



# Systemic Pharmacokinetics of Oxaliplatin After Intraperitoneal Administration by Electrostatic Pressurized Intraperitoneal Aerosol Chemotherapy (ePIPAC) in Patients with Unresectable Colorectal Peritoneal Metastases in the CRC-PIPAC Trial

Robin J. Lurvink, MD<sup>1</sup>, Rudaba Tajzai, BSc<sup>1,2</sup>, Koen P. Rovers, MD<sup>1</sup>, Emma C. E. Wassenaar, MD<sup>3</sup>, Dirk-Jan A. R. Moes, PharmD PhD<sup>4</sup>, Giulia Pluimakers, BSc<sup>2</sup>, Djamila Boerma, MD PhD<sup>3</sup>, Jacobus W. A. Burger, MD PhD<sup>1</sup>, Simon W. Nienhuijs, MD PhD<sup>1</sup>, Ignace H. J. T. de Hingh, MD PhD<sup>1,5</sup>, and Maarten J. Deenen, PharmD PhD<sup>2,4</sup>

<sup>1</sup>Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands; <sup>2</sup>Department of Clinical Pharmacy, Catharina Hospital Eindhoven, Eindhoven, The Netherlands; <sup>3</sup>Department of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands; <sup>4</sup>Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands; <sup>5</sup>GROW - School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands

## ABSTRACT

**Background.** Electrostatic pressurized intraperitoneal aerosol chemotherapy (ePIPAC) is a palliative treatment for unresectable peritoneal metastases from various primary cancers. However, little is known about the systemic pharmacokinetics of oxaliplatin after ePIPAC.

**Methods.** Twenty patients with unresectable colorectal peritoneal metastases were treated with repetitive ePIPAC monotherapy with oxaliplatin (92 mg/m<sup>2</sup>) and a simultaneous intravenous bolus of leucovorin (20 mg/m<sup>2</sup>) and 5-fluorouracil (400 mg/m<sup>2</sup>). Samples were collected during each ePIPAC: whole blood at  $t = 0, t = 5, t = 10, t = 20, t = 30, t = 60, t = 120, t = 240, t = 360$  and  $t = 1080$  min

for plasma and plasma ultrafiltrate concentrations; urine at  $t = 0, t = 1, t = 3, t = 5$  and  $t = 7$  days. Samples were analyzed using atomic absorption spectrometry. Pharmacokinetics were analyzed using nonlinear mixed-effects modeling.

**Results.** Four patients received one ePIPAC, three patients received two ePIPAC, and thirteen patients received  $\geq 3$  ePIPAC. The population pharmacokinetic models adequately described the pharmacokinetics of oxaliplatin after ePIPAC. The plasma ultrafiltrate  $C_{\max}$  of oxaliplatin reached 1.36–1.90  $\mu\text{g/mL}$  after 30 min with an  $\text{AUC}_{0-24 \text{ h}}$  of 9.6–11.7  $\mu\text{g/mL} \cdot \text{h}$ . The plasma  $C_{\max}$  reached 2.67–3.28  $\mu\text{g/mL}$  after 90 min with an  $\text{AUC}_{0-24 \text{ h}}$  of 49.0–59.5  $\mu\text{g/mL} \cdot \text{h}$ . The absorption rate constant ( $K_a$ ) was 1.13/h. Urine concentrations of oxaliplatin rapidly decreased to less than 3.60  $\mu\text{g/mL}$  in 90% of the samples at day 7.

**Discussion.** Systemic exposure to oxaliplatin after ePIPAC seemed comparable to that after systemic chemotherapy, as described in other literature. Since this is an indirect comparison, future research should focus on the direct comparison between the systemic exposure to oxaliplatin after ePIPAC and after systemic chemotherapy.

**Trial registration:** NCT03246321, Pre-results; ISRCTN89947480, Pre-results; NTR6603, Pre-results; EudraCT: 2017-000927-29, Pre-results.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1245/s10434-020-08743-9>) contains supplementary material, which is available to authorized users.

Robin J. Lurvink and Rudaba Tajzai contributed equally to this manuscript and share the first authorship.

© Society of Surgical Oncology 2020

First Received: 2 April 2020;  
Published Online: 22 June 2020

M. J. Deenen, PharmD PhD  
e-mail: maarten.deenen@catharinaziekenhuis.nl

## INTRODUCTION

Peritoneal metastases (PM) are a frequent occurrence in patients with colorectal cancer, affecting about 10–15% of patients and severely diminishing their prognosis.<sup>1–4</sup> These patients can be treated with cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (CRS and HIPEC), or with palliative systemic chemotherapy. Intraperitoneal therapies have been developed since most patients do not qualify for CRS and HIPEC, and palliative systemic chemotherapy is considered less effective against PM as compared to liver or pulmonary metastases.<sup>1,5,6</sup>

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a recently developed intraperitoneal therapy. With this technique, a low dose of chemotherapeutic agent is aerosolized into the abdominal cavity by a laparoscopic approach, theoretically leading to: (1) high intraperitoneal concentrations, but low systemic concentrations and low systemic toxicity, (2) a homogeneous distribution, and (3) deep local tissue penetration.<sup>7–15</sup> The addition of electrostatic precipitation to the aerosol could result in a greater tissue penetration of the chemotherapeutic agent (ePIPAC).<sup>16–18</sup>

During (e)PIPAC for colorectal cancer, current protocols typically use oxaliplatin at a dosage of 92 mg/m<sup>2</sup> with a simultaneous intravenous bolus of 5-fluorouracil (400 mg/m<sup>2</sup>) with leucovorin (20 mg/m<sup>2</sup>), which is considerably lower than the oxaliplatin dosage used during HIPEC (460 mg/m<sup>2</sup>).<sup>19–22</sup>

HIPEC with oxaliplatin results in high concentrations of oxaliplatin in peritoneal fluid and tumor tissue, with relatively limited systemic concentrations.<sup>20,23–26</sup> Nevertheless, the pharmacokinetics of oxaliplatin administered by PIPAC have only been investigated in one animal study, and not yet in humans.<sup>15</sup>

The CRC-PIPAC trial was performed to investigate the feasibility, safety, efficacy, systemic pharmacokinetics, quality of life, and costs of repetitive ePIPAC with oxaliplatin in patients with PM from colorectal cancer.<sup>27</sup> The current manuscript aimed to analyze the systemic pharmacokinetics of oxaliplatin in plasma, plasma ultrafiltrate, peritoneal fluid, and urine after intraperitoneal administration by ePIPAC.

## MATERIALS AND METHODS

A prospective, single-arm, open-label, phase II study was performed in two Dutch HIPEC centers. The Central Medical Ethics Committee (MEC-U, Nieuwegein, Netherlands, R17.038) and institutional review boards of the participating institutions approved of the study, and the principles of the Declaration of Helsinki were followed. The study protocol has recently been published.<sup>27</sup> Therefore, we will only provide a brief summary.

### *Patient Population*

Patients were eligible to participate if they were older than 18 years with a WHO performance status of 0–1, and were diagnosed with unresectable colorectal/appendiceal PM without systemic metastases, did not present with symptoms of obstruction, had adequate organ functions, did not have any contra-indications for laparoscopy or chemotherapy, and no previous (e)PIPACs. All patients provided written informed consent.

### *ePIPAC Procedure*

Patients were treated with repetitive ePIPAC under general anesthesia with oxaliplatin (92 mg/m<sup>2</sup>) and a simultaneous intravenous bolus of leucovorin (20 mg/m<sup>2</sup> in 10 min) and 5-fluorouracil (400 mg/m<sup>2</sup> in 15 min) every 6 weeks, and did not receive systemic therapy in between subsequent ePIPAC procedures. The intravenous bolus of leucovorin and 5-fluorouracil is infused during laparoscopic surgery, after which the intraperitoneal injection of oxaliplatin is subsequently started. Oxaliplatin was prepared in a total volume of 150 mL dextrose solution and injected through the nebulizer (CapnoPen, Capnomed GmbH, Villingendorf, Germany) in 5 min, after which the Ultravision generator (Ultravision, Alesi Surgical, Cardiff, UK) administered electrostatic precipitation to the aerosol. The electrostatic field and the 12 mm Hg capnoperitoneum were then maintained at 37 °C for another 25 min. A detailed description of the general PIPAC procedure has also been reported by Solass et al.<sup>7</sup> and Giger-Pabst et al.<sup>28</sup>

Trial treatment could have been terminated due to disease progression, toxicity, at the patient's request, or at a physician's discretion. For a complete description of the ePIPAC procedure and evaluation schedule, we refer to the study protocol.<sup>27</sup>

### *Sample Collection and Analysis*

We collected samples of whole blood, urine, and peritoneal fluid at multiple moments after each ePIPAC. Sampling was performed at each procedure to study any potential accumulation and intra-individual variation. All samples were stored at – 80 °C until analysis.

Whole blood was collected at  $t = 0, 5, 10, 20, 30, 60, 120, 240, 360,$  and 1080 min after the start of injection of oxaliplatin. Whole blood samples were immediately cooled on ice and centrifuged for 5 min at 2000×g at 4 °C. One ml from the obtained plasma was loaded on an Ultrafree Millipore membrane (Merck Millipore Ltd., Tullagreen, Carrigtwohill, Co. Cork, Ireland) and ultrafiltered for 20 min at 2000×g at 4 °C to obtain plasma ultrafiltrate (free fraction of oxaliplatin).

Single urine samples were collected pre-operatively and at  $t = 1, 3, 5,$  and  $7$  days after the injection of oxaliplatin; peritoneal fluid was collected at  $t = 30$  min after the injection of oxaliplatin.

Oxaliplatin concentrations were measured using atomic absorption spectrometry on a Thermo Fisher Solaar ICE 3500 graphite-furnace spectrophotometer with Zeeman correction (Thermo Fisher Scientific, Bremen, Germany).

### Pharmacokinetic Analysis

Pharmacokinetic parameters were estimated using two differently developed population pharmacokinetic models based on the oxaliplatin plasma and plasma ultrafiltrate concentration–time data, respectively, by non-linear mixed-effects modeling using NONMEM (V7.4, Icon Development Solutions, Ellicott City, MD, USA). The Perl-speaks-NONMEM toolkit version 4.7.0 and Pirana version 2.9.7 were used as modeling environment. Results were plotted using R statistics (v3.4.4, Boston, MA, USA) and RStudio (v1.1.453). A first-order conditional estimation method with interaction was used throughout the analysis. One, two and three compartmental pharmacokinetic models with first order elimination were compared with the observed oxaliplatin plasma and plasma ultrafiltrate concentration–time data to find the optimal fit. Model selection was based on statistical significance, goodness of fit and stability. Throughout the model building process, an altered model was chosen over a pre-cursor model if the difference in the objective functions ( $-2 \log$  likelihood) was  $> 6.63$  ( $P < 0.01$ , with 1 degree of freedom, assuming  $\chi^2$  distribution). The final population pharmacokinetic model was validated by means of a prediction corrected visual predictive check (500 runs). Subsequently, exposure ( $AUC_{0-24}$  and  $AUC_{0-48}$ ) was calculated using the individual predicted values (concentration) and time data using the trapezoidal rule with R statistics.

## RESULTS

### Patient Characteristics

Between October 2017 and April 2019, twenty patients were treated with repetitive ePIPAC: four (20%) patients only received one ePIPAC, three (15%) patients received two ePIPAC, and thirteen (65%) patients received three or more ePIPAC. All patients received the intended dose of chemotherapeutic agents. No dose reductions were required due to systemic toxicity, including peripheral neuropathy. Twelve (60%) patients were male and eight (40%) patients were female. The median age was 63.5 years. Most patients had synchronous peritoneal

metastases ( $n = 15, 75%$ ) from a right-sided ( $n = 14, 70%$ ) colorectal adenocarcinoma that had not been resected ( $n = 14, 70%$ ). Nine patients (45%) had been treated with palliative systemic chemotherapy before study inclusion, of whom eight patients received an oxaliplatin-containing regimen, and nine patients (45%) had undergone an explorative laparotomy with the intention of CRS and HIPEC, which all resulted in an open-close procedure. The baseline characteristics are provided in Table 1.

### Pharmacokinetics of Plasma and Plasma Ultrafiltrate

Oxaliplatin pharmacokinetics in plasma were best described by a 2-compartment model with first order absorption from the peritoneal compartment with first order elimination, as shown in supplementary Fig. 1. Oxaliplatin pharmacokinetics in the ultrafiltrate were best described by a 3-compartment model with first order absorption from the peritoneal compartment with first order elimination with allometric scaling. Random effect parameters for inter-individual variability in absorption, clearance, distribution volume of the central compartment and the peripheral compartment, and intercompartmental clearance were identified. The concentration–time profiles of oxaliplatin in plasma and plasma ultrafiltrate are provided in Figs. 1 and 2, respectively. Both models performed well, although the plasma model proved to be slightly more accurate than the plasma UF model due to denser sampling (goodness of fit plots as supplementary Figs. 2 and 3).

Table 2 provides the calculated estimates of the pharmacokinetic parameters of oxaliplatin in plasma and plasma ultrafiltrate (UF) after the first, second and third ePIPAC. The maximum concentration of oxaliplatin ( $C_{max}$ ) in plasma UF and in plasma varied between 1.36 and 1.90  $\mu\text{g/mL}$  and between 2.67 and 3.28  $\mu\text{g/mL}$ , respectively. The maximum concentrations of oxaliplatin in plasma UF and in plasma were reached after approximately 30 and 90 min ( $T_{max}$ ), respectively. The median plasma UF  $AUC_{0-24 \text{ h}}$  varied between 9.6 and 11.7  $\mu\text{g/mL} \cdot \text{h}$ . The median plasma  $AUC_{0-24 \text{ h}}$  varied between 49.0 and 59.5  $\mu\text{g/mL} \cdot \text{h}$ , and the median plasma  $AUC_{0-48 \text{ h}}$  varied between 95.4 and 114.9  $\mu\text{g/mL} \cdot \text{h}$ .

The  $C_{max}$ , the  $AUC_{0-24 \text{ h}}$ , and the  $AUC_{0-48 \text{ h}}$  of oxaliplatin in both plasma UF and plasma increased significantly from the first to the second and third ePIPAC.

Finally, the absorption rate constant ( $K_a$ ) was 1.13 (1.04–1.30) L/h.

### Pharmacokinetics of Urine and Peritoneal Fluid

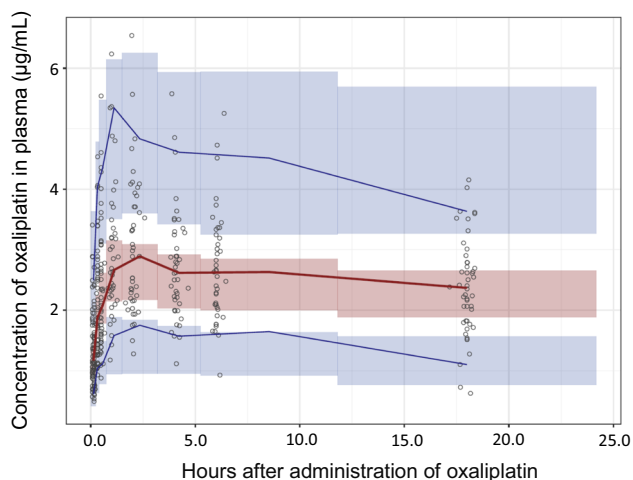
Figure 3 shows the concentration of oxaliplatin in urine during the first week after each ePIPAC. Concentrations were highest on the first day after ePIPAC after which a

**TABLE 1** Baseline characteristics

Characteristic	Category	N = 20
Gender	Male	12 (60%)
	Female	8 (40%)
Age (years)		63.5 (57.0–69.8)
Location of primary tumor	Appendix	6 (30%)
	Ascending colon	8 (40%)
	Descending colon	6 (30%)
Histology of primary tumor	(Mucinous) adenocarcinoma	11 (55%)
	(Mucinous) adenocarcinoma with SRC	7 (35%)
	LAMN	2 (10%)
Primary tumor resection	Yes	6 (30%)
	No	14 (70%)
Diagnosis of PM	Synchronous	15 (75%)
	Metachronous	5 (25%)
Previous treatment of PM	None	7 (35%)
	Palliative systemic chemotherapy	9 (45%)
	Attempt at CRS and HIPEC	9 (45%)

All values are median (IQR) or n (%)

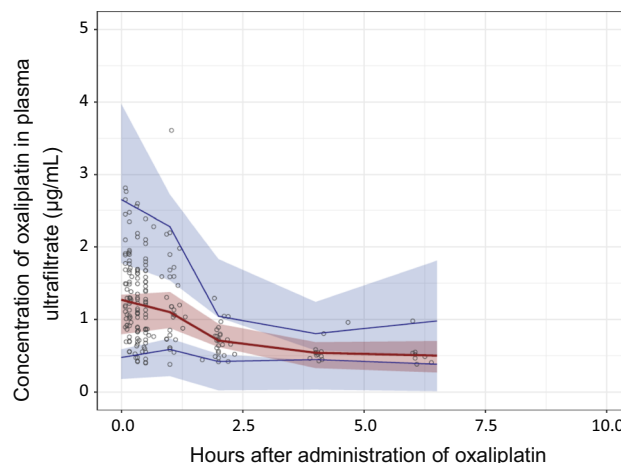
SRC Signet ring cell differentiation, LAMN low grade appendiceal mucinous neoplasm, PM peritoneal metastases, CRS cytoreductive surgery, HIPEC hyperthermic intraperitoneal chemotherapy



**FIG. 1** Prediction corrected visual predictive check for the concentration of oxaliplatin in plasma. The red line represents the median and the blue lines represent the 10th and 90th observation percentiles. The observed oxaliplatin concentrations are shown as open circles. The shaded areas represent the 95% confidence interval around each of the prediction percentiles

rapid decrease was observed. At day 3, 90% of the urine samples were below 8.70 µg/mL; at day 5, 90% of the samples were below 4.90 µg/mL; at day 7, 90% of the samples were below 3.60 µg/mL. With the applied method of analysis (AAS), no accumulation of oxaliplatin could be detected between the various ePIPAC procedures.

The concentrations of oxaliplatin in peritoneal fluid 30 min after the start of the injection are shown in Fig. 4. The

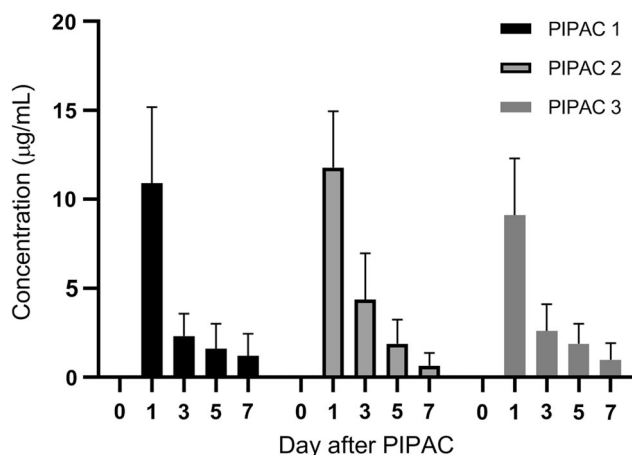


**FIG. 2** Prediction corrected visual predictive check for the concentration of oxaliplatin in plasma ultrafiltrate. The red line represents the median and the blue lines represent the 10th and 90th observation percentiles. The observed oxaliplatin concentrations are shown as open circles. The shaded areas represent the 95% confidence interval around each of the prediction percentiles

highest concentration was found after the first ePIPAC, although the differences in concentrations after the second and third ePIPAC were not statistically significant ( $p = 0.38$ ).

## DISCUSSION

This study aimed to describe the systemic pharmacokinetics of oxaliplatin administered by ePIPAC, and was the first to do so in humans. ePIPAC with oxaliplatin (92 mg/

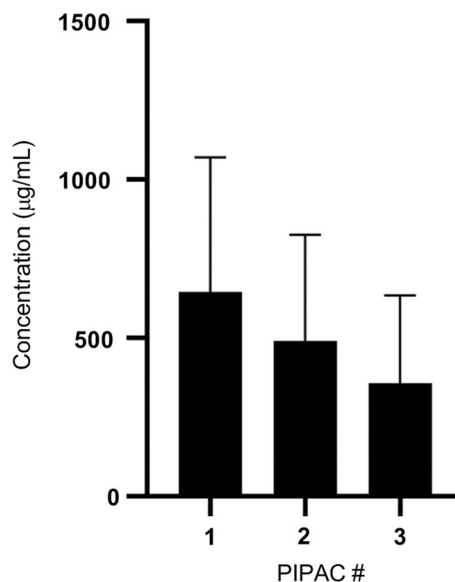


**FIG. 3** Concentration of oxaliplatin (µg/mL) in urine during the first week after injection of oxaliplatin

m<sup>2</sup>) resulted in significant systemic concentrations. After 7 days, the excretion of oxaliplatin in urine had decreased to less than 3.60 µg/mL in 90% of the samples. No accumulation of oxaliplatin was observed between the ePIPAC-procedures.

Remarkably, the C<sub>max</sub> and AUC of oxaliplatin of plasma and plasma UF increased significantly during the second and the third ePIPAC. This increase was an unexpected finding, and might potentially be due to the fact that the extent of peritoneal disease decreased during treatment, thereby obtaining a greater “healthy” surface area available for systemic drug absorption, subsequently leading to a higher AUC. However, this is only a hypothesis, and this finding of increased systemic exposure with an increasing number of PIPAC will have to be confirmed in another pharmacokinetic study.

Oxaliplatin has been part of systemic chemotherapy protocols and has been used as a HIPEC drug for several decades. The pharmacokinetics of oxaliplatin after systemic administration or intraperitoneal administration by HIPEC have been described by several research groups.



**FIG. 4** Concentration of oxaliplatin (µg/mL) in peritoneal fluid, 30 min after injection of oxaliplatin

With systemic chemotherapy, oxaliplatin is administered in a dose of 130 mg/m<sup>2</sup> or of 85 mg/m<sup>2</sup>, depending on the combination with either capecitabine (CAPOX/XELOX) in a 3-weekly schedule or 5-fluorouracil/leucovorin (FOLFOX) in a 2-weekly schedule, respectively. Since our ePIPAC regimen with oxaliplatin (92 mg/m<sup>2</sup>) and an intravenous bolus of 5-fluorouracil/leucovorin (400/20 mg/m<sup>2</sup>) resembles the oxaliplatin component of a systemic cycle of FOLFOX, we compared our pharmacokinetic results with the pharmacokinetics of systemic chemotherapy with FOLFOX as described by other studies.<sup>29,30</sup> After intravenous administration of 85 mg/m<sup>2</sup> oxaliplatin, these studies described a C<sub>max</sub> of 1.61–1.92 µg/mL in plasma and of 0.38–0.68 µg/mL in plasma UF, which is slightly lower than the C<sub>max</sub> of oxaliplatin after ePIPAC found in our study (2.67–3.28 µg/mL and 1.36–1.90 µg/mL, respectively). The most likely explanation for the lower

**TABLE 2** Pharmacokinetics of oxaliplatin in plasma and plasma ultrafiltrate

	PIPAC 1 (n = 20)	PIPAC 2 (n = 16)	PIPAC 3 (n = 13)	P value
C <sub>max</sub> plasma (µg/mL)	2.67 (2.15–3.27)	2.92 (2.36–4.14)	3.28 (2.76–4.19)	0.039
C <sub>max</sub> plasma UF (µg/mL)	1.36 (1.06–1.74)	1.38 (0.96–2.02)	1.90 (0.87–2.85)	0.016
T <sub>max</sub> plasma (min)	93 (60–233)	94 (62–169)	90 (37–122)	0.56
T <sub>max</sub> plasma UF (min)	30 (20–48)	30 (30–64)	30 (30–55)	0.57
AUC 24 h plasma (µg/mL * h)	49.0 (42.8–64.4)	59.2 (46.0–81.2)	59.5 (47.5–85.2)	0.001
AUC 24 h plasma UF (µg/mL * h)	9.6 (8.5–12.4)	11.7 (9.1–14.8)	11.7 (8.4–14.5)	0.001
AUC 48 h plasma (µg/mL * h)	95.4 (81.8–124.5)	111.0 (87.1–154.9)	114.9 (90.8–167.4)	0.001
Absorption rate constant (Ka)	1.13 (1.04–1.30)	–	–	–

All values are median (IQR)

AUC Area under the curve, C<sub>max</sub> maximum concentration; T<sub>max</sub> time to maximum concentration; UF ultrafiltrate



$C_{\max}$  of oxaliplatin after intravenous administration is that it is administered over a much longer time, up to 2–6 h, while the complete dose of oxaliplatin during ePIPAC is administered in less than 5 min. Another explanation for this difference could be the slightly higher dose of oxaliplatin used during ePIPAC, and the application of pressure and electrostatic precipitation during ePIPAC, possibly increasing absorption.<sup>9</sup>

Remarkably, the plasma AUC of oxaliplatin was comparable after intravenous administration and after ePIPAC (51.4–118.0  $\mu\text{g/mL}$  vs. 49.0–59.5  $\mu\text{g/mL}$ , respectively), whereas the plasma UF AUC of oxaliplatin was lower after intravenous administration, compared with other literature (4.3–4.8  $\mu\text{g/mL}$  vs. 9.6–11.7  $\mu\text{g/mL}$ , respectively).<sup>29,30</sup>

A much higher dose of oxaliplatin is used during HIPEC, varying from 360 to 460  $\text{mg/m}^2$ .<sup>24,26,31</sup> The  $C_{\max}$  in plasma and plasma UF following administration by HIPEC varied from 10.7 to 14.0  $\mu\text{g/mL}$  and 7.0 to 8.5  $\mu\text{g/mL}$ , respectively, which are roughly fivefold higher than the maximum concentrations of oxaliplatin after ePIPAC in our study.<sup>24,26,31</sup> This could be explained by the fivefold lower dose of oxaliplatin of 92  $\text{mg/m}^2$  that was used during ePIPAC.

In these studies, maximum concentrations of both plasma and plasma UF are reached after approximately 30 min ( $T_{\max}$ ). In our study, the plasma UF  $T_{\max}$  was 30 min as well, although the plasma  $T_{\max}$  was 90 min. This could partially be explained by the removal of oxaliplatin after 30 min of HIPEC, whereas oxaliplatin remains in the abdomen after ePIPAC, allowing further absorption.

In contrast to the  $C_{\max}$ , the AUC of plasma UF after ePIPAC is almost equal to the AUC of plasma UF after HIPEC (9.6–11.7  $\mu\text{g/mL} \cdot \text{h}$  and 13.7–14.8  $\mu\text{g/mL} \cdot \text{h}$ , respectively).<sup>24,26,31</sup> Although not the goal of ePIPAC, this suggests that equal levels of systemic exposure can be achieved with ePIPAC, and further justifies the fivefold lower dose used during ePIPAC as compared to HIPEC. Possible explanations are the application of pressure and electrostatic precipitation during ePIPAC, and the removal of chemotherapy from the abdominal cavity after 30 min of HIPEC, whereas oxaliplatin remains in the abdominal cavity after ePIPAC.

The absorption rate constant ( $K_a$ ) during ePIPAC was lower than during HIPEC (1.13/h vs. 1.40–1.42/h, respectively), which may be explained by the lower absolute dose of oxaliplatin used during ePIPAC as rate of absorption is dose-dependent with 1st order pharmacokinetics.<sup>24,26</sup>

Eveno et al. presented in-animal results of the pharmacokinetics of oxaliplatin after intravenous administration (5  $\text{mg/mL}$ ) and after PIPAC (0.028  $\text{mg/mL}$ ), resulting in a systemic concentration of 0.089  $\mu\text{g/mL}$  and 0.019  $\mu\text{g/mL}$  7 days after administration of oxaliplatin, respectively.<sup>15</sup> They found higher concentrations of oxaliplatin after

intravenous administration than after PIPAC ( $p = 0.008$ ). Unfortunately, we were not able to compare our results with Eveno et al., because their study was conducted in mice and therefore used different dosages of oxaliplatin. Also, in their study, the oxaliplatin concentration was only measured on one occasion after 7 days, which does not allow a complete pharmacokinetic analysis as was performed in our study.

### Limitations

This study has several limitations. First of all, it is limited by a small sample size and a non-controlled design, disabling direct comparison with the systemic pharmacokinetics of oxaliplatin after intravenous administration and after HIPEC. In addition to that, we were not able to accurately calculate the clearance of oxaliplatin from plasma due to too short sampling. The last sampling occasion was 18 h post-ePIPAC, after which the absorption and distribution phase proved to be not totally finished yet. This does not allow a proper estimation of the elimination phase—a final sample after, e.g., 48 h would have been required. Nonetheless, clearance and elimination rates are not expected to be different following administration by ePIPAC, HIPEC or intravenous infusion. As shown in the goodness of fit plots, the model for plasma is more accurate than the model for plasma UF, which is probably due to fewer plasma UF samples—we were not able to obtain sufficient ultrafiltrated plasma from some samples.

The sampling of peritoneal fluid was only performed once, 30 min after the start of the injection of oxaliplatin. Although this single measurement confirmed that oxaliplatin remained in the abdomen after the procedure and was thus still able to exert its anti-tumor effects, this measurement alone did not allow us to describe the AUC ratio of intraperitoneal and plasma oxaliplatin as has been described for various other drugs administered by HIPEC.<sup>32</sup>

Future research could elaborate on the direct comparison of the systemic absorption of oxaliplatin administered by ePIPAC and by systemic chemotherapy, allowing determination of the absolute bioavailability.

### Conclusion

To our knowledge, this is the first study to investigate the systemic pharmacokinetics of oxaliplatin administered by ePIPAC in humans. In conclusion, the systemic absorption of oxaliplatin administered by ePIPAC was higher than expected, reaching concentrations equal to those reached with systemic chemotherapy, as reported in other studies. This finding does not support one of the proclaimed benefits of ePIPAC: a decreased systemic

exposure and potentially less toxic profile compared with systemic administration. Additional sampling at 24 and/or 48 h after administration of ePIPAC could have increased the accuracy of the oxaliplatin plasma AUC and clearance. Oxaliplatin was mainly excreted during the first 7 days and no accumulation was observed. This allows repeated treatment with ePIPAC at 6-week intervals and potentially also more frequently without further increasing toxicity.

**ACKNOWLEDGEMENT** This study received funding from the Catharina Research Foundation and the St. Antonius Research Foundation.

**DISCLOSURE** None to declare.

## REFERENCES

- Razenberg LG, Lemmens VE, Verwaal VJ, et al. Challenging the dogma of colorectal peritoneal metastases as an untreatable condition: results of a population-based study. *Eur J Cancer*. 2016;65:113–20.
- Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49(6):1374–403.
- Klaver YL, Simkens LH, Lemmens VE, et al. Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and without targeted therapy. *Eur J Surg Oncol*. 2012;38(7):617–23.
- Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg*. 2006;243(2):212–22.
- 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(11):2717–25.
- Franko J, Shi Q, Meyers JP, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *Lancet Oncol*. 2016;17(12):1709–19.
- Solass W, Kerb R, Murdter T, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. *Ann Surg Oncol*. 2014;21(2):553–9.
- Reymond MA, Hu B, Garcia A, et al. Feasibility of therapeutic pneumoperitoneum in a large animal model using a microvaporisator. *Surg Endosc*. 2000;14(1):51–5.
- Jacquet P, Stuart OA, Chang D, Sugarbaker PH. Effects of intra-abdominal pressure on pharmacokinetics and tissue distribution of doxorubicin after intraperitoneal administration. *Anticancer Drugs*. 1996;7(5):596–603.
- Esquis P, Consolo D, Magnin G, et al. High intra-abdominal pressure enhances the penetration and antitumor effect of intraperitoneal cisplatin on experimental peritoneal carcinomatosis. *Ann Surg*. 2006;244(1):106–12.
- Solass W, Herbet A, Schwarz T, et al. Therapeutic approach of human peritoneal carcinomatosis with Dbait in combination with capnoperitoneum: proof of concept. *Surg Endosc*. 2012;26(3):847–52.
- Solass W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. *Surg Endosc*. 2012;26(7):1849–55.
- Facy O, Al Samman S, Magnin G, et al. High pressure enhances the effect of hyperthermia in intraperitoneal chemotherapy with oxaliplatin: an experimental study. *Ann Surg*. 2012;256(6):1084–8.
- Blanco A, Giger-Pabst U, Solass W, Zieren J, Reymond MA. Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Ann Surg Oncol*. 2013;20(7):2311–6.
- Eveno C, Haidara A, Ali I, Pimpie C, Mirshahi M, Pocard M. Experimental pharmacokinetics evaluation of chemotherapy delivery by PIPAC for colon cancer: first evidence for efficacy. *Pleura Peritoneum*. 2017;2(2):103–9.
- Williaert W, Sessink P, Ceelen W. Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Pleura Peritoneum*. 2017;2(3):121–8.
- Graversen M, Lundell L, Fristrup C, Pfeiffer P, Mortensen MB. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) as an outpatient procedure. *Pleura Peritoneum*. 2018;3(4):20180128.
- Kakchekeeva T, Demtroder C, Herath NI, et al. In Vivo Feasibility of Electrostatic Precipitation as an Adjunct to Pressurized Intraperitoneal Aerosol Chemotherapy (ePIPAC). *Ann Surg Oncol*. 2016;23(Suppl 5):592–8.
- Kuijpers AM, Mirck B, Aalbers AG, et al. Cytoreduction and HIPEC in the Netherlands: nationwide long-term outcome following the Dutch protocol. *Ann Surg Oncol*. 2013;20(13):4224–30.
- Elias D, Bonnay M, Puizillou JM, et al. Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. *Ann Oncol*. 2002;13(2):267–72.
- Demtroder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. *Colorectal Dis*. 2016;18(4):364–71.
- Nowacki M, Alyami M, Villeneuve L, et al. Multicenter comprehensive methodological and technical analysis of 832 pressurized intraperitoneal aerosol chemotherapy (PIPAC) interventions performed in 349 patients for peritoneal carcinomatosis treatment: An international survey study. *Eur J Surg Oncol*. 2018;44(7):991–6.
- 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(9):907–11.
- Ferron G, Dattez S, Gladieff L, et al. Pharmacokinetics of heated intraperitoneal oxaliplatin. *Cancer Chemother Pharmacol*. 2008;62(4):679–83.
- Perez-Ruixo C, Valenzuela B, Peris JE, et al. Population pharmacokinetics of hyperthermic intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis after cytoreductive surgery. *Cancer Chemother Pharmacol*. 2013;71(3):693–704.
- Chalret du Rieu Q, White-Koning M, Picaud 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(3):571–82.
- Rovers KP, Lurvink RJ, Wassenaar EC, et al. Repetitive electrostatic pressurized intraperitoneal aerosol chemotherapy (ePIPAC) with oxaliplatin as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases: protocol of a

- Dutch, multicentre, open-label, single-arm, phase II study (CRC-PIPAC). *BMJ Open*. 2019;9(7):e030408.
28. Giger-Pabst U, Tempfer CB. How to Perform Safe and Technically Optimized Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): Experience After a Consecutive Series of 1200 Procedures. *J Gastrointest Surg*. 2018;22(12):2187–93.
  29. Graham MA, Lockwood GF, Greenslade D, Brienza S, Bayssas M, Gamelin E. Clinical pharmacokinetics of oxaliplatin: a critical review. *Clin Cancer Res*. 2000;6(4):1205–18.
  30. Burz C, Berindan-Neagoe IB, Balacescu O, et al. Clinical and pharmacokinetics study of oxaliplatin in colon cancer patients. *J Gastrointest Liver Dis*. 2009;18(1):39–43.
  31. Elias DM, Sideris L. Pharmacokinetics of heated intraoperative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis. *Surg Oncol Clin N Am*. 2003;12(3):755–69.
  32. Goodman MD, McPartland S, Detelic D, Saif MW. Chemotherapy for intraperitoneal use: a review of hyperthermic intraperitoneal chemotherapy and early post-operative intraperitoneal chemotherapy. *J Gastrointest Oncol*. 2016; 7(1):45–47.

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.