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REVIEW

# Hyperthermic intraperitoneal chemotherapy with oxaliplatin for peritoneal carcinomatosis: a clinical pharmacological perspective on a surgical procedure

**Correspondence** Loek A. W. de Jong, MSc, Geert Grooteplein Zuid 10, 6525GA, Nijmegen, The Netherlands. Tel.: +31 24 361 6405; Fax: +31 24 366 8755; E-mail: loek.dejong@radboudumc.nl

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Loek A. W. de Jong[1], Fortuné M. K. Elekonawo[2], Philip R. de Reuver[2], Andre J. A. Bremers[2], Johannes H. W. de Wilt[2], Frank G. A. Jansman[3,4], Rob ter Heine[1] and Nielka P. van Erp[1]

*[1]Radboudumc, Department of Pharmacy, Radboud Institute for Health Sciences, P.O. Box 91016500, HBNijmegen, the Netherlands, [2]Radboudumc, Department of Surgery, Radboud Institute for Health Sciences, P.O. Box 91016500, HBNijmegen, the Netherlands, [3]Department of Clinical Pharmacy, Deventer Teaching Hospital, Nico Bolkesteinlaan 757416 SE Deventer, the Netherlands, and [4]University of Groningen, Groningen Research Institute of Pharmacy, PharmacoTherapy, -Epidemiology & -Economics, P.O. Box 1969700 AD Groningen, the Netherlands*

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Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has become the standard of care in the treatment of patients with peritoneal carcinomatosis of colorectal origin. The use of oxaliplatin for HIPEC has gained popularity. Although the HIPEC procedure is adopted throughout the world, major differences exist between treatment protocols regarding the carrier solution, perfusate volume, use of an open or closed technique, duration of the perfusion and application of additional flushing. These differences can influence the pharmacokinetics and pharmacodynamics of oxaliplatin and might thereby have an impact on the efficacy and/or safety of the treatment. Clinicians should be aware of the clinical importance of oxaliplatin pharmacology when performing HIPEC surgery. This review adds new insights into the complex field of the pharmacology of HIPEC and highlights an important worldwide problem: the lack of standardization of the HIPEC procedure.

## Introduction

Metastases to the peritoneal cavity, referred to as peritoneal carcinomatosis (PC), is a common phenomenon in distant metastatic colorectal cancer [1–3]. Patients with isolated metastasis to the peritoneum who are treated with palliative surgery alone or with 5-fluorouracil (**5-FU**)-based regimens have poor overall survival rates of approximately 6 months [4–6]. As a result of the introduction of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC), median overall survival has significantly increased to 63 months, with a 5-year survival rate of approximately 40% [7]. The CRS-HIPEC procedure has become the standard of care in the treatment of patients with PC of colorectal origin [8]. Adequate patient selection remains one of the main challenges as CRS-HIPEC is associated with approximately 1–3% mortality and significant morbidity in one-third of patients [7]. The most important prognostic factors that have been identified to influence the outcome after the CRS-HIPEC procedure are the extent of the



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peritoneal disease, the completeness of cytoreduction and the histological subtype of the primary tumour [9].

Different chemotherapeutic drugs can be administered in HIPEC for colorectal PC. Traditionally, **mitomycin C** (MMC) was the most commonly used drug, but for the past few years **oxaliplatin** has been used more often worldwide. Oxaliplatin is the cornerstone in the systemic treatment of patients with colorectal cancer. Results on survival in HIPEC series for CRC are comparable for MMC and oxaliplatin [10–17]. No statistically significant differences were demonstrated in survival and postoperative morbidity after HIPEC with MMC or oxaliplatin [18, 19]. As there has been no randomized phase III trial comparing MMC and oxaliplatin, there is no consensus on the intraperitoneal drug of choice. Based on the duration of the perfusion, 30 min for oxaliplatin *vs*. 90 min for MMC, oxaliplatin is the preferred drug in the CRS-HIPEC procedure for colorectal PC in many centres.

The oxaliplatin dose used for HIPEC is 3.5–5.4 times the intravenous dose of a one-off infusion delivered to patients with metastatic colorectal cancer in the various treatment regimens [20]. Although CRS-HIPEC is widely applied as the standard treatment for PC of colorectal origin, the exact procedure for HIPEC differs between institutions and surgeons. There is no consensus on the applied dose, duration, carrier solution, perfusate volume, perfusate concentration, use of an open *vs*. closed technique, or the usefulness of additional flushing with crystalloids at the end of the HIPEC procedure. These differences can play an important role in the pharmacokinetics (PK) of oxaliplatin and thereby might influence efficacy and/or safety of the HIPEC procedure. The present review provides an overview about the PK and pharmacodynamics (PD) of oxaliplatin during HIPEC procedures and the implications for clinical practice. It is surprising that a high-risk procedure as HIPEC, with a great impact on survival, has not yet been standardized.

## Analytical techniques

Oxaliplatin is highly reactive in the blood and forms a variety of hydrolysed intermediates after intravenous infusion, including monochloro- dichloro- and diaquo-platinum species [21, 22]. Up to 17 platinum-containing derivatives have been observed in plasma ultrafiltrate (UF) samples from patients [23]. These intermediates rapidly react with endogenous low-molecular-weight molecules such as glutathione, cysteine and methionine, and high-molecular-weight compounds such as albumin, globulin and haemoglobin [21, 24, 25]. At the end of a 2-h intravenous administration of oxaliplatin, approximately 40% of the administered platinum is bound to erythrocytes and approximately 33% is bound to plasma proteins [26]. The unbound platinum is generally considered as the pharmacologically active moiety [21, 22], although the relationship between free platinum and the pharmacological activity and toxicity is not as clear as for carboplatin [27]. Free platinum concentrations are a sum of active as well as inactive forms of free platinum. Some authors suggest that the parent drug oxaliplatin is the pharmacologically active moiety [24, 28, 29]. Analysis of the free fraction of the parent drug oxaliplatin has revealed a very short terminal half-life for intact oxaliplatin of only 14 min in blood [24].

Considering this, it is important to differentiate between the analytical techniques that are used for the detection of platinum derivatives when interpreting PK data. The majority of PK studies that have used the HIPEC procedure determined the platinum content by flameless atomic absorption spectrometry (AAS) [30–36], direct current plasma emission spectroscopy [37], inductively coupled plasma optical emission spectrometry [38–40] or inductively coupled plasma mass spectrometry [41, 42]. These analytical techniques measure both the parent drug oxaliplatin and other active and inactive platinum-containing complexes that are formed as a result of the high reactivity of oxaliplatin *in vivo*. This might lead to an overestimation of the concentration of active drug, as a result of nonspecificity. Two studies have investigated the PK of intact oxaliplatin during HIPEC [35, 43]. Measurement of intact oxaliplatin and total platinum content can result in large differences in PK parameter estimation, such as an oxaliplatin plasma clearance of 28.4 l $h^{-1}$ $m^{-2}$ based on intact oxaliplatin [43] *vs*. 6.68 l $h^{-1}$ $m^{-2}$ based on AAS [33]. However, the extent of drug absorbed during HIPEC (36–60% [43] *vs*. 40–68% [33]) and the volume of distribution (0.294 l $kg^{-1}$ [44] *vs*. 0.235 l $kg^{-1}$ [33]) seem to be consistent. To date, it is unknown which analytical measurement (intact oxaliplatin or the mixture of platinum derivatives) is the best surrogate marker to predict both the toxicity and efficacy of oxaliplatin-based HIPEC. Future research should be performed to provide answers to this unresolved question.

## Carrier solutions in HIPEC

The ideal carrier solution for HIPEC with oxaliplatin should provide a uniform distribution of the cytotoxic drug and heat, with minimal loss of volume during perfusion. This requires minimal transport of fluid and electrolytes from the peritoneal compartment to the plasma, and stability of the drug in the carrier solution. As oxaliplatin can react with chloride ions, causing degradation, dextrose 5% is often used as the carrier solution in oxaliplatin-based HIPEC protocols [45]. A disadvantage of the use of dextrose 5% is the inability to maintain a high intraperitoneal fluid volume, owing to rapid absorption [45]. High intraperitoneal volumes of dextrose 5% require high doses of insulin to prevent severe hyperglycaemia, causing major electrolyte disturbances during perfusion [46–49]. Other carrier solutions that have been investigated are hypertonic solutions, hypotonic solutions and isotonic high molecular weight solutions. The main disadvantage of hypertonic solutions is dilution of the drug due to fluid shift towards the peritoneal cavity [45]. Both *in vitro* and animal studies suggest that the use of hypotonic solutions can enhance platinum accumulation in tissue [50, 51]. Nevertheless, this effect could not be replicated in humans and, because of an increased risk of haemorrhage and thrombocytopenia, the use of hypotonic solutions for HIPEC with oxaliplatin is discouraged [52]. Some centres advise the use of high molecular weight solutions such as

icodextrin [40, 53]. The small differences that are found in the rate and extent of oxaliplatin absorption between glucose 5% and icodextrin 4% are deemed clinically irrelevant [53]. Promising results have been seen with the use of the peritoneal dialysis fluids Physioneal 40 dextrose 2.27% solution [35] and Dianeal PD4 dextrose 1.36% solution [54, 55], showing minimal electrolyte and glycaemic disturbances during the HIPEC procedure. The cytotoxic properties of oxaliplatin in Physioneal 40 dextrose 2.27% solution remain unchanged during the HIPEC procedure [35]. These findings support the use of perfusates containing lower concentrations of dextrose.

However, there is currently no consensus on the best type of carrier solution, showing the need for further research, as different carrier solutions might result in different outcomes.

## Drug penetration in tumour tissue

The goal of intraperitoneal administration of oxaliplatin is to obtain high local concentrations and high penetration in tumour tissue to enhance efficacy. Although tissue penetration seems important, a relationship between tissue concentration and efficacy of the HIPEC procedure has not yet been described. Given the heterogeneity of colorectal carcinoma, the optimal tissue concentration might differ for each patient, or even in different tumours within the same patient. Drug penetration is limited to only a few cell layers under the tumour surface [56]. This highlights the importance of complete cytoreduction to optimize the effect of intraperitoneally administered oxaliplatin. Elias *et al*. [30] showed that the concentration of platinum in healthy peritoneal tissue exposed to oxaliplatin solution during HIPEC is a good reflection of its concentration in peritoneal tumour tissue. A recent study collected tissue samples after HIPEC with oxaliplatin and demonstrated no significant difference ($P$ = 0.38) between the platinum concentration in peritoneal tissue and in the subjacent fascia [35].

Table 1 provides an overview of human and animal studies in which platinum tissue concentrations during the HIPEC procedure with oxaliplatin were measured. As a result of major differences in the procedure, it is hard to compare the individual studies. Factors that have been identified to have an impact on the platinum concentration in tumour tissue are hyperthermia, pressure, dose, perfusate concentration, type of carrier solution and pretreatment with 5-FU [30, 35–38, 52, 57, 58].

### *Effect of hyperthermia and pressure*

The rationale for using hyperthermia in cancer treatment relates to tumour cells being more susceptible to heat than non-malignant cells. Hyperthermia impairs DNA replication and disturbs multiple DNA repair pathways, and thus sensitizes cancer cells to cytotoxic agents, leading to increased cell death [59]. Local heating of tumours also triggers multiple antitumour immune responses and facilitates increased trafficking of immune cells between tumours and draining lymph nodes [60].

Besides intrinsic antitumour activities, hyperthermia also enhances the cytotoxicity of oxaliplatin [57, 61]. A study in rats showed that the peritoneal tissue concentration of oxaliplatin significantly increased with higher temperature [57]. An animal study in a pig model using a semi-open technique with a constant oxaliplatin concentration showed that hyperthermia (42°C) increased the tissue concentration of oxaliplatin in the visceral peritoneum compared with normothermia. High pressure also increased the oxaliplatin tissue concentration in both the visceral and parietal peritoneum compared with normal pressure [36]. High intra-abdominal pressure can be achieved using a HIPEC procedure with a closed abdominal wall [36, 62]. However, higher tissue concentrations and a homogeneous distribution of oxaliplatin in the perfusate can be achieved using the open technique [63, 64].

### *Effect of dose and concentration*

A study in rats showed that tissue distribution is significantly increased by the use of higher doses of oxaliplatin. A sixfold increase in tissue concentration was seen with a fourfold increase in dose [57]. In a phase I clinical study, an increase in tumour platinum concentration was found with every dose escalation step of 50 mg $m^{-2}$. Tumour platinum exposure increased by a factor of 1.5 between the lowest and highest dose tested, which were 260 mg $mg^{-2}$ and 460 mg $m^{-2}$, respectively [30]. HIPEC with oxaliplatin perfused at a temperature of 40°C over a period of 2 h showed a 1.3-fold increase in tumour platinum exposure between a dose of 200 mg $m^{-2}$ and of 250 mg $m^{-2}$. Nevertheless, the maximum tolerated dose for a 2-h perfusion of oxaliplatin was 200 mg $m^{-2}$ in that study [38].

Perfusate volume and perfusate concentration are important variables for PK during the HIPEC procedure. The diffusion of oxaliplatin from perfusate to peritoneal tissue and blood is driven by a concentration gradient. A higher perfusate volume of 2.5 l $m^{-2}$, instead of 2 l $m^{-2}$, decreases the intraperitoneal platinum concentration by 20% [30]. The maximal plasma concentration ($C_{max}$) and systemic exposure are similar for a 410 mg $m^{-2}$ dose of oxaliplatin in 2.5 l $m^{-2}$ and a 310 mg $m^{-2}$ dose in 2 l $m^{-2}$. This indicates that the PK and tissue penetration of oxaliplatin are influenced more by the concentration in the perfusate than by the total dose administered [30, 57]. Some publications describe the use of a standard perfusate volume of 2 l $m^{-2}$ with a fixed dose of 460 mg $m^{-2}$. In this case, all patients are treated with a fixed concentration of 230 mg $l^{-1}$ oxaliplatin in the perfusate at the beginning of the HIPEC procedure. Using perfusate volumes above 2 l $m^{-2}$, along with a fixed dose per $m^2$, might negatively influence efficacy because tumour exposure will be decreased. However, the use of fixed volumes of 2 l $m^{-2}$ can cause inadequate tissue contact time in patients with a relative large abdominal cavity. Some centres fill the abdominal cavity completely before the administration of oxaliplatin. This causes great variation in oxaliplatin concentrations and therefore is likely to influence tumour penetration and the systemic absorption of oxaliplatin, which might influence the efficacy and/or safety of the treatment.

## Table 1

Overview of human and animal studies measuring total platinum tissue exposure during the hyperthermic intraperitoneal chemotherapy procedure with oxaliplatin

| Author/year | Subjects | Treatment strategy | Oxaliplatin dose (mg m$^{-2}$) | Carrier solution | Duration, flow rate | Temperature (°C) | Flushing afterwards | Analytical method | Total platinum tissue concentration (ng mg$^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|
| **Human studies** | | | | | | | | | |
| **Elias *et al.*/ 2002 [32]** | *n* = 5 | Open coliseum technique | 260 | 5% dextrose, 2 l m$^{-2}$ | 30 min (+ approximately 10 min required to reach high homogeneous temperature), 2 l min$^{-1}$ | 42–44 | No | AAS | Tumour tissue: 228 μg g$^{-1}$ dry tissue<br>Normal peritoneum: 230 μg g$^{-1}$ dry tissue |
| | *n* = 3 | | 310 | | | | | | Tumour tissue: 248 μg g$^{-1}$ dry tissue<br>Normal peritoneum: 273 μg g$^{-1}$ dry tissue |
| | *n* = 3 | | 360 | | | | | | Tumour tissue: 327 μg g$^{-1}$ dry tissue<br>Normal peritoneum: 296 μg g$^{-1}$ dry tissue |
| | *n* = 3 + 3 | | 410 | 5% dextrose, 2.0 l m$^{-2}$ and 2.5 l m$^{-2}$ | | | | | Tumour tissue: 323 μg g$^{-1}$ dry tissue<br>Normal peritoneum: 287 μg g$^{-1}$ dry tissue |
| | *n* = 3 | | 460 | 5% dextrose, 2 l m$^{-2}$ | | | | | Tumour tissue: 339 μg g$^{-1}$ dry tissue<br>Normal peritoneum: 392 μg g$^{-1}$ dry tissue |
| **Elias *et al.*/ 2002 [54]** | *n* = 4 | Open coliseum technique | 460 | 100 mosm l$^{-1}$ dextrose, 2 l m$^{-2}$ | 30 min (+ approximately 5 min required to reach high homogeneous temperature), 2 l min$^{-1}$ | 42–44 | No | AAS | Tumour tissue: 480 ± 82 μg g$^{-1}$ dry tissue<br>Normal peritoneum: 396 ± 73 μg g$^{-1}$ dry tissue |
| | *n* = 4 | | | 150 mosm l$^{-1}$ dextrose, 2 l m$^{-2}$ | | | | | Tumour tissue: 440 ± 108 μg g$^{-1}$ dry tissue<br>Normal peritoneum: 449 ± 83 μg g$^{-1}$ dry tissue |
| | *n* = 3 | | | 200 mosm l$^{-1}$ dextrose, 2 l m$^{-2}$ | | | | | Tumour tissue: 322 ± 76 μg g$^{-1}$ dry tissue<br>Normal peritoneum: 314 ± 101 μg g$^{-1}$ dry tissue |
| | *n* = 3 (+3) | | | 300 mosm l$^{-1}$ dextrose, 2 l m$^{-2}$ | | | | | Tumour tissue: 299 ± 87 μg g$^{-1}$ dry tissue<br>Normal peritoneum: 339 ± 92 μg g$^{-1}$ dry tissue |
| **Stewart *et al.*/ 2008 [40]** | *n* = 12 | Closed | 200 | 5% dextrose, fixed volume of 3 l | 120 min, 0.8–1 l min$^{-1}$ | 40.6 ± 0.5 | Yes, with 3 l of crystalloid | ICP-OES | Tumour tissue: 15.9 ± 12.0 μg g$^{-1}$<br>Normal peritoneum: 17.7 ± 10.8 μg g$^{-1}$ |
| | *n* = 3 | | 250 | | | | | | Tumour tissue: 20.3 ± 9.7 μg g$^{-1}$<br>Normal peritoneum: 26.3 ± 14.7 μg g$^{-1}$ |
| **Löffler *et al.*/ 2017 [37]** | *n* = 9 | Not mentioned | 300 | Physioneal 40 dextrose 2.27% w/v Clear-Flex peritoneal dialysis solution, 5–6 l (different concentrations; 93.7 ± 12.2 [75.0–108.9] μg ml$^{-1}$) | 30 min, not mentioned | 42 | Not mentioned | AAS | Normal peritoneum: 50 μg g$^{-1}$ dry tissue [range 5–203 μg g$^{-1}$]<br>Subjacent fascia: 70 μg g$^{-1}$ dry tissue [range 0–103 μg g$^{-1}$] |

*(continues)*

## Table 1

(Continued)

| Author/year | Subjects | Treatment strategy | Oxaliplatin dose (mg $m^{-2}$) | Carrier solution | Duration, flow rate | Temperature (°C) | Flushing afterwards | Analytical method | Total platinum tissue concentration (ng $mg^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|
| **Animal studies** | | | | | | | | | |
| **Facy *et al.*/ 2012 [38] (in pigs)** | $n = 5$ | Semi-open | 150 mg $l^{-1}$ | 5% dextrose, 4 l | 30 min, not mentioned | 38 | Yes, with 1 l of 5% dextrose | AAS | Parietal peritoneum: 35.62 ± 8.81 μg $g^{-1}$<br>Visceral peritoneum: 5.48 ± 0.70 μg $g^{-1}$ |
| | $n = 5$ | | | | | 42 | | | Parietal peritoneum: 38.73 ± 7.74 μg $g^{-1}$<br>Visceral peritoneum: 7.99 ± 1.66 μg $g^{-1}$ |
| | $n = 5$ | Semi-open with high intra-abdominal pressure | | 5% dextrose, 8 l | | 38 | | | Parietal peritoneum: 53.61 ± 10.32 μg $g^{-1}$<br>Visceral peritoneum: 6.95 ± 1.46 μg $g^{-1}$ |
| | $n = 5$ | | | | | 42 | | | Parietal peritoneum: 66.16 ± 13.03 μg $g^{-1}$<br>Visceral peritoneum: 10.39 ± 3.49 μg $g^{-1}$ |
| **Piché *et al.*/ 2011 [59] (in rats)** | $n = 5$ | Closed | 920 | 5% dextrose, 15 ml | 25 min, 16 ml $min^{-1}$ | 37 | Yes, with 20 ml of 5% dextrose | HPLC with Phenomenex column and a precolumn of $C^{18}$ | Normal peritoneum: 5.7 ± 0.4 μg $ml^{-1}$ |
| | $n = 7$ | | | | | 40 | | | Normal peritoneum: 6.5 ± 0.3 μg $ml^{-1}$ |
| | $n = 13$ | | | | | 43 | | | Normal peritoneum: 7.9 ± 0.6 μg $ml^{-1}$ |
| | $n = 6$ | | 460 | | | 40 | | | Normal peritoneum: 2.4 ± 0.7 μg $ml^{-1}$ |
| | $n = 6$ | | 1840 | | | | | | Normal peritoneum: 15.5 ± 0.6 μg $ml^{-1}$ |
| **Pestieau *et al.*/ 2001 [39] (in rats)** | $n = 5$ | Closed | 15 mg $kg^{-1}$ | 5% dextrose, 150 ml | 90 min, 80 ml $min^{-1}$ | 35–37 | Not mentioned | DC-PES | Colonic tissue: 25 ± 9 μg $ml^{-1}$ |
| | $n = 5$ | | | | | 40–42 | | | Colonic tissue: 28 ± 6 μg $ml^{-1}$ |

AAS, atomic absorption spectrometry; DC-PES = direct current plasma emission spectroscopy; ICP-OES, inductively coupled plasma optical emission spectrometry; HPLC, high-performance liquid chromatography

## Table 2

Pharmacokinetic studies of oxaliplatin in patients undergoing the hyperthermic intraperitoneal chemotherapy procedure with oxaliplatin

| Author/year | Subjects | Treatment strategy | Oxaliplatin dose (mg $m^{-2}$) | Carrier solution | Duration, flow rate | Temperature (°C) |
|---|---|---|---|---|---|---|
| **Elias *et al.*/ 2002 [32]** | $n = 5$<br>$n = 3$<br>$n = 3$<br>$n = 3 + 3$<br>$n = 3$ | Open coliseum technique | 260<br>310<br>360<br>410<br>460 | 5% dextrose, 2 l $m^{-2}$<br>5% dextrose, 2 l $m^{-2}$ and 2.5 l $m^{-2}$<br>5% dextrose, 2 l $m^{-2}$ | 30 min (+ approximately 10 min required to reach high homogeneous temperature), 2 l $min^{-1}$ | 42–44 |
| **Elias *et al.*/ 2002 [54]** | $n = 4$<br>$n = 4$<br>$n = 3$<br>$n = 3$ (+3) | Open coliseum technique | 460 | 100 mosm $l^{-1}$ dextrose, 2 l $m^{-2}$<br>150 mosm $l^{-1}$ dextrose, 2 l $m^{-2}$<br>200 mosm $l^{-1}$ dextrose, 2 l $m^{-2}$<br>300 mosm $l^{-1}$ dextrose (=iso-osmotic), 2 l $m^{-2}$ | 30 min (+ approximately 5 min required to reach high homogeneous temperature), 2 l $min^{-1}$ | 42–44 |
| **Mahteme *et al.*/ 2008 [45]** | $n = 8$ | Open coliseum technique | 427 ± 29 | 5% dextrose, 3.2 ± 0.7 l | 30 min (+ time required to reach high homogeneous temperature), not mentioned | 41.5–43 |
| **Ferron *et al.*/ 2008 [35]** | $n = 24$ | Open coliseum technique | 360 ($n = 7$) and 460 ($n = 17$) | 5% dextrose, 2 l $m^{-2}$ | 30 min (+ approximately 8–10 min required to reach high homogeneous temperature) (12×) and 30 min (12×), 2 l $min^{-1}$ | 42–43 |
| **Chalret du Rieu *et al.*/ 2014 [36]** | $n = 58$<br>$n = 17$ | Open coliseum technique | 360<br>460 | 5% dextrose, 2 l $m^{-2}$ | 30 min (+ approximately 8–10 min required to reach high homogeneous temperature) (12×) and 30 min (63×), 2 l $min^{-1}$ | 42–43 |
| **Leinwand *et al.*/ 2013 [43]** | $n = 10$ | Closed | 250 | 5% dextrose, 2.7 ± 0.8 l | 60 min, 1 l $min^{-1}$ | Not mentioned |
| **Stewart *et al.*/ 2008 [40]** | $n = 12$<br>$n = 3$ | Closed | 200<br>250 | 5% dextrose, fixed volume of 3 l | 120 min, 0.8–1 l $min^{-1}$ | 40.6 ± 0.5 |
| **Valenzuela *et al.*/2011 [41]** | $n = 30$ | Open coliseum technique | 360 | 4% icodextrin, 2.5–6 l | 40 (range 30–60), 1 l $min^{-1}$ | 42–43 |
| **Pérez-Ruixo *et al.*/2012 [42]** | $n = 36$<br>$n = 13$ | Open coliseum technique | 364.5 ± 32.4<br>399.5 ± 94.7 | 4% icodextrin, 3.9 ± 0.8 l<br>5% dextrose, 3.6 ± 0.6 l | 37.6 ± 8.3, 1 l $min^{-1}$<br>33.8 ± 5.1, 1 l $min^{-1}$ | 42–43 |

AAS, atomic absorption spectrometry, AUC, area under the concentration–time curve; $C_{max}$, maximal plasma concentration; ICP-MS, inductively coupled plasma mass spectrometry, ICP-OES, inductively coupled plasma optical emission spectrometry; LC, liquid chromatography
[a]Unbound oxaliplatin parent drug

## PK of oxaliplatin during HIPEC

Table 2 provides an overview of PK studies of oxaliplatin in patients undergoing the HIPEC procedure.

### *Absorption of platinum from the peritoneal compartment*

In the peritoneal compartment, the great majority of administered drug is present as unbound platinum, which is

## Table 2

(Continued)

| Author/year | Flushing afterwards | Analytical method | Pharmacokinetic parameters | | | | |
|---|---|---|---|---|---|---|---|
| | | | Total platinum half-life in perfusate (min) | Total platinum | | Ultrafilterable platinum | |
| | | | | $C_{max}$ (μg ml$^{-1}$) | AUC (μg ml*h$^{-1}$) | $C_{max}$ (μg ml$^{-1}$) | AUC (μg ml*h$^{-1}$) |
| **Elias *et al.*/ 2002 [32]** | No | AAS | 40 | – | – | | 11 |
| | | | | – | – | | 14 |
| | | | | – | – | | 15 |
| | | | | – | – | | 15 |
| | | | | 13.2 | – | 8.5 | 17 |
| **Elias *et al.*/ 2002 [54]** | No | AAS | 35 | 15.0 ± 2.3 | 92.3 ± 10.1 | 8.7 ± 1.7 | 16.7 ± 2.3 |
| | | | | 13.6 ± 1.7 | 104.0 ± 12.1 | 9.1 ± 1.4 | 18.6 ± 2.6 |
| | | | | 10.4 ± 0.9 | 72.3 ± 6.3 | 7.6 ± 1.2 | 15.0 ± 1.7 |
| | | | | 12.0 ± 1.8 | 81.6 ± 7.2 | 7.8 ± 1.1 | 17.6 ± 1.9 |
| **Mahteme *et al.*/ 2008 [45]** | Yes, with an unknown amount of saline | LC with porous graphitic carbon and postcolumn derivation with sodium diethyldithiocarbamate in a microwave field followed by photometric detection | 29.5 [21.1–41.2][a] | – | – | 8.3 ± 1.8[a] | 26 220 ± 4290[a] |
| **Ferron *et al.*/ 2008 [35]** | Yes, with an unknown amount of saline | AAS | 29 [18–42] | – | – | – | 13.7 [8.0–20.0] |
| **Chalret du Rieu *et al.*/ 2014 [36]** | Yes, with an unknown amount of saline | AAS | 29.6 ± 6 | – | – | – | 16.1 ± 4.9 |
| | | | | | | | 22.9 ± 4.7 |
| **Leinwand *et al.*/ 2013 [43]** | Not mentioned | ICP-MS | – | – | 138.1 ± 33.1 mg*min l$^{-1}$ | – | – |
| **Stewart *et al.*/ 2008 [40]** | Yes, with 3 l of crystalloid | ICP-OES | 70.1 ± 23.8 | 2.2 ± 0.77 | 23.2 ± 11.4 | – | – |
| | | | 65.3 ± 10.3 | 3.2 ± 0.6 | 31.1 ± 3.0 | | |
| **Valenzuela *et al.*/2011 [41]** | Not mentioned | ICP-OES | 132 | 2.56 ± 0.9 | 87.20 ± 123.20 | – | – |
| **Pérez-Ruixo *et al.*/2012 [42]** | Not mentioned | ICP-OES | 76.8 ± 21 | 20.5 ± 4.3 | 192 ± 45.3 | – | – |
| | | | 71.4 ± 29.4 | 22.3 ± 9.1 | 213 ± 72.4 | | |

available for antitumour activity and transfer to the bloodstream. This indicates low platinum protein-binding in the perfusate solution. Although unbound platinum in the perfusate has only been studied for intraperitoneal administration of cisplatin [65, 66], this might also apply to the administration of oxaliplatin. Given the high reactivity of oxaliplatin with serum proteins such as albumin, it can be speculated that extensive cytoreduction, bleeding or severed tissue surfaces will decrease the fraction of unbound platinum in the perfusate. No significant association has been found between oxaliplatin systemic exposure and the extent of the surgery or the peritoneal cancer index [34].

Oxaliplatin is rapidly absorbed from the peritoneal compartment, with reported mean peritoneal half-lives ($t_{1/2}$s) of

29 min [33, 34], 35 min [52] and 40 min [30], indicating that approximately half of the dose is cleared from the peritoneal compartment during a 30-min HIPEC procedure. Some studies have report much longer peritoneal $t_{1/2}$s of up to 2.2 h [38–40]. The rate constant for the absorption of oxaliplatin from the peritoneal perfusate to the plasma is independent of the administered dose and shows low interpatient variability (with a coefficient of variation of 22%) [33]. Furthermore, modifications to the osmolarity of the carrier solution (with a fixed oxaliplatin concentration) do not affect systemic oxaliplatin absorption [52]. A positive correlation has been found between the percentage of systemic absorbed platinum and the body mass index (BMI) of patients [43]. This might be due to a larger peritoneal surface area in patients with a higher BMI. This could not be replicated in another study using a closed HIPEC procedure [41]. Nevertheless, it was shown that body surface area (BSA) is a predictor of systemic exposure to platinum. Patients with a higher BSA show a lower plasma oxaliplatin area under the concentration–time curve (AUC) over a 1-h closed HIPEC procedure, possibly caused by lower drug concentrations in the perfusate in these patients [41]. The peritoneal AUC and systemic AUC of oxaliplatin during HIPEC is not influenced by disease burden or the extent of peritonectomy, indicating that an intact peritoneum is not required to maintain the concentration differences between perfusate and plasma observed during HIPEC procedure [41, 67].

HIPEC performed with a sodium bicarbonate-containing carrier solution shows a fast decline of free platinum compounds in the perfusate, with a recovery of only 50% at 5 min after the start of perfusion [35]. This fast decline of free platinum compounds in the perfusate might not only be explained by absorption from the peritoneal compartment, but also by a reaction with solid tissues in the peritoneum and degradation in the perfusate solution, most probably caused by a reaction with erythrocytes and other cell types or debris circulating in the perfusate. Only a small percentage (10–15%) of the parent drug oxaliplatin is consistently detectable during 30-min HIPEC with 300 mg $m^{-2}$ oxaliplatin. This can be the result of rapid nonenzymatic transformation into reactive compounds in the perfusate. Nevertheless, it was shown that bioactivity in the perfusate was preserved during the whole 300-min HIPEC procedure [35]. When dextrose 5% is used as a carrier solution, the parent drug oxaliplatin is more stable in the perfusate, with a degradation of only 5–10% at the end of the HIPEC procedure [43]. These large differences in recovery of the parent drug oxaliplatin could be explained by different carrier solutions, given that there is a higher reactivity with sodium bicarbonate-containing carrier solutions [35]. However, both studies used different analytical methods, making it hard to compare these results adequately.

### *Systemic PK of oxaliplatin with HIPEC*

One of the advantages of intraperitoneal administration of oxaliplatin is the use of high drug doses with relatively low systemic exposure. The interindividual variability of central volume of distribution and plasma clearance is larger than for peritoneal volume of distribution and peritoneal clearance [33]. The $C_{max}$ of platinum in the plasma is reached at the end of the HIPEC procedure [31, 52]. After evacuation of the oxaliplatin solution from the abdominal cavity, the plasma concentration of platinum rapidly drops. Some studies showed a relatively small systemic exposure (AUC) that was comparable to AUC values observed after a 2-h intravenous infusion of oxaliplatin at a dose of 130 mg $m^{-2}$ [30]. Others found a twofold higher systemic exposure to the parent drug oxaliplatin after HIPEC compared with an intravenous infusion of 130 mg $m^{-2}$ oxaliplatin over 30 min [43]. Systemic exposure to oxaliplatin increases with higher doses [30, 34]. A study in rats showed that higher perfusion temperatures decreased the systemic exposure to oxaliplatin [57] and decreased drug absorption in kidney tissue [37]. The reason for these findings is unknown, but might be associated with higher reactivity in the peritoneum.

High systemic exposure to oxalipatin during HIPEC can lead to thrombocytopenia and neutropenia. The most frequently reported toxicities after HIPEC with oxaliplatin are haemoperitoneum (23%), neuropathy (19%), thrombocytopenia (13%) and ascites (4%) [34]. Although haemoperitoneum is a postoperative complication, high systemic oxaliplatin exposure can increase the risk of this condition. Neutropenia is rarely observed [34].

To date, only two studies have investigated the PK of intact oxaliplatin during HIPEC [35, 43]. Huge differences were found between the plasma clearance of unbound intact oxaliplatin (28.4 l $h^{-1}$ $m^{-2}$) [43] and total unbound platinum (6.68 l $h^{-1}$ $m^{-2}$) [33]. The systemic exposure to unbound intact oxaliplatin is about four times lower than the systemic exposure to total unbound platinum. This can be explained by the fact that, with time, the amount of intact oxaliplatin will constitute a gradually decreasing fraction of total unbound platinum as a result of reactivity with endogenous compounds [43].

### *Additional flushing*

There is no consensus about the usefulness of flushing the abdominal cavity with crystalloids at the end of oxaliplatin administration. When flushing is performed, its purpose is to minimize systemic exposure to both patient and personnel, as well as to evacuate remaining debris and clots due to the surgery and resulting bleeding. However, HIPEC without flushing might increase tumour exposure because intraperitoneal tumour cells might be exposed to high concentrations of oxaliplatin for a longer period. Currently, there is a lack of knowledge on the effect of additional flushing on oxaliplatin PK.

## PD of oxaliplatin during HIPEC

Few studies have investigated the PD of oxaliplatin during HIPEC [34, 39, 68, 69]. These studies use PK/PD models to find associations between PK parameters and PD toxicities of the treatment. It has been demonstrated that HIPEC-induced neutropenia largely depends on the duration of the HIPEC procedure and the oxaliplatin concentration in the perfusate, which is related to systemic concentrations [39]. It has been predicted that each 400 mg $l^{-1}$ increase in initial oxaliplatin concentration causes a 28% decrease in the

absolute neutrophil count (ANC) at day 7 [69]. Extending the duration of HIPEC from 30 min to 60 min is predicted to result in a 23% decrease in ANC at day 7 [69]. This is relevant because postoperative infectious complications can be expected within the first week after surgery. the main determinants for the duration and severity of HIPEC-induced thrombocytopenia are the initial oxaliplatin concentration and the duration of the HIPEC procedure [69].

The systemic exposure to oxaliplatin is associated with the severity of thrombocytopenia and the occurrence of haemoperitoneum [34]. An increase by approximately 20% in systemic oxaliplatin exposure resulted in a decrease in platelets and an increase in the chance of developing haemoperitoneum. No associations were found between either intraperitoneal or systemic oxaliplatin exposure and the onset of ascites or neuropathy [34].

The PK studies that have been performed so far suggest that higher doses of oxaliplatin could be used for the HIPEC procedure, without substantially increasing the risk of major haematological toxicity. Nevertheless, based on the data summarized above, this should be performed with great caution.

## The rationale for administration of 5-FU prior to administration of oxaliplatin

The combination of intravenous administration of oxaliplatin with 5-FU–leucovorin significantly improves antitumour efficacy in patients with metastatic colorectal cancer [70]. There is a synergistic effect of oxaliplatin and 5-FU [71], but 5-FU cannot be mixed with oxaliplatin because of incompatibility. This is the reason for the clinical use of intraoperative intravenous administration of 5-FU and leucovorin in conjunction with intraperitoneal perioperative oxaliplatin [30]. Although the peritoneum and abdominal cavity have an impaired blood supply, resulting in systemic therapy having limited efficacy, it has been demonstrated that 5-FU administered intravenously penetrates rapidly into heated tumour nodules during HIPEC [72]. The simultaneous administration of intravenous and intraperitoneal chemotherapy creates an ideal situation for enhancement of cytotoxicity in the heated tumour nodules. In a recent study in rats, intravenous administration of 5-FU enhanced the peritoneal absorption of oxaliplatin [58]. This highlights the importance of the administration of 5-FU in the management of PC of gastrointestinal origin.

## Knowledge gaps

Although several studies have investigated drug penetration in tumour tissue during the HIPEC procedure, no relationship has been found between tumour platinum exposure and clinical outcome yet. It can be assumed that tissue penetration is an important factor for optimal drug effect. However, the optimal drug concentration to attain complete tumour cell death remains unclear and might differ for individual patients and tumours. Higher tumour exposures can be achieved with the use of higher perfusate concentrations and a longer duration of procedure, but this will also cause an increased systemic absorption, which is related to toxicity. Future studies should investigate the relationship between tumour exposure and antitumour efficacy, and systemic exposure and toxicity. This will help to establish the optimal HIPEC procedure for each patient.

## Future perspectives

For patients with advanced PC who are not eligible for HIPEC with curative intent, a novel treatment has recently been introduced, called 'pressurized intraperitoneal aerosol chemotherapy (PIPAC). This technique is minimally invasive and combines the advantages of local administration with pressurized vaporization. Although no clear indication for PIPAC has yet been defined, the treatment has been reported to be feasible, well tolerated and safe [73]. However, available data are limited by small sample sizes, heterogeneity and the lack of control groups.

New techniques, such as organoid technology [74], create great opportunities for future HIPEC research. Organoids are three-dimensional stem cell cultures that self-organize into *ex vivo* 'mini-organs'. Organoids generated from colorectal carcinomas can be used to test several cytotoxic agents, concentrations, durations, temperatures and frequencies, to optimize current intraperitoneal chemotherapy. The first study to use this approach showed that oxaliplatin was the most efficient cytotoxic agent in patients with PC of colorectal cancer origin [75]. The use of organoids generated from colorectal carcinomas from individual patients will create opportunities to individualize HIPEC procedures. Future studies should investigate the opportunities that these individualized approaches may bring, which will theoretically create the optimal treatment, with high tumour exposure and efficacy and acceptable systemic exposure and toxicity.

## Conclusions

Currently, there is a wide variety of procedures and a lack of PK data in HIPEC. Several important factors can influence the PK profile of oxaliplatin in HIPEC procedures. The variety of analytical techniques and HIPEC procedures makes it difficult to compare individual studies. Although HIPEC is now widely accepted as an effective curative treatment option, the exact procedure can differ between institutions. There is a need for standardization of the first-line HIPEC procedure with oxaliplatin in patients with PC of colorectal origin. Given the complexity of the procedure, there is a need for a multidisciplinary approach, combining the expertise of surgeons, medical oncologists, perfusionists, anaesthetists and pharmacists.

### *Nomenclature of ligands*

Key ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [76].

## Competing Interests

There are no competing interests to declare.

## References


**1** Lemmens VE, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JW, de Hingh IH. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. Int J Cancer 2011; 128: 2717–25.

**2** Segelman J, Granath F, Holm T, Machado M, Mahteme H, Martling A. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. Br J Surg 2012; 99: 699–705.

**3** Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. Ann Surg 2006; 243: 212–22.

**4** Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. Br J Surg 2002; 89: 1545–50.

**5** Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, *et al*. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 2000; 88: 358–63.

**6** Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. Cancer 1989; 63: 364–7.

**7** Huang CQ, Min Y, Wang SY, Yang XJ, Liu Y, Xiong B, *et al*. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival for peritoneal carcinomatosis from colorectal cancer: a systematic review and meta-analysis of current evidence. Oncotarget 2017; 8: 55657–83.

**8** Li Y, Yu Y, Liu Y. Report on the 9th International Congress on Peritoneal Surface Malignancies. Cancer Biol Med 2014; 11: 281–4.

**9** Simkens GA, Rovers KP, Nienhuijs SW, de Hingh IH. Patient selection for cytoreductive surgery and HIPEC for the treatment of peritoneal metastases from colorectal cancer. Cancer Manag Res 2017; 9: 259–66.

**10** Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh HJ 3rd. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. Cancer 2010; 116: 3756–62.

**11** Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, *et al*. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010; 28: 63–8.

**12** Verwaal VJ, van Ruth S, Witkamp A, Boot H, van Slooten G, Zoetmulder FA. Long-term survival of peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol 2005; 12: 65–71.

**13** Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, *et al*. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2009; 27: 681–5.

**14** Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008; 15: 2426–32.

**15** Elias D, Glehen O, Pocard M, Quenet F, Goere D, Arvieux C, *et al*. A comparative study of complete cytoreductive surgery plus intraperitoneal chemotherapy to treat peritoneal dissemination from colon, rectum, small bowel, and nonpseudomyxoma appendix. Ann Surg 2010; 251: 896–901.

**16** da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. J Am Coll Surg 2006; 203: 878–86.

**17** van Leeuwen BL, Graf W, Pahlman L, Mahteme H. Swedish experience with peritonectomy and HIPEC. HIPEC in peritoneal carcinomatosis. Ann Surg Oncol 2008; 15: 745–53.

**18** Hompes D, D'Hoore A, Wolthuis A, Fieuws S, Mirck B, Bruin S, *et al*. The use of oxaliplatin or mitomycin C in HIPEC treatment for peritoneal carcinomatosis from colorectal cancer: a comparative study. J Surg Oncol 2014; 109: 527–32.

**19** van Eden WJ, Kok NFM, Woensdregt K, Huitema ADR, Boot H, Aalbers AGJ. Safety of intraperitoneal Mitomycin C versus intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis of colorectal cancer undergoing cytoreductive surgery and HIPEC. Eur J Surg Oncol 2018; 44: 220–7.

**20** Ychou M, Viret F, Kramar A, Desseigne F, Mitry E, Guimbaud R, *et al*. Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a phase II study in colorectal cancer patients with non-resectable liver metastases. Cancer Chemother Pharmacol 2008; 62: 195–201.

**21** Graham MA, Lockwood GF, Greenslade D, Brienza S, Bayssas M, Gamelin E. Clinical pharmacokinetics of oxaliplatin: a critical review. Clin Cancer Res 2000; 6: 1205–18.

**22** Brouwers EE, Tibben M, Rosing H, Schellens JH, Beijnen JH. The application of inductively coupled plasma mass spectrometry in clinical pharmacological oncology research. Mass Spectrom Rev 2008; 27: 67–100.

**23** Sanofi-aventis U.S. LLC. Eloxatin: Highlights of prescribing information. 2012. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021492s011,021759s009lbl.pdf (last accessed 27 March 2018).

**24** Ehrsson H, Wallin I, Yachnin J. Pharmacokinetics of oxaliplatin in humans. Med Oncol 2002; 19: 261–5.

**25** Desoize B, Madoulet C. Particular aspects of platinum compounds used at present in cancer treatment. Crit Rev Oncol Hematol 2002; 42: 317–25.

**26** Mani S, Graham MA, Bregman DB, Ivy P, Chaney SG. Oxaliplatin: a review of evolving concepts. Cancer Invest 2002; 20: 246–63.

**27** Takimoto CH, Remick SC, Sharma S, Mani S, Ramanathan RK, Doroshow J, *et al*. Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute Organ Dysfunction Working Group Study. J Clin Oncol 2003; 21: 2664–72.

**28** Shord SS, Bernard SA, Lindley C, Blodgett A, Mehta V, Churchel MA, *et al*. Oxaliplatin biotransformation and pharmacokinetics: a pilot study to determine the possible relationship to neurotoxicity. Anticancer Res 2002; 22: 2301–9.

**29** Jerremalm E, Wallin I, Ehrsson H. New insights into the biotransformation and pharmacokinetics of oxaliplatin. J Pharm Sci 2009; 98: 3879–85.

**30** Elias D, Bonnay M, Puizillou JM, Antoun S, Demirdjian S, El OA, *et al*. Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. Ann Oncol 2002; 13: 267–72.

**31** Elias D, Matsuhisa T, Sideris L, Liberale G, Drouard-Troalen L, Raynard B, *et al*. Heated intra-operative intraperitoneal oxaliplatin plus irinotecan after complete resection of peritoneal carcinomatosis: pharmacokinetics, tissue distribution and tolerance. Ann Oncol 2004; 15: 1558–65.

**32** Gesson-Paute A, Ferron G, Thomas F, de Lara EC, Chatelut E, Querleu D. Pharmacokinetics of oxaliplatin during open versus laparoscopically assisted heated intraoperative intraperitoneal chemotherapy (HIPEC): an experimental study. Ann Surg Oncol 2008; 15: 339–44.

**33** Ferron G, Dattez S, Gladieff L, Delord JP, Pierre S, Lafont T, *et al*. Pharmacokinetics of heated intraperitoneal oxaliplatin. Cancer Chemother Pharmacol 2008; 62: 679–83.

**34** Chalret du Rieu Q, White-Koning M, Picaud L, Lochon I, Marsili S, Gladieff L, *et al*. Population pharmacokinetics of peritoneal, plasma ultrafiltrated and protein-bound oxaliplatin concentrations in patients with disseminated peritoneal cancer after intraperitoneal hyperthermic chemoperfusion of oxaliplatin following cytoreductive surgery: correlation between oxaliplatin exposure and thrombocytopenia. Cancer Chemother Pharmacol 2014; 74: 571–82.

**35** Löffler MW, Schuster H, Zeck A, Quilitz N, Weinreich J, Tolios A, *et al*. Pharmacodynamics of oxaliplatin-derived platinum compounds during hyperthermic intraperitoneal chemotherapy (HIPEC): an emerging aspect supporting the rational design of treatment protocols. Ann Surg Oncol 2017; 24: 1650–7.

**36** Facy O, Al Samman S, Magnin G, Ghiringhelli F, Ladoire S, Chauffert B, *et al*. High pressure enhances the effect of hyperthermia in intraperitoneal chemotherapy with oxaliplatin: an experimental study. Ann Surg 2012; 256: 1084–8.

**37** Pestieau SR, Belliveau JF, Griffin H, Stuart OA, Sugarbaker PH. Pharmacokinetics of intraperitoneal oxaliplatin: experimental studies. J Surg Oncol 2001; 76: 106–14.

**38** Stewart JH, Shen P, Russell G, Fenstermaker J, McWilliams L, Coldrun FM, *et al*. A phase I trial of oxaliplatin for intraperitoneal hyperthermic chemoperfusion for the treatment of peritoneal surface dissemination from colorectal and appendiceal cancers. Ann Surg Oncol 2008; 15: 2137–45.

**39** Valenzuela B, Nalda-Molina R, Bretcha-Boix P, Escudero-Ortiz V, Duart MJ, Carbonell V, *et al*. Pharmacokinetic and pharmacodynamic analysis of hyperthermic intraperitoneal oxaliplatin-induced neutropenia in subjects with peritoneal carcinomatosis. AAPS J 2011; 13: 72–82.

**40** Pérez-Ruixo C, Valenzuela B, Peris JE, Bretcha-Boix P, Escudero-Ortiz V, Farre-Alegre J, *et al*. Population pharmacokinetics of hyperthermic intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis after cytoreductive surgery. Cancer Chemother Pharmacol 2013; 71: 693–704.

**41** Leinwand JC, Bates GE, Allendorf JD, Chabot JA, Lewin SN, Taub RN. Body surface area predicts plasma oxaliplatin and pharmacokinetic advantage in hyperthermic intraoperative intraperitoneal chemotherapy. Ann Surg Oncol 2013; 20: 1101–4.

**42** Esteban-Fernandez D, Verdaguer JM, Ramirez-Camacho R, Palacios MA, Gomez-Gomez MM. Accumulation, fractionation, and analysis of platinum in toxicologically affected tissues after cisplatin, oxaliplatin, and carboplatin administration. J Anal Toxicol 2008; 32: 140–6.

**43** Mahteme H, Wallin I, Glimelius B, Pahlman L, Ehrsson H. Systemic exposure of the parent drug oxaliplatin during hyperthermic intraperitoneal perfusion. Eur J Clin Pharmacol 2008; 64: 907–11.

**44** Pfeiffer P, Sorbye H, Ehrsson H, Fokstuen T, Mortensen JP, Baltesgard L, *et al*. Short-time infusion of oxaliplatin in combination with capecitabine (XELOX30) as second-line therapy in patients with advanced colorectal cancer after failure to irinotecan and 5-fluorouracil. Ann Oncol 2006; 17: 252–8.

**45** Kusamura S, Dominique E, Baratti D, Younan R, Deraco M. Drugs, carrier solutions and temperature in hyperthermic intraperitoneal chemotherapy. J Surg Oncol 2008; 98: 247–52.

**46** Ceelen WP, Peeters M, Houtmeyers P, Breusegem C, De Somer F, Pattyn P. Safety and efficacy of hyperthermic intraperitoneal chemoperfusion with high-dose oxaliplatin in patients with peritoneal carcinomatosis. Ann Surg Oncol 2008; 15: 535–41.

**47** De Somer F, Ceelen W, Delanghe J, De Smet D, Vanackere M, Pattyn P, *et al*. Severe hyponatremia, hyperglycemia, and hyperlactatemia are associated with intraoperative hyperthermic intraperitoneal chemoperfusion with oxaliplatin. Perit Dial Int 2008; 28: 61–6.

**48** Rueth NM, Murray SE, Huddleston SJ, Abbott AM, Greeno EW, Kirstein MN, *et al*. Severe electrolyte disturbances after hyperthermic intraperitoneal chemotherapy: oxaliplatin versus mitomycin C. Ann Surg Oncol 2011; 18: 174–80.

**49** Stewart CL, Gleisner A, Halpern A, Ibrahim-Zada I, Luna RA, Pearlman N, *et al*. Implications of hyperthermic intraperitoneal chemotherapy perfusion-related hyperglycemia. Ann Surg Oncol 2017; 25: 655–9.

**50** Smith E, Brock AP. The effect of reduced osmolarity on platinum drug toxicity. Br J Cancer 1989; 59: 873–5.

**51** Tsujitani S, Oka A, Kondo A, Katano K, Oka S, Saito H, *et al*. Administration in a hypotonic solution is preferable to dose escalation in intraperitoneal cisplatin chemotherapy for peritoneal carcinomatosis in rats. Oncology 1999; 57: 77–82.

**52** Elias D, El Otmany A, Bonnay M, Paci A, Ducreux M, Antoun S, *et al*. Human pharmacokinetic study of heated intraperitoneal oxaliplatin in increasingly hypotonic solutions after complete resection of peritoneal carcinomatosis. Oncology 2002; 63: 346–52.

**53** Perez-Ruixo C, Peris JE, Escudero-Ortiz V, Bretcha-Boix P, Farre-Alegre J, Perez-Ruixo JJ, *et al*. Rate and extent of oxaliplatin absorption after hyperthermic intraperitoneal administration in peritoneal carcinomatosis patients. Cancer Chemother Pharmacol 2014; 73: 1009–20.

**54** Mehta AM, Van den Hoven JM, Rosing H, Hillebrand MJ, Nuijen B, Huitema AD, *et al*. Stability of oxaliplatin in chloride-containing carrier solutions used in hyperthermic intraperitoneal chemotherapy. Int J Pharm 2015; 479: 23–7.

**55** Mehta AM, Huitema AD, Burger JW, Brandt-Kerkhof AR, van den Heuvel SF, Verwaal VJ. Standard clinical protocol for bidirectional hyperthermic intraperitoneal chemotherapy (HIPEC): systemic leucovorin, 5-fluorouracil, and heated intraperitoneal oxaliplatin in a chloride-containing carrier solution. Ann Surg Oncol 2017; 24: 990–7.

**56** Los G, Mutsaers PH, van der Vijgh WJ, Baldew GS, de Graaf PW, McVie JG. Direct diffusion of cis-diamminedichloroplatinum (II)

in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. Cancer Res 1989; 49: 3380–4.

**57** Piché N, Leblond FA, Sideris L, Pichette V, Drolet P, Fortier LP, *et al*. Rationale for heating oxaliplatin for the intraperitoneal treatment of peritoneal carcinomatosis: a study of the effect of heat on intraperitoneal oxaliplatin using a murine model. Ann Surg 2011; 254: 138–44.

**58** Badrudin D, Sideris L, Leblond FA, Pichette V, Cloutier AS, Drolet P, *et al*. Rationale for the administration of systemic 5-FU in combination with heated intraperitonal oxaliplatin. Surg Oncol 2018; 27: 275–9.

**59** Oei AL, Vriend LE, Crezee J, Franken NA, Krawczyk PM. Effects of hyperthermia on DNA repair pathways: one treatment to inhibit them all. Radiat Oncol 2015; 10: 165.

**60** Toraya-Brown S, Fiering S. Local tumour hyperthermia as immunotherapy for metastatic cancer. Int J Hyperthermia 2014; 30: 531–9.

**61** Rietbroek RC, van de Vaart PJ, Haveman J, Blommaert FA, Geerdink A, Bakker PJ, *et al*. Hyperthermia enhances the cytotoxicity and platinum-DNA adduct formation of lobaplatin and oxaliplatin in cultured SW 1573 cells. J Cancer Res Clin Oncol 1997; 123: 6–12.

**62** Facy O, Combier C, Poussier M, Magnin G, Ladoire S, Ghiringhelli F, *et al*. High pressure does not counterbalance the advantages of open techniques over closed techniques during heated intraperitoneal chemotherapy with oxaliplatin. Surgery 2015; 157: 72–8.

**63** Ortega-Deballon P, Facy O, Jambet S, Magnin G, Cotte E, Beltramo JL, *et al*. Which method to deliver hyperthermic intraperitoneal chemotherapy with oxaliplatin? An experimental comparison of open and closed techniques. Ann Surg Oncol 2010; 17: 1957–63.

**64** Elias D, Antoun S, Raynard B, Puizillout JM, Sabourin JC, Ducreux M, *et al*. Treatment of peritoneal carcinomatosis using complete excision and intraperitoneal chemohyperthermia. A phase I-II study defining the best technical procedures. Chirurgie 1999; 124: 380–9.

**65** Royer B, Guardiola E, Polycarpe E, Hoizey G, Delroeux D, Combe M, *et al*. Serum and intraperitoneal pharmacokinetics of cisplatin within intraoperative intraperitoneal chemotherapy: influence of protein binding. Anticancer Drugs 2005; 16: 1009–16.

**66** Royer B, Delroeux D, Guardiola E, Combe M, Hoizey G, Montange D, *et al*. Improvement in intraperitoneal intraoperative cisplatin exposure based on pharmacokinetic analysis in patients with ovarian cancer. Cancer Chemother Pharmacol 2008; 61: 415–21.

**67** de Lima Vazquez V, Stuart OA, Mohamed F, Sugarbaker PH. Extent of parietal peritonectomy does not change intraperitoneal chemotherapy pharmacokinetics. Cancer Chemother Pharmacol 2003; 52: 108–12.

**68** Perez-Ruixo C, Valenzuela B, Peris JE, Bretcha-Boix P, Escudero-Ortiz V, Farre-Alegre J, *et al*. Neutrophil dynamics in peritoneal carcinomatosis patients treated with cytoreductive surgery and hyperthermic intraperitoneal oxaliplatin. Clin Pharmacokinet 2013; 52: 1111–25.

**69** Perez-Ruixo C, Valenzuela B, Peris JE, Bretcha-Boix P, Escudero-Ortiz V, Farre-Alegre J, *et al*. Platelet dynamics in peritoneal carcinomatosis patients treated with cytoreductive surgery and hyperthermic intraperitoneal oxaliplatin. AAPS J 2016; 18: 239–50.

**70** Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, *et al*. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 2000; 18: 136–47.

**71** Van der Speeten K, Stuart OA, Sugarbaker PH. Pharmacokinetics and pharmacodynamics of perioperative cancer chemotherapy in peritoneal surface malignancy. Cancer J 2009; 15: 216–24.

**72** Van der Speeten K, Stuart OA, Mahteme H, Sugarbaker PH. Pharmacology of perioperative 5-fluorouracil. J Surg Oncol 2010; 102: 730–5.

**73** Grass F, Vuagniaux A, Teixeira-Farinha H, Lehmann K, Demartines N, Hubner M. Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis. Br J Surg 2017; 104: 669–78.

**74** Clevers H. Modeling development and disease with organoids. Cell 2016; 165: 1586–97.

**75** Roy P, Canet-Jourdan C, Annereau M, Zajac O, Gelli M, Broutin S, *et al*. Organoids as preclinical models to improve intraperitoneal chemotherapy effectiveness for colorectal cancer patients with peritoneal metastases: preclinical models to improve HIPEC. Int J Pharm 2017; 531: 143–52.

**76** Harding SD, Sharman JL, Faccenda E, Southan C, Pawson AJ, Ireland S, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. Nucl Acids Res 2018; 46: D1091–106.