Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): an open-label, single-arm, phase 3 trial

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Summary

Background Most patients with low-grade upper tract urothelial cancer are treated by radical nephroureterectomy. We aimed to assess the safety and activity of a non-surgical treatment using instillation of UGN-101, a mitomycin-containing reverse thermal gel.

Methods In this open-label, single-arm, phase 3 trial, participants were recruited from 24 academic sites in the USA and Israel. Patients (aged ≥18 years) with primary or recurrent biopsy-proven, low-grade upper tract urothelial cancer (measuring 5–15 mm in maximum diameter) and an Eastern Cooperative Oncology Group performance status score of less than 3 (Karnofsky Performance Status score >40) were registered to receive six instillations of once-weekly UGN-101 (mitomycin 4 mg per mL; dosed according to volume of patient's renal pelvis and calyces, maximum 60 mg per instillation) via retrograde catheter to the renal pelvis and calyces. All patients had a planned primary disease evaluation 4–6 weeks after the completion of initial therapy, in which the primary outcome of complete response was assessed, defined as negative 3-month ureteroscopic evaluation, negative cytology, and negative for-cause biopsy. Activity (complete response, expected to occur in >15% of patients) and safety were assessed by the investigator in all patients who received at least one dose of UGN-101. Data presented are from the data cutoff on May 22, 2019. This study is registered with ClinicalTrials.gov, NCT02793128.

Findings Between April 6, 2017, and Nov 26, 2018, 71 (96%) of 74 enrolled patients received at least one dose of UGN-101. 42 (59%, 95% CI 47–71; p<0·0001) patients had a complete response at the primary disease evaluation visit. The median follow-up for patients with a complete response was 11·0 months (IQR 5·1–12·4). The most frequently reported all-cause adverse events were ureteric stenosis in 31 (44%) of 71 patients, urinary tract infection in 23 (32%), haematuria in 22 (31%), flank pain in 21 (30%), and nausea in 17 (24%). 19 (27%) of 71 patients had study drug-related or procedure-related serious adverse events. No deaths were regarded as related to treatment.

Interpretation Primary chemoablation of low-grade upper tract urothelial cancer with intracavitary UGN-101 results in clinically significant disease eradication and might offer a kidney-sparing treatment alternative for these patients.

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Introduction

Upper tract urothelial cancer is a rare malignancy most commonly diagnosed in patients older than 70 years and is routinely treated by radical nephroureterectomy.[1] Biopsy grade coupled with cross-sectional imaging data and urine cytology have been integrated into European Association of Urology (EAU) guidelines for clinical stage stratification.[2–5] Patients with high-grade cancer are routinely offered extirpative surgery that may include segmental removal of portions of the ureter (usually distal) or, more commonly, radical nephroureterectomy. Conversely, 10–20% of patients with low-grade disease manifesting as a solitary, small (<20 mm), and favourably located lesion within the upper tract are offered kidney-preserving approaches such as endoscopic ablation.[1,5,6] Endoscopic surgery carries specific surgical risks and is associated with a high rate of local disease recurrence.[7] Ultimately, 70–80% of patients with low-grade and low-stage upper tract urothelial cancer undergo radical nephroureterectomy.[1,8,9] This procedure is associated with the typical hazards of major surgery and the additional long-term deleterious effects of renal insufficiency, exacerbation of pre-existing comorbidities, and the potential need for dialysis dependence.[7,10–12]

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Research in context

Evidence before this study

A 2018 consensus conference on upper tract urothelial cancer in Stockholm, Sweden gathered clinical and research experts to discuss existing European Association of Urology guidelines for its treatment and to add further recommendations. These recommendations were to be based on a scoping review of the literature using PubMed, Embase, and Web of Science, with search terms including "upper tract transitional cell carcinoma", "upper tract TCC", "UTTCC", "upper tract urothelial cell carcinoma", "upper tract urothelial carcinoma", "UTUC", "endoscopic management", "ureteroscopic management", "laser ablation", "percutaneous management", "PNRT", "conservative management", "ureteroscopic biopsy", "biopsy", "BCG", "mitomycin C", and "topical therapy". During the 2-day meeting, findings from the literature review were presented, discussed, challenged, and adjusted accordingly. While acknowledging the paucity of prospective data, there was consensus that kidney-sparing surgery such as endoscopic ablation should be attempted for patients with low-grade upper tract urothelial cancer. It was noted, however, that stringent follow-up is required because of a high incidence of disease recurrence associated with ureteroscopic management of this type of cancer.

Added value of this study

To our knowledge, this trial is the first prospective study to report the activity of topical chemoablation (using a mitomycin-containing reverse thermal gel) for the primary treatment of low-grade upper tract urothelial cancer. The results show that a high proportion of patients had a complete response to this induction therapy, irrespective of baseline demographics and clinical characteristics.

Implications of all the available evidence

These findings suggest that this alternative kidney-sparing treatment might be considered for patients with low-grade upper tract urothelial cancer, including those with multifocal disease and those who are not candidates for endoscopic ablation.

Early data regarding genomic analyses of low-grade urothelial bladder cancer and low-grade upper tract urothelial cancer suggest that low-grade urothelial malignancies share common genetic characteristics, irrespective of site of origin.[13] Low-grade urothelial bladder cancer is sensitive to various chemotherapeutic agents, such as mitomycin and gemcitabine, commonly recommended as adjuvant intravesical therapies following transurethral resection of bladder tumours. Drug concentration and dwell time at the target are key features of optimal topical therapy for urothelial bladder cancer; however, continuous drug dilution due to urine flow limits the benefit of aqueous topical therapy to upper tract urothelial cancer.[7–14] Previously, we reported proof-of-concept and preliminary safety for UGN-101, a reverse thermal gel formulation of mitomycin, in treating 22 patients with upper tract urothelial cancer in a compassionate use programme.[15] UGN-101 consists of mitomycin and a sterile RTGel reverse thermogelation hydrogel (UroGen Pharma, Ra'anana, Israel), which is used to reconstitute mitomycin before instillation. The reverse thermal properties of UGN-101 allow for local administration of mitomycin as a liquid, with subsequent conversion to a semi-solid gel depot following instillation into the upper tract. Normal urine flow dissolves the gel depot, allowing tissue exposure to mitomycin over a period of 4–6 h. The mechanism of tumour cell destruction by mitomycin is largely ascribed to DNA alkylation and the consequent inhibition of DNA synthesis. Modification of redox cycling, RNA inhibition, and modulation of thioredoxin reductase activity are additional activities of mitomycin.[16]

The current single-arm trial further evaluated the safety and activity of UGN-101 to chemotherapeutically ablate primary and recurrent low-grade upper tract urothelial cancer.

Methods

Study design and participants

This open-label, single-arm, phase 3 trial recruited participants in 24 academic sites in the USA and Israel (appendix p 7).

Eligible patients were aged 18 years or older with primary or recurrent biopsy-proven, low-grade upper tract urothelial cancer involving the renal pelvis or calyces (diagnosed within 2 months before screening), life expectancy of more than 24 months, and an Eastern Cooperative Oncology Group performance status score of less than 3 (with Karnofsky Performance Status score >40). Current guidelines of the EAU and the International Consultation on Urological Diseases do not make a distinction between primary and recurrent low-grade disease for risk stratification; thus, patients with either type were included in this trial. The presence of one or more low-grade lesion above the ureteropelvic junction, measuring (by direct visualisation at ureteroscopy) 5–15 mm in greatest dimension, was required for study entry. Patients with lesions larger than 15 mm were eligible for endoscopic downsizing before the initiation of treatment. Patients with multifocal cancer were included as long as any ureteral or lower urinary tract tumours were completely ablated, and patients with bilateral disease were eligible if one renal unit was removed or rendered disease-free by endoscopic ablation before enrolment (see protocol in appendix). Patients with coexisting ureteral upper tract urothelial cancer were excluded unless they could be first ablated by endoscopic or surgical resection before study entry. The study

surgeons determined whether tumours were resectable or unresectable at baseline, the latter usually because of difficult access to the lower pole of the kidney.

Patients were required to have adequate organ and bone marrow function, as determined by routine laboratory testing (leucocytes ≥3000 cells per µL, absolute neutrophil count ≥1500 cells per µL, platelets ≥100 000 per µL, haemoglobin ≥9·0 mg/dL, total bilirubin ≤1·5×upper limit of normal [ULN], aspartate aminotransferase and alanine aminotransferase ≤2·5×ULN, alkaline phosphatase ≤2·5×institutional ULN, and estimated glomerular filtration rate ≥30 mL/min). Patients who received Bacillus Calmette–Guérin treatment during the 6 months before visit 1 and those who were actively being treated or intended to be treated with systemic or intravesical chemotherapy during the duration of the study were excluded. Patients with active urinary tract infection or intractable bleeding disorders were excluded. Inclusion and exclusion criteria are summarised in the appendix (p 1).

All participants gave informed written consent. The study protocol, amendments, and related documents issued to the patients were reviewed and approved by the designated ethics committees, institutional review boards, and regulatory authorities before any procedures related to the study were undertaken. The study was performed in accordance with US Food and Drug Administration good clinical practice regulations (Code of Federal Regulations 21, parts 50, 56, and 312), and the International Conference on Harmonisation good clinical practice guidelines (E6) and clinical safety data management (E2A). An independent data monitoring committee periodically reviewed results of the trial including all available safety data. The protocol is available in the appendix.

Procedures

Eligible participants received six once-weekly treatments of UGN-101 (4 mg mitomycin per mL gel) to the renal pelvis and calyces via retrograde ureteral catheter (5–7 French catheter). The instilled volume of UGN-101 was determined in each patient by averaging three fluoroscopically guided volumetric measurements of the renal pelvis and calyces before treatment. The instilled volume of UGN-101 was not to exceed 15 mL (ie, maximum dose 60 mg). Procedures were done in a variety of clinical settings including hospital operating rooms, outpatient surgical centres, and doctor's offices, but the same kits were used in all settings. Patients received their instillations under either general or local anaesthesia; the decision to use general versus local anaesthesia was based on provider and patient preferences. Blood tests were done within 3 days before each instillation to establish acceptable laboratory values for organ and bone marrow function. In the event of a urinary tract infection or another safety indication (eg, inadequate organ function), treatment was postponed until the event had resolved. Treatment delays beyond 4 weeks due to adverse drug reaction required discontinuation of treatment. Complete blood count, renal, and liver function tests were done 1 week and 3 weeks after the last weekly instillation.

4–6 weeks after completion of initial therapy, study participants were evaluated at the primary disease evaluation by ureteroscopy, selective upper tract wash cytology, and for-cause biopsy, which was done if ureteroscopic visual inspection was suspicous for recurrent or persistent disease (ie, not clearly negatiave). The same surgeon did both the diagnostic and primary disease evaluation ureteroscopies. Cytology and histopathology slides were reviewed by local pathology laboratories (a single pathologist at each institution) and centrally (at the University of Tennessee Health Science Center, Memphis, TN, USA). The degree of response and durability of complete response for study analysis purposes were based on the local laboratory's interpretation. Patients with a complete response continued to undergo quarterly surveillance and were eligible for up to 11 monthly maintenance treatments with UGN-101 (appendix p 2). Durability of response was assessed at 6 months, 9 months, and 12 months in patients with complete response at the primary disease evaluation and was recorded dichotomously as either success (a complete response at 12 months) or failure (no longer a complete response at 12 months).

Patients with no complete response, including those achieving a partial response (defined as any decrease in tumour size or number of tumours that was not a complete response), were referred for standard-of-care therapy, as determined by the treating urologist.

Outcomes

The primary endpoint was complete response, which was defined as a negative endoscopic examination and negative cytology at the primary disease evaluation and negative for-cause biopsy when done. These measures were selected in consultation with regulatory authorities as clinically meaningful. If either biopsy or cytology results showed residual disease, the patient was classified as having no complete response.

When the primary analysis was done (data cutoff May 22, 2019), we did an interim analysis for the key secondary endpoint, which was durable response at the 12-month follow-up visit for patients showing complete response at the primary disease evaluation. A separate report will analyse this endpoint when all patients showing complete response have been followed up for at least 12 months. Further secondary endpoints were durability of the ablative effect at 3 months, 6 months, and 9 months after the primary disease evaluation visit for patients who showed a complete response at the primary disease evaluation, and to evaluate the overall clinical benefit of treatment with UGN-101. Overall clinical benefit included whether patients with partial

See Online for appendix

For the **Medical Dictionary for Regulatory Activities** see https://www.meddra.org

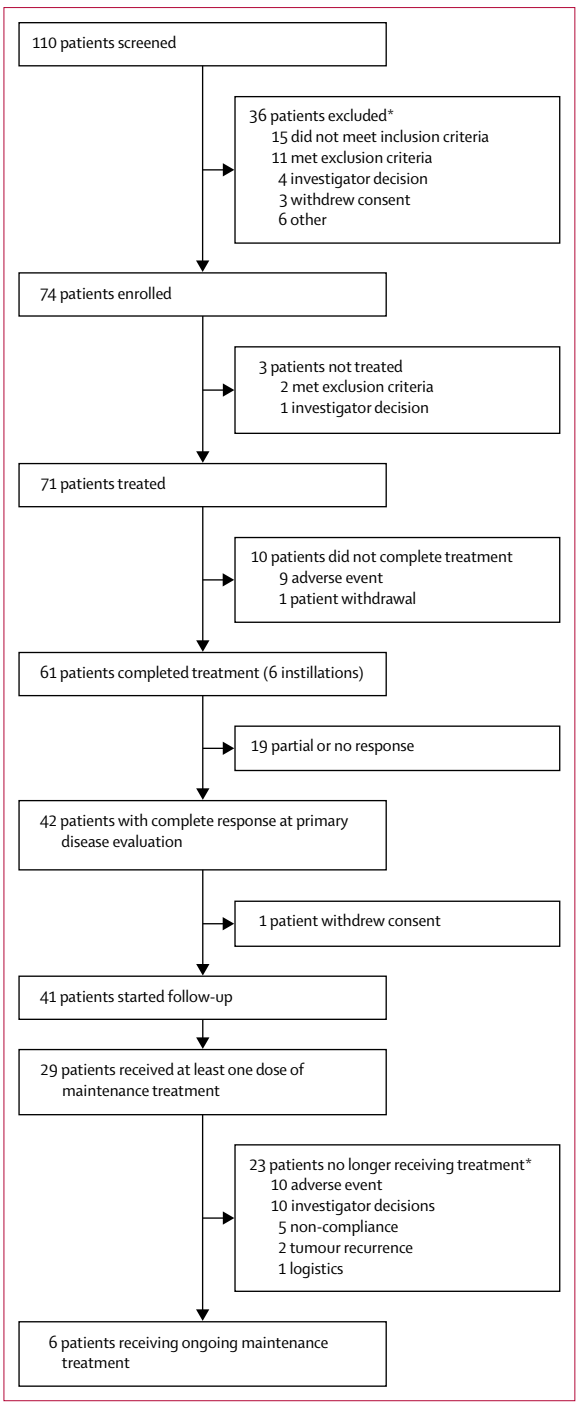

Figure 1: **Trial profile**
At the time of data cutoff, 16 patients had not yet reached the study completion visit (12 months after the primary disease evaluation); six of these were still receiving maintenance treatment. *More than one reason could be given.

response were able to have their treatment plans modifed. Pre-specified exploratory subgroup analyses for the primary and key secondary endpoints examined the potential effects of baseline demographic and clinical characteristics on outcomes.

Safety was assessed throughout the study through adverse event monitoring; adverse events were graded according to the Medical Dictionary for Regulatory Activities, version 19.1.

Statistical analysis

The single-arm design tests a novel chemoablation strategy and was chosen in consultation with regulatory authorities as the most effective way to quickly determine the activity of UGN-101, because there are no approved drugs or non-surgical ablative therapies with which UGN-101 could be compared. UGN-101 was offered as a kidney-sparing approach for patients who were current candidates for radical nephroureterectomy, and a placebo group was therefore not considered for ethical reasons.

Sample size was determined under the assumption that the primary endpoint of the study was the proportion of patients with a complete response at the primary disease evaluation visit, that the true complete response rate following treatment with UGN-101 was expected to be 30% or higher, and that the primary analysis of the primary endpoint aimed to rule out a threshold rate of 15% using a two-tailed test for binomial proportion with two-sided α of 0·05. In other words, a complete response rate of 15% was the performance goal of the study. Per protocol and under these assumptions, a sample size of 74 evaluable patients would provide a power of 88·5% to show that the observed complete response rate was superior to 15%.

The primary analysis was done using all patients who received at least one instillation of UGN-101. Assuming that the sample included 74 evaluable patients, the decision rule was to reject the null hypothesis if the number of complete responses in the sample was 18 or more. If the number of evaluable patients was not 74, the rejection area was to be updated accordingly, using the same statistical methods. The number and percentage of patients who were complete responders at the primary disease evaluation (with 95% CI and exact binomial hypothesis testing p value) are presented as a part of the primary analysis. A preplanned futility analysis was done after 20 evaluable patients had primary data at the primary disease evaluation (March, 2018), which indicated that the intervention was not futile and that the study should go forward.

All statistical analyses were carried out using SAS, version 9.4 or higher. All descriptive statistics were provided by visit (if relevant) and overall. Success for the key secondary endpoint was declared if the lower bound of the 95% CI for durability of tumour ablative effect at 12 months was greater than 40%, which was deemed to be a clinically meaningful threshold given that the 6-month rate of recurrence after endoscopic ablation is high.

The safety analysis group included all patients who received at least one instillation of UGN-101. Treatment-emergent adverse events reported by five or more patients are presented descriptively by preferred term

	All treated patients (n=71)
Age (years)	
Mean (SD)	70·4 (10·0)
Median (range)	71·0 (42·0–87·0)
Age group	
<65 years	18 (25%)
65 to <75 years	27 (38%)
≥75 years	26 (37%)
Sex	
Male	48 (68%)
Female	23 (32%)
Race or ethnicity	
White	62 (87%)
African American	4 (6%)
Hispanic	3 (4%)
Asian	2 (3%)
Current or previous history of tobacco use	56 (79%)
Two kidneys at enrolment	63 (89%)
History of upper tract urothelial cancer	37 (52%)
Previous transurethral resection of bladder tumours for urothelial bladder cancer	21 (30%)
Previous renal ablative surgery	37 (52%)
Any previous surgery related to urothelial cancer	62 (87%)

Data are n (%) unless otherwise specified.

Table 1: **Baseline characteristics**

	Measurements at baseline
Number of papillary tumours*	
Mean (SD)	2·2 (1·5)
Median (range)	2·0 (1–8)
Diameter of largest papillary tumour (mm)†	
Mean (SD)	14·8 (8·7)
Median (range)	14·0 (5–50)
Total tumour burden (mm)‡	
Mean (SD)	19·9 (13·0)
Median (range)	17·0 (5–65)
Tumour is unreachable by laser, n (%)	
Yes	34/71 (48%)
No	37/71 (52%)

Papillary tumour characteristics are given prior to debulking (if applicable). The current episode was defined as the last urothelial carcinoma finding as observed in the last ureteroscopy before or during screening (before partial fulguration if applicable). If more than one episode in the same location (above or below the ureteropelvic junction) was marked as the current episode, the number of lesions and the tumour burden within the location were calculated according to the largest record available. Bladder lesions were ignored in this analysis. *Measured in 70 patients. One patient had a lesion that was marked as flat in the case report form but later clarified by the investigator and confirmed by histology as papillary. †Measured in 67 patients. ‡Measured in 66 patients. Total tumour burden was calculated per patient as the sum over all lesions' largest diameters of papillary lesions. If at least one tumour burden calculation in the current upper urinary tract episode (above or below the ureteropelvic junction) was missing, the total tumour burden of this episode was considered missing.

Table 2: **Summary of papillary tumours for the current upper urinary tract episode in the treated population (n=71)**

and maximal severity. There were no changes to the protocol during conduct of the study and all endpoints were prespecified.

The study is registered with ClinicalTrials.gov, NCT02793128.

Role of the funding source

The funder of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report. The first author (NK), senior author (SPL), and coauthors (ES and MS) had full access to the data, and were responsible for the final decision to submit for publication.

Results

Between April 6, 2017, and Nov 26, 2018, 74 patients were enrolled in this trial, of whom 71 were treated with at least one instillation of UGN-101 (figure 1). 16 (23%) patients remained in follow-up at the data cutoff on May 22, 2019. Most patients were white, male, and older than 70 years (table 1). Data on patients' tumour characteristics at baseline are in table 2.

61 (86%) of the 71 treated patients completed six instillations of UGN-101 as per the protocol. During these six instillations and maintenance therapy, treatments were administered under general anaesthesia in about a quarter of the instillations, and with local anaesthesia or sedation in the remainder (appendix p 3). Most treatments were administered using a 7 French ureteral catheter (appendix p 4). The mean volume for all treatments was 54·4 mL (SD 14·3) with a median volume of 54·0 mL (range 21·0–90·0). Across the six instillations during the treatment period, the number of patients for whom the planned and actual instillation volume differed ranged from 12 (17%) of 71 patients at instillations 1 and 2, to 16 (26%) of 61 patients at instillation 6. No patient received a different instillation volume due to an adverse event, two patients received a different instillation volume because of technical problems, and all other differences were because of other reasons (data not shown). During the initial 6-week treatment period, ten (14%) of 71 patients discontinued treatment. The most common reasons for treatment discontinuation were adverse events (nine [13%] of 71 patients) and early withdrawal for personal reasons (one [1%] patient).

42 (59%; 95% CI 47–71; p<0·0001) of 71 patients who received at least one instillation had a complete response by the primary disease evaluation visit (table 3). 29 (41%) patients had no complete response (table 3). The median follow-up for patients with complete response was 11·0 months (IQR 5·1–12·4). Complete response at the primary disease evaluation visit as assessed by the central laboratory (37 [63%] of 59 patients) was a similar proportion to that assessed by local laboratories.

41 (98%) of 42 patients with a complete response at the primary disease evaluation entered the follow-up period,

and one (2%) did not because the patient withdrew consent before follow-up. 29 (71%) of the 41 patients who entered the follow-up period received at least one dose of maintenance therapy. Six (15%) of the 41 patients were still receiving maintenance treatment at the time of the data cutoff.

At the time of the data cutoff, 26 (63%) of 41 patients in follow-up had reached the 12-month timepoint. 20 (77%) of these 26 patients had a 12-month assessment, 14 (70%) of whom showed durability of their complete response (appendix p 5). Six (15%) of the 41 patients who had a complete response and entered follow-up had a documented recurrence during follow-up, and none progressed to high-grade or invasive cancer at the time of data cutoff. In the time-to-recurrence Kaplan-Meier analysis, durability of response was estimated at 84·2% (95% CI 71·0–97·4) 12 months after the primary disease evaluation, and the median time to recurrence was estimated as 13·0 months (95% CI 13·0–not estimable; figure 2). The durability of the responses at 3 months, 6 months, and 9 months after the primary disease evaluation visit are in the appendix (p 5). Clinical benefit was assessed for patients having partial response, but the numbers were too small for meaningful analysis.

	All treated patients (n=71)
Complete response	42 (59%)
No complete response	29 (41%)
Partial response	8 (11%)
No response	12 (17%)
High-grade patient*	6 (8%)
Indeterminate†	3 (4%)

*High-grade patients were those with the emergence of high-grade disease at primary disease evaluation that was not detected at baseline. †Indeterminate patients were those who had "undetermined" (or "not done") recorded on the case report form page "Evaluation of Response (Target Area Lesions)" at primary disease evaluation and at re-evaluation, or who had no re-evaluation. For the primary analysis these patients are deemed non-complete responders.

Table 3: **Primary disease evaluation results (local pathology)**

Exploratory subgroup analyses were done to evaluate the treatment effect on the primary and key secondary endpoints. No individual parameter seemed to have any effect on complete response at primary disease evaluation (table 4) or on durability of response 12 months after the primary disease evaluation visit (appendix p 6).

Overall, 67 (94%) of 71 patients had adverse events (table 5) of which 60 (85%) were deemed related to study drug or procedure. 26 (37%) patients had at least one serious adverse event, the most common of which were ureteric stenosis in five (7%) patients, hydronephrosis in four (6%) patients, and flank pain and urosepsis, each in three (4%) patients. One patient had life-threatening urosepsis (grade 4) that was not related to study drug or procedure. Three (4%) patients had serious adverse events that led to death, none of which was related to the study drug or procedure. The causes of death were cerebrovascular accident, failure to thrive, and unknown cause.

19 (27%) of 71 patients had study drug-related or procedure-related serious adverse events, the most frequent of which were ureteric stenosis, hydronephrosis, flank pain, urosepsis, and chronic obstructive pulmonary disease. 19 (27%) of 71 patients discontinued treatment because of an adverse event, including nine (13%) who discontinued during the initial 6-week treatment period and ten (14%) during maintenance treatment, and 13 (18%) who had study drug-related or procedure-related adverse events that led to treatment discontinuation. Of these events, the most frequent was ureteric stenosis.

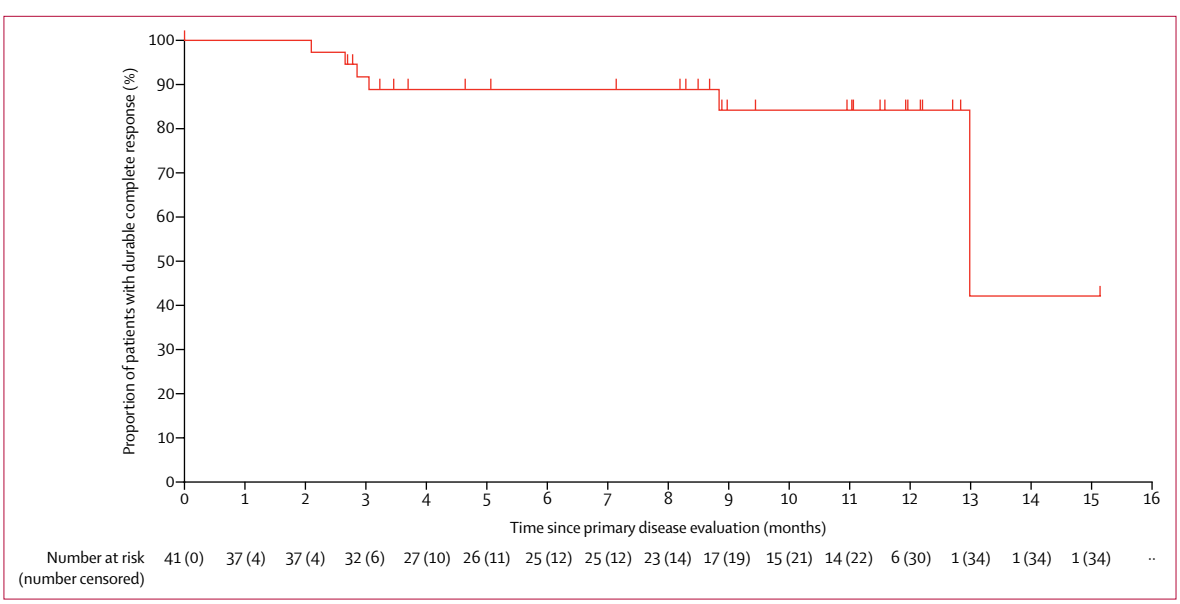

Figure 2: **Kaplan-Meier analysis for durability of complete response**

Overall, the most frequently reported adverse events (table 5) were ureteric stenosis in 31 (44%) of 71 patients, urinary tract infection in 23 (32%), haematuria in 22 (31%), flank pain in 21 (30%), and nausea in 17 (24%).

Among the adverse events of special interest, impairment of renal function was noted in 14 (20%) patients, with nine (13%) patients recovering and five (7%) not recovering, one (1%) of whom had severe renal impairment during the trial, which was assessed as related to treatment by the reporting investigator. Anaemia was observed in nine (13%) patients but was mild to moderate in severity and self-limited in all cases; in three (4%) patients it was deemed not to be treatment-related, five (7%) cases were deemed to be possibly treatment-related, and one (1%) was definitely treatment-related. Thrombocytopenia and leukopenia were observed in a small number of patients and did not rise to the level of serious adverse event in any of the affected individuals. All three (4%) cases of thrombocytopenia were possibly treatment-related, two (3%) of the leukopenia cases were considered not to be treatment-related, one (1%) was probably treatment-related, and one (1%) was definitely treatment-related. One patient (1%) had severe transient pancytopenia that was potentially related to exposure to the study drug.

To further explore the nature of the association of the treatment with urinary tract morbidity in particular, we evaluated patient-specific data related to the use of indwelling stents during or following exposure to UGN-101. 48 (68%) of 71 patients had an adverse event related to the renal urinary system, 24 (50%) of whom required transient placement of a ureteral stent. 11 (23%) of 48 patients did not require surgical intervention and an additional 11 patients required long-term stent placement (defined as an indwelling stent present at the time of data cutoff). At the time of data cutoff, two (4%) of 48 patients had developed ureteral stenosis that would have mandated permanent internal stent drainage and both individuals elected to undergo radical nephroureterectomy as an alternative. Histopathological evaluation of the radical nephroureterectomy specimen in both cases showed the absence of residual cancer.

	Patients in subgroup	Complete response, n (%)	95% CI	p value
Age (years)				0·95
<65	18	10 (55·6%)	(30·7–78·5)	
65 to <75	27	16 (59·3%)	(38·7–77·7)	
≥75	26	16 (61·5%)	(40·5–79·8)	
Gender				0·61
Male	48	27 (56·3%)	(41·1–70·6)	
Female	23	15 (65·2%)	(42·7–83·7)	
Body mass index (kg/m²)				0·80
≤30	47	27 (57·4%)	(42·1–71·8)	
>30	24	15 (62·5%)	(40·5–81·3)	
Country				0·37
USA	57	32 (56·1%)	(42·3–69·3)	
Israel	14	10 (71·4%)	(41·8–91·7)	
Pre-debulking number of papillary lesions				0·63
1	34	19 (55·9%)	(37·8–72·9)	
>1	36	23 (63·9%)	(46·2–79·2)	
Post-debulking number of papillary lesions				0·60
1	48	30 (62·5%)	(47·3–76·1)	
>1	22	12 (54·5%)	(32·2–75·7)	
Pre-debulking largest lesion diameter (mm)				0·13
≤10 mm	29	21 (72·4%)	(52·7–87·3)	
>10 mm	38	20 (52·6%)	(35·8–69·1)	
Post-debulking largest lesion diameter (mm)				0·35
≤10mm	57	36 (63·2%)	(49·3–75·6)	
>10 mm	13	6 (46·2%)	(19·2–74·9)	
Pre-debulking total tumour burden (mm)				0·046
≤17 mm	34	24 (70·6%)	(52·5–85·0)	
>17 mm	32	14 (43·8%)	(26·3–62·4)	
Post-debulking total tumour burden (mm)				0·23
≤10 mm	39	26 (66·7%)	(49·7–81·0)	
>10 mm	31	16 (51·6%)	(33·0–69·9)	
Number of treatments received				1·00
6	61	36 (59·0%)	(45·6–71·5)	
<6	10	6 (60·0%)	(26·2–87·9)	
Tumour is unresectable				1·00
No	37	22 (59·5%)	(42·0–75·3)	
Yes	34	20 (58·8%)	(40·6–75·4)	
Past urothelial carcinoma episodes				0·47
0	28	15 (53·6%)	(33·8–72·5)	
≥1	43	27 (62·8%)	(46·7–77·1)	
Past upper tract urothelial carcinoma episodes				0·81
0	37	21 (56·8%)	(39·4–73·0)	
≥1	34	21 (61·8%)	(43·5–77·9)	

Table 4: **Subgroup analysis of complete response at primary disease evaluation for all treated patients (n=71)**

Discussion

This study shows that a substantial proportion (59%) of patients with low-grade upper tract urothelial cancer can have a complete response when treated with UGN-101. The total number of recruited and eligible patients exceeded that needed to show activity based on the primary endpoint of the trial (complete response >15%). The durability of response observed at 12 months was also encouraging. Chemoablation provides therapy to the entire field affected by urothelial cancer, which may explain the relative freedom from recurrence observed so far following treatment with UGN-101.

Upper tract urothelial cancer is a therapeutic challenge for urologists because of its rarity and the divergent clinical behaviour of its two distinct histological forms (high grade and low grade).[2–5] Diagnosed patients have few therapeutic options apart from ipsilateral radical nephroureterectomy, which most patients with low-grade, low-stage disease would eventually undergo. Radical nephroureterectomy is associated with the typical risks of major surgery, including a 40% 30-day complication rate, with haematological,

	Grades 1–2	Grade 3*	Grade 4†	Grade 5‡
Any adverse event	37 (52%)	26 (37%)	1 (1%)	3 (4%)
Ureteric stenosis	25 (35%)	6 (8%)	0	0
Urinary tract infection	21 (30%)	2 (3%)	0	0
Haematuria	20 (28%)	2 (3%)	0	0
Flank pain	19 (27%)	2 (3%)	0	0
Nausea	16 (23%)	1 (1%)	0	0
Dysuria	15 (21%)	0	0	0
Renal impairment	13 (18%)	1 (1%)	0	0
Vomiting	11 (15%)	3 (4%)	0	0
Abdominal pain	12 (17%)	1 (1%)	0	0
Hydronephrosis	9 (13%)	4 (6%)	0	0
Fatigue	11 (15%)	0	0	0
Anaemia	9 (13%)	0	0	0
Back pain	9 (13%)	0	0	0
Pollakiuria	9 (13%)	0	0	0
Pruritus	9 (13%)	0	0	0
Asthenia	7 (10%)	1 (1%)	0	0
Chills	8 (11%)	0	0	0
Pyrexia	8 (11%)	0	0	0
Decreased appetite	7 (10%)	0	0	0
Bladder transitional cell carcinoma	4 (6%)	2 (3%)	0	0
Dehydration	4 (6%)	2 (3%)	0	0
Diarrhoea	6 (8%)	0	0	0
Hypertension	4 (6%)	2 (3%)	0	0
Lower abdominal pain	5 (7%)	0	0	0
Acute kidney injury	4 (6%)	1 (1%)	0	0
Constipation	5 (7%)	0	0	0
Dyspnoea	3 (4%)	2 (3%)	0	0
Headache	5 (7%)	0	0	0

Data are n (%). Patients with more than one episode of the same adverse event term were counted only once (the worst severity of that adverse event). *Other grade 3 events were thrombocytopenia, urosepsis, and pulmonary oedema, each occurring in two patients, and pelvi-ureteric obstruction, renal failure, urinary tract inflammation, urinary tract obstruction, groin pain, hyperkalaemia, pancytopenia, fall, hyperglycaemia, hypersensitivity, hypotension, syncope, ureteric obstruction, acute respiratory failure, acute cardiac failure, chronic cardiac failure, deep vein thrombosis, hyponatraemia, iron deficiency anaemia, pyelonephritis, and supraventricular tachycardia, each occurring in one patient. †The grade 4 event was urosepsis, which was not related to the study drug or procedure. ‡Causes of death (grade 5 events) were cerebrovascular accident, failure to thrive, and unknown, none of which were related to the study drug or the procedure.

Table 5: **Treatment-emergent adverse events reported by a total of five or more patients by preferred term and maximum severity in the safety analysis group (n=71)**

gastrointestinal, and infectious complications being the most common.[10] Renal loss in older patients results in a heightened risk of renal insufficiency, the exacerbation of pre-existing cardiac comorbidity, and a small but real risk of renal failure leading to dialysis dependence.[10,11,17–19] Moreover, given that the current alternative management for low-grade upper tract urothelial cancer includes repeated ureteroscopy requiring general anaesthesia, the effect of repeated anaesthesia should be considered because newly published research suggests a potentially detrimental effect on cognition in elderly patients.[20,21]

Experience with conservative management of low-grade upper tract urothelial cancer with endoscopic ablation alone is variable in the published literature, with local recurrence rates of 77–90% as seen in studies with more than 48 months of follow-up.[22–25] Although the exact local recurrence rate for this type of cancer is not uniformly reported in these studies, a report from 2016[26] suggests that up to 51% of patients might experience recurrence or incomplete treatment after only 60 days. In general, the local recurrence rate of low-grade upper tract urothelial cancer after endoscopic ablation depends on the size of the index lesion, duration of follow-up, and experience of the treating centre, but it is clearly an area that urgently needs improvement. Endoscopic tumour ablation carries surgical risks such as ureteral stenosis (10–25%), infection, and injury to the urinary tract, including perforation.[7,27] Attempts to use adjuvant topical chemotherapy have yielded equivocal results, reflecting the short dwell time achieved in the upper tract when using aqueous solutions.[7,14] The continuous flow of urine coupled with the absence of reservoir capacity in the renal pelvis and ureter preclude retention of potentially beneficial drugs delivered in aqueous solution.

Reverse thermal gels, a subclass of polymer mixtures known as hydrogels, which assume a liquid form at low temperatures and a solid gel form as the temperature is increased, have previously been used to treat macular degeneration.[28] The use described in this report is novel in the care of patients with low-grade upper tract urothelial cancer. UGN-101 is a formulation of mitomycin with a proprietary mixture of polymers designed to provide extended dwell and contact time of mitomycin with the surface of the upper urinary tract. Non-clinical studies and early human experience with UGN-101 suggest that mitomycin at a concentration of 4 mg/mL in sterile hydrogel is well tolerated and feasible for delivery to the upper urothelial tract using a retrograde ureteral catheter.[15,29] Non-clinical and clinical pharmacokinetic studies have shown a low level of systemic absorption of mitomycin.[30]

We report treatment-related morbidity that might occur as a result of recurrent instrumentation of the upper tract as well as treatment with UGN-101 for the management of upper tract urothelial cancer. Most patients in this trial required temporary ureteral stenting, which is consistent with other treatments for upper tract urothelial cancer using standard-of-care technology. Serious or grade 3 ureteral stenosis formation occurred in six (8%) of 71 patients. Two (3%) patients had delayed radical nephroureterectomy after developing clinically significant ureteral stenosis that would have required long-term stenting. The final pathology in both patients confirmed complete resolution of the cancer. Patients in this study had transient perturbation of renal function consistent with either a mechanical or pharmacological effect of treatment; however, long-term decline in renal function

following treatment was rare. Treatments were administered under general anaesthesia in about a quarter of the instillations, but the attribution of adverse events to general anaesthesia was not specified.

Patients who had a complete response after induction therapy were eligible for monthly maintenance treatments with UGN-101 for the duration of the observation period. Although most patients received at least one dose of maintenance therapy, the use of maintenance therapy was inconsistent, and few patients received full-course maintenance. Thus, we could draw no conclusions about the value of maintenance with respect to the durability of complete response in this cohort.

The 6-week treatment regimen chosen for this trial was empirically derived from generally accepted urological practice for lower urinary tract adjuvant therapy. We acknowledge that alternative dosing regimens may be useful and could form a basis for future research. The catheter used in the trial was chosen to facilitate the administration of the slightly viscous UGN-101. A 7 French catheter was used for most doses administered. In some cases, investigators used a 5 or 6 French catheter when ureteral oedema or narrowing was encountered, making use of the 7 French catheter difficult. All catheters performed acceptably in the trial, and on the basis of this experience we believe that all catheters can be used to provide treatment using UGN-101.

This study has some potential limitations. The single-arm design was chosen in consultation with regulatory authorities because most patients with low-grade upper tract urothelial cancer undergo radical nephroureterectomy, especially those with lesions not amenable to endoscopic ablation. Radical nephroureterectomy is not an appropriate comparator for an organ-sparing therapy, and endoscopic ablation is used in a small minority of patients treated typically in specialty centres. The absence of a control group introduces potential biases into the trial, including the selection of a favourable group of patients more likely to respond to UGN-101, and the possibility that both benefits and harms might be overassessed or underassessed. The status of the contralateral kidney was not required to be reported. We do not have data on persistent tumour in other parts of the urinary system. A further limitation is that neither patient-reported nor caregiver-reported outcomes were measured. Patients were treated in expert centres, and questions could therefore be raised regarding the generalisability of the study results outside of expert urological oncology practices. The small size of the study population reflects the rarity of low-grade upper tract urothelial cancer, and statistical analysis shows that the observed complete response significantly exceeded our pre-specified goals. Patients with tumours larger than 15 mm were eligible for enrolment if they underwent endoscopic downsizing by partial ablation. It is possible that these partial ablations subtly contributed to the overall beneficial effect of treatment with UGN-101.

Conservative management of low-grade upper tract urothelial cancer is based upon the understanding that the tumour grade on biopsy correlates with clinical stage. Several investigators have observed that this correlation is imperfect, with up to a third of patients with low-grade disease on biopsy having high-grade tumours on radical nephroureterectomy.[31] Large, low-grade tumours might obscure high-grade elements that elude detection on endoscopic biopsy. Accordingly, both the US National Comprehensive Cancer Network and the EAU have recommended that conservative management of low-grade upper tract urothelial cancer patients should be considered for individuals with small (<15–20 mm), solitary tumours that are favourably located.[5,32] Although our data support a conservative approach to this population, the current results in patients with multifocal tumours and disease initially considered to be endoscopically unresectable suggest that some adjustment to the current recommendations might be warranted.

In conclusion, primary chemoablation of low-grade upper tract urothelial cancer with UGN-101 resulted in complete response in a substantial proportion of patients. In patients achieving complete response after induction therapy, durable disease control was observed in the majority, although just less than half of the patients with complete response had been evaluated for continued response at 12 months at the time of data cutoff. We continue to follow up this patient cohort and will provide an update on durability when data are available, which we estimate to be in about 12 months. Ureteral stenosis was the most common adverse event associated with treatment, but serious adverse events occurred in a minority of patients. This novel kidney-sparing approach might offer an important alternative for patients with low-grade upper tract urothelial cancer and expand the treatment options for patients with tumours that are difficult to treat endoscopically.

Contributors

NK, SFM, KC, MO'D, AW, RP, IK, MK, DS-A, MS, and SPL participated in the design of the trial and SPL determined the eligibility for each patient. PMP, ES, DS-A, MS, and SPL contributed to data analysis and the initial draft of the manuscript as well as subsequent revisions. ES, MS, and SPL had full access to the data, vouch for the integrity of the data and adherence to the study protocol, and were responsible for the decision to submit the manuscript. All authors contributed to data collection, data analysis and interpretation, and the revision of the manuscript for important content.

Declaration of interests

NK, PMP, and ABS report acting as investigators and consultants for UroGen Pharma. SFM reports consultancy for UroGen Pharma and Taris Bio. BH, KC, JDR, and JL report consultancy for UroGen Pharma. MR is a consultant for Boston Scientific and Lumenis. MO'D reports acting as an investigator and consultant for UroGen Pharma, Medical Enterprises, and Photocure, grants from Abbott Molecular, and consultancy for Fidia Farmaceuticals, Theralase, and Vaxiion. JJK reports acting as an investigator for UroGen Pharma and consultancy for Boston Scientific. CW reports consultancy for Abbott Molecular. ABS reports consultancy for UroGen Pharma, Merck, and Photocure, and acting as an investigator for Patient-Centered Outcomes Research Initiative. MBA reports being an investigator and consultant for UroGen Pharma, consultancy for Precipio, International Diagnostics Lab, Advanced

Clinical, and Cell Max, and holds stocks in Core Diagnostics. ES, IK, MK, DS-A, and MS are employees of UroGen Pharma. SPL reports grants for clinical trials from UroGen Pharma, Endo, FKD Therapies, JBL Drug Laboratories, Roche/Genentech, Vaxiion, and Viventia; consultancy for UroGen Pharma, Anchiano Therapeutics, Ferring, Gerson Lehrman Group, Merck, Roche/Genentech, QED Therapeutics, and Verity, honoraria and travel support as a speaker for Nucleix and MSD Korea, advising for mlR Scientific, is a patent holder for The Cancer Genome Atlas classifier, and has received compensation in his role as Co-Editor in Chief for *Bladder Cancer* and as Co-Editor for the bladder cancer section of UpToDate. MK reports patents issued and pending related to the materials and methods for treating internal cavities, the production of thermoreversible hydrogels for therapeutic applications, and reverse thermal hydrogel preparations for use in the treatment of disorders of the urothelium. All other authors declare no competing interests.

Data sharing

The study protocol is available in the appendix (pp 8–137). Individual participant data that underlie the reported results are not available.

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