

University of Groningen

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

van Berlo-van de Laar, I R F; Brummelhuis, W J; Imholz, A L T; Schellens, J H; Huitema, A D R; Jansman, F G A

Published in:
Journal of Clinical Pharmacy and Therapeutics

DOI:
[10.1111/jcpt.12661](https://doi.org/10.1111/jcpt.12661)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van Berlo-van de Laar, I. R. F., Brummelhuis, W. J., Imholz, A. L. T., Schellens, J. H., Huitema, A. D. R., & Jansman, F. G. A. (2018). Dosing oxaliplatin in a haemodialysis patient with metastatic rectum cancer monitored by free platinum concentrations. *Journal of Clinical Pharmacy and Therapeutics*, 43(4), 574-577. <https://doi.org/10.1111/jcpt.12661>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

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

I. R. F. van Berlo – van de Laar PharmD¹ | W. J. Brummelhuis MD, PhD² |
A. L. T. Imholz MD, PhD³ | J. H. Schellens PharmD^{2,4} | A. D. R. Huitema PharmD^{2,5} |
F. G. A. Jansman PharmD, PhD^{1,6}

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

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

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

⁴Utrecht Institute of Pharmaceutical Sciences, Utrecht, The Netherlands

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

⁶Unit 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/m², folinic acid 200 mg/m², 5-FU 340 mg/m² bolus and 2040 mg/m² 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 AUC₀₋₅₀ 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/m² and folinic acid 200 mg/m² intravenous during a 2-hour infusion. 5-FU was then administered as a bolus injection of 340 mg/m², followed by continuous infusion of 5-FU 2040 mg/m² 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_{0-50} 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_{0-50} for total and free platinum are depicted in Table 1.

Freeplatinum plasma ultrafiltrate concentration-time curve

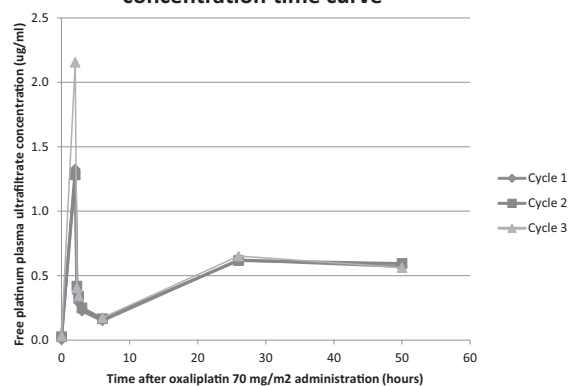


FIGURE 1 Free platinum plasma ultrafiltrate concentration-time curve

TABLE 1 Pharmacokinetic parameters of oxaliplatin 70 mg/m²

	Cycle 1	Cycle 2	Cycle 3
Total platinum			
C_0 ($\mu\text{g/mL}$)	0	0.14	0.17
C_{max} ($\mu\text{g/mL}$)	2.2	2.5	2.7
AUC_{0-50} ($\mu\text{g}\cdot\text{h/mL}$)	71.2	81.7	80.2
Free platinum			
C_0 ($\mu\text{g/mL}$)	0	0.03	0.03
C_{max} ($\mu\text{g/mL}$)	1.3	1.3	2.2
AUC_{0-50} ($\mu\text{g}\cdot\text{h/mL}$)	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 al⁹ and Gori et al⁶ 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. Hemihpatectomy 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 al¹² 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_{0-50} was $25.0 \mu\text{g}\cdot\text{h}/\text{mL}$ which was comparable with the AUC_{0-50} of Horimatsu et al¹² after a dose of $70 \text{ mg}/\text{m}^2$ ($23.6 \mu\text{g}\cdot\text{h}/\text{mL}$). 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 $70 \text{ mg}/\text{m}^2$ 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.

ACKNOWLEDGEMENTS

We thank the patient and Cornelis G. Vermeij, treating nephrologist of this patient, for cooperating in this study.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Takimoto CH, Remick SC, Sharma S, 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;21:2664-2672.
2. Massari C, Brienza S, Rotarski M, et al. Pharmacokinetics of oxaliplatin in patients with normal versus impaired renal function. *Cancer Chemother Pharmacol*. 2000;45:157-164.
3. Graham MA, Lockwood GF, Greenslade D, et al. Clinical pharmacokinetics of oxaliplatin: a critical review. *Clin Cancer Res*. 2000;6:1205-1218.
4. Summary of Product Characteristics (SmPC). Oxaliplatin Sandoz concentrate for infusion 5 mg/ml. January 2016 (1311-V5).
5. Watayo Y, Kuramochi H, Hayashi K, Nakajima G, Kamikozuru H, Yamamoto M. Drug monitoring during FOLFOX6 therapy in a rectal cancer patient on chronic hemodialysis. *Jpn J Clin Oncol*. 2010;40:360-364.
6. Gori S, Lunardi G, Inno A, et al. Pharmacokinetics of oxaliplatin in a hemodialyzed patient: chemotherapy dose adjustment and timing of dialysis. *Clin Colorectal Cancer*. 2014;13:260-263.
7. Katsumata K, Sumi T, Wada T, et al. Oxaliplatin for metastatic colon cancer in a patient with renal failure. *Clin Med Oncol*. 2008;2:97-101.
8. Shitara K, Munakata M, Muto O, et al. Hepatic arterial infusion of oxaliplatin for a patient with hepatic metastases from colon cancer undergoing hemodialysis. *Jpn J Clin Oncol*. 2007;37:540-543.
9. Horimatsu T, Miyamoto S, Morita S, et al. Pharmacokinetics of oxaliplatin in a hemodialytic patient treated with modified FOLFOX-6 plus bevacizumab therapy. *Cancer Chemother Pharmacol*. 2011;68:263-266.
10. Brouwers EE, Tibben MM, Hillebrand MJ, Joerger M, Schellens JH, Beijnen JH. Sensitive inductively coupled plasma mass spectrometry assay for the determination of platinum originating from cisplatin, carboplatin and oxaliplatin in human plasma ultrafiltrate. *J Mass Spectrom*. 2006;41:1186-1194.

11. Gamelin E, Le Bouil A, Boisdron-Celle M, et al. Cumulative pharmacokinetic study of oxaliplatin, administered every three weeks, combined with 5-fluorouracil in colorectal cancer patients. *Clin Cancer Res.* 1997;3:891-899.
12. Giacchetti S, Zidani R, Perpoint b, et al. Phase III trial of 5-fluorouracil, folinic acid, with or without oxaliplatin (OXA) in previously untreated patients with metastatic colorectal cancer (MCC). *Proc Annu Meet Am Soc Clin Oncol.* 1997;16:805.

How to cite this article: van Berlo – van de Laar IRF, Brummelhuis WJ, Imholz ALT, Schellens JH, Huitema ADR, Jansman FGA. Dosing oxaliplatin in a haemodialysis patient with metastatic rectum cancer monitored by free platinum concentrations. *J Clin Pharm Ther.* 2018;43:574–577. <https://doi.org/10.1111/jcpt.12661>