Peer Review File

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Reviewer A

In this study, the authors discussed the risk of progression in patients with BCG-unresponsive CIS of the bladder. By assessing the results of previous phase II/III clinical trials on bladder-sparing treatments for BCG-unresponsive CIS of the bladder, they concluded that the risk of progression is low.

Comment 1: They discussed about BCG-unresponsive CIS of the bladder in this study, but the title seems to include Ta-T1 NMIBC as well as CIS, so I think the title needs to be revised.

Reply 1: Thank you for taking the time to review our letter to the editor. We agree with your comment, as we focused on papers that include patients with BCG-unresponsive NMIBC with CIS, we adjusted the title accordingly.

Changes in text: Line: 1-3.

Comment 2: Generally, BCG-unresponsive disease includes BCG-refractory and BCG-relapsing tumors. The difference in the risk of progress between the two should be described.

Reply 2: Thank you for your insightful suggestion. The present study aimed to evaluate the risk of disease progression in patients with BCG-unresponsive CIS of the bladder who were enrolled in clinical trials on bladder-sparing treatments. As described in the manuscript, we encountered considerable variability in the reported data on progression outcomes, posing challenges for meaningful comparisons across trials. In this concise letter, we focused on the main difficulties we encountered in assessing progression outcomes within the included studies. These challenges included: 1) heterogeneity in the definition of disease progression, 2) the lack of fixed endpoints, 3) progression rates reported for patients who had progression after 2nd line of treatment, and 4) missing pathological and clinical tumor characteristics at the time of progression. While we acknowledge that patients with BCG-refractory versus –relapse NMIBC may have divergent progression outcomes, the heterogeneity of the studies precluded to conduct subgroup analysis. Moreover, it is important to note that, due to the limited risk of progression and low number of events (less than 10%), drawing conclusions regarding the correlation between any risk factor and the risk of progression requires adjustments in sample size and probably trial design. As such, we consider this beyond the “small scope” of this letter to the editor.

Reviewer B

The authors summarize several BCG-refractory single-arm studies and report their outcomes in a succinct manner that is easy for the reader to understand. The notion that the definition of disease progression in such trials should be standardized is well stated. I have the following comments:

Comment 1: Regarding the statement that the vast majority of patients where RC was postponed without jeopardizing oncological outcomes, Can the authors please expand on this and provide data that supports this? Do they think that there is sufficient follow-up to sustain this statement? For instance, did all studies have 2 years follow-up to assess recurrence/metastasis following cystectomy.

Reply 1: We would like to thank the reviewer for the thoughtful review. The median follow-up in the studies included was: 19.7, 36.4, 23.9, and 41 months. As such, the median follow-up was at least longer than 20 months. We agree that for a strong conclusion about progression rates the follow-up for each individual patient needs to be a minimum of 2 years. As such, we nuanced our conclusion, underlined the problem of not defining a fixed endpoint (at 2 year), and added your recommended reference (comment 3) which emphasizes this problem.

Change in text: Line 70-74. 80-81 and 96.

Comment 2: I suggest revising the statement in line 39 that this study aimed to assess the risk of disease progression, as this is a summary and commentary without analyses.

Reply 2: Thanks for your helpful input, we adjusted the text as stated below.

Change in text: Line 40 “The aim of the present study was to evaluate the risk of disease progression in patients with BCG-unresponsive CIS of the bladder who were enrolled in clinical trials on bladder-sparing treatments.”

Comment 3: Please consider adding reference PMID: 34955291, which discusses the need to define disease states and provides recommendations on design for such trials from the International Bladder Cancer Group
Reply 3: Thank you for bringing up this worthwhile suggestion.
Change in text: The reference is added in line 80-81.

Reviewer C
Great job! This is an intriguing brief overview of bladder-sparing strategies in NMIBC BCG-unresponsive patients. This area of research is broad, and I believe that future treatments for this subgroup of patients will be non-surgical.
Reply: Many thanks for your positive opinion on this letter to the editor. We agree with your idea that non-surgical treatment is the future treatment for BCG-unresponsive NMIBC.