

Mitomycin C and Capecitabine: An Additional Option as an Advanced Line Therapy in Patients with metastatic Colorectal Cancer. A Retrospective Analysis

Reviewer #1.

"This study was retrospective and could not guarantee mCRC patient homogeneity prior to the enrollment in this study."

Our study was indeed retrospective, as emphasized in the title as well as in other sections of the manuscript; the characteristics of our cohort were however, to our understanding, representative of the overall population with mCRC, as described in the literature.

"It is important to further help clinicians accurately judge the tumor characteristics after previous lines of standard chemotherapy prior to enrollment."

We thank the reviewer for highlighting the fact that it is not clear enough in the text that the patient and tumor characteristics, as described in Table 1, are indeed at the onset of MMC/Capecitabine treatment, after the completion of previous lines of treatment. This was now emphasized in the text ("Results", page 6).

"Your reference documentation is not comprehensive enough."

Following the reviewer's recommendation, we have added several references to the manuscript.

I also recommend that you give a final polish to your writing to keep your message as concise as possible."

Our professional institutional Editorial Board has now reviewed and polished the manuscript (English Editing Certificate attached).

Reviewer #2

"The first sentence of the abstract ("In recent years survival with metastatic colorectal cancer (mCRC) has improved significantly due to better management and new treatment options") is not suitable for the context of the manuscript. If the goal of this manuscript has already been achieved, then what is the need to do this research".

We thank the reviewer for his comment. We have rephrased the first sentence of the abstract of the manuscript accordingly; it now reads: "In recent years survival of patients with metastatic colorectal cancer (mCRC), though still limited, has improved significantly; clearly, when the disease becomes refractory to standard regimens, additional treatment options are needed".

"Has the previous administration of different drugs not affected the effectiveness of this (MMC/capecitabine) regimen?"

Previous lines of chemotherapy were almost invariably homogeneous and standard; we did not notice any impact of the specific previous regimens or their sequence on the effectiveness of the current regimen.

"The authors did not mention surgery in the studied patients. Is the effectiveness of the studied drugs related to previous surgery?"

Of note, most of the patients (79.1%) underwent surgery at some stage of their disease course. We did not notice any difference in the effectiveness of the studied drugs related to previous surgery.

"The study examined data from patients over a large span of time (2006-2020). The quality of patient care may have been different at different times. Does this not affect the study of authors? Can the authors examine their study in two time periods?"

Upon the reviewer's recommendation, we have now examined our results in two time periods, namely, 2006-2012 and 2013-2020, and found no apparent differences in outcome. This is not unexpected considering the overall poor outcome of the patients under this 3rd or further line of palliative treatment.

"The analysis methods are not well described in the manuscript."

The reviewer's comment is not completely clear to us; we now re-examined the description of the analysis methods in the Methods section, and found them very much detailed. We would appreciate a more specific comment.

Editorial Office's Comment

Company editor-in-chief

"Before final acceptance the author(s) must provide the English Language Certificate issued by a professional English language editing company"

Our professional institutional Editorial Board has now reviewed and polished the manuscript (certificate attached).

"The authors must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript."

We have added an "Article Highlight Section" as well as several new references to the original text.

(August 2, 2023)

Some Relevant Remarks:

- Key Words, appear already in the original text.
- Running Title, I suggest MMC/Capecitabine in metastatic colorectal cancer".
- Supportive Foundation Acknowledgement, I suppose "None"; is this correct?.
- Conflict-of-Interest, see form to be filled by each author.
- Author Contribution;
 - Design of the Study – B, M, G
 - Acquisition of Data - G
 - Data Analysis and Interpretation - G, M, B, A, Y
 - Manuscript Writing - G, M, B, A
 - Final Manuscript Approval - G, M, B, A, Y
- Institutional Review Board approval form
- Certificate of Biostatistics
- Copyright License Agreement
- Co-first authors are not permitted
- Data Sharing Statement
- References, first author's family name and initials should appear in bold; references in the text, in square brackets [1] [2], etc.
- English Editing Certificate

Unfulfilled Tasks:

- Article Highlights
- New references to be added
- =Review of our results in two different time periods
- Modify the original text accordingly with modifications in yellow.