UNIVERSIDAD MIGUEL HERNÁNDEZ

DEPARTAMENTO DE PATOLOGÍA Y CIRUGÍA

TRATAMIENTO MULTIMODAL DE LA CARCINOMATOSIS PERITONEAL MEDIANTE CIRUGÍA RADICAL Y QUIMIOHIPERTERMIA INTRAPERITONEAL PERIOPERATORIA. ANÁLISIS FARMACOCINÉTICO Y FARMACODINÁMICO DEL OXALIPLATINO TRAS SU ADMINISTRACIÓN INTRAPERITONEAL CON HIPERTERMIA.

TESIS DOCTORAL

Pedro Bretcha Boix

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Los que suscriben, **Dr. Juan José Pérez Ruixo**, Director Cientifico Senior del Departamento de Farmacologia Clinica y Farmacometria de Janssen Pharmaceutica; **Dra**. **Belén Valenzuela Jiménez**, Directora de la Unidad de Farmacoterapia Personalizada de la Plataforma de Oncología del Hospital Quirón Torrevieja; y **Dr. Francisco Javier Lacueva Gomez**, Profesor titular del Área de Cirugía, del Departamento de Cirugía de la Universidad Miguel Hernández de Elche,

CERTIFICAN:

que la investigación incluida en esta Memoria para optar al Grado de Doctor, titulada:

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ha sido realizada por Pedro Bretcha Boix, bajo su dirección y supervisión, reuniendo las condiciones necesarias para que pueda aspirar con este trabajo a la obtención del Grado de Doctor.

Para que así conste, firman el presente certificado a 22 de diciembre de 2016.

Fdo. Dr. Juan José Pérez Ruixo **Fdo. Dra. Belén Valenzuela Jiménez**

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Dra. Susana Jiménez Moreno, Directora del Departamento de Cirugía de la Facultad de Medicina de la Universidad Miguel Hernández de Elche,

CERTIFICA:

que Pedro Bretcha Boix ha realizado bajo la coordinación de este Departamento su Memoria de Tesis Doctoral, titulada:

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Cumpliendo todos los objetivos previstos, finalizando su trabajo en forma satisfactoria para su defensa pública y capacitándole para optar al Grado de Doctor.

Lo que certifico en San Juan de Alicante a 9 de Enero de 2017.

Fdo. Dra. Susana Jiménez Moreno

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PRODUCCIÓN CIENTÍFICA DEL DOCTORANDO

Las publicaciones científicas generadas por Pedro Bretcha Boix durante su doctorado y directamente asociadas a la presente Memoria de Tesis Doctoral de la Universidad Miguel Hernández son las siguientes:

- ***Pedro Bretcha***, Jose Farré, Manuel Sureda, Carlos Dussan, Juan José Pérez Ruixo, Antonio Brugarolas Masllorens. Cytoreductive surgery and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of colonic origin: outcomes after 7 years experience of a new center for peritoneal surface malignancies. Clin Transl Oncol. 2010;12: 437-42.

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A mi esposa
A mis hijos
A mis padres

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"El éxito consiste en obtener lo que se desea.
La felicidad, en disfrutar lo que se obtiene"
Emerson (1803-1882)

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Pere Bretcha Boix
Diciembre de 2016 (Alicante)

Índice

Índice de Figuras

Índice de Tablas

Lista de Abreviaturas

[Prol]	Compartment Representing Prolifereative Cells
[Transit]	Compartment Representing Maturating Cells
[Circ]	Compartment Describing Circulating Blood Cells
α	Intercept of the Power Function Quantifying the Drug Effect
5-FU	5-Fluorouracil
ALT	Alaninte Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve Concentration
AUC^N	Normalized AUC
AUC^N_{PR}	Normalized AUC_{0-1} in Peritoneum
AUC^N_{PL}	Normalized $AUC_{0-tlast}$ in Plasma
$AUC_{0-tlast}$	Individual AUC from 0 to the Last Experimental Time
β	Power Coefficient of the Power Function Quantifying the Drug Effect
BSA	Body Surface Area
C_e	Effect Compartement
CI/F	Estimated Apparent Oxaliplatin Plasma Clearance
$C^N_{max\ PL}$	Normalized C in Plasma
Circ	Circulation Compartment
Circ0	Baseline Value of the Absolute Neutrophil Count

CI	Confidence Interval
Cl	Systemic Clearance
Cl_a	Plasma Clearance
Cl_p	Intercompartmental Clearance
cm	Centimeter
C_{max}	Maximum Plasma Drug Concentration
$C_{max\ PR}$	Maximum Concentratium in Peritoneum
$C^N_{max\ PR}$	Normalized Maximum Concentratium in Peritoneum
C_{tlast}	Observed Concentration at the Last Sampling Point
CP	Carcinomatosis Peritoneal
CRS	Citoreductive Surgery
CT	Computed Tomography
CV	Coefficient of Variation
dl	Deciliter
EBE	Empirical Bayes' Estimates of Model Parameters
E_{drug}	Drug Effect
EPIC	Early Postoperative Intraperitoneal Chemotherapy
F	Oxaliplatin Absolute Bioavailability
FOCE	First-Order Conditional Estimation Method
γ	Feedback Effect on the Proliferation Process
G-CSF	Granulocyte Colony-Stimulating Factor
GOF	Goodness Of Fit
h	Hours
HIO	Hyperthermic Intraperitoneal Oxaliplatin
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
HR	Hazard Ratio

ICP-AES	Inductively Coupled Plasma Atomic Emission Spectrometry
IM_{max}	Maximum Inhibitory Effect of Surgical Stress on MTT
IIV	Between Subject Variability or Interindividual Variability
IV	Intravenous
k_{circ}	First-Order Elimination Rate Constant of the Circulating Neutrophils
k^0_{prol}	The First-Order Proliferation Rate Constant
k_{prol}	First-Order Production Rate Constant of the Sensitive Progenitor Cells
k_{tr}	First-Order Transit Rate Constant
k_p	First-Order Disappearance Rate Constant of the Surgical Stress Effect on Proliferation
Km	Kilometer
kz	Terminal Rate Constant
L	Liter
L/h	Liter per Hour
LRT	Likelihood Ratio Test
m^2	Squared Meter
mg	Miligrame
µg	Microgram
min	Minute
mL	Mililiter
MTT	Mean Transit Time from Bone Marrow to Peripheral Circulation (Blood)

MTT_0	Mean Transition Time at a Time Before Surgery
MVOF	Minimum Value of the Objective Function
ΔMVOF	Change Minimum Value of the Objective Function
n	Sample Size
NCA	Non-Compartmental Analysis
NONMEM	Non-linear Mixed Effects Models
NPDE	Normalized Prediction Distribution Errors
NPC	Numerical Predictive Check
OS	Overall-Survival
p	p-value
pcVPC	Prediction Corrected Visual Predictive Check
PCI	Peritoneal Carcinomatosis Index
PD	Pharmacodynamic
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetic
PK/PD	Pharmacokinetic and Pharmacodynamic
PSOGI	Peritoneal Surface Oncologic Group International
Q_2	Intercompartmental Flow between Central and Catenary Compartment
Q_3	Intercompartmental Flow between Central and Shallow Compartment
Q_4	Intercompartmental Flow between Central and Deep Compartment
Q_a	Plasma Clearance
RSE	Relative Standard Error
SAEM	Stochastic Approximation Expectation Maximization
SD	Mean

SP_{max}	Maximum Stimulatory Effect of Surgical Stress
SPSC	Standard Palliative Surgery and Chemotherapy
T	Duration of Peritoneal Perfusions
t1/2	Terminal Half-life
t1/2β	Beta Half-life
tlast	Last Experimental Time
ts	Start time
TNFα	Tumor Necrosis Factor
ULN	Upper Limit of Normal
USA	United States of America
V1	Central Volume of Distribution
V2	Volume of Distribution of Catenary Compartment
V3	Volume of Distribution of Shallow Compartment
V4	Volume of Distribution of Deep Compartment
Va	Volume of Distribution in Peritoneum
Vc	Central Volume of Distribution
Vc/F	Oxaliplatin Apparent Central Volume of Distribution
Vp	Peripheral Volume of Distribution
VPC	Visual Predictive Check
WHO	World of Health Organisation
$\chi 2$	Chi-Square Test

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CAPÍTULO I.

Introducción y Objetivos

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1. *Introducción.*

La carcinomatosis peritoneal (CP) es una afectación de la serosa peritoneal, tanto visceral como parietal, por tumores mayoritariamente de origen gastrointestinal y ginecológicos aunque también existen los primarios de peritoneo como son el mesotelioma y el seroso-papilar primario. Representa una forma de progresión tumoral desalentadora y considerada como estadio IV sin diferenciarse de otras localizaciones metastásicas (1).

La metástasis peritoneal es un proceso de múltiples fases incluyendo el desprendimiento de células tumorales del tumor primario, la adhesión al peritoneo visceral o parietal, la invasión del espacio submesotelial, la angiogénesis y la proliferación celular allí donde asienten.

La CP suele manifestarse de forma muy diversa, desde escasos implantes milimétricos adyacentes al tumor primario, hasta la ocupación de todo el abdomen y la pelvis por masas tumorales voluminosas. El tamaño y la extensión de la enfermedad peritoneal no influyen en la definición del término CP. La mayoría de los pacientes con CP evolucionan hacia la obstrucción intestinal, la formación de ascitis, la caquexia tumoral o la combinación de todas ellas. El término CP se asocia con tumores muy avanzados y/o estadios tumorales terminales sin posibilidades terapéuticas curativas.

El tratamiento habitual de la CP es de índole paliativo mediante el uso de quimioterapia sistémica asociada o no a la cirugía. Estos tratamientos consiguen períodos de supervivencia limitados que varían según el origen del tumor, la histología y la extensión de la CP. Un estudio prospectivo y multicéntrico que incluyó a pacientes con CP de origen gástrico, colorrectal y pancreático demostró la relación de la mediana de supervivencia con el origen del tumor y el volumen de la enfermedad peritoneal, siendo la supervivencia de tan sólo 3,1, 5,2 y 2,1 meses, respectivamente (2). En otros trabajos publicados antes del año 2002, y que incluyeron series extensas de pacientes con CP de origen colorrectal, las supervivencias medias referidas fueron de 5 a 9 meses (3). Protocolos más actuales de quimioterapia sistémica que contemplan nuevos fármacos como el oxaliplatino o el irinotecán, solos o en asociación con otros tratamientos biológicos, consiguen prolongar la supervivencia de estos pacientes a 21,5-24 meses (4, 5).

La evolución natural y la respuesta a los quimioterápicos administrados por vía sistémica en la enfermedad peritoneal son significativamente peores que en otras localizaciones metastásicas, como la hepática o la pulmonar (4). Hasta la fecha, no se ha publicado ningún estudio que haya valorado la respuesta de los pacientes con enfermedad metastásica exclusiva peritoneal a estas nuevas líneas de

quimioterápicos. Es excepcional que un paciente diagnosticado de CP y sometido a cualquier tipo de tratamiento paliativo permanezca vivo a los 5 años del tratamiento.

El peritoneo es la primera línea de defensa contra la diseminación peritoneal de un cáncer abdominal. Es conocido que las células cancerígenas se implantan hasta 100 veces más eficientemente en el peritoneo traumatizado que en el intacto. A su vez la formación de fibrina inmediatamente tras el trauma quirúrgico favorece el atrapamiento de células malignas convirtiéndose en zonas de santuario terapéutico para el tratamiento sistémico.

En los últimos años, se ha incrementado el interés por la diseminación peritoneal de los tumores, debido a los mejores resultados clínicos conseguidos con los tratamientos multimodales y a los recientes conocimientos sobre el desarrollo y el crecimiento tumoral peritoneal, que han permitido considerar la CP como una enfermedad locorregional subsidiaria de beneficiarse de un tratamiento de intensificación terapéutica regional, tal y como actualmente se realiza con éxito en el tratamiento de la enfermedad metastásica a nivel hepático (6).

En 1989, Paul H. Sugarbaker estableció las bases de un tratamiento multidisciplinar en la CP que asocia la cirugía citorreductora radical y la administración inmediata de quimioterápicos a nivel intraperitoneal, con o sin hipertermia, orientados a erradicar el tumor microscópico residual tras la cirugía (7, 8).

El pronóstico de los pacientes con CP sometidos a tratamiento multidisciplinar está relacionado directamente con la extensión de la CP y la consecución de una cirugía radical (9) siendo el objetivo la extirpación de todo el tumor de la cavidad abdominal sin dejar ningún residuo tumoral macroscópico visible mediante resecciones viscerales y técnicas de peritonectomia descritas por el mismo autor (7, 8). Este tipo de cirugía suele denominarse “citorreducción completa” (CRS). La extensión y distribución de la enfermedad tumoral peritoneal debe ser establecida por completo antes de iniciar el proceso de la cirugía radical, y para ello se han descrito varios sistemas de clasificación siendo el más usado el índice de carcinomatosis peritoneal (PCI en inglés) descrito en su día por Sugarbaker (7).

El PCI combina la distribución de los implantes tumorales y el tamaño de los mismos (LS: lesión size en inglés) con el fin de determinar una puntuación. LS-0 indica que no se evidencia tumor; LS-1 indica la existencia de implantes tumorales hasta 0,5 cm; LS-2 cuando los implantes están entre 0,5 y 5 cm; y LS-3 cuando son mayores de 5 cm. La distribución del tumor se determina según 13 regiones abdominopelvicas definidas, de manera que el PCI tiene un rango posible de 0 a 39.

Tras finalizar la cirugía de citorreducción (CRS) el cirujano debe indicar el grado conseguido. Una puntuación CC-0 indica que no queda tumor visible tras la citorreducción; CC-1 cuando los nódulos restantes son < 2,5 mm; CC-2 cuando éstos son entre 2,5 mm y 2,5 cm y CC-3 cuando son > 2, 5 cm o confluencia de nódulos irresecables en cualquier localización. El principal factor que imposibilita la CRS es la afectación masiva del intestino delgado o su mesenterio, ya que supondría una extensa resección intestinal (10). En la carcinomatosis de origen colorectal, la obstrucción biliar o la gran afectación del ligamento gastrohepático generalmente se asocia a imposibilidad de conseguir un CC-0 (11). De ahí la importancia de la adecuada selección preoperatoria de los pacientes.

La quimioterapia administrada de forma regional pretende alcanzar concentraciones altas de un agente citotóxico en un punto determinado del organismo. Administrada por vía intraperitoneal permite realizar un tratamiento muy intensivo de los tumores localizados en la cavidad abdominal en relación con la dosis de fármacos utilizada. El objetivo primario de la quimioterapia intraperitoneal es conseguir la máxima interacción fármaco/tumor minimizando los efectos secundarios derivados de su paso a la ciruculación sistémica. Las concentraciones tisulares logradas con los quimioterápicos cuando se administran en la cavidad peritoneal son del orden de 20 a 400 veces superiores a las conseguidas mediante la administración endovenosa, y los gradientes de concentración peritoneo/plasmáticos de 20:1 a 1.400:165 (12). El máximo beneficio citotóxico se consigue cuando la administración de quimioterapia se realiza inmediatamente después de la cirugía, antes del "atrapamiento" celular tumoral por la fibrina y de la compartimentación de la cavidad abdominal por las adherencias posquirúrgicas.

La asociación del calor a la quimioterapia intraperitoneal potencia el efecto terapéutico regional de algunos quimioterápicos y provoca un "shock tóxico" directo sobre las células tumorales. La hipertermia *in vitro* provoca la destrucción de las células tumorales cuando se alcanzan temperaturas de 43ºC. En cambio las células normales resisten temperaturas de hasta 45ºC (13).

La hipertermia ha demostrado su eficacia clínica antitumoral en diversos estudios aleatorizados, ya sea como mecanismo directo por la mayor termosensibildad de las células tumorales o debido al efecto potenciador que ejerce sobre la radioterapia y la quimioterapia. A nivel clínico, los mayores efectos tumoricidas de la hipertermia se consiguen entre 41 y 43ºC. La pérdida de un grado de temperatura significa dividir por 10 la eficacia y por encima de 43ºC puede aparecer toxicidad, expresada fundamentalmente por lesiones sobre la permeabilidad de la membrana peritoneal y la viabilidad del intestino delgado (14).

El grupo internacional de oncología de la superficie peritoneal (PSOGI siglas en inglés) reunido en Madrid en el año 2004 y posteriormente en San Diego en el año 2006, acordó referirse a este

procedimiento como HIPEC (hyperthermic intraperitoneal chemotherapy) con la intención de consensuar diversos protocolos de tratamiento en la carcinomatosis peritoneal (15, 16).

Este abordaje comprende un cambio conceptual en cuanto a la administración de la quimioterapia, tanto por la ruta como por el momento en el que se propone respecto al acto quirúrgico. El fármaco idóneo para su uso intraperitoneal perioperatorio con hipertermia debe cumplir una série de características como son la capacidad de penetrar en el tumor, tener una baja difusión hacia el espacio subperitoneal del endotelio capilar para evitar una excesiva exposición sistémica al fármaco, poseer una actividad citotóxica sinérgica con la temperatura y no ser dependiente del ciclo celular (16, 17). Así, se prefieren fármacos que se eliminen del cuerpo rápidamente y, por tanto, los compuestos hidrofílicos de elevado peso molecular con limitada permeabilidad a través de la membrana peritoneal son preferibles a compuestos lipofílicos de bajo peso molecular y elevada permeabilidad. En este sentido, la actividad citotóxica de cisplatino, mitomicina C, carboplatino, paclitaxel, irinotecan y oxaliplatino se ve reforzada con la hipertermia y justifica su evaluación como agentes en HIPEC.

Uno de los fármacos más utilizados en el contexto de HIPEC es el oxaliplatino ya que cumple los criterios anteriormente citados. Se trata de un fármaco activo frente una gran variedad de tipos de tumores sólidos y más concretamente para el tratamiento del cáncer colorrectal. Es un agente atractivo para el uso en HIPEC ya que su citotoxicidad se ve aumentada significativamente por la hipertermia y su penetración intratumoral es óptima (18). Además se ha evidenciado que la citorreducción quirúrgica seguida de HIPEC con oxaliplatino prolonga la supervivencia media de 23,9 a 62,7 meses y aumenta la tasa de supervivencia a 5 años de 13% a 51% con respecto a la cirugía paliativa estándar y quimioterapia sistémica (19). Sin embargo, después de su administración intravenosa aumenta el riesgo de toxicidad hematológica y neuropatía sensorial periférica de forma dosis-dependiente. Por tanto, es primordial lograr la máxima exposición de oxaliplatino en la cavidad peritoneal con un acceso mínimo a la circulación sistémica con el fin de encontrar el equilibrio adecuado entre la actividad citotóxica loco-regional y el riesgo de toxicidad sistémica. En este sentido, diversos estudios Fase I evidencian que la dosis máxima tolerada de oxaliplatino intraperitoneal en condiciones hipertérmicas (HIO) es de 200 a 460 mg/m^2 administrado durante 0,5 a 2 h (20).

En estos estudios, el oxaliplatino mostró un comportamiento farmacocinético lineal tiempo independiente, tanto en plasma como en peritoneo. A nivel peritoneal experimentó una disminución exponencial de las concentraciones con una vida media de 30 a 40 minutos, y en plasma experimentó un aumento de las concentraciones hasta alcanzar la concentración máxima (C_{max}) poco después del final de la infusión intraperitoneal. El valor medio de la constante aparente de absorción (k_a) del oxaliplatino de peritoneo al plasma es de 1,4 h^{-1} (21, 22, 23). Después del tratamiento con HIPEC, las

concentraciones plasmáticas de oxaliplatino descienden de manera bi-exponencial, similar a lo que sucede tras una administración intravenosa. A una dosis de 460 mg/m^2 de oxaliplatino se obtiene una C_{max} 25 veces mayor en peritoneo (330 µg/mL) que en plasma (13.2 mg/mL), que se traduce en una mayor exposición del tumor al oxaliplatino y, potencialmente, en un tratamiento más eficaz para la CP que la administración intravenosa (24). Sin embargo, los parámetros farmacocinéticos obtenidos a partir de las concentraciones plasmáticas alcanzadas tras HIPEC varían considerablemente entre estudios reflejando diferencias en relación a el analito (ultrafiltrado frente a platino total), método de análisis para la detección de platino en plasma (espectroscopía de absorción atómica, cromatografía líquida, o de espectrometría de emisión atómica acoplada a plasma), y la solución de soporte utilizada (soluciones isotónicas, hipotónicas o hipertónicas) (25). En este contexto, no es sorprendente que las estimaciones en la semivida plasmática de oxaliplatino oscilaran entre 12,9 horas a 37,5 horas y 40 horas, mientras que el volumen de distribución se estimó entre 15 L y 19 L (20).

En estos estudios, también se describen la neutropenia y trombocitopenia como las reacciones adversas más frecuentes relacionadas con el oxaliplatino (17). Stewart *y col.* (21) comprobaron que el grado de toxicidad hematológica está relacionada con la tasa de absorción sistémica de oxaliplatino a la dosis de 250 mg/m^2 administrados durante 2 h.

Si bien la primera fase del tratamiento multimodal, es decir la citorreducción, queda bien definida, existen multitud de incógnitas en todo lo relativo a la perfusión intraperitoneal debido a las diversas variables que interactúan. La mayoría de los protocolos existentes administran el fármaco de acuerdo con la superficie corporal, tal y como se suele realizar en el ámbito de la oncología médica, sin evaluar la diversidad de fenotipos de los individuos. Debe tenerse en cuenta que, a una misma superficie corporal, puede haber diferencias en la capacidad volumétrica abdominal traduciéndose en una dilución o concentración de una misma dosis de fármaco. Esta circunstancia claramente incide en la exposición de la célula tumoral al fármaco. Otra de las variables fundamentales que obviamente incide en la exposición loco-regional del fármaco es la duración de la perfusión intraperitoneal, que a su vez condicionará la toxicidad sistémica.

En los estudios de la adecuada exposición del fármaco al tumor puede tener interés la solución de dilución utilizada durante la perfusión. En el ámbito quirúrgico se han realizado estudios con distintas soluciones administradas a nivel de la cavidad abdominal con el objetivo de minimizar las inevitables adherencias postquirúrgicas causantes de morbilidad tardía en forma de oclusión intestinal o síndrome adherencial. Su mecanismo de acción es mediante la separación física por hidroflotación de las superficies peritoneales dañadas. Una de las soluciones más prometedoras es la de icodextrina al 4% por ser un coloide isotónico de alto peso molecular. Esta característica la hace inócua para la membrana

peritoneal y permite que se mantenga el volumen instilado durante los primeros días del postoperatorio, momento en el que existe el máximo proceso inflamatorio y reparación mesotelial que deriva en la formación de adherencias (26). Los estudios realizados han demostrado la acción osmótica de este coloide que permite la retención del fluido en la cavidad peritoneal durante 4 días (27). Estas bondades de la icodextrina al 4% puede ser interesante para ser considerada en el HIPEC, ya que podría mantener el volumen intraperitoneal de forma más estable durante la perfusión, y por tanto hipotéticamente mantener una concentración estable del fármaco minimizando la absorción del mismo al torrente circulatorio. De esta forma también podría disminuir la toxicidad sistémica en el postoperatorio de estos pacientes.

Por otro lado el uso de suero glucosado al 5% como solución para la perfusión con oxaliplatino plantea efectos colaterales indeseados como son la hiperglucemia, hiponatremia y acidosis láctica durante el HIPEC y en el postoperatorio inmediato, requiriendo de vigilancia exhaustiva durante el procedimiento (28). Esto es así por tratarse de una solución isotónica de bajo peso molecular, y por ende fácil de atravesar la membrana peritoneo plasmática.

Este complejo procedimiento multimodal se asocia a una relativamente elevada morbilidad (30-60%), potencial mortalidad (1-10%) y a una prolongada estancia hospitalaria (29-32). Todo ello requiere de un esfuerzo por parte de los equipos multidisciplinares que conllevará una inevitable curva de aprendizaje para optimizar los resultados tanto a corto plazo en el postoperatorio temprano, como en términos de supervivencia libre de enfermedad y global. Para conseguir resultados adecuados es preciso establecer grupos de trabajo que agrupe a los profesionales de las distintas disciplinas implicadas en el manejo de los pacientes con CP mediante un programa asistencial específico que permita la interrelación personal, la difusión del conocimiento y el abordaje transversal del proceso terapéutico.

2. *Objetivos.*

Por todo lo expuesto en el epígrafe anterior los objetivos de esta memoria de tesis doctoral han sido los siguientes:

1.- Implementar el tratamiento multimodal radical de la CP en un centro hospitalario y analizar el beneficio clínico de la cirugía citorreductora seguida de HIPEC en pacientes diagnosticados de CP de origen colorrectal.

2.- Caracterizar la relación entre la exposición peritoneal-sistémica (farmacocinética) y la toxicidad hematológica (farmacodinámica) del oxaliplatino tras su administración intraperitoneal intraoperatoria con hipertermia.

3.- Evaluar el uso de dos vehículos de perfusión (icodextrina al 4% y dextrosa al 5%) desde el punto de vista quirúrgico, clínico y económico.

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CAPÍTULO II.

Cytoreductive surgery and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of colonic origin. Outcomes after 7 years' experience of a new center for peritoneal surface malignancies.

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1. *Abstract.*

Introduction: Peritoneal carcinomatosis is a relatively frequent situation in the natural history of colorectal cancer and is associated with a dismal prognosis. Promising results have been shown after radical cytoreduction followed by intraperitoneal chemohyperthermic perfusion. The aim our study was to assess the outcomes after treating patients with peritoneal carcinomatosis of colonic origin by means of cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) followed by early postoperative intraperitoneal chemotherapy (EPIC).

Methods: Tumour resection was performed in accordance with the guidelines for oncologic surgery. Selective peritonectomies and remnant nodule electroevaporation were performed with the aim of achieving a complete cytoreduction. Peritoneal perfusion was carried out according to the Coliseum technique at 0.5–1 L/min, and chemotherapy was administered at 42ºC for 40–90 min. Mitomycin C 10–12.5 mg/m^2 or oxaliplatin 360 mg/m^2 was used. Postoperative intraperitoneally administered 5-fluorouracil (5-FU) (650 mg/m^2 per day) was given for 5 consecutive days.

Results: Twenty patients were treated from 2001 to 2008. The mean peritoneal cancer index was 11 (range 2–39). Fifteen patients had undergone complete cytoreductive surgery. The morbidity was 40%. There was one case of death due to bone marrow aplasia. Ten patients had recurrence; five of them underwent salvage surgery. Two patients were treated with a second HIPEC. Actuarial overall survival and progression-free survival were 36% and 30% at 5 years, respectively, with a median follow-up of 18 (range 8–28) months.

Conclusions: Cytoreductive surgery combined with HIPEC is a feasible technique that might increase patient survival. It represents a potential cure for selected patients who have no other alternatives.

2. *Introduction.*

Despite curative surgery, between 20–30% of colorectal cancer patients develop local relapse. Peritoneal carcinomatosis is a frequent sign of therapeutic failure in patients with colorectal cancer and has been considered a sign of widespread disease and a therapeutic challenge, as it is treated palliatively and the outcome is inevitably fatal. Actually, most patients with peritoneal carcinomatosis die within the first year. Patients often suffer from disabling symptoms due to local tumour progression that is

much faster than in other oncologic patients. Therefore, treatment of this condition has focused more on the location of the disease than on its histology. In recent years, newer chemotherapeutic regimens have become available for patients with metastases from colorectal cancer. Although the response rates to these treatments have improved, long-term survival remains limited. In fact, these trials included patients with systemic metastases. However, there is no current data in the literature to support systemic chemotherapy as the standard of care of peritoneal carcinomatosis [1–3]. Despite the poor prognosis of this condition, there has been an interest in treating it since the 1980s. Different therapies have been examined, such as the use of intraperitoneal chemotherapy. This procedure appears to be the most promising; consists of a combination of exeresis and the maximum possible dose of regional chemotherapy. Drug concentrations in the peritoneal area are expected to be much higher than those obtained after administering chemotherapy through the systemic pathway. The action of these drugs is boosted by heat, which in itself has a cytotoxic effect [4–7]. Dr. Paul H. Sugarbaker is considered the father of this technique. However, at a meeting of the international medical community held in Madrid in 2004, it was agreed that this technique should be referred to as HIPEC [8]. The objective of this study was to assess in our centre the viability of cytoreductive surgery plus HIPEC followed by early postoperative intraperitoneal chemotherapy (EPIC) to treat peritoneal carcinomatosis of colonic origin.

3. *Materials and Methods.*

The study was carried out in the Hospital San Jaime between 2001 and 2008 as part of a programme to study and treat malignant diseases of the peritoneum. The study was approved by the Institute's Ethics and Clinical Trials Committee, and all patients signed the specific informed consent form for this procedure after being told about the associated benefi ts and risks. Inclusion criteria were patients with colorectal carcinomatosis, synchronous or metachronous carcinomatosis, no extra-abdominal metastasis, no evidence of bowel obstruction and a satisfactory cardiorespiratory and renal status. Exclusion criteria were unresectable primary tumours, renal or cardiac failure and a World Health Organisation (WHO) performance scale >2. The workup included a complete colonoscopic evaluation as well as a computed tomography (CT) scan of the chest, abdomen and pelvis to evaluate the extent of peritoneal dissemination. A positron emission tomography (PET) scan was performed when there was any question of extra-abdominal disease [9].

Surgical procedure

Firstly, a balanced general anaesthetic was administered, and all hemodynamic parameters were carefully monitored. Subsequently, a medial xiphopubic laparotomy was carried out and the entire abdominal cavity examined. Tumour load was assessed and the peritoneal cancer index (PCI) obtained [4]. The abdomen was divided into 13 areas numbered from zero to 12, as described by Sugarbaker [10]. Cytological samples and biopsies were taken from each area. Resection of the primary tumour when present was carried out according to oncological criteria (lymphadenectomy with the correct margins). In carcinomatosis with the primary tumour in situ and in metachronous cases, peritonectomies and debulking was carried out as required. In other words, extensive systematic peritonectomies were not performed. The mesenteric peritoneum was not extensively removed, but acceptable small-bowel resections guided by maximal tumour volume locations were performed. Remaining malignant granulations were destroyed using electrosurgical fulguration. The aim was to leave no macroscopic tumours. Anastomoses were not carried out until perfusion of the abdominal cavity had been completed. The cytoreduction obtained by surgery was considered complete (CCR-0) when no residual implants remained. When residual implants persisted, they were classified as CCR-1 if they were <2.5 mm, CCR-2 between 2.5 mm and 2.5 cm and CCR-3 if >2.5 cm [11].

Peritoneal chemotherapy

In all cases, the open coliseum technique was used, following Sugarbaker's description [4]. Four 36-Fr drains were connected to a continuous closed circuit, and two intraperitoneal thermal probes were placed to obtain a proper temperature feedback. The rollers of an extracorporeal circulation machine, set at a speed of 500 mL/min, were used to deliver the perfusate. The circuit passed through a heat exchanger, which raised the temperature to 48ºC. Once the temperature was obtained, the drug was diluted in 3–5 L of 5% dextrose peritoneal dialysis fluid. During perfusion, the surgeon distributed the fluid in the cavity intermittently, and special attention was paid to the hemodynamic parameters. The temperature of the liquid on the abdominal cavity fluctuated between 42º and 43ºC. The length of the perfusion varied between 40 and 90 min, depending on which drug was administered. Afterwards, the infusion liquid was evacuated. The first seven patients of our series were treated with mitomycin C according to the protocol described by Sugarbaker elsewhere [12, 13]. Following the seminar publication of Elias et al. [14, 15], we initiated a phase I dose escalation study with oxaliplatin followed by 5-fluorouracil (5-FU) in peritoneal surface malignancy patients, including patients with primary diagnosis of colorectal cancer, among other studies. However, we did not administered IV chemotherapy 1 h before the intraperitoneal perfusion, as in Elias protocol. Six patients with a diagnosis of colorectal

cancer were also part of a phase I study in which the initial oxaliplatin dose, 90 mg/m^2 , was escalated up to 360 mg/ m^2 according to a modified Fibonacci scheme [6]. Twentyfour hours after completing the surgical procedure, 650 mg/m^2 of 5-FU was administered intraperitoneally daily for 5 consecutive days. Each dose was kept for 24 h in the peritoneum before its removal. After reaching oxaliplatin at a dosage of 360 mg/m^2 in the absence of dose-limiting toxicities, 24 additional patients were recruited to receive this dose level in order to expand our experience with this protocol, which has been proven to be safe up to date. Actually, results of the phase 1 study are subject of a separate manuscript that is currently under preparation. All patients in the study remained in the intensive care unit for the 5 days of the EPIC. Once a patient had been discharged from the hospital, clinical, analytical and radiological follow-ups were carried out after a month and subsequently every 3 months.

Statistical analysis

Data were analysed using the S plus version 6.0 for Windows (Insightful, Seattle, WA, USA). The Kaplan–Meier test was used to analyse progression-free (PFS) and overall (OS) survival, stratified by PCI, CCR. Due to the limited sample size of our series, a p value of 0.10 was selected as a cutoff for statistical significance. However, the nature of the analysis was purely exploratory or hypothesis generating, and no confirmatory claims can be derived from it. Thus, the point estimate of the hazard ratio (HR), the associated 95% confidence intervals (CIs) and the p values were determined to assist in evaluating the association between CCR or PCI and PFS or OS, and therefore should be cautiously interpreted.

4. *Results.*

Patient's characteristics

During the study period, 75 procedures were performed in 69 patients with diverse aetiology (ovary in 24, colon in 20, appendicular in eight, gastric in nine, endometrial in five, primary peritoneal in two and mesothelioma in one). Twenty patients were diagnosed with peritoneal carcinomatosis after colorectal cancer diagnosis: 12 women and eight men. The mean age was 55.5 (range 25–78) years. Primary tumours were found in the following locations: right colon in six patients, transverse colon in one, left colon in ten and rectum in three. In addition, 12 patients were diagnosed as being metachronous. Therefore, they had already undergone surgical interventions, mainly in other centres. All patients but one had received prior systemic chemotherapy. Five patients presented liver metastases that were treated

during the same surgical intervention either with metatarsectomies or radiofrequency ablation. HIPEC was carried out immediately after resection of the primary tumour, if present, with peritoneal disease resection.

Surgical procedure

The mean PCI was 11 (range 2–39). By the end of surgery, 15 patients could be considered CCR-0 resections, one CCR-1, and four CCR-2. There was no intraoperative mortality, and the procedure was completed in all cases. The average length of the operation was 7 h (range 5–9 h). There was one case of postoperative mortality due to grade IV aplasia. Overall, 40% of patients experienced toxicity of severity grade II–IV. It was distributed as follows: two cases of hemoperitoneum, one of anastomotic dehiscence, two of sepsis, one of biliary fistula, one intestinal fistula and one subphrenic abscess. Reoperation had to be carried out on two patients due to a haemoperitoneum and biliary fistulae. The average length of hospitalisation was 17.8 (range 10–48) days.

Chemotherapy

The average temperature measured with an oesophageal catheter was 38.5ºC (range 37–39.5ºC). The average temperature in the abdominal cavity was 42ºC (range 39–43ºC). No intolerance to hyperthermia was observed. In 16 patients, EPIC was carried out during the 5 established days. In four cases, treatment had to be suspended for sepsis in one patient, biliary fistulae in one and severe abdominal pain in two.

Relapse and survival results

There were two deaths during the study period: one in the late postoperative period, as mentioned above, and the other from a myocardial infarct 3 months after surgery. Disease progression was observed in ten patients during the followup period: in the lungs in two, liver in three, peritoneum in five, anastomosis in one and retroperitoneum in one. Salvage surgery was carried out in five cases. Two patients underwent a second HIPEC. One of them was disease free at 19 months but the other died at 18 months due to tumour progression. Six patients were alive and disease free as this was written. Seven of them had survived for >2 years. Results of the overall Kaplan–Meier analysis for OS and PFS, stratified by PCI and CCR, are shown in Figs. II-1–II-6. Actuarial OS and PFS according to the Kaplan–Meier test was 36% (95% CI: 18.1–72.7) (Fig. II-1) and 30% (95% CI: 12.5–72) (Fig. II-4) at 5 years, respectively, with a median follow-up of 18 (range 8–28) months. When patients were divided according to whether they had a PCI above or below 13 and the completeness of cytoreduction, statistically

significant differences in OS were seen (Figs. II-2-II-3) but not in PFS (Figs. II-5-II-6), probably due to the limited sample size.

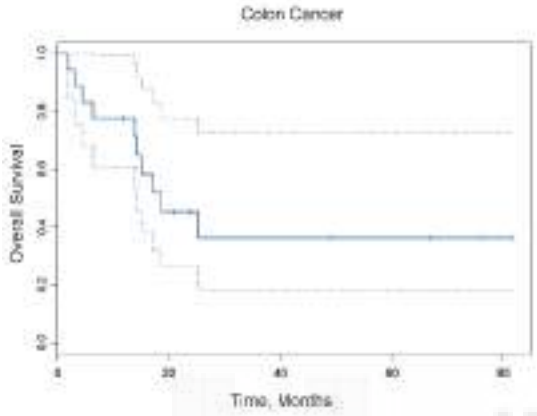

Fig II-1: Kaplan Meier curve for overall survival

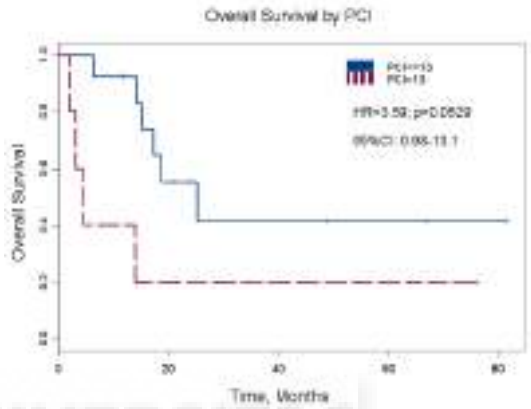

Fig II-3: Kaplan Meier curve for overall survival stratified by peritoneal cancer index

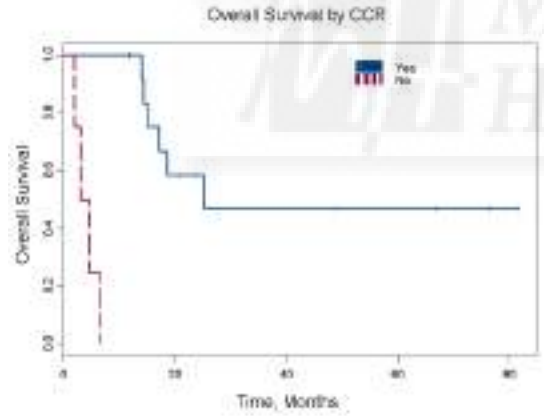

Fig II-2: Kaplan Meier curve for overall survival stratified by completeness of cytoreduction

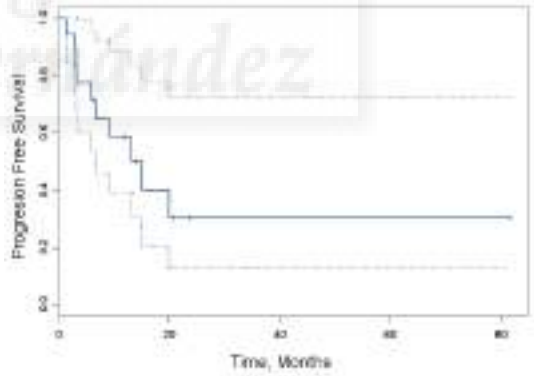

Fig III-4: Kaplan Meier curve for progression free survival

5. *Discussion.*

The incidence of colorectal cancer is increasing in the Western world. In Spain alone, 20,000 new cases are diagnosed per year. Of these, 25% develop peritoneal carcinomatosis, the natural course of which is associated with an average survival of 6 months [16]. Peritoneal carcinomatosis can occur at the same time as the primary tumour or in relapse after surgical resection. In the first case, cell dissemination is spontaneous after the tumour has invaded the serosa or perforated the affected organ. In the second case, carcinomatosis can even occur in the absence of lymphatic or hematogenous metastases. Dissemination of tumour cells in the peritoneum can be spontaneous or occur during surgery, by mechanisms such as the formation of tumour emboli as a result of pressure, escape of malignant cells when cutting the lymphatic vessels or spread of such cells in the peritoneal cavity during surgical dissection. Subsequently, these cells usually invade or perforate the serosa. Once the primary tumour has been ablated, cell-growth factors involved in cicatrization stimulate the growth of viable malignant cells that are trapped or found in intraabdominal blood clots or in fibrin in traumatised peritoneal surfaces. As these cells are trapped, it is difficult to reach them with systemic chemotherapy. Thus, such chemotherapy becomes less effective and may even have no effect [4, 13, 17]. Since 1980, new methods for treating patients with tumour dissemination in the peritoneum have appeared in the literature. Such patients are difficult to treat both therapeutically and emotionally; the initial therapy has failed and a rapid and progressive loss in quality of life is experienced [18]. In 1982, Sugarbaker proposed that peritoneal dissemination of certain cancers was a locoregional stage of the disease [11]. Therefore, he developed a therapeutic alternative based on surgical treatment of the macroscopic peritoneal disease by means of radical cytoreductive surgery, followed by HIPEC to treat the residual microscopic disease.

The surgery reduces the peritoneal disease to a minimum size and frees the patient of all adherences. This creates optimal conditions in which to increase the efficacy of cytostatic drugs.

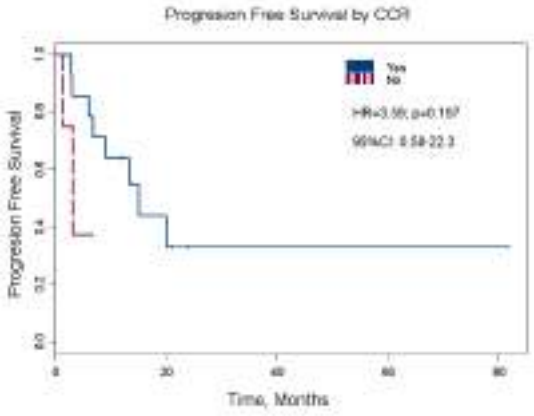

Fig II-5: Kaplan Meier curve for progression free survival stratified by completeness of cytoreduction

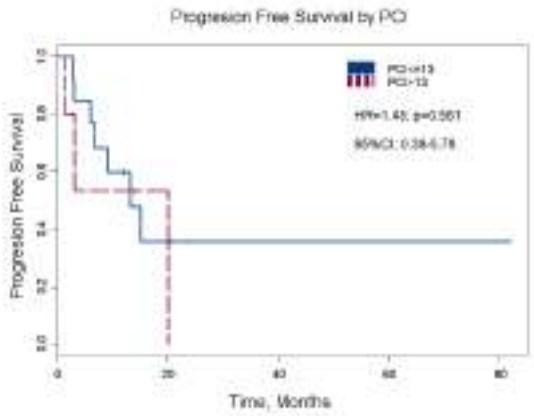

Fig II-6: Kaplan Meier curve for progression free stratified by peritoneal cancer index

Using this therapeutic approach, 5-year survival rates of 30% and 50% were obtained in selected groups of patients who had previously been considered terminal. Similar results were reported by other groups after using this complex technique [12, 14, 18–23]. A multicentric study involving 506 patients with peritoneal carcinomatosis of colonic origin demonstrated a better prognosis after complete cytoreduction and HIPEC than after incomplete surgery alone (the average survival was 32.4 *vs*. 8.4 months). The 5-year survival rate was 31% [24]. Verwaal et al. carried out the first phase III study using this procedure. They randomised 105 patients with peritoneal carcinomatosis due to colorectal cancer.

Half of the patients were given standard treatment, whereas the other group was treated with surgery + HIPEC. After an average follow-up period of 21.6 months, survival of the first group was 12.6 months and that of the HIPEC group 22.4 months, p = 0.032. In the HIPEC group, only one patient died out of the 18 who underwent complete cytoreduction (CCR-1). Fourteen patients died out of the 21 who had a residual tumour after surgery that was <2.5 mm (CCR-1a). Seven patients died in the follow-up period out of the ten who had extensive residual disease after surgery [25]. The same group analysed the results of 117 patients treated with cytoreduction + HIPEC. In this case, the 5-year survival rate was 43% [26]. Initially, our group administered the drugs following Sugarbaker's protocols [12]. However, data from papers by Elias et al., who administered oxaliplatin (460 mg/m^2) and 5-FU (400 mg/m^2) with endovenous leucovorin (20 mg/m^2) 1 h prior to the perfusion [27] showed the best results published to date (a 5-year survival rate of 48.5% with a median of 60.1 months of follow-up). Therefore, we decided to change our protocol while maintaining the EPIC. Two patients presented grade IV aplasia after administration of oxaliplatin at the described dose (one case in the colon and one in the ovary).

Therefore, we undertook a dose escalation study in groups of three patients, beginning with oxaliplatin 90 mg/m^2 and increasing 60 mg/m^2 until reaching dose-limiting toxicity at 360 mg/m^2. The role of EPIC is still not clearly defined. Some studies report that it has no benefits [28]. However, our group is of the opinion that intraperitoneal and early postoperative chemotherapy should be used to achieve the maximum effect. In early postoperative chemotherapy, specific cellcycle drugs maintained in the peritoneal cavity for long periods before the inevitable process of adherence formation should have added value [29, 30]. Clearly, a combination of two aggressive treatments entails greater morbidity and mortality rates. However, these rates are similar to those found in the other complex surgical procedures frequently used in oncologic surgery [31, 32]. Therefore, morbidity and mortality in our series was in line with that described in the literature.

Some studies have shown that a carcinomatosis index >13 according to Sugarbaker's rating, and an incomplete cytoreduction have a poor prognosis. Our experience supports the result of these studies with respect to OS. Although PFS was not statistically associated with PCI and CCR, the HR indicated a trend to worse outcome in patients with PCI >13 and incomplete cytoreduction. Thus, it appears that when surgery cannot be radical and there is not enough reduction in tumour volume, HIPEC is not indicated, as the benefi ts in terms of survival are minimal [13, 24, 32–34]. Consequently, the results presented suggest that the appropriate selection of the patients who can benefi t from this treatment is critical. In our case, we followed the criteria adopted by the Peritoneal Surface Oncology Group in 2006 [9]. We can compare the situation of isolated peritoneal carcinomatosis to that of isolated liver metastasis, in which good long-term survival rates can be obtained by performing surgical exeresis of macroscopic disease and subsequently administration of systemic treatment for the residual microscopic disease. The combination of cytoreductive surgery and perioperative intraperitoneal chemotherapy in peritoneal carcinomatosis of colorectal origin leads to 5-year survival rates similar to those published for resection of liver metastasis of the same origin [8, 35]. Further studies should assess the potential benefi ts and risks associated with the optimisation of the different components of this treatment, such as the drug and its dose, the length of HIPEC, the level of hyperthermia and the extent of debulking. Standardisation of treatment protocols as well as conducting phase II and III multi-institutional studies have been suggested as the path towards better understanding the treatment of this disease and optimising clinical outcomes [36]. The results described in this paper show the potential treatment modality. Selecting the patients appropriately, fine tuning the technical procedures and increasing the availability of new chemotherapy drugs should lead to a substantial improvement in results. Combining this therapy with other locoregional or systemic therapeutic methods will pave the way for new promising lines of work for a group of patients who currently have no other option than palliative care.

6. *Conflict of interest*

This manuscript has not been published and is not under consideration for publication elsewhere. All authors have read the manuscript and have approved this submission. The authors report no conflict of interest.

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8. *Annex II-1. Original Publication: "Cytoreductive surgery and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosisof colonic origin: outcomes after 7 years' experience of a new centre for peritoneal surface malignancies".*

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RESEARCH ARTICLES

Cytoreductive surgery and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of colonic origin: outcomes after 7 years' experience of a new centre for peritoneal surface malignancies

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Abstract
Introduction Peritoneal carcinomatosis is a relatively frequent situation in the natural history of colorectal cancer and is associated with a dismal prognosis. Promising results have been shown after radical cytoreduction followed by intraperitoneal chemohyperthermic perfusion. The aim our study was to assess the outcomes after treating patients with peritoneal carcinomatosis of colonic origin by means of cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) followed by early postoperative intraperitoneal chemotherapy (EPIC).
Methods Tumour resection was performed in accordance with the guidelines for oncologic surgery. Selective peritonectomies and remnant nodule electroevaporation were performed with the aim of achieving a complete cytoreduction. Peritoneal perfusion was carried out according to the Coliseum technique at 0.5–1 L/min, and chemotherapy was administered at 42°C for 40–90 min. Mitomycin C 10–12.5 mg/m² or oxaliplatin 300 mg/m² was used. Postoperative intraperitoneally administered 5-fluorouracil (5-FU) (650 mg/m² per day) was given for 5 consecutive days.
Results Twenty patients were treated from 2001 to 2008. The mean peritoneal cancer index was 11 (range 2–39). Fifteen patients had undergone complete cytoreductive surgery. The morbidity was 40%. There was one case of death due to bone marrow aplasia. Ten patients had recurrence; five of them underwent salvage surgery. Two patients were treated with a second HIPEC. Actuarial overall survival and progression-free survival were 36% and 30% at 5 years, respectively, with a median follow-up of 18 (range 8–28) months.
Conclusions Cytoreductive surgery combined with HIPEC is a feasible technique that might increase patient survival. It represents a potential cure for selected patients who have no other alternatives.

Keywords Colorectal cancer · Peritoneal carcinomatosis · Intraperitoneal chemotherapy · Intraoperative chemotherapy · Peritoneal surface malignancy · HIPEC · Peritoneal perfusion

Introduction

Despite curative surgery, between 20–30% of colorectal cancer patients develop local relapse. Peritoneal carcinomatosis is a frequent sign of therapeutic failure in patients with colorectal cancer and has been considered a sign of widespread disease and a therapeutic challenge, as it is treated palliatively and the outcome is inevitably fatal. Actually, most patients with peritoneal carcinomatosis die within the first year. Patients often suffer from disabling symptoms due to local tumour progression that is much faster than in other oncologic patients. Therefore, treatment of this condition has focused more on the location of the disease than on its histology.

In recent years, newer chemotherapeutic regimens have become available for patients with metastases from col-

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orectal cancer. Although the response rates to these treatments have improved, long-term survival remains limited. In fact, these trials included patients with systemic metastases. However, there is no current data in the literature to support systemic chemotherapy as the standard of care of peritoneal carcinomatosis [1–3].

Despite the poor prognosis of this condition, there has been an interest in treating it since the 1980s. Different therapies have been examined, such as the use of intraperitoneal chemotherapy. This procedure appears to be the most promising; consists of a combination of exeresis and the maximum possible dose of regional chemotherapy. Drug concentrations in the peritoneal area are expected to be much higher than those obtained after administering chemotherapy through the systemic pathway. The action of these drugs is boosted by heat, which in itself has a cytotoxic effect [4–7].

Dr. Paul H. Sugarbaker is considered the father of this technique. However, at a meeting of the international medical community held in Madrid in 2004, it was agreed that this technique should be referred to as HIPEC [8].The objective of this study was to assess in our centre the viability of cytoreductive surgery plus HIPEC followed by early postoperative intraperitoneal chemotherapy (EPIC) to treat peritoneal carcinomatosis of colonic origin.

Materials and methods

The study was carried out in the Hospital San Jaime between 2001 and 2008 as part of a programme to study and treat malignant diseases of the peritoneum. The study was approved by the Institute's Ethics and Clinical Trials Committee, and all patients signed the specific informed consent form for this procedure after being told about the associated benefits and risks. Inclusion criteria were patients with colorectal carcinomatosis, synchronous or metachronous carcinomatosis, no extra-abdominal metastasis, no evidence of bowel obstruction and a satisfactory cardiorespiratory and renal status. Exclusion criteria were unresectable primary tumours, renal or cardiac failure and a World Health Organisation (WHO) performance scale >2. The workup included a complete colonoscopic evaluation as well as a computed tomography (CT) scan of the chest, abdomen and pelvis to evaluate the extent of peritoneal dissemination. A positron emission tomography (PET) scan was performed when there was any question of extra-abdominal disease [9].

Surgical procedure

Firstly, a balanced general anaesthetic was administered, and all hemodynamic parameters were carefully monitored. Subsequently, a medial xiphopubic laparotomy was carried out and the entire abdominal cavity examined. Tumour load was assessed and the peritoneal cancer index (PCI) obtained [4]. The abdomen was divided into 13 areas numbered from zero to 12, as described by Sugarbaker [10]. Cytological samples and biopsies were taken from each area. Resection of the primary tumour when present was carried out according to oncological criteria (lymphadenectomy with the correct margins). In carcinomatosis with the primary tumour in situ and in metachronous cases, peritonectomies and debulking was carried out as required. In other words, extensive systematic peritonectomies were not performed. The mesenteric peritoneum was not extensively removed, but acceptable small-bowel resections guided by maximal tumour volume locations were performed. Remaining malignant granulations were destroyed using electrosurgical fulguration. The aim was to leave no macroscopic tumours. Anastomoses were not carried out until perfusion of the abdominal cavity had been completed.

The cytoreduction obtained by surgery was considered complete (CCR-0) when no residual implants remained. When residual implants persisted, they were classified as CCR-1 if they were <2.5 mm, CCR-2 between 2.5 mm and 2.5 cm and CCR-3 if >CC3 [11].

Peritoneal chemotherapy

In all cases, the open coliseum technique was used, following Sugarbaker's description [4]. Four 36-Fr drains were connected to a continuous closed circuit, and two intraperitoneal thermal probes were placed to obtain a proper temperature feedback. The rollers of an extracorporeal circulation machine, set at a speed of 500 ml/min, were used to deliver the perfusate. The circuit passed through a heat exchanger, which raised the temperature to 48°C. Once the temperature was obtained, the drug was diluted in 3–5 L of 5% dextrose peritoneal dialysis fluid. During perfusion, the surgeon distributed the fluid in the cavity intermittently, and special attention was paid to the hemodynamic parameters. The temperature of the liquid on the abdominal cavity fluctuated between 42° and 43°C. The length of the perfusion varied between 40 and 90 min, depending on which drug was administered. Afterwards, the infusion liquid was evacuated.

The first seven patients of our series were treated with mitomycin C according to the protocol described by Sugarbaker elsewhere [12, 13]. Following the seminar publication of Elias et al. [14, 15], we initiated a phase I dose-escalation study with oxaliplatin followed by 5-fluorouracil (5-FU) in peritoneal surface malignancy patients, including patients with primary diagnosis of colorectal cancer, among other studies. However, we did not administered IV chemotherapy 1 h before the intraperitoneal perfusion, as in Elias protocol. Six patients with a diagnosis of colorectal cancer were also part of a phase I study in which the initial oxaliplatin dose, 90 mg/m², was escalated up to 360 mg/

m^2 according to a modified Fibonacci scheme [6]. Twenty-four hours after completing the surgical procedure, 650 mg/m^2 of 5-FU was administered intraperitoneally daily for 5 consecutive days. Each dose was kept for 24 h in the peritoneum before its removal. After reaching oxaliplatin at a dosage of 360 mg/m^2 in the absence of dose-limiting toxicities, 24 additional patients were recruited to receive this dose level in order to expand our experience with this protocol, which has been proven to be safe up to date. Actually, results of the phase 1 study are subject of a separate manuscript that is currently under preparation.

All patients in the study remained in the intensive care unit for the 5 days of the EPIC. Once a patient had been discharged from the hospital, clinical, analytical and radiological follow-ups were carried out after a month and subsequently every 3 months.

Statistical analysis

Data were analysed using the S plus version 6.0 for Windows (Insightful, Seattle, WA, USA). The Kaplan–Meier test was used to analyse progression-free (PFS) and overall (OS) survival, stratified by PCI, CCR. Due to the limited sample size of our series, a p value of 0.10 was selected as a cutoff for statistical significance. However, the nature of the analysis was purely exploratory or hypothesis generating, and no confirmatory claims can be derived from it. Thus, the point estimate of the hazard ratio (HR), the associated 95% confidence intervals (Cis) and the p values were determined to assist in evaluating the association between CCR or PCI and PFS or OS, and therefore should be cautiously interpreted.

Results

Patient's characteristics

During the study period, 75 procedures were performed in 69 patients with diverse aetiology (ovary in 24, colon in 20, appendicular in eight, gastric in nine, endometrial in five, primary peritoneal in two and mesothelioma in one). Twenty patients were diagnosed with peritoneal carcinomatosis after colorectal cancer diagnosis: 12 women and eight men. The mean age was 55.5 (range 25–78) years. Primary tumours were found in the following locations: right colon in six patients, transverse colon in one, left colon in ten and rectum in three. In addition, 12 patients were diagnosed as being metachronous. Therefore, they had already undergone surgical interventions, mainly in other centres. All patients but one had received prior systemic chemotherapy. Five patients presented liver metastases that were treated during the same surgical intervention either with metatarsectomies or radiofrequency ablation. HIPEC was carried out immediately after resection of the primary tumour, if present, with peritoneal disease resection.

Surgical procedure

The mean PCI was 11 (range 2–39). By the end of surgery, 15 patients could be considered CCR-0 resections, one CCR-1, and four CCR-2. There was no intraoperative mortality, and the procedure was completed in all cases. The average length of the operation was 7 h (range 5–9 h). There was one case of postoperative mortality due to grade IV aplasia. Overall, 40% of patients experienced toxicity of severity grade II–IV. It was distributed as follows: two cases of hemoperitoneum, one of anastomotic dehiscence, two of sepsis, one of biliary fistula, one intestinal fistula and one subphrenic abscess. Reoperation had to be carried out on two patients due to a haemoperitoneum and biliary fistulae. The average length of hospitalisation was 17.8 (range 10–48) days.

Chemotherapy

The average temperature measured with an oesophageal catheter was 38.5°C (range 37–39.5°C). The average temperature in the abdominal cavity was 42°C (range 39–43°C). No intolerance to hyperthermia was observed. In 16 patients, EPIC was carried out during the 5 established days. In four cases, treatment had to be suspended for sepsis in one patient, biliary fistulae in one and severe abdominal pain in two.

Relapse and survival results

There were two deaths during the study period: one in the late postoperative period, as mentioned above, and the other from a myocardial infarct 3 months after surgery. Disease progression was observed in ten patients during the follow-up period: in the lungs in two, liver in three, peritoneum in five, anastomosis in one and retroperitoneum in one. Salvage surgery was carried out in five cases. Two patients underwent a second HIPEC. One of them was disease free at 19 months but the other died at 18 months due to tumour progression. Six patients were alive and disease free as this was written. Seven of them had survived for >2 years.

Results of the overall Kaplan–Meier analysis for OS and PFS, stratified by PCI and CCR, are shown in Figs. 1–6. Actuarial OS and PFS according to the Kaplan–Meier test was 36% (95% CI: 18.1–72.7) (Fig. 1) and 30% (95% CI: 12.5–72) (Fig. 4) at 5 years, respectively, with a median follow-up of 18 (range 8–28) months. When patients were divided according to whether they had a PCI above or below 13 and the completeness of cytoreduction, statistically significant differences in OS were seen (Figs. 2-3) but not in PFS (Figs. 5-6), probably due to the limited sample size.

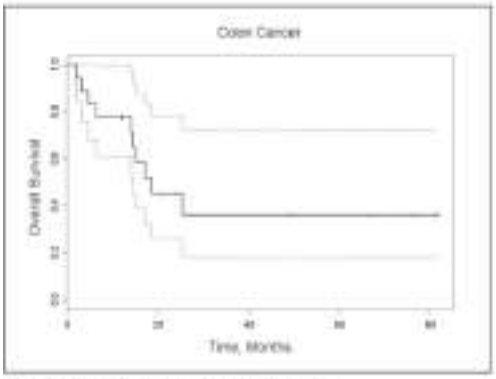

Fig. 1 Kaplan–Meier curve for overall survival

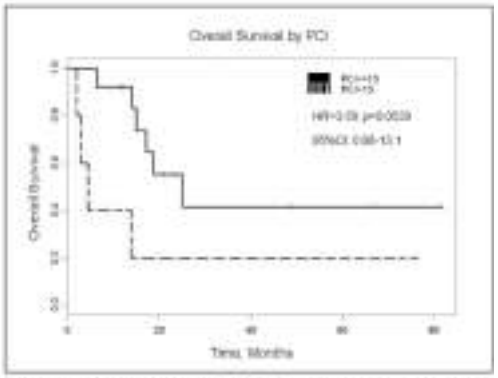

Fig. 3 Kaplan Meier curve for overall survival stratified by peritoneal cancer index

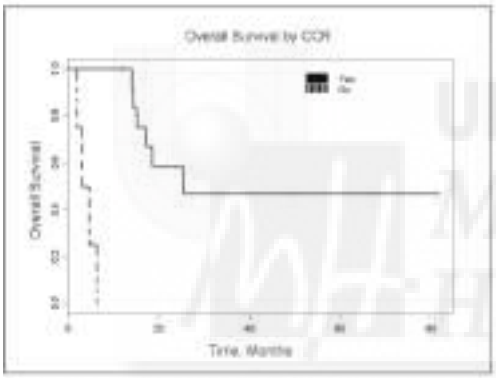

Fig. 2 Kaplan Meier curve for overall survival stratified by completeness of cytoreduction

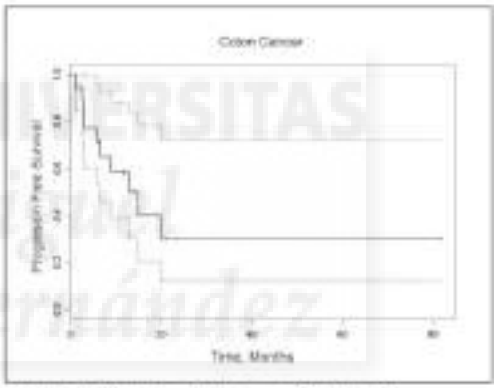

Fig. 4 Kaplan Meier curve for progression free survival

Discussion

The incidence of colorectal cancer is increasing in the Western world. In Spain alone, 20,000 new cases are diagnosed per year. Of these, 25% develop peritoneal carcinomatosis, the natural course of which is associated with an average survival of 6 months [16]. Peritoneal carcinomatosis can occur at the same time as the primary tumour or in relapse after surgical resection. In the first case, cell dissemination is spontaneous after the tumour has invaded the serosa or perforated the affected organ. In the second case, carcinomatosis can even occur in the absence of lymphatic or hematogenous metastases. Dissemination of tumour cells in the peritoneum can be spontaneous or occur during surgery, by mechanisms such as the formation of tumour emboli as a result of pressure, escape of malignant cells when cutting the lymphatic vessels or spread of such cells in the peritoneal cavity during surgical dissection. Subsequently, these cells usually invade or perforate the serosa.

Once the primary tumour has been ablated, cell-growth factors involved in cicatrization stimulate the growth of viable malignant cells that are trapped or found in intra-abdominal blood clots or in fibrin in traumatised peritoneal surfaces. As these cells are trapped, it is difficult to reach them with systemic chemotherapy. Thus, such chemotherapy becomes less effective and may even have no effect [4, 13, 17]. Since 1980, new methods for treating patients with tumour dissemination in the peritoneum have appeared in the literature. Such patients are difficult to treat both therapeutically and emotionally; the initial therapy has failed and a rapid and progressive loss in quality of life is experienced [18].

In 1982, Sugarbaker proposed that peritoneal dissemination of certain cancers was a locoregional stage of the disease [11]. Therefore, he developed a therapeutic alternative based on surgical treatment of the macroscopic peritoneal disease by means of radical cytoreductive surgery, followed by HIPEC to treat the residual microscopic disease.

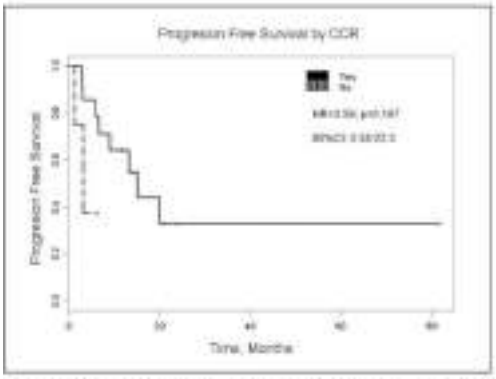

Fig. 5 Kaplan Meier curve for progression free survival stratified by completeness of cytoreduction

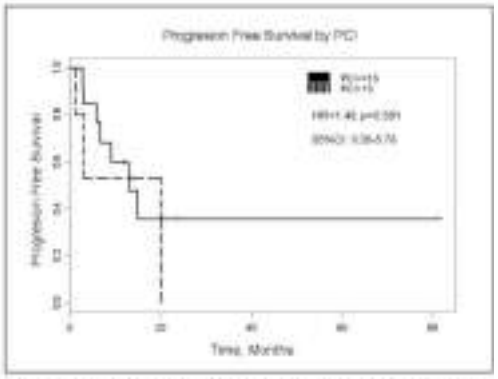

Fig. 6 Kaplan Meier curve for progression free survival stratified by peritoneal cancer index

The surgery reduces the peritoneal disease to a minimum size and frees the patient of all adherences. This creates optimal conditions in which to increase the efficacy of cytostatic drugs. The antineoplastic effects of the chemotherapy are enhanced by heat, as this causes an increase in cell permeability and changes in the active transport of the drugs and alterations in cell metabolism.

Using this therapeutic approach, 5-year survival rates of 30% and 50% were obtained in selected groups of patients who had previously been considered terminal. Similar results were reported by other groups after using this complex technique [12, 14, 18–23].

A multicentric study involving 506 patients with peritoneal carcinomatosis of colonic origin demonstrated a better prognosis after complete cytoreduction and HIPEC than after incomplete surgery alone (the average survival was 32.4 vs. 8.4 months). The 5-year survival rate was 31% [24]. Verwaal et al. carried out the first phase III study using this procedure. They randomised 105 patients with peritoneal carcinomatosis due to colorectal cancer. Half of the patients were given standard treatment, whereas the other group was treated with surgery + HIPEC. After an average follow-up period of 21.6 months, survival of the first group was 12.6 months and that of the HIPEC group 22.4 months, $p = 0.032$. In the HIPEC group, only one patient died out of the 18 who underwent complete cytoreduction (CCR-1). Fourteen patients died out of the 21 who had a residual tumour after surgery that was <2.5 mm (CCR-1a). Seven patients died in the follow-up period out of the ten who had extensive residual disease after surgery [25]. The same group analysed the results of 117 patients treated with cytoreduction + HIPEC. In this case, the 5-year survival rate was 43% [26].

Initially, our group administered the drugs following Sugarbaker's protocols [12]. However, data from papers by Elias et al., who administered oxaliplatin (460 mg/m^2) and 5-FU (400 mg/m^2) with endovenous leucovorin (20 mg/m^2) 1 h prior to the perfusion [27] showed the best results published to date (a 5-year survival rate of 48.5% with a median of 60.1 months of follow-up). Therefore, we decided to change our protocol while maintaining the EPIC. Two patients presented grade IV aplasia after administration of oxaliplatin at the described dose (one case in the colon and one in the ovary). Therefore, we undertook a dose escalation study in groups of three patients, beginning with oxaliplatin 90 mg/m^2 and increasing 60 mg/m^2 until reaching dose-limiting toxicity at 360 mg/m^2.

The role of EPIC is still not clearly defined. Some studies report that it has no benefits [28]. However, our group is of the opinion that intraperitoneal and early postoperative chemotherapy should be used to achieve the maximum effect. In early postoperative chemotherapy, specific cell-cycle drugs maintained in the peritoneal cavity for long periods before the inevitable process of adherence formation should have added value [29, 30]. Clearly, a combination of two aggressive treatments entails greater morbidity and mortality rates. However, these rates are similar to those found in the other complex surgical procedures frequently used in oncologic surgery [31, 32]. Therefore, morbidity and mortality in our series was in line with that described in the literature.

Some studies have shown that a carcinomatosis index >13 according to Sugarbaker's rating, and an incomplete cytoreduction have a poor prognosis. Our experience supports the result of these studies with respect to OS. Although PFS was not statistically associated with PCI and CCR, the HR indicated a trend to worse outcome in patients with PCI >13 and incomplete cytoreduction. Thus, it appears that when surgery cannot be radical and there is not enough reduction in tumour volume, HIPEC is not indicated, as the benefits in terms of survival are minimal [13, 24, 32–34]. Consequently, the results presented suggest that the appropriate selection of the patients who can benefit from this treatment is critical. In our case, we fol-

lowed the criteria adopted by the Peritoneal Surface Oncology Group in 2006 [9].

We can compare the situation of isolated peritoneal carcinomatosis to that of isolated liver metastasis, in which good long-term survival rates can be obtained by performing surgical exeresis of macroscopic disease and subsequently administration of systemic treatment for the residual microscopic disease. The combination of cytoreductive surgery and perioperative intraperitoneal chemotherapy in peritoneal carcinomatosis of colorectal origin leads to 5-year survival rates similar to those published for resection of liver metastasis of the same origin [8, 35].

Further studies should assess the potential benefits and risks associated with the optimisation of the different components of this treatment, such as the drug and its dose, the length of HIPEC, the level of hyperthermia and the extent of debulking. Standardisation of treatment protocols as well as conducting phase II and III multi-institutional studies have been suggested as the path towards better understanding the treatment of this disease and optimising clinical outcomes [36]. The results described in this paper show the potential treatment modality. Selecting the patients appropriately, fine tuning the technical procedures and increasing the availability of new chemotherapy drugs should lead to a substantial improvement in results. Combining this therapy with other locoregional or systemic therapeutic methods will pave the way for new promising lines of work for a group of patients who currently have no other option than palliative care.

Conflict of interest This manuscript has not been published and is not under consideration for publication elsewhere. All authors have read the manuscript and have approved this submission. The authors report no conflict of interest.

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CAPÍTULO III.

Pharmacokinetic and Pharmacodynamic Analysis of Hyperthermic Intraperitoneal Oxaliplatin-Induced Neutropenia in Subjects with Peritoneal Carcinomatosis

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1. *Abstract.*

The objective of this study was to characterize the pharmacokinetics and the time course of the neutropenia-induced by hyperthermic intraperitoneal oxaliplatin (HIO) after cytoreductive surgery in cancer patients with peritoneal carcinomatosis. Data from 30 patients who received 360 mg/m^2 of HIO following cytoreductive surgery were used for pharmacokinetic–pharmacodynamic (PK/PD) analysis. The oxaliplatin plasma concentrations were characterized by an open two-compartment pharmacokinetic model after first-order absorption from peritoneum to plasma. An oxaliplatin-sensitive progenitor cell compartment was used to describe the absolute neutrophil counts in blood. The reduction of the proliferation rate of the progenitor cells was modeled by a linear function of the oxaliplatin plasma concentrations. The typical values of oxaliplatin absorption and terminal half-lives were estimated to be 2.2 and 40 h, with moderate interindividual variability. Oxaliplatin reduced the proliferation rate of the progenitor cells by 18.2% per mg/L. No patient's covariates were related to oxaliplatin PK/PD parameters. Bootstrap and visual predictive check evidenced the model was deemed appropriate to describe oxaliplatin pharmacokinetics and the incidence and severity of neutropenia. A peritoneum oxaliplatin exposure of 65 and 120 mg·L/h was associated with a 20% and 33% incidence of neutropenia grade 4. The time course of neutropenia following HIO administration was well described by the semiphysiological PK/PD model. The maximum tolerated peritoneum oxaliplatin exposure is 120 mg L/h and higher exposures should be avoided in future studies. We suggest the prophylactic use of granulocyte colony stimulating factor for patients treated with HIO exposure higher than 65 mg L/h.

2. *Introduction*

For many patients with peritoneal carcinomatosis (PC) secondary to intra-abdominal cancers, tumor progression in the peritoneum is the sole life-limiting component of disease and one of the most common causes of cancer incurability. However, there are no PC treatment approved by regulatory agencies, and the development of new therapies to manage this life-threatening condition could fulfill an unmet medical need. In this context, several Phase I/II clinical studies in gastric cancer (1–3), mesothelioma (4), colorectal (5), or ovarian carcinoma (6) have shown promising results in treating macroscopic PC with cytoreductive surgery and residual PC with hyperthermic intraperitoneal chemotherapy (HIPEC) (7). The rationale for this treatment is based on experimental studies showing that drug penetration is limited to a few cell layers under the surface of the tumor (8), and consequently, intraperitoneal chemotherapy must be immediately administered after the cytoreductive surgery in order to achieve the maximal cytotoxic activity on residual tumor cells before they get trapped in the postoperative fibrin adhesions (9). In addition, the intratumoral cytotoxic activity can be enhanced by

administering highly permeable drugs at relatively high doses with hyperthermia. The efficacy of this approach has been evidenced in Phase III studies in colorectal cancer patients (10,11).

The ideal drug for HIPEC should penetrate into the tumor, have a low diffusion into the subperitoneal space and capillary endothelial in order to avoid excessive drug systemic exposure, and have a temperature dependent cytotoxic activity. Therefore, drugs rapidly metabolized and/or excreted from the Body should be preferred over others as they should decrease the systemic exposure and the risk of toxicity. Consequently, large hydrophilic compounds with limited permeability across an intact peritoneal membrane have been preferred to small lipophilic compounds (12). In this context, cisplatin (13), mytomicin C (14), carboplatin (15), paclitaxel (16), irinotecan (17), and oxaliplatin (18) have been used as chemotherapy agents in HIPEC because their cytotoxic activity is enhanced with hyperthermia. Although comparative studies across these drugs have not been performed to date, the results obtained with oxaliplatin are encouraging. In a retrospective analysis in patients with resectable PC, Elias et al. have shown that surgical cytoreduction followed by HIPEC with oxaliplatin prolongs median survival from 23.9 to 62.7 months and increase the 5-year survival rate from 13% to 51% with respect to standard palliative surgery and chemotherapy (19).

Oxaliplatin, a diaminocyclohexane–platinum compound active in a variety of solid tumor types, licensed in the USA and Europe for the treatment of colorectal cancer, is an attractive agent for HIPEC because its cytotoxicity is significantly increased by hyperthermia (20,21) and the intratumoral penetration is optimal (22). However, systemic exposure to oxaliplatin increases the risk of hematological toxicity and peripheral sensory neuropathy, which have been described as dose-limiting toxicities after intravenous treatment (23). Therefore, it is important to achieve the maximum oxaliplatin exposure in the peritoneal cavity with minimum access to systemic circulation, in order to balance the cytotoxic activity and the risk of toxicity. Several Phase I dose-escalation studies in subjects with PC were conducted to determine the maximum tolerated dose of hyperthermic intraperitoneal oxaliplatin (HIO) and characterized its pharmacokinetics (PK) as a single agent (24–26). In these studies, intraperitoneal doses ranging from 200 to 460 mg/m^2 were administered during 0.5 to 2 h and oxaliplatin exhibited linear and time-independent PK in both plasma and peritoneum. While oxaliplatin peritoneal concentrations decline in an exponential manner with a half-life of 30 to 40 min (22, 27, 28), oxaliplatin plasma concentrations increase to reach the maximum shortly after the end of the intraperitoneal infusion. The mean value of apparent oxaliplatin absorption rate constant (k_a) from peritoneum to plasma was close to 1.4 h^{-1} (22, 27, 28). After treatment with HIO, oxaliplatin plasma concentrations declined in a bi-exponential manner resembling to the PK profiles observed after an intravenous administration. At an oxaliplatin dose level of 460 mg/m^2, the peak concentration (C_{max}) was estimated to be 25-fold

higher in peritoneum (330 μg/mL) than in plasma (13.2 μg/mL) (24,25) which indicates an increased oxaliplatin tumor exposure and, potentially, a more efficacious treatment for residual PC than its intravenous administration. However, the pharmacokinetic parameters obtained from plasma concentrations achieved following HIO vary substantially from one study to others reflecting differences in relation to (1) the analyte (ultrafiltrate vs total platinum), (2) analytical method for measuring plasma platinum content (atomic absorption spectroscopy, liquid chromatography, or inductively coupled plasma atomic emission spectrometry), and (3) the carrier solution used (isotonic, hypotonic, or hypertonic solutions) (29). In this context, is not surprising that the estimated oxaliplatin plasma clearance ranged from 6.68 L/h/m^2 (27) to 28.4 L/h/m^2 (28), while the volume of distribution is estimated to be 15 L (27). In these studies, the most frequent and severe adverse events related with oxaliplatin were neutropenia and thrombocytopenia (24–27). Stewart et al. (26) reported that hematologic toxicity grade was related to the extent and the rate of oxaliplatin systemic absorption at 250 mg/m^2 administered during 2 h. However, to date, there are not quantitative longitudinal analyses exploring the effect of oxaliplatin pharmacokinetics on the time course of hematological toxicity after its intraperitoneal administration. In this study, we characterize the oxaliplatin pharmacokinetics in peritoneum and plasma when is administered in an icodextrin 4% carrier solution and establish its relationship with the time course of absolute neutrophil counts (ANC) in patients with PC receiving HIO after cytoreductive surgery. A semi-mechanistic population pharmacokinetic and pharmacodynamic (PK/PD) model previously developed (30) was used to analyze the data and the effect of patient demographics and/or physiopathological factors on oxaliplatin PK/PD parameters. Finally, the relationship between oxaliplatin concentrations in peritoneum, the duration of the HIO and the incidence of severe neutropenia was explored in order to establish the maximum tolerated oxaliplatin exposure, which will be critical to optimize the design of future clinical studies with oxaliplatin in this setting.

3. *Material and Methods*

Study Design and Subject Eligibility Criteria.

Data from 30 subjects included in a single-arm study investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of HIO after cytoreductive surgery were analyzed. Adult patients were eligible if they had confirmation of PC without extra-abdominal metastasis. Other eligibility criteria included a World Health Organization performance status of 0 to 2, anticipated life expectancy of at least 3 months. Previous anticancer radiation therapy and/or chemotherapy, if given, had to be discontinued for at least 4 weeks before entry into the study, or 6 weeks in the case of

pretreatment with nitrosoureas or mitomycin C. Patients were required to have a negative pregnancy test (only for female patients with reproductive potential), and normal hepatic and renal function, defined as bilirubin ≤1.5 times the upper limit of normality, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 times the upper limit of normality, and serum creatinine ≤1.5 times the upper limit of normality. An acceptable bone marrow function, defined as white blood cells >3.5 $x10^9$/L, neutrophil count >1.5 $x10^9$/L, and platelets >100.0 $x10^9$/L was needed. Patients with one or more of the following criteria were not selected: active infection; central nervous system metastases; peripheral neuropathy >grade 2; allogenic transplant; prior extensive radiation therapy (>25% of bone marrow reserve); prior bone marrow transplantation or high dose chemotherapy with bone marrow or stem cell rescue; concurrent radiation therapy, chemotherapy, hormonal therapy, or immunotherapy; participation in a clinical trial involving an investigational drug in the past 30 days or concurrent enrollment in another investigational trial; and any coexisting medical condition that was likely to interfere with study procedures and/or results.

The study was conducted at the USP Hospital San Jaime (Torrevieja, Spain) between 2006 and 2009 in accordance with principles for human experimentation as defined in the International Conference on Harmonization for Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study was approved by the corresponding Investigational Review Board and informed consent was obtained from each subject after being advised of the potential risks and benefits, as well as, the investigational nature of the study (31). The primary tumor type of the eligible patients were ovarian (n=10), colorectal (n=9), appendiceal (n=5), gastric (n=3), endometrial (n=2), and primary papilar (n=1). A summary of patient characteristics at baseline is presented in Table III-1.

Surgical Procedure.

A xiphopubic midline laparotomy was carried out to examine the tumor load in the abdominal cavity. To obtain the peritoneal cancer index (32), the abdomen was divided into 13 areas numbered from 0 to 12, as described elsewhere (33), and cytological samples and biopsies were taken from each area. Resection of the primary tumor when present was carried out according to regional lymphadenectomy with correct margins. In carcinomatosis with the primary tumor in situ and in metachronous cases, peritonectomies and debulking were carried out as required and extensive systematic peritonectomies were not performed. The mesenteric peritoneum was not extensively removed, and acceptable small bowel resections were guided by maximal tumor volume locations. Remaining malignant granulations were destroyed using electrosurgical fulguration. This aggressive surgical cytoreduction was performed with the aim to reach complete resection or, if not possible, to

resect all visible tumor lesions larger than 2.5 mm. Anastomoses were carried out after the perfusion of the abdominal cavity was completed. The cytoreduction obtained by surgery was considered complete CC_0 (no residual implants remained), incomplete CC_1 (residual implants <2.5 mm persisted), incomplete CC_2 (residual implants ≥2.5 mm, but <2.5 cm persisted) or incomplete CC_3 (residual implants ≥2.5 cm persisted) (34).

Hyperthermic Intraperitoneal Oxaliplatin.

An open coliseum technique was used according to the procedure previously described (35). Four 36-Fr drains were connected to a continuous closed circuit, and two intraperitoneal thermal probes were placed in order to obtain a proper temperature feedback. Briefly, a Tenckhoff inflow catheter was placed centrally in the abdomen and four outflow catheters were inserted through separate stab incisions in the abdominal wall. Both the inflow and outflow catheters were connected to a perfusion pump and heat exchanger. The skin of the abdomen was attached to a retractor ring, and the abdominal cavity was covered with a plastic sheet with a small opening in the center allowing entrance for the surgeon's hands to stir the abdominal contents in order to deliver a more uniform drug distribution and heat to the intra-abdominal surfaces. The rollers of an extracorporeal circulation machine (Performer LRT, Rand) were set at a speed of 1,000 mL/min to deliver the perfusate, 4% icodextrin solution. The circuit passed through a heat exchanger which raised the temperature to 48°C. The perfusate temperature on the abdominal cavity fluctuated between 42°C and 43°C. Once the temperature was achieved, oxaliplatin 360 mg/m^2 was administered. The perfusate volume varied from patient to patient depending on the peritoneal surface area and, approximately, 2.5 to 6.0 L were employed. On average, the HIO mean duration was 40 min (range 30–60 min). After the end of perfusion, the solution was evacuated. During the next five postoperative days, 5-fluorouracil (5-FU) was administered at a dose of 15 mg/kg intraperitoneally in 1 h infusion through a 14-Fr catheter in order to potentiate the oxaliplatin cytotoxic effect (36).

Sample Collection and Bioanalytical Methods.

Peritoneal fluid and venous blood samples were collected immediately after the oxaliplatin administration and then every 10 min until the end of the peritoneal perfusion. Additional venous blood samples were drawn at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, 24, and 28 h after the end of the peritoneal perfusion. All samples were collected in S-monovette® tubes, centrifuged at 3,500 rpm for 10 min and were stored at −80°C until analysis. Total platinum in peritoneal fluid and plasma was measured using a validated assay based on inductively coupled plasma atomic emission spectrometry.

The lower limit of quantification was 0.5 mg/L. Over the validated range of the assay (0.5 to 30 mg/L for plasma samples and 5 to 300 mg/L for peritoneal fluid samples), the mean intra- and inter-assay coefficients of variation were lower than 9.5% and 7.7%, respectively. Blood samples for the determination of ANC were collected before the surgery and, afterwards, daily until patient completely recovered from the hematological toxicity. ANC were determined using an automated hematology analyzer (Beckman Coulter, Inc. AcT5diff AL, Fullerton, CA, USA).

Tabla III-1 Summary of Patient Characteristics at Baseline

Subject characteristics (N=30)	Mean (SD)	Range
Age (year)	57.9 (10.5)	32.0–75.0
Body Weight (kg)	69.3 (12.1)	42.0–90.0
Body Surface Area (m^2)	1.7 (0.2)	1.4–2.0
Sex (%)		
Male	40	
Female	60	
ALT (IU/L)	45.1 (20.1)	19.0–100
AST (IU/L)	38.9 (19.4)	10.0–83.0
Alkaline Phosphatase (IU/L)	234 (108)	52–467
Total Bilirubin (µmol/L)	0.6 (0.3)	0.2–1.6
Serum Albumin (g/L)	33.3 (10.6)	14.9–50.5
Total Protein (g/L)	59.8 (11.6)	38.8–79.3
Creatinine Clearance[a] (mL/min)	85.3 (32.9)	23.2–150.0
Hemoglobin (g/dL)	11.3 (1.5)	6.4–13.0
Leukocyte Count $x10^9$/L	7.7 (4.2)	0.4–17.8
Neutrophil $\times10^9$/L	7.5 (5.8)	1.7–26.5
Platelets $\times10^9$/L	261 (139)	115–716
Liver metastases		
No (%)	83.3	
Yes (%)	16.7	
Peritoneal Carcinomatosis Index	8.6	0.0–39.0
Complete Cytoreduction		
No (%)	33.3	
Yes (%)	66.7	

Continuous variables are expressed as mean (standard deviation) and range, whereas categorical variables are expressed as percentage (%)

[a]Creatinine Clearance was calculated using the Cockroft and Gault's formula and values higher than 150 mL/min were truncated to 150 mL/min

Pharmacokinetic and Pharmacodynamic Model Development

Software. Nonlinear mixed-effects modeling using the first-order conditional (FOCE) method implemented in (37) was used to develop the population PK/PD model and to conduct model-based simulations. Compilations were achieved using DIGITAL Visual Fortran Version 6.6C. Graphical and all other statistical analyses were performed using S-Plus 6.1 Professional Edition (Insightful, Seattle, WA, USA).

Pharmacokinetic and Pharmacodynamic Model. Oxaliplatin concentrations in peritoneal fluid evidenced a monoexponential decay, and consequently, oxaliplatin in the peritoneal fluid was assumed to be absorbed into plasma according to a linear process, characterized by the first-order absorption rate constant, k_a (Fig. III-1). As oxaliplatin concentration in the peritoneal fluid were available, the absorption process was parameterized in terms of peritoneum to plasma clearance (Q_a) and volume of distribution in the peritoneum (V_a); thus k_a was calculated as a secondary parameter (Q_a/V_a). Based on the graphical exploratory analysis, the oxaliplatin disposition in plasma was characterized by an open two-compartment model with linear elimination and nonspecific distribution to peripheral tissues (Fig. III- 1). This model was parameterized in terms of systemic clearance (Cl), intercompartmental flow (Q_2), central volume of distribution (V_c), and peripheral volume of distribution (V_p). As the oxaliplatin absolute bioavailability (F) after intraperitoneal administration is not known, F was fixed to 1; therefore, the estimated model parameters were apparent. The corresponding differential equations for each compartment were:

$$\frac{dA}{dt} = -\frac{Q_a}{V_a} \cdot A = -k_a \cdot A \qquad (1)$$

$$\frac{dC}{dt} = \frac{Q_a}{V_a} \cdot A - \frac{Q_2}{V_c} \cdot C - \frac{Cl}{V_c} \cdot C + \frac{Q_2}{V_p} \cdot P \qquad (2)$$

$$\frac{dP}{dt} = \frac{Q_2}{V_c} \cdot C - \frac{Q_2}{V_p} \cdot P \qquad (3)$$

where A, C, and P represent the oxaliplatin concentrations in peritoneal fluid, plasma, and peripheral compartment, respectively.

The semi-mechanistic model proposed by Friberg et al. (30) was used to describe the ANC time course as a function of oxaliplatin concentrations (Fig. III-1). The backbone structure of the model

consists in five compartments: one compartment represents the proliferative cells [*Prol*], such as stem cell and other progenitor cells; three transit compartments with maturating cells [*Transit*]; and one compartment of the circulating blood cells [*Circ*]. A maturation chain, with transit compartments and first-order rate constants *(k_{tr})* accounts for the lag time between the oxaliplatin administration and the observed neutropenic effects in blood. The generation of new cells in [*Prol*] was dependent on the number of cells in that compartment, which is consistent with the mechanism of self-renewal or mitosis. The first-order proliferation rate constant, kprol, determines the rate of cell division, together with the feedback mechanism from the circulating cells.

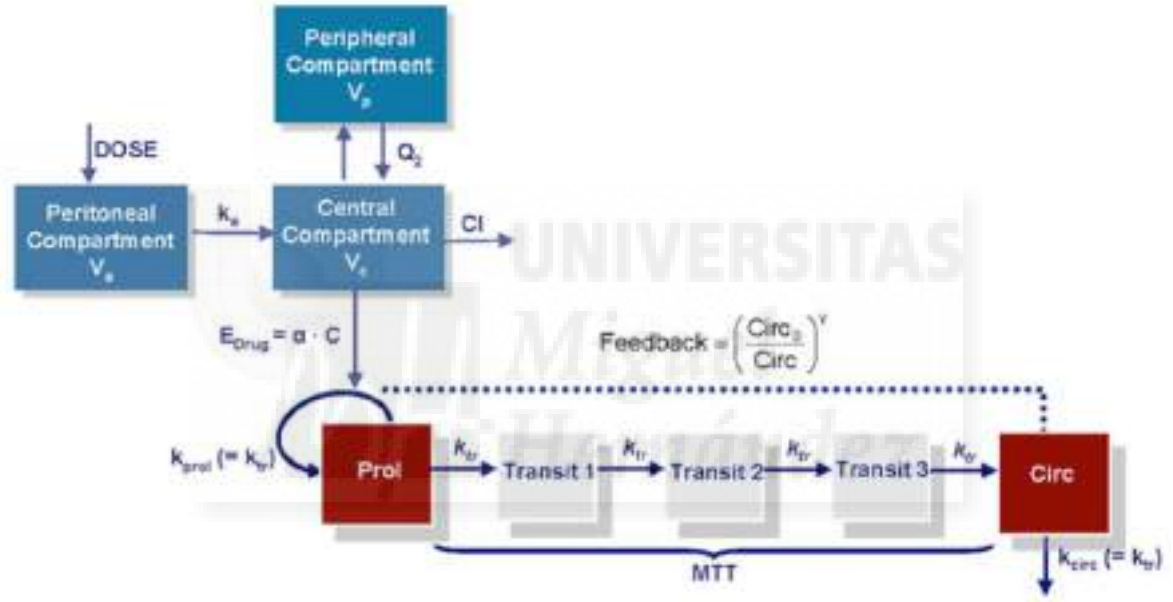

Figure III-1. Schematic of the semi-mechanistic population PK/PD model

The feedback loop was necessary to describe the rebound of ANC compared to the baseline values ($Circ_0$) and was incorporated into the model as $(Circ_0/Circ)^{\gamma}$ as previously suggested (35).

$$\frac{dProl}{dt} = k_{\text{Prol}} \cdot Prol \cdot \left(\frac{Circ_0}{Circ}\right)^{\gamma} \cdot \left(1 - E_{\text{Drug}}\right) - k_{\text{tr}} \cdot Prol \quad (4)$$

$$\frac{dTransit_1}{dt} = k_{\text{tr}} \cdot Prol - k_{\text{tr}} \cdot Transit_1 \quad (5)$$

$$\frac{dTransit_2}{dt} = k_{\text{tr}} \cdot Transit_1 - k_{\text{tr}} \cdot Transit_2 \quad (6)$$

$$\frac{dTransit_3}{dt} = k_{\text{tr}} \cdot Transit_2 - k_{\text{tr}} \cdot Transit_3 \quad (7)$$

$$\frac{dCirc}{dt} = k_{\text{tr}} \cdot Transit_3 - k_{\text{Circ}} \cdot Circ \quad (8)$$

The oxaliplatin plasma concentrations were assumed to reduce the proliferation rate according to a linear function (E_{Drug}):

$$E_{\text{Drug}} = \alpha \cdot C \quad (9)$$

where α is the slope of the linear relationship between E_{Drug} and C, and C is derived based on the empirical Bayesian estimates of the individual pharmacokinetic parameter obtained from the oxaliplatin population pharmacokinetic model previously described.

In the transit compartments, it was assumed that the only loss of cells is into the next compartments; therefore, the random loss of precursor cells was assumed to be negligible. As the proliferative cells differentiate into more mature cell types, the concentration of cells is maintained by cell division. At steadystate, before administering oxaliplatin, dProl/dt is equal to 0 and, therefore, $k_{Prol}=k_{tr}$. As the ANC data collected did not contain enough information to estimate independently k_{Circ}, itwas fixed to the population mean half life of neutrophils previously determined, 0.07 h−1 (30). To improve the interpretability, the mean transit time (MTT) was estimated as follows:

$$\text{MTT} = \frac{n+1}{k_{\text{tr}}} \quad (10)$$

where n is the number of transit compartments. MTT represents the time taken for the neutrophil to reach the circulation after leaving the proliferative compartment. Thus the structural model parameters to be estimated were the system-related parameters: $Circ_0$, MTT, and γ, and the drug-related parameter, α.

The effect of 5-FU on the inhibition of the proliferation rate and/or stimulation of the killing rate of the progenitor cells was assumed to be negligible because the low intrinsic neutropenic effects of 5-FU (38) and the relatively low doses administered, which lead to a negligible systemic exposure as evidence by the large proportion (81.5%) of 5-FU plasma concentration below the limit of quantification (0.04 mg/L).

Statistical Model. The interindividual (or between subjects) variability (IIV) in the PK/PD model parameters was assumed to follow the lognormal distribution and, consequently, an exponential error model was used. Residual variability in oxaliplatin peritoneal concentrations, oxaliplatin plasma concentrations, or ANC was evaluated using an additive error model after natural logarithmic transformation of the observations and model predictions. The magnitude of interindividual and residual variability was expressed approximately as a coefficient of variation.

Model Selection Criteria. The improvement of the fit obtained for each model was assessed in several ways. First, the resulting NONMEM-generated minimum value of the objective function (MVOF) was used to perform the likelihood ratio test. This test is based on the change in the MVOF (ΔMVOF), which is equal (up to a constant) to minus twice the log-likelihood of the data and is asymptotically distributed like χ^2 with the degrees of freedom equal to the number of parameters added to the model. ΔMVOFs of −10.83 or −12.12 were required to reach statistical significance at $p \leq 0.0010$ or $p \leq 0.0005$ for the inclusion or exclusion of one fixed effect in nested models, respectively. These stringent statistical criteria were used to avoid the inclusion of weak and clinically no relevant effects. In addition, the improvement in the fit was assessed by the reduction in the IIVand residual variability, the precision in parameter estimates, and the examination of diagnostic plots, and shrinkage (39).

Model Qualification. A nonparametric bootstrap was used as internal evaluation method to qualify the estimates of the PK/PD model parameters (40) using WINGS for NONMEM (N. Holford, Version 6.16, Auckland, New Zealand). The mean and the 95% confidence intervals of the parameter estimates from the bootstrap replicates were compared with the estimated parameters from the original dataset. In addition, a visual predictive check was performed on the time course of the 5th, 50th, and 95th percentile of the oxaliplatin peritoneal and plasma concentrations and the ANC (41).

Model-Based Simulations. Based on the PK/PD model developed, simulations were undertaken in order to explore the role of the initial oxaliplatin concentration in the peritoneum (and therefore the dose) and the duration of the HIO on the incidence of neutropenia grade 4 or grade 4 lasting at least 5 days. For a total of 12 oxaliplatin concentrations (0, 25, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, and 300 mg/L), the daily ANC was simulated for four different HIO durations (30, 40, 50, and 60 min) and the incidence of neutropenia grade 4 or grade 4 lasting at least 5 days was computed. For each scenario, 1,000 virtual subjects were simulated.

4. *Results*

Pharmacokinetics. A total of 140 and 338 oxaliplatin concentrations from peritoneum and plasma, respectively, were available for the PK analysis. The mean (SD) of the Cmax in peritoneum and plasma was determined to be 82.30 (17.76) mg/L at 6.36 (7.13) min after the start of HIO and 2.56 (0.90) mg/L at 35.97 (8.20) min after the start of HIO, respectively. Moreover, the mean (SD) of the area under the curve concentration vs. time curve (AUC) in peritoneum and plasma was determined to be 1,150 (348) and 87.20 (123.20) mg·h/L, respectively.

The time course of plasma concentrations following HIO was best described by an open two-compartment disposition model with nonspecific distribution to a peripheral compartment, linear elimination from the central compartment, and first-order absorption from peritoneum to plasma. Figure III-2 displays the goodness-of-fit plots for oxaliplatin peritoneal concentrations (upper panels) and oxaliplatin plasma concentrations (mid-panels), which showed a normal random scatter around the identity line and indicated the absence of significant bias. The final estimates of the pharmacokinetic parameters and the results of the non-parametric bootstrap analysis are presented in Table III-2. Except for Q_2, between subject variability was estimated for all of the PK parameters, with acceptable shrinkage (<0.3). The population estimates of model parameters were very similar to the mean of the 684 bootstrap replicates that minimized successfully and were contained within the 95% confidence intervals obtained from the bootstrap analysis, suggesting an acceptable accuracy of the parameters estimates.

The precision of the fixed effects estimates was also good, with relative standard error (RSE) lower than 34%, while the RSE for the random effect ranged from 30% to 70%. The results of the visual predictive check performed are depicted in Fig. III-3. In this figure, the blue areas cover the 95% confidence interval of the 5^{th}, 50^{th}, and 95^{th} percentiles of the model-based prediction for peritoneal or plasma concentrations and red solid lines represent the observed 5^{th}, 50^{th}, and 95^{th} percentiles of the

peritoneal or plasma concentrations. This figure evidence that the PK model developed is appropriate to describe the time course of peritoneal and plasma oxaliplatin concentrations and their associated variability observed in cancer patients with PC.

Pharmacodynamics. A total of 678 ANC values were available for the PK/PD analysis. The mean (SD) of the $Circ_0$ was determined to be $7.47x10^9$/L (5.78x109/L) and remains relatively constant until the 4 to 6 days after drug administration when ANC begin to decline and reached a nadir approximately 11 to 14 days after the start of the HIO. The median ANC nadir determined was $3.09x10^9$/L and showed large variability with values ranging from 0.03 to $10.31x10^9$/L. The incidence of patients with neutrophil count less than $1.00\cdot10^9$/L and $0.5\cdot10^9$/L, suggestive of neutropenia at least grades 3 and 4, respectively, was 17% and 10%, respectively. The infusion duration for the three patients that developed neutropenia grade 4 was 35, 45, and 45 min, and the corresponding ANC nadir was $0.0023x10^9$/L, $0.028x10^9$/L and $0.13x10^9$/L.

The model proposed by Friberg *et al*. (30) fits the ANC profiles reasonably well. Figure III- 2 displays the goodness-of-fit plots for ANC (lower panels), which also showed a normal random scatter around the line of identity and indicate an absence of bias. The final estimates of the PD parameters and the results of the non-parametric bootstrap analysis are presented in Table II. Between subject variability was estimated for $Circ_0$ and α with acceptable shrinkage (0.077 and 0.224, respectively). The shrinkage for MTT was determined to be 0.391. The population estimates of model parameters were very similar to the mean of the 964 bootstrap replicates that minimized successfully, and were contained within the 95% confidence intervals obtained from the bootstrap analysis, suggesting an acceptable accuracy of the PD parameters. The precision of the fixed effects estimates was acceptable, with RSE lower than 36.6%. In addition, the precision for the random effect parameters was also adequate with RSE ranging from 27.5% to 53.2%. The results of the visual predictive check performed are depicted in Fig. III-2 and evidence that the model developed is appropriate to describe the time course of ANC in cancer patients following cytoreductive surgery and HIO.

The exploratory graphical analysis of the effect of age, sex, body weight, serum creatinine, albumin, serum ALT, serum AST, total bilirubin, hemoglobin, and hematocrit did not suggest any correlation between these covariates and PK/ PD parameters. Therefore, given the limited number of subjects included in the current analysis, a formal analysis of covariate effects on PK/PD parameters was not attempted.

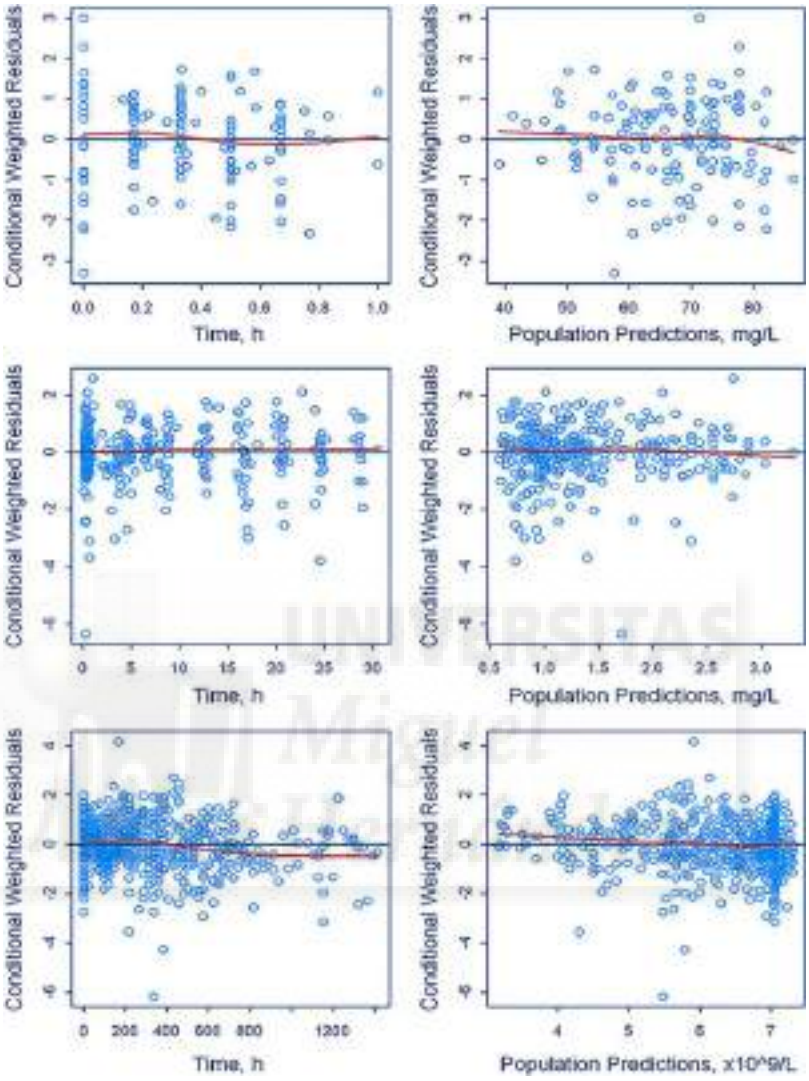

Figure III-2. Conditional weighted residuals *vs*. time and conditional weighted residuals *vs*. population predictions for peritoneal (*upper panels*) and plasma (*mid panels*) oxaliplatin concentrations, and absolute neutrophils counts (*lower panels*)

Model-Based Simulations. Deterministic simulations (Fig. III-4, upper panels) clearly show that the neutropenia is reversible, short-lasting, and non-cumulative. In addition, the initial HIO concentration (and the oxaliplatin dose) and the infusion duration are the main determinants of the severity and the duration of the neutropenia. As a consequence of the linear drug effect model, Fig. III-

4 (upper panels) shows that a proportional increase in the oxaliplatin exposure will lead to a proportional decrease in the ANC nadir. In addition, extending the duration of the HIO administration, for a given initial oxaliplatin concentration in the peritoneum, will increase the severity and duration of the neutropenia as it is directly related to the oxaliplatin exposure in peritoneum.

The relationship between initial HIO concentration and the incidence of severe neutropenia is also displayed in Fig. III-4 (lower panels) as a function of the infusion duration. In this figure, the incidence of neutropenia grade 4 appears linearly related to the initial HIO concentration and the slope of that linear relationship also depends of the infusion duration. Actually, a 60-min infusion of

Table III-2 Parameter Estimates and Bootstrap Analysis of the HIO Populaiton Pharmakokinetic and Pharmakodinamic Model

	Original dataset	Nonparametric bootstrap	
Model parameters	Estimate [a,b]	Mean [a]	95% Confidence interval
Pharmacokinetic model			
Q_a (L/h)	2.70	2.80 (17.3)	1.91–3.86
V_a (L)	8.33	8.32 (4.48)	7.61–9.09
Cl/F (L/h)	1.61	1.65 (33.4)	0.71–2.85
Q_2/F (L/h)	77.0	79.4 (18.6)	56.7–112.0
V_c/F (L)	19.2	20.0 (25.2)	11.4–30.8
V_p/F (L)	72.8	75.3 (17.2)	50.1–103.9
Interindividual variability (CV %)			
ω_{Qa}	34.1	34.1 (30.6)	23.4–44.2
ω_{Va}	17.7	17.4 (38.3)	10.1–23.5
$\omega_{CL/F}$	85.6	93.4 (69.6)	38.2–159.0
$\omega_{Vc/F}$	57.9	56.0 (69.8)	15.1–84.2
$\omega_{Vp/F}$	23.5	24.4 (69.0)	6.70–39.3
Residual variability (CV %)			
$\sigma_{1\ (plasma)}$	14.7	14.5 (16.8)	12.0–16.8
$\sigma_{2\ (peritoneum)}$	16.5	16.3 (27.9)	12.6–21.0
Pharmacodynamic model			
System related parameters			
$Circ_0$ ($\cdot 10^9$/L)	7.05 (6.88)	7.07 (6.75)	6.26–8.09
MTT (h)	118 Fixed	–	–
γ	0.135 (11.9)	0.133 (25.4)	0.016–0.209
Drug-related parameter α (L/mg)	0.182 (36.5)	0.181 (62.8)	0.048–0.505
Interindividual variability (CV %) ω_{Circ0}	42.3 (27.5)	40.6 (29.6)	27.3–52.1
ω_{MTT}	32.8 (53.2)	31.2 (155.9)	5.6–75.6
ω_{α}	141 (31.7)	145 (160.7)	73–250
Residual variability (CV %)			
σ	49.7 (17.6)	49.1 (19.4)	41.1–58.7

[a] Results expressed as parameter (RSE relative standard error of parameter estimate, %)
[b] The covariate step failed. Therefore, RSE of PK parameters are not provided

oxaliplatin starting at peritoneal concentration of 65 mg/L leads to a 20% incidence of neutropenia Grade 4. However, a 30-min infusion starting at the same oxaliplatin concentration leads to a 12% incidence of neutropenia Grade 4. Thus, shorter HIO reduce the incidence of severe neutropenia, while the initial oxaliplatin dose administered to achieve an initial 65 mg/L concentration remains the same in both cases.

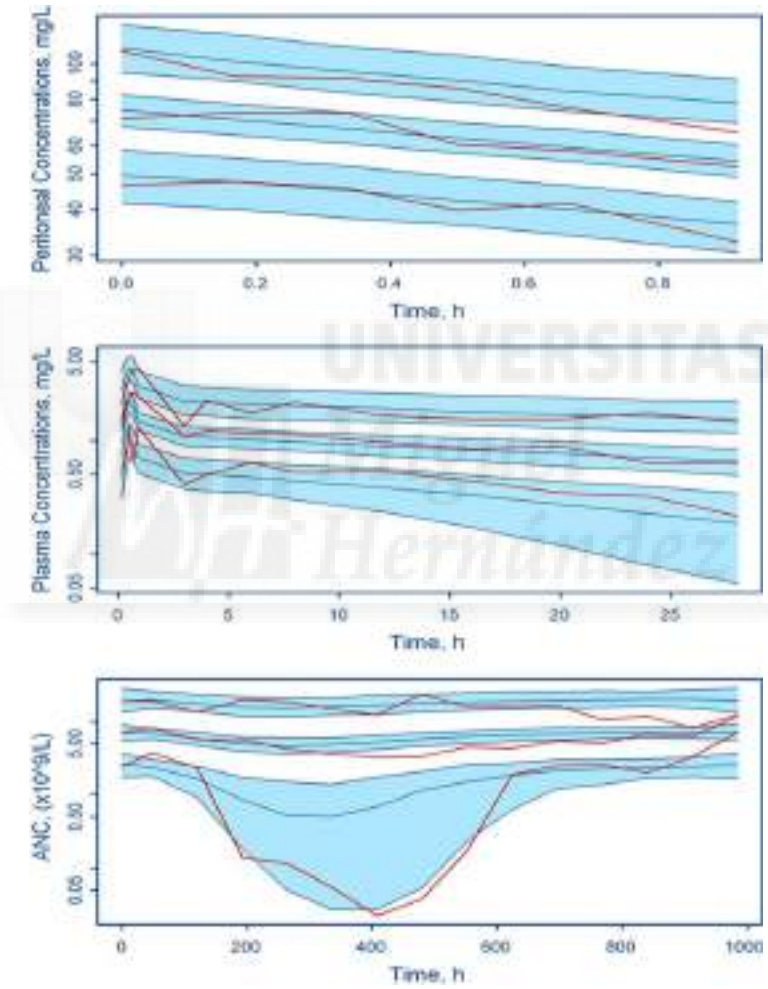

Figure III-3 Time course of the 5th, 50th, and 95th percentiles of the peritoneal (*upper panel*) and plasma (*mid panel*) oxaliplatin concentration and absolute neutrophils counts (*lower panel*) and their associated model-based prediction of the 95% confidence interval.

According to Fig. III- 4 (lower left panel), a 20% incidence of neutropenia Grade 4 is also expected following a 30-min infusion starting at peritoneal oxaliplatin concentration of 105 mg/L. Interestingly, the area under the peritoneal oxaliplatin concentration versus time curve (AUC) following a 60-min infusion starting at 65 mg/L concentration is the same than the AUC following a 30-min infusion starting at Fig. III-3. Time course of the 5th, 50th, and 95th percentiles of the peritoneal (upper panel) and plasma (mid panel) oxaliplatin concentration and absolute neutrophils counts (lower panel)

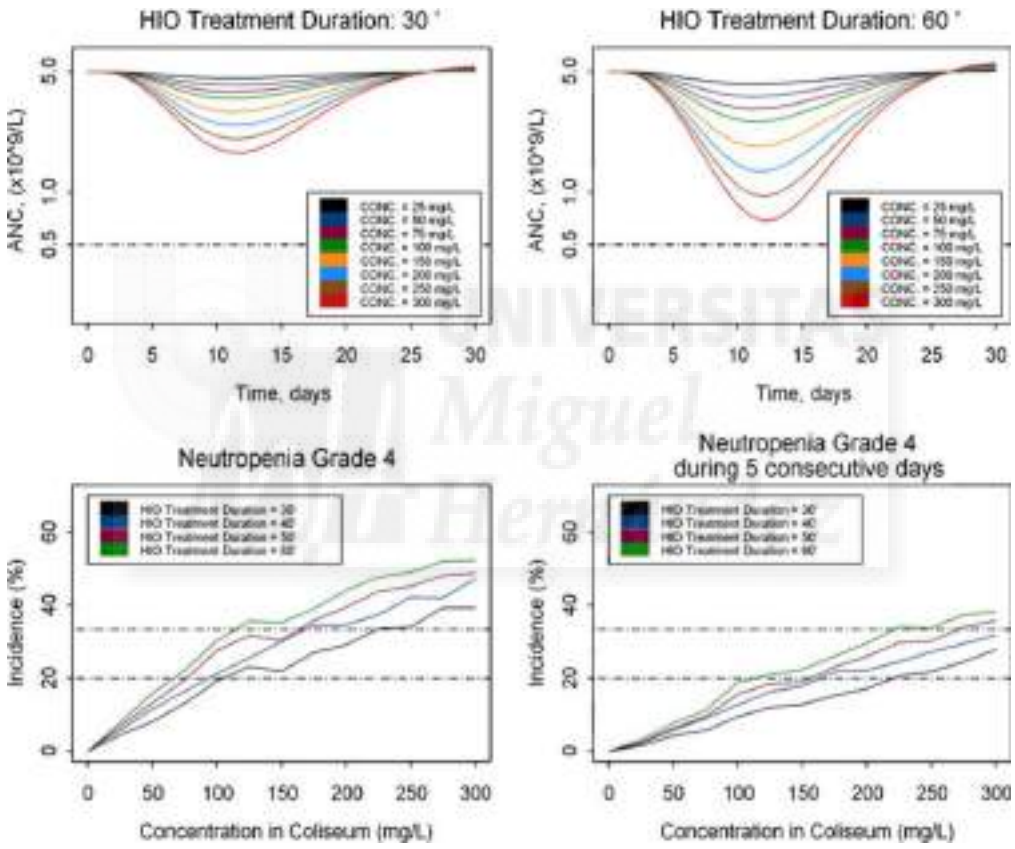

Figure III-4 Effect of initial oxaliplatin concentration in peritoneum and HIO treatment duration on the time course of neutrophil counts (*upper panels*) and on the incidence of neutropenia grade 4 and grade 4 lasting at least 5 days (*lower panels*).

and their associated model-based prediction of the 95% confidence interval oxaliplatin concentration of 105 mg/L. Consequently, these two dosing regimens leads to an incidence of neutropenia grade 4, for

which primary prophylaxis with granulocytecolony stimulating factors is recommended. Furthermore, a 60-min infusion starting at 120 mg/L concentration is associated with a 33% incidence of neutropenia grade 4, which determine the maximum tolerated exposure. Similarly, HIO exposure of 120 and 225 mg· h/L are associated with a 20% and 33% incidence of neutropenia grade 4 lasting more than 5 days Fig. III- 4 (lower right panel).

5. *Discussion*

In this study, the oxaliplatin pharmacokinetics in peritoneum and plasma has been characterized in cancer patients with PC treated with cytoreductive surgery followed by HIO. Regarding the oxaliplatin plasma disposition, the typical volume of the central compartment and the alpha half-life ($t_{1/2\alpha}$) were estimated to be 19.2 L and 0.14 h, respectively, and were similar to the PK parameters previously reported by Ferron et al. (27) and Massari et al. (42) The beta half-life ($t_{1/2\beta}$) determined in the current study, 40 h, was similar to that observed by Massari et al. (37.5 h) after 2-h intravenous infusion of oxaliplatin 130 mg/m^2 but was longer than the $t_{1/2\beta}$ reported by Ferron et al. (12.9 h). A possible explanation of these differences is the limited sampling period used to characterize the oxaliplatin pharmacokinetics in Ferron et al. study, as compared to the others studies. It becomes very difficult to accurately estimate oxaliplatin $t_{1/2\beta}$ based on plasma samples collected only up to 8 h after the start of HIO administration. Sampling schedules including plasma concentration collected beyond 24 h should provide a more accurate estimation of the $t_{1/2\beta}$ for total oxaliplatin.

The peritoneum to plasma ratio of oxaliplatin C_{max}, 32.1, was similar to a previously reported value for ultrafiltrate platinum concentrations (24, 28). However, the apparent oxaliplatin peritoneal half-life ($t_{1/2a}$=Ln(2)/k_a), equivalent to the oxaliplatin absorption half-life from peritoneum to plasma, 2.2 h, was considerably higher than the values reported previously (0.5–0.7 h) (25–27), probably because different carrier solution has been used in the current study.While all the previous pharmacokinetic studies of HIO were performed using isotonic 5% dextrose as carrier solution, this study reports, for the first time, the HIO pharmacokinetics in plasma and peritoneumusing isotonic 4% icodextrin as carrier solution. Icodextrin is a macromolecule that, theoretically, should reduce oxaliplatin clearance from the peritoneal cavity and, consequently, the $t_{1/2a}$ should be longer. On the other hand, the ratio estimated of the AUCs in peritoneum and plasma was 13.19, which is in line with the values previously reported (28) for ultrafiltrate platinum using isotonic 5% dextrose as carrier solution. Probably, other factors, including differences in the surgical procedures, the extracorporeal circulation machines, the oxaliplatin

absolute bioavailability and the analyte and bioanalytical method, could contribute to explain the differences in the absorption half-life from peritoneum to plasma across the studies conducted with dextrose at 5% vs icodextrin at 4%. Therefore, further studies comparing oxaliplatin absorption with both carrier solutions are necessary to quantify the icodextrin effect on oxaliplatin absorption.

In this study, the relationship between oxaliplatin pharmacokinetics and the time course of ANC in patients with PC receiving HIO after cytoreductive surgery was also investigated by applying a semi-mechanistic population PK/PD model previously developed (30). The relationship between oxaliplatin plasma concentrations and drug effect was described by a linear function and the slope of the linear drug effect was estimated to be 0.182 L/mg. It appears that oxaliplatin neutropenic potency is about 28% higher than the estimated neutropenic potency for carboplatin in monotherapy, after correcting for the differences in the free fraction between the two drugs (43). The 5th, 50th, and 95th percentiles of the oxaliplatin peak inhibition of the proliferative rate of precursor cells into the Prol were determined to be 13.13, 44.23, and 564.33, respectively. With respect to the system related parameters, the estimated of Circ0 was consistent with ANC normal values. The MTT could not be estimated correctly with the available data and, therefore, was fixed to 118 h as previously reported in the literature (30, 44–48). The estimated γ value, 0.135, was also similar to those obtained previously for other anticancer drugs, such as irinotecan (0.132) or topotecan (0.120) (30, 49). Interindividual and residual variabilities were moderate to large, consistent with that observed for other drugs (30).

Model-based simulations revealed that HIO induced neutropenia is reversible, short-lasting, and largely dependent on the intensity of the dose administered (or concentration in the peritoneum) and the duration of the HIO treatment. Figure III-4 (upper panels) shows that increasing the dose (or the initial concentration in the peritoneum) and/or extending the HIO duration leads to a greater fluctuation in ANC values and consequently increases the likelihood of severe neutropenia. Simulations also indicated that it is possible to reduce the degree of neutropenia by employing treatment regimens with shorter HIO duration, while the overall amount of dose administered (and the initial oxaliplatin concentration in the peritoneum) remains the same. Quantitatively, simulations suggest that the maximum tolerated HIO exposure is 120 mg·h/L. However, primary prophylaxis with granulocyte-colony stimulating factors should be considered if HIO exposure is higher than 65 mg·h/L in order to prevent severe neutropenia as recommended by the guidelines (50).

In summary, a semi-mechanistic pharmacokinetic and pharmacodynamic model has been developed to account for the effect of oxaliplatin on myelosupression. This model has been successfully applied for the first time to describe the time course of ANC in cancer patients with diagnosis of PC

treated with HIO, using 4% icodextrin as carrier solutions. Model-based simulations suggest that targeting HIO exposure not higher than 120 mg·h/L is safe and, however, at exposure higher than 65 mg·h/L the primary prophylaxis with granulocyte- colony stimulating factors support recommended. The model developed is useful to optimize the design of future clinical studies.

6. *Acknowledgments*

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8. *Annex III-1. Original Publication: Pharmacokinetic and Pharmacodynamic Analysis of Hyperthermic Intraperitoneal Oxaliplatin-Induced Neutropenia in Subjects with Peritoneal Carcinomatosis.*

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Research Article

Pharmacokinetic and Pharmacodynamic Analysis of Hyperthermic Intraperitoneal Oxaliplatin-Induced Neutropenia in Subjects with Peritoneal Carcinomatosis

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Abstract. The objective of this study was to characterize the pharmacokinetics and the time course of the neutropenia induced by hyperthermic intraperitoneal oxaliplatin (HIO) after cytoreductive surgery in cancer patients with peritoneal carcinomatosis. Data from 30 patients who received 360 mg/m² of HIO following cytoreductive surgery were used for pharmacokinetic-pharmacodynamic (PK/PD) analysis. The oxaliplatin plasma concentrations were characterized by an open two-compartment pharmacokinetic model after first-order absorption from peritoneum to plasma. An oxaliplatin-sensitive progenitor cell compartment was used to describe the absolute neutrophil counts in blood. The reduction of the proliferation rate of the progenitor cells was modeled by a linear function of the oxaliplatin plasma concentrations. The typical values of oxaliplatin absorption and terminal half-lives were estimated to be 2.2 and 48 h, with moderate interindividual variability. Oxaliplatin reduced the proliferation rate of the progenitor cells by 18.2% per mg/L. No patient's covariates were related to oxaliplatin PK/PD parameters. Bootstrap and visual predictive check evidenced the model was deemed appropriate to describe oxaliplatin pharmacokinetics and the incidence and severity of neutropenia. A peritoneum oxaliplatin exposure of 65 and 120 mg·L/h was associated with a 28% and 55% incidence of neutropenia grade 4. The time course of neutropenia following HIO administration was well described by the semiphysiological PK/PD model. The maximum tolerated peritoneum oxaliplatin exposure is 120 mg·L/h and higher exposures should be avoided in future studies. We suggest the prophylactic use of granulocyte colony stimulating factor for patients treated with HIO exposure higher than 65 mg·L/h.

KEY WORDS: hyperthermic intraperitoneal chemotherapy (HIPEC); NONMEM; oxaliplatin; peritoneal carcinomatosis; pharmacodynamics; pharmacokinetics.

INTRODUCTION

For many patients with peritoneal carcinomatosis (PC) secondary to intra-abdominal cancers, tumor progression in the peritoneum is the sole life-limiting component of disease and one of the most common causes of cancer incurability. However, there are no PC treatment approved by regulatory agencies, and the development of new therapies to manage this life-threatening condition could fulfill an unmet medical need. In this context, several Phase I/II clinical studies in gastric cancer (1–3), mesothelioma (4), colorectal (5), or ovarian carcinoma (6) have shown promising results in treating macroscopic PC with cytoreductive surgery and residual PC with hyperthermic intraperitoneal chemotherapy (HIPEC) (7). The rationale for this treatment is based on experimental studies showing that drug penetration is limited to a few cell layers under the surface of the tumor (8), and consequently, intraperitoneal chemotherapy must be immediately administered after the cytoreductive surgery in order to achieve the maximal cytotoxic activity on residual tumor cells before they get trapped in the postoperative fibrin adhesions (9). In addition, the intratumoral cytotoxic activity can be enhanced by administering highly permeable drugs at relatively high doses with hyperthermia. The efficacy of this approach has been evidenced in Phase III studies in colorectal cancer patients (10,11).

The ideal drug for HIPEC should penetrate into the tumor, have a low diffusion into the subperitoneal space and capillary endothelial in order to avoid excessive drug systemic exposure, and have a temperature dependent cytotoxic activity. Therefore, drugs rapidly metabolized and/or excreted from the body should be preferred over others as they should decrease the systemic exposure and the risk of toxicity. Consequently, large hydrophilic compounds with limited permeability across an intact peritoneal membrane have been preferred to small lipophilic compounds (12). In this context,

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cisplatin (13), mytomicin C (14), carboplatin (15), paclitaxel (16), irinotecan (17), and oxaliplatin (18) have been used as chemotherapy agents in HIPEC because their cytotoxic activity is enhanced with hyperthermia. Although comparative studies across these drugs have not been performed to date, the results obtained with oxaliplatin are encouraging. In a retrospective analysis in patients with resectable PC, Elias *et al.* have shown that surgical cytoreduction followed by HIPEC with oxaliplatin prolongs median survival from 23.9 to 62.7 months and increase the 5-year survival rate from 13% to 51% with respect to standard palliative surgery and chemotherapy (19).

Oxaliplatin, a diaminocyclohexane–platinum compound active in a variety of solid tumor types, licensed in the USA and Europe for the treatment of colorectal cancer, is an attractive agent for HIPEC because its cytotoxicity is significantly increased by hyperthermia (20,21) and the intratumoral penetration is optimal (22). However, systemic exposure to oxaliplatin increases the risk of hematological toxicity and peripheral sensory neuropathy, which have been described as dose-limiting toxicities after intravenous treatment (23). Therefore, it is important to achieve the maximum oxaliplatin exposure in the peritoneal cavity with minimum access to systemic circulation, in order to balance the cytotoxic activity and the risk of toxicity. Several Phase I dose-escalation studies in subjects with PC were conducted to determine the maximum tolerated dose of hyperthermic intraperitoneal oxaliplatin (HIO) and characterized its pharmacokinetics (PK) as a single agent (24–26). In these studies, intraperitoneal doses ranging from 200 to 460 mg/m^2 were administered during 0.5 to 2 h and oxaliplatin exhibited linear and time-independent PK in both plasma and peritoneum. While oxaliplatin peritoneal concentrations decline in an exponential manner with a half-life of 30 to 40 min (22,27,28), oxaliplatin plasma concentrations increase to reach the maximum shortly after the end of the intraperitoneal infusion. The mean value of apparent oxaliplatin absorption rate constant (k_a) from peritoneum to plasma was close to 1.4 h^{-1} (22,27,28). After treatment with HIO, oxaliplatin plasma concentrations declined in a bi-exponential manner resembling to the PK profiles observed after an intravenous administration. At an oxaliplatin dose level of 460 mg/m^2, the peak concentration (C_{max}) was estimated to be 25-fold higher in peritoneum (330 μg/mL) than in plasma (13.2 μg/mL) (24,25) which indicates an increased oxaliplatin tumor exposure and, potentially, a more efficacious treatment for residual PC than its intravenous administration. However, the pharmacokinetic parameters obtained from plasma concentrations achieved following HIO vary substantially from one study to others reflecting differences in relation to (1) the analyte (ultrafiltrate *vs* total platinum), (2) analytical method for measuring plasma platinum content (atomic absorption spectroscopy, liquid chromatography, or inductively coupled plasma atomic emission spectrometry), and (3) the carrier solution used (isotonic, hypotonic, or hypertonic solutions) (29). In this context, is not surprising that the estimated oxaliplatin plasma clearance ranged from 6.68 L/h/m^2 (27) to 28.4 L/h/m^2 (28), while the volume of distribution is estimated to be 15 L (27).

In these studies, the most frequent and severe adverse events related with oxaliplatin were neutropenia and thrombocytopenia (24–27). Stewart *et al.* (26) reported that hematologic toxicity grade was related to the extent and the rate of oxaliplatin systemic absorption at 250 mg/m^2 administered during 2 h. However, to date, there are not quantitative longitudinal analyses exploring the effect of oxaliplatin pharmacokinetics on the time course of hematological toxicity after its intraperitoneal administration. In this study, we characterize the oxaliplatin pharmacokinetics in peritoneum and plasma when is administered in an icodextrin 4% carrier solution and establish its relationship with the time course of absolute neutrophil counts (ANC) in patients with PC receiving HIO after cytoreductive surgery. A semi-mechanistic population pharmacokinetic and pharmacodynamic (PK/PD) model previously developed (30) was used to analyze the data and the effect of patient demographics and/or physiopathological factors on oxaliplatin PK/PD parameters. Finally, the relationship between oxaliplatin concentrations in peritoneum, the duration of the HIO and the incidence of severe neutropenia was explored in order to establish the maximum tolerated oxaliplatin exposure, which will be critical to optimize the design of future clinical studies with oxaliplatin in this setting.

MATERIALS AND METHODS

Study Design and Subject Eligibility Criteria. Data from 30 subjects included in a single-arm study investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of HIO after cytoreductive surgery were analyzed. Adult patients were eligible if they had confirmation of PC without extra-abdominal metastasis. Other eligibility criteria included a World Health Organization performance status of 0 to 2, anticipated life expectancy of at least 3 months. Previous anticancer radiation therapy and/or chemotherapy, if given, had to be discontinued for at least 4 weeks before entry into the study, or 6 weeks in the case of pretreatment with nitrosoureas or mitomycin C. Patients were required to have a negative pregnancy test (only for female patients with reproductive potential), and normal hepatic and renal function, defined as bilirubin ≤1.5 times the upper limit of normality, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 times the upper limit of normality, and serum creatinine ≤1.5 times the upper limit of normality. An acceptable bone marrow function, defined as white blood cells >3.5 × 10^9/L, neutrophil count >1.5 × 10^9/L, and platelets >100.0 × 10^9/L was needed. Patients with one or more of the following criteria were not selected: active infection; central nervous system metastases; peripheral neuropathy >grade 2; allogenic transplant; prior extensive radiation therapy (>25% of bone marrow reserve); prior bone marrow transplantation or high dose chemotherapy with bone marrow or stem cell rescue; concurrent radiation therapy, chemotherapy, hormonal therapy, or immunotherapy; participation in a clinical trial involving an investigational drug in the past 30 days or concurrent enrollment in another investigational trial; and any coexisting medical condition that was likely to interfere with study procedures and/or results.

The study was conducted at the USP Hospital San Jaime (Torrevieja, Spain) between 2006 and 2009 in accordance with principles for human experimentation as defined in the

International Conference on Harmonization for Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study was approved by the corresponding Investigational Review Board and informed consent was obtained from each subject after being advised of the potential risks and benefits, as well as, the investigational nature of the study (31). The primary tumor type of the eligible patients were ovarian ($n=10$), colorectal ($n=9$), appendiceal ($n=5$), gastric ($n=3$), endometrial ($n=2$), and primary pupilar ($n=1$). A summary of patient characteristics at baseline is presented in Table I.

Surgical Procedure. A xiphopubic midline laparotomy was carried out to examine the tumor load in the abdominal cavity. To obtain the peritoneal cancer index (32), the abdomen was divided into 13 areas numbered from 0 to 12, as described elsewhere (33), and cytological samples and biopsies were taken from each area. Resection of the primary tumor when present was carried out according to regional lymphadenectomy with correct margins. In carcinomatosis with the primary tumor *in situ* and in metachronous cases, peritonectomies and debulking were carried out as required and extensive systematic peritonectomies were not performed. The mesenteric peritoneum was not extensively removed, and acceptable small bowel resections were guided by maximal tumor volume locations. Remaining malignant granulations were destroyed using electrosurgical fulguration. This aggressive surgical cytoreduction was performed with the aim to reach complete resection or, if not possible, to resect all visible tumor lesions larger than 2.5 mm. Anastomoses were carried out after the perfusion of the abdominal cavity was completed. The cytoreduction obtained by surgery was considered complete CC0 (no residual implants remained), incomplete CC1 (residual implants <2.5 mm persisted), incomplete CC2 (residual implants ≥2.5 mm, but <2.5 cm persisted) or incomplete CC3 (residual implants ≥2.5 cm persisted) (34).

Table I. Summary of Patient Characteristics at Baseline

Subject characteristics ($N=30$)	Mean (SD)	Range
Age (year)	57.9 (10.5)	32.0–75.0
Body Weight (kg)	69.3 (12.1)	42.0–90.0
Body Surface Area (m^2)	1.7 (0.2)	1.4–2.0
Sex (%)		
Male	40	
Female	60	
ALT (IU/L)	45.1 (20.1)	19.0–100
AST (IU/L)	38.9 (19.4)	10.0–83.0
Alkaline Phosphatase (IU/L)	234 (108)	52–467
Total Bilirubin (μmol/L)	0.6 (0.3)	0.2–1.6
Serum Albumin (g/L)	33.3 (10.6)	14.9–50.5
Total Protein (g/L)	59.8 (11.6)	38.8–79.3
Creatinine Clearance[a] (mL/min)	85.3 (32.9)	23.2–150.0
Hemoglobin (g/dL)	11.3 (1.5)	6.4–13.6
Leukocyte Count $x10^9$/L	7.7 (4.2)	0.4–17.8
Neutrophil $\times10^9$/L	7.5 (5.8)	1.7–26.5
Platelets $\times10^9$/L	261 (139)	115–716
Liver metastases		
No (%)	83.3	
Yes (%)	16.7	
Peritoneal Carcinomatosis Index	8.6	0.0–39.0
Complete Cytoreduction		
No (%)	33.3	
Yes (%)	66.7	

Continuous variables are expressed as mean (standard deviation) and range, whereas categorical variables are expressed as percentage (%).
[a]Creatinine Clearance was calculated using the Cockroft and Gault's formula and values higher than 150 mL/min were truncated to 150 mL/min

Hyperthermic Intraperitoneal Oxaliplatin. An open coliseum technique was used according to the procedure previously described (35). Four 36-Fr drains were connected to a continuous closed circuit, and two intraperitoneal thermal probes were placed in order to obtain a proper temperature feedback. Briefly, a Tenckhoff inflow catheter was placed centrally in the abdomen and four outflow catheters were inserted through separate stab incisions in the abdominal wall. Both the inflow and outflow catheters were connected to a perfusion pump and heat exchanger. The skin of the abdomen was attached to a retractor ring, and the abdominal cavity was covered with a plastic sheet with a small opening in the center allowing entrance for the surgeon's hands to stir the abdominal contents in order to deliver a more uniform drug distribution and heat to the intra-abdominal surfaces. The rollers of an extracorporeal circulation machine (Performer LRT, Rand) were set at a speed of 1,000 mL/min to deliver the perfusate, 4% icodextrin solution. The circuit passed through a heat exchanger which raised the temperature to 48°C. The perfusate temperature on the abdominal cavity fluctuated between 42°C and 43°C. Once the temperature was achieved, oxaliplatin 360 mg/m^2 was administered. The perfusate volume varied from patient to patient depending on the peritoneal surface area and, approximately, 2.5 to 6.0 L were employed. On average, the HIO mean duration was 40 min (range 30–60 min). After the end of perfusion, the solution was evacuated. During the next five postoperative days, 5-fluorouracil (5-FU) was administered at a dose of 15 mg/kg intraperitoneally in 1 h infusion through a 14-Fr catheter in order to potentiate the oxaliplatin cytotoxic effect (36).

Sample Collection and Bioanalytical Methods. Peritoneal fluid and venous blood samples were collected immediately after the oxaliplatin administration and then every 30 min until the end of the peritoneal perfusion. Additional venous blood samples were drawn at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, 24, and 28 h after the end of the peritoneal perfusion. All samples were collected in S-monovette® tubes, centrifuged at 3,500 rpm for 10 min and were stored at −80°C until analysis. Total platinum in peritoneal fluid and plasma was measured using a validated assay based on inductively coupled plasma atomic emission spectrometry. The lower limit of quantification was 0.5 mg/L. Over the validated range of the assay (0.5 to 30 mg/L for plasma samples and 5 to 300 mg/L for peritoneal fluid samples), the mean intra- and inter-assay coefficients of variation were lower than 9.5% and 7.7%, respectively. Blood samples for the determination of ANC were collected before the surgery and, afterwards, daily until patient completely recovered from the hematological toxicity. ANC were determined using an automated hematology analyzer (Beckman Coulter, Inc. AcT5diff AL, Fullerton, CA, USA).

Pharmacokinetic and Pharmacodynamic Model Development

Software. Nonlinear mixed-effects modeling using the first-order conditional (FOCE) method implemented in NONMEM VI software package (ICON, Hanover, MD) (37) was used to develop the population PK/PD model and to conduct model-based simulations. Compilations were achieved using DIGITAL Visual Fortran Version 6.6C. Graphical and all other statistical analyses were performed using S-Plus 6.1 Professional Edition (Insightful, Seattle, WA, USA).

Pharmacokinetic and Pharmacodynamic Model. Oxaliplatin concentrations in peritoneal fluid evidenced a monoexponential decay, and consequently, oxaliplatin in the peritoneal fluid was assumed to be absorbed into plasma according to a linear process, characterized by the first-order absorption rate constant, k_a (Fig. 1). As oxaliplatin concentration in the peritoneal fluid were available, the absorption process was parameterized in terms of peritoneum to plasma clearance (Q_a) and volume of distribution in the peritoneum (V_a); thus k_a was calculated as a secondary parameter (Q_a/V_a). Based on the graphical exploratory analysis, the oxaliplatin disposition in plasma was characterized by an open two-compartment model with linear elimination and nonspecific distribution to peripheral tissues (Fig. 1). This model was parameterized in terms of systemic clearance (Cl), intercompartmental flow (Q_2), central volume of distribution (V_c), and peripheral volume of distribution (V_p). As the oxaliplatin absolute bioavailability (F) after intraperitoneal administration is not known, F was fixed to 1; therefore, the estimated model parameters were apparent. The corresponding differential equations for each compartment were:

$$\frac{dA}{dt} = -\frac{Q_a}{V_a} \cdot A = -k_a \cdot A \quad (1)$$

$$\frac{dC}{dt} = \frac{Q_a}{V_a} \cdot A - \frac{Q_2}{V_c} \cdot C - \frac{Cl}{V_c} \cdot C + \frac{Q_2}{V_p} \cdot P \quad (2)$$

$$\frac{dP}{dt} = \frac{Q_2}{V_c} \cdot C - \frac{Q_2}{V_p} \cdot P \quad (3)$$

where A, C, and P represent the oxaliplatin concentrations in peritoneal fluid, plasma, and peripheral compartment, respectively.

The semi-mechanistic model proposed by Friberg *et al.* (30) was used to describe the ANC time course as a function of oxaliplatin concentrations (Fig. 1). The backbone structure of the model consist in five compartments: one compartment represents the proliferative cells [*Prol*], such as stem cell and other progenitor cells; three transit compartments with maturating cells [*Transit*]; and one compartment of the circulating blood cells [*Circ*]. A maturation chain, with transit compartments and first-order rate constants (k_tr) accounts for the lag time between the oxaliplatin administration and the observed neutropenic effects in blood. The generation of new cells in [*Prol*] was dependent on the number of cells in that compartment, which is consistent with the mechanism of self-renewal or mitosis. The first-order proliferation rate constant, k_{prol}, determines the rate of cell division, together with the feedback mechanism from the circulating cells. The feedback loop was necessary to describe the rebound of ANC compared to the baseline values ($Circ_0$) and was incorporated into the model as $(Circ_0/Circ)^\gamma$ as previously suggested (35). The feedback function is governed by the γ parameter, which reflects the increase in self-replication rate occurring when circulating cells are depleted. The differential equations describing the reference model were as follows:

$$\frac{dProl}{dt} = k_{Prol} \cdot Prol \cdot \left(\frac{Circ_0}{Circ}\right)^{\gamma} \cdot (1 - E_{Drug}) - k_{tr} \cdot Prol \quad (4)$$

$$\frac{dTransit_1}{dt} = k_{tr} \cdot Prol - k_{tr} \cdot Transit_1 \quad (5)$$

$$\frac{dTransit_2}{dt} = k_{tr} \cdot Transit_1 - k_{tr} \cdot Transit_2 \quad (6)$$

$$\frac{dTransit_3}{dt} = k_{tr} \cdot Transit_2 - k_{tr} \cdot Transit_3 \quad (7)$$

$$\frac{dCirc}{dt} = k_{tr} \cdot Transit_3 - k_{Circ} \cdot Circ \quad (8)$$

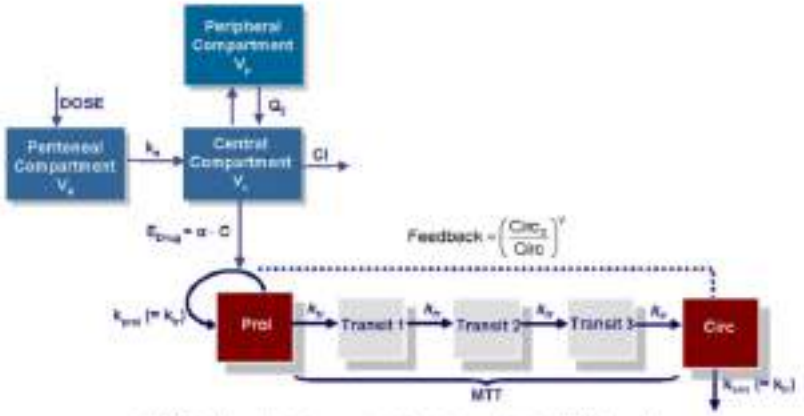

Fig. 1. Schematic of the semi-mechanistic population PK/PD model

The oxaliplatin plasma concentrations were assumed to reduce the proliferation rate according to a linear function (E_{Drug}):

$$E_{Drug} = a \cdot C \quad (9)$$

where a is the slope of the linear relationship between E_{Drug} and C, and C is derived based on the empirical Bayesian estimates of the individual pharmacokinetic parameter obtained from the oxaliplatin population pharmacokinetic model previously described.

In the transit compartments, it was assumed that the only loss of cells is into the next compartment; therefore, the random loss of precursor cells was assumed to be negligible. As the proliferative cells differentiate into more mature cell types, the concentration of cells is maintained by cell division. At steady-state, before administering oxaliplatin, $dProl/dt$ is equal to 0 and, therefore, $k_{Prol} = k_{tr}$. As the ANC data collected did not contain enough information to estimate independently k_{Circ_0} it was fixed to the population mean half life of neutrophils previously determined, 0.07 h^{-1} (30). To improve the interpretability, the mean transit time (MTT) was estimated as follows:

$$\mathrm{MTT} = \frac{n+1}{k_{tr}} \quad (10)$$

where n is the number of transit compartments, MTT represents the time taken for the neutrophil to reach the circulation after leaving the proliferative compartment. Thus the structural model parameters to be estimated were the system-related parameters: $Circ_0$, MTT, and γ, and the drug-related parameter, a.

The effect of 5-FU on the inhibition of the proliferation rate and/or stimulation of the killing rate of the progenitor cells was assumed to be negligible because the low intrinsic neutropenic effects of 5-FU (38) and the relatively low doses administered, which lead to a negligible systemic exposure as evidence by the large proportion (81.5%) of 5-FU plasma concentration below the limit of quantification (0.04 mg/L).

Statistical Model. The interindividual (or between subjects) variability (IIV) in the PK/PD model parameters was assumed to follow the lognormal distribution and, consequently, an exponential error model was used. Residual variability in oxaliplatin peritoneal concentrations, oxaliplatin plasma concentrations, or ANC was evaluated using an additive error model after natural logarithmic transformation of the observations and model predictions. The magnitude of interindividual and residual variability was expressed approximately as a coefficient of variation.

Model Selection Criteria. The improvement of the fit obtained for each model was assessed in several ways. First, the resulting NONMEM-generated minimum value of the objective function (MVOF) was used to perform the likelihood ratio test. This test is based on the change in the MVOF (ΔMVOF), which is equal (up to a constant) to minus twice the log-likelihood of the data and is asymptotically distributed like χ^2 with the degrees of freedom equal to the number of parameters added to the model. ΔMVOFs of −10.83 or −12.12 were required to reach statistical significance at $p \leq 0.0010$ or $p \leq 0.0005$ for the inclusion or exclusion of one fixed effect in nested models, respectively. These stringent statistical criteria were used to avoid the inclusion of weak and clinically no relevant effects. In addition, the improvement in the fit was assessed by the reduction in the IIV and residual variability, the precision in parameter estimates, and the examination of diagnostic plots, and shrinkage (39).

Model Qualification. A nonparametric bootstrap was used as internal evaluation method to qualify the estimates of the PK/PD model parameters (40) using WINGS for NONMEM (N. Holford, Version 6.16, Auckland, New Zealand). The mean and the 95% confidence intervals of the parameter estimates from the bootstrap replicates were compared with the estimated parameters from the original dataset. In addition, a visual predictive check was performed on the time course of the 5th, 50th, and 95th percentile of the oxaliplatin peritoneal and plasma concentrations and the ANC (41).

Model-Based Simulations. Based on the PK/PD model developed, simulations were undertaken in order to explore the role of the initial oxaliplatin concentration in the peritoneum (and therefore the dose) and the duration of the HIO on the incidence of neutropenia grade 4 or grade 4 lasting at least 5 days. For a total of 12 oxaliplatin concentrations (0, 25, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, and 300 mg/L), the daily ANC was simulated for four different HIO durations (30, 40, 50, and 60 min) and the incidence of neutropenia grade 4 or grade 4 lasting at least 5 days was computed. For each scenario, 1,000 virtual subjects were simulated.

RESULTS

Pharmacokinetics. A total of 140 and 338 oxaliplatin concentrations from peritoneum and plasma, respectively, were available for the PK analysis. The mean (SD) of the C_{max} in peritoneum and plasma was determined to be 82.30 (17.76) mg/L at 6.36 (7.13) min after the start of HIO and 2.56 (0.90) mg/L at 35.97 (8.20) min after the start of HIO, respectively. Moreover, the mean (SD) of the area under the curve concentration *vs.* time curve (AUC) in peritoneum and plasma was determined to be 1,150 (348) and 87.20 (123.20) mg·h/L, respectively.

The time course of plasma concentrations following HIO was best described by an open two-compartment disposition model with nonspecific distribution to a peripheral compartment, linear elimination from the central compartment, and first-order absorption from peritoneum to plasma. Figure 2 displays the goodness-of-fit plots for oxaliplatin peritoneal concentrations (upper panels) and oxaliplatin plasma concentrations (mid-panels), which showed a normal random scatter around the identity line and indicated the absence of significant bias. The final estimates of the pharmacokinetic parameters and the results of the non-parametric bootstrap analysis are presented in Table II. Except for Q_2, between subject variability was estimated for all of the PK parameters, with acceptable shrinkage (<0.3). The population estimates of model parameters were very similar to the mean of the 684 bootstrap replicates that minimized successfully and were contained within the 95% confidence intervals obtained from the bootstrap analysis, suggesting an acceptable accuracy of the parameters estimates.

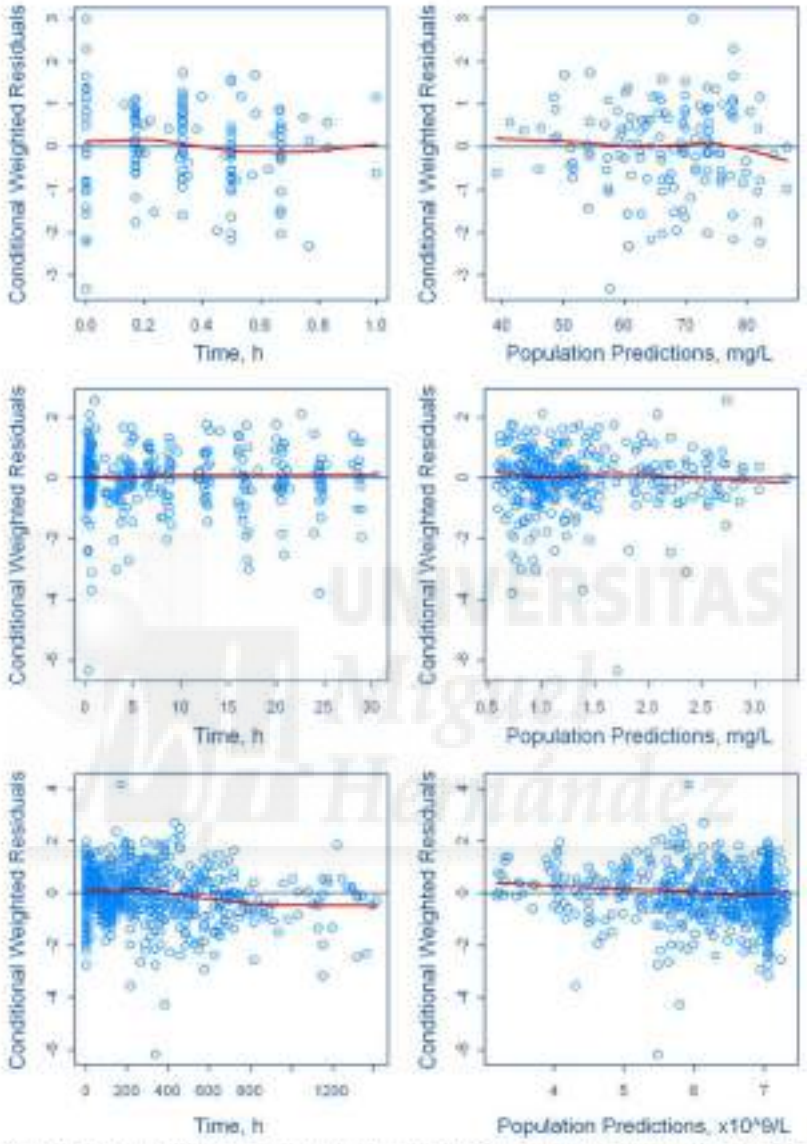

Fig. 2. Conditional weighted residuals *vs* time and conditional weighted residuals *vs* population predictions for peritoneal (*upper panels*) and plasma (*mid panels*) oxaliplatin concentrations, and absolute neutrophils counts (*lower panels*)

The precision of the fixed effects estimates was also good, with relative standard error (RSE) lower than 34%, while the RSE for the random effect ranged from 30% to 70%.

The results of the visual predictive check performed are depicted in Fig. 3. In this figure, the blue areas cover the 95% confidence interval of the 5th, 50th, and 95th percentiles of the model-based prediction for peritoneal or plasma concentrations and red solid lines represent the observed 5th, 50th, and 95th percentiles of the peritoneal or plasma concentrations. This figure evidence that the PK model developed is appropriate to describe the time course of peritoneal and plasma oxaliplatin concentrations and their associated variability observed in cancer patients with PC.

Pharmacodynamics. A total of 678 ANC values were available for the PK/PD analysis. The mean (SD) of the $Circ_0$ was determined to be $7.47 \cdot 10^9$/L ($5.78 \cdot 10^9$/L) and remains relatively constant until the 4 to 6 days after drug

Table II. Parameter Estimates and Bootstrap Analysis of the HIO Population Pharmacokinetic and Pharmacodynamic Model

Model parameters	Original dataset	Nonparametric bootstrap	
	Estimate[a,b]	Mean[a]	95% Confidence interval
Pharmacokinetic model			
Q_c (L/h)	2.70	2.80 (17.3)	1.91–3.86
V_c (L)	8.33	8.32 (4.48)	7.61–9.09
Cl/F (L/h)	1.61	1.65 (33.4)	0.71–2.85
Q_p/F (L/h)	77.0	79.4 (18.6)	56.7–112.0
V_c/F (L)	19.2	20.0 (25.2)	11.4–30.8
V_p/F (L)	72.8	75.3 (17.2)	50.1–103.9
Interindividual variability (CV %)			
$\omega_{Q/F}$	34.1	34.3 (30.6)	23.4–44.2
$\omega_{V_c/F}$	17.7	17.4 (38.3)	10.1–23.5
$\omega_{Cl/F}$	85.6	85.4 (69.6)	38.2–159.0
$\omega_{V_p/F}$	57.9	56.0 (69.8)	15.1–84.2
$\omega_{V_p/F}$	23.5	24.4 (69.0)	6.70–39.3
Residual variability (CV %)			
σ_1 (proximal)	14.7	14.5 (16.8)	12.0–16.8
σ_2 (peritoneum)	16.5	16.3 (27.9)	12.6–21.0
Pharmacodynamic model			
System related parameters			
$Circ_0$ ($\cdot 10^9$/L)	7.05 (6.88)	7.07 (6.75)	6.26–8.09
MTT (h)	118 Fixed	–	–
γ	0.135 (11.9)	0.133 (25.4)	0.016–0.209
Drug related parameter			
α (L/mg)	0.382 (36.5)	0.381 (62.8)	0.048–0.505
Interindividual variability (CV %)			
ω_{Circ0}	42.3 (27.5)	40.6 (29.6)	27.3–52.1
ω_{MTT}	32.8 (53.2)	31.2 (155.9)	5.6–75.6
ω_α	141 (31.7)	145 (160.7)	73–250
Residual variability (CV %)			
σ	40.7 (17.6)	40.1 (19.4)	41.1–58.7

[a] Results expressed as parameter (*RSE*: relative standard error of parameter estimate, %).
[b] The covariate step failed. Therefore, RSE of PK parameters are not provided.

administration when ANC begin to decline and reached a nadir approximately 11 to 14 days after the start of the HIO. The median ANC nadir determined was $3.09 \cdot 10^9$/L and showed large variability with values ranging from 0.03 to $10.31 \cdot 10^9$/L. The incidence of patients with neutrophil count less than $1.0 \cdot 10^9$/L and $0.5 \cdot 10^9$/L, suggestive of neutropenia at least grades 3 and 4, respectively, was 17% and 10%, respectively. The infusion duration for the three patients that developed neutropenia grade 4 was 35, 45, and 45 min, and the corresponding ANC nadir was $0.0023 \cdot 10^9$/L, $0.028 \cdot 10^9$/L and $0.13 \cdot 10^9$/L.

The model proposed by Friberg *et al.* (30) fits the ANC profiles reasonably well. Figure 2 displays the goodness-of-fit plots for ANC (lower panels), which also showed a normal random scatter around the line of identity and indicate an absence of bias. The final estimates of the PD parameters and the results of the non-parametric bootstrap analysis are presented in Table II. Between subject variability was estimated for $Circ0$ and α with acceptable shrinkage (0.077 and 0.224, respectively). The shrinkage for MTT was determined to be 0.391. The population estimates of model parameters were very similar to the mean of the 964 bootstrap replicates that minimized successfully, and were contained within the 95% confidence intervals obtained from the bootstrap analysis, suggesting an acceptable accuracy of the PD parameters. The precision of the fixed effects estimates was acceptable, with RSE lower than 36.6%. In addition, the precision for the random effect parameters was also adequate with RSE ranging from 27.5% to 53.2%. The results of the visual predictive check performed are depicted in Fig. 3 and evidence that the model developed is appropriate to describe the time course of ANC in cancer patients following cytoreductive surgery and HIO.

The exploratory graphical analysis of the effect of age, sex, body weight, serum creatinine, albumin, serum ALT, serum AST, total bilirubin, hemoglobin, and hematocrit did not suggest any correlation between these covariates and PK/PD parameters. Therefore, given the limited number of subjects included in the current analysis, a formal analysis of covariate effects on PK/PD parameters was not attempted.

Model-Based Simulations. Deterministic simulations (Fig. 4, upper panels) clearly show that the neutropenia is reversible, short-lasting, and non-cumulative. In addition, the initial HIO concentration (and the oxaliplatin dose) and the infusion duration are the main determinants of the severity and the duration of the neutropenia. As a consequence of the linear drug effect model, Fig. 4 (upper panels) shows that a proportional increase in the oxaliplatin exposure will lead to a proportional decrease in the ANC nadir. In addition, extending the duration of the HIO administration, for a given initial

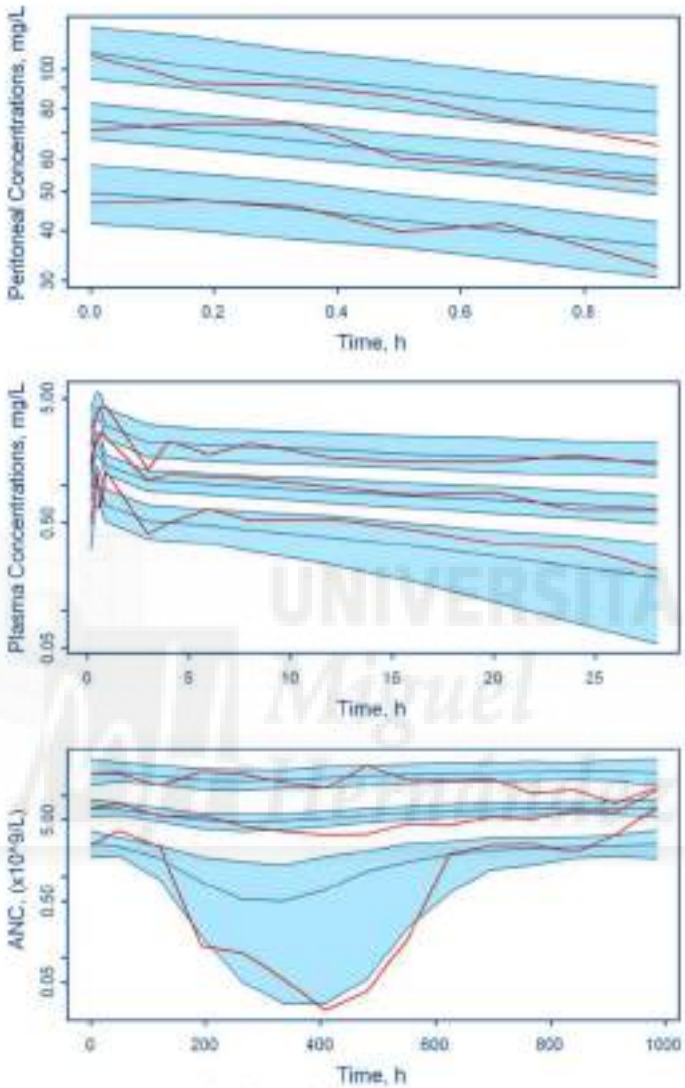

Fig. 3. Time course of the 5th, 50th, and 95th percentiles of the peritoneal (*upper panel*) and plasma (*mid panel*) oxaliplatin concentration and absolute neutrophils counts (*lower panel*) and their associated model-based prediction of the 95% confidence interval

oxaliplatin concentration in the peritoneum, will increase the severity and duration of the neutropenia as it is directly related to the oxaliplatin exposure in peritoneum.

The relationship between initial HIO concentration and the incidence of severe neutropenia is also displayed in Fig. 4 (lower panels) as a function of the infusion duration. In this figure, the incidence of neutropenia grade 4 appears linearly related to the initial HIO concentration and the slope of that linear relationship also depends of the infusion duration. Actually, a 60-min infusion of oxaliplatin starting at peritoneal concentration of 65 mg/L leads to a 20% incidence of neutropenia Grade 4. However, a 30-min infusion starting at the same oxaliplatin concentration leads to a 12% incidence of neutropenia Grade 4. Thus, shorter HIO reduce the incidence of severe neutropenia, while the initial oxaliplatin dose administered to achieve an initial 65 mg/L concentration remains the same in both cases.

According to Fig. 4 (lower left panel), a 20% incidence of neutropenia Grade 4 is also expected following a 30-min infusion starting at peritoneal oxaliplatin concentration of 105 mg/L. Interestingly, the area under the peritoneal oxaliplatin concentration *versus* time curve (AUC) following a 60-min infusion starting at 65 mg/L concentration is the same than the AUC following a 30-min infusion starting at

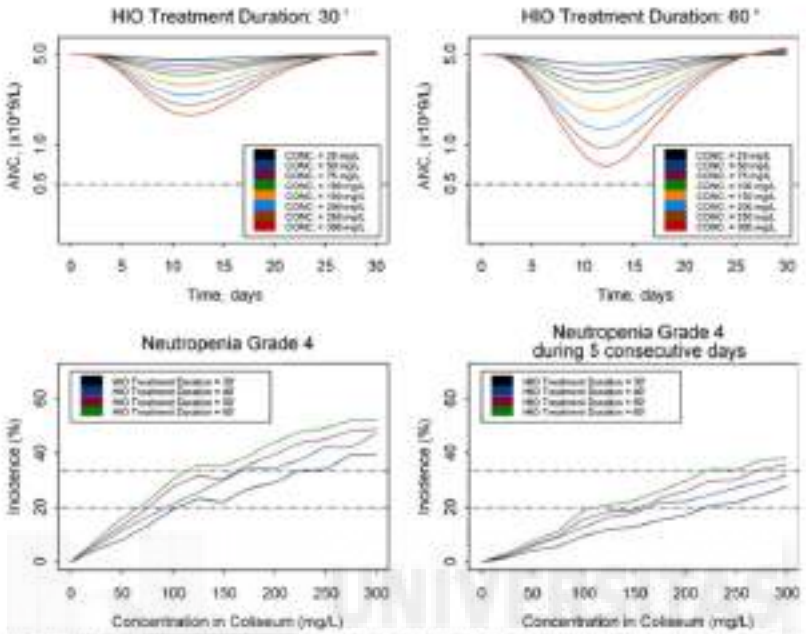

Fig. 4. Effect of initial oxaliplatin concentration in peritoneum and HIO treatment duration on the time course of neutrophil counts (*upper panels*) and on the incidence of neutropenia grade 4 and grade 4 lasting at least 5 days (*lower panels*)

oxaliplatin concentration of 105 mg/L. Consequently, these two dosing regimens leads to an incidence of neutropenia grade 4, for which primary prophylaxis with granulocyte-colony stimulating factors is recommended. Furthermore, a 60-min infusion starting at 120 mg/L concentration is associated with a 33% incidence of neutropenia grade 4, which determine the maximum tolerated exposure. Similarly, HIO exposure of 120 and 225 mg h/L are associated with a 20% and 33% incidence of neutropenia grade 4 lasting more than 5 days Fig. 4 (lower right panel).

DISCUSSION

In this study, the oxaliplatin pharmacokinetics in peritoneum and plasma has been characterized in cancer patients with PC treated with cytoreductive surgery followed by HIO. Regarding the oxaliplatin plasma disposition, the typical volume of the central compartment and the alpha half-life ($t_{1/2\alpha}$) were estimated to be 19.2 L and 0.14 h, respectively, and were similar to the PK parameters previously reported by Ferron *et al.* (27) and Massari *et al.* (42) The beta half-life ($t_{1/2\beta}$) determined in the current study, 40 h, was similar to that observed by Massari *et al.* (37.5 h) after 2-h intravenous infusion of oxaliplatin 130 mg/m^2 but was longer than the $t_{1/2\beta}$ reported by Ferron *et al.* (12.9 h). A possible explanation of these differences is the limited sampling period used to characterize the oxaliplatin pharmacokinetics in Ferron *et al.* study, as compared to the others studies. It becomes very difficult to accurately estimate oxaliplatin $t_{1/2\beta}$ based on plasma samples collected only up to 8 h after the start of HIO administration. Sampling schedules including plasma concentration collected beyond 24 h should provide a more accurate estimation of the $t_{1/2\beta}$ for total oxaliplatin.

The peritoneum to plasma ratio of oxaliplatin C_{max}, 32.1, was similar to a previously reported value for ultrafiltrate platinum concentrations (24,28). However, the apparent oxaliplatin peritoneal half-life ($t_{1/2\alpha}$=Ln(2)/k_a), equivalent to the oxaliplatin absorption half-life from peritoneum to plasma, 2.2 h, was considerably higher than the values reported previously (0.5–0.7 h) (25–27), probably because different carrier solution has been used in the current study. While all the previous pharmacokinetic studies of HIO were performed using isotonic 5% dextrose as carrier solution, this study reports, for the first time, the HIO pharmacokinetics in plasma and peritoneum using isotonic 4% icodextrin as carrier solution. Icodextrin is a macromolecule that, theoretically, should reduce oxaliplatin clearance from the peritoneal cavity and, consequently, the $t_{1/2\alpha}$ should be longer. On the other hand, the ratio estimated of the AUCs in peritoneum and plasma was 13.19, which is in line with the values previously reported (28) for ultrafiltrate platinum using isotonic 5% dextrose as carrier solution. Probably, other factors, including differences in the surgical procedures, the extracorporeal circulation machines, the oxaliplatin absolute bioavailability and the analyte and bioanalytical method, could contribute to explain the differences in the absorption half-life from peritoneum to plasma across the studies conducted with dextrose at 5% *vs* icodextrin at 4%. Therefore, further studies comparing oxaliplatin absorption with both carrier solutions are necessary to quantify the icodextrin effect on oxaliplatin absorption.

In this study, the relationship between oxaliplatin pharmacokinetics and the time course of ANC in patients with PC receiving HIO after cytoreductive surgery was also investigated by applying a semi-mechanistic population PK/PD model previously developed (30). The relationship between oxaliplatin plasma concentrations and drug effect was described by a linear function and the slope of the linear drug effect was estimated to be 0.182 L/mg. It appears that oxaliplatin neutropenic potency is about 28% higher than the estimated neutropenic potency for carboplatin in monotherapy, after correcting for the differences in the free fraction between the two drugs (43). The 5th, 50th, and 95th percentiles of the oxaliplatin peak inhibition of the proliferative rate of precursor cells into the *Prol* were determined to be 13.13, 44.23, and 564.33, respectively. With respect to the system related parameters, the estimated of $Circ_0$ was consistent with ANC normal values. The *MTT* could not be estimated correctly with the available data and, therefore, was fixed to 118 h as previously reported in the literature (30,44–48). The estimated γ value, 0.135, was also similar to those obtained previously for other anticancer drugs, such as irinotecan (0.132) or topotecan (0.120) (30,49). Interindividual and residual variabilities were moderate to large, consistent with that observed for other drugs (30).

Model-based simulations revealed that HIO induced neutropenia is reversible, short-lasting, and largely dependent on the intensity of the dose administered (or concentration in the peritoneum) and the duration of the HIO treatment. Figure 4 (upper panels) shows that increasing the dose (or the initial concentration in the peritoneum) and/or extending the HIO duration leads to a greater fluctuation in ANC values and consequently increases the likelihood of severe neutropenia. Simulations also indicated that it is possible to reduce the degree of neutropenia by employing treatment regimens with shorter HIO duration, while the overall amount of dose administered (and the initial oxaliplatin concentration in the peritoneum) remains the same. Quantitatively, simulations suggest that the maximum tolerated HIO exposure is 120 mg·h/L. However, primary prophylaxis with granulocyte-colony stimulating factors should be considered if HIO exposure is higher than 65 mg·h/L in order to prevent severe neutropenia as recommended by the guidelines (50).

In summary, a semi-mechanistic pharmacokinetic and pharmacodynamic model has been developed to account for the effect of oxaliplatin on myelosupression. This model has been successfully applied for the first time to describe the time course of ANC in cancer patients with diagnosis of PC treated with HIO, using 4% icodextrin as carrier solutions. Model-based simulations suggest that targeting HIO exposure not higher than 120 mg·h/L is safe and, however, at exposure higher than 65 mg·h/L the primary prophylaxis with granulocyte-colony stimulating factors support is recommended. The model developed is useful to optimize the design of future clinical studies.

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CAPÍTULO IV.

Population pharmacokinetics of hyperthermic intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis after cytoreductive surgery.

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1. *Abstract.*

Purpose*:* To characterize the hyperthermic intraperitoneal oxaliplatin (HIO) pharmacokinetics in peritoneum and plasma in patients with peritoneal carcinomatosis (PC) after cytoreductive surgery (CRS).

Methods: Data from 36 patients receiving HIO diluted in isotonic 4% icodextrin were combined with data from 13 patients receiving HIO diluted in isotonic 5% dextrose. Total oxaliplatin in peritoneal and plasma fluids were used to characterize an open two-compartment disposition model with linear distribution and elimination and firstorder absorption from peritoneum to plasma using NONMEM software. The effect of patient- and treatment-related covariates on oxaliplatin pharmacokinetic parameters was explored.

Results: The typical value (interindividual variability, %) in k_a, CL, and V_{ss} were 0.57 h^{-1} (43%), 1.71 L h^{-1} (39%), and 77 L (65%), respectively. No significant effect of age, body surface area, sex, creatinine clearance, liver metastases, PC index, and complete cytoreduction on pharmacokinetic parameters was found. A 12–15 % reduction in peritoneal volume of distribution was observed in patients receiving HIO diluted in 5 % dextrose relative to those patients receiving HIO diluted in 4% icodextrin.

Conclusions: The integration of peritoneal and plasma data demonstrated oxaliplatin linear absorption from peritoneum to plasma, non-specific distribution to a peripheral compartment, and linear elimination from the central compartment when HIO was administered with isotonic carrier solutions to PC patients who underwent CRS. Only the effect of the carrier solution had an impact in the peritoneal volume of distribution, but its clinical relevance seems to be limited, especially for short HIO infusions (< 60 min).

2. *Introduction*

Peritoneal carcinomatosis (PC) arises from widespread metastases of tumors in the peritoneal cavity and is generally considered to be an untreatable terminal disease [1]. Besides standard palliative surgery and chemotherapy (SPSC), there are no specific PC treatments approved by regulatory agencies;

therefore, the development of new treatments to manage this life-threatening condition could fulfill an unmet medical need [2]. A retrospective analysis in patients with resectable PC of colorectal origin has shown that cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin prolongs median survival from 24 to 63 months and increases the 5-year survival rate from 13 to 51 % with respect to SPSC [3]. The efficacy of CRS, along with HIPEC, for the PC treatment was reported in a Phase II study in ovarian cancer [4], and also in two Phase III studies in colorectal and gastric cancers [5, 6]. Recently, a metaanalysis of CRS with HIPEC and/or early postoperative intraperitoneal chemotherapy (EPIC) has shown a statistically significant survival benefit over SPSC (hazard ratio: 0.55; 95 % CI: 0.40–0.75) in PC of colorectal origin [7]. These results justify further clinical research and development of this aggressive treatment, particularly in situations where long-term survival is hardly ever seen (e.g., PC of non-gynecologic origin) [8, 9].

Oxaliplatin is an attractive agent for HIPEC because its cytotoxicity is significantly increased by hyperthermia and its intratumoral penetration is also optimal [10, 11].

Therefore, the goal of the hyperthermic intraperitoneal oxaliplatin (HIO) for PC treatment is to achieve the maximum oxaliplatin exposure in the unresected tumor nodules and residual tumor cells in the peritoneal cavity with minimum oxaliplatin access to the systemic circulation in order to balance its cytotoxic activity and the risk of hematological toxicity and peripheral sensory neuropathy, which are the dose-limiting toxicities after intravenous (IV) oxaliplatin [12].

Several Phase I dose-escalation studies in PC patients were conducted to characterize the pharmacokinetics in peritoneum and plasma and determine the HIO maximumtolerated dose [2, 13 – 15]. In these studies, intraperitoneal doses of oxaliplatin ranging from 200 to 460 mg/m^2, diluted in isotonic or hypotonic solutions, were administered during 0.5–2 h, and usually, pharmacokinetic parameters were obtained by non-compartmental pharmacokinetic analysis in separate settings (peritoneum or plasma). Oxaliplatin evidenced linear and time-independent pharmacokinetics in both peritoneum and plasma. Following 460 mg/m^2 dosing, the maximum HIO concentration (C_{max}) in peritoneum (330 mg /L^{-1}) [13] was 130-fold higher than plasma C_{max} after IV administration (2.59 mg/ L^{-1}) of 130 mg/m^2 [14], which indicates HIO is potentially more efficacious treatment for residual PC than IV oxaliplatin. Peritoneal concentrations decline exponentially with a half-life ranging from 0.5 to 2.2 h, while plasma concentrations increase to reach the peak shortly after the end of the intraperitoneal infusion.

After treatment with HIO, oxaliplatin plasma concentrations decline in a biexponential manner resembling to the pharmacokinetic profiles observed after IV administration. While the oxaliplatin

apparent central volume of distribution (V_c/F) was estimated to be between 15 and 20 L [2, 15], the estimated apparent oxaliplatin plasma clearance (Cl/F) varied substantially across studies (range: 1.61–3.71 L h^{-1}) [2, 15], reflecting differences in relation to the analyte, the analytical method, and the carrier solution tonicity, among other factors [16].

Our goal was to simultaneously characterize peritoneum and plasma oxaliplatin pharmacokinetics when HIO is administered with two different carrier solutions (5% dextrose and 4% icodextrin) and explore the effect of patient- and treatment-related covariates on HIO pharmacokinetics in PC patients who underwent CRS.

3. *Materials and methods*

Study Design and Subject Eligibility Criteria

Data were obtained from two single-arm studies (Study A and Study B) that investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of HIO after CRS [17]. In these studies, adult patients were eligible if they had confirmation of PC without extra-abdominal metastasis. Other eligibility criteria included a World Health Organization performance status of 0–2 and anticipated life expectancy of at least 3 months. Previous anticancer radiation therapy and/or chemotherapy, if given, had to be discontinued for at least 4 weeks before entry into the study or 6 weeks in the case of pretreatment with nitrosoureas or mitomycin C. Patients were required to have a negative pregnancy test (only for female patients with reproductive potential) and normal hepatic and renal function, defined as bilirubin ≤ 1.5 times the upper limit of normality (9 ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 (xULN), and serum creatinine ≤ 1.5 (x ULN). An acceptable bone marrow function, defined as neutrophil count > 1.5 x 10^9 L^{-1}, hemoglobin >10 g/$dL^{-1,}$ and platelets >100.0 x10^9 L^{-1}, was also needed. Patients with one or more of the following criteria were not selected: active infection, central nervous system metastases, peripheral neuropathy grade >2, allogenic transplant, prior extensive radiation therapy (> 25 % of bone marrow reserve), prior bone marrow transplantation or high-dose chemotherapy with bone marrow or stem cell rescue, concurrent radiation therapy, chemotherapy, hormonal therapy, immunotherapy, participation in a clinical trial involving an investigational drug in the past 30 days or concurrent enrollment in another investigational trial, and any coexisting medical condition that was likely to interfere with study procedures and/or results.

The studies were conducted in accordance with principles for human experimentation as defined in the International Conference on Harmonization for Good Clinical Practice guidelines and the

principles of the Declaration of Helsinki. The study was approved by the corresponding Investigational Review Board, and informed consent was obtained from each subject after being advised of the potential risks and benefits, as well as the investigational nature of the study.

Surgical procedure

A xiphopubic midline laparotomy was carried out to examine the tumor load in the abdominal cavity. To obtain the PC index [18], the abdomen was divided into 13 areas numbered from 0 to 12, as described elsewhere [19]. Cytological samples and biopsies were taken from each area. Resection of the primary tumor when present was carried out according to regional lymphadenectomy with correct margins. In PC with the primary tumor in situ and in metachronous cases, peritonectomies and debulking were carried out as required and extensive systematic peritonectomies were not performed. The mesenteric peritoneum was not extensively removed, and acceptable small-bowel resections were guided by maximal tumor volume locations. Remaining malignant granulations were destroyed using electrosurgical fulguration. This aggressive CRS was performed with the aim to reach complete resection or, if not possible, to resect all visible tumor lesions larger than 2.5 mm. Anastomoses were carried out after the perfusion of the abdominal cavity was completed. The CRS was considered complete if no residual implants remained [20].

Hyperthermic intraperitoneal oxaliplatin

An open coliseum technique was used according to the procedure previously described [18]. Four 36-Fr drains were connected to a continuous closed circuit, and two intraperitoneal thermal probes were placed in order to obtain a proper temperature feedback. Briefly, a Tenckhoff inflow catheter was placed centrally in the abdomen, and four outflow catheters were inserted through separate stab incisions in the abdominal wall. Both the inflow and outflow catheters were connected to a perfusion pump and heat exchanger. The skin of the abdomen was attached to a retractor ring, and the abdominal cavity was covered with a plastic sheet with a small opening in the center allowing entrance for the surgeon's hands to stir the abdominal contents and deliver a more uniform drug distribution and heat to the intra-abdominal surfaces. The rollers of an extracorporeal circulation machine (Performer LRT, Rand) were set at a speed of 1 L min-1 to deliver the carrier solution. The circuit passed through a heat exchanger which raised the temperature to 48ºC. The perfusate temperature on the abdominal cavity fluctuated between 42º and 43ºC.

Once the temperature was achieved, oxaliplatin dose was administered. In Study A, patients received HIO diluted in isotonic 4 % icodextrin, whereas in Study B, patients received HIO diluted in

isotonic 5 % dextrose. After the end of perfusion, the solution was evacuated. During the next five postoperative days, 19 of 36 patients in Study A received EPIC based on the administration of 5-fluorouracil (5-FU) at a dose of 15 mg kg-1 in 1-h infusion through a 14-Fr catheter in order to potentiate the oxaliplatin cytotoxic effect [21].

Sample Collection and Bioanalytical Methods

Peritoneal fluid and venous blood samples were collected immediately after the oxaliplatin administration and then every 10 min until the end of the peritoneal perfusion. Additional venous blood samples were drawn at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, 24, and 28 h after the end of the peritoneal perfusion. All samples were collected in Sarstedt lithium-heparin monovette tubes, centrifuged at 3,500 rpm for 10 min, and stored at - 80 C until analysis. All samples were previously digested with nitric acid at 0.65 %. Total platinum in peritoneum and plasma was measured using a validated assay through inductively coupled plasma atomic emission spectrometry (ICP-AES, model ULTIMA, JOBIN–YVON, France). This methodology has been widely used for quantification of platinum compounds in human plasma samples [22 –24]. The lower limit of quantification was 0.5 mg/L. Over the validated range of the assay (0.5–30 mg/L for plasma samples and 5–300 mg/L for peritoneal fluid samples), the mean intra- and interassay coefficients of variation were lower than 9.5 and 7.7 %, respectively. Total platinum concentrations of each sample were transformed into oxaliplatin concentrations according to their molecular weights before conducting the pharmacokinetic analysis.

Software

An exploratory non-compartmental pharmacokinetic analysis (NCA) was performed with WinNonlin Professional (Version 4.0.1; Pharsight Corp., Mountain View, CA, USA). The population pharmacokinetic analysis was conducted by nonlinear mixed-effects modeling using the firstorder conditional (FOCE) method implemented in NONMEM VII version 7.1.2. software package (ICON, Hanover, MD) [25], and the compilations were achieved using gfortran compiler, for Windows. PsN 3.4.2 tool was used to conduct a nonparametric bootstrap stratified by study. Wings for NONMEM (Auckland, New Zealand) was used to conduct a randomization test. Graphical and all other statistical analyses were performed using S-Plus 6.1 Professional Edition (Insightful, Seattle, WA, USA)

Exploratory Non-Compartmental Pharmacokinetic Analysis (NCA)

A NCA for peritoneal and plasma concentration–time data was performed in order to explore the lack of differences in pharmacokinetic parameters across the two studies analyzed. Individual

oxaliplatin C_{max} at peritoneum and plasma was determined by direct observation of the raw data. Individual AUC from 0 to the last experimental time (t_{last}) (AUC_{0}–t_{last}) was calculated using the linear/log trapezoidal method. While the use of $AUC_{0–tlast}$ instead of AUC_{0}–∞ in peritoneum is justified because the oxaliplatin concentration in peritoneum after the drug removal is 0, the justification for using $AUC_{0–tlast}$ for plasma concentrations is based on the magnitude of the extrapolation from t_{last} to ∞, which is higher than 20 % in all subjects as expected from the long terminal half-life of oxaliplatin in plasma and the sampling schedule implemented [26]. The terminal rate constant (k_z) was determined from the slope of the terminal log-linear portion of the peritoneal and plasma concentration–time curves, and the terminal half-life ($t_{1/2}$) was calculated as ln2/ (k_z) for both peritoneum and plasma, respectively.

In order to compare the pharmacokinetic parameters C_{max}, $AUC_{0–tlast}$, and $t_{1/2}$ across both studies, several normalizations in C_{max} and $AUC_{0–tlast}$ parameters were necessary to control the differences between patients with respect to oxaliplatin doses administered, the volume of the carrier solution used and the duration of peritoneal perfusions (T).

Since C_{max} in peritoneum ($C_{max\ PR}$) was related to the oxaliplatin dose (D, mg m^{-2}) and the carrier solution volume (V, L), which both vary across patients, individual C_{max} values were normalized for a standard dose of 360 mg m^{-2} and 1 L of carrier solution, according to Eq.1:

$$C^{N}_{\max PR} = \frac{C_{\max PR} \cdot V \cdot 360}{D} \quad (1)$$

where $C^{N}_{\max PR}$ represents the normalized $C_{max\ PR}$. Similarly, $AUC_{0–tlast}$ in peritoneum depends on D and T, which also varies across patients. Consequently, the individual $AUC_{0–tlast}$ values in peritoneum were normalized for a standard dose of 360 mg m^{-2} dose and 1-h duration of peritoneal perfusion, according to Eq.2:

$$AUC^{N}_{PR} = \frac{AUC_{0-tlast} + AUC_{tlast-1}}{D} \cdot 360 = \frac{AUC_{0-tlast} + \frac{C_{tlast}}{\lambda z} \cdot \left[1 - e^{-\lambda z \cdot (1-tlast)}\right]}{D} \cdot 360 \quad (2)$$

where AUC^{N}_{PR} represents the normalized $AUC_{0–1}$ in peritoneum and C_{tlast} represents the observed concentration at the last sampling point, t_{last}.

Normalizations were also undertaken for non-compartmental parameters derived from the plasma oxaliplatin concentrations. Since plasma C_{max} and $AUC_{0-tlast}$ depend on the amount of oxaliplatin absorbed during HIO, which at the same time depends on D and T, C_{max} and $AUC_{0-tlast}$ were normalized according to the following equations:

$$C^{N}_{\max PL}\frac{C_{\max}\cdot 360}{D\cdot(1-\exp^{-\lambda z\cdot T})} \quad (3)$$

$$\mathrm{AUC}^{N}_{PL}=\frac{\mathrm{AUC}_{0-tlast}\cdot 360}{D\cdot(1-\exp^{-\lambda z\cdot T})} \quad (4)$$

where $C^{N}_{\max PL}$ and AUC^{N}_{PL} represent the normalized C_{max} and $AUC_{0-t_{last}}$ in plasma, respectively. Finally, the ratio of the geometric means of the C^{N}_{max} AUC^{N} and $t_{1/2}$ between the two studies and the associated confidence interval (CI) and p values were calculated for peritoneum and plasma [27].

Population Pharmacokinetic Analysis

Based on the exploratory graphical analysis, oxaliplatin in the peritoneal fluid was assumed to be absorbed into plasma according to a linear process, characterized by the first-order absorption rate constant, k_a. As oxaliplatin concentrations in peritoneum were available, the absorption process was parameterized in terms of peritoneum to plasma clearance (Cl_a) and volume of distribution in the peritoneum (V_a); thus, k_a was calculated as a secondary parameter as Cl_a/V_a. Moreover, the oxaliplatin disposition in plasma was characterized by an open two-compartment model with linear elimination and non-specific distribution to peripheral tissues. This model was parameterized in terms of systemic clearance (Cl), intercompartmental clearance (Cl_p), central volume of distribution (V_c), and peripheral volume of distribution (V_p). As the oxaliplatin absolute bioavailability (F) after intraperitoneal administration cannot be estimated from the available data, the estimated model parameters were considered apparent. Because the system of differential equation is linear, ADVAN5 subroutine in NONMEM was used. The interindividual (or between subjects) variability (IIV) in the pharmacokinetic model parameters was assumed to follow the lognormal distribution, and consequently, an exponential error model was used. Residual variability in oxaliplatin peritoneal and plasma concentrations was evaluated using an additive error model after natural logarithmic transformation of the observations and model predictions. The magnitude of interindividual and residual variability was expressed approximately as a coefficient of variation.

Model selection criteria

The improvement in the fit obtained for each model was assessed in several ways. First, the resulting NONMEM- generated minimum value of the objective function (MFOV) after fitting the models evaluated was used to perform the likelihood ratio test (LRT). This test is based on the change in the minimum value of the objective function (MVOF), which is equal (up to a constant) to minus twice the log-likelihood of the data and is asymptotically distributed like v^2 with the degrees of freedom equal to the number of parameters added to the model. For hierarchical models, a ΔMVOF of 3.84 was required to reach statistical significance ($p = 0.05$) for the addition of one fixed effect. In addition, the improvement in the model fit by including covariates into the population pharmacokinetic model was assessed by the reduction in the IIV, residual variability, the reduction in the standard errors, and the examination of diagnostic plots.

Covariate analysis

The population pharmacokinetic model described was fitted to the data, and the empirical Bayes' estimates (EBE) of the individual pharmacokinetic parameters were computed using a ''POSTHOC'' feature in NONMEM in order to screen the influence of covariates on model parameters. The covariates selected for this analysis were age, body surface area, sex, creatinine clearance, liver metastases, PC index, complete cytoreduction, and study. The screening was conducted only on model parameters where the shrinkage was lower than 0.3 and was based on visual graphical inspection and stepwise linear regression of the relationships between the EBE of individual model parameters and the covariates. Covariates with statistically significant ($p < 0.05$) and potentially clinically relevant ($r^2 > 0.2$) effect on the model parameters during the screening analysis were further tested in NONMEM by forward inclusion ($p < 0.05$) and backward elimination ($p < 0.01$) in order to be incorporated into the population model [28]. Continuous covariates were evaluated using power equations after centering on the median, whereas categorical covariates were incorporated into the model as index variable as indicated in Eq. 5 for a binary variable:

$$P_i = P_R \cdot e^{\varphi \cdot x} \cdot e^{\eta_i}, \quad \text{where } \eta_i \approx N(0, \omega^2) \qquad (5)$$

where P_i is the individual pharmacokinetic parameter for i the subject; P_R represents the geometric mean of the selected model parameter in patients with the reference category of the binary covariate ($x = 0$), x is a dummy variable that takes the value 0 in patients with the reference category and 1 for patients within the test category, and e^{Φ} represents the ratio of the parameter geometric mean between the two

categories. Two different approaches were used to compute the CI of the covariate effect. In the first approach, CI was calculated from the asymptotic standard error, while in the second approach the CI was obtained by nonparametric bootstrap stratified by study [29]. The p value associated with the covariate effect was derived from both the LRT and the randomization test [30].

Model Evaluation

Three complementary methods were employed to evaluate the model: nonparametric bootstrap stratified by study [31], normalized prediction distribution errors (NPDE) [32], and visual predictive check (VPC) [33].

4. *Results*

Overall, 49 patients (36 from Study A and 13 from Study B) were available for the analysis. The primary tumor type was colorectal (n = 17), ovarian (n = 15), appendiceal (n = 10), gastric (n = 3), endometrial (n = 3), and primary papillary (n = 1). The perfusate volume varied from patient to patient depending on the peritoneal surface area, and approximately 2.5–6.0 L was employed. On average, the HIO mean duration was 36.6 min (range: 30–60 min). Descriptive statistics of the patient baseline characteristics stratified by study are shown in Table 1. Similar covariate distribution was found across both studies with no statistically significant differences in both patient and treatment characteristics at baseline.

A total of 222 and 576 oxaliplatin concentrations from peritoneum and plasma, respectively, were available to characterize the oxaliplatin pharmacokinetics in cancer patients with PC treated with HIO after CRS. Peritoneal oxaliplatin concentration showed a rapid, exponential decrease during the duration of the peritoneal perfusion. The peak plasma concentration of oxaliplatin was observed shortly after the end of the peritoneal perfusion and, subsequently, decayed rapidly in a biexponential fashion, resulting in a limited systemic exposure. The results of the exploratory NCA are presented in Table IV-2. The NCA parameters C^N_{max}, AUC^N , and $t_{1/2}$ in both peritoneum and plasma showed no statistically significant differences between both studies. The 90 % CI of the Study B-to-Study A ratio of geometric means included 1 and fell within 0.8 to 1.25 for C^N_{max}, AUC^N, and $t_{1/2}$ in both peritoneum and plasma.

The population pharmacokinetic analysis evidenced the time course of peritoneal oxaliplatin concentration was well described by a first-order elimination process. Furthermore, plasma concentrations following HIO were best described by an open two-compartment disposition model with

nonspecific distribution to a peripheral compartment, linear elimination from the central compartment, and first-order absorption from peritoneum to plasma. Figures IV- 1 and IV-2 display the goodness-of-fit plots for oxaliplatin peritoneal and plasma concentrations, respectively.

Table IV-1 Patient and treatment characteristics at baseline stratified by study

Patient and treatment characteristics at baseline	Study A[a] (N = 36)	Study B[a] (N = 13)	p value[b]
Age (years)	57.7 (11.6)	58.2 (12.8)	0.89
Body weight (kg)	69.3 (12.1)	69.1 (12.7)	0.95
Body surface area (m^2)	1.7 (0.2)	1.8 (0.2)	0.78
Sex (%)			
Male	39	38	0.98
Female	61	62	
ALT (IU L^{-1})	50.6 (42.4)	35.0 (6.8)	0.35
AST (IU L^{-1})	43.2 (45.5)	34.6 (13.4)	0.63
Alkaline phosphatase (IU L^{-1})	189 (90)	212 (63)	0.60
Total bilirubin (µmol L^{-1})	0.6 (0.3)	0.6 (0.3)	0.93
Serum albumin (g L^{-1})	46.2 (5.8)	42.1 (1.7)	0.78
Total protein (g L^{-1})	66.7 (12.3)	70.9 (8.8)	0.50
Creatinine clearance (mL min^{-1})[c]	80.5 (29.2)	79.7 (34.0)	0.95
Hemoglobin (g dL^{-1})	11.6 (2.0)	11.8 (1.1)	0.71
Leukocyte Count ($x10^9 L^{-1}$)	7.2 (3.8)	7.2 (3.4)	0.99
Neutrophil ($x10^9 L^{-1}$)	4.7 (3.6)	4.6 (3.5)	0.92
Platelets ($x10^9 L^{-1}$)	286 (155)	261 (127)	0.61
Liver metastases			
Yes (%)	86.1	84.6	0.84
No (%)	13.9	15.4	
Peritoneal carcinomatosis index	12.3 (12.3)	11.0 (10.8)	0.73
Complete cytoreduction			
Yes (%)	27.8	7.7	0.14
No (%)	72.2	92.3	
Oxaliplatin dose (mg m^{-2})	364.5 (32.4)	399.5 (94.7)	0.59
Volume carrier solution (L)	3.9 (0.8)	3.6 (0.6)	0.20
Duration HIO (min)	37.6 (8.3)	33.8 (5.1)	0.13

The observed versus model-predicted plots (upper panels in Figs. IV-1, IV-2) showed a normal random scatter around the identity line and indicated the absence of significant bias or model misfit.

Similarly, the distribution of conditional weighted residual (middle panels in Figs. IV- 1, IV-2) [34] and NPDE (lower panels in Figs. IV-1, IC-2) as a function of the population predictions (left panels in Figs. IV-1, IV2) and time (right panels in Figs. IV- 1, IV-2) did not show any trend that evidences model inadequacy [32]. Actually, the mean and standard deviation of the NPDE for peritoneal concentrations were - 0.01 (95 %CI: - 0.13 to 0.13) and 0.98 (95 %CI: 0.86 to 1.08), respectively, while the mean and standard deviation of the NPDE for plasma concentration were 0.04 (95 %CI: - 0.04 to 0.11) and 0.91(95 %CI: 0.85 to 0.98), respectively. This result confirms the model accuracy and precision because the mean and standard deviation of the NPDE for both peritoneal and plasma concentrations were very close to 0 and 1, respectively.

The final estimates of the pharmacokinetic model parameters and the results of the nonparametric bootstrap analysis stratified by study are presented in Table IV-3. Except for Cl_p, IIV was estimated for all the model parameters, and the shrinkage was $<\chi$20 %, except for V_c . Furthermore, the population estimates for the final model parameters were very similar to the mean of the 500 bootstrap replicates that minimized successfully and were contained within the 95 % CI obtained from the bootstrap analysis. The precision of the parameter estimates was good with relative standard error (RSE) lower than 15 % for fixed effects and lower than 50 % for random effects. In addition, the results of the VPC depicted in Fig. IV-3 evidence the model developed is appropriate to describe the time course of peritoneal and plasma oxaliplatin concentrations and their associated variability in cancer patients with PC after CRS and, therefore, can be used to assess the covariate effects in model parameters. Within the range of covariate values analyzed, the graphical and statistical screening analyses evidenced a Integligible effect of the age, body surface area, sex, creatinine clearance, liver metastases, PC index, and complete cytoreduction on pharmacokinetic model parameters. Only study type had a direct impact in the V_a. The mean (SD) of V_a in Study A was estimated to be 3.9 (0.7) L, while the mean (SD) of V_a in Study B was 3.1 (0.6) L. The p values associated with the inclusion of the study type as a covariate for V_a in NONMEM were 0.01 and 0.03 for the LRT and the randomization test, respectively. On the other hand, the Study B-to-Study A ratio of the geometric means for V_a (and its asymptotic 90 % CI) was estimated to be 0.86 (0.74–0.91), which was very similar to the results obtained from the nonparametric bootstrap stratified by study, 0.87 (90 % CI: 0.78–0.92).

5. *Discussion*

We aimed to simultaneously characterize the peritoneal and plasma time course of oxaliplatin concentrations when HIO was administered with isotonic carrier solutions to patients with PC who underwent CRS and evaluate the effect of several covariates in the oxaliplatin peritoneal and plasma pharmacokinetic parameters. The descriptive statistics of both patient and treatment characteristics at baseline showed a similar covariate distribution across the studies included in the analysis, with no statistically significant differences among them.

Table IV-2 Non-compartmental pharmakokinetic parameters stratified by study

Site	Pharmacokinetic parameter	Study A[a] (N = 35) [c]	Study B[a] (N = 13)	Mean ratio: Study B/ study A (90 % CI)	p value[b, c]
Peritoneum	C_{maxN} (mg L_{-1})	676 (150)	698 (193)	1.03 (0.93–1.13)	0.71
	AUC^N (mg h L^{-1})	132 (25.0)	150 (44.7)	1.13 (1.00–1.23)	0.18
	$t_{1=2}$ (h)	1.28 (0.35)	1.19 (0.49)	0.89 (0.80–1.02)	0.28
Plasma	C_{maxN} (mg L_{-1})	20.5 (4.30)	22.3 (9.10)	1.05 (0.93–1.17)	0.47
	AUC^N (mg h L^{-1})	192 (45.3)	213 (72.4)	1.08 (0.95–1.22)	0.34
	$t_{1=2}$ (h)	33.7 (28.2)	31.3 (16.7)	0.93 (0.80–1.05)	0.36

[a] Results are expressed as mean (standard deviation)
[b] Continuous variables were compared with t test. Shapiro–Wilk test was used for assessing normal distributions. Levene's test was used for checking the equality of variances
[c] One subject was excluded from the NCA due to limited data to compute non-compartmental parameters

Although the unbound oxaliplatin fraction is considered to be the active drug, the absence of proteins to which oxaliplatin can bind in peritoneal fluid and the high correlation determined between unbound and total platinum plasma levels for oxaliplatin (r^2 = 0.98) [35] justify that total oxaliplatin concentrations in peritoneum and plasma were used to conduct this population pharmacokinetic analysis, similarly to what was recently done and reported in other publications in the same target population [2, 15].

The exploratory NCA showed that the ratio between peritoneal and plasma C_{max} was around 33 and reflects that high oxaliplatin peritoneal exposure was achieved with a low oxaliplatin access to the systemic circulation. This local regional exposure advantage was also observed by Elias *et al*. [13].

Furthermore, the estimated AUCs in peritoneum and plasma, as well as the oxaliplatin absorption half-life ($t_{1/2}$), were consistent with those values reported elsewhere [36]. However, the mean of the oxaliplatin plasma elimination half-life was estimated to be 32.1 h, which is consistent with the beta half-life ($t_{1/2b}$) previously reported (32–38 h) after 1- or 2-h intravenous infusion of oxaliplatin 130 mg m^{-2} [14], and Valenzuela et al. (40 h) after CRS followed by HIO [2], but longer than the $t_{1/2b}$ reported by Ferron et al. (12.9 h), probably because of the differences in the sampling schedules [15]. Even though the differences in the volume of perfusate and duration of HIPEC were not statistically significant across the two studies analyzed, the C_{max} and AUC_0–t_{last} in peritoneum and plasma were normalized by different functions of dose, volume of perfusate, and/or duration of HIPEC in order to avoid the potential confounding effect. After normalizing, the non-compartmental parameters showed no statistically significant differences between both studies, and the 90 % CI of the mean ratio of all parameters analyzed included 1 and fell within 0.8–1.25.

Study A and Study B were pooled for a joint population pharmacokinetic analysis, which evidenced the oxaliplatin absorption and elimination half-lives were very similar to those estimated from the NCA analysis. In addition, the oxaliplatin plasma disposition was characterized by a volume of distribution at the steady state of 77.0 L, which was similar to the value reported by Ferron et al. (65.1 L) [15] and Massari *et al*. (69.7 L) [14]. The apparent plasma clearance of oxaliplatin was estimated to be 1.71 L/h^{-1} very similar to the one reported by Valenzuela et al. (1.61 L/h^{-1}) [2]. However, Ferron et al. reported an apparent plasma clearance higher than the obtained in the present study (3.71 L/h^{-1}). This fact probably is due to the sample protocol design because Ferron et al. collected samples until 8 h, while in this study, samples were collected until 28 h. The IIV in model parameters was moderate and ranged from 21.4 % in V_a to 58.2 % in V_p. Interestingly, the IIV observed in the pharmacokinetic parameters determining the oxaliplatin plasma disposition was higher than that observed for the pharmacokinetic parameters which determine the peritoneal concentrations. This phenomenon has been previously observed in other population pharmacokinetic studies of HIO [2,15]. Age, body surface area, sex, creatinine clearance, liver metastases, PC index, and complete cytoreduction did not influence HIO pharmacokinetic parameters to a significant extent.

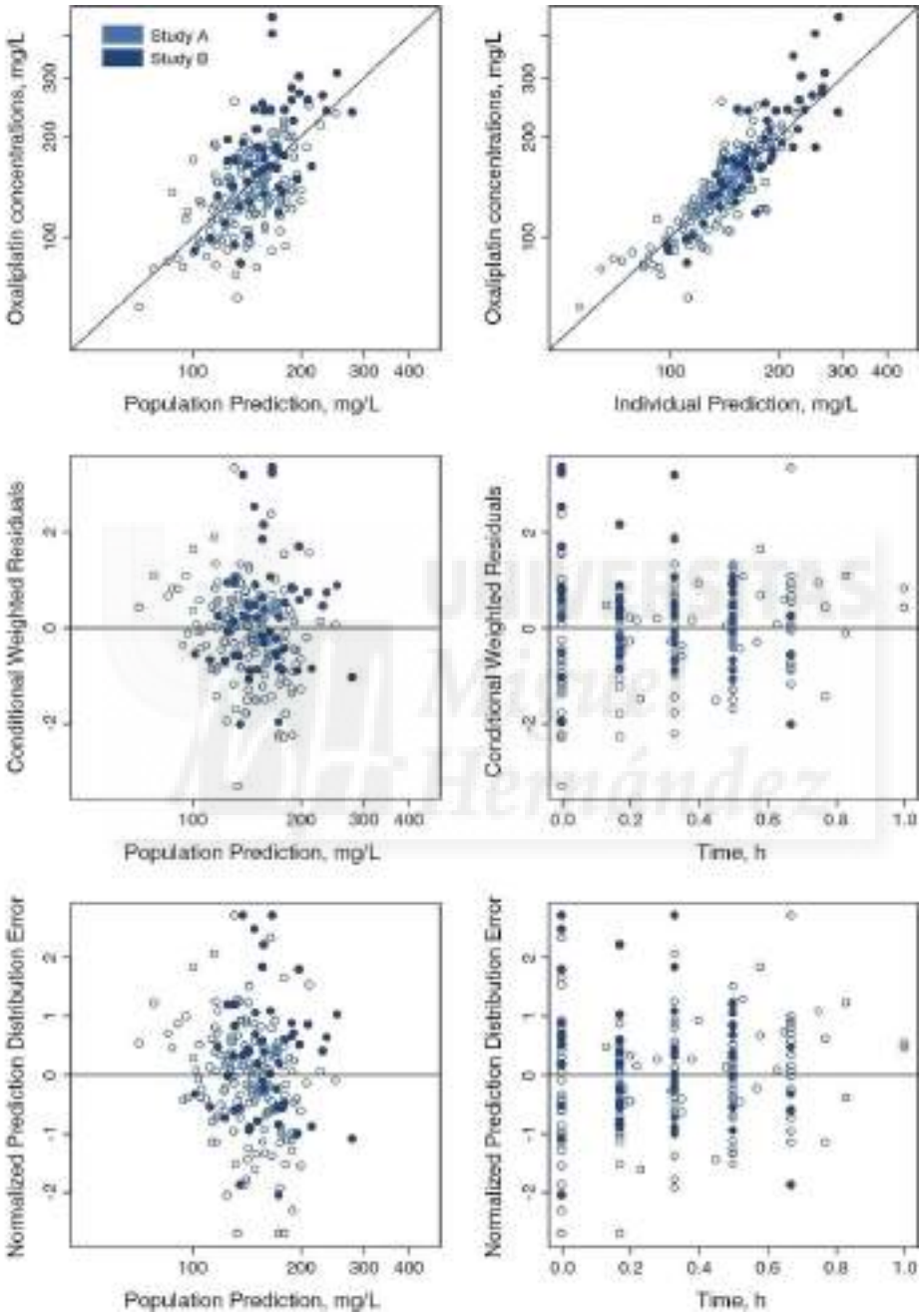

Figure IV-1 Goodness of fit plots for oxaliplatin peritoneal concentrations stratified by study

Since the LRT is approximate by a $\chi 2$ distribution and this approximation might not be optimal at lower sample sizes, a randomization test was conducted to determine the exact p value in assessing the covariates with potential effect on oxaliplatin pharmacokinetics. Both LRT and randomization test confirmed the study effect on the V_a parameter. The 12–15 % reduction in V_a for Study B, relative to Study A, might be explained by the carrier solutions used. While in Study A patients received HIO diluted in 4 % icodextrin, in Study B patients received HIO diluted in 5 % dextrose. The choice of a carrier solution and its tonicity plays an important role in the penetration of chemotherapeutic agents into tumor cells and its peritoneal absorption [16]. Hypotonic solutions have been associated with high incidence (50 %) of postoperative peritoneal bleeding and severe thrombocytopenia and are not currently used [37]. Hypertonic solutions are not suitable for HIPEC since the fluid shift inward to the peritoneal cavity dilutes the intraperitoneal drug concentration and reduces drug exposure [38]. Isotonic salt or 5 % dextrose solutions are the solutions most frequently employed for HIPEC. However, their solute absorption through the peritoneum makes difficult to maintain a prolonged high intraperitoneal fluid volume and, consequently, may limit the HIPEC duration [39]. In theory, isotonic high molecular weight solutions should be able to maintain the intraperitoneal fluid volume due to its lack of absorption and therefore have a higher drug availability in the peritoneal cavity relative to isotonic salt or 5 % dextrose solutions [16, 40]. Icodextrin, an a -1-4-linked glucose polymer of 12,000 to 20,000 D, diluted at 4 % is an isotonic high molecular weight solution widely used for peritoneal dialysis that has also been employed as carrier solution for HIO [2, 16]. To date, no formal comparison on the effect of carrier solutions in HIOhas been reported. The reduction in V_a in the dextrose group could be due to the net absorption of the dextrose and would confirm the theoretical hypothesis that isotonic high molecular weight solutions, like icodextrin, are able to maintain the intraperitoneal fluid volume because these compounds are not absorbed. Furthermore, this phenomenon might also explain the lack of difference in normalized C_{max} and AUC observed in the non-compartmental analysis. Indeed, non-compartmental parameters in peritoneum were calculated using the theoretically administered carrier solution volume, which was assumed to be constant during HIO duration. If future studies confirm that the perfusate volume varies during HIPEC, then the conclusions derived from the non-compartmental analysis should be interpreted with caution. The clinical relevance of the difference in V_a can be inferred from a previous pharmacokinetic–pharmacodynamic model for HIO [3]. Stochastic model-based simulations undertaken indicated that incidence of neutropenia Grade 4 lasting at least 5 days following HIO might be about 15 % higher for the 5 % dextrose relative to 4 % icodextrin at the target peritoneal exposure of 200 $mg \cdot h/L^{-1}$.

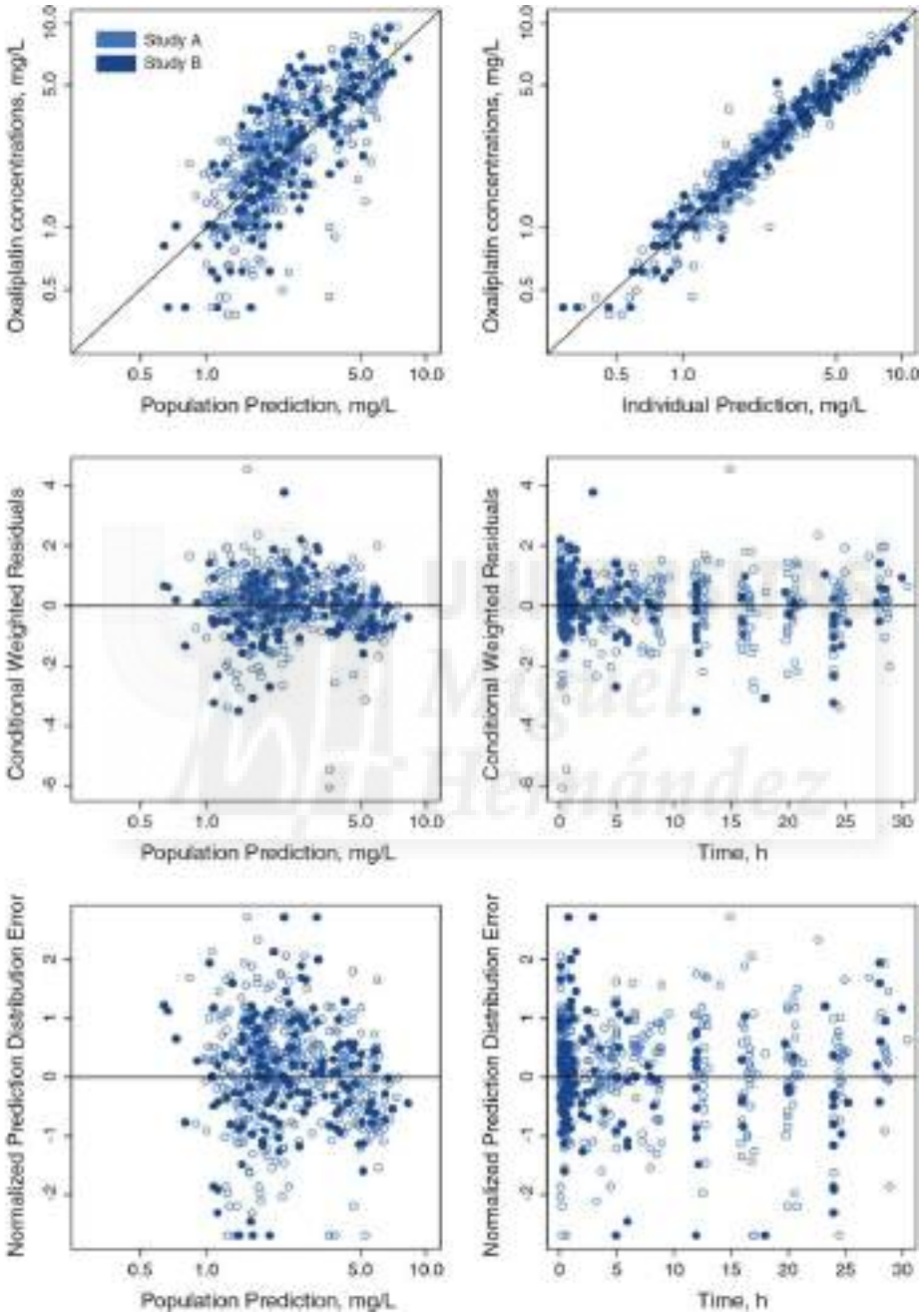

Figure IV-2 Goodness of fit plots for oxaliplatin peritoneal concentrations stratified by study

Therefore, using 5 % dextrose, instead of 4 % icodextrin, as carrier solution for 30- and 120-min HIO would result in less than one additional patient with neutropenia Grade 4 lasting more than 5 days for every 67 and 23 patients treated, respectively. These results suggest that the clinical relevance of the

Table IV-3 Parameter estimates and bootstrap analysis of the HIO population pharmacokinetic model

	Estimate	Mean	95 % CI
Cl_a (L h^{-1})	2.03 (10.6)	2.01 (10.5)	1.58–2.40
V_a study A (L)	3.90 (3.6)	3.89 (4.3)	3.74–4.04
V_a study B (L)	3.10 (4.7)	3.12 (5.2)	2.89–3.35
Cl (L h^{-1})	1.71 (13.0)	1.70 (13.5)	1.25–2.15
Cl_p (L h^{-1})	34.9 (10.0)	34.9 (10.0)	28.1–41.8
V_c (L)	19.7 (12.2)	19.4 (12.7)	14.6–24.2
V_p (L)	57.3 (13.4)	57.1 (13.6)	43.4–73.7
Interindividual variability (CV %)			
x_{Cla}	39.0 (11.7)	37.7 (12.0)	29.1–47.0
x_{Va}	21.4 (18.1)	20.9 (14.4)	14.8–26.9
x_{CL}	44.3 (26.9)	43.9 (20.7)	28.3–64.5
x_{Vc}	22.6 (19.4)	22.1 (50.0)	0.23–46.7
x_{Vp}	58.2 (41.2)	55.5 (25.5)	30.0–84.0
Residual variability (CV %) r			
	18.3 (6.3)	18.2 (6.0)	16.2–20.3

[a]Results expressed as parameter (RSE, relative standard error of parameter estimate, %)

difference between 4 % icodextrin and 5 % dextrose is limited for short infusion durations (i.e., 30 min). In this situation, the direct cost saved in using 5 % dextrose (1.38 € L^{-1}) instead of 4 % icodextrin (97.40 € L^{-1}) is expected to be higher than the direct cost associated with the treatment for the additional severe neutropenia events that may happen in using 5 % dextrose over 4 % icodextrin. However, if the HIO duration is prolonged up to 120 min, further studies are needed to evaluate the clinical equivalence between the 5 %dextrose and 4 % icodextrin and its potential economic impact.

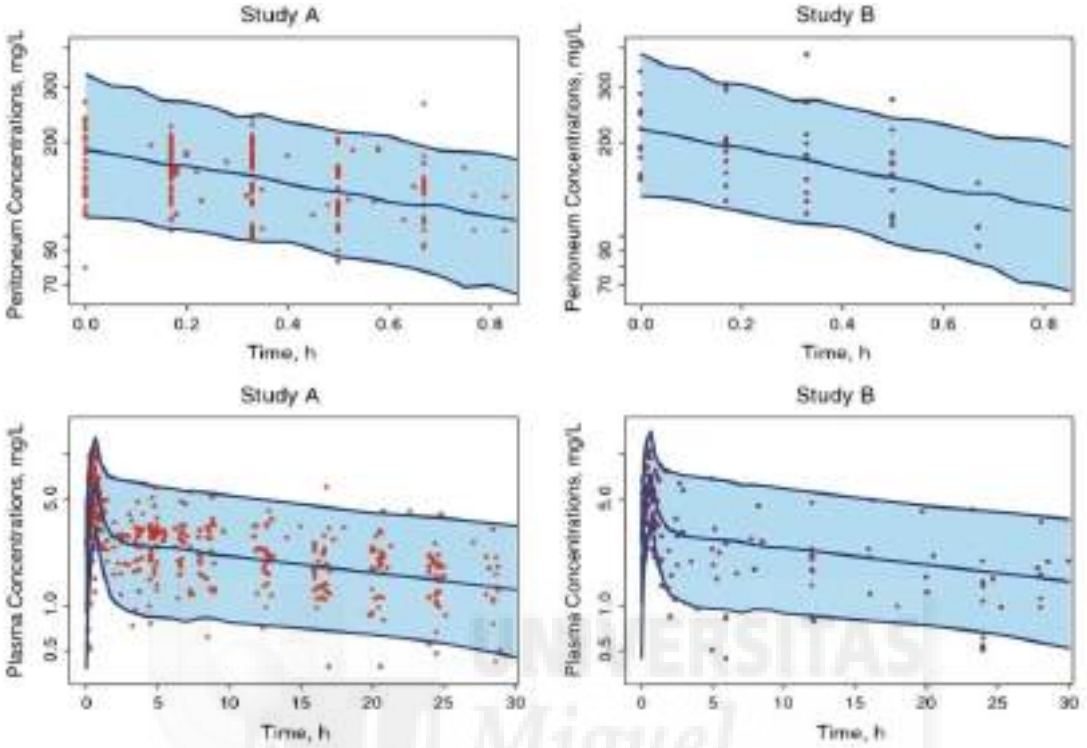

Figure IV-3: Time course of the observed peritoneal (upper panels) and plasma (*lower panels*) oxaliplatin concentrations for Study A (*left panels*) and Study B (*right panels*) and their associated model-based 95 % prediction intervals.

In summary, an open two-compartment disposition model with non-specific distribution to a peripheral compartment, linear elimination from the central compartment, and first-order absorption from peritoneum to plasma managed to properly characterize the peritoneal and plasma time course of oxaliplatin concentrations when HIO was administered with isotonic carrier solutions to PC patients who underwent CRS. The 12–15 % reduction in peritoneal volume of distribution observed in patients receiving HIO diluted in 5 % dextrose relative to that in patients receiving HIO diluted in 4 % icodextrin supports the theoretical hypothesis that isotonic high molecular weight solutions are able to maintain the intraperitoneal fluid volume longer. The clinical relevance of this finding is limited for short HIO durations, and further studies are needed to elucidate the clinical equivalence at longer HIO duration.

6. *Acknowledgments*

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7. *Conflict of interest*

The author(s) indicated no potential conflicts of interest.

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9. Annex IV-1. Original Publication: Population pharmacokinetics of hyperthermic intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis after cytoreductive surgery.

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ORIGINAL ARTICLE

Population pharmacokinetics of hyperthermic intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis after cytoreductive surgery

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Abstract
Purpose To characterize the hyperthermic intraperitoneal oxaliplatin (HIO) pharmacokinetics in peritoneum and plasma in patients with peritoneal carcinomatosis (PC) after cytoreductive surgery (CRS).
Methods Data from 36 patients receiving HIO diluted in isotonic 4 % icodextrin were combined with data from 13 patients receiving HIO diluted in isotonic 5 % dextrose. Total oxaliplatin in peritoneal and plasma fluids were used to characterize an open two-compartment disposition model with linear distribution and elimination and first-order absorption from peritoneum to plasma using NONMEM software. The effect of patient- and treatment-related covariates on oxaliplatin pharmacokinetic parameters was explored.
Results The typical value (interindividual variability, %) in λ_z, CL, and V_c were 0.57 h^{-1} (43 %), 1.71 L h^{-1} (39 %), and 77 L (65 %), respectively. No significant effect of age, body surface area, sex, creatinine clearance, liver metastases, PC index, and complete cytoreduction on pharmacokinetic parameters was found. A 12–15 % reduction in peritoneal volume of distribution was observed in patients receiving HIO diluted in 5 % dextrose relative to those patients receiving HIO diluted in 4 % icodextrin.
Conclusions The integration of peritoneal and plasma data demonstrated oxaliplatin linear absorption from peritoneum to plasma, non-specific distribution to a peripheral compartment, and linear elimination from the central compartment when HIO was administered with isotonic carrier solutions to PC patients who underwent CRS. Only the effect of the carrier solution had an impact in the peritoneal volume of distribution, but its clinical relevance seems to be limited, especially for short HIO infusions (<60 min).

Keywords Hyperthermic intraperitoneal chemotherapy (HIPEC) · Oxaliplatin · Peritoneal carcinomatosis · Population pharmacokinetics

Disclaimer: The views expressed in this article are the personal views of the authors reflecting their scientific knowledge of this topic and should not be understood or quoted as being made on behalf of the companies where the authors currently work.

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Introduction

Peritoneal carcinomatosis (PC) arises from widespread metastases of tumors in the peritoneal cavity and is generally considered to be an untreatable terminal disease [1]. Besides standard palliative surgery and chemotherapy (SPSC), there are no specific PC treatments approved by regulatory agencies; therefore, the development of new treatments to manage this life-threatening condition could fulfill an unmet medical need [2]. A retrospective analysis in patients with resectable PC of colorectal origin has shown that cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) with

oxaliplatin prolongs median survival from 24 to 63 months and increases the 5-year survival rate from 13 to 51 % with respect to SPSC [3]. The efficacy of CRS, along with HIPEC, for the PC treatment was reported in a Phase II study in ovarian cancer [4], and also in two Phase III studies in colorectal and gastric cancers [5, 6]. Recently, a meta-analysis of CRS with HIPEC and/or early postoperative intraperitoneal chemotherapy (EPIC) has shown a statistically significant survival benefit over SPSC (hazard ratio: 0.55; 95 %CI: 0.40–0.75) in PC of colorectal origin [7]. These results justify further clinical research and development of this aggressive treatment, particularly in situations where long-term survival is hardly ever seen (e.g., PC of non-gynecologic origin) [8, 9].

Oxaliplatin is an attractive agent for HIPEC because its cytotoxicity is significantly increased by hyperthermia and its intratumoral penetration is also optimal [10, 11]. Therefore, the goal of the hyperthermic intraperitoneal oxaliplatin (HIO) for PC treatment is to achieve the maximum oxaliplatin exposure in the unresected tumor nodules and residual tumor cells in the peritoneal cavity with minimum oxaliplatin access to the systemic circulation in order to balance its cytotoxic activity and the risk of hematological toxicity and peripheral sensory neuropathy, which are the dose-limiting toxicities after intravenous (IV) oxaliplatin [12].

Several Phase I dose-escalation studies in PC patients were conducted to characterize the pharmacokinetics in peritoneum and plasma and determine the HIO maximum-tolerated dose [2, 13–15]. In these studies, intraperitoneal doses of oxaliplatin ranging from 200 to 460 mg m^{-2}, diluted in isotonic or hypotonic solutions, were administered during 0.5–2 h, and usually, pharmacokinetic parameters were obtained by non-compartmental pharmacokinetic analysis in separate settings (peritoneum or plasma). Oxaliplatin evidenced linear and time-independent pharmacokinetics in both peritoneum and plasma. Following 460 mg m^{-2} dosing, the maximum HIO concentration (C_{max}) in peritoneum (330 mg L^{-1}) [13] was 130-fold higher than plasma C_{max} after IV administration (2.59 mg L^{-1}) of 130 mg m^{-2} [14], which indicates HIO is potentially more efficacious treatment for residual PC than IV oxaliplatin. Peritoneal concentrations decline exponentially with a half-life ranging from 0.5 to 2.2 h, while plasma concentrations increase to reach the peak shortly after the end of the intraperitoneal infusion.

After treatment with HIO, oxaliplatin plasma concentrations decline in a biexponential manner resembling to the pharmacokinetic profiles observed after IV administration. While the oxaliplatin apparent central volume of distribution (Vc/F) was estimated to be between 15 and 20 L [2, 15], the estimated apparent oxaliplatin plasma clearance (Cl/F) varied substantially across studies (range: 1.61–3.71 L h^{-1}) [2, 15], reflecting differences in relation to the analyte, the analytical method, and the carrier solution tonicity, among other factors [16].

Our goal was to simultaneously characterize peritoneum and plasma oxaliplatin pharmacokinetics when HIO is administered with two different carrier solutions (5 % dextrose and 4 % icodextrin) and explore the effect of patient- and treatment-related covariates on HIO pharmacokinetics in PC patients who underwent CRS.

Materials and methods

Study design and subject eligibility criteria

Data were obtained from two single-arm studies (Study A and Study B) that investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of HIO after CRS [17]. In these studies, adult patients were eligible if they had confirmation of PC without extra-abdominal metastasis. Other eligibility criteria included a World Health Organization performance status of 0–2 and anticipated life expectancy of at least 3 months. Previous anticancer radiation therapy and/or chemotherapy, if given, had to be discontinued for at least 4 weeks before entry into the study or 6 weeks in the case of pretreatment with nitrosoureas or mitomycin C. Patients were required to have a negative pregnancy test (only for female patients with reproductive potential) and normal hepatic and renal function, defined as bilirubin ≤1.5 times the upper limit of normality (×ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN, and serum creatinine ≤1.5 × ULN. An acceptable bone marrow function, defined as neutrophil count >1.5 × 10^9 L^{-1}, hemoglobin >10 g dL^{-1}, and platelets >100.0 × 10^9 L^{-1}, was also needed. Patients with one or more of the following criteria were not selected: active infection, central nervous system metastases, peripheral neuropathy grade >2, allogenic transplant, prior extensive radiation therapy (>25 % of bone marrow reserve), prior bone marrow transplantation or high-dose chemotherapy with bone marrow or stem cell rescue, concurrent radiation therapy, chemotherapy, hormonal therapy, immunotherapy, participation in a clinical trial involving an investigational drug in the past 30 days or concurrent enrollment in another investigational trial, and any coexisting medical condition that was likely to interfere with study procedures and/or results.

The studies were conducted in accordance with principles for human experimentation as defined in the International Conference on Harmonization for Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study was approved by the corresponding Investigational Review Board, and informed consent was

obtained from each subject after being advised of the potential risks and benefits, as well as the investigational nature of the study.

Surgical procedure

A xiphopubic midline laparotomy was carried out to examine the tumor load in the abdominal cavity. To obtain the PC index [18], the abdomen was divided into 13 areas numbered from 0 to 12, as described elsewhere [19]. Cytological samples and biopsies were taken from each area. Resection of the primary tumor when present was carried out according to regional lymphadenectomy with correct margins. In PC with the primary tumor in situ and in metachronous cases, peritonectomies and debulking were carried out as required and extensive systematic peritonectomies were not performed. The mesenteric peritoneum was not extensively removed, and acceptable small-bowel resections were guided by maximal tumor volume locations. Remaining malignant granulations were destroyed using electrosurgical fulguration. This aggressive CRS was performed with the aim to reach complete resection or, if not possible, to resect all visible tumor lesions larger than 2.5 mm. Anastomoses were carried out after the perfusion of the abdominal cavity was completed. The CRS was considered complete if no residual implants remained [20].

Hyperthermic intraperitoneal oxaliplatin

An open coliseum technique was used according to the procedure previously described [18]. Four 36-Fr drains were connected to a continuous closed circuit, and two intraperitoneal thermal probes were placed in order to obtain a proper temperature feedback. Briefly, a Tenckhoff inflow catheter was placed centrally in the abdomen, and four outflow catheters were inserted through separate stab incisions in the abdominal wall. Both the inflow and outflow catheters were connected to a perfusion pump and heat exchanger. The skin of the abdomen was attached to a retractor ring, and the abdominal cavity was covered with a plastic sheet with a small opening in the center allowing entrance for the surgeon's hands to stir the abdominal contents and deliver a more uniform drug distribution and heat to the intra-abdominal surfaces. The rollers of an extracorporeal circulation machine (Performer LRT, Rand) were set at a speed of 1 $L \cdot min^{-1}$ to deliver the carrier solution. The circuit passed through a heat exchanger which raised the temperature to 48 °C. The perfusate temperature on the abdominal cavity fluctuated between 42 and 43 °C.

Once the temperature was achieved, oxaliplatin dose was administered. In Study A, patients received HIO diluted in isotonic 4 % icodextrin, whereas in Study B, patients received HIO diluted in isotonic 5 % dextrose. After the end of perfusion, the solution was evacuated. During the next five postoperative days, 19 of 36 patients in Study A received EPIC based on the administration of 5-fluorouracil (5-FU) at a dose of 15 $mg \cdot kg^{-1}$ in 1-h infusion through a 14-Fr catheter in order to potentiate the oxaliplatin cytotoxic effect [21].

Sample collection and bioanalytical methods

Peritoneal fluid and venous blood samples were collected immediately after the oxaliplatin administration and then every 10 min until the end of the peritoneal perfusion. Additional venous blood samples were drawn at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, 24, and 28 h after the end of the peritoneal perfusion. All samples were collected in Sarstedt lithium-heparin monovette® tubes, centrifuged at 3,500 rpm for 10 min, and stored at −80 °C until analysis. All samples were previously digested with nitric acid at 0.65 %. Total platinum in peritoneum and plasma was measured using a validated assay through inductively coupled plasma atomic emission spectrometry (ICP-AES, model ULTIMA, JOBIN-YVON, France). This methodology has been widely used for quantification of platinum compounds in human plasma samples [22–24]. The lower limit of quantification was 0.5 mg/L. Over the validated range of the assay (0.5–30 mg/L for plasma samples and 5–300 mg/L for peritoneal fluid samples), the mean intra- and interassay coefficients of variation were lower than 9.5 and 7.7 %, respectively. Total platinum concentrations of each sample were transformed into oxaliplatin concentrations according to their molecular weights before conducting the pharmacokinetic analysis.

Software

An exploratory non-compartmental pharmacokinetic analysis (NCA) was performed with WinNonlin® Professional (Version 4.0.1; Pharsight Corp., Mountain View, CA, USA). The population pharmacokinetic analysis was conducted by nonlinear mixed-effects modeling using the first-order conditional (FOCE) method implemented in NONMEM VII version 7.1.2. software package (ICON, Hanover, MD) [25], and the compilations were achieved using gfortran compiler, for Windows. PsN 3.4.2 tool was used to conduct a nonparametric bootstrap stratified by study. Wings for NONMEM (Auckland, New Zealand) was used to conduct a randomization test. Graphical and all other statistical analyses were performed using S-Plus 6.1 Professional Edition (Insightful, Seattle, WA, USA).

Exploratory non-compartmental pharmacokinetic analysis (NCA)

A NCA for peritoneal and plasma concentration–time data was performed in order to explore the lack of differences in pharmacokinetic parameters across the two studies analyzed. Individual oxaliplatin C_{max} at peritoneum and plasma was determined by direct observation of the raw data. Individual AUC from 0 to the last experimental time (t_{last}) ($AUC_{0-tlast}$) was calculated using the linear/log trapezoidal method. While the use of $AUC_{0-tlast}$ instead of $AUC_{0-\infty}$ in peritoneum is justified because the oxaliplatin concentration in peritoneum after the drug removal is 0, the justification for using $AUC_{0-tlast}$ for plasma concentrations is based on the magnitude of the extrapolation from t_{last} to ∞, which is higher than 20 % in all subjects as expected from the long terminal half-life of oxaliplatin in plasma and the sampling schedule implemented [26]. The terminal rate constant (λz) was determined from the slope of the terminal log-linear portion of the peritoneal and plasma concentration–time curves, and the terminal half-life ($t_{1/2}$) was calculated as $\ln 2/(\lambda z)$ for both peritoneum and plasma, respectively.

In order to compare the pharmacokinetic parameters C_{max}, $AUC_{0-tlast}$ and $t_{1/2}$ across both studies, several normalizations in C_{max} and $AUC_{0-tlast}$ parameters were necessary to control the differences between patients with respect to oxaliplatin doses administered, the volume of the carrier solution used and the duration of peritoneal perfusions (T).

Since C_{max} in peritoneum ($C_{max\ PR}$) was related to the oxaliplatin dose (D, mg m^{-2}) and the carrier solution volume (V, L), which both vary across patients, individual C_{max} values were normalized for a standard dose of 360 mg m^{-2} and 1 L of carrier solution, according to Eq. 1:

$$C^{N}_{max\,PR} = \frac{C_{max\,PR} \cdot V \cdot 360}{D} \quad (1)$$

where $C^{N}_{max\,PR}$ represents the normalized $C_{max\ PR}$. Similarly, $AUC_{0-tlast}$ in peritoneum depends on D and T, which also varies across patients. Consequently, the individual $AUC_{0-tlast}$ values in peritoneum were normalized for a standard dose of 360 mg m^{-2} dose and 1-h duration of peritoneal perfusion, according to Eq. 2:

$$AUC^{N}_{PR} = \frac{AUC_{0-tlast} + AUC_{tlast-1}}{D} \cdot 360 = \frac{AUC_{0-tlast} + \frac{C_{last}}{\lambda z} \cdot \left[1 - e^{-\lambda z \cdot (1 - tlast)}\right]}{D} \cdot 360 \quad (2)$$

where AUC^{N}_{PR} represents the normalized AUC_{0-1} in peritoneum and C_{last} represents the observed concentration at the last sampling point, t_{last}.

Normalizations were also undertaken for non-compartmental parameters derived from the plasma oxaliplatin concentrations. Since plasma C_{max} and $AUC_{0-tlast}$ depend on the amount of oxaliplatin absorbed during HIO, which at the same time depends on D and T, C_{max} and $AUC_{0-tlast}$ were normalized according to the following equations:

$$C^{N}_{max\,PL} \frac{C_{max} \cdot 360}{D \cdot (1 - \exp^{-\lambda z \cdot T})} \quad (3)$$

$$AUC^{N}_{PL} = \frac{AUC_{0-tlast} \cdot 360}{D \cdot (1 - \exp^{-\lambda z \cdot T})} \quad (4)$$

where $C^{N}_{max\,PL}$ and AUC^{N}_{PL} represent the normalized C_{max} and $AUC_{0-tlast}$ in plasma, respectively. Finally, the ratio of the geometric means of the C^{N}_{max}, AUC^{N} and $t_{1/2}$ between the two studies and the associated confidence interval (CI) and p values were calculated for peritoneum and plasma [27].

Population pharmacokinetic analysis

Based on the exploratory graphical analysis, oxaliplatin in the peritoneal fluid was assumed to be absorbed into plasma according to a linear process, characterized by the first-order absorption rate constant, k_a. As oxaliplatin concentrations in peritoneum were available, the absorption process was parameterized in terms of peritoneum to plasma clearance (Cl_a) and volume of distribution in the peritoneum (V_a); thus, k_a was calculated as a secondary parameter as Cl_a/V_a. Moreover, the oxaliplatin disposition in plasma was characterized by an open two-compartment model with linear elimination and non-specific distribution to peripheral tissues. This model was parameterized in terms of systemic clearance (Cl), intercompartmental clearance (Cl_p), central volume of distribution (V_c), and peripheral volume of distribution (V_p). As the oxaliplatin absolute bioavailability (F) after intraperitoneal administration cannot be estimated from the available data, the estimated model parameters were considered apparent. Because the system of differential equation is linear, ADVAN5 subroutine in NONMEM was used. The interindividual (or between subjects) variability (IIV) in the pharmacokinetic model parameters was assumed to follow the lognormal distribution, and consequently, an exponential error model was used. Residual variability in oxaliplatin peritoneal and plasma concentrations was evaluated using an additive error model after natural logarithmic transformation of the observations and model predictions. The magnitude of interindividual and residual variability was expressed approximately as a coefficient of variation.

Model selection criteria

The improvement in the fit obtained for each model was assessed in several ways. First, the resulting NONMEM-

generated minimum value of the objective function (MFOV) after fitting the models evaluated was used to perform the likelihood ratio test (LRT). This test is based on the change in the minimum value of the objective function (ΔMVOF), which is equal (up to a constant) to minus twice the log-likelihood of the data and is asymptotically distributed like χ^2 with the degrees of freedom equal to the number of parameters added to the model. For hierarchical models, a ΔMVOF of 3.84 was required to reach statistical significance ($p = 0.05$) for the addition of one fixed effect. In addition, the improvement in the model fit by including covariates into the population pharmacokinetic model was assessed by the reduction in the IIV, residual variability, the reduction in the standard errors, and the examination of diagnostic plots.

Covariate analysis

The population pharmacokinetic model described was fitted to the data, and the empirical Bayes' estimates (EBE) of the individual pharmacokinetic parameters were computed using a "POSTHOC" feature in NONMEM in order to screen the influence of covariates on model parameters. The covariates selected for this analysis were age, body surface area, sex, creatinine clearance, liver metastases, PC index, complete cytoreduction, and study. The screening was conducted only on model parameters where the shrinkage was lower than 0.3 and was based on visual graphical inspection and stepwise linear regression of the relationships between the EBE of individual model parameters and the covariates. Covariates with statistically significant ($p < 0.05$) and potentially clinically relevant ($r^2 > 0.2$) effect on the model parameters during the screening analysis were further tested in NONMEM by forward inclusion ($p < 0.05$) and backward elimination ($p < 0.01$) in order to be incorporated into the population model [28]. Continuous covariates were evaluated using power equations after centering on the median, whereas categorical covariates were incorporated into the model as index variable as indicated in Eq. 5 for a binary variable:

$$P_i = P_X \cdot e^{\theta \cdot x} \cdot e^{\eta_i}, \quad \text{where } \eta_i \approx N(0, \omega^2) \tag{5}$$

where P_i is the individual pharmacokinetic parameter for ith subject; P_X represents the geometric mean of the selected model parameter in patients with the reference category of the binary covariate ($x = 0$). x is a dummy variable that takes the value 0 in patients with the reference category and 1 for patients within the test category, and e^{θ} represents the ratio of the parameter geometric mean between the two categories. Two different approaches were used to compute the CI of the covariate effect. In the first approach, CI was calculated from the asymptotic standard error, while in the second approach the CI was obtained by nonparametric bootstrap stratified by study [29]. The p value associated with the covariate effect was derived from both the LRT and the randomization test [30].

Model evaluation

Three complementary methods were employed to evaluate the model: nonparametric bootstrap stratified by study [31], normalized prediction distribution errors (NPDE) [32], and visual predictive check (VPC) [33].

Results

Overall, 49 patients (36 from Study A and 13 from Study B) were available for the analysis. The primary tumor type was colorectal ($n = 17$), ovarian ($n = 15$), appendiceal ($n = 10$), gastric ($n = 3$), endometrial ($n = 3$), and primary papillary ($n = 1$). The perfusate volume varied from patient to patient depending on the peritoneal surface area, and approximately 2.5–6.0 L was employed. On average, the HIO mean duration was 36.6 min (range: 30–60 min). Descriptive statistics of the patient baseline characteristics stratified by study are shown in Table 1. Similar covariate distribution was found across both studies with no statistically significant differences in both patient and treatment characteristics at baseline.

A total of 222 and 576 oxaliplatin concentrations from peritoneum and plasma, respectively, were available to characterize the oxaliplatin pharmacokinetics in cancer patients with PC treated with HIO after CRS. Peritoneal oxaliplatin concentration showed a rapid, exponential decrease during the duration of the peritoneal perfusion. The peak plasma concentration of oxaliplatin was observed shortly after the end of the peritoneal perfusion and, subsequently, decayed rapidly in a biexponential fashion, resulting in a limited systemic exposure. The results of the exploratory NCA are presented in Table 2. The NCA parameters C^N_{max}, AUC^N, and $t_{1/2}$ in both peritoneum and plasma showed no statistically significant differences between both studies. The 90 % CI of the Study B-to-Study A ratio of geometric means included 1 and fell within 0.8 to 1.25 for C^N_{max}, AUC^N, and $t_{1/2}$ in both peritoneum and plasma.

The population pharmacokinetic analysis evidenced the time course of peritoneal oxaliplatin concentration was well described by a first-order elimination process. Furthermore, plasma concentrations following HIO were best described by an open two-compartment disposition model with nonspecific distribution to a peripheral compartment, linear elimination from the central compartment, and first-order absorption from peritoneum to plasma. Figures 1 and 2

Table 1 Patient and treatment characteristics at baseline stratified by study

Patient and treatment characteristics at baseline	Study A[a] ($N = 36$)	Study B[a] ($N = 13$)	p value[b]
Age (years)	57.3 (11.6)	58.2 (12.8)	0.89
Body weight (kg)	69.3 (12.1)	69.1 (12.7)	0.95
Body surface area (m^2)	1.7 (0.2)	1.8 (0.2)	0.78
Sex (%)			
Male	39	38	0.98
Female	61	62	
ALT (IU L^{-1})	30.6 (42.4)	35.0 (6.8)	0.35
AST (IU L^{-1})	43.2 (45.5)	34.6 (13.4)	0.63
Alkaline phosphatase (IU L^{-1})	180 (90)	212 (63)	0.60
Total bilirubin (μmol L^{-1})	0.6 (0.3)	0.6 (0.3)	0.93
Serum albumin (g L^{-1})	46.2 (5.8)	42.1 (1.7)	0.78
Total protein (g L^{-1})	66.7 (12.3)	70.9 (8.8)	0.50
Creatinine clearance (mL min^{-1})[c]	80.5 (29.2)	79.7 (34.0)	0.93
Hemoglobin (g dL^{-1})	11.6 (2.0)	11.8 (1.1)	0.71
Leukocyte Count ($\times 10^9$ L^{-1})	7.2 (3.8)	7.2 (3.4)	0.99
Neutrophil ($\times 10^9$ L^{-1})	4.7 (3.6)	4.6 (3.5)	0.92
Platelets ($\times 10^9$ L^{-1})	286 (155)	261 (127)	0.61
Liver metastases			
Yes (%)	86.1	84.6	0.84
No (%)	13.9	15.4	
Peritoneal carcinomatosis index	12.3 (12.3)	11.0 (10.8)	0.75
Complete cytoreduction			
Yes (%)	27.8	7.7	0.14
No (%)	72.2	92.3	
Oxaliplatin dose (mg m^{-2})	364.5 (32.4)	399.5 (94.7)	0.59
Volume carrier solution (L)	3.9 (0.8)	3.6 (0.6)	0.20
Duration HIO (min)	37.6 (8.3)	33.8 (5.1)	0.13

[a] Continuous variables are expressed as mean (SD), whereas categorical variables are expressed as percentage (%)

[b] Continuous variables were compared with t test or Mann–Whitney U test. Shapiro–Wilk test was used for assessing normal distributions. Levene's test was used for checking the equality of variances. Categorical variables were analyzed by chi-squared or Fisher's exact test

[c] Creatinine clearance was calculated using the Cockroft and Gault's formula, and values higher than 150 mL min^{-1} were truncated to 150 mL min^{-1}

display the goodness-of-fit plots for oxaliplatin peritoneal and plasma concentrations, respectively. The observed versus model-predicted plots (upper panels in Figs. 1, 2) showed a normal random scatter around the identity line and indicated the absence of significant bias or model misfit. Similarly, the distribution of conditional weighted residual (middle panels in Figs. 1, 2) [34] and NPDE (lower panels in Figs. 1, 2) as a function of the population predictions (left panels in Figs. 1, 2) and time (right panels in Figs. 1, 2) did not show any trend that evidences model inadequacy [32]. Actually, the mean and standard deviation of the NPDE for peritoneal concentrations were −0.01 (95 %CI: −0.13 to 0.13) and 0.98 (95 %CI: 0.86 to 1.08), respectively, while the mean and standard deviation of the NPDE for plasma concentration were 0.04 (95 %CI: −0.04 to 0.11) and 0.91 (95 %CI: 0.85 to 0.98), respectively. This result confirms the model accuracy and precision because the mean and standard deviation of the NPDE for both peritoneal and plasma concentrations were very close to 0 and 1, respectively.

The final estimates of the pharmacokinetic model parameters and the results of the nonparametric bootstrap analysis stratified by study are presented in Table 3. Except for Cl_p, IIV was estimated for all the model parameters, and the shrinkage was <20 %, except for V_c. Furthermore, the population estimates for the final model parameters were very similar to the mean of the 500 bootstrap replicates that minimized successfully and were contained within the 95 %CI obtained from the bootstrap analysis. The precision of the parameter estimates was good with relative standard error (RSE) lower than 15 % for fixed effects and lower than 50 % for random effects. In addition, the results of the VPC depicted in Fig. 3 evidence the model developed is appropriate to describe the time course of peritoneal and plasma oxaliplatin concentrations and their associated variability in cancer patients with PC after CRS and, therefore, can be used to assess the covariate effects in model parameters.

Within the range of covariate values analyzed, the graphical and statistical screening analyses evidenced a negligible effect of the age, body surface area, sex, creatinine clearance, liver metastases, PC index, and complete cytoreduction on pharmacokinetic model parameters. Only study type had a direct impact in the V_p. The mean (SD) of V_p in Study A was estimated to be 3.9 (0.7) L, while the mean (SD) of V_p in Study B was 3.1 (0.6) L. The p values associated with the inclusion of the study type as a covariate for V_p in NONMEM were 0.01 and 0.03 for the LRT and the randomization test, respectively. On the other hand, the Study B-to-Study A ratio of the geometric means for V_p (and its asymptotic 90 % CI) was estimated to be 0.86 (0.74–0.91), which was very similar to the results obtained from the nonparametric bootstrap stratified by study, 0.87 (90 % CI: 0.78–0.92).

Discussion

We aimed to simultaneously characterize the peritoneal and plasma time course of oxaliplatin concentrations when HIO was administered with isotonic carrier solutions to patients with PC who underwent CRS and evaluate the effect of several covariates in the oxaliplatin peritoneal and plasma pharmacokinetic parameters. The descriptive statistics of both patient and treatment characteristics at

Table 2 Non-compartmental pharmacokinetic parameters stratified by study

Site	Pharmacokinetic parameter	Study A[a] ($N = 35$)[c]	Study B[a] ($N = 13$)	Mean ratio: Study B/ study A (90 % CI)	p value[b, c]
Peritoneum	C^{ss}_{max} (mg L^{-1})	676 (150)	698 (193)	1.03 (0.93–1.13)	0.71
	AUC^{ss} (mg h L^{-1})	132 (25.0)	150 (44.7)	1.13 (1.00–1.23)	0.18
	$t_{1/2}$ (h)	1.28 (0.35)	1.19 (0.49)	0.89 (0.80–1.02)	0.28
Plasma	C^{ss}_{max} (mg L^{-1})	20.5 (4.30)	22.3 (9.10)	1.05 (0.93–1.17)	0.47
	AUC^{ss} (mg h L^{-1})	192 (45.3)	213 (72.4)	1.08 (0.95–1.22)	0.34
	$t_{1/2}$ (h)	33.7 (28.2)	31.3 (16.7)	0.93 (0.80–1.05)	0.36

[a] Results are expressed as mean (standard deviation)

[b] Continuous variables were compared with t test. Shapiro–Wilk test was used for assessing normal distributions. Levene's test was used for checking the equality of variances

[c] One subject was excluded from the NCA due to limited data to compute non-compartmental parameters

baseline showed a similar covariate distribution across the studies included in the analysis, with no statistically significant differences among them.

Although the unbound oxaliplatin fraction is considered to be the active drug, the absence of proteins to which oxaliplatin can bind in peritoneal fluid and the high correlation determined between unbound and total platinum plasma levels for oxaliplatin ($r^2 = 0.98$) [35] justify that total oxaliplatin concentrations in peritoneum and plasma were used to conduct this population pharmacokinetic analysis, similarly to what was recently done and reported in other publications in the same target population [2, 15].

The exploratory NCA showed that the ratio between peritoneal and plasma C_{max} was around 33 and reflects that high oxaliplatin peritoneal exposure was achieved with a low oxaliplatin access to the systemic circulation. This local regional exposure advantage was also observed by Elias et al. [13]. Furthermore, the estimated AUCs in peritoneum and plasma, as well as the oxaliplatin absorption half-life ($t_{1/2}$), were consistent with those values reported elsewhere [36]. However, the mean of the oxaliplatin plasma elimination half-life was estimated to be 32.1 h, which is consistent with the beta half-life ($t_{1/2\beta}$) previously reported (32–38 h) after 1- or 2-h intravenous infusion of oxaliplatin 130 mg m^{-2} [14], and Valenzuela et al. (40 h) after CRS followed by HIO [2], but longer than the $t_{1/2\beta}$ reported by Ferron et al. (12.9 h), probably because of the differences in the sampling schedules [15]. Even though the differences in the volume of perfusate and duration of HIPEC were not statistically significant across the two studies analyzed, the C_{max} and AUC_{0-last} in peritoneum and plasma were normalized by different functions of dose, volume of perfusate, and/or duration of HIPEC in order to avoid the potential confounding effect. After normalizing, the non-compartmental parameters showed no statistically significant differences between both studies, and the 90 % CI of the mean ratio of all parameters analyzed included 1 and fell within 0.8–1.25.

Study A and Study B were pooled for a joint population pharmacokinetic analysis, which evidenced the oxaliplatin absorption and elimination half-lives were very similar to those estimated from the NCA analysis. In addition, the oxaliplatin plasma disposition was characterized by a volume of distribution at the steady state of 77.0 L, which was similar to the value reported by Ferron et al. (65.1 L) [15] and Massari et al. (69.7 L) [14]. The apparent plasma clearance of oxaliplatin was estimated to be 1.71 L h^{-1} very similar to the one reported by Valenzuela et al. (1.61 L h^{-1}) [2]. However, Ferron et al. reported an apparent plasma clearance higher than the obtained in the present study (3.71 L h^{-1}). This fact probably is due to the sample protocol design because Ferron et al. collected samples until 8 h, while in this study, samples were collected until 28 h. The IIV in model parameters was moderate and ranged from 21.4 % in V_a to 58.2 % in V_p. Interestingly, the IIV observed in the pharmacokinetic parameters determining the oxaliplatin plasma disposition was higher than that observed for the pharmacokinetic parameters which determine the peritoneal concentrations. This phenomenon has been previously observed in other population pharmacokinetic studies of HIO [2, 15]. Age, body surface area, sex, creatinine clearance, liver metastases, PC index, and complete cytoreduction did not influence HIO pharmacokinetic parameters to a significant extent.

Since the LRT is approximate by a χ^2 distribution and this approximation might not be optimal at lower sample sizes, a randomization test was conducted to determine the exact p value in assessing the covariates with potential effect on oxaliplatin pharmacokinetics. Both LRT and randomization test confirmed the study effect on the V_c parameter. The 12–15 % reduction in V_c for Study B, relative to Study A, might be explained by the carrier solutions used. While in

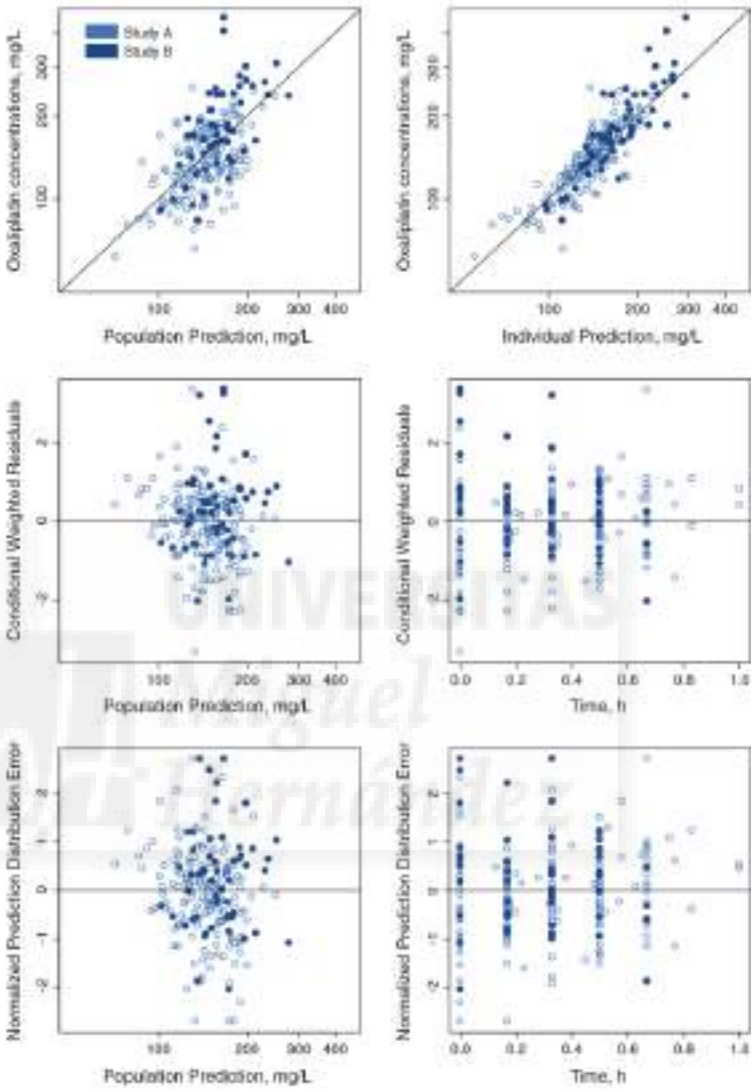

Fig. 1 Goodness of fit plots for oxaliplatin peritoneal concentrations stratified by study

Study A patients received HIO diluted in 4 % icodextrin, in Study B patients received HIO diluted in 5 % dextrose. The choice of a carrier solution and its tonicity plays an important role in the penetration of chemotherapeutic agents into tumor cells and its peritoneal absorption [16]. Hypotonic solutions have been associated with high incidence (50 %) of post-operative peritoneal bleeding and severe thrombocytopenia and are not currently used [37]. Hypertonic solutions are not suitable for HIPEC since the fluid shift inward to the peritoneal cavity dilutes the intraperitoneal drug concentration and reduces drug exposure [38]. Isotonic salt or 5 % dextrose solutions are the solutions most frequently employed for HIPEC. However, their solute absorption through the peritoneum makes difficult to maintain a prolonged high intraperitoneal fluid volume and, consequently, may limit the HIPEC duration [39]. In theory, isotonic high molecular weight solutions should be able to maintain the intraperitoneal fluid volume due to its lack of absorption and

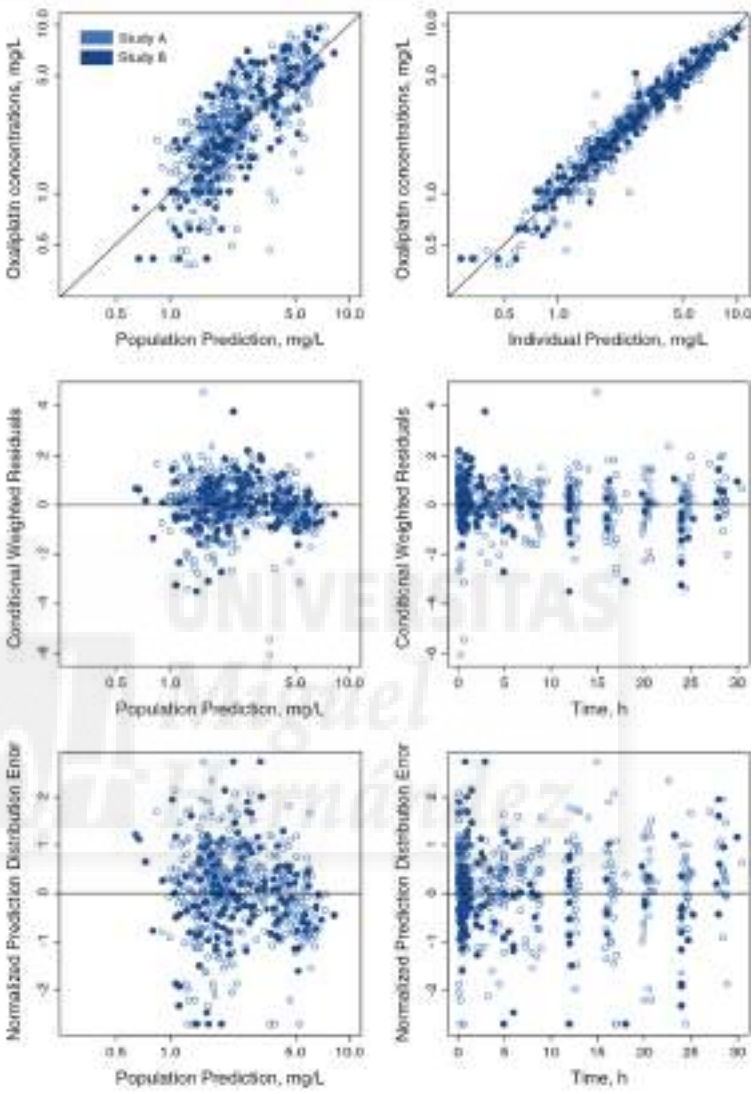

Fig. 2 Goodness of fit plots for oxaliplatin plasma concentrations stratified by study

therefore have a higher drug availability in the peritoneal cavity relative to isotonic salt or 5 % dextrose solutions [16, 40]. Icodextrin, an α-1-4-linked glucose polymer of 12,000 to 20,000 D, diluted at 4 % is an isotonic high molecular weight solution widely used for peritoneal dialysis that has also been employed as carrier solution for HIO [2, 16]. To date, no formal comparison on the effect of carrier solutions in HIO has been reported. The reduction in V_c in the dextrose group could be due to the net absorption of the dextrose and would confirm the theoretical hypothesis that isotonic high molecular weight solutions, like icodextrin, are able to maintain the intraperitoneal fluid volume because these compounds are not absorbed. Furthermore, this phenomenon might also explain the lack of difference in normalized C_{max} and AUC observed in the non-compartmental analysis. Indeed, non-compartmental parameters in peritoneum were calculated using the theoretically administered carrier solution volume, which was assumed to be constant

Table 3 Parameter estimates and bootstrap analysis of the HIO population pharmacokinetic model

Pharmacokinetic model parameters	Original dataset	Nonparametric bootstrap (N = 500 replicates)	
	Estimate	Mean	95 % CI
Cl_p (L h^{-1})	2.05 (10.6)	2.01 (10.5)	1.58–2.40
V_c study A (L)	3.90 (3.6)	3.89 (4.3)	3.74–4.04
V_c study B (L)	3.10 (4.7)	3.12 (5.2)	2.89–3.35
Cl (L h^{-1})	1.71 (13.0)	1.70 (13.5)	1.25–2.15
Cl_p (L h^{-1})	34.9 (10.0)	34.9 (10.0)	28.1–41.8
V_c (L)	19.7 (12.2)	19.4 (12.7)	14.6–24.2
V_p (L)	57.3 (13.4)	57.1 (13.6)	43.4–73.7
Interindividual variability (CV %)			
ω_{Cl_p}	39.0 (11.7)	37.7 (12.0)	29.1–47.0
ω_{V_c}	21.4 (18.1)	20.9 (14.4)	14.8–26.9
ω_{Cl}	44.5 (26.9)	43.9 (20.7)	28.3–64.5
ω_{V_c}	22.6 (19.4)	22.1 (50.0)	0.23–46.7
ω_{V_p}	58.2 (41.2)	55.5 (25.5)	30.0–84.0
Residual variability (CV %)			
σ	18.3 (6.3)	18.2 (6.0)	16.2–20.3

[a] Results expressed as parameter (RSE, relative standard error of parameter estimate, %)

during HIO duration. If future studies confirm that the perfusate volume varies during HIPEC, then the conclusions derived from the non-compartmental analysis should be interpreted with caution. The clinical relevance of the difference in V_c can be inferred from a previous pharmacokinetic–pharmacodynamic model for HIO [3]. Stochastic model-based simulations undertaken indicated that incidence of neutropenia Grade 4 lasting at least 5 days

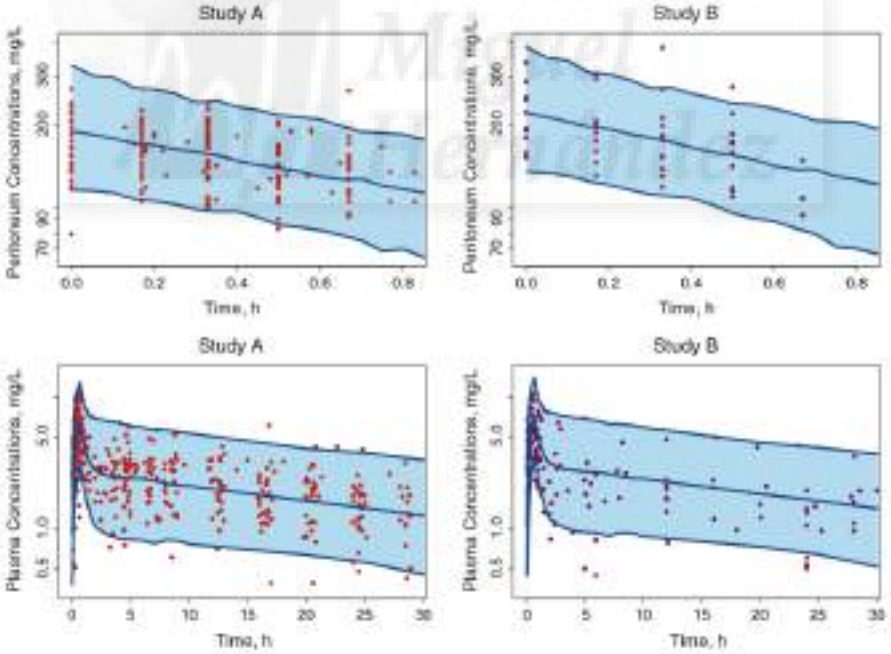

Fig. 3 Time course of the observed peritoneal (*upper panels*) and plasma (*lower panels*) oxaliplatin concentrations for Study A (*left panels*) and Study B (*right panels*) and their associated model-based 95 % prediction intervals

following HIO might be about 15 % higher for the 5 % dextrose relative to 4 % icodextrin at the target peritoneal exposure of 200 mg h L^{-1}. Therefore, using 5 % dextrose, instead of 4 % icodextrin, as carrier solution for 30- and 120-min HIO would result in less than one additional patient with neutropenia Grade 4 lasting more than 5 days for every 67 and 23 patients treated, respectively. These results suggest that the clinical relevance of the difference between 4 % icodextrin and 5 % dextrose is limited for short infusion durations (i.e., 30 min). In this situation, the direct cost saved in using 5 % dextrose (1.38 € L^{-1}) instead of 4 % icodextrin (97.40 € L^{-1}) is expected to be higher than the direct cost associated with the treatment for the additional severe neutropenia events that may happen in using 5 % dextrose over 4 % icodextrin. However, if the HIO duration is prolonged up to 120 min, further studies are needed to evaluate the clinical equivalence between the 5 % dextrose and 4 % icodextrin and its potential economic impact.

In summary, an open two-compartment disposition model with non-specific distribution to a peripheral compartment, linear elimination from the central compartment, and first-order absorption from peritoneum to plasma managed to properly characterize the peritoneal and plasma time course of oxaliplatin concentrations when HIO was administered with isotonic carrier solutions to PC patients who underwent CRS. The 12–15 % reduction in peritoneal volume of distribution observed in patients receiving HIO diluted in 5 % dextrose relative to that in patients receiving HIO diluted in 4 % icodextrin supports the theoretical hypothesis that isotonic high molecular weight solutions are able to maintain the intraperitoneal fluid volume longer. The clinical relevance of this finding is limited for short HIO durations, and further studies are needed to elucidate the clinical equivalence at longer HIO duration.

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Conflict of interest The author(s) indicated no potential conflicts of interest.

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CAPÍTULO V.

Resumen

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1. *Cytoreductive surgery and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of colonic origin. Outcomes after 7 years' experience of a new center for peritoneal surface malignancies.*

El cáncer colorectal representa la segunda neoplasia del varón y la tercera en la mujer. En el momento del diagnóstico aproximadamente un 10% de los pacientes cursan con enfermedad metastásica y el 50% de lo afectados desarrollará enfermedad a distancia durante su evolución. Aproximadamente el 25% de los pacientes presentarán una carcinomatosis peritoneal, estando el curso natural de la enfermedad asociado a una esperanza de vida muy limitada, así como a una rápida y progresiva pérdida en la calidad de vida. El tratamiento estándar de esta situación considerada un signo de diseminación del cáncer colorectal (estadio IV), ha sido la realización de abordajes quirúrgicos para paliar los síntomas (esencialmente de obstrucción intestinal) y la administración de quimioterapia sistémica. Clásicamente, este planteamiento se ha asociado a medianas de supervivencia de 6 a 9 meses (1, 2). Debe reconocerse una progresiva mejoría de la supervivencia de este grupo de pacientes conforme los fármacos y esquemas terapéuticos han ido evolucionando hasta llegar a la situación actual que ofrece una supervivencia mediana de 24 meses con la asociación de las terapias biológicas (3). A pesar de ello, la supervivencia a largo plazo sigue siendo muy limitada.

En los años 80 con los estudios de Sugarbaker hay un cambio del paradigma, pasando a considerar esta situación como una afectación de una región anatómica y abandonando el concepto de diseminación metastásica a distancia. Este autor diseña un abordaje multimodal, esto es una cirugía citorreductora máxima asociada a la administración de quimioterapia intraperitoneal intraoperatoria con hipertermia (HIPEC). Con este abordaje, el cirujano trata la afectación macroscópica con las técnicas de peritonectomia descritas por dicho investigador, y la enfermedad microscópica residual es tratada a continuación mediante una perfusión de quimioterapia bajo condiciones de hipertermia. Con este planteamiento se han publicado resultados de supervivencia a los 5 años del 30-50% en grupos seleccionados de pacientes (4, 5).

El presente estudio se basó en los protocolos descritos por Sugarbaker con el uso de mitomicina C en la perfusión y 5-fluoruracilo intraperitoneal (5-FU) durante los 5 días del postoperatorio inmediato (EPIC) (6); pero a partir de los resultados publicados por Elias con oxaliplatino intraperitoneal (460 mg/m^2) y 5-FU (400 mg/m^2) con leucovorin (20 mg/m^2) endovenoso (5) reportando una supervivencia

a los 5 años del 48.5%, se optó por su modificación. Se inició un estudio fase I de escalada de dosis según el método de Fibonacci en grupos de tres pacientes, a partir de 90 mg/m^2 de oxaliplatino e incrementando a razón de 60 mg/m^2 hasta alcanzar la dosis limitante de toxicidad en 360 mg/m^2. A partir de esa dosis la serie se expansionó con 24 pacientes y se mostró adecuada por su seguridad. Se continuó la administración de quimioterapia en el postoperatorio precoz (EPIC) con 5-FU intraperitoneal (650mg/m^2) durante los 5 días del postoperatorio, tal y como describió Sugarbaker.

Se incluyeron 20 pacientes afectos de CP de origen colorectal de los 75 procedimientos que conformaban la serie, con un índice de carcinomatosis medio de 11. Doce de los pacientes se encontraban en una situación metacrónica, por tanto, habían sido intervenidos previamente, y 5 de ellos presentaban metástasis hepáticas sincrónicas. Salvo un paciente, los restantes habían recibido quimioterapia sistémica. Se consiguió una citorreducción completa en el 75% de los casos (sin implantes residuales tras la cirugía) y todos los pacientes completaron el tratamiento multimodal intraoperatorio. La temperatura media de la cavidad abdominal fue de 42ºC (rango: 39-43ºC) y no se observó ningún caso de intolerancia a la hipertermia. Tras el procedimiento, el 80% de los pacientes recibieron EPIC durante los siguientes 5 días. En 4 casos hubo que suspender dicho tratamiento por sepsis (n=1), fístula biliar (n=1) y por dolor severo (n=2). Un 40% de los pacientes presentaron toxicidad grado II-IV requiriendo dos de ellos reintervención en el postoperatorio temprano.Sólo hubo un caso de mortalidad por aplasia medular grado 4. La estancia media hospitalaria fue de 17.8 días (rango: 10-48 dias).

Durante el seguimiento se observó progresión de la enfermedad en 10 casos, a nivel pulmonar [n=2], hepático [n=3] y peritoneal [n=5]. Se realizó cirugía de rescate en cinco de ellos, destacando la práctica de re-HIPEC en dos casos. Uno de los pacientes se encontraba libre de enfermedad a los 19 meses y el otro falleció por progresión a los 18 meses.

La supervivencia actuarial y el periodo libre de enfermedad de la serie de pacientes fueron del 36% y del 30% a los 5 años, respectivamente, con un seguimiento mediano de 18 meses.

Se analizó a los pacientes con relación a un índice de carcinomatosis por encima o debajo de 13 y de acuerdo con la consecución o no de una citorreducción completa, y se obtuvieron diferencias significativas en la supervivencia global, aunque no en el periodo libre de enfermedad, probablemente por la limitación de la muestra.

2. *Pharmacokinetic and Pharmacodynamic Analysis of Hyperthermic Intraperitoneal Oxaliplatin-Induced Neutropenia in Subjects with Peritoneal Carcinomatosis.*

El oxaliplatino es un agente atractivo para el tratamiento con HIPEC debido a su sinergía con la hipertermia y por su óptima penetración intratumoral. Sin embargo, su exposición sistémica incrementa el riesgo de toxicidad hematológica y neuropatia sensorial periférica. Por tanto, es primordial alcanzar la máxima exposición de oxaliplatino en la cavidad peritoneal con el mínimo acceso a la circulación sistémica.

Los diversos estudios existentes muestran diferencias sustanciales en los parámetros farmacocinéticos de oxaliplatino obtenidos tras HIPEC con relación a: el analito (platino ultrafiltrado frente a platino total), el método de medición y por último las distintas soluciones usadas en la perfusión. En este contexto no es sorprendente que el rango estimado de aclaramiento plasmático del oxaliplatino varíe desde 6.68 L/h/m^2 hasta 28.4 L/h/m^2 con un volumen de distribución estimado de 15 L. En estos estudios la toxicidad severa más frecuente se relaciona con la neutropenia y trombocitopenia (7, 8).

Hasta la fecha no hay ningún análisis cuantitativo longitudinal explorando el efecto de la farmacocinética del oxaliplatino en el curso de su toxicidad hematológica tras su administración intraperitoneal. En el presente estudio se caracteriza la farmacocinética del oxaliplatino en el peritoneo y en plasma cuando es administrado con una solución de icodextrina al 4% y se establece su relación con el curso temporal del recuento absoluto de neutrófilos (ANC) en pacientes con CP tratados con cirugía de citorreducción máxima y HIPEC.

Los pacientes incluidos en el estudio presentaban diversos orígenes de tumor primario: ovario [10 casos], colorectal [9], apendicular [5], gástrico [3], endometrio [2] y papilar [1]. Todos ellos recibieron 360 mg/m^2 de oxaliplatino durante la perfusión. El tiempo de perfusión medio fue de 40 minutos (rango 30-60 minutos). Durante los cinco días siguientes a la cirugía se administró 15 mg/kg de 5-fluorouracilo durante 23 horas a través de un catéter peritoneal para potenciar el efecto citotóxico.

Tras la administración del fármaco se extrajeron muestras de sangre y de líquido peritoneal cada 10 minutos hasta concluir la perfusión. Posteriormente, en plasma, se tomaron muestras durante un periodo máximo de muestreo de 28 horas hasta un total de 12 muestras. El platino total se analizó usando un ensayo validado basado en espectrometría de emisión atómica. También se tomaron muestras de sangre para realizar un hemograma hasta la completa recuperación de la toxicidad hematológica. Para

el estudio farmacocinético el número total de muestras disponibles fue de 140 concentraciones de oxaliplatino peritoneal, y 338 concentraciones plasmáticas.

La caracterización de las concentraciones plasmáticas de oxaliplatino se realizó con un modelo farmacocinético bicompartimental tras una absorción peritoneo/plasmática de primer orden. Para describir la cuenta absoluta de neutrófilos en plasma se usó un modelo compartimental de progenitores celulares sensible al oxaliplatino. La reducción del ratio de proliferación de las células progenitoras fue modelada siguiendo una función linear de las concentraciones plasmáticas del oxaliplatino. Para el desarrollo del modelo farmacocinético/farmacodinámico (PK/PD) y para llevar a cabo las simulaciones basadas en el mismo, se utilizó la modelación no linear mixta con el método condicional de primer orden. Como modelo dinámico se utilizó el modelo de granulopoiesis descrito por Friberg y col. (9) a partir de 678 ANC. Este modelo ha sido ampliamente utilizado para describir la mielosupresión producida por una gran variedad de agentes antineoplásicos y se consideró como punto de partida en esta Memoria de Tesis Doctoral. A su vez se estudió la relación entre las concentraciones de oxaliplatino en peritoneo, la duración de la perfusión y la incidencia de neutropenia severa, para establecer la exposición máxima tolerable.

Los valores de absorción y semivida del oxaliplatino se estimaron en 2,2 y 40 h con una variabilidad interindividual moderada. Estos valores fueron considerablemente superiores a los descritos en otros trabajos (10), y probablemente se debe al uso de distinta solución de transporte. En los estudios farmacocinéticos previos se había usado suero con dextrosa al 5%, y en cambio este estudio es el primero que realiza el análisis farmacocinético del oxaliplatino en HIPEC usando como solución la icodextrina al 4%. Esta es una solución isotónica de alto peso molecular y que teóricamente ayudaría a reducir la difusión del fármaco a través de la barrera peritoneo/plasmática. A pesar de ello, el ratio estimado del área bajo la curva en peritoneo y plasma fue de 13,19, estando en consonancia con los reportados en los estudios realizados con dextrosa al 5% (11). Por tanto, la diferencia en el tiempo de vida media de absorción peritoneo/plasmatico del oxaliplatino debe atribuirse a otros factores como: diferencias en el procedimiento quirúrgico, máquinas de perfusión, biodisponibilidad del oxaliplatino absoluto y del analito y finalmente en los métodos de análisis.

El aclaramiento plasmático de oxaliplatino resultó ser 1,61L/h con una variabilidad interpaciente del 85%. El volumen de distribución en compartimento central fue de 19,2 L, con una variabilidad inter-paciente del 85,6 %. El volumen de distribución en estado estacionario del oxaliplatino fue de 92 L, es decir la suma del volumen central y periférico (19,2 + 72.8 = 92 L). Se observó que el oxaliplatino redujo la ratio de proliferación de las células progenitoras un 18.2% por mg/L.

El modelo farmacodinámico que mejor describió la relación entre las concentraciones de oxaliplatino sobre la proliferación de los precursores de ANC fue el modelo lineal, ya que mejoró de forma estadísticamente significativa la bondad del ajustado de otros modelos (potencial, E_{max} o E_{max} sigmoide) que no convergieron de forma satisfactoria, probablemente porque no se alcanzó el efecto máximo dentro del rango de concentraciones plasmáticas evaluado.

Por otro lado, se incluyó un efecto feedback sobre el tiempo medio de tránsito de las células precursoras a neutrófilos, que mejoró de forma estadísticamente significativa la descripción de los datos experimentales. Fisiológicamente, este mecanismo concuerda con la reducción del tiempo de colonias de granulocitos. Dentro del ámbito de valores evaluado, ninguna de las covariables (edad, sexo, peso, creatinina plasmática, albúmina plasmática, ALT, AST séricas, bilirrubina total, hemoglobina y hematocrito) estuvo asociada con los parámetros del modelo. Por tanto, ajustes de dosis en base a ellas no influyeron en la gravedad o duración de la mielosupresión asociada a oxaliplatino en la población a estudio.

El modelo desarrollado fue internamente validado mediante el test predictivo visual y el bootstrap no paramétrico y evidenciaron que era apropiado para describir la farmacocinética del oxaliplatino, así como la evolución temporal del ANC y puede utilizarse para realizar simulaciones que permitan comprender mejor el efecto de la intensidad de dosis, el régimen de dosificación, o la duración de la perfusión intraperitoneal en la incidencia de neutropenia severa.

Las simulaciones determinísticas claramente evidenciaron la reversibilidad de la neutropenia, su corta duración y su efecto no acumulativo. Como consecuencia del modelo lineal del efecto del oxaliplatino, se observó que la concentración inicial y la duración de la perfusión fueron los principales determinantes de la severidad y duración de la neutropenia. Se observó que un aumento proporcional de la exposición del oxaliplatino condujo a un descenso proporcional del nadir de ANC. Así mismo, la extensión de la duración del HIPEC para una misma concentración de oxaliplatino en peritoneo, incrementó la severidad y duración de la neutropenia ya que esta directamente relacionada con la exposición del fármaco al peritoneo.

Tras las simulaciones realizadas se observó que una exposición peritoneal de 65 y 120 mg/L de oxaliplatino durante 60 minutos se asoció a una incidencia de neutropenia grado 4 del 20% y 30% respectivamente; y que con una duración de 30 minutos a una concentración de 65 mg/L y 105 mg/L obtendría un 20% de neutropenia grado 4. La máxima dosis tolerada se fijó en 120 mg/L durante una perfusión de 60 minutos ya que se asoció a un 33% de neutropenia grado 4 de más de 5 días de duración.

Respecto al efecto del 5-fluorouracilo intraperitoneal sobre el ANC, el estudio asumió que era despreciable dado el escaso efecto neutropenico del fármaco y por las bajas dosis administradas, estando de hecho el 81.5% de las muestras plasmáticas por debajo del límite de cuantificación.

Por tanto, el estudio concluye que la exposición máxima tolerada del oxaliplatino administrado a nivel peritoneal es de 120 mg L/h y que debe evitarse dosis superiores. En esta línea se sugiere el uso profiláctico de factores estimuladores de colonias de granulocitos en aquellos pacientes que vayan a tener una exposición superior a 65 mg L/h intraperitoneal.

3. *Population Pharmacokinetics of Hyperthermic Intraperitoneal Oxaliplatin in Patients with Peritoneal Carcinomatosis after Cytoreductive Surgery.*

Es conocida la relevancia de la solución transportadora en la penetración del fármaco a la célula tumoral y en la absorción peritoneal. Las soluciones hipotónicas se han asociado a una alta incidencia de hemorragia peritoneal postoperatoria y a trombocitopenia severa. En cambio, las soluciones hipertónicas no parecen adecuadas ya que provocan un movimiento de fluido hacia el peritoneo y por tanto diluyen la concentración de fármaco reduciendo la exposición del mismo. Por otro lado, las soluciones salinas y de dextrosa al 5% son isotónicas y las más usadas en HIPEC, si bien su fácil absorción a través de la barrera peritoneo/plasmática hace difícil mantener un alto volumen de fluido intraperitoneal y puede limitar la duración del HIPEC. Teóricamente las soluciones isotónicas de alto peso molecular como la icodextrina al 4%, deberían mantener el volumen de perfusión a lo largo del tiempo y por tanto tener una mayor disponibilidad de fármaco a nivel peritoneal. Hasta la fecha no se han realizado estudios comparando el efecto de las distintas soluciones de transporte en HIPEC.

El objetivo en este estudio ha sido caracterizar la farmacocinética del oxaliplatino en peritoneo y plasma comparando dos soluciones transportadoras durante el HIPEC (dextrosa 5% e icodextrina 4%). Como objetivos secundarios también se consideraron parámetros clínicos como la complejidad quirúrgica, diferencias en el postoperatorio y finalmente el posible impacto económico de la utilización de una u otra solución.

Los datos del estudio se recogieron de dos cohortes paralelas con objeto de investigar la seguridad, tolerancia, farmacocinética y farmacodinamia. Se recogieron los datos de 36 pacientes afectos de carcinomatosis peritoneal de diversos orígenes y tratados mediante cirugía citorreductora

máxima con HIPEC usando la solución isotónica de icodextrina al 4% (brazo de estudio A) y otros 13 pacientes sometidos al mismo tratamiento, pero utilizando la solución isotónica de dextrosa al 5% durante la perfusión (brazo de estudio B). El volumen perfundido varió entre los pacientes dependiendo del área de superficie peritoneal (2,5-6 L), y la duración media de la perfusión fue de 36.6 min (rango 30-60 min.).

Se recogieron un total de 222 y 576 muestras de la concentración peritoneal y plasmática de oxaliplatino respectivamente. El esquema de toma de muestras y bioanálisis fue el mismo que el utilizado en el Artículo II de la presente Memoria de Tesis Doctoral. Los datos de las dos cohortes se modelaron conjuntamente para caracterizar la farmacocinética de oxaliplatino con distintas soluciones portadoras. Se realizó un estudio comparativo entre ambas grupos evidenciando que la absorción y vida media de eliminación de oxaliplatino eran muy similares a las estimadas con el análisis farmacocinético no compartimental. La disposición plasmática de oxaliplatino fue caracterizada por un volumen de distribución basal de 77.0 L. El aclaramiento plasmático de oxaliplatino fue estimado de 1,71 L h^{-1} . La variabilidad entre individuos de los parametros farmacocineticos del modelo fue moderada y osciló entre 21,4 % en el volumen de distribución plasmático a 58,2 % en el volumen de distribución periférico. De hecho, dicha variabilidad interindividual fue superior en las concentraciones plasmáticas que en las peritoneales. La edad, superficie corporal, sexo, aclaramiento de creatinina, presencia de metástasis hepáticas, PCI y grado de CRS obtenido, no influenciaron de forma significativa los parámetros farmacocinéticos del HIPEC.

La reducción en el volumen peritoneal del 12-15% en el brazo B del estudio respecto al brazo A, se puede explicar por la distinta solución transportadora usada. La elección de la solución y su tonicidad tiene importancia en la penetración del agente quimioterápico en la célula tumoral y en la absorción peritoneal. Esta reducción del volumen podría explicarse por la absorción neta de dextrosa y confirmaría la hipótesis teórica según la cual las soluciones isotónicas de alto peso molecular son capaces de mantener el volumen intraperitoneal ya que sus componentes no son absorbidos.

El modelo farmacodinámico desarrollado en el Artículo II de esta memoria de Tesis Doctoral se utilizó para realizar simulaciones estocásticas que indicaron que la incidencia de neutropenia grado 4 de como mínimo 5 días de duración tras HIPEC puede ser un 15% superior en el grupo de dextrosa 5% frente al grupo de icodextrina 4% para una exposición peritoneal de 200 mg·h/L. Sin embargo, en los pacientes incluidos en el estudio no hubo diferencias significativas relacionadas con la toxicidad hematológica, ni manejo quirúrgico ni complicaciones postoperatorias.

Por otro lado, el uso de dextrosa al 5% como solución de transporte en lugar de icodextrina al 4% durante 30 y 120 minutos de HIO resultará en menos de un paciente adicional con neutropenia grado 4 prolongada por cada 67 y 23 pacientes tratados, respectivamente. Estos resultados sugieren que la relevancia clínica de esta diferencia esa limitada por ser el tiempo de perfusión corto. En esta situación puede ser más costo-efectivo el uso de dextrosa al 5% (1,38 € L^{-1}) en lugar de la icodextrina al 4 % (97,40 € L^{-1}), dada la pequeña diferencia en cuanto a neutropenia severa. En caso de querer prolongar la duración de la perfusión hasta 120 minutos, habría que realizar más estudios para elucidar la equivalencia clínica entre ambas soluciones transportadoras.

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CAPÍTULO VI.

Conclusiones

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1. El tratamiento multimodal que combina la citorreducción quirúrgica máxima con la perfusión de quimiohipertermia administrada en el acto operatorio, es una técnica factible con una morbi-mortalidad aceptable en pacientes seleccionados afectos de una carcinomatosis peritoneal de origen colorectal.

   El índice de carcinomatosis peritoneal y la consecución de una citorreducción completa impactan significativamente en la supervivencia global, no así en el periodo libre de enfermedad, probablemente por la limitación de la muestra.

2. La farmacocinética de oxaliplatino tras su administración intraperitoneal diluido en la solución portadora de icodextrina al 4% en el tratamiento de los pacientes afectos de una carcinomatosis peritoneal, ha sido adecuadamente descrita para la dosis de 360 mg/m^2 mediante un modelo bicompartimental abierto con una distribución no específica a un compartimento periférico, una eliminación lineal desde el compartimento central y una absorción de primer orden peritoneo-plasmática

3. El modelo farmacocinético/farmacodinámico desarrollado describe adecuadamente la evolución temporal del recuento absoluto de los neutrófilos tras la administración intraperitoneal de oxaliplatino en el contexto de CRS + HIPEC. La variabilidad interpaciente fue moderada y ninguna covariable afectó de manera significativa a los parámetros del modelo. Las simulaciones basadas en el modelo desarrollado demuestran que la gravedad y la duración de la neutropenia están directamente influenciada por la duración de la perfusión y la concentración inicial de oxaliplatino en el espacio peritoneal y que esta toxicidad hematológica es reversible y de corta duración.

4. La utilización de dextrosa al 5% como vehículo de perfusión en lugar de icodextrina al 4% no afecta al manejo quirúrgico ni postoperatorio del paciente afecto de carcinomatosis peritoneal. La farmacocinética de oxaliplatino resultó ser esencialmente similar en ambas cohortes con una ligera reducción del volumen peritoneal en el grupo de dextrosa que podría explicarse por la absorción neta de dextrosa y confirmaría la hipótesis teórica según la cual las soluciones isotónicas de alto peso molecular son capaces de mantener el volumen intraperitoneal, ya que sus componentes no son absorbidos.

5. Las simulaciones realizadas con el modelo farmacocinético/farmacodinámico desarrollado en el Artículo II de esta Memoria de Tesis Doctoral indican que el uso de dextrosa al 5% como solución de transporte en lugar de icodextrina al 4% durante 30 y 120 minutos de HIPEC

resultará en menos de un paciente adicional con neutropenia grado 4 prolongada por cada 67 y 23 pacientes tratados, respectivamente. Estos resultados sugieren que la relevancia clínica de esta diferencia esta limitada por ser el tiempo de perfusión corto. En esta situación puede ser más costo-efectivo el uso de dextrosa al 5% por ser hasta 70 veces más económico, dada la pequeña diferencia en cuanto a neutropenia severa.