Pharmacokinetics of sunitinib in hemodialysis

Clear-cell renal carcinoma is the most common cancer of the kidney [1]. Up to 30% of patients with renal-cell carcinoma present with metastatic disease [2, 3] and recurrence develops in ~40% of affected patients treated for a localized tumor [2, 4]. Long-term dialysis is a risk factor since prevalence in hemodialysis and renal transplant patients is 40–100 times higher than in the general population [6, 7]. Sunitinib is an orally administered inhibitor of tyrosine kinase targeting the vascular endothelial growth factor receptor and the platelet-derived growth factor receptor. Sunitinib given as first-line treatment in metastatic renal-cell carcinoma has shown clinical activity in a phase III randomized trial, with a median progression-free survival significantly longer (11 months) than in the interferon alfa group (5 months) and a higher objective response rate (31% versus 6%, \( P < 0.001 \)) as compared with interferon alfa [5]. Sunitinib and its main metabolite, SU12662, are mainly eliminated in the feces and only 15%–20% of the dose is cleared by the kidney [8]. So far, no pharmacokinetic (PK) data of sunitinib have been reported in patients with renal failure or under hemodialysis. We report a PK analysis of sunitinib and its main metabolite in two hemodialysed patients.

patients

Case 1: A 62-year-old man was diagnosed with intracaval neoplastic extension secondary to left clear-cell carcinoma. He underwent a nephrectomy for a pT3pN1M0 tumor and removal of the intracaval thrombosis extending into the right atrium. Despite a 5-month compassionate 50 mg daily sunitinib and maintained anticoagulation, intracaval thrombosis remained stable and the patient depended on hemodialysis.

Case 2: a 23-year-old man underwent a nephrectomy for a T3N2M1 tumour on a single kidney. The patient was put on a thrice per week hemodialysis program after the nephrectomy. Despite IL-2–interferon-alfa cytokine protocol and a 6-month period of 3 mg/kg of bevacizumab every 2 weeks, the patient experienced increased tumor volume and exhibited enlarged lomboaortic lymph nodes. Bevacizumab was replaced by sunitinib.

sunitinib treatment and hemodialysis

Both patients received sunitinib once daily (50 mg/day) orally for 4 weeks every 6 weeks.

Hemodialysis was carried out for 4 h, three times weekly. A F60 polysulfone dialyzer (surface area 2.1 m²) with dual lumen catheter was used for patient 1. For patient 2, a polyacrylonitrile dialyzer (surface area 1.6 m²) with double-needle access to a radial arteriovenous fistula was used. The dialyzate flow rate was constant at 500 ml/min and the blood flow rate was 300 ml/min. After obtaining patient informed consents, a sunitinib PK evaluation was carried out at steady state, i.e. at the end of the 1-month and 6-month treatment period in patients 1 and 2, respectively.

PK analysis

Steady state is reached 10–14 days after starting treatment. Blood samples (3 ml on EDTA-containing tubes) were collected just before the daily intake and then 6, 8, 10, 11, 13, 15, 17, 19, and 24 h after sunitinib oral administration. For patient 1, blood collection was carried out on day 27 (on-dialysis day) and day 28 (off-dialysis day) of cycle 1. For patient 2, blood collection was carried out on day 27 (on-dialysis day) and day 28 (off-dialysis day) of cycle 5. In both patients, the 4-h dialysis session started 6 h after the drug intake. Paired arterial and venous blood samples were carried out simultaneously 2 h after the start of the session.

Sunitinib and its metabolite SU12662 were measured using an high-performance liquid chromatography (HPLC) developed and validated in the Oncopharmacology Unit of Centre Antoine Lacassagne. Briefly, 500 µl of plasma spiked with ZD6474 (0.1 µg/ml final concentration) as internal standard was extracted with 4 ml of ter-butyl methyl ether. After evaporation, the residue was reconstituted in 200 µl of the HPLC mobile phase (ammonium formate 20 mM pH 3.25/acetonitril, 60/40) and separated on a Superoxel ODS 5 µm HPLC column (4.6 × 250 mm, flow rate 0.8 ml/min).

Detection was carried out at 369 nm. Recovery rates were 74% and 70% for sunitinib and SU12662, respectively. The limit of quantification was 1 ng/ml for both sunitinib and SU12662.
Area under the concentration–time curve (AUC) was computed according to trapezoidal rule. AUC 0–24h corresponding to the steady-state AUC between two oral intakes was calculated. The total body clearance (CL) was computed as the daily dose divided by the AUC0–24h.

Influence of hemodialysis was studied by means of the extraction ratio $E$ and hemodialysis clearance $CL_{HD}$. PK parameters obtained in the two patients were compared with those of subjects with normal renal function receiving 50 mg daily (Table 1) [8].

Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 2.0. Evaluation was carried out at the end of each cycle of treatment.

Results and discussion

Sunitinib and SU12662 PK parameters are depicted in Table 1. For patient 1, $AUC_{0–24h}$ of sunitinib and SU12662 measured on an off-dialysis day were 2100 and 1123 ng/ml.h and were 207 and 130 ng/ml.h for patient 2, respectively (Table 1). This 10-fold difference in sunitinib concentrations between two patients receiving the same daily dose reflects the wide interpatient variability already reported in literature [8].

Two hours after the start of hemodialysis, arterial and venous sunitinib concentrations were 168 and 157 ng/ml for patient 1 and 27 and 29 ng/ml for patient 2; those of SU12662 were 207 and 130 ng/ml.h for patient 2, respectively (Table 1). This 10-fold difference in sunitinib concentrations between two patients receiving the same daily dose reflects the wide interpatient variability already reported in literature [8].

The sunitinib PK parameters of these two hemodialyzed patients were therefore in the range of the reference values reported in patients with normal renal function (Table 1). No dose-limiting toxicity (fatigue, hypertension, skin discoloration, hand–foot syndrome, nausea, vomiting, and abdominal pain) was observed during the study. However, both cases experienced grade 2 mucosal inflammation.

Conclusion

Present data obtained in patients with renal insufficiency undergoing hemodialysis suggest that sunitinib administered at a dose of 50 mg per day for 4 weeks is well tolerated and leads to plasma concentrations and PK characteristics similar to those reported in patients with normal renal function. In addition, sunitinib seems not to be dialyzable and therefore administration may be at anytime before or after the hemodialysis session. These preliminary results deserve further confirmation on larger cohort of patients.

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References


Table 1. Pharmacokinetic parameters of sunitinib in two hemodialyzed patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patient 1</th>
<th></th>
<th>Patient 2</th>
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<th>Reference values at steady state</th>
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<td>50 mg Daily</td>
<td>50 mg Daily</td>
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<td>SU12662 metabolite</td>
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<tr>
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</table>

$CH_{HD}$, hemodialysis clearance: $[(Ca – Cv) \times Qb]/Ca$; $Ca$, concentration entering the dialyzer (ng/ml); $Cv$, concentration leaving the dialyzer (ng/ml); $Qb$, blood flow (ml/min); CL, total body clearance; $E$, extraction coefficient (%); $CL_{HD}/Qb$, NA, not available.

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