Long-Term Survival Outcomes with Intravesical Docetaxel for Recurrent Nonmuscle Invasive Bladder Cancer After Previous Bacillus Calmette-Guérin Therapy

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Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin

CIR = complete initial response

DSS = disease specific survival

MMC = mitomycin C

NMIBC = nonmuscle invasive bladder cancer

OS = overall survival

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Purpose: Docetaxel is a safe agent for intravesical therapy. Adding monthly maintenance treatments can extend response durability. We report our cumulative experience with intravesical docetaxel in a larger cohort with extended followup.

Materials and Methods: A total of 54 patients received salvage intravesical docetaxel for bacillus Calmette-Guérin refractory nonmuscle invasive bladder cancer between 2003 and 2012, including 18 treated during the original phase I trial. All patients received 6 weekly instillations of intravesical docetaxel. After the phase I trial, those with a complete response to induction treatment were offered single dose monthly maintenance treatments for a total of up to 12 months of docetaxel therapy. Recurrence was defined as positive biopsy or urine cytology. Recurrence-free, disease specific and overall survival was determined by Kaplan-Meier analysis.

Results: Median followup was 39.1 months. Of the 54 patients 32 (59%) had a complete initial response after induction therapy, including 18 who received additional monthly maintenance treatments. Median time to recurrence in initial responders treated with vs without docetaxel maintenance was 39.3 vs 19.0 months. One and 3-year recurrence-free survival rates for the entire cohort were 40% and 25%, respectively. Of the 54 patients 17 (24%) underwent radical cystectomy at a median of 24 months of followup. Five-year disease specific and overall survival rates were 85% and 71%, respectively.

Conclusions: Intravesical docetaxel appears to be a promising agent with significant efficacy and durability for bacillus Calmette-Guérin refractory nonmuscle invasive bladder cancer. Adding maintenance treatments may increase the duration of recurrence-free survival.

Key Words: urinary bladder; urinary bladder neoplasms; therapies, investigational; docetaxel; administration, intravesical

SINCE the original reports of intravesical BCG for superficial bladder cancer, now more appropriately termed NMIBC,[1] BCG has become a primary intravesical agent for managing NMIBC in North America.[2,3] It is supported by the American Urological Association as first line treatment for carcinoma in situ, and as prophylaxis to prevent recurrence after resection of T1 and high grade Ta tumors.[4] In 2005 Sylvester et al performed a meta-analysis of 9 randomized trials comparing BCG to intravesical chemotherapy, including MMC, epirubicin and doxorubicin, for carcinoma in situ with or without concurrent papillary tumors.[5] These studies showed a 68% complete response

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rate after BCG compared to 51% after chemotherapy. At a median of 3.6 years of followup 47% of patients treated with BCG remained disease free compared to 26% of those who received chemotherapy. Several series also demonstrated decreased recurrence and progression when BCG was used after transurethral resection of papillary tumors.[6–9] To our knowledge no intravesical chemotherapy to date has been superior to BCG in treatment naïve patients with NMIBC.

Unfortunately, treatment options are limited for patients with recurrence after BCG therapy. Repeat BCG courses with or without interferon are often administered but the response rate to additional courses of BCG induction therapy is only 20% after 2 or more failed courses.[10] Also, the high frequency of toxicity associated with BCG makes it difficult for some patients to tolerate further therapy.[4] Patients with BCG refractory NMIBC have a 50% chance of disease progression and should be considered for cystectomy[10] but many are unwilling or unable to undergo this procedure. Novel agents are needed to treat these patients at high risk.

In 2006 the results of a phase I trial of intravesical docetaxel for BCG refractory NMIBC were reported.[11] Docetaxel, a microtubule depolymerization inhibitor with antitumor activity for a wide variety of cancers,[12–15] showed a 56% response rate with minimal toxicity after a single 6-week course of intravesical instillation in 18 patients treated in the phase I dose escalation protocol. In a larger cohort of 33 patients only 36% experienced grade 1 or 2 local toxicity with no grade 3 or 4 local toxicity or systemic toxicity observed.[16] Since other agents have been more effective with the addition of maintenance therapy, subsequent patients were treated with the same 6-week induction, followed by up to 9 monthly instillations if cystoscopy at 3 months revealed a response.[17,18]

We analyzed the long-term efficacy and durability of intravesical docetaxel in a large cohort with extended followup.

MATERIALS AND METHODS

We queried an institutional review board approved, prospectively captured database and identified 54 patients who received salvage intravesical docetaxel for recurrent NMIBC after BCG failure between 2003 and 2012. Each patient was treated in the past with at least 1 complete 6-week course of intravesical BCG with or without interferon and had experienced recurrence or progression after therapy. All patients underwent cystoscopy with transurethral resection 1 to 6 weeks before induction therapy with docetaxel. No marker lesions were left in the bladder. The risks and benefits of this and alternative treatments were discussed and informed consent was obtained for each patient before therapy initiation.

Intravesical docetaxel was prepared and administered as previously described.[11] For each treatment docetaxel was reconstituted with polysorbate 80 in 0.9% sodium chloride. A dose escalation scheme was used in the first 18 patients treated with doses ranging from 5 to 75 mg for a final concentration of 0.125 to 0.75 mg/ml for administration. All subsequent patients received the maximum dose of 75 mg/100 ml normal saline. Before instillation the bladder was emptied by sterile urethral catheterization. The docetaxel solution was then instilled in the bladder during 5 minutes. Patients retained the drug for 2 hours before voiding. The drug was administered weekly for 6 weeks during induction therapy. All patients treated after the dose escalation trial who responded to induction therapy were offered monthly maintenance instillations starting 3 months after induction therapy for a maximum of 9 maintenance treatments (total of 1 year of therapy). Patients were monitored for local toxicity throughout the duration of treatment. Toxicity outcomes were previously reported in a subset of the current cohort.[11,16]

The initial response after induction treatment was assessed by cystoscopy with biopsies of the urothelium and urine cytology 6 weeks after the sixth docetaxel instillation. Patients were considered to have a CIR if they had negative biopsy and cytology results. All patients with positive biopsies or cytology after induction therapy were classified as having no initial response.

Patients with a CIR were monitored by quarterly cystoscopy with urine cytology and biopsies as well as periodic computerized tomography. Recurrence-free survival was measured from pre-induction cystoscopy to the time of the most recent negative cystoscopy. Death from bladder cancer and other causes was determined from medical records and the Social Security Death Index. Treatment efficacy was measured using the CIR rate after induction therapy and Kaplan-Meier survival analyses of recurrence-free survival, DSS and OS.[19] All statistical analysis was performed using Stata®/SE, version 9.2.

RESULTS

Six women and 48 men with BCG refractory NMIBC who received a 6-week induction course of intravesical docetaxel at our institution were identified for analysis (see table). Median age was 72 years (range 36 to 90). Median followup was 39.1 months (range 5 to 93). All patients previously received BCG, including 28 with BCG alone and 26 with BCG plus interferon (see table). A total of 16 patients (30%) previously received intravesical chemotherapy, including 12 treated with MMC. Most patients had undergone at least 2 prior courses of intravesical therapy.

At post-induction cystoscopy 32 patients (59%) had a CIR to intravesical docetaxel. One and 3-year recurrence-free survival rates for the entire cohort of 54 patients were 40% and 25%, respec-