Author's response to reviews

Title: Carmustine (BCNU) for recurrent glioblastoma multiforme: efficacy, toxicity and prognostic factors

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Author's response to reviews: see over
Submission of the revised manuscript (MS: 9473240532616158)
Carmustine (BCNU) for recurrent glioblastoma multiforme: efficacy, toxicity and prognostic factors

Dear Doctor Norton,

Thank you very much for the possibility to submit a revision of our manuscript “BCNU for recurrent glioblastoma multiforme: efficacy, toxicity and prognostic factors.” We have extensively studied the comments of the reviewers and integrated them into the revised manuscript. Enclosed you will find a document with a point-to-point response to the concerns as well as the revised manuscript (one version to track changes, one version without the possibility to track changes).

With best regards

Thomas Reithmeier
Response for Alfredo Quinones-Hinojosa

Thank you very much for your important remarks. We integrated them into the revised manuscript and below you will find our point-to-point answers to your concerns.

1. Defining BCNU treatment in the abstract early on is important, whether systemic or local. Because local BCNU in the form of Gliadel for high grade gliomas has been extensively studied, both alone and with adjuvant temozolomide, the novelty of this study would be greater with systemic study.

We incorporated this point in the abstract.

2. The concept of previous relapses needs to be elaborated. In these patients, is each relapse equal to a resection? In these relapses, what was the incidence of BCNU, temozolomide use, or radiation therapy?

In the section patients’ characteristics on page 8 primary therapy as well as the treatment of previous relapses is described. To clarify this point we have incorporated the following table in the manuscript.

<table>
<thead>
<tr>
<th>First relapse</th>
<th>Second relapse</th>
<th>Third relapse</th>
<th>Fourth relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCNU</td>
<td>30</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Resection</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LINAC radiosurgery</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Local immunotoxin administration</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alternative chemotherapy (cilengitide)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: Treatment modalities in the relapse situation

3. Defining “macroscopically total resection” more specifically would be helpful. For example is it equivalent to gross total resection (versus near total resection)?

Macroscopically total resection is equivalent to gross total resection. Therefore we changed “macroscopically total resection” into “gross total resection”

4. In evaluation of prognostic factors: table 2, was there any correlation with gross total resection prior to recurrence?

We performed a statistically evaluation of this point and added the results into the manuscript. Gross total resection prior to recurrence is a negative prognostic factor for overall survival and progression free survival.

5. In evaluation of recurrent disease, it is often important to know the time since diagnosis of primary tumor. Though overall survival may change, a change in the time since initial diagnosis would help interpreting this info. It is unclear in table 1 if “time from initial diagnosis to start of BCNU” refers to diagnosis of recurrence or initial tumor.

The time span refers to diagnosis of the initial tumor. Therefore we changed “time from initial
diagnosis to start of BCNU” into “Time for diagnosis of initial tumor to start of BCNU”.

6. Would it be possible to describe location of tumors as a variable? We added this information in the section patients’ characteristics

7. When describing toxicities, were there any trends among those patients that showed adverse effects? Those that had more previous relapses for example? We also looked at this point and found that all patients with bone marrow toxicities had a temozolomide pretreatment had two or more cycles of BCNU and a stereotactic biopsy. This information was added to the toxicity section.

8. No mention was made of follow up time in this patients group (mean, range, standard deviation) Thank you for pointing this out. We added the median follow-up time to the results section. This is a more appropriate measure than mean, range, sd, for failure time variables. A corresponding remark and reference was added to the statistics section.

9. There is a figure 3 referred to in the second paragraph of progression free and overall survival in the results, though no such figure exists. We corrected this.

Response for Antonio Silvani

Thank you very much for your important remarks. We integrated them into the revised manuscript and below you will find our point-to-point answers to your concerns.

The population study is very heterogeneous as: tumor history and previous treatment: One methodically limitation of retrospective studies is the heterogeneous patient population, which is included in the discussion (page 12, last paragraph)

Problem of pseudoprgression is not discussed and a comment about the strategy of drugs combination for the problem of MGMT mediated chemoresistance is needed. The problem of pseudoprogresion and MGMT mediated chemoresistance is now included in the discussion on page 12 and 13 and might explain in part the dismal PFS rate of our patients.

How many BCNU cycles have been administered in the patient that developed lung fibrosis? In the patients with lung fibrosis three cycles of BCNU were administered and we added this information into the “Toxicity section”.

Conclusion: Is it not clear why this treatment could be considered in older patients and in low performance patients. As neither age nor KPS were identified as prognostic factors we concluded that BCNU might be an option for these patients after exploiting standard chemotherapy protocol (Stupp scheme and intensified temozolomide scheme)

Response for Renato v La Rocca

Thank you very much for your important remarks. We integrated them into the revised manuscript and below you will find our point-to-point answers to your concerns.
Data for efficacy of BCNU in glioblastoma are very limited in the literature, especially in the relapse situation in the temozolomide area and with regard to toxicity. These are important data as BCNU is one of the few drugs approved for treatment of GBM by the FDA and can be used as a benchmark to evaluate the efficacy and toxicity of the wide range of experimental chemotherapeutic protocols which are administrated to glioblastoma patients. The value and actuality of retrospective analysis of cisplatinum and BCNU chemotherapy in primary glioblastoma patients has recently been demonstrated by the paper of Antonio Silvani, published in the Journal of Neurooncology in 2009. Therefore we are convinced that our study is suitable for publication in BMC Cancer.

A retrospective analysis of MGMT promoter methylation and correlation with response to BCNU therapy could strengthen the results of this descriptive manuscript.

The discussion does not note the option of BCNU-impregnated wafer insertion.

We mentioned and discussed this point of missing data with respect to the MGMT status extensively in the discussion section as well as the use of Gliadel wafers.

BCNU appears to be a valuable therapeutic option for recurrent glioblastomas is perhaps an overstatement.

We agree with this notice of concern and pointed out that BCNU is a therapeutic option when no other validated treatment modalities are available and that the high rate of toxicity has to be considered.