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TOPIC PAPER

Emerging therapies in the management of high-risk non-muscle invasive bladder cancer (HRNMIBC)

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Abstract

Purpose BCG is the gold standard in management of high-risk non-muscle invasive bladder cancer (HRNMIBC). However, in patients who fail BCG, there are few effective intrasvesical options. This review aims to explore standard and emerging therapies in HRNMIBC.

Methods A non-systematic literature review was performed using Medline and PubMed. Literature focused on HRNMIBC and BCG failure studies, with particular attention to Phase II and III clinical trials.

Results The only FDA approved therapy for BCG failure patients in Valrubicin. Patients with HRNMIBC and BCG failure patients are at increased risk for progression and death from bladder cancer. There are a variety of clinical trials exploring different therapeutic approaches such as immunotherapy, vaccines, radiotherapy, and gene therapy. These trials are showing some promise in the early reporting phase.

Conclusion Despite limited intravesical treatment options in BCG failure patients, there are several promising therapies currently being developed and several with promising early results.

Keywords Non-muscle invasive bladder cancer · BCG failure · Immunotherapy · Vaccines

Introduction

Bladder cancer is the 5th most common malignancy in men and 10th most common cancer in woman. There will be an estimated 81,190 new cases of bladder cancer and 17,240 bladder cancer deaths predicted in 2018 in the United States. Approximately, 75% of newly diagnosed bladder cancer is Non-Muscle Invasive Bladder Cancer (NMIBC) [1]. The recurrence rates vary from 50 to 70% with a 10–40% risk of disease progression [2, 3]. NMIBC is a heterogeneous group of tumors and it is, therefore, important to identify and risk stratify individuals with a higher rate of recurrence and progression. With the recent explosion of immune-oncology therapies in the metastatic patient population, similar principles are being applied to NMIBC. This review will highlight the current standard of care with high-risk non-muscle invasive bladder cancer (HRNMIBC) and emerging therapies currently being examined in Phase II and Phase III clinical trials.

Definition of HRNMIBC

The most important risk factor for progression of NMIBC is grade. Tumor characteristics such as multiplicity, tumor size > 3 cm, presence of CIS and prior treatment with BCG have been implicated as prognostic indicators of recurrence. There have been multiple nomograms and risk tables designed in an attempt to predict disease recurrence and progression in the NMIBC patient [2, 3]. Based on the available literature, the American Urological Association (AUA) has updated the NMIBC guidelines in 2016 and has suggested a risk stratification strategy in NMIBC. Low-risk patients include those with Low-Grade Ta (LGTa solitary) tumors ≤ 3 cm and Papillary Urothelial Neoplasm of Low Malignant Potential. Intermediate Risk patients include

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LGTa recurrences within 1 year, solitary LGTa > 3 cm, multifocal LGTa, HGTa tumors ≤ 3 cm, LGT1. High-risk patients are defined as having HGT1, recurrent HGTa, HGTa > 3 cm or multifocal, carcinoma in situ (CIS), Bacillus Calmette–Guerin (BCG) failure in HG patient, variant histology, lymphovascular invasion, or any HG prostatic urethra involvement [4]. The European Association of Urology (EAU) definition of HRNMIBC is similar to that of the AUA stance on HNMIBC, with the exception that all T1 tumors regardless of grade are defined as high-risk.

Standard of care treatment high-risk NMIBC

Role of repeat transurethral resection of bladder tumor (TURBT)

Repeat TURBT has been advocated for since the late 1990s after studies at that time determined up to 76% of patients had residual tumor and 29% of patients were upstaged at repeat TURBT resulting in change in management in a third of patients [5]. The value of repeat TURBT in HG T1 was explored further to evaluate how a complete visual resection at TURBT impacts upstaging at re-resection. When surgeons feel that a complete resection has been performed, upstaging to T2 at repeat TURBT fell to 8%, but 33% still harbored high-grade disease [6, 7].

In addition to the detection of persistent tumor burden and upstaging patients, the pathology on the repeat TURBT can be utilized as a prognostic indicator. Residual T1 disease at time of repeat TURBT has been associated with increased risk of disease recurrence and progression [7]. Patients with residual T1 at re-TURBT have a 2-year recurrence-free survival of only 26.1% and a 23.2% risk of progression to muscle invasive disease (versus only 6% in other stages of NMIBC) [8]. Herr et al. evaluated a cohort of HGT1 patients treated with BCG and noted that 82% of patients with residual HGT1 on re-TURBT progressed to MIBC within 5 years compared with 19% of patients without T1 on restaging TURBT [9]. If residual HGT1 on repeat TURBT is found, clinicians should counsel patients on radical cystectomy rather than intravesical therapy due to increased rates of progression.

Patients with T1 and concomitant CIS are at the highest risk, with progression rates around 50% and a 34% risk of death from bladder cancer [10]. Data from the European Association for Research and Treatment of Cancer (EORTC) suggest that patients with HGT1 and CIS have rates of progression ranging from 29 to 74% at 1 and 5 years, respectively (compared to 10% and 29% in pts with T1 alone) [11]. However, only around 10% of patients in the EORTC data received BCG, reflecting more of a natural history of untreated patients, overestimating the progression rates [11, 12]. A meta-analysis of 15,215 patients showed that HGT1, with associated CIS, carried a two-fold risk of progression when compared to HGT1 alone. Overall 5-year recurrence, progression and cancer-specific survival were 42, 21 and 87%, respectively, for all HGT1 cancers in this study [13].

Role of blue-light (BLC) TURBT in HRNMIBC

Traditional recurrence rates of NMIBC after white light TURBT have been reported to be as high as 41, 61, 73 and 75% at 2, 12, 36 and 60 months, respectively [14]. Due to the high rates of recurrence and upstaging seen on white light re-turbt, new cystoscopic techniques have emerged such as photodynamics (PDD) in an effort to improve the accuracy of cystoscopy. White light cystoscopic (WLC) detection of CIS can be as poor as 60.5% [14]. A recent meta-analysis evaluating TURBT with fluorescent light cystoscopy (5-aminolevulinic acid or hexaminolevulinic acid) improved detection rates of CIS to around 90% [15]. Hexaminolevulinate (HAL) (Hexvix, Cysview, Photocure) was approved by the FDA in 2010. A meta-analysis of HAL with BLC was associated with improved detection rates of HGTa, T1, and CIS, leading to decreased recurrence rates at 12 months (34.5% vs 45.4% BLC vs WLC) [16]. Although fluorescent cystoscopy has been associated with improved recurrence-free survival rates at 1 and 2 years, progression to MIBC did not differ between WLC and BLC groups [17].

Ultimately, BLC assists the urologist in the management of HRNMIBC by accurately detecting more high-risk tumors, which ultimately may lead to a reduction in progression rates.

BCG therapy

BCG is the gold standard adjuvant treatment for patients with HRNMIBC. Multiple studies have shown that BCG leads to both a reduction in recurrence and progression [18–20]. Currently, the AUA and EAU recommend induction BCG (6 weeks) followed by 1–3 years of maintenance, depending on risk. These results are based on meta-analyses of the SWOG and EORTC studies that used a maintenance schedule consisting of three weekly instillations at 3, 6, 12, 18, 24, and 36 months [20, 21]. Despite aggressive therapy, around 20–40% with HRNMIBC will progress and another significant percentage will not tolerate treatment. These patients require second-line therapy; most of which outside of RC is not effective. This has prompted further exploration into this patient population.

Defining BCG failures

Discussing and understanding the nuances associated with the management of BCG and HRNMIBC are an important issue that is often not well understood. Defining the terms associated with BCG failure is not only important for communication between physicians and patients but it also carries prognostic significance.

Adequate BCG

To determine if a patient has failed BCG, it is critical to ensure they received an adequate course of BCG. From a BCG failure trial design standpoint, an adequate course of BCG is defined as at least five of six intended weekly induction treatments (one induction course) and at least two additional weekly maintenance treatments or a second re-induction in a 6-month time period.

BCG intolerant

During the course of either induction or maintenance BCG, there will be some patients that do not tolerate the treatment due to adverse side effects. When patients cannot complete their intended BCG treatment course because of symptoms, this is termed BCG intolerant.

BCG refractory

BGG refractory patients are at the highest risk for progression to muscle invasive disease. These patients have persistent high-risk disease despite adequate BCG at their 6-month cystoscopy. There is some debate on timing. Some clinicians feel that 3 months may be the most important time frame and others feel that urologists should wait until the 6-month time point, as some of the patients with persistent disease at 3 months will respond at 6 months. Most agree that if patients progress to a more advanced stage (i.e., CIS to HG T1) at the 3-month cystoscopy that these patients may be at even higher risk of progression to MIBC and should consider "early" cystectomy. The main goal of managing HRNMIBC is walking the fine line between preserving a patients' bladder with effective intravesical treatment, but not allowing them progress to MIBC. If the urologist waits until muscle invasion, they have waited too long.

A Memorial Sloan Kettering Study examined the prognostic differences between BCG refractory and BCG relapsing patients and found that progression-free survival was 18 months for BCG refractory and 52 months for BCG relapsing, respectively [22]. At last follow-up, 47% (8/17) patients had died from bladder cancer in the BCG refractory group compared to 20% (3/15) in the BCG relapsing patients. Furthermore, progression to muscle invasive disease in this population has been reported to be between 50 and 70% in the first 12 months on surveillance [22].

BCG relapsing

BCG relapsing is defined as patients who receive adequate induction BCG and respond and are determined to be disease free at 6 months. The patient may undergo maintenance BCG for a period of time and then recur. The type of recurrence is important and carries prognostic information. Patients that recur with HGNMIBC (CIS, HGTa, HGT1) have a more worrisome prognosis than those that recur with low-risk NMIBC. A study from MD Anderson examined 917 patients who underwent induction BCG and identified 66 patients with a Ta recurrence and 18 patients with a T1 recurrence. This study demonstrated that an HG Ta recurrence at 3 months after induction BCG portends a similar prognosis as that of HG T1. The recurrence rate for these patients was 62% at 1 year with a progression rate of 17% at 1 year. However, no patients who recurred with LG Ta experience progression with a median follow-up of 74 months [23]. This study suggests that a HG Ta or T1 recurrence at 3 months are significant events that carry a similar prognosis. Patients with LG Ta have an extremely favorable prognosis and patients can be managed conservatively.

BCG failure FDA-approved therapies

When patients with HRNMIBC fail BCG treatment, there are very few effective options outside of radical cystectomy. Intravesical chemotherapeutic agents including mitomycin C, doxorubicin, and thiotepa have been used with limited success with less than 20% remaining tumor free at 5 years [24]. Multiple randomized controlled trials have shown that progression rates are not impacted by cytotoxic chemotherapy [25]. Intravesical chemotherapy may not be effective because chemotherapy is only active when tumor is present. Therefore, prophylactic chemotherapy is not logical in the absence of disease. However, due to the dearth of options available in this setting, chemotherapy agents were still evaluated.

Valrubicin is an analog of doxorubicin that is lipid soluble and inhibits DNA and RNA synthesis, partially by topoisomerase II inhibition [26]. Unlike doxorubicin, valrubicin traverses cell membranes into the cytoplasm of cells and has lower systemic toxicity. This makes this drug ideal for

intravesical instillation [27]. Greenberg et al. evaluated intravesical valrubicin in patients (32) with BCG refractor NMIBC, including 22% with CIS. This study showed initial promise with a complete response rate of 41% (13 patients). However, only 6 patients were BCG failure patients with a response rate of 33% (2) [28]. In the BCG failure population, Steinberg and Dinney et al. reported on long-term outcomes in 80 patients treated with valrubicin for BCG refractory disease in NMIBC. At 2-year follow-up, the complete response rate was 18% [29, 30]. This led to valrubicin getting FDA approval for use in patients with BCG refractory CIS who are not candidates for RC. Despite FDA approval, valrubicin is not a particulary effective drug in BCG refractory patients.

Role of IFN-α in NMIBC

Similar to BCG inducing an immune response, it was thought that perhaps interferon-alpha (IFN-α) would induce a similar type of response leading to equivocal results. IFN-α monotherapy was evaluated in a double-blind randomized control trial versus placebo in patients with CIS and other HRNMIBC as first line; however, the success rate for CIS was only around 15% with a mean follow-up of 43 months. In patients with HG T1, IFN-α was found to be no better than placebo [31]. Despite the low success rate, IFN-α concomitant with BCG therapy in BCG failure patients has seen some success. Several single institutional studies have reported disease-free states between 50 and 60% in patients with HRNMIBC who have failed at least one course of induction BCG, with follow-up ranging from 12 to 30 months [32–34]. This approach seems to be especially good for single BCG failures with CIS only, with 45% 3-year disease-free survival [33]. However, BCG refractor CIS that has failed at least 2 induction courses of BCG has been shown to have a disease-free survival rate of only 23% at 24 months follow-up [35]. Of note, none of the studies showed a benefit in survival or clinical progression rates in patients receiving BCG and IFN-α over those receiving BCG alone. This type of treatment should not be advocated in patients with true BCG refractory disease.

Thermo-chemotherapy

Thermo-chemotherapy focuses on the idea that traditional intravesical chemotherapeutic regimens do not penetrate the bladder wall and not efficient in their cytotoxic properties. The thermal effect theoretically allows better drug penetration and may prove to be more efficacious that traditional intravesical methods. Recently, thermo-chemotherapy with mitomycin C (MMC) at a bladder wall temperature of 42C was evaluated in 111 patients with papillary NMIBC after BCG therapy. Maintenance therapy for 6 weeks on a weekly basis was compared to non-maintenance therapy [36]. They found that the recurrence rate was 39% and 61% in the maintenance and non-maintenance groups, respectively. Based on these results, the author's concluded that hyperthermia and MMC are effective in BCG refractors papillary disease without a significant risk of progression (3%) [36].

Intra-arterial chemotherapy

To investigate the effects of intra-arterial chemotherapy on T1 stage bladder cancer (Bca) and evaluate patient outcome with bladder-preserving treatment approaches, Zefu Liu et al. retrospectively evaluated 238 patients with HG T1, where 62 patients refused cystectomy, 141 had intravesical chemotherapy, and 35 patients underwent immediate RC [37]. The bladder preservation group received cisplatin intra-arterial chemotherapy plus gemcitabine. The RC and intra-arterial chemotherapy group both had superior PFS and CSS when compared to the intravesical chemotherapy group. However, there was no difference in PFS and OS in the RC versus intra-arterial chemotherapy groups, suggesting oncologic equivalence in this retrospective study [37]. While these data are interesting and hypothesis generating, ideally these patients should be enrolled in a prospective trial.

Gemcitabine and docetaxel

Gemcitabine has been shown to be effective in patients with HRNMIBC who have failed prior BCG therapy. A phase II study was performed to evaluated gemcitabine induction plus maintenance in the BCG refractory space. However, less than 30% of patients remained disease free at 12 months of follow-up [38]. Recently, there has been a renewed interest in combination therapy with gemcitabine and intravesical docetaxel. Forty-five patients with BCG refractory NMIBC were offered 6 weekly instillations of gemcitabine followed immediately by docetaxel. They achieved some success with a 1-year DFS rate of 54% that declined to 34% at 2 years. These data suggest an alternative treatment for those patients who refuse or are unfit for cystectomy {Steinberg:2015en}.

Ongoing Phase II and III clinical trials in HRNMIBC

Over the last few years, there has been an explosion in drug research for both muscle invasive and NMIBC. Currently, there are over 25 clinical trials in the United States in the non-muscle invasive population. Here, we will highlight

several key trials in the Phases II and III in the HRNMIBC and BCG failure population (Table 1).

Immunotherapy blockade mechanisms in HRNMIBC

Atezolizumab (anti-PDL-1) was the first immunotherapy drug approved in the muscle invasive bladder cancer patient population. This class of drug is called an immune checkpoint and it is a monoclonal antibody that targets tumor-associated antigens. Immune checkpoints refer to co-inhibitory receptors that can be expressed either on the T cell or the tumor cell. These co-stimulatory molecules can either suppress or augment the adaptive immune response. The main immune checkpoints that will be discussed are the anti-cytotoxic T Lymphocyte antigen 4 (CTLA4), anti-programmed cell death 1 (PD-1), and anti-programmed cell death ligand 1 (PDL-1). A critical interaction needed in T cell activation is the B7-CD28 binding, which activates the T cell. CTLA-4 is exclusively expressed on the T cell and competitively competes with CD28 for the binding domain of B7 on the antigen-presenting cell (APC), resulting in deactivation of the T cell (Fig. 1). Inhibitors of CTLA4 can bind to CTLA4, preventing interaction with B7, resulting in the activation of the T cell. PD1 is expressed typically on the T cell. Binding of PD1 to PDL-1, which can be expressed on tumor cells, NK cells, or APCs, results in deactivation of the T cell and reduction in the inflammatory cytokine cascade [39, 40]. Inhibitory molecules against PD1 and PDL-1 can, therefore, prevent deactivation of the T cell and promote a more robust immune response.

Many of these principles elucidated in MIBC are being applied to the NMIBC patient population through a variety of clinical trials, a few of which will be highlighted (Fig. 1) [40].

Table 1 Phase II and III trials in HRNMIBC

Agent	Mechanism	Clinical trial #	NMIBC space	Route	Primary outcome	Secondary outcome	Phase
Immunotherapy							
Atezolizumab	PDL-1 inhibitor	NCT02844816	BCG failure	IV	CR	PFS, OS	II
Pembrolizumab (PD1)	PD1 inhibitor	NCT02625961	BCG failure	IV	CR	PFS	II
BCG + ALT-803	IL-15 Superagonist	NCT02138734	BCG Naïve	Intravesical	CR	PFS	II
Nivolumab plus BMS-986,205	PD1 and indoleamine 2,3-dioxygenase 1 inhibitor	NCT03519256	BCG failure	IV	CR in CIS	PFS	II
Vaccines							
HS-410	Vaccine against bladder tumor antigens	NCT02010203	BCG failure	IV	PFS	CR	II
ALT-801	Fusion protein improve T cell binding domain on IL-2	NCT01625260	BCG failure	IV	PFS,safety	CR	IB/II
PANVAC + BCG	Pox viral vector	NCT02015104	BCG failure	IV + intravesical	PFS	Tumor antigen response	II
Gene therapy							
Instiladrin (rAd-IFN/Syn-3)	Adenovirus vector containing IFN alpha-2b gene	NCT01687244	BCG failure	Intravesical	CR	PFS	II/III
CG0070	Oncolytic vector + production GM-CSF[a]	NCT02365818	BCG failure	Intravesical	CR	PFS	II
Drug delivery system							
Albumin-bound Paclitaxel	Paclitaxel arrests the cell cycle in the G_2-M phase	NCT03081858	BCG failure	Intravesical	CSS	PFS,CR	II
Radiation therapy							
RTOG 0926	Cisplatin +radiation	NCT00981656	HG T1	IV and Radiation	RC-free rate	PFS,OS	II

[a]GM-CSF granulocyte macrophage-colony stimulating factor

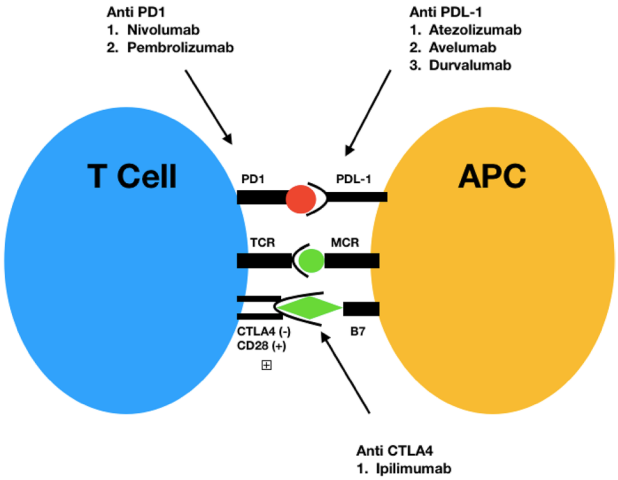

Fig. 1 Immune blockade mechanisms blockade mechanisms in NMIBC

Alterations of tumor micro environment and immune system

Atezolizumab in treating patients with recurrent BCG-unresponsive NMIBC

This is a phase II trial in patients with CIS, HGTa, or HG T1 who have failed prior BCG therapy. Patients receive atezolizumab intravenously (IV) every 21 days for up to 17 courses. The primary objective is to estimate complete response rates (CR) at 25 weeks. Other secondary and tertiary objectives include progression-free survival, cystectomy-free survival, and overall survival. Additionally, they hope to identify predictors of survival by utilizing immunohistochemistry to stratify by PDL-1 status (Fig. 1).

Study of pembrolizumab (MK-3475) in participants with high-risk non-muscle invasive bladder cancer (MK-3475-057/KEYNOTE-057)

This study is almost identical to the above atezolizumab study including having the same inclusion and exclusion criteria. Pembrolizumab is a monoclonal antibody against PD1 which is located on the lymphocytes. This receptor is generally designed to prevent the immune system from destroying its native tissue. Cancers tend to manufacture proteins that bind to PD1 on the lymphocyte, shutting down that immune response. In this study, patients receive 200 mg IV every 3 weeks for up to 24 months. The primary endpoint is CR rates and disease-free survival (Fig. 1).

A study of intravesical BCG in combination with ALT-803 in patients with non-muscle invasive bladder cancer

This is a Phase IB/IIB-randomized, open-label study of intravesical ALT-803 plus BCG versus BCG alone in BCG naïve patients with HGNMIBC. ALT-803 is an IL-15 superagonist that simultaneously mobilizes both the innate and adaptive immune response. It has a profound stimulatory effect on both NK cells and T cells. The primary outcome is CR rates. This has shown promise in preclinical studies as well as Phase 1b studies in lung cancer. The concept behind this study is that the intravesicle BCG leads to local immune response in the bladder that can be further augmented by ALT803.

A Study of Nivolumab or Nivolumab Plus Experimental Medication BMS-986205 With or Without Bacillus Calumette–Guerin (BCG) in BCG Unresponsive Bladder Cancer That Has Not Invaded Into the Muscle Wall of the Bladder

This is a phase II trial with 4 treatment arms in the NMIBC BCG-unresponsive space. Nivolumab is PD1 inhibitor and BMS-986205 is medication taken oral that inhibits indoleamine 2,3-dioxygenase 1 (IDO1). This enzyme is responsible for the oxidation of tryptophan into the metabolite kynurenine, which is immunosuppressive. BMS-986205 specifically binds to IDO1 and decreases kynurenine in tumor cells, activating various immune cells in both the innate and adaptive immune response while also reducing the amount of tumor-associated regulatory T cells (Tregs). This trial has 4 arms. Arm 1 is nivolumab alone. Arm 2 is nivolumab plus BCG. Arm 3 is nivolumab plus BMS-986205. Arm 4 is nivolumab plus BMS-986205 plus BCG. The primary outcome is the percentage of CIS patients who have a CR.

Vaccines

Vaccines are being revisited in cancer therapy. Vaccines have a definitive advantage over other treatment options. Theoretically if a vaccine is effective, there should be no need for additional treatments as is needed for monoclonal antibody therapy. The vaccine to the cancer should create adaptive immunity that will not only eradicate tumor but also create lifelong protection against future recurrence and progression. In the BCG unresponsive space, there are three current trials being investigated (ALT-801, PANVAC, and HS-410) [41].

HS-410

Vesigenurtacel-L (HS-410) is a novel vaccine comprising an allogeneic cell line, selected for high expression of a series of bladder tumor antigens (neoantigens) and transfected with gp96-Ig and hsp90B1 (heat shock protein). Upon being delivered to a recipient's own antigen-presenting cells (APCs), the neoantigens, in particular (GP96), stimulate CD8+ cytotoxic T cells. This is thought to augment the patient's own BCG-induced immune response to bladder cancer-specific targets. The phase II preliminary results were recently reported in 78 patients with recurrence-free survival (RFS) being the primary endpoint. Preliminary results reported that RFS rates for BCG and low-dose HS-410, BCG, and high-dose HS-410, and BCG and placebo were 65.4, 65.45, and 76.9%, respectively. There was no statistically significant difference in RFS between HS-410 and placebo. However, the patients exposed to the vaccine developed immune responses to tumor-associated peptides [41].

Study of ALT-801 in patients with BCG failure NMIBC

ALT-801 is a fusion protein that changes the T cell receptor binding domain on IL-2. This IL-2 with the novel fusion protein significantly augments ALT-801 over the natural form of IL-2. The effective is thought to be further augmented by the administration of gemcitabine in this trial. This Phase Ib/II trial is investigating safety, tolerability, and cancer recurrence rates up to 13 weeks in patients with high-grade Ta, T1, or Tis NMIBC.{Annels:2015gy}.

Study of Bacillus Calmette–Guerin (BCG) combined with PANVAC versus BCG alone in adults with high-grade non-muscle invasive bladder cancer who failed at least 1 course of BCG

PANVAC is a poxviral vector-based vaccine. The patients' immunologic responses were assessed by following three tumor-specific antigens (mucin-1, Brachyury, and carcinoembryonic enzyme (CEA)). Preliminary data for the first 16 patients were reported at the AUA annual meeting in 2017. In the PANVAC and BCG combination arm noted an increase in CD8 T-cells and antigen-specific T cell responses to CEA, mucin-1, and brachyury. Thus far in the trial, the authors concluded that BCG plus PANVAC induced an immunological response greater than BCG alone. No clinical data were available [42].

Genetic therapy

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

Instiladrin (rAd-IFN/Syn-3) is a non-replicating adenovirus that contains a vector containing the human IFN alpha-2b gene. This drug also contains Syn-3, which augments transduction of the virus into the urothelium and cancer cells. The idea is that the adenovirus inserts the gene into the cells, which start manufacturing IFN alpha locally into the bladder. Phase I and phase II trials have demonstrated detectable levels of IFN alpha in the urine [43]. The clinical data were recently reported. After 12 months of follow-up, 35% (14/40) remained disease free of an HG tumor recurrence [44]. This data is compelling and will be interesting to evaluate the data as the trial matures.

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

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 [45]. This drug both lyses tumor cells and directly leads to production of GM-CSF. The intravesical instillation of CG-0700 has been shown to be safe, with a complete response rate of 48.6% at 10.4 months. The interim results of the phase II study were reported at the 2017 AUA. Of the 45 patients (24 CIS, 8 CIS +Ta, 4 CIS +T1, 6 Ta, 1 T1), the overall CR rate at 6 months was 47%. The CR was best for CIS (50%). Patients with T1 had much poorer response rates (0% for pure T1, 33% for T1 +Ta) [46].

Drug delivery systems

Intravesical nanoparticle albumin-bound paclitaxel for recurrent non-muscle-invasive bladder cancer after previous Bacillus Calmette–Guérin therapy

This is a new type of treatment that utilizes various properties of molecules to more effectively deliver drugs to the target. Nanoparticle albumin-boud paclitaxel (nab-Paclitaxel) stabilizes microtubules and arrests the cell cycle in the G_2-M phase [47]. The results for the Phase II trial were reported. Although the cancer specific survival rate was 91%, only 18% remained disease free at a median follow-up of 5 years [48].

Radiation therapy

Phase II protocol for patients with stage T1 bladder cancer to evaluate selective bladder-preserving treatment by radiation therapy concurrent with cisplatin chemotherapy following a thorough TURBT (RTOG 0926)

In muscle invasive bladder cancer, tri-modal therapy with maximal TURBT, radiation, and chemotherapy is currently being investigated. Preliminary single institutional data suggest that cancer-specific survival rates may rival radical cystectomy in properly selected patients [49]. Historically, radiation monotherapy for NMIBC has not been effective [50]. However, there is a renewed interested in the utilization of radiation therapy concomitantly with immune-oncology agents such as PD1/PDL-1 inhibitors in the treatment of both MIBC and NMIBC. Radiation typically is thought to work by inducing double strand DNA breaks that result in apoptosis and cell death. Radiation-induced cell death can both stimulate the immune system or can be immunosuppressive, depending on the dose. Historically, clinicians are familiar with the abscopal effect, where treatment of the primary tumor causes regression of metastatic sites. Although the exact mechanism is unclear, it is thought that radiation induces an intense inflammatory response of both the innate and adaptive immune system that leads to tumor antigen recognition and an adaptive mediated destruction of cancer cells [51]. Immuno-oncology drugs, such as anti-PDL/PDL-1/CTLA-4 inhibitors, can augment the immune infiltrate induced by radiotherapy by overcoming resistance mechanisms and re-activating the T-cell [51]. These radiotherapy applications are now being applied in the NMIBC setting [51].

Radiation therapy is currently being investigated in a Phase II trial (RTOG 0926) that is investigating outcomes in patients with BCG refractory HG T1 disease. The overall endpoint is evaluating the rate of freedom from RC at 3 years. Radiation therapy (RT) is likely going to be paired with PD1 and PDL-1 inhibitors and may further add to augment immunotherapy in the future. However, there are numerous unknowns associated with RT. For example, the timing and the radiation dose per fraction seem to be important parameters determining the modulation of the immune response. Perhaps, low-dose RT induces a more robust immune response and is less immunosuppressive than standard dose RT. These are factors that will continue to evolve and immunotherapy treatment for cancer continues to progress.

Conclusions

The treatment of HRNMIBC, particularly in BCG failure patients, remains challenging. These patients are at high risk of progression to MIBC and death from bladder cancer. Currently, there are poor intravesical options for second-line treatment and RC remains the gold standard. However, there are many clinical trials underway examining different therapeutic approaches in an effort to provide safe and effective bladder sparing options.

Author contributions RW: Protocol/project development-yes, data collection or management-yes, data analysis-N/A, manuscript writing/editing-writing and editing. BA, M.D.: Protocol/project development-yes, data collection or management-yes, data analysis-N/A, manuscript writing/editing-writing and editing. GDS, M.D.: Protocol/project development-yes, data collection or management-no, data analysis-N/A, manuscript writing/editing-editing.

Compliance with ethical standards

Conflict of interest Gary Steinberg: I am a scientific advisor/consultant for the following companies: Heat Biologics, Cold Genesys, PhotoCure, Merck, Roche/Genentech, Taris Biomedical, MDxHealth, Fidia Farmaceuticals, Urogen, Spectrum Pharmaceuticals, Biocancell, Epivax Oncology, Natera, FKD, Synergo, BMS, Boston Scientific, Ferring Pharmaceuticals, QED. Ryan Werntz: none. Brittany Adamic: none.

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