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CASE REPORT

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Dosing oxaliplatin in a haemodialysis patient with metastatic rectum cancer monitored by free platinum concentrations

I. R. F. van Berlo – van de Laar PharmD[1] | W. J. Brummelhuis MD, PhD[2] | A. L. T. Imholz MD, PhD[3] | J. H. Schellens PharmD[2,4] | A. D. R. Huitema PharmD[2,5] | F. G. A. Jansman PharmD, PhD[1,6]

[1]Department of Clinical Pharmacy, Deventer Hospital, Deventer, The Netherlands

[2]Department of Clinical Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

[3]Department of Internal Medicine, Deventer Hospital, Deventer, The Netherlands

[4]Utrecht Institute of Pharmaceutical Sciences, Utrecht, The Netherlands

[5]Department of Clinical Pharmacy, University Medical Centre Utrecht, Utrecht, The Netherlands

[6]Unit of PharmacoTherapy, -Epidemiology &-Economics, Groningen Research Institute of Pharmacy (GRIP), University of Groningen, Groningen, The Netherlands

Correspondence
I. R. F. van Berlo – van de Laar, Department of Clinical Pharmacy, Deventer Hospital, Deventer, The Netherlands.
Email: i.vanberlo-vandelaar@dz.nl

Summary

What is known and objective: Oxaliplatin in combination with fluorouracil and folinic acid is one of the preferred chemotherapeutic options in the treatment of metastatic rectum cancer. However, oxaliplatin is contraindicated in patients with a creatinine clearance <30 mL/min and dosing guidelines in patients on haemodialysis have not been established.

Case summary: A 77-year-old haemodialysis patient with metastatic rectum cancer was treated with FOLFOX and bevacizumab (oxaliplatin 70 mg/m^2, folinic acid 200 mg/m^2, 5-FU 340 mg/m^2 bolus and 2040 mg/m^2 continuous infusion during 44 hours and bevacizumab 5 mg/kg) every three weeks. Haemodialysis started immediately after infusion of oxaliplatin. The oxaliplatin dose was monitored by measuring free platinum ultrafiltrate concentrations. The $AUC_{0\text{-}50}$ of free platinum plasma ultrafiltrate after cycles 1-3, respectively, was 24.3, 24.7 and 25.8 μg*h/mL. The C_{max} was, respectively, 1.3, 1.3 and 2.2 μg/mL. There was no accumulation of free platinum detectable. The patient experienced no toxicity, and after 3 cycles, the CT scan showed a decrease in the liver metastases after which hemihepatectomy and metastasectomy were performed without any complications. A CT scan 6 months after the surgery showed no new liver metastases. However, lymphatic metastasis was diagnosed for which palliative treatment was started.

What is new and conclusion: Dosing oxaliplatin in a haemodialysis patient monitored by free platinum concentrations was effective, safe and feasible in clinical practice. Further research is needed to determine the best pharmacokinetic parameter or combination of parameters and corresponding target values to further optimize the oxaliplatin dose for the individual haemodialysis patient.

KEYWORDS
colorectal cancer, FOLFOX, free platinum concentration, haemodialysis, oxaliplatin

1 | WHAT IS KNOWN AND OBJECTIVE

The number of haemodialysis patients with colorectal cancer is increasing as a result of earlier recognition of colorectal cancer and improvements in dialysis treatments. Oxaliplatin in combination with fluorouracil and folinic acid represents the standard adjuvant treatment in colorectal cancer and is also one of the preferred chemotherapeutic options in the metastatic setting. Oxaliplatin binds covalently to DNA forming inter- and intrastrand cross-links that block DNA transcription and replication ultimately resulting in cell death. Major side effects are mild

myelosuppression, moderate nausea and vomiting, and dose-limiting neuropathies.[1] Oxaliplatin is mainly eliminated through the kidneys. There is a strong correlation between glomerular filtration rate (GFR) and drug clearance measured as free platinum concentrations and also between GFR and free platinum area under the curve (AUC).[1-3] Formally, oxaliplatin is contraindicated in patients with a creatinine clearance <30 mL/min and dosing guidelines in patients on haemodialysis have not been established.[4] Only a few case reports of dosing oxaliplatin in haemodialysis patients have been published to date.[5-9] In this study, we investigated whether dosing of oxaliplatin in a haemodialysis patient with metastatic rectum cancer monitored by measuring free platinum plasma concentrations was effective, safe and feasible in clinical practice.

2 | DETAILS OF THE CASE

A 77-year-old male patient with renal insufficiency and chronic haemodialysis (3 times a week) since 2015 was diagnosed with metastatic rectum cancer in February 2016. The treatment plan consisted of neoadjuvant FOLFOX and bevacizumab followed by hemihepatectomy and metastasectomy. The combination chemotherapy consisted of the following: bevacizumab 5 mg/kg intravenous followed by oxaliplatin 70 mg/m^2 and folinic acid 200 mg/m^2 intravenous during a 2-hour infusion. 5-FU was then administered as a bolus injection of 340 mg/m^2, followed by continuous infusion of 5-FU 2040 mg/m^2 during 44 hours. A 4-hour haemodialysis session was started immediately after the bolus injection of 5-FU. For dialysis, a polyflux 170F dialyser and acetic acid-free dialysate containing Na 138, K 2.0, Ca 1.5, bicarbonate 34 mmol/L and glucose 1 g/L were used. The blood flow rate was set at 300 mL/min and the dialysate flow rate at 500 mL/min.

The oxaliplatin dose was based on the report of Horimatsu et al.[9] Because of formal instructions to consider dose reduction in 5-FU in renal failure, the dose of 5-FU was lowered by 15%. Because the elimination of bevacizumab is not dependant on renal function, the standard dose was maintained. The cycle was repeated every three weeks conform the report of Horimatsu et al.[9]

Free and total platinum concentrations were measured during the first 3 cycles. Blood samples were collected: before the start of oxaliplatin (t = 0 hour) and at the end of the oxaliplatin infusion (just before dialysis [t = 2 hour], t = 2.25 hour, t = 2.5 hour, t = 3 hour, t = 6 hour [at the end of the dialysis], t = 26 hour and t = 50 hour [just before the next dialysis session]). The blood samples were immediately centrifuged at 2000 g for 5 minutes. 1 mL of plasma per sample was centrifuged at 2000 g during 10 minutes in a 30-kD cut-off filter from Millipore. The ultrafiltrate and the remaining plasma samples were transported by a courier (storage condition −20°C) to the analysing laboratory. Free platinum and total platinum concentrations were measured by inductively coupled plasma mass spectrometry before the next cycle of chemotherapy as previously described.[10] The $AUC_{0\text{-}50}$ was calculated using the trapezoidal method. Figure 1 shows the free platinum concentrations during the 3 cycles. The results of the pharmacokinetic parameters C_0, C_{max} and the $AUC_{0\text{-}50}$ for total and free platinum are depicted in Table 1.

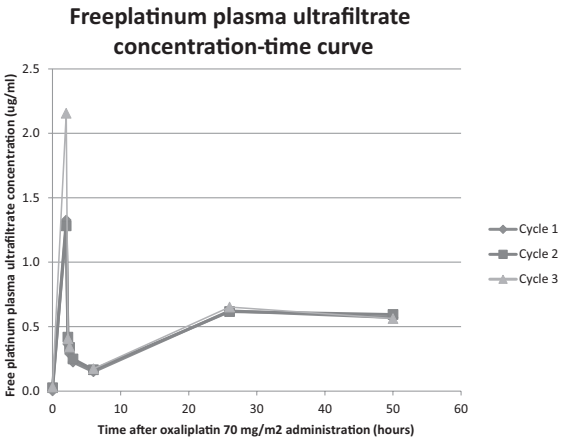

FIGURE 1 Free platinum plasma ultrafiltrate concentration-time curve

TABLE 1 Pharmacokinetic parameters of oxaliplatin 70 mg/m^2

	Cycle 1	Cycle 2	Cycle 3
Total platinum			
C_0 (μg/mL)	0	0.14	0.17
C_{max} (μg/mL)	2.2	2.5	2.7
$AUC_{0\text{-}50}$ (μg*h/mL)	71.2	81.7	80.2
Free platinum			
C_0 (μg/mL)	0	0.03	0.03
C_{max} (μg/mL)	1.3	1.3	2.2
$AUC_{0\text{-}50}$ (μg*h/mL)	24.3	24.7	25.8

AUC, area under the curve.

Adverse effects, blood pressure and laboratory parameters (myelosuppression) were monitored after each cycle. The C_{max} and the observed AUC were compared with the results published by Horimatsu et al[9] and Gori et al[6] to determine whether dose adaption was necessary. After 3 cycles, the efficacy was reviewed by performing a CT scan. The CT scan showed a decrease in the liver metastases according to the RECIST 1.1 criteria, and there was no indication of metastasis elsewhere in the body. Hemihepatectomy and metastasectomy were performed without any complications. A control CT scan 1 week after the surgery showed a fluid collection at the resection plane (differential diagnosis seroma, haematoma, biloma). One month later, a proctoscopy was performed because of rectal blood loss. There was no local recurrence of rectum carcinoma seen. Six months later, the liver fluid collection was encapsulated and slightly decreased. However, this CT scan showed lymphatic metastasis for which palliative treatment was started.

3 | WHAT IS NEW AND CONCLUSION

In plasma, oxaliplatin is rapidly and extensively converted into metabolites that rapidly form inactive conjugates. The pharmacokinetics

of unbound platinum in plasma ultrafiltrate after oxaliplatin administration is triphasic. The short initial alpha phase represents the rapid clearance of the biologically intact oxaliplatin and its metabolites via irreversibly binding to albumin and erythrocytes and via distribution into tissue compartments. The subsequent beta phase reflects the renal clearance of platinum-containing products. Finally, the long gamma phase is hypothesized to represent the slow release of platinum products arising from degradation of cellular macromolecules. Urinary elimination is the predominant route of elimination of free platinum.[1,3]

The generally accepted approach for monitoring platinum-containing anticancer agents, like carboplatin, is to determine platinum product concentrations as free platinum in plasma ultrafiltrate and total platinum in plasma. Free platinum in plasma ultrafiltrate is thought to represent the pharmacological and toxicological active fraction in blood.[1,10]

For oxaliplatin, the relation between free platinum AUC and pharmacological activity and toxicity is not as clear as for carboplatin.[1] The free platinum AUC is correlated with the GFR, but in several reports, the exposure of free platinum was not related to toxicity. However, the cumulative dose for neurotoxicity in these reports was not achieved and few patients were included.[1,2,11] When measuring free platinum concentrations, platinum from active as well as inactive forms is included. Possibly, the increased platinum exposure seen in renal-impaired patients with oxaliplatin is explained by inactive metabolites. Carboplatin is less rapidly inactivated and is less highly protein bound resulting in increased renal clearance. Consequently, platinum AUC after carboplatin is possibly more closely linked to its biological activity compared to oxaliplatin.

The findings of Giacchetti et al[12] suggest that the antitumor activity of oxaliplatin does not correlate with the AUC of free platinum, but haematological toxicity correlates with the C_{max}. In our patient, the average free platinum $AUC_{0\text{-}50}$ was 25.0 μg*h/mL which was comparable with the $AUC_{0\text{-}50}$ of Horimatsu et al[12] after a dose of 70 mg/m^2 (23.6 μg*h/mL). It was also comparable with other reported case reports of oxaliplatin in haemodialysis patients.[6] The free platinum concentration-time curve in our patient showed a bimodal pattern with peaks at 2 and 26 hours after oxaliplatin administration. This is also described in other case reports.[5-9] The second peak is not seen in patients with normal renal function and may be caused by the dissociation of the platinum bound to plasma proteins and blood cells or by redistribution of platinum from tissue. In patients with normal renal function, it is likely that free platinum is rapidly eliminated by renal excretion, so no second peak is observed. Because the second peak influences the AUC significantly, in some reports a dosing interval of 3 weeks is used instead of 2 weeks.[3,9] The C_{max} we measured was significantly higher than reported in literature. However, the determination of the maximum concentration after infusion of drugs with a fast initial distribution is challenging and is associated with high variation. Because this relatively high C_{max} did not result in haematological toxicity, the AUC was comparable with literature and there was no significant accumulation of free platinum, we maintained the dose of oxaliplatin at 70 mg/m^2 every 3 weeks.

Further research is needed to determine the best pharmacokinetic parameter or combination of parameters and corresponding target values to further optimize the oxaliplatin dose for the individual haemodialysis patient.

In this study, we have shown that treatment of a metastatic rectum cancer haemodialysis patient with an adapted FOLFOX and bevacizumab scheme in which oxaliplatin dosing is monitored by measuring free platinum concentrations is effective, safe and feasible in clinical practice.

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CONFLICT OF INTEREST

None to declare.

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