Editorial Commentary

Ablative therapy with UGN-102 for low-grade intermediate risk non-muscle-invasive bladder cancer: ready for primetime?

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Non-muscle-invasive bladder cancer (NMIBC) is a heterogenous disease with widely variable treatment options and outcomes depending on risk stratification. Per American Urological Association (AUA) guidelines, intermediate risk (IR) NMIBC is characterized by either a low-grade (LG) T1 tumor, a solitary high-grade (HG) Ta <3 cm non-recurrent tumor, or LG Ta tumor with certain features including recurrent within 1 year, tumor size >3 cm, or multifocal disease (1). Thus, IR NMIBC is by definition a heterogeneous disease state. While patients with high-risk NMIBC have meaningful risk for progression and death, the primary concern with IR NMIBC is a 15–70% chance of recurrence and need for quality-of-life impacting management, due to an associated <5% risk of progression to muscle invasive bladder cancer (1). There is a non-negligible operative risk with procedures under anesthesia in the predominantly elderly and comorbid bladder cancer population, as well as morbidity from repetitive resection and intravesical therapy (2). Therefore, recent efforts have been directed towards decreasing the morbidity associated with transurethral resection of bladder tumor (TURBT) and adjuvant intravesical chemotherapy for IR NMIBC.

Aqueous mitomycin has been utilized for chemoablation of NMIBC in the DeBlaCa-13 study, where patients received an intensive course of intravesical mitomycin, and compared to TURBT and adjuvant intravesical chemotherapy, had an overall decrease in the number of TURBTs performed and comparable 12-month recurrence-free survival (RFS) (3). Furthermore, chemoablative reverse thermal gel with mitomycin has been used successfully in the treatment of LG upper tract urothelial carcinoma in an effort to avoid the morbidity associated with repeated endoscopic procedures or nephroureterectomy (4).

In this timely study published by Prasad *et al.*, the ATLAS trial compared treatment with a chemoablative reverse thermal gel containing mitomycin called UGN-102 versus TURBT alone for patients with LG IR NMIBC (5). This was a prospective phase 3 trial of 282 patients with LG IR NMIBC diagnosed on cold cup biopsy, while leaving tumor in situ. Patients either received UGN-102 with or without TURBT or TURBT alone. Both groups were found to have similar complete response (CR) rates (65% for UGN-102 group and 64% for TURBT group) and rates of disease progression 3 months after surgery. Disease-free survival (DFS) was found to be superior in the UGN-102 arm with 72% DFS at 15 months compared to 50% in the TURBT monotherapy group. Durability of response was also superior in the UGN-102 group at 18 months (5).

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While this study is of significant interest, there are some notable limitations. First, the study was terminated early, prior to half of the accrual goal being reached, rendering the trial underpowered to perform hypothesis testing. As the authors acknowledge, DFS was defined differently in each group—residual LG disease at 3 months was considered a DFS event in the TURBT monotherapy group but not in the UGN-102 group. This departs from typical clinical trial design that utilizes CR. In fact, the Society for Immunotherapy of Cancer (SITC) and the International Bladder Cancer Group (IBCG) recently presented a consensus statement that recommends CR as the primary outcome for studies investigating ablative therapy for low and IR NMIBC (6). These organizations define recurrence as histologically proven tumor of any grade or stage within the bladder, progression to muscle invasive disease, or clinical stage/grade progression, rather than residual tumor at 3-month per the ATLAS trial (6). Next, the control TURBT arm could have allowed for adjuvant intravesical therapy, as it is expected to have high rates of recurrence with TURBT alone (1). Both a single dose of intravesical chemotherapy as well as repeated instillations have both been shown to provide an absolute risk reduction of recurrence: 27% and 13–14%, respectively (7,8). For IR patients, both of these treatment modalities should be offered to patients and may explain some of the difference in DFS as one group received intravesical therapy at the time of surgery and the other did not. In the chemoablative DaBlaCa-13 study, the definition of DFS was the same for both groups and in the control group patients received adjuvant intravesical therapy (3). Lastly, there was a large number of patients with missing DFS data in both groups, making it difficult to interpret the results of the study. In particular, in the control TURBT arm, of the 85 patients who did not have a DFS event, only 49 were disease free at the end of the study with the remaining 36 patients either having no post-TURBT assessment or withdrew from or violated the study.

The aim to limit the morbidity of treatment for IR NMIBC is laudable and should be taken in the context of an improving side effect profile for traditional resection and adjuvant intravesical therapies. The true morbidity of TURBT is understudied and certainly an area that needs research focus. The authors of the ATLAS trial contextualized TURBT morbidity with a study that utilized the National Surgical Quality Improvement Program database, which showed a 5.1% 30-day complication rate, 3.7% hospital readmission rate, and 0.8% 30-day mortality after TURBT. Upon granular assessment, patient-specific risk factors increasing complication rate included ASA score 3–5, poor functional status, CHF, renal failure, and bleeding disorders (9). Therefore, the goal of avoiding TURBT in these highest-risk patients is compelling, while this does not seem necessary in lower risk groups, since the standard of care utilizing TURBT followed by adjuvant intravesical chemotherapy provides established oncologic benefit with acceptable toxicity.

The direct toxicity associated with adjuvant intravesical therapy for IR NMIBC seems to be decreasing over time. Sequential intravesical gemcitabine and docetaxel (Gem/Doce) has consistently shown clinical efficacy and an optimal safety profile amongst patients with various types of pathology and risk factors (10-12). With respect to IR NMIBC, a recent retrospective cohort of 77 patients with IR disease treated with Gem/Doce demonstrated 2-year RFS of 71% amongst the entire cohort and 79% amongst those that were treatment naïve, which compares similarly to BCG or single agent chemotherapy (10). A follow-up multi-institution series of 182 patients with LG IR NMIBC treated either with Gem/Doce or BCG demonstrated no difference in oncologic outcomes between groups. Importantly, Gem/Doce is consistently well-tolerated across studies, with 2.9–3.9% of patients unable to a complete induction course, and 2.6–4.0% of patients with Grade 3+ treatment-related adverse events (10,11).

In summary, we commend the authors of the ATLAS trial for moving the field of NMIBC forward with the important goal of limiting morbidity of treatment for IR NMIBC. There seems to be potential to add UGN-102 to the armamentarium of treatment options for NMIBC, particularly for patients with significant medical comorbidities that are unable to safely undergo a TURBT, or those with very high-volume or unresectable LG tumors where chemoablation is imperative. Therefore, we recommend further careful study of this agent to improve treatment options for patients with LG IR NMIBC.

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