Title

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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

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Study Need and Importance: The standard of care for treatment of low-grade intermediate-risk nonmuscle-invasive bladder cancer (LG IR NMIBC) is transurethral resection of bladder tumor (TURBT), typically performed under general anesthesia. As LG IR NMIBC is a highly recurrent malignancy, patients often endure repeated surgeries that may be associated with significant postoperative and long-term morbidity. We sought to evaluate the efficacy and safety of a nonsurgical alternative for the treatment of LG IR NMIBC offered by UGN-102—a mitomycin-containing reverse thermal gel—which can be administered on an outpatient basis in an office setting.

What We Found: Primary chemoablation using UGN-102 resulted in complete eradication of disease in a substantial number of patients (65%) 3 months after treatment initiation, with sustained durability up to 12 months (estimated probability of durable response 12 months after treatment initiation was 73%). A total of 13 patients (32%) had documented disease recurrence. Adverse events were generally mild or moderate in severity.

Limitations: The primary limitation of this study is its open-label, single-arm design. The absence of a control group complicates interpretation of treatment effect and permits only indirect evaluation of the efficacy and safety of UGN-102 chemoablation compared with TURBT.

Interpretations for Patient Care: UGN-102 chemoablation is a nonsurgical, minimally invasive procedure that can be performed in a physician's office and results in clinically significant treatment response with demonstrated durability. Treatment with UGN-102 may provide an alternative to repetitive TURBT surgery for patients with LG IR NMIBC. A more definitive assessment of the role UGN-102 may play in patient care must await results from an ongoing phase 3, randomized, controlled trial of UGN-102 versus TURBT (NCT04688931).

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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

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Abbreviations and Acronyms

AE = adverse event
CR = complete response
HG = high-grade
IR = intermediate-risk
ITT = intent-to-treat
LG = low-grade
NMIBC = nonmuscle-invasive bladder cancer
TEAE = treatment-emergent adverse event
TURBT = transurethral resection of bladder tumor
UC = urothelial carcinoma
UTUC = upper tract urothelial carcinoma

Purpose: Low-grade intermediate-risk nonmuscle-invasive bladder cancer (LG IR NMIBC) is a recurrent disease, thus requiring repeated transurethral resection of bladder tumor under general anesthesia. We evaluated the efficacy and safety of UGN-102, a mitomycin-containing reverse thermal gel, as a primary chemoablative therapeutic alternative to transurethral resection of bladder tumor for patients with LG IR NMIBC.

Materials and Methods: This prospective, phase 2b, open-label, single-arm trial recruited patients with biopsy-proven LG IR NMIBC to receive 6 once-weekly instillations of UGN-102. The primary end point was complete

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response (CR) rate, defined as the proportion of patients with negative endoscopic examination, negative cytology and negative for-cause biopsy 3 months after treatment initiation. Patients with CR were followed quarterly up to 12 months to assess durability of treatment effect. Safety and adverse events were monitored throughout the trial.

Results: A total of 63 patients (38 males and 25 females 33–96 years old) enrolled and received ≥1 instillation of UGN-102. Among the patients 41 (65%) achieved CR at 3 months, of whom 39 (95%), 30 (73%) and 25 (61%) remained disease-free at 6, 9 and 12 months after treatment initiation, respectively. A total of 13 patients had documented recurrences. The probability of durable response 9 months after CR (12 months after treatment initiation) was estimated to be 73% by Kaplan-Meier analysis. Common adverse events (incidence ≥10%) included dysuria, urinary frequency, hematuria, micturition urgency, urinary tract infection and fatigue.

Conclusions: Nonsurgical primary chemoablation of LG IR NMIBC using UGN-102 resulted in significant treatment response with sustained durability. UGN-102 may provide an alternative to repetitive surgery for patients with LG IR NMIBC.

Key Words: urinary bladder neoplasms; mitomycin; clinical trial, phase II

Bladder cancer is the sixth most common cancer in the United States, with an estimated 81,400 new cases diagnosed in 2020.[1] At the time of diagnosis, 75% of patients present with nonmuscle-invasive bladder cancer (NMIBC).[2,3] NMIBC includes a clinically heterogeneous group of cancers with a wide range of recurrence and progression probabilities.[4,5] Treatment guidelines recommend classifying patients with NMIBC as being at low, intermediate or high risk for disease recurrence and/or progression.[2,4,6] While the management of low-risk and high-risk patients appears clear, the best treatment option for intermediate-risk (IR) patients is uncertain.[3] It is estimated that low-grade (LG) IR NMIBC represents approximately 25% of newly diagnosed bladder cancer cases in the U.S.[7]

The standard of care for treatment of LG IR NMIBC is transurethral resection of bladder tumor (TURBT), usually performed under general anesthesia.[4,8] Instillation of adjuvant intravesical chemotherapy is recommended by U.S. national guidelines, but the peer-reviewed literature suggests this is not frequently done in clinical practice for reasons ranging from fear of permanent damage to the bladder to inconvenience to lack of confirmation of malignancy.[9–13] Adjuvant intravesical immunotherapy is also recommended, but the national shortage of bacillus Calmette-Guérin has complicated this therapeutic approach for patients with IR NMIBC.[14] Therefore, patients with LG IR NMIBC are most commonly managed by repetitive TURBTs under general anesthesia with its attendant risks.[15–21]

UGN-102 is an investigational agent designed for primary nonsurgical treatment of LG IR NMIBC, and to potentially obviate the need for repetitive TURBTs. UGN-102 consists of mitomycin and a proprietary reverse thermal hydrogel (UroGen Pharma, Ra'anana, Israel) used to reconstitute mitomycin before instillation. The reverse thermal properties of UGN-102 allow for local administration of mitomycin as a liquid in a cooled state, with subsequent conversion to a semi-solid gel depot at body temperature following instillation. The gel slowly disintegrates and is excreted by normal urine flow, allowing for sustained release of mitomycin over a period of 4 to 6 hours. The prolonged exposure of tumor cells to mitomycin is expected to improve chemoablation compared with aqueous preparations of the drug. The mechanism of tumor cell destruction by mitomycin is largely ascribed to DNA alkylation and consequent inhibition of DNA synthesis.[22] The current single-arm trial evaluated the efficacy and safety of UGN-102 as a primary chemoablative therapy in patients with histologically confirmed LG IR NMIBC.

MATERIALS AND METHODS

Study Design and Population

This phase 2b, open-label, single-arm trial was conducted from October 15, 2018 to October 21, 2020 at 20 sites in the U.S. and Israel. Eligible patients were ≥18 years old with LG NMIBC (Ta) diagnosed using cold cup biopsy (with visible tumor left in situ) and negative voiding cytology for high-grade (HG) disease within 6 weeks before screening. IR disease was defined as having 1 or 2 of the following: presence of multiple tumors, solitary tumor >3 cm and/or recurrence (≥1 occurrence of LG NMIBC within 1 year of the current diagnosis).[6] Patients were required to have adequate organ and bone marrow function as determined by routine laboratory testing (leukocytes ≥3,000 cells per μl, absolute neutrophil count ≥1,500 cells per μl, platelets ≥100,000 per μl, hemoglobin ≥9.0 gm/dl, total bilirubin ≤1.5 × upper limit of normal, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≤2.5 × upper limit of normal and estimated glomerular filtration rate ≥30 ml/min).

Patients with past or present muscle-invasive or metastatic urothelial carcinoma (UC), concurrent upper tract UC (UTUC) and patients with a history of carcinoma in situ within the previous 5 years, HG papillary UC within the previous 2 years or those who had received bacillus Calmette-Guérin treatment for UC within the previous 2 years were excluded.

All patients provided written informed consent before initiating any study-related procedure. The trial protocol, amendments and informed consent form were approved by the institutional review board at each participating site (IRB No. TC-BC-12). The trial was conducted in compliance with the Declaration of Helsinki, International Council for Harmonization guidelines and the U.S. Code of Federal Regulations Title 21, parts 50, 56 and 312. The study is registered with ClinicalTrials.gov (NCT03558503).

Procedures

Eligible patients received 6 once-weekly intravesical instillations of UGN-102 (75 mg mitomycin in 56 ml admixture with reverse thermal hydrogel to equal 1.33 mg/ml). In the event of a urinary tract infection or another safety reason (eg inadequate organ function), treatment could be postponed for up to 4 weeks until the event resolved. The ablative effect of UGN-102 was evaluated at the 3-month visit, which occurred 4 to 6 weeks after the last weekly instillation and 3 months after treatment initiation. Response was determined based on visual assessment (cystoscopy), biopsy of remaining lesions (if applicable) and voided urine cytology. If cystoscopy indicated no remaining tumors and urine cytology was negative, the patient had no detectable disease and was considered a complete response (CR). If the bladder was free of tumor endoscopically but cytology was positive, the investigator was required to exclude UTUC and occult carcinoma of the bladder or urethra. If UTUC was confirmed, the patient was considered to have CR. If any lesions were detected, even if they appeared necrotic, a biopsy was taken from the suspect tissue. If the biopsy was negative for cancer, the case was considered CR, and if the biopsy was positive, the case was considered non-CR. Patients who achieved CR continued to have monthly telephone contacts to document any adverse events (AEs) and were assessed for evidence of disease recurrence at 6, 9 and 12 months after the first instillation of UGN-102. Patients considered nonCR discontinued the study and continued with standard of care therapy as determined by their treating physicians.

Outcomes

The primary efficacy end point was CR rate, defined as the percentage of patients with CR at the 3-month visit. The secondary efficacy end point was durable CR in patients who achieved CR at the 3-month visit, defined as the percentage of patients with no detectable disease at 6, 9 and 12 months after treatment initiation. In addition to the durable CR rate, the duration of CR was defined as time from the date of evidence of CR at the 3-month visit to the earliest date of recurrence as determined using the date of cystoscopy, biopsy or cytology, whichever occurred first.

Safety was assessed throughout the study. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

SAS® software was used to perform all data analyses. Sample size was determined based on an expectation that 60% of patients would achieve CR. Assuming a 10% dropout rate, approximately 66 patients were to be recruited to provide adequate power to establish that the observed CR rate was superior to 45%. The primary analysis was performed using all patients who received at least 1 instillation of UGN-102 (intent-to-treat [ITT] analysis set). A test for binomial proportions was used to derive the exact 2-sided 95% CI for the CR rate using the Clopper-Pearson method. Subgroup analyses of the primary end point, including frequency and percentage of CR and exact 95% CIs, were conducted for descriptive purposes.

Point estimates and 2-sided exact 95% binomial CIs (Clopper-Pearson method) for durable CR rate at 6, 9 and 12 months after treatment initiation were summarized using all patients who achieved CR at the 3-month visit (3-month CR analysis set). Duration of CR was estimated using the Kaplan-Meier method. If a patient did not have a recurrence, the patient was censored at the date of the last adequate disease assessment or date of death.

Analyses of AEs were performed using the ITT analysis set, which was identical to the safety analysis set. Treatment-emergent AEs (TEAEs) reported for $\geq$3 patients were summarized descriptively by preferred term and maximal severity.

RESULTS

A total of 63 patients were enrolled in the trial and treated with $\geq$1 instillation of UGN-102 (fig. 1). Of

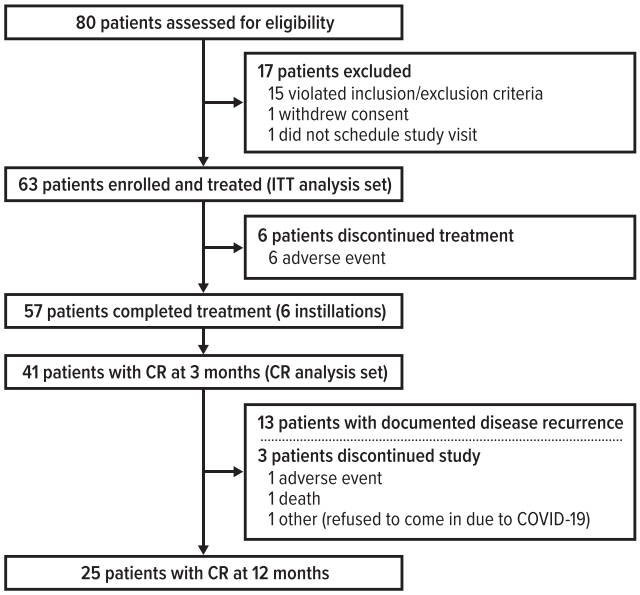

Figure 1. Flow diagram.

these patients 57 (90%) completed 6 instillations of UGN-102 according to protocol and 6 patients discontinued treatment due to an AE. Median age was 68.0 years (range 33–96), 57% of patients were ≥65 years old and 40% of patients were ≥75 years old (table 1). Most patients were male (60%) and Caucasian (87%). A total of 49 patients (78%) had recurrent LG NMIBC and 28 (44%) had a previous episode within 1 year of the current diagnosis. Patients with recurrence underwent a median of 3.0 prior TURBTs (range 0–13), with 37 (76%) having ≥2 prior TURBTs and 28 (57%) having ≥3 prior TURBTs. Among patients with data available, 50/61 (82%) had multiple visible tumors and 17/61 (28%) had tumors >3 cm.

A total of 41 patients (65%) achieved CR at 3 months after treatment initiation (95% CI 52.0, 76.7; table 2). Among 22 patients who were nonCR, 20 showed evidence of persistence or worsening of disease, including 5 who had HG papillary UC and/or UC in situ, suggesting under grading at the time of diagnosis. Of the 41 patients with CR, 39 (95%), 30 (73%) and 25 (61%) remained free of disease at 6, 9 and 12 months after treatment initiation, respectively (table 3). A total of 13 patients (32%) had disease recurrence (2 of whom were determined to have a more aggressive tumor than diagnosed at screening, which was considered evidence of disease progression), and 3 patients terminated the study early: 1 due to an AE, 1 due to death, and 1 patient was unable to complete the study due to concerns about COVID-19. The median duration of CR was not estimable (fig. 2). However, the probability of durable response 9 months after CR (12 months after treatment initiation) estimated by the Kaplan-Meier method was 72.5% (95% CI 54.4, 84.3; supplementary table 1, https://www.jurology.com). Subgroup analyses of the primary and key secondary end points are presented in supplementary figures 1 and 2 (https://www.jurology.com).

Overall, 57 of 63 patients (90%) experienced TEAEs and 40 (63%) had TEAEs that were considered related to study drug or procedure (supplementary table 2, https://www.jurology.com). Five patients (8%) had ≥1 serious TEAE, none of which was considered related to study drug or procedure. One patient experienced 4 serious TEAEs (cardiac disorder, hematuria, pneumonia and Klebsiella pneumonia), 1 patient experienced 2 serious TEAEs (chronic obstructive pulmonary disease and stress cardiomyopathy) and 3 patients each experienced 1 serious TEAE (acute myeloid

Table 1. *Patient characteristics (ITT analysis set)*

Characteristic	All Treated Pts (63)	
Age (yrs):		
Mean (SD)	70.5	(11.7)
Median (range)	68.0	(33.0–96.0)
No. age group (%):		
<65 yrs	27	(42.9)
65 to <75 yrs	11	(17.5)
≥75 yrs	25	(39.7)
No. gender (%):		
Male	38	(60.3)
Female	25	(39.7)
No. race:		
Caucasian	55	(87.3)
Asian	3	(4.8)
Hispanic	3	(4.8)
African American	1	(1.6)
Other	1	(1.6)
No. tumor size (%):*		
≤3 cm	44	(72.1)
>3 cm	17	(27.9)
No. tumors (%):*		
Single	11	(18.0)
Multiple	50	(82.0)
No. visual appearance of lesions (%):		
Papillary	63	(100.0)
Flat	2	(3.2)
Other	2	(3.2)
No. tumor staging (%):		
Noninvasive papillary Ca	62	(98.4)
Other†	2	(3.2)
No. tumor grading (%):		
Papillary urothelial Ca, LG	62	(98.4)
Papillary urothelial neoplasm of low malignant potential	1	(1.6)
Other	2	(3.2)
No. any previous LG NMIBC episode (%)	49	(77.8)
No. previous LG NMIBC episode within 1 yr of current diagnosis (%)	28	(44.4)
No. prior TURBTs:‡		
Mean (SD)	4.0	(3.3)
Median (range)	3.0	(0.0–13.0)
No. prior TURBTs (%):‡		
0	2	(4.1)
1	10	(20.4)
2	9	(18.4)
≥3	28	(57.1)
Days since last TURBT at day 1 (%):§		
≤365	23	(48.9)
>365	24	(51.1)

A patient may have more than 1 result for classification of tumor staging, grading and visual appearance of lesions.
* Measured in 61 patients.
† Staging was reported as "noninvasive papillary carcinoma (Ta)" and "sessile but LG" for 1 patient, and as "papillary urothelial carcinoma, low-grade, no extension into lamina propria identified, muscularis propria not sampled" for 1 patient.
‡ Measured in 49 patients.
§ Measured in 47 patients.

Table 2. *Complete response at 3-month visit (ITT analysis set)*

	All Treated Pts (63)	
	No. (%)*	Exact 95% CI†
Complete response	41 (65.1)	(52.0, 76.7)
Noncomplete response	22 (34.9)	
Evidence of persistence/worsening of disease‡	20 (31.7)	
Indeterminate	2 (3.2)	

* Percentages are computed using total number as denominator.
† Exact 95% CI for CR rate is computed using Clopper-Pearson method.
‡ Five patients were determined by investigator to have HG papillary urothelial carcinoma and/or UC in situ at 3-month visit. Given that all 5 patients were determined by investigator to have LG papillary UC at screening, these cases likely represent under staging/under grading at time of diagnosis rather than true disease progression.

Table 3. *Durability of complete response (3-month CR analysis set)*

	Durable Complete Response Rate			
Time Point*	No./N1 (%)†	Exact 95% CI‡	No./N2 (%)§	Exact 95% CI‡
6 mos (3 mos after CR at 3-month visit)	39/41 (95.1)	(83.5, 99.4)	39/40 (97.5)	(86.8, 99.9)
9 mos (6 mos after CR at 3-month visit)	30/41 (73.2)	(57.1, 85.8)	30/39 (76.9)	(60.7, 88.9)
12 mos (9 months after CR at 3-month visit)	25/41 (61.0)	(44.5, 75.8)	25/38 (65.8)	(48.6, 80.4)

N1, number of patients who achieved CR at 3-month visit; N2, number of evaluable patients who reached followup visit with durable CR or evidence of disease recurrence.
* Time points of 6, 9 and 12 months are relative to start of study treatment.
† Percentages are computed using N1 as denominator (ie all patients in 3-month CR analysis set are included in denominator for computing durable CR rate).
‡ Exact 95% CIs for durable CR rates are computed using Clopper-Pearson method.
§ Percentages are computed using N2 as denominator (ie evaluable patients who terminated study early or patients who had indeterminate response are excluded from denominator for computing durable CR rate).

leukemia, gastroenteropancreatic neuroendocrine tumor disease and metastatic urothelial carcinoma). The event of acute myeloid leukemia was life-threatening, and the event of cardiac disorder in a 91-year-old male resulted in death (table 4). The event of metastatic UC likely represents invasive or HG disease not diagnosed at screening. Computerized tomography 6 months after the last study treatment revealed extensive lymph node spread. The location of primary cancer was unconfirmed but suspected to be the bladder. Cystoscopy and cytology were negative from the 3-month visit through end of study. Six patients (10%) had $\geq$1 TEAE leading to treatment discontinuation, all of which were considered related to study drug or procedure. One patient experienced 3 TEAEs leading to treatment discontinuation (dysuria, micturition urgency and penile erythema), and 5 patients each experienced 1 TEAE leading to treatment discontinuation (lower urinary tract symptoms in 2, hand dermatitis in 1, generalized rash in 1 and urinary retention in 1).

The most frequently reported TEAEs were dysuria in 26 of 63 patients (41%), urinary frequency in 13 (21%), hematuria in 10 (16%), micturition urgency and urinary tract infection in 9 (14%), and fatigue in 7 (11%; table 4). Regarding TEAEs of special interest (ie lower urinary tract symptoms, allergic reactions, voiding interruption due to urethral/penile edema, genitourinary infections, inadvertent or accidental exposure to UGN-102 and bone marrow suppression), 43 of 44 patients (98%) had events that were mild or moderate in severity and 35 (80%) had events that resolved during the study. Among the 9 cases with TEAEs of special interest that did not resolve, 6 events were considered not related to study drug or procedure.

DISCUSSION

In the current study, 63 patients with biopsy-proven LG IR NMIBC received induction chemoablative therapy with UGN-102 and 41 (65%) achieved CR at 3 months after treatment initiation. Of these 41

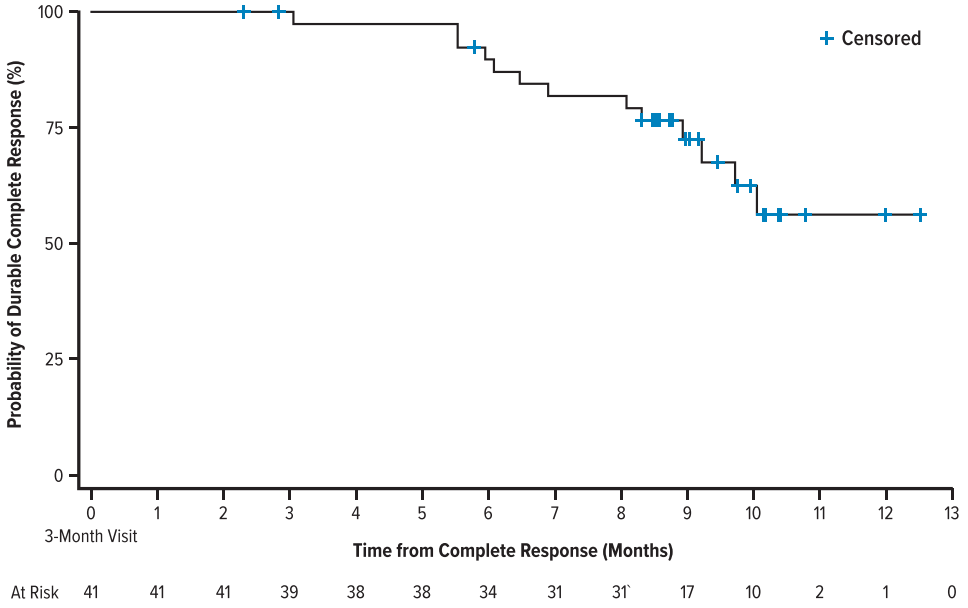

Figure 2. Kaplan-Meier plot of duration of CR (3-month CR analysis set).

Table 4. *TEAEs reported in ≥3 patients by preferred term and maximum severity (ITT analysis set)*

TEAE Preferred Term	No. Treated Pts (%)			
	Grades 1–2*	Grade 3†	Grade 4‡	Grade 5§
Pts with any TEAE	50 (79.4)	5 (7.9)	1 (1.6)	1 (1.6)
Dysuria	26 (41.3)	0	0	0
Pollakiuria	13 (20.6)	0	0	0
Hematuria	9 (14.3)	1 (1.6)	0	0
Micturition urgency	9 (14.3)	0	0	0
Urinary tract infection	9 (14.3)	0	0	0
Fatigue	7 (11.1)	0	0	0
Urinary incontinence	5 (7.9)	0	0	0
Accidental exposure to product	4 (6.3)	0	0	0
Nocturia	4 (6.3)	0	0	0
Pruritus genital	4 (6.3)	0	0	0
Urinary retention	4 (6.3)	0	0	0
Vulvovaginal discomfort	4 (6.3)	0	0	0
Bladder spasm	3 (4.8)	0	0	0
Constipation	3 (4.8)	0	0	0
Genital discomfort	3 (4.8)	0	0	0
Lower urinary tract symptoms	3 (4.8)	0	0	0
Penile edema	2 (3.2)	1 (1.6)	0	0
Rash generalized	3 (4.8)	0	0	0
Sinusitis	3 (4.8)	0	0	0

Total of 63 patients were treated.
Percentages are computed using total number treated as denominator. Patients with more than 1 episode of same AE are counted only once (under worst severity category).
* Severity grades are defined as 1, mild; 2, moderate; 3, severe or medically significant; 4, life-threatening; 5, fatal.
† Other grade 3 events were arthralgia, chronic obstructive pulmonary disease, gastroenteropancreatic neuroendocrine tumor disease, Klebsiella pneumonia and metastatic urothelial carcinoma, each occurring in 1 patient.
‡ Grade 4 event was acute myeloid leukemia, which was not related to study drug or procedure.
§ Cause of death (grade 5 event) was cardiac disorder (reported term: exacerbation of chronic heart disease), which was not related to study drug or procedure.

patients 25 (61%) remained disease-free 9 months after achieving CR (12 months after treatment initiation). Among the 41 patients who initially achieved CR, 13 had documented disease recurrence during followup, including 2 patients whose tumors were determined to be more aggressive than diagnosed at screening and thus evidenced disease progression. The probability of durable response was estimated to be 72.5% by Kaplan-Meier analysis. The median duration of response was not reached. Treatment with UGN-102 was generally well tolerated. AEs were primarily mild or moderate in severity, and no study drug or procedure-related serious TEAEs were reported.

Due to the recurrent nature of the disease (30% to 50% of cases recur at 1 year),[2] patients with LG IR NMIBC often undergo repeated TURBT, a surgical procedure with well-defined risks that include failure to cure, bleeding requiring unplanned hospital admission and bladder perforation.[16,18–20,23] In addition, recently published evidence suggests that repetitive TURBT is independently associated with an increased mortality risk.[17] Finally, the repeated use of general anesthesia in the elderly may predispose to cognitive decline.[24,25]

Studies of aqueous preparations of mitomycin suggest that chemoablation with mitomycin may obviate the need for surgery in some patients or reduce the perioperative morbidity associated with surgery secondary to lower volume disease, and may be associated with fewer clinically significant AEs.[26,27] UGN-102 is a formulation of mitomycin with a proprietary mixture of polymers designed to prolong dwell and contact time of mitomycin with the surface of the bladder cavity, potentially leading to improved chemoablation compared with aqueous preparations of mitomycin.

The primary limitation of the current study is the single-arm design. While these data appear to demonstrate a benefit of avoidance of surgery in a clinically meaningful proportion of patients, patients who are under graded at diagnosis or who do not achieve a complete response to chemoablation with UGN-102 may be at risk for disease progression. The absence of a control group in this study complicates the interpretation of treatment effect and permits only indirect comparisons with the safety of TURBT. The results of the current study warrant further investigation of UGN-102 in an ongoing phase 3, randomized, controlled trial vs TURBT (NCT04688931).

CONCLUSIONS

Nonsurgical primary chemoablation of LG IR NMIBC using UGN-102 results in a clinically significant treatment response with demonstrated durability. UGN-102 may provide an alternative to repetitive TURBT surgery for patients with LG IR NMIBC.

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UroGen Pharma.

CONFLICTS OF INTEREST

JL, DM, JDR and DSa report acting as investigators and consultants/advisors for UroGen Pharma; KC, BH, NDS and ABS report serving as consultants/advisors for UroGen Pharma; NG, SL, MM, AM, SR, MS and ES are full-time employees of UroGen Pharma; MT reports serving as an assistant editor for *The Journal of Urology*®; KKC, AC, RD'A, YE, BF, WCH, LK, MK, SK, AS, DSc, AT and MV report no direct or indirect commercial financial incentive associated with publishing the article.

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EDITORIAL COMMENTS

IR bladder cancer represents a heterogeneous group with high propensity for recurrence. Given the limited options in adjuvant therapy, the authors present very encouraging results on the use of UGN-102, a mitomycin-containing reverse thermal gel, as a chemoablative option for LG IR patients. Of the 63 patients enrolled, 65% showed CR at 3 months after initial treatment, with an impressive 12-month recurrence-free survival of 73% and a tolerable side effect profile with low discontinuation rate.

The cohort closely represented a real-world practice of recurrent bladder cancer patients, of which many were heavily pre-treated with a median of 3 prior TURBTs (range 0–13) before treatment initiation. In the present study, patients had cold cup biopsies with tumors left in situ, so the true impact of TURBT + UGN-102 on recurrence outcomes remains to be seen, as these are apt to be even better after complete resection. Thus, it is likely the therapeutic benefit of UGN-102 would remain in clinical scenarios.

The authors cautiously discuss the benefits of avoiding repeat TURBT and its inherent perioperative surgical and anesthetic risks for a generally frail cancer population given the chemoablative effect of UGN-102 on remaining LG tumor sites. Hence, accurate histopathological staging is critical given the apparently poor efficacy for those with HG disease and those unable to achieve CR at 3 months (~32% developed persistent or worsening disease).

Overall, this is an important addition to the literature for an under studied patient population. This well-designed study provides valuable prospective data on nonsurgical chemoablation of LG IR bladder cancer with sustained durability. Consequently, UGN-102 may provide an alternative treatment to repeat TURBT in highly select cases. The true clinical benefit will be clarified with the ongoing phase 3 study evaluating UGN-102 chemoablation versus TURBT alone.

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IR bladder cancer is a heterogeneous category with 1-year recurrence rates ranging of 24% to 36% in those treated primarily with TURBT and post-operative intravesical chemotherapy.[1] Improving the efficacy, safety and tolerability of re-treatment is therefore critical.

Here, the authors report a phase 2b single-arm study of UGN-102, a mitomycin-containing reverse thermal gel, for the chemoablation of LG IR bladder cancer in lieu of standard repeat TURBTs. Of the 63 patients enrolled (all with visible tumor remaining following diagnostic biopsy), they found that 65% of patients achieved CR at 3 months, and in those who responded the likelihood of CR at 12 months was 73%. This was a well-selected group of IR patients who had the expected risk factors for tumor progression and recurrence. Included in the cohort are 78% with recurrent disease, 28% with tumors >3 cm, 82% with multiple tumors and 76% with multiple prior TURBTs. Drug-related TEAEs were experienced in nearly two-thirds of the treatment group and account for a 10% discontinuation rate. While the risks of surgery/anesthesia are significant, the adverse effects and tolerability of traditional mitomycin C are not negligible, and we recognize that chemical cystitis, hematuria and severe adverse effects may represent challenges to tolerability with more widespread use.[2,3]

Overall, this was a well-designed and reported phase 2 trial with promising outcomes. Given the applicability of nonsurgical management to medically high-risk groups, it will be interesting to review the comorbidity profile and tolerability in a phase 3 controlled comparison with TURBT, which is certainly merited.

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