

January 27, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7561-review.doc).

Revised Title: NOVEL AGENTS AND NEW THERAPEUTIC APPROACHES FOR THE TREATMENT OF MULTIPLE MYELOMA

Author: Roberto Ria, Antonia Reale, Angelo Vacca

Name of Journal: *World Journal of Methodology*

ESPS Manuscript NO: 7561

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer:

Reviewer #1 suggestions: The first sentence in the page 10 is not completed: "The risk of neurotoxicity early in the disease course represent the major contra."? -Add references to table 1 -I suggest to add more tables in each section summarizing the contents in simplified way with references -Try to reduce the references list to the most important ones (reference about 28 pages / 55 total)

(1) The first sentence in the page has been changed in: "The risk of neurotoxicity early in the disease course rapresents the major unfavorable factor" in the revised text.

(2) References were not added in table 7 (table 1 in the old text) because of the exceeding number of references. A review regarding developing monoclonal antibodies has been cited in the revised text and in the table caption.

(3) New tables 1 to 6 have been added in the revised text. No tables for new and newest drugs has been added since there are no approved therapies outside clinical trials at today.

(4) The reference list has been reduced. The large number of studies and clinical trials on multiple myeloma do not allow further reduction in the number of references without compromising the correctness of the manuscript.

Reviewer #2 suggestions: 1. Include the details up to year 2013 and the tread in figure 1. Also include references as an extra column. 2. Include reference in Table 2 as an extra column. 3. Please include some schematic diagram and the chemical structures of some important compounds. 4. The title "NOVEL AGENTS AND FUTURE DIRECTIONS IN MULTIPLE MYELOMA" is very unclear. Either it should focus on MULTIPLE MYELOMA detection or therapy or some thing else. The title of the manuscript should be changed to clearly address the content of the manuscript.

5. Check grammar of the manuscript.

Reply:

(1) Figure 1 has been updated as suggested by the Reviewer but no references have been added because of the exceeding number of references. A review regarding the history of myeloma therapy has been cited in the figure 1 caption and in the revised text.

(2) References were not added in table 7 (table 1 in the old text) because of the exceeding number of references. A review regarding developing monoclonal antibodies has been cited in the revised text and in the table caption.

(3) New figures 2 and 3 with the chemical structure of IMiDs and proteasome inhibitors have been added and cited in the revised text.

(4) The title has been changed according to reviewer criticism to NOVEL AGENTS AND NEW THERAPEUTIC APPROACHES FOR THE TREATMENT OF MULTIPLE MYELOMA.

(5) The grammar of the manuscript has been revised by two native speakers of English (Dr. Antonia Reale and Dr. Cecilia Perillo).

Reviewer #3 suggestion: 1) Encourage a revision - look at the scope of this journal and introduce some aspect to meet that. 2) Keep most of the substance on therapies. 3) Future Therapies - Expand here and introduce the novel methodological issues in choosing the right patient and the right way to follow-up to ensure issues such as lead time bias are excluded. Also highlight that with so many agents how we decide on the agents chosen. Are there novel methodological molecular epidemiological methods to select and follow patients. Table - introduce a third column for comments - in this could suggest when this agent will be considered etc. I have enclosed a PDF with some comments. These are general suggestions which the authors has to put together in a workable context.

Reply:

(1 and 2) We think that the discussion of the rationale of treatment strategy in patients with multiple myeloma fill with the scope of the journal.

(3) These agents are now in the development phase in relapsed/refractory patients (the majority of them are in phase 1/2 clinical trials) and their use is limited to clinical trials. To date we cannot establish when and in which patients the newest drugs are useful. Their use should be limited to patients enrolled in clinical trials until their conclusion and until the role of these newest drugs in myeloma therapy will be clarified. Finally, the regulatory agencies (FDA for USA and EMA for Europe) should approve the regular use of these drugs before their clinical use outside of clinical trials. These last phrases has been added in the revised text.

(4) Reviewer's comments in the attached PDF:

The title has been changed according to reviewer criticism to NOVEL AGENTS AND NEW THERAPEUTIC APPROACHES FOR THE TTREATMENT OF MULTIPLE MYELOMA.

The phrase: "We will also comment on the methodological aspects needed to brings these trials into reality" has not been added in the Abstract of the revised text because they do not represent the focus of our manuscript.

The phrase: "Thus, render the decision of the best therapy represent a difficult issue" has been changed into "Thus, the choice of the best treatment is a difficult issue" in the Abstract of the

revised text.

The phrase: "...their use is still not approved outside of clinical trials " has been added in the Abstract of the revised text.

The phrase: "In this paper we review the novel agents that could shape future directions for MM management" has been added in the Introduction of the revised text. The phrase: "We discuss this in the context of novel methods needed to recruit patients, monitor therapy, follow-up and reintervene" has not been added in the revised text because no new methods are needed to recruit patients. Moreover, "monitor therapy and follow-up" are not the objects of this paper.

There are no relevant bias to discuss.

There are no methodology issues to insert since there are only clinical issues in the choice of therapies.

The novel/early screening and diagnostics for detecting MM are outside the scope and objectives of this review.

The issues of the trial's design and the ethical aspects are outside the scope and objectives of this review

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Methodology*.

Sincerely yours,

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