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LETTER TO THE EDITOR

Acute hepatic failure following monotherapy with sunitinib for ovarian cancer

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To the editor

Sunitinib (Sutent; Pfizer Pharmaceuticals Group, New York, NY, USA) is an orally administered vascular endothelial growth factor (VEGF) receptor tyrosine-kinase inhibitor (RTK) with demonstrated cytotoxic activity against various malignant diseases [1, 2]. We present the case of a 49-year-old patient who died of fulminant hepatic failure following third-line monotherapy with sunitinib for ovarian cancer. The patient was diagnosed with stage IIb ovarian cancer in 2002 and after R0 surgery; she received first-line chemotherapy. In 2006, second-line chemotherapy was started for disease recurrence, leading to a complete remission after six cycles. Nine months later, a tumor measuring 37 × 42 × 50 mm in the area of the left iliac vein was diagnosed again by CT scan. An explorative laparotomy was performed revealing an entirely inconspicuous abdominal cavity except for a tumorous lesion on the left pelvic wall, about 50 mm cranial of the inguinal ligament. The tumor was removed and histology revealed a lymph node metastasis of the ovarian cancer. Additional lymph nodes, multiple biopsies of the abdominal cavity and diaphragm, as well as peritoneal fluid cytology showed no evidence of metastatic disease. Since recurrence occurred nine months after second-line therapy, necessity of third-line chemotherapy was discussed with the patient, but she refused due to toxicities experienced with the previous treatments. At this point, the possibility of oral therapy with sunitinib was discussed. Sunitinib inhibits, amongst others, the RTKs: platelet derived growth factor (PDGF), VEGF c-KIT (produced by the KIT gene) and colony stimulating factor (CSF)-1 whose expression has been reported in ovarian cancer [1, 3]. The risks and possible complications due to side effects of sunitinib were explained to the patient and she was thoroughly informed about prohibited co-medication during the treatment. Sunitinib therapy was started, at a dose of 50 mg given orally once daily for 4 weeks every 6 weeks. Vital signs and laboratory analysis at the start of therapy were within normal limits. No toxicities except common terminology criteria for adverse events (CTCAE) grade 2 fatigue occurred during the first 4 weeks of therapy. On day 26 of the treatment, the patient presented with CTCAE grade 4 fatigue and an Eastern Cooperative Oncology Group (ECOG) performance status of 3 and was hospitalized. Abnormal laboratory reports included bilirubin 1.1 mg/dl; alanine aminotransferase (ALT) 52.5 U/l; aspartate aminotransferase (AST) 49.2 U/l; gamma glutamyl transpeptidase (γGT) 83.4 U/l; and thyroidea stimulating hormone (TSH) 27.22 mIU/l. She received 75 μg Levothyroxin daily for hypothyroidism as concomitant medication. A cranial CT scan did not reveal any abnormality. Therapy with sunitinib was stopped. Twelve hours after admission, the physical condition of the patient and laboratory results had dramatically worsened. Her conscious state deteriorated, she became hypoxic and was transferred to the Intensive Care Unit for intubation and supportive measures. Liver function deteriorated rapidly (Fig. 1), hepatitis serology was negative for HBsAg, and AntiHCV, AntiHBs was 281.2 IU/l. The patient died of liver failure 29 h after hospitalization, despite maximum supportive therapy measures. Immediate family members did not agree with an autopsy. Nevertheless, we believe that the liver failure was associated

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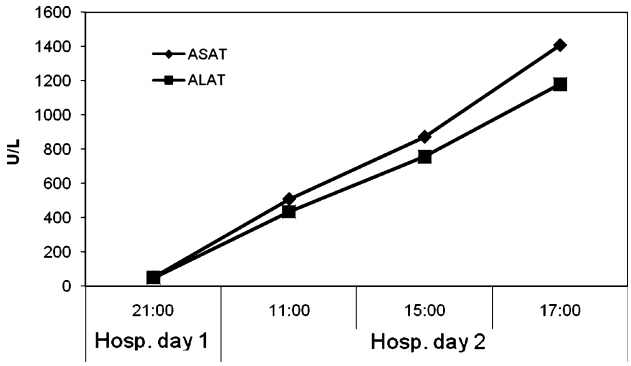

Fig. 1 After 26 days of sunitinib, liver enzymes surged uncontrollably

with sunitinib because there were no other possible causal factors for liver function decay and the patient was not receiving any other drugs that could increase the hepatic toxicity of sunitinib. Reported side effects following sunitinib treatment are fatigue, nausea, diarrhea, anorexia, constipation, hypothyreosis, neutropenia, thrombocytopenia and asymptomatic lipase elevations [1, 4]. Most dose-limiting adverse events are reversible after discontinuation of treatment [1], however, some are fatal, even in patients without predisposing factors. To our knowledge, this is the first case of sunitinib-induced liver failure in a patient with normal liver function and no liver disease at the start of therapy. In one phase II trial presented at the 2007 American Society of Clinical Oncology (ASCO), there were 4 deaths as a result of treatment-related liver failure [5, 6] on full dose sunitinib-therapy (50 mg/day) in patients with unresectable hepatocellular carcinoma (HCC). There were no deaths related to liver failure in another trial presented at ASCO 2007 on unresectable HCC where patients received 37.5 mg sunitinib daily [7]. Eligibility criteria in these trials included only patients with adequate organ function, but the grade 5 toxicity cases were not individually evaluated. Additionally, the time frame that the organ failure occurred was not mentioned. Unresectable HCC itself represents a risk factor for the development of liver failure over time. Further on, it is unclear whether liver failure occurs only in patients receiving full dose therapy or which mechanisms were accountable for liver toxicity by sunitinib. Further studies addressing this issue are warranted. There is an increasing number of patients treated with sunitinib in phase II/III trials for several solid tumors. Furthermore, sunitinib is becoming widely used for renal cell cancer and GIST-tumors [2]. It is therefore important that clinicians are aware of this dramatic complication, which can also occur in patients with no tumor load and normal liver function at the start of therapy.

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