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SHORT COMMUNICATION

Pharmacokinetics of trabectedin on hemodialysis: an application for the management of cancer patients with end-stage renal disease

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Abstract
Purpose The pharmacokinetics of trabectedin has never been reported in patients with impaired renal function or in patients on hemodialysis.
Methods We examined trabectedin PK in a patient on hemodialysis, starting trabectedin therapy at a standard dose for recurrence of a retroperitoneal myxoid liposarcoma that had occurred under immunosuppressive drugs for kidney transplant.
Results As compared with a population with normal renal function, the study patient presented a higher C_{max} and AUC, with lower clearance, terminal half-life, and volume of distribution. The low dialysis clearance, accounting for a minor part of the total body clearance and the absence of detectable trabectedin in the dialysate samples, suggests that hemodialysis does not efficiently clear trabectedin. Trabectedin tolerance was good.
Conclusions This case reports for the first time the feasibility of trabectedin therapy in a hemodialyzed patient. Given the rising incidence of cancer in patients with end-stage renal disease, it is crucial to provide data that improve the management of anticancer drugs in dialyzed patients.

Keywords Trabectedin · Ecteinascidin · Pharmacokinetics · Hemodialysis · End-stage renal disease · Dialysis

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Introduction

Trabectedin, also known as ecteinascidin 743, is a marine-derived alkaloid that interacts with the minor groove of DNA and interferes with various transcription factors, DNA-binding proteins, and DNA repair pathways [1]. Trabectedin is a high molecular weight molecule (761.84 g/mol) that binds extensively to plasma proteins has a long half-life, a large distribution volume, and is extensively cleared by hepatic metabolism involving mainly CYP3A4 [2–5]. The incidence of patients under chronic dialysis who later develop cancer is a growing concern [6]. The management of such patients is extremely difficult due to the scarcity of pharmacokinetic studies for patients with a renal

clearance under 30 ml/min [7]. These patients should not be systematically denied treatment on the basis of their end-stage kidney disease but rather should be offered dosage adjustments and adaptation to dialysis. This is critical to guarantee antitumor efficacy and tolerance in these frail patients [6]. To our knowledge, the pharmacokinetics (PK) of trabectedin has never been reported in patients with impaired renal function or in patients on hemodialysis (HD). We thus examined trabectedin PK in a patient on HD, starting trabectedin therapy at a standard dose for a multifocal recurrence of a retroperitoneal myxoid liposarcoma (RML). PK characteristics of our patient were compared with PK data from the literature obtained in a population of patients with normal kidney function [8].

Materials and methods

Patient

A 59-year-old woman was referred for relapse of RML to the Nice Cancer Center in November 2009. She had been operated on for a RML grade II in June 2001 (nephro-ureterectomy, splenectomy, and lombo-aortic dissection). Complete resection of the tumor mass was followed by 6 courses of MAID chemotherapy (mesna, doxorubicin, ifosfamide, dacarbazine) until October 2001. The patient had kidney failure following chemotherapy, probably due to ifosfamide-related tubulopathy. She underwent HD for end-stage kidney disease from 2004 to December 2008. In December 2008, she received a kidney graft. Her transplant did not yield sufficient kidney function to avoid dialysis but allowed residual diuresis. Immunosuppressive treatment consisted of tacrolimus and sevelamer hydrochloride. Eleven months later, in November 2009, her annual CT scan revealed an unresectable multifocal recurrence around operative clips. The patient was WHO status 1. She had a creatinine clearance of 6 ml/min and 450 cc/day residual diuresis; she had only minor fluid overload and was relieved of 1–1.5 kg per dialysis session. Given the potential risk of immunosuppressive drugs promoting tumor recurrence, immunosuppressive treatment was stopped in November 2009 and the graft was removed in January 2010. CT scan showed tumor progression in March 2010. Trabectedin (Yondelis®) was started on April 19, 2010 at the standard dose of 1.5 mg/m² as a 24 h i.v. infusion once every 3 weeks (body surface area 1.45 m^2). Dexamethasone (20 mg i.v.) was administered before trabectedin infusion. Trabectedin PK was examined at the first course of treatment. The patient had signed informed consent, and the institutional board had approved the procedure in agreement with the Declaration of Helsinki. In June 2010, after 2 trabectedin cycles, the patient had normal liver tests and no myelosuppression. Trabectedin tolerance was good. In October 2010, CT scan showed tumor progression with areas of necrosis. Trabectedin was stopped. The patient died in November 2010, after progression to two other treatment lines.

Pharmacokinetic analysis

Blood samples (4 ml on heparinized tubes) were collected during the first trabectedin course, before the infusion (duration, 24 h 50 min) and at the following times after the start of infusion: 2, 6 h 15 min, 23 h 45 min (i.e., 65 min before the end of infusion), 25 h 20 min (i.e., 30 min after the end of infusion), 26 h 30 min, 76 h 25 min, 124 h 20 min, 196 h 30 min, 364 h 40 min, and 500 h 35 min. HD began 3 h 15 min after the end of the infusion and lasted 3 h 30 min. Six additional blood samples were taken during the HD, at the input and at the output of the dialyzer, at start time (28 h 5 min), mid-time (29 h 50 min) and end time (31 h 35 min) of the dialysis session (Fig. 1). Also, dialysate samples were collected at mid-time and end time of the dialysis session. Blood samples were immediately centrifuged and plasma and dialysate were stored at −80°C until analysis. Trabectedin concentrations (total drug) were analyzed using miniaturized high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry [9, 10]. The limit of quantification was 26 pg/ml in plasma and 250 pg/ml in dialysate samples.

Phoenix Winnonlin 6.1 software (Tripos L.P.) was used for non-compartmental analysis (NCA) of the concentration–time profile to obtain the area under the plasma concentration (AUC) from time 0 to infinity, the elimination rate (k_{el}), the elimination half-life ($0.693/k_{el}$), the maximum plasma concentration (C_{max}), and the volume of distribution at steady state (V_{ss}).

PK parameters of control patients with normal renal (creatinine ≤1.5-fold ULN) and hepatic (bilirubin ≤1.5-ULN, AST, and ALT ≤2.5-fold ULN) functions were obtained from a population PK model developed for trabectedin on 603 patients, with the same analytical assay, using NONMEM V level 1.1 software [8]. Based on this population PK model, a Monte Carlo simulation of 1,000 replicates was performed with sampling times corresponding to those of our HD patient, until the last measurable point (196 h 30 min). We thus simulated the 90% confidence interval (CI) of trabectedin concentrations versus time in this control population (blue area in Fig. 1a). We then focused on the 5th, 50th, and 95th percentile of this simulated control population and further applied a PK NCA to these quantiles so as to compare PK parameters of the HD patient with those of the simulated control population, based on the same methodological approach (Table 1).

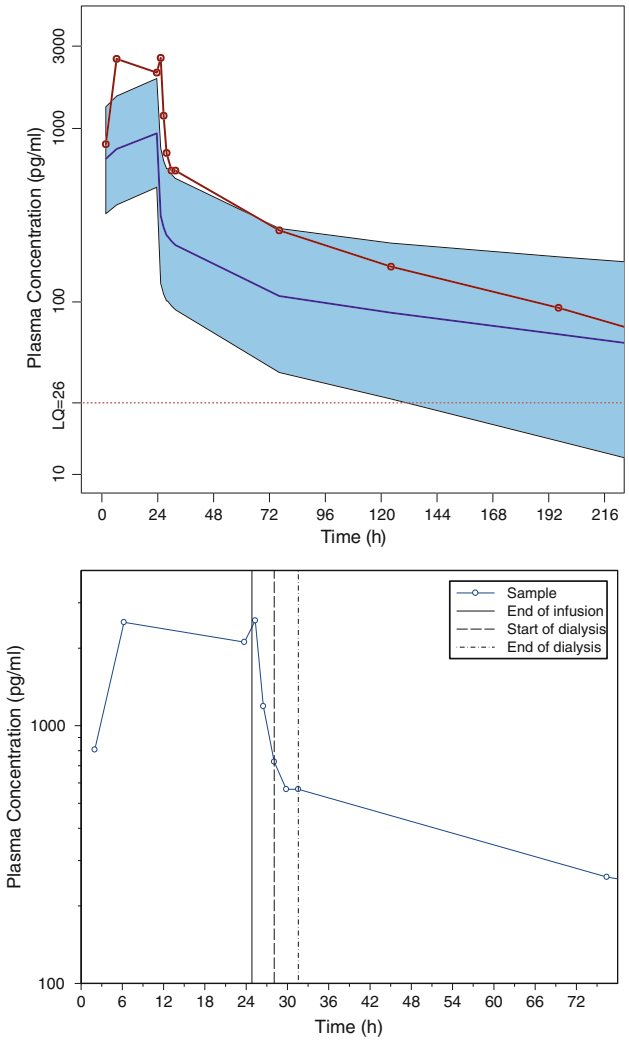

Fig. 1 **a** Trabectedin PK profile (semilog plot over 216 h) of the study patient (*red line*) and of a simulated control population with normal renal function (the *blue line* indicates the median value and the *shaded blue area* indicates the 90% CI comprised between the 5th and the 95th percentile). See the "Materials and methods" section for description of PK data in the control population. LQ means limit of quantification. **b** Trabectedin PK profile (semilog plot over 72 h) of the study patient. Trabectedin infusion started at T0 and ended at 24 h 50 min (*continuous line*). The HD started 3 h 15 min after the end of infusion (*dashed line*) and lasted 3 h 30 min (*dotted line*)

Results

The trabectedin PK profile of our patient is depicted in Fig. 1 and Table 1, which also illustrate the trabectedin PK obtained in a simulated control population with normal kidney function, receiving the same standard dose. As compared with control patients with normal kidney function, the study patient exhibited a higher C_{max} (above the 95th percentile of the control population) and a lower elimination half-life and volume of distribution (below the 5th percentile of the control population). Also, the AUC of our patient was twofold that of the median value of the control population and her total body clearance were half that of the median value of the control population, although comprised within their respective 95% CIs. Dialysis clearances computed from plasma concentrations measured at the input and at the output of the dialyzer were 3.6, 0.31, and 0.54 l/h at start, middle, and end times of the dialysis session, respectively, demonstrating that the dialyzer had a very low ability to extract trabectedin from blood. Accordingly, the levels of trabectedin in dialysate samples were below the limit of quantification.

Discussion

A first striking observation is that the present patient developed a multifocal recurrence 11 months after immunosuppressive therapy, although occurring more than 8 years after complete tumor resection. An increased risk of malignancy is a recognized complication of immunosuppressive drugs. This risk is related to the intensity, duration, and type of treatment [11]. A 2- to 5-year remission is usually required before indicating a graft. However, this may be too short for malignancies with a long-term relapse potential, such as low-grade liposarcomas.

The standard treatment for relapsed unresectable retroperitoneal liposarcomas (RURL) is ifosfamide-based chemotherapy. Despite its association with uromitexan, ifosfamide is responsible for 6–10% renal failures. It is thus important to have an efficient second-line therapy in RURL patients failing under ifosfamide and having developed a renal failure. As trabectedin has been approved for relapsed liposarcomas in patients with normal kidney function [12] and is not cleared by the kidney [3], it may offer a drug of choice in RURL patients with renal failure. Trabectedin therapy was thus initiated for this patient on chronic HD.

Trabectedin PK has never been reported in patients with creatinine clearance under 30 ml/min. We presently documented trabectedin PK in a patient on HD with impaired renal function, receiving a standard dose (1.5 mg/m^2) similar to that given to patients with normal kidney function. Trabectedin infusion was administered before the dialysis session. Table 1 shows that trabectedin C_{max}, half-life, and volume of distribution observed in the present HD patient are located outside of the 90% CI of reference values computed in patients with normal renal function [8]. In our patient, C_{max} and $AUC_{0-infinity}$ were approximately twofold higher than median values and total body clearance half that of a population with normal renal function. Unexpectedly, elimination half-life of the study patient was twofold shorter (81 h) than that observed in normal kidney patients (median 165 h). This suggests that trabectedin elimination from the body was not impaired, but rather increased in our

Table 1 Description of trabectedin PK parameters

	Study patient with impaired renal function on HD	Simulated control population with normal renal function		
		5th percentile	50th percentile	95th percentile
Dose (mg/m^2)	1.5	1.5	1.5	1.5
C_{max} (ng/ml)	2.56	0.46	0.94	1.95
$AUC_{0-infinity}$ (ng h/ml)	106.3	18.1	53.7	147.2
Total body clearance (l/h)	20.5	120.3	40.6	14.8
Elimination half-life (h)	81	91	165	229
V_{SS} (liters)	1,175	7,442	6,035	3,497

patient. A possible explanation for this short half-life compared with a population with normal renal function, along with elevated C_{max}, AUC, and reduced clearance, may be the low volume of distribution of our patient, which was estimated at around 1,200 liters, whereas 90% CI computed in the control population was 3,497–7,445 liters. Also, interesting is the data from Supko et al. [13] who examined trabectedin PK in 69 adult patients with normal renal function receiving 24-h continuous infusion at the standard dose. These authors reported a very large inter-patient variability in Cmax, $AUC_{0-infinity}$, and total body clearance, with coefficient of variation between 42 and 45%, suggesting that the PK values presently observed in our patient may lie within the variability reported in patients with normal renal function.

Additional information came from trabectedin measurements in plasma at the dialyzer input and output, as well as in the dialysate itself. Dialysis clearances, accounting for 17.6, 1.5, and 2.6% of the total body clearance at the start, middle, and end of dialysis, respectively, were low. This observation, along with the absence of any quantifiable amount of trabectedin in the dialysate, strongly suggests that HD does not eliminate trabectedin. This concords well with literature data reporting that renal elimination is a minor route in total trabectedin clearance, with less than 1% of a trabectedin dose recovered in urine as unchanged drug [4, 5]. Therefore, trabectedin PK changes in patients with impaired renal function are unlikely to occur.

In total, it is presently not possible to impute the trabectedin PK pattern of our patient to her renal function impairment. Such a PK profile may be explained by other unidentified individual characteristics, possibly including modifications in hepatic metabolism. Further PK studies of trabectedin in patients with end-stage renal function are thus required in order to confirm the present observation on a larger number of patients. The fact that the patient tolerated trabectedin treatment well at full dose, along with the fact that trabectedin AUC was elevated, even though comprised within the 90% CI of the control population, can serve as a guide for other HD patients. In conclusion, this case report shows the feasibility of trabectedin therapy in hemodialyzed patients. It is critical that the increasing incidence of patients with end-stage renal disease who later develop cancer foster larger pharmacokinetics studies in order to improve the management of anticancer drugs in this emerging population.

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Conflict of interest A. Soto-Matos and C. Fernandez-Teruel work for PharmaMar. Other authors have none.

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