Author's response to reviews

Title: An adult patient with Nijmegen Breakage Syndrome and Hodgkins Lymphoma

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Version: 2
Date: 21 November 2013

Author's response to reviews: see over
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Version: 2 Date: 10 November 2013 Author’s response to reviews: see over
Reviewer's report

Title: An adult patient with Nijmegen Breakage Syndrome and Hodgkin Lymphoma

Version: 1 Date: 30 September 2013

Reviewer: Takayuki Saitoh

Reviewer's report:

This article reporting Hodgkin lymphoma with Nijmegen Breakage Syndrome provides an interesting case report. The manuscript is well written and the conclusion is well balanced.

Major comments:
1) The diagnosis of NBS in this report is unsatisfactory. Because the sequencing showed no mutation. There was no family history in this patient. The patient presented here was included into the Nijmegen Breakage Registry because of characteristic clinical signs and symptoms, i.e. microcephaly, immunodeficiency and chromosomal instability. Among the cases published within the first report of the Nijmegen Breakage Registry in 2000 (Arch Dis Child), in nine out of 55 (16%) patients no mutation was identified and 37 children (67%) presented without any family history. This is now stated in the manuscript.

Minor comment
1) The authors should discuss the dose of chemotherapy in details. Even if the patient has no organ failure, the previous report suggested that the patient should be given a decreased dose of chemotherapy. Because the chemotherapy drug affects the cytotoxic effect for tumors using DNA repair pathway.

The exact doses of chemotherapy given are now stated within the manuscript and were the following:
- cycle 1: Cyclophosphamide 375 mg/m\(^2\), Doxorubicin 12.5 mg/m\(^2\), Vincristin 2 mg total dose: initially cyclophosphamide dose was reduced to limit hematotoxicity, doxorubicin dose was adjusted to poor liver function.
- cycle 2 (3 weeks later), d1: Doxorubicin 19 mg/m\(^2\), Bleomycin 2.5 mg/m\(^2\), Vinblastin 4.4 mg/m\(^2\), Dacarbazin 194 mg/m\(^2\): in the second cycle doxorubicin was still applied in a lower dose to account for hepatic dysfunction, bleomycin was thought to be particularly toxic since it induces DNA breaks, especially in kidney failure like in our patient, as this cycle was applied while the patient was still recovering from severe sepsis also Vinblastin and Dacarbazin were reduced to limit the risk of neutropenic infection. Additionally, pegfilgrastim was given und days 4 and 19 to prevent prolonged neutropenia.
In the following cycles we increased the different chemotherapy doses step-wise to full or – for dacarbazine – 75% dose:
- cycle 2, d15: Doxorubicin 25 mg/m², Bleomycin 5 mg/m², Vinblastin 6 mg/m², Dacarbazin 281 mg/m²
- cycle 3, d1 (four weeks after cycle 2): Doxorubicin 25 mg/m², Bleomycin 10 mg/m², Vinblastin 6 mg/m², Dacarbazin 281 mg/m²,
- cycles 3, d15 and 4, dd1 and 15 each like cycle 3, d1

With regard to the optimal doses to be applied no clear standard in such patients is currently defined. We agree with the reviewer that based on the literature (childhood HL) a reduced dosage could have been maintained throughout the treatment. Regarding the very aggressive biology of the patient’s HL and a considerable likelihood that the patient would not undergo the standard number of cycles for stage IV disease, and also due to compliance issues we however opted to use the described dosages. The risk for second malignancy resulting from treatment is clearly stated within the Conclusions section of the manuscript.

2) The patient had severe organ failure with first diagnosis. Probably the liver failure comes from the infiltration. How about the renal failure?
The patient presented with high fever and multi organ failure. The origin of renal failure could have been either sepsis or high cell turn-over but was certainly aggravated by hypovolemia (high fever without adequate fluid substitution) and hepato-renal mechanisms. Tumor infiltration of the kidneys appears unlikely as this was not identified on initial magnetic resonance scan. This is now stated within the manuscript.

3) The patient had severe complication of infection and polyneuropathy. The authors should discuss the adverse events.
In fact, the patient described here suffered from two episodes of severe infection, both from fungi rather than bacteria. It has been described that the incidence of fungal infections is higher in NBS patients due to reduced cellular and humoral immunity (Gregorek et al, Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2009). In our patient, who had never suffered from infectious complications before, chemotherapy-induced neutropenia might have tipped him over the edge to systemic fungal infection. As suggested by the Reviewer this important consideration was included into the manuscript.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Reviewer's report

Title: An adult patient with Nijmegen Breakage Syndrome and Hodgkins Lymphoma

Version: 1 Date: 1 October 2013

Reviewer: Srdjan Pasic

Reviewer's report:
Ms "An adult patient with Nijmegen Breakage Syndrome and Hodgkins Lymphoma"
can be accepted with minor corrections and spelling mistakes (e.g. ESR) to BMC Hematology
The spelling errors were corrected. No other specific comments to be addressed.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interest