Reviewer's report

Title: Results from the 5-year, phase IV RENEW (Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis) Study

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Reviewer: E. Ann Yeh

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Rivera et al. discuss results from a registry-based study of long-term effects of mitoxantrone in patients with worsening multiple sclerosis. 509 patients from 46 MS centers were included. The results of the study are similar to that found in other studies of mitoxantrone safety, namely that approximately 5% of patients suffered from decreased LV ejection fraction, that therapy related leukemia was present in a small number of patients, and that persistent amenorrhea was present in a significant number of patients. The authors analyze data from all patients, but long-term follow up data was available for less than half of the patients.

Below are some suggestions:

(1) Minor essential revision: P. 4 last line: please clarify “menses absent on >= 2 consecutive treatment visits and do not resume”. Do the authors mean “without return of menses during the course of the study”?

(2) Major compulsory revision: It would be important for the authors to clarify in the abstract that long term data were only available for fewer than half of the patients who were started on mitoxantrone.

(3) Discretionary revision: Timing. It would be helpful if the authors discussed the timing of the onset of the cardiac events and mitoxantrone-related leukemias.

(4) Discretionary revision: What was the reason for the discontinuation of therapy in these patients?

(5) Minor essential revision: The authors note serious infection in a number of patients. Could they clarify which infections were reported?

(6) Major compulsory revision: In all figures except first the authors describe differences between groups with or without cardiac events. Could the authors please provide the p values so that it is clear whether there is a statistically significant difference between the groups when making this comparison?

(7) Minor essential revision: Figure legends: this is confusing. There seem to be figures numbered up to figure 7, but only legends for figures 1-5. Based on the text, I believe the figures are simply mislabelled. The numbering of the figures is also not very clear, sometimes overlapping with wording above (figure 6). I believe that figures 3a and 3b, as well as 4a and b are mislabelled, as is figure 5 (now labelled as figure 7).

(8) Minor essential revision: Concluding paragraph – the concluding paragraph is
worded a bit strongly in support of the therapy. It seems that the authors can only actually state that significant side effects, as noted in previous reports, were seen, and that caution must be used if mitoxantrone is prescribed, noting the necessity of close follow up for haematological, cardiac and neoplastic complications.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests