Intravesical docetaxel for high-risk non-muscle invasive bladder cancer after Bacillus Calmette-Guérin failure

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Background: There are limited bladder-preserving therapeutic options for patients with high-risk non-muscle invasive bladder cancer (NMIBC) after failed Bacillus Calmette-Guérin (BCG) therapy. Salvage intravesical docetaxel therapy was described in 2006 but has not been validated outside of the original institution. In this study, we presented the first external report on the oncologic outcomes of intravesical docetaxel.

Methods and materials: We identified 13 patients with high-risk NMIBC treated with ≥1 course of intravesical BCG who received salvage intravesical docetaxel. Recurrence-free survival (RFS) was estimated using the Kaplan–Meier method. Associations of clinicopathologic features with RFS were evaluated using Cox regression.

Results: Median age was 75.2 years, and 46.2% of patients were male. Of the patients 92.3% had a prior diagnosis of high-grade T1 disease, 38.5% had a prior diagnosis of carcinoma in situ, and 46.2% had received ≥2 courses of BCG. Only 1 (7.7%) patient experienced docetaxel-related toxicity. Nine (69.2%) patients had a complete response at initial post-docetaxel cystoscopy. During a median follow-up of 12.0 (interquartile range 5.0–11.8) months, a total of 7 (53.8%) patients developed recurrence. Median time to recurrence was 10.1 (interquartile range 4.3–11.6) months. Estimated RFS at 6-, 12-, 18-, and 24-months was 75%, 50%, 50%, and 25%, respectively. Three (23.1%) patients ultimately underwent cystectomy. On univariable analysis, multiple courses of induction BCG were associated with decreased RFS, although this did not reach statistical significance (hazard ratio 4.69, \( p=0.08 \)).

Conclusions: In this first external validation study, intravesical docetaxel was associated with excellent response rates and intermediate-term RFS among patients with high-risk NMIBC after failed BCG therapy.

Keywords: Bacillus Calmette-Guérin; Docetaxel; Intravesical instillation; Nonmuscle invasive bladder cancer

1. Introduction

Adjuvant intravesical bacillus Calmette-Guérin (BCG) is standard of care in the management of patients with high-risk non-muscle invasive bladder cancer (NMIBC) following endoscopic resection.1–3 However, up to 50% of patients fail BCG therapy and represent an important index case for disease management.4,5 While early radical cystectomy (RC) is recommended for high-risk NMIBC after failed BCG therapy due to the increased mortality risk among such patients, RC is associated with substantial morbidity and potential quality of life changes.6–8 Accordingly, bladder-preserving therapeutic options are critical for this group of patients.

Multiple intravesical agents have been evaluated to address this important knowledge gap, including valrubicin,6 gemcitabine,7 docetaxel,8 adenoviral vectors,9 and combination or sequential agents.10,11 However, no salvage intravesical agent has been established for the management of BCG failure due to poor efficacy or limited data. Indeed, valrubacin is the only FDA-approved agent for BCG-refractory NMIBC, but it is associated with a 2-year response rate of only 8%.12

Intravesical docetaxel has been associated with a promising initial response rate of approximately 60% and 3-year recurrence-free survival (RFS) of 25%, although the data are limited to a single center.13–15 Given its relative safety and reported efficacy, intravesical docetaxel represents an appealing salvage therapy after BCG failure. In this study, we report our experience with salvage intravesical docetaxel for high-risk NMIBC after failed BCG therapy, which is the first external validation study to our knowledge.
2. Materials and methods

2.1. Study population and clinicopathologic features

After obtaining Institutional Review Board approval, we identified 13 patients aged ≥18 years with Ta, T1, or carcinoma in situ (CIS) urothelial carcinoma of the bladder, who received salvage intravesical docetaxel after failing 1 or more courses of intravesical BCG.

Clinicopathologic features recorded included age at predocetaxel recurrence, sex, Charlson comorbidity index, smoking status, tumor stage at initial diagnosis and at predocetaxel recurrence, tumor grade at initial diagnosis and at predocetaxel recurrence, characteristics of prior BCG therapy (agent[s] used, number of courses), and time from last treatment to BCG failure. BCG failure was categorized as refractory, unresponsive, relapsing, or intolerant. With regard to docetaxel administration, we recorded initial response after docetaxel induction, utilization of maintenance docetaxel therapy, time to recurrence after docetaxel induction, tumor grade and stage at postdocetaxel recurrence, and clinical management of postdocetaxel recurrence. Docetaxel-related toxicity, categorized according to symptoms, was retrospectively assessed by using a prespecified data collection sheet. Delayed toxicity was considered in patients who presented with symptoms after 2 weeks following completion of all 6 cycles of induction therapy.

2.2. Intravesical docetaxel protocol

Each patient provided written informed consent prior to receipt of intravesical docetaxel. Induction therapy consisted of 6 weekly instillations. Before each instillation, a urinalysis was performed to exclude urinary infection. During each instillation, a Foley catheter was placed using sterile technique to drain the bladder. Then, 75 mg of docetaxel in 100 mL of 0.9% sterile saline was instilled into the bladder. The patient was instructed to hold the medication for 2 h or as long as tolerated. Patients were instructed to notify a physician with any adverse reactions. Postdocetaxel cystoscopy was performed approximately 6 weeks after the 6th instillation. If surveillance cystoscopy demonstrated suspicious findings, endoscopic resection was performed to establish pathologic diagnosis. In the absence of recurrence, patients were recommended to complete monthly maintenance docetaxel for 12 months.

2.3. Clinical follow-up

In the absence of recurrence, cystoscopic surveillance was performed every 3 months for the first 2 years, then every 6 months for the next 2 years, and annually thereafter. Endoscopic resection was performed if suspicious findings were identified on surveillance cystoscopy to establish pathologic diagnosis. Initial response following induction docetaxel was classified as complete response if no tumor was identified; partial response if lower grade and/or stage tumor was identified than prior to docetaxel; persistent disease if the same grade and stage tumor was identified; or disease progression if higher grade and/or stage tumor was identified. Recurrences were managed in accordance with clinical guidelines at the discretion of the treating physician.

2.4. Histopathologic evaluation

To examine for potential treatment-related morphologic changes following docetaxel, a single urologic pathologist (A.A.) reviewed the histopathologic material from 7 patients who developed postdocetaxel recurrence, including transurethral resection (TUR) specimens and RC specimens. For each patient, the specimen obtained immediately before and after administration of the docetaxel therapy was reviewed to examine the effect of chemotherapy on normal tissue and tumor. Histologic changes were categorized and summarized by using frequency counts and percentages.

2.5. Statistical analysis

Baseline characteristics were summarized using medians/interquartile ranges (IQR) and frequency counts/percentages. Response after induction docetaxel was summarized with frequency counts/percentages. Follow-up time for RFS was calculated as the time from the last recurrence before induction docetaxel (i.e., the TUR immediately preceding docetaxel induction) to the date of last follow-up or pathologically-confirmed recurrence event (ie, date of TUR after docetaxel). RFS was estimated using the Kaplan–Meier method. The associations of baseline characteristics with RFS were evaluated using univariable Cox regression models. Multivariable analysis was not performed due to the small number of events.

Statistical analysis was performed by using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and p-value < 0.05 was considered to be statistically significant.

3. Results

A total of 13 patients received salvage intravesical docetaxel for NMIBC recurrence after 1 or more courses of intravesical BCG. Baseline characteristics are summarized in Table 1. The median age prior to docetaxel was 75.2 (IQR 66.3–78.4) years, and 46.2% of patients were male. Prior to docetaxel, 46.2% of the cohort received ≥2 courses of induction BCG; 92.3% had a prior diagnosis of high-grade T1 tumor, and 38.5% had a prior diagnosis of CIS. BCG failure was classified as refractory in 69.2% of patients and intolerant in 30.8%. Median time to BCG failure was <12 months in 84.6% of patients. Tumor stage prior to docetaxel was T1 in 7 (53.8%) patients, T1 + CIS in 1 (7.7%) patient, and CIS in 2 (15.4%) patients.

All patients completed the full 6-instillation induction course of intravesical docetaxel; no patient discontinued induction therapy due to toxicity. Only 1 (7.7%) patient experienced docetaxel-related toxicity during induction therapy in the form of urinary tract infection (Table 2). Clinicopathologic outcomes after intravesical docetaxel therapy are summarized in Table 3. A total of 9 (69.2%) patients had a complete response to induction docetaxel, while 4 (30.8%) patients demonstrated persistent disease. There were 9 (69.2%) patients who received monthly maintenance docetaxel with a median of 11 instillations per patient.

Median follow-up for the cohort was 12.0 (IQR 5.0–18.1) months. During this time, 7 (53.8%) patients developed recurrence at a median of 10.1 (IQR 4.8–11.6) months (Fig. 1). Estimated RFS at 6-, 12-, 18-, and 24-month was 75%, 50%, 50%, and 25%. All recurrences were non-muscle invasive disease. Of these, 2 (28.6%) patients were treated with early RC while 5 (71.4%) were managed with endoscopic resection with or without additional intravesical therapy. There was 1 additional patient who progressed to RC at a later time.

The associations of baseline characteristics with RFS were evaluated using univariable Cox regression (Table 4). History of ≥2 induction BCG courses was associated with increased risk of disease recurrence, although this did not reach statistical
significance (hazard ratio 4.69; 95% confidence interval 0.84–26.03; \( p = 0.08 \)).

As an exploratory analysis to identify potential treatment-related morphologic changes following docetaxel, we reviewed histopathologic specimens in the 7 patients who developed postdocetaxel recurrence and compared the morphologic features of normal tissue and tumor with those of the specimen obtained immediately prior to administration of docetaxel. The most prominent morphological alterations observed after docetaxel administration included expansion of the tumor cytoplasm (n = 7, 100%), nuclear enlargement (n = 3, 43%), squamous metaplasia (with or without keratinization; n = 2, 29%), and cytoplasmic clearing (n = 1, 14%). Cytoplasmic expansion was also noted in the benign urothelium when it is available. Representative images are provided as Figure 2.

### Table 1

Baseline characteristics (n = 13).

| Patient characteristics | Values |
|-------------------------|--------|
| Age, y                  | Median (IQR) 75.2 (66.3–78.4) |
|                         | Range   62.0–85.6 |
| Sex, n (%)              | Male 6 (46.2) |
|                         | Female 7 (53.8) |
| Charlson comorbidity index, median (IQR) | 1 (1, 2) |
| Smoking status, n (%)   | Never 3 (23.1) |
|                         | Former 9 (69.2) |
|                         | Current 1 (7.7) |
| Tumor stage at initial diagnosis, n (%) | GS 0 |
|                         | Ta 1 (7.7) |
|                         | Ta + CIS 0 |
|                         | T1 12 (92.3) |
|                         | T1 + CIS 0 |
| Tumor stage prior to docetaxel, n (%) | GS 2 (15.4) |
|                         | Ta 3 (23.1) |
|                         | Ta + CIS 0 |
|                         | T1 7 (53.8) |
|                         | T1 + CIS 1 (7.7) |
| Tumor grade at initial diagnosis, n (%) | Low 1 (7.7) |
|                         | High 12 (92.3) |
| Tumor grade prior to docetaxel, n (%) | Low 1 (7.7) |
|                         | High 12 (92.3) |
| Prior diagnosis of CIS, n (%) | 5 (38.5) |
| Prior diagnosis of high-grade T1, n (%) | 12 (92.3) |
| Prior therapy with BCG, n (%) | 10 (76.9) |
|                         | With interferon 3 (23.1) |
| Total number of prior courses of induction BCG, n (%) | 1 7 (53.8) |
|                         | 2 5 (38.5) |
|                         | 3 or more 1 (7.7) |
| Classification of BCG failure, n (%) | Refractory 9 (69.2) |
|                         | Unresponsive 0 |
|                         | Relapsing 0 |
|                         | Intolerant 4 (30.8) |
| Prior BCG maintenance (with any course), n (%) | Yes 5 (38.5) |
|                         | No 8 (61.5) |
| Timing of BCG failure from last treatment, n (%) | First surveillance cystoscopy 11 (84.6) |
|                         | <12 months 0 |
|                         | 12–24 months 1 (7.7) |
|                         | >24 months 1 (7.7) |

### Table 2

Docetaxel-related toxicity during induction therapy.

| Feature                          | Number of patients (%) |
|----------------------------------|------------------------|
| Experienced any toxicity         | 1 (7.7)                |
| Toxicity symptoms                |                        |
| Frequency                        | 0                      |
| Urgency                          | 0                      |
| Dysuria                          | 0                      |
| Hematuria                        | 0                      |
| Facial flushing                  | 0                      |
| Rash                             | 0                      |
| Urinary tract infection          | 1 (7.7)                |
| Other                            | 0                      |

### Table 3

Clinicopathologic outcomes after intravesical docetaxel therapy.

| Feature                                                                 | Number of patients (%) |
|-------------------------------------------------------------------------|------------------------|
| Received monthly maintenance docetaxel                                  | 9 (69.2)               |
| Number of monthly maintenance                                            | 11 (8–14)              |
| instillations (n = 9); median (IQR)                                     |                        |
| Initial response after induction therapy                                 |                        |
| Complete response                                                        | 9 (69.2)               |
| Partial response                                                          | 0                      |
| Persistent disease                                                        | 4 (30.8)               |
| Disease progression                                                       | 0                      |
| Patients with recurrence (at any time after induction docetaxel)         | 7 (53.8)               |
| Recurrence at first surveillance postdocetaxel                           | 4 (30.8)*              |
| Staging at first recurrence                                             |                        |
| CIS                                                                      | 2 (28.6)*              |
| Ta                                                                       | 1 (14.3)               |
| Ta + CIS                                                                 | 0                      |
| T1                                                                       | 3 (42.9)               |
| T1 + CIS                                                                 | 1 (14.3)               |
| T2+                                                                      | 0                      |
| Grade at first recurrence                                               |                        |
| Low                                                                      | 0                      |
| High                                                                     | 7 (100.0)              |
| Management of first recurrence                                          |                        |
| TUR + surveillance                                                       | 1 (14.3)               |
| TUR + docetaxel                                                          | 3 (42.9)               |
| TUR + alternate therapy                                                  | 1 (14.3)               |
| Cystectomy                                                               | 2 (28.6)               |
| Chemotherapy                                                             | 0                      |
| Progression to cystectomy (at any time)                                  | 3 (23.1%)              |
| Months to recurrence (among those who recurred)                          |                         |
| Median (IQR)                                                             | 10.1 (4.8–11.6)        |
| Range                                                                    | 3.7–23.5               |
| Months follow-up                                                         |                         |
| Median (IQR)                                                             | 12.0 (5.0–18.1)        |
| Range                                                                    | 3.4–27.7               |

*One patient had a RC after initial cystoscopy due to large tumors on bladder wall. No TUR of bladder tumor was performed. Stage and grade based on RC pathology, not TUR of bladder tumor.
4. Discussion

In this study, salvage intravesical docetaxel was associated with an encouraging initial response rate of 69% and relatively durable efficacy with 24-month RFS of 25%. Treatments were well tolerated, without any discontinuation due to docetaxel-related toxicity. Although the study cohort is relatively small, this is the first external report, to the best of our knowledge, to support the oncologic efficacy of intravesical docetaxel outside of the initial reports. Furthermore, although there was no control arm, the study population comprised NMIBC patients at highest risk of recurrence and progression. These results suggest that intravesical docetaxel should be further examined in larger studies as a readily available, safe, and potentially efficacious bladder-preserving treatment strategy for patients with high-risk NMIBC after failed BCG therapy.

Intravesical docetaxel was initially described in phase I dose-escalation study by McKiernan et al.,[14] which demonstrated minimal toxicity and no systemic absorption. In that study, 56% of patients demonstrated a complete response at first post-docetaxel cystoscopy. The authors have since reported on their expanded experience with intravesical docetaxel, including monthly maintenance therapy.[8,12,13] In the largest report of 54 patients with BCG-refractory NMIBC, 59% achieved a complete initial response, with 1- and 3-year RFS of 40% and 25%. Our results reinforced these observations, with very similar complete initial response and RFS rates.

A number of other intravesical agents, including both intravesical immunotherapy and intravesical chemotherapy, have been explored for the management of high-risk NMIBC after BCG failure, but none has been established as standard of care due to inconsistent efficacy or limited data.[4] Intravesical valrubicin is the only FDA-approved agent for BCG-refractory CIS, despite a 2-year response rate of only 8%.[6] Intravesical gemcitabine has also been evaluated in multiple studies. In a meta-analysis, intravesical gemcitabine was associated with reduced recurrence rates compared to other intravesical agents, although the treatment effect varied by study population and comparator arm.[16] Other studies have reported efficacy of combination therapies, including combination intravesical gemcitabine and mitomycin C.[17,18] Most recently, a phase II study of recombinant adenovirus interferon alfa with syn3 (Ad-IFNa/Syn3) demonstrated an encouraging 35% 12-month RFS, with a phase III trial currently ongoing.[9]

This is also the first report, to the best of our knowledge, to describe the impact of docetaxel therapy on morphological

| Feature | Hazard ratio (95% confidence interval) | p |
|---------|--------------------------------------|---|
| Age (y) | 0.97 (0.88–1.08) | 0.59 |
| Female sex | 0.82 (0.16–4.08) | 0.81 |
| Charlson index | 1.74 (0.77–3.90) | 0.18 |
| Prior therapy with BCG + interferon (vs. BCG alone) | 1.53 (0.28–8.39) | 0.62 |
| Multiple courses of induction BCG (vs. 1) | 4.69 (0.84–26.03) | 0.08 |
| Prior BCG maintenance (vs. no maintenance) | 1.10 (0.22–5.50) | 0.91 |
| Smoking status (vs. never) | 0.52 (0.09–2.87) | 0.45 |
| Predocetaxel T stage | | |
| Ta | Ref | Ref |
| T1 or CIS | 1.97 (0.23–16.9) | 0.54 |
| Predocetaxel T stage | | |
| Ta | Ref | Ref |
| Tis | 3.38 (0.20–55.9) | 0.39 |
| T1 (± CIS) | 1.78 (0.20–16.0) | 0.61 |
| Prior diagnosis of Tis (vs. No) | 2.56 (0.50–13.1) | 0.26 |

Ref = reference category.
changes in histopathology specimens. We observed that all specimens demonstrated expansion of the tumor cytoplasm after docetaxel administration \( (n = 7, 100\%) \), as well as nuclear enlargement and squamous metaplasia in a subset of patients. These observations may be clinically relevant when examining postdocetaxel pathologic specimens to ensure accurate interpretation.

The present study has several limitations. Most importantly, it is retrospective and no control arm was utilized. Therefore, while the efficacy results are encouraging, it is not possible to attribute the treatment effect to intravesical docetaxel or to compare with competing salvage intravesical agents. In addition, the study cohort was small, which precluded the ability to perform multivariable analysis, and was limited to a single academic institution. Finally, we were unable to evaluate cancer-specific survival given short follow-up duration.

Despite these limitations, within the context of multiple investigational salvage intravesical agents after BCG failure, the
present study suggests that intravesical docetaxel holds promise
given its ubiquitous availability at cancer centers, ease of
administration, and encouraging response rates. Larger studies
and comparison to control arms are needed to validate these
results.

5. Conclusion
Salvage intravesical docetaxel was well tolerated, and associated
with an encouraging initial response rate of 69% and 24-month
RFS of 25%. Intravesical docetaxel should be further examined
in larger studies as a readily available, safe, and potentially
efficacious bladder-preserving treatment strategy for patients
with high-risk NMIBC after failed BCG therapy.

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Statement of ethics
This study was approved by the local institutional review board
(IRB) and conducted in accordance with the principles of the
Declaration of Helsinki.

Conflict of interest statement
The authors declare that they have no financial conflict of interest
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Author contributions
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