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Experience with Sequential Intravesical Gemcitabine and Docetaxel as Salvage Therapy for Non-Muscle Invasive Bladder Cancer

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Abstract Patients with high-grade muscle invasive bladder cancer (NMIBC) receive intravesical therapy with bacillus Calmette-Guérin (BCG) as the well-established standard-of-care. However, even with prompt induction of intravesical therapy, approximately 40 % of patients will recur within 2 years. For patients who fail BCG, options include radical cystectomy, repeat BCG therapy, or alternative intravesical salvage therapy. In this review, we will discuss the most recent published evidence on salvage intravesical therapy with an emphasis on a more in-depth report of our therapeutic strategy with sequential gemcitabine and docetaxel intravesical therapy for this treatment-refractory population. In addition, we will provide practical advice on our approach to this challenging patient population including the use of operative staging to aid early identification of treatment failures.

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Introduction

The diagnosis of non-muscle invasive bladder cancer (NMIBC) comprises approximately 75 % of all new bladder cancer diagnoses [1]. According to American Urological Association (AUA) and European Association of Urology (EUA) guidelines, first-line treatment in the management of NMIBC includes complete transurethral resection of bladder tumor followed by intravesical therapy with bacillus Calmette-Guérin (BCG) for intermediate or high-risk tumors [2, 3]. Current evidence supports intravesical BCG immunotherapy in NMIBC given its ability to reduce disease recurrence, disease progression, and improve disease-specific survival [4]. Despite the importance of BCG in this setting, population-based assessment of guideline-based care for NMIBC has identified that BCG is underutilized and surveillance is suboptimal [5].

Even in those patients who receive appropriate BCG therapy and surveillance, complete response rate to BCG therapy remains suboptimal and many patients will fail. Treatment failure with BCG occurs in 37–45 % of patients with NMIBC followed for 2 years, and a multi-center randomized trial showed no difference in recurrence in those BCG naïve patients who received interferon or megadose vitamin supplementation [6]. Thus, this patient population carries a significant burden of unknowns—which specific patient will progress to life-threatening muscle-invasive disease and what the appropriate treatment option should be. In this review, we will provide an overall framework for the discussion of options and present more in-depth

discussion of the available intravesical options with a focus on gemcitabine and docetaxel.

Definition of BCG Unresponsive NMIBC

Several patient- and disease-specific factors (gender, age, grade, multiplicity, associated carcinoma in situ) have been reported [7] and validated [8] as prognostic factors in NMIBC in addition to recurrence pattern. When attempting to stratify recurrence patterns, terminologies such as "BCG-refractory" and "BCG-resistant" were created but never gained widespread utilization. Recently, at the 2015 Genitourinary Cancers Symposium, an expert panel defined a new replacement term of "BCG unresponsive" for those patients who were treated with adequate BCG and are least likely to benefit from further intravesical BCG therapy. Criteria to meet this definition of BCG unresponsive include a timeframe of recurrence within 6 months, along with either T1 high-grade disease following initial induction course or recurrence with high-grade disease (CIS, Ta) after two courses of intravesical BCG-based therapy. This definition becomes important in the context of discussion of treatment options.

Options for Non-BCG Unresponsive Disease

Cystectomy The preferred treatment for BCG failure patients with high-risk NMIBC based on the AUA and EAU guidelines is proceeding to radical cystectomy [2, 3]. This approach is supported by the overall concept of prompt cystectomy from the initial bladder cancer diagnosis [9], and, more specifically, retrospective data that has shown BCG failure patients with high-risk NMIBC had improved survival with an earlier rather than a delayed cystectomy [10]. A prospective randomized trial comparing early cystectomy to salvage intravesical therapies for high-risk superficial bladder cancer has not been performed and is unlikely to ever occur due to the divergent treatment options which would create significant accrual challenge in terms of patient preference for bladder salvage. Despite the potential oncologic benefit of cystectomy, it is well established that radical cystectomy is associated with significant potential morbidity and measurable short- and long-term mortalities [11].

BCG or BCG/Interferon Some patients may be unfit for cystectomy because of medical comorbidity. There is also a subset of BCG failure patients with a strong preference for bladder preservation that refuse cystectomy despite being counseled about the risks of disease progression. In this context, it becomes important to have a working understanding of available salvage intravesical therapy options. Additionally, the need for safe and efficacious salvage chemotherapeutic alternatives to BCG is becoming increasingly important, as BCG shortages remain an issue [12]. As it is known that significant variability exists in molecular complexity and immune responsiveness of urothelial cancer [13], the exploration of alternative options further explores the theory that "one size does not fit all" for the treatment of NMIBC.

For those who do not meet the definition of BCG unresponsive disease (diagnosis >6 months after the last BCG or less than T1 disease within 6 months), repeat induction BCG remains an option. The success rate of repeated BCG is an approximately 35 % 2-year recurrence-free rate in the prior published literature in historic cohorts [14, 15]. While not directly compared to BCG alone, BCG/interferon (IFN) combination therapy has demonstrated a 45 % 2-year RFS in non-BCG naïve patients [16].

Options for BCG Unresponsive Disease

Cystectomy For patients with BCG unresponsive disease, patient counseling should include discussion that there is a substantial risk of disease recurrence and potentially disease progression. Counseling and shared decision-making should include consideration of radical cystectomy, and for those that do not pursue cystectomy, there should be close follow-up with the goal of early identification of treatment failures (see "Identifying Failures: Formal Restaging Protocol" section below).

Salvage Intravesical Therapies Valrubicin is a semisynthetic anthracycline and is currently the only FDA-approved intravesical therapy for CIS patients who have failed BCG. An open-label multi-center non-comparative trial of 90 CIS patients who had failed at least one BCG course showed that the recurrence-free survival in this cohort was 18–21 % at 6 months and 8 % at 30 months [17]. Because of the moderate success rate and large health-care cost with its use (over US$20,000 for full induction and maintenance treatment cycle in a cost implication analysis [18]), utilization of valrubicin remains less than ideal.

Gemcitabine is a non-vesicant chemotherapeutic drug, which is a deoxycytidine nucleoside analog that blocks replication and causes cell apoptosis. A phase II trial with monotherapy gemcitabine in 30 BCG-refractory patients reported that 21 % of patients were recurrence free at 1 year [19]. Other phase II trials have demonstrated variable efficacy at 1 year [20–22]. Skinner et al. reported on the results of a phase III trial in which 47 patients with two previous BCG failures received 2 g of intravesical gemcitabine weekly for 6 weeks of induction, followed by monthly maintenance for 1 year [23]. Recurrence-free survival was 28 % at 1 year and 21 % at 2 years. With its good tolerability, moderate efficacy, and low rate of progression, gemcitabine monotherapy can be

considered for salvage therapy in select patients, though its efficacy may be supplemented as part of combination therapy, as will be discussed later.

Docetaxel is an anti-mitotic chemotherapeutic agent which inhibits tubulin disassembly, thereby stopping cell division. One report of long-term evaluation of 53 patients treated with 75 mg intravesical docetaxel with monthly maintenance instillations showed a recurrence-free rate of 40 % at 1 year and 25 % at 3 years [24]. Docetaxel monotherapy is an option for BCG failure patients given its excellent tolerability and reasonable efficacy or may be used as a component of combination therapy as discussed below.

At our institution, combination of intravesical gemcitabine and mitomycin C chemotherapy has been offered as a salvage option for NMIBC in the treatment of high-risk patients. Patients received six weekly treatments with sequential intravesical gemcitabine (1 g) and mitomycin C (40 mg) chemotherapy. Our pilot experience in a pooled analysis with two other institutions reported recurrence-free results of 48 % at 1 year and 38 % at 2 years [25•]. Subsequently, the mitomycin shortage in 2009 halted further use and emphasized the development of additional intravesical salvage therapeutic options [26]. Following the mitomycin shortage, our institution transitioned to sequential gemcitabine and docetaxel as salvage therapy for patients with NMIBC.

Pilot Experience with Gemcitabine and Docetaxel Salvage Therapy

To determine whether dual sequential intravesical gemcitabine and docetaxel is effective in treating NMIBC, we treated 45 patients with recurrent NMIBC following BCG therapy and reported the results in 2015 [27••]. Patients were treated with six weekly instillations. Treatment was sequential instillations of 1 g gemcitabine for 1.5 h, followed by 37.5 mg docetaxel for 2 h. If patients were found to be disease free at restaging, they received monthly maintenance therapy for 2 years.

The optimal order of drug administration has not been completely defined, but at our institution, we determine drug sequence based upon fundamental principles of drug mechanism of action. Gemcitabine is a deoxycytidine nucleoside analog that inhibits DNA synthesis and promotes apoptosis. Since this drug requires active DNA synthesis for incorporation and effectiveness, it should be administered before docetaxel. Docetaxel exerts its chemotherapeutic effect by inhibiting microtubule disassembly and preventing cell division. These two mechanisms work in concert and should be given in the correct sequence.

In our patient review, treatment tolerance was reasonable, as only 5 of 45 patients were unable to tolerate a full induction course (all of whom had baseline lower urinary tract symptoms and a history of intolerance to prior intravesical therapy). Treatment success was defined as no recurrence of bladder cancer and no cystectomy for intolerable bladder symptoms. Median overall follow-up was 15 months, and median follow-up for treatment success was 6 months in all patients and 13 months for responders. Treatment success was 66 % at first surveillance, 54 % at 1 year, and 34 % at 2 years after induction completion.

It is important to also assess whether patients had significant disease progression during the delay to cystectomy. Ten patients underwent cystectomy at a median of 5.6 months from the beginning of induction, of which eight were performed for disease recurrence. Of importance, only one patient had disease progression to T4 disease based on prostatic stromal invasion and all surgical margins and lymph nodes were negative. Gemcitabine/docetaxel is a promising new therapy and, to our knowledge, the only non-device-assisted salvage therapy to date to demonstrate >50 % recurrence-free survival at 1 year of follow-up.

Practical Advice for Administering Gemcitabine and Docetaxel Salvage Therapy

Sequential intravesical gemcitabine and docetaxel is a salvage chemotherapy treatment option that can be easily implemented by practicing urologists in both community and academic settings. Gemcitabine and docetaxel are both FDA-approved anti-cancer drugs which should be readily available to be prepared by a pharmacist for administration.

Gemcitabine is a non-vesicant agent with limited systemic absorption that is well tolerated in the bladder but can still be irritating to the bladder and cause moderate nausea if absorbed across an inflamed or denuded bladder surface. It is recommended that all patients be treated with 1300 mg oral sodium bicarbonate the evening before and morning of every treatment instillation. Alkalinization of the urine helps to minimize the irritative side effects of the very acidic gemcitabine solution (gemcitabine solution has a pH of 2.5). Providers can substitute potassium citrate for patients on sodium restriction. Zofran may also be used to help treat gemcitabine-induced nausea. As with all intravesical therapies, providers should advise patients to avoid diuretics and restrict fluids, especially caffeine, in the morning of treatment to minimize drug dilution and maximize drug concentration.

The instructions provided to nursing are as follows: an indwelling catheter is placed and the bladder is drained completely. One gram of gemcitabine in 50 mL of sterile water is instilled into the bladder via the catheter, which is then plugged. The solution is retained for 90 min then drained. Forty milligrams (two 20 mg vials with a volume of 2 cc each) of docetaxel is diluted in 50 cc saline (final volume of 54 cc) is

then instilled into the bladder via Foley catheter. The solution is retained for 2 h and then drained.

Identifying Failures: Formal Restaging Protocol

An important aspect of treatment with intravesical salvage therapies is the risk of disease progression and the need to balance the oncologic safety with bladder preservation. Catalona et al. have shown that each additional course of BCG following the initial BCG failure carries a 7 % actuarial risk of disease progression [14]. Recently, Millan-Rodriguez and colleagues have reported disease progression in 8 % of patients at 1 year with high-risk NMIBC with a mortality rate of 1 % [28]. Therefore, in order to identify early recurrence and mitigate the risk of disease progression, our institution recommends formal restaging.

Our restaging protocol involves evaluation under anesthesia with cystoscopy, bladder barbotage cytology, bilateral upper tract barbotage cytologies, bilateral retrograde pyelograms, random bladder biopsies, and prostatic urethral biopsies in men. Our published experience with 126 restaging procedures was a heavily pretreated population with 51 % of patients having recurrence [29]. We identified that if evaluation was only cystoscopy and cytology, then 25 % of recurrences would have been missed on routine surveillance. We therefore concluded that this rate of additional identified disease justifies formal operative restaging in an effort to identify treatment failures as early as possible.

Limitations of Salvage Therapy

The limitation of nearly all salvage intravesical therapy options is the lack of a comparator arm and the lack of extended long-term follow-up. This makes direct comparison of different regimens very difficult. The introduction of novel intravesical therapy without the benefit of true comparison against the standard therapy has the potential to yield similar or worse outcomes in the absence of a comparator arm. However, the combination of a relatively favorable response rate in this heavily pretreated population creates an additional intravesical salvage therapy option with gemcitabine and docetaxel.

Conclusions

Currently, there is no randomized control trial comparing available salvage intravesical therapies and no evidence-based treatment algorithm to guide urologists in salvage intravesical therapy for the treatment of recurrent NMIBC following BCG failure. This complicates the ability of urologists to engage in shared decision-making with their patients when it comes to determining the most appropriate next step in management. The urologist must discuss the oncologic safety and risk of disease progression during salvage intravesical therapies with the patient when deciding further treatments. Patients with at least one prior BCG failure and recurrent NMIBC disease remain a very difficult population to treat, and a working knowledge of guidelines-based case is vital. Herein, we have presented several available salvage intravesical therapies in addition to our pilot experience with sequential intravesical gemcitabine and docetaxel therapy. For those patients who opt for salvage intravesical therapy, the definition of optimal management continues to evolve as our experience with alternative treatment options grows.

Compliance with Ethical standards

Conflict of Interest Kyla N. Velaer, Ryan L. Steinberg, Lewis J. Thomas, Michael A. O'Donnell, and Kenneth G. Nepple each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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