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Long-term Clinical Outcomes of a Phase I Trial of Intravesical Docetaxel in the Management of Non–muscle-invasive Bladder Cancer Refractory to Standard Intravesical Therapy

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Abstract

OBJECTIVES—To report the long-term clinical outcomes and durability of response after treatment with induction intravesical docetaxel. Most novel agents used to treat bacillus Calmette-Guerin refractory high-grade non–muscle-invasive (NMI) bladder cancer are evaluated only after short follow-up periods. Our previously published phase I trial demonstrated that docetaxel is a safe agent for intravesical therapy with minimal toxicity and no detectable systemic absorption. We sought to determine long-term clinical outcomes after treatment with intravesical docetaxel.

METHODS—Eighteen patients with recurrent Ta (n = 7), T1 (n = 5), and Tis (n = 6) transitional cell carcinoma who experienced treatment failure with at least 1 prior intravesical therapy completed the phase I trial. Docetaxel was administered as 6 weekly intravesical instillations using a dose-escalation model terminated at 0.75 mg/mL. Efficacy was evaluated by interval cystoscopy with biopsies when indicated, cytology, and computed tomography imaging. Follow-up consisted of quarterly cystoscopy, cytology, computed tomography, and biopsy when indicated.

RESULTS—With a median follow-up of 48.3 months, 4 patients (22%) have demonstrated a complete durable response and currently remain disease-free without further treatment. Three patients (17%) had a partial response, defined as a single NMI recurrence with no further therapy for bladder cancer. Eleven patients (61%) failed treatment, and required another intervention. One patient developed stage progression. No delayed toxicities were noted. The median disease-free survival time was 13.3 months.

CONCLUSIONS—After 4 years of follow-up without maintenance therapy, intravesical docetaxel has demonstrated the ability to prevent recurrence in a select number of patients with refractory NMI bladder cancer and warrants further investigation.

In 2008, it was estimated that 68 810 new cases of bladder cancer will be diagnosed in the United States. In addition, 14 100 people will die from this disease, making bladder cancer the fourth leading cause of cancer in men and the eighth leading cause of cancer in women in the United States.¹ Non–muscle-invasive (NMI) bladder cancer accounts for 70%–80% of

these cases, and has a variable clinical course. The cornerstone of diagnosis and treatment of NMI bladder cancer is transurethral resection of bladder tumor (TURBT). However, the risk of recurrence of NMI bladder cancer treated with TURBT alone ranges from 45–80%.^{2,3}

In individuals with high-risk clinical and pathological features (Ta, T1, and Tis) the use of adjuvant induction intravesical therapy to prevent recurrence or progression has become the standard of care. BCG (bacillus Calmette-Guerin), live attenuated tuberculosis vaccine, after TURBT has been shown to reduce the risk of recurrence by approximately 40% as compared with TURBT alone.^{4,5} However, recurrence rates following 1 induction course of BCG are 46% and 69% with 5- and 10-year follow-up, respectively.^{6,7} When currently available intravesical agents fail to control disease, patients are faced with the prospect of radical cystectomy and urinary diversion. Reluctance to accept this intervention is often hinged on an expected decrease in quality of life or comorbid medical conditions that preclude major surgery. Currently, there are no clearly beneficial intravesical salvage chemotherapeutic alternatives for these refractory patients.

Docetaxel (Taxotere; Sanofi Aventis, Bridgewater, NJ; [(2R,3S)-*N*-carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5 β ,20-epoxy-1, 2 α ,4, 7 β ,10 β ,13 α -hexahydroxytax-11-en-9-1 4-acetate 2 benzoate, trihydrate]) is a cytotoxic chemotherapeutic agent derived from the needles of *Taxus baccata*.⁸ It exerts its chemotherapeutic effect by stabilizing microtubules against depolymerization, resulting in M-phase cell cycle arrest and cell death.⁸ In preclinical studies, docetaxel has been shown to be one of the most effective agents in inhibiting growth in human bladder tumor cell lines at concentrations as low as 0.1 μ M. It has exhibited the ability to suppress clonal growth in 100% of cell lines tested at this concentration.⁹

A phase I trial to assess the safety and tolerability of intravesical docetaxel was performed, and included 18 patients with high-grade, NMI, BCG-refractory bladder cancer.⁸ These patients had failed a mean of 3 prior induction courses of intravesical therapy. Intravesical docetaxel was administered once weekly for 6 weeks using a dose escalation model. The intravesical dwell time was 2 hours, and serum levels of docetaxel were monitored 2 hours after voiding with high pressure liquid chromatography. In our previously published study, no grade 3 or 4 toxicities were observed and no dose-limiting toxicity was encountered in this trial. The initial previously published evaluation done after 4 weeks with biopsy and cytology showed that 10 (56%) of 18 patients had a complete response (negative biopsy and negative cytology), 2 (11%) had a partial response (negative biopsy and positive cytology), and 6 (33%) had no response (positive biopsy). Given the limited data in this experimental population, our current objective is to report the long-term clinical outcomes and durability of response after treatment with induction intravesical docetaxel.

MATERIAL AND METHODS

All 18 patients included in the initial phase I clinical trial of intravesical docetaxel for the treatment of NMI transitional cell carcinoma of the urinary bladder (Ta, T1, Tis) had continued follow-up at Columbia University Medical Center. To be included in this study group, initially all patients had documented evidence of recurrent, high-grade, NMI bladder

cancer that was refractory to standard intravesical therapy, including BCG, mitomycin, interferon, or any combination of the above. All patients were found to be medically unstable or refused cystectomy. All grossly visible disease was resected before enrollment and no marker lesion was left. Other inclusion criteria were age ≥ 18 , ability to read and understand and sign informed consent, ECOG performance status of 0 or 1, peripheral neuropathy grade 1, adequate hematopoietic and hepatic parameters, negative pregnancy test in women of childbearing age, and consent to using effective contraception while on treatment and for 3 months after their participation in the study.

The long-term follow-up of these patients consisted of cystoscopy every 3 months and urine cytology, abdominal and pelvic computed tomography scan, and biopsy when indicated. If a patient remained disease-free for 2 years, then he/she was subsequently evaluated with cystoscopy every 6 months. No maintenance therapy was given. Additional therapies at relapse were administered at patients' and physicians' discretion; thus, the long-term outcomes of interest were defined as follows: a durable complete response (DCR) was defined as remaining disease-free without any further intervention. A durable partial response (DPR) was defined as NMI recurrence requiring TURBT but no further treatment. No durable response was defined as recurrence prompting either cystectomy or further pharmacologic therapy. Progression was defined as progression to T2 or greater.

RESULTS

A total of 18 patients were enrolled in the study (Table 1). All of these patients had continued follow-up after completion of the clinical trial and were included in the long-term analysis. None of the patients experienced any delayed toxicities. With a median of 48 months of follow-up, 4 (22%) of 18 patients had a durable complete response, 3 (17%) had a DPR, and 11 (61%) had no durable response. No observable correlation occurred between dose and long-term response. Notably, 39% of patients (DCR and DPR) remain disease-free without any further intravesical therapy or cystectomy (Table 2). Of the 11 patients who had no durable response, 4 patients had further intravesical therapy but have not undergone cystectomy, 6 patients underwent cystectomy, and 1 patient refused cystectomy and subsequently died of metastases. One of 6 cystectomy patients underwent this procedure at an outside institution and died of a postoperative complication. None of the patients who ultimately underwent cystectomy had occult nodal metastases. Additionally, 16 of 18 patients did not exhibit progression of disease, including specifically those who elected further treatment (Table 3). Therefore, progression-free survival among these patients was 89%. The 2 patients with progression in this calculation included the patient who refused cystectomy and the patient who died of a postoperative complication after cystectomy.

A Kaplan–Meier survival curve was generated to further depict disease-free survival maintained without further intravesical treatment or cystectomy. In this extremely high-risk group of patients who have failed multiple prior intravesical treatments, it is reasonable to define success as those patients who remain disease-free without further medical treatment or cystectomy. The 3 patients who underwent an additional TURBT to maintain disease-free status as previously described are included as successes. Disease-free survival at 1- and 2-

years after completion of intravesical docetaxel treatment was 61% and 44%, respectively. The median disease-free survival time was 13.3 months (Fig. 1).

COMMENT

Intravesical treatment with BCG remains the most common therapy for high-grade, NMI bladder cancer. It has been highly effective in delaying time to recurrence in this disease; however, for patients who fail BCG therapy, the prognosis is poor. The definitive treatment for these patients remains radical cystectomy. However, in a rapidly aging population with higher rates of comorbid conditions, this option is not often feasible or desirable for the patient. The current effective alternative medical options available to these patients with BCG-refractory, high-grade, NMI bladder cancer are limited.

After failing 1 course of BCG, failure rates with subsequent courses continue to rise a maximum of 80% by the third course of BCG.¹⁰ Alternate chemotherapeutic agents such as valrubicin and mitomycin C exist for the treatment of BCG-refractory bladder cancer, but failure rates have been reported to be as high as 56% and 77%, respectively.^{11,12} Our study population comprised individuals with highly resistant disease who had failed an average of 3 prior induction cycles of the most efficacious intravesical agents available at the time. Although efficacy was not the primary objective in this phase I trial, the initial 4 week follow-up data showed the presence of activity in 12 (67%) of 18 patients treated with an induction course of intravesical docetaxel.⁸ The small population size and design of the study do not allow for any substantial claims to be made regarding the efficacy of intravesical docetaxel.

Given the promising initial results of intravesical docetaxel, it was critical to examine the durability of this therapeutic agent. Many experimental trials report on the initial response seen within months of treatment initiation. It is also vital to continue to follow up these patients to accurately characterize the long-term outcomes that can be expected. This long-term evaluation suggests that docetaxel may provide a subset of high-risk patients with the possibility of DCR for high-risk, NMI bladder cancer.

CONCLUSIONS

With a median follow-up of 48.3 months, a single course of intravesical docetaxel seems to prevent recurrence in patients who are refractory to prior intravesical therapy. Among 18 treated patients, 39% are disease-free without cystectomy or further intravesical therapy, and progression-free survival among this group was 89%. Given these results and the need for intravesical chemotherapeutic alternatives, taxane-based intravesical chemotherapy remains a promising agent in the treatment of non-muscle-invasive bladder cancer.

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Figure 1.
Disease-free survival maintained without further intravesical treatment or cystectomy.

Table 1

Patient demographics (no. of patients = 18) from initial cohort included in phase I clinical trial of intravesical docetaxel

Characteristic	No. Patients
Age, y	
Mean	75
Range	39–89
Sex	
Male	16
Female	2
Inclusion	
Refused surgery	16
Medically inoperable	2
ECOG status	
0	18
Clinical stage	
Tis	5
Ta	7
T1	1
Ta + Tis	1
T1 + Tis	4
Prior therapy with BCG	18
BCG alone	9
BCG + IFN	9
Prior therapy with BCG + chemotherapy	4
Mitomycin	2
Valrubicin	1
Thiotepa	1

ECOG = eastern cooperative oncology group; BCG = bacillus Calmette-Guerin; IFN = interferon.

Table 2

Individual long-term outcomes with a median follow-up of 48.3 months

Dose (mg)	Pretrial Stage	Additional Treatment	Status	Long-term Response
5	Tis	None	NED	DCR
10	HG Ta	None	NED	DCR
20	Tis	None	NED	DCR
75	Tis	None	NED	DCR
5	HG Ta	TURBT	NED	DPR
40	HG Ta	TURBT	NED	DPR
60	T1	TURBT	DOC	DPR
5	T1 + Tis	Phase I gene therapy	NED	NDR
20	HG Ta	Docetaxel	NED	NDR
20	HG Ta	Phase I gene therapy	DOC	NDR
60	HG Ta	Phase I gene therapy	NED	NDR
10	HG Ta + Tis	Cystectomy	DOC	NDR
10	Tis	Cystectomy	NED	NDR
40	HG Ta	Refused cyst	DOD	NDR
40	Tis	Cystectomy	NED	NDR
60	T1 + Tis	Cystectomy	DOD [*]	NDR
75	T1	Cystectomy	NED	NDR
75	T1 + Tis	Cystectomy	NED	NDR

^{*} Patient died of postoperative complication.

NED = no evidence of disease; DOC = died of other cause; DOD = died of disease; DCR = durable complete response; DPR = durable partial response; NDR = no durable response.

Table 3

Stage before additional treatment among patients in the no durable response group

Dose (mg)	Pretrial Stage	Stage Before Additional Treatment	Additional Treatment	Pathological Stage	Status
5	T1 + Tis	HG Ta + Tis	Phase I gene therapy		NED
20	HG Ta	LG Ta	Docetaxel		NED
20	HG Ta	HG Ta + Tis	Phase I gene therapy		DOC
60	HG Ta	LG Ta	Phase I gene therapy		NED
10	HG Ta + Tis	HG Ta	Cystectomy	HG pTa	DOC
10	Tis	HG Ta + Tis	Cystectomy	pT1	NED
40	HG Ta	T1	Refused cystectomy		DOD
40	Tis	Tis	Cystectomy	pT1	NED
60	T1 + Tis	T1	Cystectomy	pT1	DOD*
75	T1	T1 + Tis	Cystectomy	pT1	NED
75	T1 + Tis	T1	Cystectomy	pT1	NED

* Patient died of postoperative complication.