Author's response to reviews

Title: Acute Liver Toxicity with Ifosfamide in Treatment of Sarcoma: a case report

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Author's response to reviews: see over
Dear Associate Editor,

Thank you very much for reviewing the manuscript ‘Acute liver toxicity with ifosfamide in treatment of sarcoma: a case report’. Below are revisions made in response to your comments. The changes are highlighted in red in the revised article.

1. Introduction – the words ‘product literature’ is replaced with ‘product package insert’

2. Table 1 of introduction– the list of adverse effects of ifosfamide is truncated to include those of >1% incidence only, and the table caption is changed to ‘Significant adverse effects of ifosfamide, per product package insert’

3. Paragraph 1 of case presentation – the ethnicity of the case patient is included

4. Paragraph 4 of case presentation – the dosing frequency of methylene blue is rewritten as TID from TDS

5. Paragraph 5 of case presentation – the discussion of ammonia in encephalopathy is omitted, and the corresponding reference (Bhatia et al.) is also omitted.

6. Paragraph 5 of case presentation – the section is rewritten more concisely and now reads: ‘Despite this her confusion persisted and blood tests revealed that at day one after finishing chemotherapy, she had developed a dramatic deterioration in liver function tests, with a 250-fold rise in alanine aminotransferase (ALT), and abnormal liver synthetic function and renal function (see table 2). The development of encephalopathy within 7 days of onset of jaundice constitutes hyperacute liver failure. There was a modestly elevated ammonia level at 77µmol/l (normal <50) accompanying the encephalopathy. These findings were attributed to ifosfamide use, based on temporal relationship and the subsequent normalisation on drug withdrawal. Apart from her mental state, the clinical examination was unremarkable. In particular, there was no fever, rash or arthralgia to suggest hypersensitivity drug reaction. The clinical features of drug-induced liver failure are difficult to differentiate from acute liver failure of other aetiologies.’

7. Paragraph 6 of case presentation – the final sentence is re-written to: ‘A brain CT scan excluded intracerebral causes of acute confusion, and showed a normal brain without significant cerebral oedema, which may be associated with higher grades of hepatic encephalopathy.’

8. Paragraph 7 of case presentation – the line ‘management advice was sought from the local liver unit...’ is omitted

9. Paragraph 7 of case presentation – the contents of cocodamol is explained in parathesis

10. Paragraph 2 of discussion – the description of Kosmas’ report is made more concise, and now reads: ‘There is one report of a patient with breast cancer and extensive liver...’
metastases, but no pre-treatment deterioration in liver function, who developed acute liver failure and subsequently died after treatment with ifosfamide and docetaxel, although there was also a rise in uric acid and tumour lysis could have contributed.’

11. Paragraph 3 of discussion – Figure 1 is referenced as adapted from the references Zhang et al. and Tascilar et al.

12. Conclusion – the conclusion is re-written as suggested

13. Reference list and corresponding references – these are adapted following the omission of the Bhatia et al. reference

I hope you will find these changes satisfactory and I would like to thank you again for considering this manuscript for publication in the Journal of Medical Case Reports.

Yours sincerely,

Dr. Michelle Cheung