Editorial Commentary

Chemoablation with UGN-102 in intermediate-risk non-muscle invasive bladder cancer, are we there yet?

Daniel A. González-Padilla[1]^, José Daniel Subiela[2]^, Felipe Villacampa-Aubá[1]^

[1]Department of Urology, Clínica Universidad de Navarra, Madrid, Spain; [2]Department or Urology, Hospital Universitario Ramón y Cajal, IRYCIS, Universidad de Alcalá, Madrid, Spain

Correspondence to: Daniel A. González-Padilla, MD. Department of Urology, Clínica Universidad de Navarra, C. Marquesado de Sta. Marta, 1, 28027 Madrid, Spain. Email: dgonzalezp@unav.es.

Comment on: Prasad SM, Huang WC, Shore ND, *et al.* Treatment of Low-grade Intermediate-risk Nonmuscle-invasive Bladder Cancer With UGN-102 ± Transurethral Resection of Bladder Tumor Compared to Transurethral Resection of Bladder Tumor Monotherapy: A Randomized, Controlled, Phase 3 Trial (ATLAS). J Urol 2023;210:619-29.

Keywords: Bladder cancer; urothelial carcinoma; chemoablation; ablation; UGN-102

Submitted Nov 08, 2023. Accepted for publication Feb 21, 2024. Published online Apr 03, 2024.
doi: 10.21037/tau-23-563
View this article at: https://dx.doi.org/10.21037/tau-23-563

Recurrent low-grade (LG) non-muscle invasive bladder cancer (NMIBC) presents a considerable clinical challenge for urologists worldwide. This malignancy is characterized by a notable tendency for frequent recurrence coupled with a relatively low progression rate (1), as a result, it significantly affects the patient's quality of life, primarily due to the necessity of multiple surgeries, intravesical therapies, and regular surveillance through cystoscopies (2,3). Moreover, it imposes a substantial economic burden, considering NMIBC's high cost for healthcare systems globally (4).

While the impact of LG NMIBC on survival is minimal, there is a crucial need to advance treatments that can effectively reduce recurrence rates. The current management paradigm when a LG recurrence is diagnosed via cystoscopy and a negative urine cytology is to offer a transurethral resection of the bladder (TURB) with or without a post-operative single instillation with further adjuvant intravesical chemotherapy instillations for up to 1 year (5,6).

A few randomized trials have been published using chemoablation (i.e., to treat the tumors with intravesical chemotherapy only, and skipping TURB) 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 (7), or CALIBER which randomized patients to four once-weekly MMC 40 mg intravesical instillations *vs.* TURB, with a complete response of 37% in the chemoablation arm, both at the 3-month mark (8).

The results of the ATLAS trial conducted from January 2021 to March 2023, have been published by Prasad *et al.* in the October 2023 issue of the *Journal of Urology*. This was a randomized, controlled, open-label trial with a 1:1 randomization sequence. The trial evaluated the efficacy and safety of intravesical chemoablation with UGN-102, a novel reverse thermal hydrogel, containing 75 mg of MMC in 56 mL admixture. The reverse thermal properties of UGN-102 allow the administration of MMC as a liquid with subsequent conversion to a semi-solid gel, allowing for contact with the bladder for 4 to 6 hours, the gel slowly disintegrates and is urinated (9).

This study included patients with NMIBC classified as intermediate risk (defined as having one or two of the following: multiple tumors, solitary tumor >3 cm, and/

^ ORCID: Daniel A. González-Padilla, 0000-0002-5853-8845; José Daniel Subiela, 0000-0003-4176-8174; Felipe Villacampa-Aubá, 0000-0001-6779-6945.

Table 1 Complete response rates in similar previously published chemoablation trials (non comprehensive table)

Trial	ATLAS (9)	OPTIMA II (12)	DaBlaCa-13 (7)	Caliber (8)	Racioppi *et al.* (13)
Regimen used	6 weekly instillations (UGN-102)	6 weekly instillations (UGN-102)	3 times a week for 2 weeks (40 mg MMC)	4 weekly instillations (40 mg MMC)	3 times a week for 2 weeks (40 mg MMC)
Complete response	65% at 3 months	65% at 3 months	57% at 6–8 weeks	37% at 3 months	66% at 9 months

MMC, mitomycin C.

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) (10). These patients were subsequently randomized into two groups. The first group received UGN-102 (administered as six weekly instillations) with or without TURB, while the second group received TURB alone, which was considered the standard of care in this trial. The primary endpoint of the study was disease-free survival (DFS).

Authors report a complete response rate of 65% in the UGN-102 arm and 64% in the TURB arm at the 3-month mark. Furthermore, the estimated probability of DFS 15 months after randomization indicated 72% for the UGN-102 arm and 50% for the TURB arm. In the UGN-102 arm, the most frequently observed adverse events included dysuria (30%), micturition urgency (18%), nocturia (18%), and pollakiuria (16%) without meaningfully impacting the quality of life (as per EORTC-QLQ-NMIBC24) (9).

The main limitation of this trial, and openly acknowledged by the authors, is the premature termination of the study by the sponsor, who opted to 'pursue an alternative development strategy'. This decision was made with 282 patients recruited, which amounts to only 45% of the originally intended sample size of 632 participants necessary to achieve an 80% power to detect a hazard ratio of 0.77. Consequently, this termination places constraints on the interpretation of the data, limiting it to a descriptive analysis. While not directly applicable to this context, it is worth noting that early termination for benefit in randomized controlled trials has historically presented challenges in the interpretation of the data showing implausibly large treatment effects (11).

UGN-102 has previously undergone testing in a similar context in the OPTIMA II trial, a phase 2b study that involved 63 patients diagnosed with intermediate-risk NMIBC (using the same definition as the ATLAS trial). The OPTIMA II trial used the same treatment regimen, consisting of six weekly instillations. The results revealed a 65% complete response rate at the 3-month assessment. Notably, among the 41 patients with complete response, 25 (61%) maintained a disease-free status at the 12-month follow-up (12), which falls within the expected numbers from previous reports of intermediate-risk NMIBC (1).

Results of these two trials warrant acknowledgment of the efforts made by the authors. However, it is imperative to consider these findings in relation to previous chemoablation trials that have reported similar treatments (six to eight instillations of intravesical MMC) and comparable complete response rates summarized in *Table 1*. This leads us to question whether UGN-102 provides any additional advantages over conventional MMC chemoablation assuming an increased cost is likely.

Moreover, there are several concerns to consider when interpreting this trial.

(I) The trial was designed to evaluate results 3 months after randomization, which means 3 months (give or take) after the TURB in the control arm but only 6 weeks after the 6-week course of treatment with UGN-102, which introduces an imbalance in favor of the UGN-102 arm as only 6 weeks have elapsed since the end of treatment, while the TURB arm has had 12 weeks to develop a recurrence.

(II) The study protocol adopted differing definitions for 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.

(III) The observed high rate of progression to high-grade disease in both arms (7% at 3 months and

11% at 15 months) raises concerns regarding the suitability of including patients in such trials without prior histological confirmation of LG disease (beyond cold cup biopsy and urine cytology). Notably, only 41% of the patients had undergone a prior TURB. Perhaps these treatments should be reserved for recurrent rather than primary tumors, especially given that the EORTC and EAU21 calculators estimate a progression risk of below 5% at 1 year for these patients.

(IV) As the primary endpoint of the trial was DFS with a 24-month follow-up, the control arm can be considered "sub-standard" as no adjuvant chemotherapy instillations were allowed, and hence these patients were kept from receiving the best available care, the current accepted standard of care per American and European guidelines is to give adjuvant chemotherapy instillations for up to 1 year after TURB (5,6,14).

In conclusion, the ATLAS trial was an unsuccessful attempt to prove the utility of UGN-102 in clinical practice, probably methodological limitations and slow recruitment were perhaps the reasons why the sponsor itself decided to stop the trial and launch ENVISION (NCT05243550) in early 2022, a phase 3 single-arm trial with similar characteristics but with no TURB involved, just 1 year after starting ATLAS trial. 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 (7,13). Hopefully, ENVISION will finally show if UGN-102 can be used to keep some patients away from the operative room for a meaningful period of time, which is, of course a clinically relevant end-point, we shall eagerly await the final results by 2028.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Andrology and Urology*. The article has undergone external peer review.

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-563/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-563/coif). F.V.A. reports payments by Roche Pharma to give lectures about bladder cancer. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466-5; discussion 475-7.
2. Siracusano S, Silvestri T, Bassi S, et al. Health-related quality of life after BCG or MMC induction for non-muscle invasive bladder cancer. Can J Urol 2018;25:9480-5.
3. González-Padilla DA, González-Díaz A, Guerrero-Ramos F, et al. Quality of life and adverse events in patients with nonmuscle invasive bladder cancer receiving adjuvant treatment with BCG, MMC, or chemohyperthermia. Urol Oncol 2021;39:76.e9-76.e14.
4. Lee LJ, Kwon CS, Forsythe A, et al. Humanistic and Economic Burden of Non-Muscle Invasive Bladder Cancer: Results of Two Systematic Literature Reviews. Clinicoecon Outcomes Res 2020;12:693-709.
5. Babjuk M, Burger M, Capoun O, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). Eur Urol 2022;81:75-94.
6. Laukhtina E, Abufaraj M, Al-Ani A, et al. Intravesical

Therapy in Patients with Intermediate-risk Non-muscle-invasive Bladder Cancer: A Systematic Review and Network Meta-analysis of Disease Recurrence. Eur Urol Focus 2022;8:447-56.
7. Lindgren MS, Bue P, Azawi N, et al. The DaBlaCa-13 Study: Short-term, Intensive Chemoresection Versus Standard Adjuvant Intravesical Instillations in Non-muscle-invasive Bladder Cancer-A Randomised Controlled Trial. Eur Urol 2020;78:856-62.
8. Mostafid AH, Porta N, Cresswell J, et al. CALIBER: a phase II randomized feasibility trial of chemoablation with mitomycin-C vs surgical management in low-risk non-muscle-invasive bladder cancer. BJU Int 2020;125:817-26.
9. Prasad SM, Huang WC, Shore ND, et al. Treatment of Low-grade Intermediate-risk Nonmuscle-invasive Bladder Cancer With UGN-102 ± Transurethral Resection of Bladder Tumor Compared to Transurethral Resection of Bladder Tumor Monotherapy: A Randomized, Controlled, Phase 3 Trial (ATLAS). J Urol 2023;210:619-29.
10. Sylvester RJ, Rodríguez O, Hernández V, et al. European Association of Urology (EAU) Prognostic Factor Risk Groups for Non-muscle-invasive Bladder Cancer (NMIBC) Incorporating the WHO 2004/2016 and WHO 1973 Classification Systems for Grade: An Update from the EAU NMIBC Guidelines Panel. Eur Urol 2021;79:480-8. Erratum in: Eur Urol 2023;83:e140-1.
11. Bassler D, Montori VM, Briel M, et al. Early stopping of randomized clinical trials for overt efficacy is problematic. J Clin Epidemiol 2008;61:241-6.
12. Chevli KK, Shore ND, Trainer A, et al. Primary Chemoablation of Low-Grade Intermediate-Risk Nonmuscle-Invasive Bladder Cancer Using UGN-102, a Mitomycin-Containing Reverse Thermal Gel (Optima II): A Phase 2b, Open-Label, Single-Arm Trial. J Urol 2022;207:61-9.
13. Racioppi M, Di Gianfrancesco L, Ragonese M, et al. Chemoablation with Intensive Intravesical Mitomycin C Treatment: A New Approach for Non-muscle-invasive Bladder Cancer. Eur Urol Oncol 2019;2:576-83.
14. Holzbeierlein JM, Bixler BR, Buckley DI, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline: 2024 Amendment. J Urol 2024;211:533-8.

Cite this article as: González-Padilla DA, Subiela JD, Villacampa-Aubá F. Chemoablation with UGN-102 in intermediate-risk non-muscle invasive bladder cancer, are we there yet? Transl Androl Urol 2024;13(4):639-642. doi: 10.21037/tau-23-563

