

Peer Review File

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Reviewer A

Authors present an excellent critique of the ATLAS trial riddled with design flaws.:

Author should discuss if proper control for (UGN-102 + TURB) should have been TURB+ mitomycin 75mg dissolved in 56mL and held for 1h in bladder as past clinical study (PMID: 2495144) showed that dwell time of 1h significantly reduced the recurrence rate compared to the dwell time of 0.5h with higher urine levels of mitomycin (PMID: 3131943)

Although, treatment effects on recurrence should be evaluated at same time on bladder cancer patients with recorded history of recurrence and not new patients.

Reply to Reviewer A: It is indeed a good point to mention the ideal control arm in this scenario, we agree that MMC for 1 hour is standard of care (TURBT + adjuvant instillation), yet many dosing schemes have been published including different induction and maintenance schedules with 30mg and 40mg and with other drugs (e.g. Epirubicin) making it impossible to specify a concrete “best” standard of care, but we can certainly mention that adjuvant instillations with chemotherapy for up to 1 year if the way to go.

Changes in the text: we added the following sentence in lines 73-75: *“the current accepted standard of care per American and European guidelines is to give adjuvant chemotherapy instillations for up to one year after TURB(3,4,8).”*

Reviewer B

General:

Informative piece on UGN-102. The title of the article is misleading as it primarily discusses the new trials on UGN-102 therapy. Furthermore, a proper introduction to/reflection on chemoablation, with studies showing its original effectivity, is lacking.

Reply 1: We appreciate pointing this out, it is indeed a good suggestion, while both UGN-102 trials have been focused in chemoablation we should discuss it in more detail.

Changes made:

***We changed the title to:** “Chemoablation with UGN-102 in intermediate-risk non-muscle invasive bladder cancer, are we there yet?”

***We added the following text to the introduction:** *A few randomized trials have been published using chemoablation as an alternative to surgery with promising results, like DaBlaCa-13 which randomized patients to intravesical mitomycin C (MMC, 40 mg/40 ml) three times a week for 2 weeks vs TURB + six weekly adjuvant instillations, with a complete response of 57% in the chemoablation arm(5), or CALIBER which randomized patients to four once-weekly MMC 40mg intravesical instillations vs TURB, with a complete response of 37% in the chemoablation arm, both at the 3 month mark(6) --- lines 17-24.*

We also added to the introduction the objective of the trial, which was to test chemoablation with UGN-102, in lines 27-29 it now reads: *The trial evaluated the efficacy and safety of intravesical chemoablation with UGN-102.*

In addition, I believe that limitation 5 (sentence 103) should be discussed while presenting the trial (sentence 37 onwards). This is not a properly conducted RCT, and this should be mentioned whilst introducing the study.

Reply 2. Nice suggestion, we moved that point as requested. That point now can be found in lines 56-64.

Furthermore, a clear definition of intermediate risk has been updated per the EAU guidelines 2023, with some of the previous intermediate risk NMIBC patients now falling into the high risk categories, there is no reflection on this.

Lastly

sentence 26-27: "it significantly effects .." source? → we added two references, thank you.

Sentence 63: "Intermediate risk", how was this defined? → we added the sentence: (using the same definition as the ATLAS trial)

Sentence 69-70 "the results ... the authors" can be deleted for word count → done

sentence 77: "we acknowledge ... authors themselves." can be deleted or revised. → sentence deleted as unnecessary.

Sentence 114- onwards: no reflection of the Optima II trial, and a proper reflection on the question posed in the title: are we there yet? is lacking. → great point, **we added the following sentence to the**

conclusion: *So far, ATLAS and Optima-II trials have failed to demonstrate if UGN-102 is worth it as a chemoablation agent, with similar results to passive MMC instillations previously published(7,15).*

Reply 3: Good point, now the paragraph reads: This study included patients with NMIBC classified as intermediate risk (defined as having 1 or 2 of the following: multiple tumors, solitary tumor >3 cm, and/or recurrence of LG NMIBC within 1 year of the current diagnosis), *it is relevant to mention that the definition of intermediate risk does not entirely match the latest classification of the European Association of Urology (EAU)(8).*

Reviewer C

please see below for some comments regarding your editorial

1. consider changing "chemoablation" in the title as the drug itself does not ablate the tumor, it is just prolonged local chemotherapy , moreover chemoablation is never mentioned in the text elsewhere.

Reply 1: We made several changes addressing this, please see comments to reviewer B, these should suffice we think.

2. classification of intermediate risk disease varies depending on the guidelines, for example small TaHG is considered intermediate risk tumor as per AUA guidelines and high risk as per EAU guidelines.

Reply 2: Agree, clarifications have been made, please see comments to reviewer B.

3. TURBT alone is not the SOC for intermediate risk disease even for recurrences < 12 months, so I agree that the ATLAS trial was biased

Reply 3: NA

4. please explain the use of the phrase "deemed neoadjuvant" (line 87) it does not make sense

Reply 4: Thank you for pointing this out, the paragraph now reads:

The study protocol adopted differing definitions for disease-free survival (DFS) for each treatment group.

In the TURB arm, the presence of a bladder tumor during the 3-month cystoscopy was considered a

treatment failure, whereas in the UGN-102 arm, it was not, those patients would undergo TURB and UGN-102 was considered 'neoadjuvant', hence not indicative of treatment failure. This classification favorably impacts the experimental arm, as these patients underwent two treatments (UGN-102 + TURB), whereas the control arm solely received the resection.

5. consider referencing the article by Sountoulides P, et al. How well do we manage non-muscle invasive bladder tumors? A UK audit of real-life practices. *Urologia*. 2020 Aug;87(3):142-148. doi: 10.1177/0391560319899303. Epub 2020 Jan 21. PMID: 31959070. It discussed the controversies in the clinical application of the guidelines

Reply 5: While the paper is interesting, it is a small UK sample and an internal audit, we believe such discussion is beyond the scope of this editorial.

Reviewer D

The authors have presented an excellent review of the ATLAS trial, including the limitations of the study that should be considered when interpreting the results.

- Provide a clear definition for chemoablation in the text. Is chemoablation considered intravesical treatment only without TURBT?

Reply 1: Good suggestion, we added the following sentence in lines 17-18: "*chemoablation (i.e. to treat the tumors with intravesical chemotherapy only and skipping TURB)*"

- The authors should consider mention of sequential, intravesical gemcitabine-docetaxel use in the intermediate risk-NMIBC space (<https://doi.org/10.1016/j.euo.2023.06.011>). While the results of these studies are retrospective in nature, they may be the limited guiding data while awaiting 4-5 years for results of clinical trials. Perhaps mention of alternative agents to MMC variants such as UGN-102 will guide readers to this information.

Reply 2: While we do agree on the promising results of Gem/Doce in intermediate and high risk NMIBC we think that mentioning the different alternatives of adjuvant chemotherapy is beyond the scope of this editorial and would force us to mention all the alternatives and their results, which due to space constraints is not feasible.

- Formatting: consistently place the citations at the end of the sentence, rather than in the middle. Use all TURBT or all TURB, avoiding the inconsistent use of either.

Reply 3: Thank you for pointing this out, manuscript has been revised and corrected.