Author's response to reviews

Title: Lenalidomide in heavily pretreated refractory diffuse large B-cell lymphoma

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Author's response to reviews: see over
Michael Kidd  
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RE: Revision of manuscript ID: 1904907835129808

Dear Dr. Kidd:

Thank you for the reviewers’ comments on our manuscript, now titled “Lenalidomide in Heavily Pretreated Refractory Diffuse Large B-cell Lymphoma: A Case Report.” We are pleased that the reviewers would consider this manuscript for publication in Journal of Medical Case Reports after satisfactory revision. The manuscript has been revised to address all of the reviewers’ comments, and a point-by-point response to these suggestions is attached. My coauthors and I believe that these changes have improved the manuscript, and the thoughtful reviews are appreciated.

Please direct all correspondence to my attention or contact me by telephone at +48 602 338290 or by e-mail at wojciech.jurczak@lymphoma.pl with any questions. I look forward to hearing from you.

Sincerely,

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Attachment: Response to Reviewers
EDITORIAL COMMENTS

Editorial Comment #1: Please include the study design in your title, i.e. Case Report. For example: A presenting with B in C: a case report.

Response to Comment #1: Per your request, “a case report” was added to the end of the previous title and now reads “Lenalidomide in Heavily Pretreated Refractory Diffuse Large B-cell Lymphoma: A Case Report.”

Editorial Comment #2: Please include the ethnicity of the patient in the abstract and case presentation sections.

Response to Comment #2: We agree that the ethnicity of the patient is important and have included this information in the abstract (page 2, under “Case Presentation”) and Case Presentation (page 5, first paragraph) sections of the manuscript.

Editorial Comment #3: Please include the patient’s gender (male/female).

Response to Comment #3: We agree that the patient’s gender is an important piece of information and have added this information to the abstract (page 2, under “Case Presentation”) and Case Presentation (page 5, first paragraph) sections of the manuscript.

Editorial Comment #4: Please change the “Background” section header to “Introduction”.

Response to Comment #4: As requested, the “Background” section header was changed to “Introduction” and can be found on page 3 of the manuscript.

Editorial Comment #5: Please do not include sub-headings in the “Case Presentation” section.

Response to Comment #5: All sub-headings were removed from the “Case Presentation” section of the manuscript.

Editorial Comment #6: Please remove dates of confinement in the “Case Presentation” section.

Response to Comment #6: As requested and to help maintain the anonymity of the patient, the specific years he received treatment were removed from the text (pages 5-9), appropriate figures (Figure 2 and Figure 4) and figure legends (page 20). The specific years were replaced with general year labels. For example, December 2008 is now referred to as December of year 1, May 2009 is now May of year 2, etc.
Editorial Comment #7: Please remove the patient’s details, hospital name and dates of confinement in the figure files, as this may jeopardize the anonymity of the patient.

Response to Comment #7: It is important to protect the patient’s identity; per your request, all patient information, hospital names, and dates have been removed from Figure 5.

Editorial Comment #8: Please be informed that each figure of the manuscript should be submitted as a single file.

Response to Comment #8: The figures are being resubmitted as 5 separate files alongside the revised manuscript.

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REVIEWER 1 COMMENTS
Comments to the Author

This is an interesting case report about lenalidomide in DLBCL. The patient received multiple treatments, and in particular lenalidomide was given as fourth-line treatment, concurrently with rituximab at first, then alone, and concurrently with palliative radiotherapy.

Reviewer 1, Comment #1: Why didn’t the patient receive radiotherapy after the first-line in the area of bulky cervical lymph node?

Response to Comment #1: The disease was dispersed and localized in the stomach and in other lymph nodes. For this reason, radiotherapy of only one lesion was not performed.

Reviewer 1, Comment #2: There is little proof that lenalidomide has been determined to treat the 4th relapse, since the patient was treated with radiotherapy in each anatomical site of relapse. Furthermore, there is no proof that the adenopathy of the neck (5-10mm) after lenalidomide discontinuation is really disease, since dimensions are not pathologic and both the PET scans before and after this finding were not positive in the neck, and no biopsy was performed.

Response to Comment #2: The reviewer is correct; no biopsy was performed after the 4th relapse (as indicated in Figure 2, the last one was in year 3, or 2009).
Reviewer 1, Comment #3: The authors should explain the timing of the infections during lenalidomide treatment, which could explain also the small adenopathy.

Response to Comment #3: We agree that the timing of the infections during lenalidomide treatment might be of interest to some readers. Therefore, per your request, we have added the months and year of the infections to the manuscript. On pages 8-9 of the manuscript, we have included this information and have a sentence that now reads, “The patient developed 2 infections: sinusitis in March of year 5, which was treated with amoxicillin, and herpes (varicella zoster virus infection limited to skin of left cheek, with severe neuralgia) from July to October of year 5, which was treated with acyclovir and analgesics.”

Reviewer 1, Comment #4: Based on this clinical case, lenalidomide was not important in achieving the response, but certainly was extremely important in the MAINTENANCE of the response achieved by chemotherapy and radiotherapy, and this could be the main topic of the case report. In particular, there are very few reports regarding the concurrent use of lenalidomide and radiotherapy, and this could be an interesting point in the discussion, e.g. explaining the potential molecular mechanisms by which lenalidomide could prolong the response to palliative radiotherapy.

Response to Comment #4: The radiotherapy used for this case was administered as 1-day, low-dose irradiation to relieve the severe pain the patient was suffering. Radiotherapy was not used with curative intent. Additionally, bone lesions from the sternum that were verified with histopathology did not respond to chemotherapy, but vanished with lenalidomide treatment. We believe that this was not the result of maintenance therapy and that the response observed in this chemotherapy-resistant patient was due to lenalidomide.

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REVIEWER 2 COMMENTS

Comments to the Author

Introduction to the case report is very well written. Lenalidomide mechanism of action is expertly described and comprehensive review of clinical trials utilizing lenalidomide alone or in combination with chemotherapy in DLBCL is provided.

Reviewer 2, Comment #1: Activity of lenalidomide in DLBCL, particularly in non-GCB DLBCL is very well described and known. Even though lenalidomide is not approved by FDA for use in DLBCL, based on the knowledge gained from the trials which the authors have listed in the case report, it is widely used for the relapsed/refractory DLBCL in the US. Thus, I don't believe that this case report is a novelty and provide additional knowledge.

Response to Comment #1: Treatment for patients that fail front-line R-CHOP therapy is not well established and this case report presents a detailed treatment plan for a chemotherapy-resistant
patient who received fourth-line lenalidomide plus rituximab as well as radiotherapy followed by maintenance lenalidomide. This treatment regimen is not well represented in current literature and provides useful information for clinicians treating patients with similar aggressive DLBCL.

**Reviewer 2, Comment #2:** Case report is very long and sometime repetitive. It should be more concise.

**Response to Comment #2:** To shorten the case report section, the detailed dosing regimen has been removed from the text and compiled instead into a new Table 1, “Treatment Regimen for Heavily Pretreated Patient With DLBCL.” We have also edited the text to remove redundancy and summarize information throughout the manuscript.

**Reviewer 2, Comment #3:** Immunohistochemical markers listed (CD20, MUM1, Ki67, CD5) are not enough for Hans classification of GCB vs non-GCB.

**Response to Comment #3:** We agree that there are not enough data to classify the patient as non-GCB per Hans classification. Unfortunately, no additional immunohistochemical data (such as CD10 or BCL6) are available. Therefore, the description of this patient as non-GCB has been removed from the manuscript.

**Reviewer 2, Comment #4:** It would be very important to identify whether this patient had “double hit” or “triple hit” DLBCL. Relapsed double hit DLBCL has extremely poor prognosis and the activity of lenalidomide in double hit DLBCL is not well known. Showing activity of lenalidomide in double hit DLBCL will be more original and novel.

**Response to Comment #4:** Although we agree that classifying the patient as “double hit” or “triple hit” would be of interest, no additional immunohistochemical data (such as BCL6 or MYC) are available for this patient.

**Reviewer 2, Comment #5:** Dosing of lenalidomide is not clear- it is stated as 25 mg daily first time and 10 mg daily q21d out of 28 days. If the patient tolerated 25 mg well, why was the dose decreased?

**Response to Comment #5:** The lenalidomide dose was reduced because of grade 3 neutropenia. To clarify this rationale for the reader, the following sentence has been added on page 8 of the manuscript, “Due to grade 3 neutropenia as classified by Common Terminology Criteria for Adverse Events (version 4.0), the lenalidomide dose was reduced from 25 to 10 mg.”
REVIEWER 3 COMMENTS

Comments to the Author

Reviewer 3, Comment #1: This case report is focused on lenalidomide as salvage treatment for this reason, the manuscript would benefit from a reduction in length. For instance the description of the medical history prior the period that led to the treatment with lenalidomide has to be substantially reduced. Overall the authors report here a heavily pretreated DLBCL patient treated with multiple lines of rituximab containing chemotherapies, including high dose chemotherapy and ASCT and successfully salvaged with lenalidomide.

Response to Comment #1: To shorten the case report section, the detailed dosing regimen has been removed from the text and compiled into a new Table 1, “Treatment Regimen for Heavily Pretreated Patient With DLBCL.” Efforts have also been made to reduce the text overall.

Reviewer 3, Comment #2: This of course is a favourable case, but did the authors treat only this patient with lenalidomide?

Response to Comment #2: No; other DLBCL patients have been treated with lenalidomide outside the clinical trial discussed in the manuscript. Currently, more than a dozen patients are being treated as part of this trial.

Reviewer 3, Comment #3: In the same frame time how many patients, if any, have been treated with lenalidomide in the authors’ institution and what was the response rate? The authors mentioned in the discussion that they treated other patients with lenalidomide. It is important to have this information to know how lenalidomide effectively works in the authors’ hands.

Response to Comment #3: As described above, no additional DLBCL patients have been treated with lenalidomide outside the clinical trial discussed in the manuscript. Currently, more than a dozen patients are being treated as part of this trial.

Introduction

Reviewer 3, Comment #4: Line 88. The sentence that the addition of lenalidomide to rituximab-chemotherapy in first-line treatment overcomes the negative prognostic impact of the non-GCB subtype should be mitigated because the data come only from subset analysis of two studies in a very limited number of patients.

Response to Comment #4: To clarify the number of studies and population size in the aforementioned trials, we have updated this sentence on page 4 of the manuscript to read “In this setting, several small (<70 patients), phase 2 studies have demonstrated that the addition of lenalidomide improved progression-free survival and overcame the negative prognostic impact.
of the non-GCB subtype on patient outcome” and included references for both Vitolo et al. 2014 and Nowakowski et al. 2013. In addition, we have added the statement, “An ongoing phase 2, randomized trial (NCT01856192) is currently comparing progression-free survival in GCB and non-GCB DLBCL patients treated with first-line lenalidomide combined with R-CHOP versus R-CHOP alone” to demonstrate that further investigation of the combination of lenalidomide with R-CHOP is ongoing.

Case report

Reviewer 3, Comment #5: Line 163. Central Nervous Involvement. The authors stated that the patient had CNS involvement but this is based only on suspicious clinical symptoms with neither imaging studies nor spinal fluid positive for that. Was flow cytometry on CSF performed?

Response to Comment #5: We agree that CNS involvement was based on suggestive symptoms without lesions in CT (measured in January of year 4 and February of year 4) and MRI (measured in January of year 4). Few cells were obtained in the cytology of the CSF; as a result, flow cytometry could not be performed.

Reviewer 3, Comment #6: However the paragraph should be reworded stating that CNS involvement was only a clinical suspect without a definitive diagnosis.

Response to Comment #6: The CNS involvement was suggestive and this was addressed on page 7, paragraph 2 of the manuscript. To clarify this concept, the statements now read, “Beginning in January of year 4, the patient began to present unspecified, transient symptoms suggestive of central nervous system (CNS) involvement: headaches and signs of VII cranial nerve paralysis. Although this conclusion could not be definitively diagnosed by lumbar puncture with cerebrospinal fluid (CSF) cytology and repeated imaging studies (CT and magnetic resonance imaging), intrathecal liposomal cytarabine was given as CNS prophylaxis.”

Reviewer 3, Comment #7: When the patient started lenalidomide there were two bone lesions and few months later there were additional bone lesions indicating progressive disease. The authors reported that radiotherapy was given. Please provide exactly the details of radiotherapy given, i.e. to all bone lesions? This is the most important criticism because the response seen later could be simply due to radiotherapy and not to lenalidomide.

Response to Comment #7: All the radiotherapy that was administered to the patient is shown in Figure 4. It should be noted that on each occasion, radiotherapy was administered as 1-day, low-dose irradiation to relieve the severe pain the patient was suffering. Radiotherapy was not used with curative intent. Details of the radiotherapy regimens have been added to Table 1 of the manuscript and are as follows:
April of year 4: Radiotherapy (8 Gy) was administered to the bone lesions in the proximal regions of the left scapula, the left humerus, and the femur, as well as the medial parts of the tibia and fibula.

June of year 4: Radiotherapy (6 Gy) was administered to bone lesions in the right ilium and the right scapula.

April of year 5: Radiotherapy was administered to bone lesions in the distal regions of the femur and the proximal regions of the tibia and fibula.

June of year 5: Radiotherapy was administered to bone lesions in the epiphyses of the knee joints and the right ankle.

**Reviewer 3, Comment #8:** Were there other lesions to monitor whose response could prove the positive effect of lenalidomide? Indeed we must be sure that the positive response is due to lenalidomide and not to radiotherapy given to multiple sites as suggested by figure 4.

**Response to Comment #8:** The only lesions observed in the patient are reported in Figure 4. No additional lesions were shown in PET-CT scans.

**Discussion**

**Reviewer 3, Comment #9:** Line 253. The authors say that their treatment was based on the original scheme reported by Zinzani et al. Indeed Zinzani reported Lenalidomide 20 mg + rituximab as others. The usual dose of Lenalidomide when is associated with rituximab is 20 mg. Why the authors have chosen 25 mg?

**Response to Comment #9:** The reviewer is correct; the 25 mg dosing scheme is more similar to that published by Wiernik PH, et al. 2008 and Witzig TE, et al. 2011, who administered 25 mg lenalidomide. This reference has been corrected and can be found on page 10, paragraph 2 of the manuscript.

**References**

**Reviewer 3, Comment #10:** Consider reducing the number of references.

**Response to Comment #10:** We appreciate the reviewer’s suggestion; however, we believe it is important to include a thorough background of the current literature in the Introduction section of the manuscript. Inclusion of references was required to accomplish this.
Reviewer 3, Comment #11: Reference 15. In the time the authors have submitted their manuscript, the final results of the study of the Italian group have been reported as a full paper in Lancet Oncology (Vitolo U, Chappella A et al, May 2014), please substitute this reference (that is the ASH presentation) with the full paper.

Response to Comment #11: As requested, the Chiappella et al. reference on page 3 of the manuscript has been updated to include the most recent Lancet Oncology publication from Vitolo et al. and is now reference #18.

Figures

Reviewer 3, Comment #12: Figure 3 can be omitted.

Response to Comment #12: Immunohistochemistry data are difficult to describe in text, so we feel it is necessary to keep this figure for the visual clarification of these results.