Author's response to reviews

Title: Memory loss during lenalidomide treatment: a report on two cases

Authors:

Adeline Rollin-sillaire (adeline.rollin@chru-lille.fr)
Xavier Delbeuck (xavier.delbeuck@chru-lille.fr)
Marianne Pollet (marianne.pollet@chru-lille.fr)
Marie-Anne Mackowiak (marie-anne.mackowiak@chru-lille.fr)
Pierre Lenfant (pierre.lenfant@chru-lille.fr)
Marie-Pierre Noel (marie-pierre.noel@chru-lille.fr)
Thierry Facon (thierry.facon@chru-lille.fr)
Xavier Leleu (xavier.leleu@chru-lille.fr)
Florence Pasquier (florence.pasquier@chru-lille.fr)
Emilie Lerhun (emilie.lerhun@chru-lille.fr)

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Author's response to reviews: see over
Dear Christopher Morrey,

Please find enclosed a revised manuscript (MS: 1429284928705049) that we wish to publish as a Case report in the BMC Pharmacology and Toxicology which is entitled “Memory loss during lenalidomide treatment: a report on two cases”. We describe the case of two patients who developed a severe and rapidly progressive cognitive impairment, involving mostly episodic memory with loss of independence in activities of daily living during lenalidomide-based treatment for multiple myeloma. Chemo-brain induced by lenalidomide may induce particular cognitive disorders. This is a possible unusual side effect of this medication; no major cognitive impairment with impact on activities of daily living was described so far with lenalidomide. The drug’s putative neurotoxicity is probably promoted by specific risk factors (such as previous chemotherapy, prior mild cognitive impairment, age and the presence of cerebrovascular lesions). The publication of this Case report in your journal will contribute to the better medical knowledge of possible lenalidomide’s side effects and could change clinical practice.

All co-authors have participated in the work, all have seen and agree with the content of the manuscript. We take full responsibility for the data. We have full access to all of the data.

Xavier Leleu received grant support, lecture fees and board honoraria from Celgene. Thierry Facon received lecture fees and board honoraria from Celgene. The others co-authors do not disclose any financial conflict.

We certify that this manuscript is not under review at any other publication.

We hope this article would be now suitable for publication in the BMC Pharmacology and Toxicology.
The point-by-point response is as follows:

**Editor’s comments:**

We would first like to thank Dr. Christopher Morrey for his useful comments. We hope to have addressed each point adequately.

We recommend that you ask a native English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/authors/authorfaq/editing.

The manuscript has been corrected by a native English speaker (PhD in Biochemistry and a professional medical writer for the last 10 years). We believe that any remaining language issues will be minor questions of personal style, rather than grammar or idiom.

**Conclusions**

It light of the referees reports it is essential that you moderate the conclusions that can be drawn from the case report. As Referee 2 suggests it is critical that you deemphasize a cause and effect relationship (since it is not proven beyond a reasonable doubt) but rather word the manuscript in an effort to increase awareness to the potential neurotoxicity of this agent among treating physician who may otherwise be reluctant to associate lenalidomide with such a side effect.

Thank you for your suggestion. We have now toned down our conclusions (page 13). The drug’s putative neurotoxicity is probably promoted by specific risk factors (such as previous chemotherapy, prior mild cognitive impairment, age and the presence of cerebrovascular lesions) and clearly does not occur in all treated patients.

**Limitations**

Please clearly state the limitations of this work in your manuscript.

The limitations are now clearly stated in the Discussion section (page 11). We particularly focused on the Naranjo Adverse Drug Reaction on Probability Scale, which was 6 out of 13 for the first patient and 5 out of 13 for the second - suggesting a probable causal relationship between the adverse event and lenalidomide administration.
Referee: 1

We first would like to thank Dr. Andreas Argyriou for his useful comments. We hope to have addressed each point adequately.

The cases presented do not convincingly support a potential association between memory loss and lenalidomide therapy.

P1 had cognitive deficit before the initiation of lenalidomide therapy. Memory problems worsened after its administration, but again this decline occurred while several other severe co-morbidities emerged.

We agree that patient 1 had mild cognitive impairment (with prominent dysexecutive dysfunction) prior to lenalidomide therapy. Nevertheless, two months after initiation of lenalidomide, the memory impairment worsened markedly, with the appearance of an amnesic syndrome and a negative impact on activities of daily living. The loss of 10 points for the free recall index and 15 points for the total recall index in the Free and Cued Selective Reminding Test (FCSRT) is a very acute, unexpected event and could not be ascribed to progression of cognitive impairment potentially induced by previous chemotherapy. By way of an example drawn from practice in our memory clinic, a worsening or improvement in the FCSRT score of this magnitude was never observed while prospectively monitoring a cohort of 85 patients with mild cognitive impairment over a 6-month period.

We performed a wide range of paraclinical investigations (MRI, lumbar puncture and many laboratory tests but did not find any explanatory infectious, vascular, metabolic or paraneoplastic co-morbidities. We now explain this more clearly in the Discussion section (pages 10-11).

We agree that the second decline in the patient’s health status (with asthenia, anorexia, apathy and somnolence) might have corresponded to a state of delirium with an infectious cause. However, neuropsychological assessments were not performed at that time.

P2 was an elderly patient with a brain MRI showing diffuse white matter lesions and a global atrophy.

We agree with your comment. Nevertheless, neither the patient nor his wife reported the presence of cognitive difficulties prior to initiation of lenalidomide or during previous chemotherapy regimens.

The overall atrophy and cerebrovascular lesions seen on MRI and the patient’s age might explain the very poor cognitive tolerance of lenalidomide. The latter could be also due to other comorbidities (such as prodromal AD for example). However the recovery of independence in ADL after the withdrawal of lenalidomide highlights an acute phenomenon. These various conditions and comorbidities could be risk factors for chemo brain.

The Use of the Naranjo adverse drug reaction probability score is highly recommended before one can conclude on a potential association between a drug and a toxicity.

Thank you for this suggestion. The Naranjo Adverse Drug Reaction Probability Scale score was 6 out of 13 for the first patient and 5 out of 13 for the second - suggesting a probable causal relationship between the adverse event and lenalidomide administration. We have now included these scores in the Discussion section (page 11).
The details of the scores are as follow:

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Do not know</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>+2</td>
<td>+2</td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>4. Did the adverse event reappear when the drug was re-administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5. Are there an alternative causes (other than drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td>+2</td>
<td>-1</td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

**Quality of written English:** Needs some language corrections before being published

The manuscript has been corrected by a native English speaker (PhD in Biochemistry and a professional medical writer for the last 10 years). We believe that any remaining language issues will be minor questions of personal style, rather than grammar or idiom.
Referee: 2

We first would like to thank Dr. Rachid Baz for his useful comments. We hope to have addressed each point adequately.

The authors report involves 2 patients who developed cognitive impairment while on lenalidomide highlighting this previously unreported toxicity of this agent. The main weakness of the paper is that they have not established causality with a high degree of certainty and beyond reasonable doubt and other possible causative factors could be at play. Nonetheless, they have engaged in considerable evaluations for the cognitive impairment including SPECT and have shown an element of reversibility after discontinuation of the offending agent (s). This does strengthen the evidence of causality to some extent.

Overall I would recommend deemphasizing a cause and effect relationship (since it is not proven beyond a reasonable doubt) but rather word the manuscript in an effort to increase awareness to the potential neurotoxicity of this agent among treating physician who may otherwise be reluctant to associate lenalidomide with such a side effect.

Thank you for your suggestion. We have now toned down our conclusions in the Conclusion section (page 13). The drug’s putative neurotoxicity is probably promoted by specific risk factors (such as previous chemotherapy, prior mild cognitive impairment, age and the presence of cerebrovascular lesions) and clearly does not occur in all treated patients. We have also included the Naranjo Adverse Drug Reaction on Probability Scale, which was 6 out of 13 for the first patient and 5 out of 13 for the second - suggesting a probable causal relationship between the adverse event and lenalidomide administration. These scores feature in the Discussion section (page 11).

The following Minor Essential revisions / questions are suggested

1- I would recommend editorial assistance with respect to improving grammatical errors and readability.

We thank you for your suggestion. The manuscript has been corrected by a native English speaker (PhD in Biochemistry and a professional medical writer for the last 10 years). We believe that any remaining language issues will be minor questions of personal style, rather than grammar or idiom.

2- I would suggest the use of generic drug names rather than trade name as in the case of bortezomib throughout the manuscript.

We now use the generic name throughout the manuscript (in the case report section (pages 7 and 8) and the Discussion section (page 11).

3- When in relation to high dose therapy did patient 1 develop his cognitive impairment? In addition, did this impairment improved prior to starting lenalidomide?
The onset of cognitive complaint for Patient 1 was about 6 months after starting the first cycle of chemotherapy. He was not receiving any antineoplastic agents at this time, since the latter had been withdrawn after the autograft. The first neuropsychological examination was performed 13 months after the onset of the cognitive complaints. Patient 1 was re-examined 6 months after the first neuropsychological examination (and 1 month after starting lenalidomide). He did not report a decrease in cognitive impairment. An impact on activities of daily living was also noted at that time (cessation of car driving because of an accident, development of apathy, inability to dispensing his medication, unpaid bills, etc.) and led to hospitalization.

The second neuropsychological examination was performed 2 months after the initiation of lenalidomide. We now mention the time intervals between the various examinations in the case report section (pages 6 and 7).

4- It would be important to note that penetration of the drug through an intact blood brain barrier is distinct than penetration through a blood brain barrier in a patient with cerebral lesions and does not necessarily imply that lenalidomide would penetrate to the CNS. the sedative effects of thalidomide would suggest that drug does penetrate the CNS but lenalidomide does not have sedating properties.

We agree that penetration of a drug through an intact blood-brain barrier differ from penetration through a potentially damaged blood-brain barrier (i.e. in a patient with brain lesions).

For Patient 1, blood brain barrier appeared to be intact because there was no spread of gadolinium contrast on MRI. However, in view of lenalidomide’s molecular weight and lipophilicity, some of the drug would probably have crossed the apparently intact blood-brain barrier. Patient 2 did not receive any gadolinium injections. His brain atrophy and vascular lesions may have enabled lenalidomide to cross the blood-brain barrier more easily.

It is difficult to draw firm conclusions in this respect, which could only be resolved by analyzing brain tissue.

The various suspected mechanisms of blood brain barrier penetration include a direct neurotoxic effect of the drug, oxidative stress and DNA damage, induced hormonal changes, immune dysregulation, cytokine release, vascular injury and blood clotting in small vessels and a genetic predisposition. We have included these points in the Discussion section (page 13).

Yours sincerely,

Adeline Rollin-Sillaire, MD

Emilie Le Rhun, MD