Reviewer's report

Title: Induction therapy with bortezomib and dexamethasone followed by autologous stem cell transplantation versus autologous stem cell transplantation alone in the treatment of AL amyloidosis: a randomized controlled trial

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Reviewer: Giampaolo Merlini

Reviewer's report:

In this trial, Huang et al. compared autologous stem cell transplant (SCT) alone and SCT preceded by 2 cycles of bortezomib and dexamethasone (BD) in renal AL amyloidosis and found that BD-SCT grants a higher rate of complete responses and longer survival. The Authors should be commended for undertaking the demanding task of performing a randomized trial in AL amyloidosis.

Major compulsory revisions

• Selection bias. One hundred percent of patients had renal involvement. This is probably a selection bias since the study was conducted in a nephrology institution, and should be acknowledged and in the manuscript. I would also suggest to reflect this in the Title (e.g. “… in the treatment of renal AL amyloidosis …”).
• The sample size is too small to allow patients stratification based on known risk factors, as well as to allow a subgroup analysis.
• In the introduction, the combination of melphalan and dexamethasone, besides treatment based on novel agents, should also be mentioned.
• In the Methods section the Authors state that patients “who met the criteria for MM” were excluded. The criteria used to define multiple myeloma should be reported in detail. Were only patients with symptomatic multiple myeloma excluded? If patients with “high” plasma cell infiltrate were excluded even if they did not have symptoms related to their tumor burden, this could have resulted in a relevant selection bias. Indeed, the median plasma cell infiltrate (3%) is significantly lower than expected.
• Hematologic and cardiac response should be assessed according to the novel criteria of the International Society of Amyloidosis (J Clin Oncol 2012; 30): 4541-9).
• The criteria used to define progression should be described in great detail, since there are no updated consensus criteria for progression in AL amyloidosis.
• The response rate to BD, before SCT should be reported in the text in greater detail. The Authors should comment on the rationale for transplanting patients with AL amyloidosis without multiple myeloma, who achieve CR with BD.
• The first paragraph of the Discussion repeats concepts and data already
presented in the Introduction and could be significantly reduced.

- Previous experiences with adjuvant BD following ASCT should be mentioned, discussed, and compared with the approach proposed in this manuscript.

- Table 2. The proportion of patients (if any) with NT-proBNP >8500 ng/L (advanced stage III) should be reported, as well as that of subjects with dFLC >180 mg/L (a level known to affect prognosis).

- Also, in Table 2, it is not clear how data are presented (median and range, mean and standard deviation or both?).

- In Table 3, ITT response rates should be reported (i.e. calculated at 24 months in 20 and 23 patients for the BD-SCT and SCT arm, respectively).

- Univariate analysis. BNP and proteinuria should also be tested as dichotomized variables. NT-proBNP should be included. Cardiac stage III should be tested as a separate variable (there was no survival difference between stage I and II in this series). The use of MEL 140 should also be tested. The multivariate models should be changed accordingly.

Minor essential revisions

- In the abstract the Authors should report the rate of hematologic response after BD and before SCT in the BD-SCT arm, as well as response rates at 3 and 6 months post transplant in both arms.

- Results, line 8 from bottom. “Nephritic” should probably read “nephrotic”.

- Table 2. The upper reference limit for alkaline phosphatase should be reported.

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests