

## Letters to the Editor

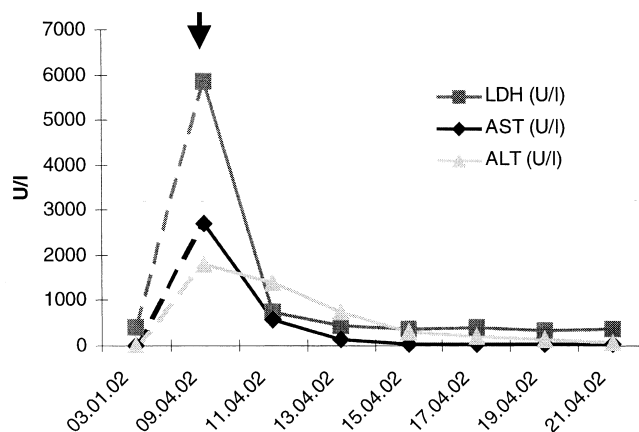
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### Severe hepatic toxicity due to thalidomide in relapsed multiple myeloma

Thalidomide has shown efficacy in the treatment of advanced refractory multiple myeloma even after autologous stem-cell transplantation [1] and has been evaluated alone or in combination in the treatment of various solid and hematological malignancies [2–4]. Both antiangiogenic activity [5] and the immunomodulatory properties of thalidomide are proposed mechanisms for its beneficial effects [6]. Common side-effects during treatment with thalidomide are sedation, constipation, skin rash and peripheral neuropathy. Less frequently bradycardia, hypotension and hypothyroidism have been described [7]. However, life-threatening toxicity due to thalidomide has occurred as toxic epidermal necrolysis [1], and in combination with steroids or anthracycline-based chemotherapy an increased incidence of thromboembolic events has been observed [8].

We report a 62-year-old female patient with refractory multiple myeloma who developed severe liver toxicity during treatment with thalidomide. The patient was diagnosed with multiple myeloma (IgG  $\kappa$ ) stage II A, in 1993. She did not respond to either the initial chemotherapy with melphalan and prednisone in 1995 or the subsequent five cycles of chemotherapy with vincristine, doxorubicin and dexamethasone 1 year later. An attempt to collect autologous peripheral stem cells was unsuccessful. In 1997, she was treated with six cycles of vinorelbine and dexamethasone and had a minor response with regard to the para-protein excretion.

Owing to progressive disease with painful osteolytic lesions and renal impairment, treatment with thalidomide (200 mg/day) and dexamethasone (40 mg/day for 4 days twice per month) was initiated in October 2001. Again, a minor response could be documented after 2 months of treatment by the decline in the para-protein. Three months later, pulmonary embolism occurred and the patient received oral anticoagulation with phenprocoumon; however, treatment with thalidomide and dexamethasone was not discontinued. Seven months after initiation of thalidomide, the patient rapidly developed malaise, progressive weakness and peripheral neuropathy. She presented with flapping tremor and elevated transaminases ( $50 \times$  upper normal value) indicating severe liver damage; bilirubin, alkaline phosphatase, calcium and potassium were within their normal ranges. Serology revealed no acute infection with hepatitis virus A, B or C. She had impaired renal function (creatinine 250  $\mu\text{mol/l}$ ), anemia (hemoglobin 9.0 g/dl) and hypoalbuminemia (28 g/l). While on oral anticoagulation, prothrombin time was decreased to 14% (international



**Figure 1.** Biochemistry results before and after thalidomide cessation (arrow).

normalized ratio 4.0). There were no clinical signs of cardiac failure: the ejection fraction according to cardiac ultrasound was 67%.

The patient had been under medication with trimipramine, transdermal fentanyl and co-trimoxazole (double-strength tablets three times per week) for >4 years and with monthly pamidronate infusions for >6 years, without any significant clinical or laboratory side-effects. We suspected toxicity due to thalidomide and stopped the drug; all other medication remained unchanged. Of note, aspartate aminotransferase declined to normal values 6 days after thalidomide withdrawal (Figure 1, arrow) and alanine aminotransferase after 7 days. Since the elevation of transaminases resolved rapidly, a liver biopsy was not performed. This prompt resolution after the cessation of thalidomide strongly suggests that thalidomide was the causative agent of the hepatic toxicity. So far, thalidomide-associated hepatitis, which had resolved 1 week after withdrawal of thalidomide and dexamethasone, has only been described in a female with chronic asymptomatic hepatitis C infection, who was treated for plasma cell leukemia [9].

With the increasing use of thalidomide in various indications, several previously rare and possibly unrecognized side-effects may emerge. Based on our findings we recommend regular monitoring of liver enzymes during thalidomide treatment.

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