Promising management of pazopanib-induced liver toxicity

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To the Editor,

Pazopanib (Votrient™ GlaxoSmithKline) is approved by the FDA and EMA for treatment of patients with advanced renal cell cancer (mRCC) and patients with non-adipocytic advanced soft tissue sarcoma (STS) who received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo)adjuvant therapy [1,2]. Unfortunately, 7–9% of the patients develop grade 3 or 4 liver toxicity and even fatal hepatotoxicity has been reported [3]. Manufacturer guideline states that patients with elevated transaminases of $>8\times$ upper limit of normal (ULN) should interrupt pazopanib until they return to $\leq 3\times$ ULN. Subse-

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quently, pazopanib can be reintroduced at a reduced dose of 600 mg once daily (OD). If transaminase elevations of $>3\times$ULN recur, pazopanib should be permanently discontinued [4]. Patients with mRCC can switch to other equipotent angiogenesis inhibitors with different toxicity profiles [5]. Unfortunately for STS patients no other angiogenesis inhibitors are available. Pazopanib is often the last resort and discontinuation has large clinical consequences. The underlying mechanism of pazopanib-induced hepatotoxicity is not yet unraveled, however, limited clinical information suggests that it might be immune mediated [6]. If autoimmune inflammation indeed underlies pazopanib-induced hepatotoxicity, corticosteroids could potentially overcome this problem. Based on this hypothesis, we treated two STS patients with prednisolone after re-elevation of transaminase when pazopanib was restarted at a reduced dose of 600 mg OD.

Case reports

Case one is a 47-year-old male patient with advanced synovial sarcoma since 2010. He was previously treated with doxorubicin followed by ifosfamide. Metastases were located in the lungs only. He used no co-medication. He started pazopanib 800 mg OD with normal ALT, AST, and bilirubin levels at baseline. After seven weeks he developed hepatotoxicity with transaminases of $>8\times$ULN. No physical adverse events or hypersensitivity symptoms were reported.

Case two is a 55-year-old female patient with advanced synovial sarcoma since February 2014. She was previously treated with combination chemotherapy consisting of doxorubicin and ifosfamide. She had multiple lung lesions and one metastasis in the adrenal gland, with normal ALT, AST, and bilirubin levels at baseline and three weeks after start with pazopanib treatment (800 mg OD). In Week 5 she suddenly developed hepatotoxicity with transaminase values of $>8\times$ULN. Similarly, no clinical symptoms were reported. In both cases no indications of liver metastases were present.

Both patients interrupted pazopanib, and liver enzymes were monitored once weekly. After recovering to $\leq 3\times$ULN, pazopanib was restarted at a reduced dose of 600 mg OD according to the drug label. Both patients developed recurrent hepatotoxicity, with transaminases of $>8\times$ULN within one week which implied discontinuing pazopanib. Instead we started prednisolone orally at 30 mg OD while continuing pazopanib at the reduced dose of 600 mg OD. The patients were well informed about the risks and gave consent for this experimental closely monitored continuation of pazopanib. Liver enzymes were

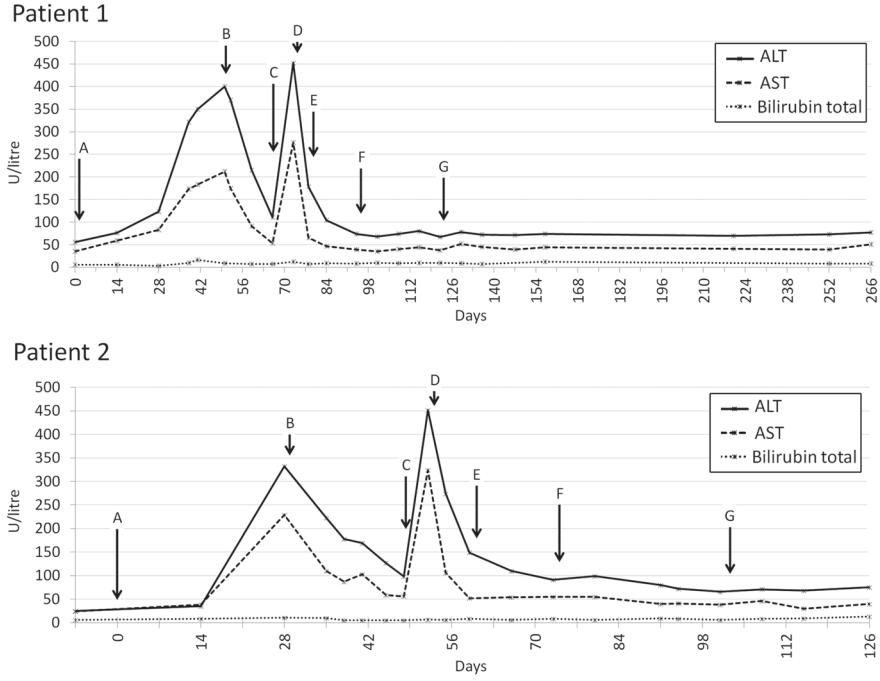

Figure 1. Liver enzymes. ALT (range male: <45 U/l, range female: <35 U/l); AST (range male: <35 U/l; range female: <30 U/l); bilirubin total [range (fe)male: <17U/l]. A: start pazopanib at 800 mg OD; B: liver toxicity of $>8\times$ULN (CTCAE grade 3) therefore stop pazopanib; C: toxicity reduced to $\leq 3\times$ULN (CTCAE grade 0) therefore restart at reduced dose of 600 mg pazopanib OD; D: recurrent toxicity $>10\times$ULN (CTCAE grade 3) therefore start prednisolone 30 mg OD + continue pazopanib 600 mg OD; E: decreasing transaminases therefore continue prednisolone at 15 mg OD + pazopanib 600 mg OD; F: decreasing transaminases therefore continue prednisolone at 10 mg OD + pazopanib 600 mg OD; G: decreasing transaminases therefore continue prednisolone at 5 mg OD + pazopanib 600 mg OD.

monitored 3–5 days after starting prednisolone, showing a rapid decrease. After one week prednisolone was reduced to 15 mg OD. Transaminase levels continued to decrease and prednisolone was diminished to 10 mg, and later 5 mg OD as toxicity had returned to $\leq 3 \times$ ULN. No adverse events were experienced from prednisolone. Both patients continued pazopanib at 600 mg OD with confirmed stable disease during 38 weeks for Patient 1, and 18 weeks for Patient 2. Serum trough levels of pazopanib were measured under prednisolone treatment to confirm adequate exposure. Patients 1 and 2 had pazopanib levels of 26 mg/l and 22 mg/l, respectively. The target pazopanib exposure in patients with mRCC is 20.5 mg/l, which both patients met [7]. However, the target exposure in patients with STS needs to be defined yet. Liver serology for hepatitis B and C tested negative in both cases. In conclusion, both patients showed rapid decrease of transaminases, sustaining after reducing the dose of prednisolone, and consequently pazopanib could be continued (Figure 1).

Discussion

In patients with advanced STS therapeutic options are scarce. Pazopanib is the only licensed oral tyrosine kinase inhibitor for non-adipocytic soft tissue sarcoma. Therefore pazopanib discontinuation due to toxicity has major impact. Although our observations have to be explored further, we believe that management as described could be applied under close monitoring of liver enzymes to patients with pazopanib-induced hepatotoxicity, in particular when no therapeutic alternatives exist.

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