

Reviewer #1:

Specific Comments to Authors: Glioblastoma is a fast-growing and aggressive brain tumor with a median survival of only 12-15 months. Leptomeningeal dissemination (LMD) is a severe complication of GBM raising diagnostic and therapeutic challenges in clinical routine. In this study, the authors combined methotrexate with systemic chemotherapy to treat LMD patients. They revealed the median overall survival of glioblastoma patients with leptomeningeal dissemination after receiving systemic chemotherapy in combination with intrathecal methotrexate is a bit longer than the regular chemotherapy regimen. The major issue for the combination regimen is the mild improvement in median overall survival time and the small patient number. There are several minor issues listed as follows.

Q1: Line number is recommended to put forward opinions about revision.

Response: thanks for your good advice, already add line number.

Q2: Are there patients who were only treated with a regular chemotherapy regimen in the trial? Or all of the 26 patients were treated in a combination of methotrexate?

Response: all of the 26 patients were treated with methotrexate and systemic chemotherapy.

Q3: Fig 2, please indicate what is the chemotherapy in this combination therapy. Is it TMZ or other chemotherapy drugs?

Response: thanks for your good advice, the chemotherapy regimen used is described in detail. Page19, line 10-11.

Reviewer #2:

Specific Comments to Authors: I would like to thank the authors to take out time to conduct this important study. I have a few comments (major and minor) as below and I believe they need to be addressed before this article can be considered for a potential publication

Q1: One of the major limitations of the study is the design, as the authors are building a case for efficacy of a medication, which can be best done in a prospective clinical trial or at-least prospective observational designs. This has to be addressed in more details in the limitations.

Response: thanks for your good advice, we have discussed the limitations of this retrospective study in more detail, as detailed in Page 13, line 13-19.

Q2: Additionally, the title needs to have the word retrospective analysis or any alternate work clearly indicating the study design.

Response: we have changed the title to "Intrathecal methotrexate in combination with systemic chemotherapy in glioblastoma patients with leptomeningeal dissemination: a retrospective analysis".

Q3: Another concern that I have is that there is no comparative group, even if this is a retrospective design there could have been a comparative group of patients who for one reason or the other did not receive ITC MTX.

Response: The cases we collected are mainly based on the hospital's medical record system. Since untreated patients do not enter the hospital inpatient system, we cannot find the detailed treatment information of these patients. Therefore, there was no control

批注 [A1]: The title is within the 18-word count limit of the journal.

group, and the historical survival data of GBM combined with LMD were used as a reference.

Q4: I do not think in this current scenario it is appropriate to comment on effectivity and safety profile as these measures need a comparator. Authors can address this by changing the theme of the manuscript from effectivity and safety to something like “clinical outcomes of GBM patients who received ITC MTX”.

Response: thanks for your reasonable advice, we have changed inappropriate expression to “This study aimed to estimate the clinical outcomes of combination therapy in GBM patients with LMD.” P5, line 27-28.

Q5: Sample size is small and has not been justified as to what level of power will this sample size give to inference these results.

Response: yes, agreed.

Q6: I do understand that the authors have touched on all the above limitations and rightfully so, I would advise them to change the theme of this manuscript away from finding effectiveness and safety profile.

Response: yes, agreed. We have changed the aim of this study from finding effectiveness and safety to estimate the clinical outcomes of combination therapy.

Q7: Some important and highly relevant studies have not been discussed (such as 10.1007/s11060-014-1486-2)

Response: thanks for your advice, we have added this study into the discussion part. P10, line 24-28.

Q8: Minor grammar polishing is required throughout the manuscript.

Response: thank you for pointing this out, we have had the manuscript language polished again.