NYU Langone Health

Department of Urology
Case of the Month

Recurrent High-Risk Non-Muscle-Invasive Bladder Cancer

CASE PRESENTATION AND TREATMENT HISTORY

The patient was a white male in his seventies with a history of atrial fibrillation, morbid obesity (BMI 38), gout, hypertension, type 2 diabetes mellitus, lower urinary tract symptoms, and a long history (9+ years) of recurrent high-grade (HG) non-muscle-invasive bladder cancer (NMIBC) despite multiple courses of intravesical therapy, including immunotherapy and chemotherapy.

The patient was initially diagnosed with T1 HG NMIBC in 2011 and received induction Bacillus Calmette-Guérin (BCG) immunotherapy for 6 instillations between 9/2011 and 11/2011. He tolerated therapy well, and subsequent transurethral resection of bladder tumor (TURBT) in 1/2012 demonstrated no evidence of carcinoma. He subsequently received maintenance BCG of 3 weekly instillations between 5/2012 and 11/2012.

In May 2013, repeat TURBT revealed Ta HG recurrence. The patient then received re-induction BCG with 6 weekly instillations through July 2013. Follow-up TURBT in September 2013 revealed recurrent Ta HG and carcinoma in situ (CIS) disease.

In October 2013, the patient received 2 weekly instillations of mitomycin-C followed by 4 BCG instillations from 10/2013 through 11/2013 followed by 5 additional instillations of mitomycin-C from 3/2014 through 4/2014. He then received BCG + mitomycin-C for 4 instillations from 4/22/2014 through 5/2014 followed by BCG for 5 instillations from 5/2014 through 6/2014.

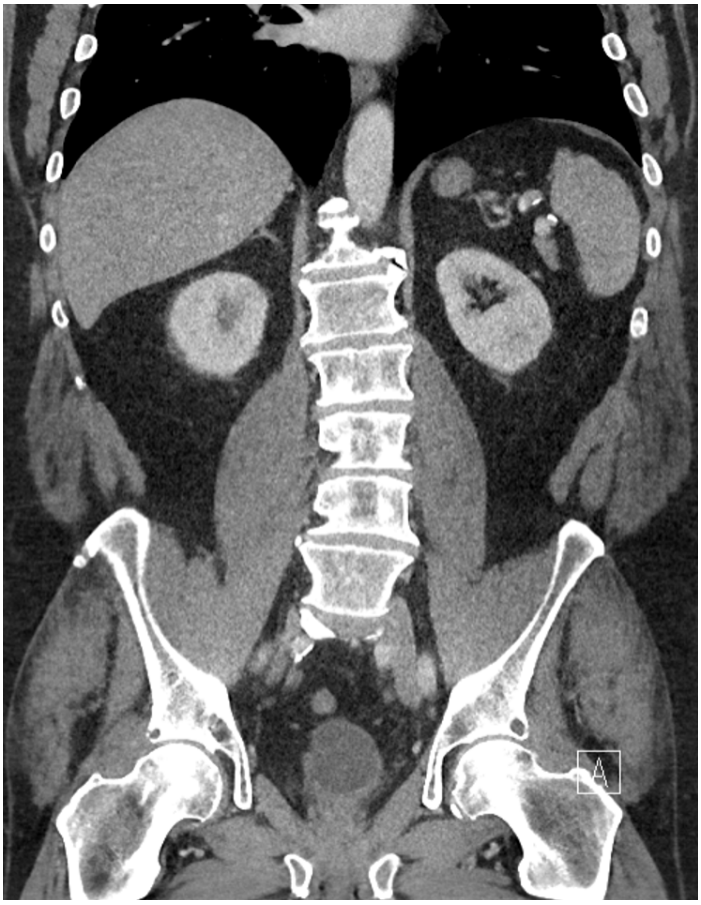
Despite this regimen, TURBT on 6/2016 demonstrated CIS.

Beginning in November 2016, the patient receiving re-induction BCG plus interferon (IFN)-α for 6 instillations from 11/2016 through 12/2016. TURBT in 3/2017 demonstrated no evidence of disease. The patient received 3 weekly instillations of maintenance BCG plus IFN-α in June 2017 and January 2018. In October 2018, the patient had positive urinary cytology, and in November 2018, TURBT revealed CIS. The patient then received valrubicin for 6 weekly instillations in January and February 2019. In March 2019, CT revealed bladder wall thickening with no evidence of extravesical spread.

EVALUATION AT NYU LANGONE HEALTH

The patient presented to NYU Langone Health for evaluation and management. Repeat TURBT in 5/2019 demonstrated CIS. The patient's physical examination was pertinent for morbid obesity (BMI 38) and atrial fibrillation. Laboratory values were pertinent for serum creatinine 1.3 mg/dL and glucose 182 mg/dL.

Figure 1. Patient's CT urogram prior to enrollment in clinical trial at NYU Langone.



TREATMENT AND MANAGEMENT

The patient was seen by both urologic oncology and medical oncology. He was diagnosed with BCG-unresponsive CIS of the bladder. He was counseled on standard of care based on American Urological Association (AUA), European Association of Urology (EAU), and National Comprehensive Cancer Network (NCCN) guidelines. Radical cystectomy was discussed as the standard of care as well as other therapies, such as investigational agents/clinical trials. The patient was referred to the Bladder Cancer Advocacy Network website. In consultation with the NYU Langone bladder cancer team, the patient enrolled in CheckMate 9UT (ClinicalTrials.gov identifier: NCT03519256), a randomized study with 4 treatment arms: nivolumab; nivolumab + BCG; nivolumab + linrodostat (an oral indoleamine 2,3-dioxygenase 1 inhibitor); and nivolumab + linrodostat + BCG.

The patient was randomized to the 3-drug arm (nivolumab + linrodostat + BCG) and began treatment in 8/2019. At the cycle 4 visit in 11/2019, the patient reported development of a diffuse blistering ulceration of the upper and lower lips and oral mucosa, without significant pain but with some intolerance of hard foods. He developed similar lesions on the left side of the glans and several well-circumscribed, discrete, raised erythematous nodules scattered on the arms and torso and lower extremities. He had no systemic complaints, including no fevers/chills. Treatment was put on hold and the patient was referred to dermatology and underwent biopsy, which

demonstrated lichenoid dermatitis. He was prescribed topical treatments, with symptomatic improvement. He resumed cycle 4 in 11/2019. He underwent first response assessment with cystoscopy/TURBT in 1/2020 and central review was consistent with a complete response (CR).

Prior to cycle 7, the patient developed hematuria in the context of coumadin toxicity and was hospitalized briefly, with resolution after coumadin reversal.

At the 6-month point, the patient underwent surveillance cystoscopy and biopsy for disease assessment. Cystoscopy was consistent with small capacity bladder with incontinence, multifocal necrotic tumor as well as papillary/sessile tumor in the right and left lateral walls, posterior walls, and trigone, with >5.0 cm bladder involved. Multiple biopsies of abnormal areas were performed, as well as "bladder mapping" as per study protocol. Pathology revealed extensive acute and chronic inflammation and CIS of the right lateral wall, anterior bladder wall, and prostatic urethra.

The patient was counseled to undergo radical cystectomy and urinary diversion. It was explained that urinary diversion through orthotopic neobladder continent urinary reconstruction was relatively contraindicated secondary to the prostatic urethral involvement with urothelial cell carcinoma.

At the time of surgery, the patient was noted to have bilateral hydroureteronephrosis, dense pelvic lymph nodes with some enlarged lymph nodes, and dense scar tissue and fibrosis, with a small thick-walled bladder. He was also noted to have a very short, thick wall intestinal mesentery. The surgery was uncomplicated and the patient was discharged home on postoperative day 6. His final pathology revealed bladder ulceration and inflammation and pTCis involving the bladder, prostatic urethra, and prostatic ducts, N0, margins negative. The patient is doing well, shows no evidence of disease, and is functioning well with his ileal conduit.

COMMENT

This complicated case addresses the challenge and difficulty in the management of high-risk (HR) NMIBC, particularly in patients for whom BCG has failed. These patients are at high risk of progression to muscle invasion and death from bladder cancer. Currently, there are limited intravesical and systemic options approved for second-line treatment, with radical cystectomy the gold standard. However, there are a number of ongoing clinical trials examining different therapeutic approaches in an effort to provide safe and effective bladder-sparing options.

Bladder cancer is the sixth most common cancer in the United States, accounting for 4.6% of all new cancer diagnoses. There were approximately 81,400 new cases of bladder cancer and 17,670 bladder cancer deaths in the United States in 2019. Approximately 75% to 85% of these cases present initially with NMIBC (1, 2). NMIBC consists of tumors confined to the mucosa (TCis), Ta, and submucosa (T1). Patients with NMIBC may have disease recurrences and progression to muscle-invasive bladder cancer (MIBC) despite surgical treatment with TURBT. Patients with stage T1 (submucosal invasion) HG, TCis, and Ta HG (>3.0 cm, multifocal, or any recurrent Ta HG) are at high risk for recurrence and progression (3, 4). Intravesical BCG immunotherapy is the most effective treatment and adjuvant therapy for reducing disease recurrence and progression of HR NMIBC (5-11). Approximately 70% of patients with NMIBC achieve CR with BCG therapy; however, many patients with HR disease do not maintain remission (8-13). Up to 60% of patients can have disease recurrence within 1 year, with this figure increasing to 80% within 15 years (9, 12). In addition, within 5 years, 20% to 40% of patients for whom BCG fails will progress to MIBC (10-13), with 6% to 15% of patients progressing with metastasis to the pelvic lymph nodes and/or beyond (14).

Intravesical BCG

In 1990, the FDA approved intravesical BCG for TCis on the basis of several clinical trials. BCG is thought to exert its antitumor effects through direct and indirect mechanisms (9,15). In addition to triggering apoptosis or necrosis upon internalization by bladder cancer cells (direct effect), BCG increases antigen expression and cytokine release from tumor cells, leading to immune cell (e.g., granulocytes, CD4+ and CD8+ lymphocytes, natural killer (NK) cells, γδ T cells, and macrophages) recruitment and immune-mediated cytotoxicity (indirect effect). Lamm et al. reviewed 34 series and noted an average CR rate of 72% in 1,354 patients treated with BCG for TCis of the bladder (15, 16). A South West Oncology Group (SWOG) study was performed to compare the standard induction 6-week BCG regimen to a 6 plus 3 regimen, consisting of a 6-week induction followed by an additional 3 weekly treatments at 3 months. The overall CR rate increased from 56% to 82% with the additional 3 weekly treatments (15).

Current AUA and EAU recommendations are for induction BCG (6 weeks) followed by 1 to 3 years of maintenance BCG, depending on risk. These recommendations are based on meta-analyses of the SWOG and European Organisation for Research and Treatment of Cancer (EORTC) studies that used a maintenance schedule of 3 weekly instillations at 3, 6, 12, 18, 24, and 36 months (17). However, the vast majority of these patients did not complete the 3-year schedule because of treatment toxicity. And despite multiple instillations of BCG, about 20% to 40% of patients with HR NMIBC will have disease progression. Moreover, there has been a worldwide BCG shortage since 2019. Because of the shortage, induction BCG treatment is prioritized, with maintenance BCG being given with reduced dosage and sparingly, depending on BCG supply. In general, few patients are receiving a year of maintenance BCG.

BCG-Unresponsive Disease

Several studies have demonstrated that patients who progress to MIBC from NMIBC have worse outcomes than patients who initially present with MIBC, suggesting that delaying cystectomy in patients with NMIBC may allow the disease to progress to an incurable state (18-24). These patients have a high likelihood of locally advanced disease, lymph node metastases, and diminished survival despite radical cystectomy. This all too frequent clinical scenario has led to a new BCG classification: BCG-unresponsive disease, which refers to patients who are at the highest risk of progression after receiving adequate BCG (which means an induction course and at least one maintenance course) and who had: [1] no response to BCG treatment and new or recurrent T1 HG disease at 3 months or [2] TCis persistence/recurrence at 6 months or within 12 months of the last BCG instillation or [3] Ta/T1 HG recurrence or relapse within 6 months of the last BCG treatment despite an initial CR (25). In addition, there is an increased incidence of upper tract recurrences in patients with multifocal NMIBC with multiple recurrences and multiple courses of intravesical therapy (26-28).

Patients with BCG-unresponsive disease face a difficult dilemma. Cystectomy is highly curative but is associated with short- and long-term morbidity. Bladder preservation may offer superior quality of life (QoL) outcomes; however, treatments for patients with BCG-unresponsive disease are not curative in most cases (29). The bladder cancer in the patient discussed in this case was clearly BCG unresponsive and he was at high risk of progression and metastases.

The current AUA/Society of Urologic Oncology (SUO) and NCCN guidelines for BCG-unresponsive NMIBC state that patients should be offered radical cystectomy, with "alternative therapy" as an option. Patients with recurrent NMIBC have improved survival in early compared to delayed cystectomy (when the pathologic stage is T2 or greater), and cure rates for patients with HR NMIBC are over 90% with upfront cystectomy (20, 21). A retrospective study in patients with

recurrent HR NMIBC found that early cystectomy was associated with a 2-year survival of 92% compared to only 52% in those with delayed cystectomy (20). Similarly, a retrospective study including patients with recurrent HR NMIBC despite BCG found a lower risk of death among patients who underwent cystectomy as opposed to those who had further BCG (21). Despite these concerns, many patients and providers are wary of the risks and QoL implications of radical cystectomy and prefer treatments that offer bladder preservation (30, 31). Furthermore, many patients with bladder cancer are elderly and have comorbid conditions that put them at higher risk for complications related to radical cystectomy (32, 33).

The patient presented in this case received multiple bladder-sparing approaches over a number of years. His multiple medical comorbidities, including diabetes, chronic renal insufficiency, hypertension, atrial fibrillation, and morbid obesity, influenced management of his bladder cancer. As with many patients and providers, alternatives to radical cystectomy are commonly employed despite the significant risk of disease progression and death from metastatic bladder cancer. In addition to intravesical BCG, this patient received combinations of immunotherapy and intravesical chemotherapy as well as intravesical chemotherapy alone. What follows is a review of the literature pertaining to the treatments the patient in this case study received as well as a review of current ongoing or completed studies.

Literature Review of Treatments

Similar to the immune response to intravesical BCG, it was thought that IFN-α would induce synergy with BCG. IFN-α and IFN-β inhibit angiogenesis (34-35), and IFN-α directly induces apoptosis in human bladder cancer cells by inducing autocrine tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) production (36-40). It is now well established that IFN-α controls dendritic cell maturation and antigen presentation and promotes tumor recognition by T cells and NK cells and that these effects likely play more important roles in tumor growth inhibition than do IFN-α's direct effects on tumor cells (36-40). However, like IFN-γ, IFN-α induces programmed death ligand 1 (PD-L1) expression (40), which may limit tumor immune recognition and which almost certainly inhibits T-cell activation. (This mechanism of action will also be relevant in the discussion below of the oncolytic vaccine nadofaragene firadenovec, which is being studied for bladder cancer.)

Clinically, the intravesical combination of BCG plus IFN-α led to equivocal results. IFN-α monotherapy was evaluated in patients with TCis and other HR NMIBC despite treatment with BCG; the success rate was approximately 15%. In patients with T1 HG, IFN-α was found to be no better than placebo at 43 months of follow-up (41). Despite, the low success rate, IFN-α concomitant with BCG therapy in patients for whom BCG has failed has seen some success. Several single institutional nonrandomized studies have reported disease-free rates between 50% and 60% in patients with HR NMIBC for whom BCG therapy failed after at least one course of induction BCG, with follow-up ranging from 12 to 30 months (42-44). In these studies, patients with TCis had a 45% 3-year disease-free survival rate if they were treated after a single induction course of BCG (42). However, none of the studies demonstrated a benefit in survival or in clinical progression rates in patients receiving BCG and IFN-α over those receiving BCG alone (45). Therefore, the combination of BCG plus IFN-α is no longer recommended for patients with BCG-refractory or unresponsive disease.

Another innovative immunotherapeutic approach for HR NMIBC being tested is N-803 (Anktiva). N-803 is a mutant IL-15-based immune-stimulatory fusion protein complex (IL-15RαFc) that promotes proliferation and activation of NK cells and CD8+ T cells but not regulatory T cells (Tregs). N-803 is believed to be potentially synergistic with intravesical BCG, which acts via the induction of various cytokines, tumor necrosis factor, TRAIL, NK cells, and γδ T cells. BCG-naive HR NMIBC patients treated with intravesical N-803 plus BCG had durable CRs for up to 24 months.

QUILT-3.032, an open-label, multicenter phase II/III study with BCG-unresponsive HG NMIBC patients, is ongoing (ClinicalTrials.gov identifier: NCT03022825). In the interim analysis, patients received intravesical N-803 plus BCG, induction and maintenance. The CR rate for patients with TCis with/without concomitant resected papillary disease (9 treated patients not reported on) was 72% (N=51/71); for patients achieving a CR, the probability of maintaining the CR for 12 months was 59%, with a median duration of CR of 19 months. Of note, patients with TCis at the initial 3-month evaluation were retreated. Low-grade treatment-related adverse events (AEs) were typically lower urinary tract symptoms, with no immune-related serious AEs noted. To date, 10 of 80 (12.5%) patients proceeded to radical cystectomy. With the observed strong efficacy and a serious AE rate of 1%, N-803 represents a novel treatment option for patients with BCG-unresponsive disease (Clinical trial information: NCT03022825) (45). Longer follow-up is forthcoming. It will be interesting to assess the efficacy of N-803 alone without BCG especially in the era of BCG shortage.

Several studies have also been conducted to investigate combination therapy with BCG and mitomycin-c or IFN to improve efficacy and reduce disease recurrence and progression, although results have been mixed and have largely failed to demonstrate a clear benefit over BCG monotherapy (46-48). The first FDA-approved intravesical chemotherapy agent for patients with BCG-refractory/intolerant TCis was valrubicin, a semisynthetic analog of doxorubicin that exerts its chemotherapeutic effect on nucleic acid metabolism. The pivotal trial evaluating 90 patients found a CR (disease-free at 6 months) rate of 21% (19/90), with 37% (7/19) of the patients remaining disease-free at median follow-up of 30 months (49). A follow-up open-label study treated patients with 6 or 9 weekly intravesical valrubicin (800 mg) instillations. In the 2 trials combined, there were 170 patients (80 and 90 patients, respectively). In both studies, the CR rate was 18%, with 86% of patients experiencing local bladder AEs, mostly mild to moderate (49-50). Despite these results, valrubicin is used relatively infrequently today because of concerns about lack of durability of response to therapy. Of note, valrubicin has not been given with maintenance therapy in any study to date.

If intravesical treatment options fail, radical cystectomy with urinary diversion/reconstruction is the standard of care with the greatest likelihood of cure of the disease (51, 52). Radical cystectomy may prevent local progression but also carries a high risk for postoperative complications and reduced QoL. In addition, not all patients are eligible for cystectomy because of advanced age or severe comorbidities. Because of the life-altering consequences and potentially reduced QoL associated with radical cystectomy, many patients refuse to undergo the surgery. Therefore, there remains an urgent need for novel therapies to provide a nonsurgical second-line treatment option.

Pembrolizumab is a programmed death receptor-1 (PD-1)-blocking antibody that binds PD-1 with high affinity and selectivity, preventing PD-1 from interacting with its ligands PD-L1 and PD-L2 (53). Pembrolizumab provides effective and durable antitumor activity against multiple cancers. The effectiveness of pembrolizumab monotherapy in treating locally advanced and metastatic urothelial carcinoma has been demonstrated in the phase III KEYNOTE-045 (ClinicalTrials.gov identifier NCT02256436) (54) and phase II KEYNOTE-052 (ClinicalTrials.gov identifier NCT02335424) studies. PD-1 is an immune checkpoint receptor expressed on activated T cells that modulates immune response (55). Tumor cells may block the binding of PD-1, PD-L1, and PD-L2 to avoid immune recognition, for example, by expressing PD-L1, which binds PD-1 on activated T cells, allowing tumor cells to escape immune-mediated cytotoxicity (54-56). Altered PD-1 pathway activation has been implicated in disease recurrence and progression and in BCG resistance in patients with NMIBC (57-59). Moreover, tumor PD-L1 expression is significantly increased after BCG treatment and is associated with reduced 5-year recurrence-free survival and overall survival (57-60). Therefore, targeting the PD-1/PD-L1 pathway has emerged as a therapeutic option for patients with NMIBC (61).

The safety and efficacy of pembrolizumab was investigated in KEYNOTE-057 (ClinicalTrials.gov Identifier: NCT02625961), a multicenter, open-label, single-arm trial that enrolled 148 patients with HR NMIBC, 102 of whom had BCG-unresponsive CIS with or without papillary tumors (62). Pembrolizumab was administered as a 200 mg IV infusion once every 3 weeks. The median patient age was 73 years and 64% of the patients had TCis alone without concomitant papillary disease. The 3-month CR rate was 40% (95% CI, 30.6%-50.4%). Furthermore, among 41 patients who achieved a CR at 3 months, 59% maintained the CR for a median duration of 17 months. Among the 41 patients with a CR at 3 months, 15 (37%) patients subsequently experienced recurrent NMIBC, with none of these patients progressing to muscle-invasive or metastatic disease. AEs were seen in 97% of patients, with 29% experiencing a grade 3-5 AE and with discontinuation due to an AE in 10% and discontinuation due to a serious AE in 4%. Treatment-related AEs occurred in 66 (65%) patients and were most frequently pruritus (10.7%), fatigue (9.7%), diarrhea (8.7%), hypothyroidism (5.8%), and maculopapular rash (5.8%). There were no treatment-related deaths. The immune-mediated AE rate was 18.4% (63). On the basis of this study, the FDA approved pembrolizumab in January 2020 for the treatment of patients with BCG-unresponsive, HR NMIBC with CIS with or without papillary tumors who are ineligible for or who have elected not to undergo cystectomy.

Building on these results is CheckMate-9UT, an ongoing phase II combination immunotherapy trial, sponsored by Bristol Myers Squibb, for patients with BCG-unresponsive NMIBC, taking place at NYU Langone's Perlmutter Cancer Center and Department of Urology. CheckMate-9UT has 4 treatment arms: nivolumab; nivolumab + BCG; nivolumab + linrodostat; and nivolumab + linrodostat + BCG. Nivolumab is a PD-1 inhibitor FDA approved for metastatic bladder cancer and linrodostat is an oral medication that inhibits the enzyme indoleamine 2, 3-dioxygenase 1 (IDO1). IDO1 is responsible for the oxidation of tryptophan into the metabolite kynurenine, which leads to the activation of Tregs and myeloid-derived suppressor cells and to the suppression of NK cells and effector T cells (64) in the tumor microenvironment. Linrodostat specifically binds to IDO1 and decreases kynurenine in tumor cells, thus activating both the innate and the adaptive immune response while also reducing the amount of tumor-associated Tregs. The primary outcome is the percentage of CIS patients who have a CR (65).

Another novel approach to treating BCG-unresponsive HR NMIBC is with intravesical oncolytic virus vaccines. Intravesical nadofaragene firadenovec (rAd-IFNα/Syn3; Adstiladrin) is a nonreplicating adenovirus with a vector that contains the human IFN-α-2b gene. It also contains Syn3, which augments transduction of the virus into the urothelium and cancer cells. The adenovirus inserts the gene into the cells, which start manufacturing IFN-α locally in the bladder. Phase I and phase II trials have demonstrated detectable levels of IFN-α in the urine (66). According to clinical data reported in 2020 from the open-label phase II/III trial, intravesical Adstiladrin in BCG-unresponsive HR NMIBC patients demonstrated a 3-month CR rate of 60% in all enrolled and treated patients (53% CR in patients with TCis with/without Ta or T1 tumors, and 73% freedom from HG recurrence in patients with HR Ta or T1 tumors only). At 12 months, 30.5% of all patients (24% of patients with TCis with/without Ta or T1 tumors and 44% of those with HG Ta or T1 tumors only) were free from HG recurrence (67, 68). Of note, the Adstiladrin regimen is one intravesical instillation every 3 months.

In addition, another oncolytic virus vaccine (CG0070) is being evaluated in an open-label, single-arm, phase II multicenter safety and efficacy study in patients with BCG-unresponsive NMIBC. CG0070 is an oncolytic adenovirus that allows for selective viral replication in tumor cells and encodes for production of granulocyte macrophage-colony stimulating factor (GM-CSF) by targeting the retinoblastoma tumor suppressor pathway (69-70). This drug both lyses tumor cells and directly leads to production of GM-CSF, a potent immune-stimulatory cytokine. The intravesical instillation of CG0700 has been shown to be safe, with a CR rate of 49% at 10.4 months (70). The interim results

of the phase II study were reported at the AUA meeting in 2017. Of the 45 HR BCG-resistant/refractory patients treated (38 TCis with/without Ta or T1 tumors, 7 HR Ta or T1 tumors only), the overall CR rate at 6 months was 47%. The CR was best for TCis (50%). Patients with T1 tumors had poorer response rates (0% for pure T1, 33% for T1 + Ta). We will be opening shortly a trial titled Phase 2, Single Arm Study of CG0070 Combined with Pembrolizumab in Patients with Non Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG). This trial will address the potential resistance mechanism of PDL-1 induction noted with immune cell death (71).

Successful management of HG NMIBC is a balancing act between overtreatment with radical cystectomy resulting in morbidity and reduced QoL and under treatment resulting in bladder cancer progression and death. As interest grows in bladder-sparing approaches and novel salvage intravesical trials to delay or avoid radical cystectomy, the importance of careful patient selection and appropriate decision-making for timely radical cystectomy cannot be overstated. However, data are lacking on outcomes for patients who do not respond to additional salvage intravesical regimens and who ultimately undergo radical cystectomy. Packiam et al. recently assessed the largest retrospective comparative series of patients with HG NMIBC who received salvage intravesical therapy. There were several key findings, including that patients who received a salvage intravesical therapy did not have inferior cancer-specific or overall survival, which persisted after controlling for covariates (72). Thus, there is the potential to offer patients with BCG-unresponsive disease nonsurgical options as well as radical cystectomy. In most trials to date, patients with HG NMIBC recurrence or persistence at 3 months are withdrawn from the trial. It may be reasonable to consider continuing treatment for one more cycle.

We have a number of ongoing clinical trials for HR NMIBC at NYU Langone's Perlmutter Cancer Center. These trials are using BCG plus pembrolizumab for patients whose NMIBC has recurred despite induction BCG and BCG plus sasanlimab, a novel PD-1 inhibitor delivered subcutaneously, for HR BCG-naive NMIBC patients. In addition to these trials, we have a number of trials in the pipeline, including the soon-to-open CG0070 plus pembrolizumab trial mentioned above and: A Phase 1/2 Study of EG-70 as an Intravesical Administration to Patients with BCG-Unresponsive NMIBC, sponsored by EnGene Inc. and using a DNA delivery system for RIG-I and IL-12 cytokines that stimulate the innate and adaptive immune system; A Randomized Phase 2 Study of Erdafitinib Versus Investigator Choice of Intravesical Chemotherapy in Subjects Who Received Bacillus Calmette-Guérin (BCG) and Recurred With High Risk Non-Muscle-Invasive Bladder Cancer (NMIBC) and FGFR Mutations or Fusions; and A Phase 2b Clinical Study Evaluating Efficacy and Safety of TAR-200 in Combination with Cetrelimab (PD-1 inhibitor), TAR-200 Alone (a novel delivery system that resides in the bladder and slowly releases gemcitabine into the bladder), or Cetrelimab Alone in Participants with High-Risk Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Intravesical Bacillus Calmette-Guerin (BCG).

FINAL THOUGHTS

The patient in this case study had a prolonged history of HR NMIBC that persisted and recurred despite multiple intravesical and subsequently systemic immunotherapy regimens. Throughout his prolonged course, he was at high risk for disease recurrence in his upper urinary tract and urethra and for metastatic disease. This patient's case demonstrates the clinical conundrum with recurrent/persistent HR NMIBC despite intravesical BCG therapy. Is it safe to preserve the bladder while deferring or avoiding radical cystectomy and urinary reconstruction?

REFERENCES

1. National Cancer Institute. SEER cancer stat facts: bladder cancer. https://seer.cancer.gov/statfacts/html/urinb.html
2. Boustead GB, Fowler S, Swamy R, Kocklebergh R, Hounsome L. Stage, grade and pathological characteristics of bladder cancer in the UK: British Association of Urological Surgeons (BAUS) urological tumour registry. *BJU Int*. 2014;113(6):924-930.
3. Babjuk M, Bohle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol*. 2017;71(3):447-461.
4. Bladder cancer: diagnosis and management of bladder cancer. © NICE (2015) Bladder cancer: diagnosis and management of bladder cancer. *BJU Int.* 2017;120(6):755-765.
5. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. *J Urol*. 2016;196(4):1021-1029.
6. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Bladder Cancer (Version 4.2019). https://www.nccn.org/professionals/physiciangls/pdf/bladder.pdf
7. Millan-Rodriguez F, Chéchile-Toniolo G, Salvador-Bayarri J, Palou J, Algaba F, Vicente-Rodriguez J. Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. *J Urol*. 2000;164(3 Pt 1):680-684.
8. BCG Live (for intravesical use) TICE® BCG. Package insert. Organon USA Inc. February 2009. https://www.fda.gov/media/76396/download
9. Saluja M, Gilling P. Intravesical bacillus Calmette-Guérin instillation in non-muscle-invasive bladder cancer: a review. *Int J Urol*. 2018;25(1):18-24.
10. van ben Bosch S, Alfred Witjes J. Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. *Eur Urol*. 2011;60(3):493-500.
11. Sarosdy MF, Lamm DL. Long-term results of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. *J Urol*. 1989;142(3):719-722.
12. Brake M, Loertzer H, Horsch R, Keller H. Long-term results of intravesical bacillus Calmette-Guérin therapy for stage T1 superficial bladder cancer. *Urology*. 2000;55(5):673-678.
13. Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *J Urol*. 2017;197(2S):S142-S145.
14. Wiesner C, Pfitzenmaier J, Faldum A, Gillitzer R, Melchior SW, Thüroff JW. Lymph node metastases in non-muscle invasive bladder cancer are correlated with the number of transurethral resections and tumor upstaging at radical cystectomy. *BJU Int*. 2005;95(3):301-305.
15. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol*. 2000;163(4):1124-1129.
16. Lamm DL (1995) BCG immunotherapy for transitional-cell carcinoma in situ of the bladder. *Oncology (Williston Park)*. 1995;9(10):947-952, 955, discussion 955-965.
17. Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. *Eur Urol*. 2013;63(3):462-472.
18. Shen PL, Lin ME, Hong YK, He XJ. Bladder preservation approach versus radical cystectomy for high-grade non-muscle-invasive bladder cancer: a meta-analysis of cohort studies. *World J Surg Oncol*. 2018;16(1):197.
19. Pang KH, Noon AP. Selection of patients and benefit of immediate radical cystectomy for non-muscle invasive bladder cancer. *Transl Androl Urol*. 2019;8(1):101-107.
20. Jäger W, Thomas C, Haag S, et al. Early vs delayed radical cystectomy for 'high-risk' carcinoma not invading bladder muscle: delay of cystectomy reduces cancer-specific survival. *BJU Int*. 2011;108(8 Pt 2):E284-E288.
21. Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J Urol*. 2001;166(4):1296-1299.
22. Raj GV, Herr H, Serio AM, et al. Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. *J Urol*. 2007;177(4):1283-1286, discussion 1286.
23. Schrier BP, Hollander MP, van Rhijn BW, Kiemeney LA, Witjes JA. Prognosis of muscle-invasive bladder cancer: difference between primary and progressive tumours and implications for therapy. *Eur Urol*. 2004;45(3):292-296.
24. Breau R. H, Karnes RJ, Farmer SA, et al. Progression to detrusor muscle invasion during urothelial carcinoma surveillance is associated with poor prognosis. *BJU Int*. 2014;113(6):900-906.
25. Lerner SP, Dinney C, Kamat A, et al. Clarification of bladder cancer disease states following treatment of patients with intravesical BCG. *Bladder Cancer*. 2015;1(1):29-30.
26. Sanderson KM, Cai J, Miranda G, Skinner DG, Stein JP. Upper tract urothelial recurrence following radical cystectomy for transitional cell carcinoma of the bladder: an analysis of 1,069 patients with 10-year followup. *J Urol*. 2007;177(6):2088-2094.
27. Tran W, Serio AM, Raj GV, et al. Longitudinal risk of upper tract recurrence following 334 radical cystectomy for urothelial cancer and the potential implications for long-term surveillance. *J Urol*. 2008;179(1):96-100.
28. Umbreit EC, Crispen PL, Shimko MS, Farmer SA, Blute ML, Frank I. Multifactorial, site-specific recurrence model after radical cystectomy for urothelial carcinoma. *Cancer*. 2010;116(14):3399-3407.
29. Babjuk M, Böhle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol*. 2017;71(3):447-461.
30. Woldu SL, Bagrodia A, Lotan Y. Guideline of guidelines: non-muscle-invasive bladder cancer. *BJU Int*. 2017;119(3):371-380.
31. Shabsigh A, Korets R, Vora KC, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *Eur Urol*. 2009;55(1):164-174.
32. Boström PJ, Kössi J, Laato M, Nurmi M. Risk factors for mortality and morbidity related to radical cystectomy. *BJU Int*. 2009;103(2):191-196.
33. Liberman D, Lughezzani G, Sun M, et al. Perioperative mortality is significantly greater in septuagenarian and octogenarian patients treated with radical cystectomy for urothelial carcinoma of the bladder. *Urology*. 2011;77(3):660-666.
34. Correa AF, Theisen K, Ferroni M, et al. The role of interferon in the management of BCG refractory nonmuscle invasive bladder cancer. *Adv Urol*. 2015;2015:656918.
35. Dinney CP, Bielenberg DR, Perrotte P, et al. Inhibition of basic fibroblast growth factor expression, angiogenesis, and growth of human bladder carcinoma in mice by systemic interferon-alpha administration. *Cancer Res*. 1998;58(4):808-814.
36. Izawa JI, Sweeney P, Perrotte P, et al. Inhibition of tumorigenicity and metastasis of human bladder cancer growing in athymic mice by interferon-beta gene therapy results partially from various antiangiogenic effects including endothelial cell apoptosis. *Clin Cancer Res*. 2002;8(4):1258-1270.

37. Papageorgiou A, Lashinger L, Millikan R, et al. Role of tumor necrosis factor-related apoptosis-inducing ligand in interferon induced apoptosis in human bladder cancer cells. *Cancer Res*. 2004;64(24):8973-8979.
38. Sadler AJ, Williams BR. Interferon-inducible antiviral effectors. *Nat Rev Immunol*. 2008;8(7):559-568.
39. Spaapen RM, Leung MY, Fuertes MB, et al. Therapeutic activity of high-dose intratumoral IFN-β requires direct effect on the tumor vasculature. *J Immunol*. 2014;193(8):4254-4260.
40. McCracken MN, Cha AC, Weissman IL. Molecular pathways: activating T cells after cancer cell phagocytosis from blockade of CD47 "Don't Eat Me" signals. *Clin Cancer Res*. 2015;21(16):3597-3601.
41. Portillo J, Martin B, Hernandez R, et al. Results at 43 months' follow-up of a double-blind, randomized, prospective clinical trial using intravesical interferon alpha-2b in the prophylaxis of stage pT1 transitional cell carcinoma of the bladder. *Urology*. 1997;49(2):187-190.
42. Lam JS, Benson MC, O'Donnell MA, et al. Bacillus Calmete [sic]-Guérin plus interferon-alpha2B intravesical therapy maintains an extended treatment plan for superficial bladder cancer with minimal toxicity. *Urol Oncol*. 2003;21(5):354-360.
43. O'Donnell MA, Krohn J, DeWolf WC. Salvage intravesical therapy with interferon-alpha 2b plus low dose bacillus Calmette-Guerin is effective in patients with superficial bladder cancer in whom bacillus Calmette-Guerin alone previously failed. *J Urol*. 2001;166(4):1300-1304, discussion 1304-1305.
44. Punnen SP, Chin JL, Jewett MAS. Management of bacillus Calmette-Guerin (BCG) refractory superficial bladder cancer: results with intravesical BCG and interferon combination therapy. *Can J Urol*. 2003;10(2):1790-1795.
45. Chamie K, Chang S, Gonzalgo ML, et al. Phase II/III clinical results of IL-15RαFc superagonist N-803 with BCG in BCG-unresponsive nonmuscle invasive bladder cancer (NMIBC) carcinoma in situ (CIS) patients. Abstract presented at Genitourinary Cancers Symposium. American Society of Clinical Oncology Virtual meeting. February 11-13, 2021.
46. Shepherd AR, Shepherd E, Brook NR. Intravesical bacillus Calmette-Guerin with interferon-alpha versus intravesical bacillus Calmette-Guerin for treating non-muscle-invasive bladder cancer. *Cochrane Database Syst Rev*. 2017;3(3):CD012112.
47. Deng T, Liu B, Duan X, Zhang T, Cai C, Zeng G. Systematic review and cumulative analysis of the combination of mitomycin C plus bacillus Calmette-Guérin (BCG) for non-muscle-invasive bladder cancer. *Sci Rep*. 2017;7(1):3172.
48. Hemdan T, Johansson R, Jahnson S, et al. 5-Year outcome of a randomized prospective study comparing bacillus Calmette-Guérin with epirubicin and interferon-α2b in patients with T1 bladder cancer. *J Urol*. 2014;191(5):1244-1249.
49. Steinberg G, Bahnson R, Brosman S, Middleton R, Wajsman Z, Wehle M. Efficacy and safety of valrubicin for the treatment of bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. *J Urol*. 2000;163(3):761-777.
50. Dinney CP, Greenberg RE, Steinberg GD. Intravesical valrubicin in patients with bladder carcinoma in situ and contraindication to or failure after bacillus Calmette-Guérin. *Urol Oncol*. 2013;31(8):1635-1642.
51. Mason SJ, Downing A, Wright P, et al. Health-related quality of life after treatment for bladder cancer in England. *Br J Cancer*. 2018;118(11):1518-1528.
52. Winters BR, Wright JL, Holt SK, Dash A, Gore JL, Schade GR. Health related quality of life following radical cystectomy: comparative analysis from the Medicare Health Outcomes Survey. *J Urol*. 2018;199(3):669-675.
53. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci U S A*. 2002;99(19):12293-12297.
54. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376(11):1015-1026.
55. Stenehjem DD, Tran D, Nkrumah MA, Gupta S. PD1/PDL1 inhibitors for the treatment of advanced urothelial bladder cancer. *Onco Targets Ther*. 2018;11:5973-5989.
56. Boorjian SA, Sheinin Y, Crispen PL, et al. T-cell coregulatory molecule expression in urothelial cell carcinoma: clinicopathologic correlations and association with survival. *Clin Cancer Res*. 2008;14(15):4800-4808.
57. Inman BA, Sebo TJ, Frigola X, et al. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. *Cancer*. 2007;109(8):1499-1505.
58. Fukumoto K, Kikuchi E, Mikami S, et al. Clinical role of programmed cell death-1 expression in patients with non-muscle-invasive bladder cancer recurring after initial bacillus Calmette-Guérin therapy. *Ann Surg Oncol*. 2018;25(8):2484-2491.
59. Hashizume A, Umemoto S, Yokose T, et al. Enhanced expression of PD-L1 in non-muscle-invasive bladder cancer after treatment with bacillus Calmette-Guerin. *Oncotarget*. 2018;9(75):34066-34078.
60. Nakanishi J, Wada Y, Matsumoto K, Azuma M, Kikuchi K, Ueda S. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. *Cancer Immunol Immunother*. 2007;56(8):1173-1182.
61. Kamat AM, Shore N, Hahn N, et al. KEYNOTE-676: Phase III study of BCG and pembrolizumab for persistent/recurrent high-risk NMIBC. *Future Oncol*. 2020;16(10):507-516.
62. US Food and Drug Administration. PEMBROLIZUMAB-P057V01MK3475 Advisory Committee Briefing Document. December 17, 2019. https://www.fda.gov/media/133542/download
63. A Study of Nivolumab or Nivolumab Plus Experimental Medication BMS-986205 With or Without Bacillus Calumette [sic]-Guerin (BCG) in BCG Unresponsive Bladder Cancer That Has Not Invaded Into the Muscle Wall of the Bladder (CheckMate 9UT).
64. Liu M, Wang X, Wang L, et al. Targeting the IDO1 pathway in cancer: from bench to bedside. *J Hematol Oncol*. 2018;11(1):100.
65. Luke JJ, Tabernero J, Joshua A, et al. BMS-986205, an indoleamine 2, 3-dioxygenase 1 inhibitor (IDO1i), in combination with nivolumab (nivo): Updated safety across all tumor cohorts and efficacy in advanced bladder cancer (advBC). *J Clin Oncol*. 2019;37(7 suppl):358.
66. Dinney CP, Fisher MB, Navai N, et al. Phase I trial of intravesical recombinant adenovirus mediated interferon-α2b formulated in Syn3 for bacillus Calmette-Guérin failures in nonmuscle invasive bladder cancer. *J Urol*. 2013;190(3):850-856.
67. Boorjian SA, Shore ND, Canter D, et al. Intravesical rad-IFNα/Syn3 for patients with high-grade, bacillus Calmette-Guérin (BCG) refractory or relapsed non-muscle invasive bladder cancer: a phase II randomized study. *J Clin Oncol*. 2017;35(6 suppl):279.
68. Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. *Lancet Oncol*. 2021;22(1):107-117.
69. Boehm BE, Svatek RS. Novel therapeutic approaches for recurrent nonmuscle invasive bladder cancer. *Urol Clin North Am*. 2015;42(2):159-168.
70. Packiam VT, Lamm DL, Barocas DA, et al. An open label, single-arm, phase II multicenter study of the safety and efficacy of CG0070 oncolytic vector regimen in patients with BCG-unresponsive non-muscle-invasive bladder cancer: interim results. *Urol Oncol*. 2018;36(10):440-447.
71. Packiam VT, Johnson SC, Steinberg GD. Non-muscle-invasive bladder cancer: Intravesical treatments beyond Bacille Calmette-Guérin. *Cancer*. 2017;123(3):390-400.
72. Packiam VT, Labbate CV, Boorjian SA, et al. The association of salvage intravesical therapy following BCG with pathologic outcomes and survival after radical cystectomy for patients with high-grade non-muscle invasive bladder cancer: a multi-institution analysis. *Urol Oncol*. 2021;20;S1078-S1439(21)00003-X. Online ahead of print.

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