Author's response to reviews

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

Authors:

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Author's response to reviews: see over
Dear Editors and Reviewers,

Thank you very much for considering the manuscript “Liver toxicity with use of ifosfamide in synovial sarcoma” for publication, and for the very helpful reviews. I have made revisions to the manuscript and have listed the specific changes below. I have attached the edited article with the revisions highlighted.

Reviewer: Neelesh Sharma

1. Wording in Abstract paragraph 3 and Case presentation paragraph 3 and 5 is revised as suggested.

2. Comment on clinical examination is added in paragraph 5 of Case Presentation. “Her clinical state was attributed to acute liver failure with encephalopathy secondary to ifosfamide, based on the temporal relationship between onset of liver derangement and drug intake, 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 liver failure of other aetiologies.”

3. Table 2 is edited to include laboratory normal range and explanation of abbreviations in the caption

4. Please see changes for the second reviewer regarding the full list of concurrent medications

5. Wording in paragraph 1 of Discussion is revised as suggested

6. Paragraph 3 of Discussion is revised to better explain the role of chloroacetaldehyde in causing the differential toxicity profile between ifosfamide and cyclophosphamide, with inclusion of the reference from Tascilar et al. as suggested, to highlight this point. “Nephrotoxicity, as characterised by Fanconi syndrome and glomerular damage, is more common in children, and is much more prevalent with ifosfamide than cyclophosphamide. Approximately 45% of the therapeutic dose of ifosfamide is metabolised into CAA via N-dechloroethylation, whereas only 10% of cyclophosphamide is converted to CAA. Thus, the nephrotoxicity of ifosfamide has been attributed to this metabolite.”

7. A diagram showing the metabolism of ifosfamide is added in Figure 1, to further explain the relationship between the metabolites and adverse effects of ifosfamide and cyclophosphamide.

8. The reference list is edited with addition of the Tascilar et al. reference.

Reviewer: Su Young Kim
1. Further detail on the concurrent medications administered during and after chemotherapy is described in paragraphs 3, 8, 11 of Case Presentation.

2. The role of measuring ifosfamide metabolites in this clinical context is commented on in the last paragraph of Discussion, in reference to a postulated mechanism for hepatotoxicity.

   “It is possible that ifosfamide, in susceptible individuals, may cause hepatotoxicity via acrolein. However, if acrolein is implicated then mesna should have a role in protecting against liver injury - this patient did not have any evidence of urothelial toxicity, e.g. haematuria, to indicate a failure of mesna in neutralising the acrolein produced. However idiosyncratic drug reaction to ifosfamide may also involve a completely different pathway due to individual metabolic variance. Measurement of ifosfamide metabolites requires specific liquid chromatography techniques and is not readily available outside of research studies, but in this case the demonstration of an unusually high level of acrolein, for example, may have been of clinical value to elucidate the mechanism of idiosyncratic hepatotoxicity.”

Reviewer: Michael Michael

1. Mesna was used during the administration of ifosfamide as is now described in paragraph 3 of Case Presentation along with a fuller description of the chemotherapy regime used. The potential role for hepatic protection is discussed in the last paragraph of Discussion.

2. The patient’s body mass index was not specifically mentioned but there was mention of her body surface area, calculated from height and weight, which dictated the dosage of chemotherapy given. Her BMI was 22, so the increased risk of hepatotoxicity in obesity was less likely in this case.

3. A liver biopsy was not performed for this patient and was not suggested by the liver team which was consulted. The diagnosis of drug-induced liver injury and the role of biopsy is discussed in the first paragraph of Discussion, and an additional reference used. “Most hepatotoxic reactions associated with chemotherapy agents are idiosyncratic, due to immunological reactions or variations in host metabolic response, and are not dose-dependent [6]. Immune-mediated drug reactions tend to show a latency of 1-5 weeks, associated with hypersensitivity features such as fever, rash, eosinophilia, and autoantibody positivity. Metabolic-mediated reactions lack these features. Biopsy of liver in acute drug reaction may show cytolytic or cholestatic features, or evidence of vascular injury. While certain drugs are known to cause specific types of injury, the type of injury in idiosyncratic drug reaction can be of variable morphology. Liver biopsy can be performed when drug-induced liver injury is suspected, along with imaging and laboratory investigations to exclude other causes, but key to the diagnosis is the temporal relationship of drug exposure and clinical picture. A validated diagnostic scale has been developed to aid diagnosis of drug-induced liver injury. It is based on the time correlation with drug use and withdrawal, response to re-exposure, previous reports of liver injury and exclusion of alternative causes [7.]”
4. CT was not performed as the patient’s ultrasound did not show evidence of fatty infiltration which is the first imaging modality to show this change (Norris, S. 2006)

5. The conclusion is revised to address the cautions for physicians when using ifosfamide and indeed any drugs, for their potential to cause liver and other adverse effects. “The nature of idiosyncratic drug reactions is that they are rare and unpredictable, therefore it is difficult to take precautions. This case report documents the hepatotoxic potential of ifosfamide, but more importantly alerts clinicians to the potential of adverse effects in any medication. In the case of ifosfamide, regular monitoring of liver enzymes and other blood parameters along with patients’ clinical conditions would allow early detection of unusual side effects. The most important management in drug-induced liver injury is to stop the offending agent.”

In addition, the authors have decided to change the title of the article to ‘Acute Liver Toxicity with Ifosfamide in Treatment of Sarcoma: a case report’, which we feel better describes the case and its clinical relevance.

I hope you will find these changes satisfactory and I would like to thank you again for considering this article for publication.

Best wishes,

Dr. Michelle Cheung