Fatal hepatotoxicity associated with 6-mercaptopurine therapy

Sir,

The cytotoxic drug 6-mercaptopurine is a purine antagonist used in the remission maintenance regimen for standard risk childhood and adult acute lymphoblastic leukaemia. The UK Medical Research Council (MRC) protocols for acute lymphoblastic leukaemia were based on both mercaptopurine and methotrexate according to biological response, i.e., neutropenia and thrombocytopenia. Careful haematological monitoring is mandatory throughout maintenance therapy to avoid serious marrow toxicity, which may be prolonged. Mercaptopurine is reported to have hepatotoxic side effects such as dose reduction or withdrawal is advised in cases of hepatic impairment.

We report a case of fatal hepatotoxicity without overt marrow suppression in the maintenance treatment of adult acute lymphoblastic leukaemia. A 68-year-old man was referred to our unit in February 1994 for investigation of severe pancytopenia. Peripheral blood and bone marrow morphology together with immunophenotyping confirmed the diagnosis of pre-B acute lymphoblastic leukaemia. The patient underwent standard acute lymphoblastic leukaemia induction and early intensification regimes following entry to the MRC UK acute lymphoblastic leukaemia X trial. Maintenance therapy was delayed through prolonged cytopenia but was commenced in May 1994 and consisted of daily mercaptopurine 75 mg/m², weekly methotrexate 20 mg/m² and monthly intravenous vincristine 1.5 mg/m² with five-day courses of oral prednisolone 40 mg/m². Liver function tests were normal on starting maintenance therapy. Due to persistent problems with cytopenia, 40% doses of mercaptopurine and methotrexate were introduced and then increased to a maximum of 75%. Therapy was well tolerated without cytopenia but with mild elevation in both serum alanine transaminase and aspartate transaminase with normal serum bilirubin levels. Shortly after the fifth monthly cycle of vincristine, prednisolone, mercaptopurine and methotrexate, all treatment was stopped due to a marked elevation in serum bilirubin to 155 µmol/l (normal range 1–24 µmol/l), aspartate transaminase 182 IU/l (normal range 5–40 IU/l), alanine transaminase 149 IU/l (normal range 5–76 IU/l) and alkaline phosphatase 143 IU/l (normal range 36–125 IU/l). Apart from oral frusamide there was no other concomitant therapy taken. Ultrasound examination excluded biliary obstruction. Hepatitis serology and microbiological cultures were negative. Liver function continued to deteriorate with progressive jaundice, bilirubin rising to 600 µmol/l, aspartate transaminase to 132 IU/l, and alkaline phosphatase to 152 IU/l. In spite of intensive supportive therapy his condition deteriorated, developing hepatic encephalopathy with renal failure resulting in death. Post-mortem examination showed no evidence of biliary obstruction. Autopsy histology revealed marked intracellular and intracanicular cholestasis, focal bile inlets and mild intercellular fibrosis. There was mild condensation of the reticular framework with scattered hepatocytes in islets.

The hepatotoxic effects of mercaptopurine are well documented but reports to the Committee on Safety of Medicines since 1963 amount to two cases only, including one fatality (personal communication). The characteristic features are a combination of intrahepatic cholestasis and parenchymal cell necrosis. These effects are usually reversible on discontinuation of the drug, although deaths both in leukemic and non-leukemic patients have been reported. The Data Sheet indicates that hepatotoxic reactions are most common when daily doses exceed 2.5 mg/kg. The maximum daily dose in our patient received was 1.8 mg/kg, being similar to the two cases reported by Schorey et al. We would recommend that, whilst careful haematological monitoring is essential when prescribing mercaptopurine, due attention is given to regular liver function assessment. Elevation of serum bilirubin, in particular, may forewarn of impending cholestasis which may prove fatal.

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US residency programme

Sir,

As a recent graduate of the UK junior doctor system before moving to the US, I read Dr Salter’s comparison of the two systems’ with great interest.

I agree with Dr Salter that several aspects of the residency programme in the US are worth exploring for the UK, such as the matching programme – much fairer than the scramble for house jobs I went through, and improved feedback to junior staff about their progress by consultants, for example. Like him, I am also struck by how the mixture of ‘service’ commitment and education is balanced much more in favour of education in the US and that this is almost always the benefit of junior staff. While realising that this may be a luxury that hospitals in the UK may not be able to afford (or willing) to afford currently, one aspect of the American system could be copied at no extra cost (and perhaps even a saving). This is the fact that, once matched into a residency programme, a junior doctor works in one hospital or group of hospitals for a three year period, rotating through different departments. This seems a distinct advantage over the system I went through, changing jobs – though luckily not cities – every six months. I considered myself very lucky when I managed to land a job as senior house officer in a single hospital, lasting a whole year. Otherwise, two or three months into a job I would have to re-apply for the next, hoping it didn’t mean I would have to move home too.

Of course, every six months there was also a new telephone/bleep system to learn, a new laundry room to find, a new personnel department to hassle, a new consultant to ask for a reference – and more job interviews.

While staying in one place may not suit everyone, I think that it would benefit most junior doctors training in medicine (the general practice trainees do it, after all). It would give some well-needed stability as well as being a more efficient and cheaper option for the hospitals (fewer interviews). The only drawback may be that it could create an elite brand of junior doctor in the ‘best’ hospitals, but then that already exists. As they say here, ‘Hey, that’s life!’

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Books received


