British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 2120–2122 2120

CASE REPORT

Pharmacogenetic analysis of irreversible severe cisplatin-induced nephropathy: a case report of a 27-year-old woman

Correspondence Maarten Deenen, PharmD, PhD, Department of Clinical Pharmacy, Catharina Hospital Eindhoven, Michelangelolaan 2, 5623 EJ Eindhoven, The Netherlands. Tel.: +31 40 239 8795; Fax: +31 40 239 8385; E-mail: maarten.deenen@catharinaziekenhuis.nl

Received 21 December 2016; **Revised** 3 April 2017; **Accepted** 11 April 2017

Corine de Jong[1], Stefan Sanders[1], Geert-Jan Creemers[2], Artur M. Burylo[3], Margot Taks[1], Jan H.M. Schellens[4,5] and Maarten J. Deenen[1,6]

[1]Department of Clinical Pharmacy, Catharina Hospital, Eindhoven, The Netherlands, [2]Department of Internal Medicine, Catharina Hospital, Eindhoven, The Netherlands, [3]Department of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands, [4]Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands, [5]Faculty of Science, Utrecht Institute of Pharmaceutical Sciences (UIPS), Division of Clinical Pharmacology and Pharmaco-epidemiology, Utrecht University, Utrecht, The Netherlands, and [6]Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands

Keywords cisplatin, genotyping, nephrotoxicity, pharmacogenomics

In this report we describe a young patient diagnosed with bulky FIGO stage IIIb squamous cell cervix carcinoma with severe and irreversible nephropathy after three weekly low-doses of cisplatin. Besides several known risk factors such as hypomagnesemia and hypoalbuminemia, the patient also proved to be homozygously polymorphic for two polymorphisms within the *COMT* gene (c.615 + 310C>T and c.616–367C>T). As *COMT* polymorphism has been associated with cisplatin-induced ototoxicity, its effect on nephrotoxicity of cisplatin should be the subject of further investigation.

Tables of Links

TARGETS
Enzymes [2]
Catechol-O-methyltransferase (COMT)

LIGANDS
Cisplatin

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Cisplatin is a widely used anticancer drug for the treatment of various solid tumours, including gastric, ovarian, testicular and lung cancer. Treatment with cisplatin is frequently associated with severe side effects such as nephrotoxicity, neurotoxicity and ototoxicity [3]. Despite intensive prophylactic measures, kidney damage occurs in one-third of patients and remains the most important complication that may limit further treatment [4]. Susceptibility to cisplatin nephrotoxicity is known to vary between individuals. Identified risk factors include co-administration with nephrotoxic agents, smoking, age, hypomagnesemia and hypoalbuminemia [5]. In addition,

DOI:10.1111/bcp.13309

genetic variations in genes involved in the pharmacological pathway of cisplatin may affect response and toxicity. In particular, polymorphism in genes involved in cisplatin cellular uptake such as the organic cation transporter 2 (*OCT2*); metabolism, i.e. glutathione S-transferases 1 (*GST1*); DNA repair, like the excision repair cross-complementation groups (*ERCC1*, *ERCC2*); and other pharmacodynamic candidate genes such as catechol-O-methyltransferase (*COMT*), have shown to be associated with nephrotoxicity [6–9]. Although cisplatin toxicity is in most cases largely reversible, this report describes a young patient with persistent severe nephropathy after three doses of low-dose cisplatin therapy.

A 27-year-old Caucasian woman was referred to our hospital with vaginal bleeding and abdominal pain. The patient had no further medical history besides an asymptomatic pelvic kidney and no history of smoking or intake of any nephrotoxic agent. She was diagnosed with bulky FIGO stage IIIb squamous cell cervix carcinoma with pelvic and presacral lymph nodes with right-sided hydronephrosis. Renal function improved after double J ureteral stent placement (serum creatinine level 87 μmol l^{-1}). Treatment was started with induction chemotherapy consisting of three cycles carboplatin (with a target area under the curve (AUC) of five) plus paclitaxel (175 mg m^{-2}) once every 3 weeks. The second and third cycle of carboplatin/paclitaxel were both postponed for 1 week due to haematological toxicity with stable creatinine clearance.

Radiologic evaluation after three cycles showed partial response of the primary tumour and lymph nodes remained stable. One month after the last cycle of carboplatin/paclitaxel, chemoradiation was initiated. Definitive chemoradiotherapy comprised weekly intravenous administration of cisplatin 40 mg m^{-2} and 25 fractions of 1.8 Gy radiotherapy besides 3 * 8 Gy brachytherapy in weeks five, six and seven. After three cycles of cisplatin, serum creatinine level increased to 147 μmol l^{-1} and platelets decreased to 40 * 10^9 l^{-1}. Cisplatin therapy was discontinued but both radiation and brachytherapy were continued. At day 31, the patient was hospitalized for 16 days because of further deterioration of kidney function (AKI grade 3, creatinine 432 μmol l^{-1}) and progressive pancytopenia (leukocytes 1.7 * 10^9 l^{-1}, neutrophils 0.84 * 10^9 l^{-1}, haemoglobin 4.9 mmol l^{-1}, platelets 21 * 10^9 l^{-1}) (Figure 1). In addition, hypoalbuminaemia (30 g l^{-1}) and hypomagnesaemia (0.66 mmol l^{-1}) were noted. At time of hospital discharge, the patient's serum creatinine level was still 228 μmol l^{-1}. Six months later, no improvement of renal function had occurred – the serum creatinine levels remained above 200 μmol l^{-1} (AKI grade 2) (Figure 1).

In order to elucidate potential causes of the observed irreversible nephropathy, a pharmacogenomic analysis was performed, for which informed consent for genotyping and publication as case report was obtained from the patient. Polymorphisms in five candidate genes (*COMT*, *ERCC1*, *ERCC2*, *GSTP1*, *OCT2*) were determined by PCR (Taqman assay). The tested polymorphisms in *ERCC1* (c.197G>T (rs3212986)), *ERCC2* (c.934C>T (rs1799793)), *GSPT1* (313A>G (rs1695)) and *OCT2* (c.808G>T (rs316019)) proved to be wild-type. Interestingly, however, both tested polymorphisms in *COMT* proved to be homozygously polymorphic (*COMT* c.615 + 310C>T (rs4646316) and c.616-367C>T (rs9332377)). Of note, both polymorphisms have previously been associated with cisplatin-induced ototoxicity [10, 11]. The COMT enzyme is dependent on the S-adenosylmethionine (SAM) methyl donor substrate in the methionine pathway and involved in the inactivation of catecholamine neurotransmitters. Despite the fact that its precise function with regard to hearing loss of cisplatin has not yet fully been unravelled, a putative mechanism for cisplatin toxicity could be mediated through increased levels of SAM as result of reduced COMT activity. In a recent mice model study, administration of both SAM and cisplatin increased cisplatin toxicity by 3–6.2-fold compared to cisplatin alone, as monitored by renal dysfunction [12]. Furthermore, whether *COMT* polymorphisms are also

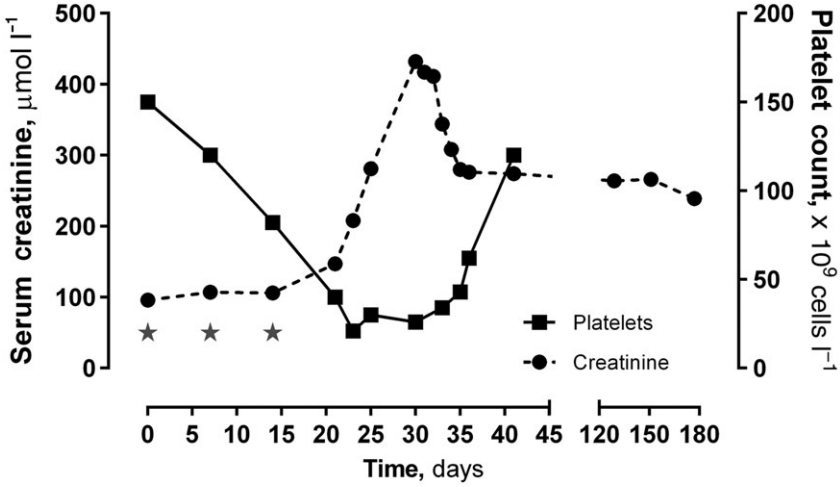

Figure 1

Serum creatinine levels and platelet counts in the peripheral blood of the patient after cisplatin therapy. Time is measured in days after the start of the chemotherapy, which is day 0. Stars indicate administration of cisplatin 40 mg m^{-2} on day 0, 7 and 14

associated with nephrotoxicity of cisplatin in humans has thus far not yet been studied. We prudentially hypothesize that based on the known association of *COMT* polymorphism with ototoxicity, plus the observed homozygosity of both polymorphisms in this young patient that led to reduced COMT activity, this may have contributed to the irreversible and severe kidney damage. With minor allele frequencies of the *COMT* polymorphisms of 16% and 24%, respectively [11], it would be interesting to explore the effect of these polymorphisms on cisplatin-induced nephrotoxicity in a *COMT* KO mice model and in an appropriate patient population.

Besides a potential genetic susceptibility, several other risk factors may have additionally contributed to kidney damage in this young woman. Cisplatin has a high plasma protein binding of more than 90%; malnutrition and hypoalbuminaemia may consequently result in a higher fraction of unbound cisplatin, with a potentially increased risk of toxicity. Hypomagnesaemia was noted, which is also associated with nephrotoxicity [13]. It is not likely that the existing hydronephrosis, for which a double J stent was placed successfully, contributed to kidney failure. Since pelvic kidney-sparing radiotherapy was performed, radiation damage is not likely. Besides, no other concomitant nephrotoxic drugs were used.

In summary, homozygosity of two *COMT* polymorphisms (c.615 + 310C>T and c.616–367C>T) was demonstrated in a patient with persisting nephrotoxicity after three low doses of cisplatin. Besides additional risk factors, including hypomagnesaemia and hypoalbuminaemia, *COMT* polymorphisms may have contributed to the severe kidney damage. Based on the known association of *COMT* polymorphism with cisplatin-induced ototoxicity, association analysis with nephrotoxicity should be the subject of further investigation.

Competing Interests

There are no competing interests to declare.

References

1 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44: D1054–68.

2 Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE, *et al*. The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. Br J Pharmacol 2015; 172: 6024–109.

3 Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of cisplatin nephrotoxicity. Toxins (Basel) 2010; 2: 2490–518.

4 Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: a review. Am J Med Sci 2007; 334: 115–24.

5 Arrieta O, Michel Ortega RM, Villanueva-Rodriguez G, Serna-Thomé MG, Flores-Estrada D, Diaz-Romero C, *et al*. Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. BMC Cancer 2010; 10: 50.

6 Khrunin AV, Moisseev A, Gorbunova V, Limborska S. Genetic polymorphisms and the efficacy and toxicity of cisplatin-based chemotherapy in ovarian cancer patients. Pharmacogenomics J 2010; 10: 54–61.

7 Liu HE, Bai KJ, Hsieh YC, Yu MC, Lee CN, Chang JH, *et al*. Multiple analytical approaches demonstrate a complex relationship of genetic and nongenetic factors with cisplatin- and carboplatin-induced nephrotoxicity in lung cancer patients. Biomed Res Int 2014; 2014: 937429.

8 Sullivan I, Salazar J, Majem M, Pallarés C, Del Rio E, Páez D, *et al*. Pharmacogenetics of the DNA repair pathways in advanced non-small cell lung cancer patients treated with platinum-based chemotherapy. Cancer Lett 2014; 353: 160–6.

9 Lu C, Spitz MR, Zhao H, Dong Q, Truong M, Chang JY, *et al*. Association between glutathione S-transferase pi polymorphisms and survival in patients with advanced nonsmall cell lung carcinoma. Cancer 2006; 106: 441–7.

10 Ross CJ, Katzov-Eckert H, Dubé MP, Brooks B, Rassekh SR, Barhdadi A, *et al*. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat Genet 2009; 41: 1345–9.

11 Hagleitner MM, Coenen MJ, Patino-Garcia A, de Bont ES, Gonzalez-Neira A, Vos HI, *et al*. Influence of genetic variants in TPMT and COMT associated with cisplatin induced hearing loss in patients with cancer: two new cohorts and a meta-analysis reveal significant heterogeneity between cohorts. PLoS One 2014; 9: e115869.

12 Ochoa B, Bobadilla N, Arrellin G, Herrera LA. S-Adenosyl-L-methionine increases serum BUN and creatinine in cisplatin-treated mice. Arch Med Res 2009; 40: 54–8.

13 Kidera Y, Kawakami H, Sakiyama T, Okamoto K, Tanaka K, Takeda M, *et al*. Risk factors for cisplatin-induced nephrotoxicity and potential of magnesium supplementation for renal protection. PLoS One 2014; 9: e101902.