

11-April-2020

Dear Editor,

Thank you very much for your kind e-mail, which gave us the possibility to revise our manuscript. We emended the paper according to the reviewers' comments. We hope this revision will make our manuscript better to be accepted in your journal. Please find enclosed the revised manuscript with suggested changes. Each comment has been answered accordingly in the manuscript and each text that has been altered was highlighted red in the revised manuscript.

We hope that the revised version will fulfill the requirements for publication in the World Journal of Gastroenterology.

Thank you very much.

Title: Adjuvant chemotherapy in older adults with stage II and III colon cancer: perspectives from the lens of clinical trials and real-world evidence.

Authors: Atul Batra, Rodrigo Rigo, Dropen Sheka, Winson Y Cheung

Name of Journal: World Journal of Gastrointestinal Oncology

Manuscript Type: Review

Manuscript no: 54885

Comment: It is a clear, structured and informative review concerning the lens of clinical trials and real-world evidence in the adjuvant chemotherapy in older adults with stage II and III colon cancer. This text is purported to be concise, but, in my opinion, is sometimes a little too "radical" regarding questions still matter of debate: For example, the question of quality of life in the elderly is affirmative and decided, while other convincing arguments do exist in the literature ("there is recognition that older adults are less willing to endure the side-effects of chemotherapy, as compared to younger patients"). This question should have been more discussed.

Response: Thank you for the comments. We have further discussed this question in the section on "quality of life". The following has been added to the text.

This should not be presumed for all older patients with cancer and individual preferences must

be known when discussing the benefits and risks of chemotherapy. Further, increased anxiety and depression have been reported in older individuals at diagnosis of cancer[81]. However, older adults who know about the diagnosis and prognosis of cancer are able to better cope with the anxiety compared with those who do not know the details[82] Therefore, an informed decision-making with older adults is likely to improve the psychosocial aspects of quality of life.

Comment: The question of the benefit of adjuvant chemotherapy in older patients with stage II colon cancer is still questioned and should have been more discussed too. The reference given to illustrate the absence of benefit on survival is lacking. Knowledge are lacking regarding the benefit/risk balance to help in decision-making for these patients in routine practice. I agree with the general conclusions of this review.

Response: We have further discussed this issue in the section on “stage II colon cancer in older adults”.

This raises the question of benefit of adjuvant chemotherapy in older adults with stage II colon cancer. The SIOG recommendations on treatment of older adults with stage II colon cancer acknowledge the limited data in this clinical situation. However, older age by itself should not be an exclusion criterion to offer adjuvant chemotherapy in stage II colon cancer with high-risk features. Thus, a discussion with older patients with high-risk stage II colon cancer regarding a small potential benefit and possible toxicities must be conducted while considering patients preferences.

The reference has been added.

Comment: As the authors state, available data from real-world evidence are limited by inherent selection bias and confounding by indication while individuals belonging to advanced age groups frequently do not or cannot participate in clinical trials. Despite these limits, real-world data may be used to address patient groups ineligible for clinical trials. Real-world data are derived from numerous various sources. I would underline the importance of using a validated statistical methodology to analyze real-world data with the aim of making results “all other things being equal”. The authors should discuss this constraint.

Response: We have added the following in the conclusions section, as suggested.

However, further real-world evidence using novel statistical methods eliminating such confounding and biases is likely to throw further light on controversies which are unlikely to be resolved by future clinical trials.