Pharmacokinetics of sunitinib in an obese patient with a GIST

Sunitinib is a potent inhibitor of a variety of receptor tyrosine kinases including vascular endothelial growth factor receptors (1, 2 and 3), fetal liver tyrosine kinase receptor 3, stem-cell factor receptor (KIT), platelet-derived growth factor receptors (alpha and beta) and colony-stimulating factor-1 receptor. It is approved for the treatment of imatinib-resistant gastrointestinal stromal tumours (GISTs) and metastatic renal cell cancer. Data about the pharmacokinetics of sunitinib in seriously obese patients are lacking. We here report the pharmacokinetic data of such an obese GIST patient treated with sunitinib.

case

An obese [weight 126.4 kg, height 1.69 m, body mass index (BMI) 44.3 kg/m²] 42-year-old male patient presented with abdominal pain, a palpable abdominal mass and iron deficiency anaemia. Analysis showed a large GIST originating from the stomach, which was deemed primarily irresectable. Treatment with imatinib (400 mg orally once daily) was started with subsequent decreased activity and volume reduction of the tumour on the 2-[fluorine-18]fluoro-2-deoxy- d-glucose– positron emission tomography–computed tomography (FDG-PET-CT) scan. Resection of the tumour was not possible since the risk of operation-related complications was considered too high due to obesity-induced intubation problems in the past. Two years later, the patient had progressive disease with a second abdominal lesion. We switched to sunitinib 50 mg orally once daily in the 4 weeks on/2 weeks off schedule. At that time, the patient weighed 134 kg (BMI 46.9 kg/m²) and did not use any co-medication. Blood samples were collected baseline and 1, 2, 3, 4, 6, 8, 12 and 24 h after first dosing and a steady-state sample at days 8 and 15 after start of treatment of pharmacokinetic analysis. Plasma levels of sunitinib were quantified using a validated liquid chromatographic assay with tandem mass spectrometric detection. Four months later, the FDG-PET-CT scan showed progressive disease. He complained about melena and accompanying diarrhoea. At this point, the clinical condition of the patient was rapidly deteriorating and therefore the patient was not considered suitable for any experimental antitumour treatment. Best supportive care was provided.

Unfortunately, the pharmacokinetic data became available after deterioration of the patient’s condition. The area under the curve (AUC) (0–24 h) was 0.261 mg h/l, which is 30%–50%
lower than reported (Figure 1) [1, 2]. The steady-state levels of sunitinib on day 8 (19.9 ng/ml) and day 15 (25.2 ng/ml) were ~70% lower than expected based on the literature [1, 2]. The apparent distribution volume was larger (3639 l), but was normal when corrected for body weight.

discussion and conclusion

We report significantly lower plasma sunitinib levels in an obese GIST patient compared with historical controls in the literature [1, 2]. Sunitinib is metabolised by cytochrome P-450 (CYP 3A4) to an active metabolite, SU12662, which is further metabolised to an inactive moiety. Sunitinib and SU12662 have similar biochemical activity and potency. The $T_{\text{max}}$ is reached within 6–12 h. The half-life time is 40–60 h for sunitinib and 80–110 h for SU12662. Steady-state concentrations are reached after 10–14 days of continuous treatment. Sunitinib and SU12662 have a large volume of distribution (2230 l), indicating a good tissue penetration. Steady-state levels between 50 and 100 ng/ml are considered to be pharmacologically active [3]. There is limited pharmacokinetic information about sunitinib and body weight. The degrees of variability between body surface area (BSA)-normalised and fixed dosing were comparable for sunitinib and SU12662 in a simulation in a phase I study [1]. However, no information is provided about the BSA or body weight in the patient characteristics. Remarkably, Food and Drug Administration (FDA) approval text states that body weight has significant effects on the clearance and distribution volume of sunitinib and SU12662. But no dose adjustment for body weight is required since the final population pharmacokinetic covariate analysis for body weight did not produce a reduction in interindividual variability. It is questionable whether these results are based on patient populations that include patients with an excessive body weight comparable to our patient.

In patients with renal cell cancer, higher AUCs of sunitinib are correlated significantly with the response rate, time to progression and overall survival [4]. Although the determination of sunitinib plasma levels is currently not widespread possible, it seems considerable to use intrapatient dose escalation based on pharmacokinetic analysis for obese patients. The FDA approval text permits dose increases to a maximum of 87.5 mg daily based on individual safety and tolerability.

In the described patient, the pharmacokinetic information became available after sunitinib was stopped because of progressive disease. During his treatment, we could not increase the dose because of complaints of melena and diarrhea. The primary GIST was located in the stomach and could be the cause of the melena. However, the patient refused to undergo a gastroscopy. The diarrhea could be secondary to the melena. Since there is no known relationship between diarrhea and dose or AUC of sunitinib, it remains possible that although below clinical active plasma sunitinib levels were found, the diarrhea was caused by sunitinib.

Remarkably, only limited pharmacokinetic and pharmacodynamic data of sunitinib are available. Since the widespread use of sunitinib (and other multiple tyrosine kinase inhibitors) for renal cell cancer and GIST, more data on pharmacokinetics are warranted, as is shown in the described patient.

In conclusion, in patients with severe obesity, plasma levels of sunitinib can be below clinical active level, and thus individual pharmacokinetic data is required to guide treatment in the most optimal way.

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