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TOPIC PAPER

Updates on the use of intravesical therapies for non-muscle invasive bladder cancer: how, when and what

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Abstract

Introduction Intravesical therapy has been an important aspect of the management of non-muscle invasive bladder cancer (NMIBC) for 40 years. Bacillus Calmette–Guerin (BCG) is considered standard of care for intermediate and high-grade non-invasive disease, yet understanding the nuances of subsequent intravesical therapy is important for any provider managing bladder cancer. Herein, we review the literature and describe optimal use of intravesical therapies for NMIBC.

Methods A comprehensive search of the medical literature was performed and highlighted in this review of intravesical therapy for NMIBC.

Results Post-resection intravesical Mitomycin C therapy for low-risk disease remains an important component of care, and gemcitabine now has level-one evidence demonstrating efficacy in this setting but is not yet a guideline recommendation. BCG intravesical therapy remains the most effective therapy preventing recurrence and progression of intermediate and high-risk NMIBC. Adequately characterizing BCG-failure is critical in determining the next step in management which includes radical cystectomy, additional intravesical immunotherapy, chemotherapy with intravesical gemcitabine ± docetaxel and clinical trials.

Conclusions Intravesical therapy remains the mainstay of treatment for NMIBC and bladder preservation. Intravesical induction BCG followed by maintenance therapy remains standard of care for intermediate and high-risk patients. Detailing the timing and characteristics of recurrence after intravesical therapy is crucial in determining subsequent treatment recommendations. Current clinical trials focus on systemic immunotherapy and enhancing the intravesical immune response by augmenting the delivery mechanism.

Keywords Non-muscle invasive bladder cancer · Intravesical therapy · BCG failure

Introduction

Bladder cancer is the 4th most common cancer diagnosed in men and 11th most common cancer in women in the United States [1]. Approximately 75,000 new cases of bladder cancer were diagnosed in 2017, of which over 70% of these cases were non-muscle invasive bladder cancer (NMIBC) [2, 3]. Transurethral resection of bladder tumor (TURBT) removing all visible tumor with adequate surgical margins to the depth of the muscularis propria has been a keystone in managing NMIBC for over 40-year [4–6]. Complete TURBT is essential in maximizing the potential effectiveness of adjuvant intravesical therapies [7]. New technologies to enhance visualization such as photodynamic diagnosis (florescence cystoscopy) and narrow band imaging have demonstrated improved cancer detection and are part of guideline recommendations when available [4, 5]. A repeat TURBT is recommended for all T1 disease to avoid missing potential muscle invasion; as such upstaging after repeat TURBT ranges from 24 to 49% which changes management [8]. Guidelines advocate for repeat TURBT within 4–6 weeks of resection to accurately stage and enhance response to intravesical therapy [9, 10].

The American Urologic Association (AUA)/Society of Urologic Oncology (SUO), European Association of Urology (EAU) and International Bladder Cancer Group (IBCG) recommend risk stratification of tumors after complete

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TURBT and the following general algorithm. Low-risk patients should receive a single perioperative dose of intravesical chemotherapy. Intermediate-risk patients are recommended to receive induction intravescial chemotherapy or BCG followed by 1 year of maintenance therapy if a complete response is achieved. For high-risk patients induction bacillus Calmette–Guerin (BCG) followed by 3 years of maintenance therapy for complete responders is recommended [4, 5].

Though there is renewed interest in cancer immunotherapy over the last few years, immunomodulation with BCG therapy has remained an effective treatment for NMIBC since it was first reported in 1976 [11]. BCG administration, however, has not been uniform which may contribute to failures and controversies still exist [12, 13]. Furthermore, as new therapies emerge the current intravesical therapy landscape is changing rapidly [14, 15]. Management of NMIBC requires consistent, repeated evaluation and therapies that contribute to treatment related morbidity and costs. As such, understanding current and future intravesical therapies is critical in managing NMIBC. The purpose of this review is to promote adherence to current guideline recommendations, provide an update in the use of intravesical therapies for NMIBC, and describe the importance of characterizing intravesical treatment failures.

Literature search

A comprehensive search of PubMed and MEDLINE using the English language was performed using the following terms individually or in combination in the context of NMIBC: "non-muscle invasive bladder cancer," "intravesical therapy," "intravesical treatment," "BCG," "immunotherapy," "recurrence," "progression," "BCG failure," "salvage intravesical therapy," "intravesical chemotherapy," "BCG failure," "BCG refractory," "BCG resistant," "BCG intolerant," "BCG unresponsive," "BCG relapsing," "high-risk," "intermediate-risk," "low-risk." The initial list of selected articles was further focused with the input of all the authors and reviewer commentary. References were condensed to fit the constraints of the journal requirements and literature within the last decade was prioritized.

Risk stratification

Non-muscle invasive bladder cancer includes patients with low-grade (LG) and high-grade (HG) pathology and Ta, T1 and CIS staging. Grade is critical in establishing risk of NMIBC, and HG disease has always been considered high-risk [4, 5, 16]. Five year rates of recurrence and progression range from 30 to 78% and 1–21%, respectively. High-grade lesions, multifocal tumors, large tumor size, prior recurrences and presence of CIS also predict recurrence and progression [17–19]. Qualifying tumors as low, intermediate and high-risk is, therefore, important to stratify cases according to their probability of recurrence and progression, and to guide adjuvant and surveillance care. The American Urologic Association (AUA)/Society of Urologic Oncology (SUO) and European Association of Urology (EAU) endorse risk stratification of NMIBC cases (Table 1) [4, 5]. Importantly, both guidelines emphasize grade, multifocality and size as critical features in determining risk.

Although the AUA/SUO and EAU guidelines appear similar in risk stratifying NMIBC, there are differences with treatment implications. First, the EAU intermediate risk group is a definition of exclusion. The AUA and

Table 1 2016 guideline risk stratification

	2016 AUA/SUO guidelines [5]	2016 EAU guidelines [4]
Low risk	LG solitary Ta, ≤ 3 cm	Primary, solitary Ta, LG/G1, < 3 cm, no CIS
	Papillary urothelial neoplasm of low malignant potential	
Intermediate risk	Recurrence within 1 year, low grade Ta	All tumors not defined in the two adjacent categories (between the category of low and high risk)
	Solitary low grade Ta, > 3 cm	
	Low grade Ta, multifocal	
	High grade Ta, ≤ 3 cm	
	Low grade T1	
High risk	High grade T1	T1 tumor
	Any recurrent, high grade Ta	HG/G3 tumor
	High grade Ta, > 3 cm (or multifocal)	CIS
	Any CIS	Multiple and recurrent and large (> 3 cm) Ta G1G2 tumors (all conditions must be present in the point)
	Any BCG failure in high grade case	
	Any variant histology	
	Any high grade prostatic urethral involvement	

International Bladder Cancer Group (IBCG) support the most simple and direct definition of intermediate risk bladder cancer: multiple or recurrent low grade Ta tumors [4, 5, 16]. The AUA/SUO guidelines suggest low-grade T1 lesions are intermediate risk, whereas EAU guidelines suggest any T1 lesion is high risk. Additionally, EAU guidelines require that multiple and recurrent and large Ta low-grade tumor features be present for high-risk categorization, whereas these tumors would fit into the intermediate risk AUA category. For intermediate risk tumors, maintenance BCG (after induction BCG) is recommended by EAU guidelines and considered optional by AUA guidelines [4, 5]. Both guidelines recommend repeat TURBT followed by induction and maintenance BCG for at least 1 year for high-risk disease.

The heterogeneity of intermediate risk NMIBC has been highlighted in recent literature and is an important point to consider for further clinical trial designs [20, 21]. The IBCG has emphasized the variety of cases that can be classified as intermediate risk disease and recommend qualifying these cases based on the number of risk factors present [e.g.: multiple tumors, tumor ≥ 3 cm, recurrence < 1 year, and frequent recurrences (> 1 per year)] [21]. Treatment algorithms emphasize preventing over treatment of favorable intermediate-risk tumors (e.g.: guideline based intermediate risk patients with zero aforementioned risk factors) and tailoring more aggressive treatment for unfavorable intermediate-risk patients (e.g.: guideline based intermediate-risk patient with ≥ 3 aforementioned risk factors). These new directions in risk stratification have implications for choice and administration schedule of intravesical therapy.

Primary (BCG naïve) intravesical therapy

Postoperative intravesical therapy for low-risk NMIBC

The biologic rational for delivery of single postoperative dose of intravesical chemotherapy is based on the antitumor effects against tumor cells suspended in the bladder and residual tumor cells at the base of the resection bed following TURBT. Guideline recommendations support the use of a single postoperative intravesical dose of chemotherapy [e.g.: mitomycin C (MMC) or epirubicin] immediately after TURBT for patients with low-risk NMIBC [4, 5, 16].

A contemporary meta-analysis of randomized trials including 2278 patients reported a risk of recurrence reduction by 35% [hazard ratio (HR) 0.65; 95% confidence interval (CI) 0.58–0.77, $p < 0.001$] and absolute risk reduction of 14% at 5 years. Study patients received intravesical Thiotepa 30 mg/50 ml (one study from the 1980s), mitomycin C 40 mg/40 ml (4 studies), pirarubicin 30 mg/30 ml (one study) or epirubicin 100 mg/100 ml (5 studies) [22]. However, a postoperative instillation did not reduce the rate of recurrence in patients with prior recurrences, more than one recurrence per year, or patients with European Organization for Research and Treatment of Cancer (EORTC) recurrence score ≥ 5 [19]. Instillation did not prolong the time to progression or death from bladder cancer, suggesting that progression may be more related to inherent tumor biology. Overall estimates of recurrence for TURBT alone vs. TURBT + perioperative intravesical chemotherapy are 20 vs 10% at 12 months and 25 vs. 15% at 24 months, respectively [20].

Optimal timing of perioperative intravesical chemotherapy is within 24 h. Clinical trial data supports the importance of immediate instead of delayed delivery of intravesical chemotherapy after TURBT for low-risk NMIBC [23].

Despite clinical trial evidence and guideline recommendations, the use of intravesical chemotherapy after TURBT in the United States is limited [24]. The most recent clinical trial data from the US suggests that intravesical gemcitabine immediately following TURBT reduced the risk of recurrence in patients with low-risk NMIBC. This randomized trial of 406 patients reports a recurrence risk reduction of 47% for patients receiving intravesical gemcitabine (2 g/100 ml saline) vs. placebo (HR 0.53, 95% CI 0.35–0.81; $p = 0.001$) without differences in adverse events [14]. In the US, MMC is a common chemotherapeutic agent. However, given concerns of drug availability, adverse side effects such as cystitis, impairing healing characterized by long-standing fibrosis and dystrophic mucosal changes, as well as cost, use of MMC for intravesical perioperative instillation is limited among US urologists [24–27]. Intravesical gemcitabine is well tolerated, available, less expensive than MMC, and now has proven efficacy reducing the rate or recurrence for NMIBC [14]. Although a head to head comparison of intravesical gemcitabine to MMC does not exist, this therapy is a good option for urologists treating NMIBC.

Induction and maintenance intravesical therapy for intermediate-risk NMIBC

Adjuvant intravesical chemo or immunotherapy (BCG) is indicated for intermediate-risk disease and supported by EAU and AUA/SUO guidelines [4, 5, 16]. However, there are differences in clinical trial definitions of intermediate-risk that impact therapy selections and the guidelines do not agree on the recommendation of induction therapy alone or induction with maintenance therapy. In comparing the effectiveness of BCG vs MMC, numerous randomized control trials and meta-analyses have shown that induction BCG with maintenance is superior to either MCC or epirubicin with maintenance for intermediate-risk patients [28–30]. Malmstrom et al. conducted one of the most robust meta-analysis including 9 trials and 2820 individual patients data (74%

intermediate-risk) revealing a 32% reduction in recurrence risk for BCG vs. MMC maintenance therapy [29]. Furthermore, for intermediate- and high-risk patients, randomized trial data have demonstrated long-term superiority of intravesical BCG over epirubicin for disease free survival, distant metastasis, overall and disease-specific survival [30]. Randomized trial data support the use of full dose 1-year BCG maintenance therapy opposed to 1/3 dose BCG for intermediate-risk patients [31].

Induction and maintenance intravesical therapy for high-risk NMIBC

Guidelines are congruent for high-risk disease management [4, 5]; disease invasive into the lamina propria requires repeat TURBT and induction intravesical BCG followed by maintenance therapy for those who completely respond to induction. All experts recommend maintenance therapy; EAU guidelines recommend at least 1–3 years of maintenance therapy, and AUA recommends 3-years of maintenance BCG therapy. Best results are obtained by the Southwest Oncology Group (SWOG) 8507 dose schedule for a full 3 years of maintenance therapy [6, 32]. EORTC randomized trial data have confirmed that full dose, 3-year maintenance BCG reduces recurrences but not death or progression compared to 1-year maintenance therapy (HR 1.61; 95% CI 1.13–2.30) [31]. Meta-analysis data support the use of maintenance intravesical BCG compared to maintenance chemotherapy for improved recurrence-free survival (HR 0.41; 95% CI 0.3–0.56) [33].

Optimal BCG induction and maintenance schedule

The original 6-week intravesical BCG induction course remains effective today [11]. Alternative induction schedules do not seem to have an advantage and optimizing BCG administration has been emphasized in expert consensus statements [6]. The SWOG 8507 maintenance BCG regimen was designed based on the concept of repeat immunomodulation improving the magnitude and durability of response. The regimen is initiated 3 months after completion of 6-week, weekly induction BCG instillation. Patients receive cystoscopy and weekly BCG instillations for 3 weeks at 3, 6, 12, 18, 24, 30 and 36 months [32].

Other maintenance schedules such as monthly, quarterly and biannual schedules compared to induction BCG only have failed to demonstrate significant reduction in recurrence in several randomized control trials [34–37]. It is also important to note that 3-week BCG maintenance also reduces disease progression, metastasis and improved overall survival according to two randomized trials [30, 32]. Another consideration is the differential effectiveness of BCG strains. In a large retrospective study of over 2000 patients, Connaught BCG was more effective in prolonging time to recurrence than the TICE strain when maintenance therapy was not given. However, with maintenance therapy TICE was more effective than Connaught. Time to progression and overall survival was similar between the two strains [38].

In comparison to non-immunotherapy intravesical instillation (epirubicin), two studies have illustrated reduced rates of recurrence, metastasis and overall survival with maintenance BCG [30, 39]. Data comparing the utility of BCG vs BCG augmented with interferon-alpha are not robust enough to recommend this therapy for induction or maintenance [40]. Indeed intravesical BCG has withstood the test of time and remains the most effective and gold-standard therapy for NMIBC.

Definition of BCG failure

BCG failure is generally considered recurrence or progression during therapy [16]. However, accurately defining BCG failure is important to better specify the characteristics of failure. Clinical trial data comparing salvage therapies after BCG are quite heterogeneous, in part due to inconsistent definitions and reporting methods. Updated consensus-based definitions of BGC failure are outlined in Table 2 [20].

BCG failure categories include BCG refractory, BCG relapsing, BCG intolerant and BCG unresponsive. It is important to highlight two specific aspects of these classifications. First, the 6-month evaluation time point is to specifically identify patients who do not respond to induction and maintenance therapy at all (BCG refractory) compared to those who achieve a disease-free state after adequate BCG at 6-month but have recurrent high-grade disease within 6-month of last BCG treatment (BCG relapsing). Evidence suggests that 25–60% of BCG relapsing patients will response to a second round of BCG induction and this remains part of guideline recommendations [4, 5, 32, 33, 41]. However, outcomes are not as successful with BCG refractory patients [42]. The BCG unresponsive classification includes patients who fail two courses of BCG with persistent or recurrent disease within 6–12 months (i.e.: BCG refractory and BCG relapsing disease), and indicates the highest risk of additional treatment failure and disease progression [43–46].

Second, the implication of adequate BCG therapy shown in Table 2 is important. Recent clinical trial design has strictly defined adequate BCG therapy as patients who received at least five of six planned induction intravesical treatments and have received as least two of the three scheduled weekly instillations (per cycle) for maintenance therapy within a 6 month period. Standardized definitions of therapy

Table 2 BCG failure classifications. Adapted from Kamat et al. [20]

Classification	Description
BCG refractory	Persistent high-grade disease at 6 months after adequate induction and maintenance therapy[a] or any stage/grade progression by 3 months after the first BCG cycle. Example: recurrent high-grade disease at 3 months after initial Ta/T1 high-grade or CIS
BCG relapsing	Recurrent high-grade disease after achieving a disease-free state of ≥ 6 months after adequate[a] BCG induction and maintenance therapy Early relapse: < 12 months; Intermediate relapse: 12–4 month; late relapse: > 24 months
BCG unresponsive [53]	BCG refractory and BCG relapsing disease as described occurring within 6 months of last BCG exposure for patients on maintenance therapy. These patients are at highest risk for recurrence and progression
BCG intolerant	Disease persistence due to patient intolerance of adequate BCG[a]

[a]Adequate BCG induction is defined as when patients have received at least five of six planned induction intravesical treatments and at least two of three weekly instillations (one cycle) for maintenance therapy within a 6 month period

are important for maintain consistency in therapy and regulating clinical trial design [20].

Second-line, salvage or rescue intravesical therapy options

Conventional intravesical chemotherapy (mitomycin, valrubicin)

In patients who have failed intravesical BCG, conventional intravesical chemotherapy is of limited use. Subset analyses of a prior prospective comparison of intravesical BCG vs mitomycin studies have reported a 19% 3-year disease free survival in only 21 patients with mixed histology [47]. Overall, conventional intravesical chemotherapy after BCG failure is not recommended [6].

Valrubicin is the only FDA-approved intravesical mediation specifically for BCG-refractory CIS. Approval was given for a 21% complete response rate at 3 and 6 months following treatment, yet only 9% of patients remain disease free at 2 years, and it is not effective for patients with concomitant T1 disease [48]. Later investigation revealed a diminished response rate to 4% at 24 months [49]. As a result, this agent is rarely used, and not often recommend.

Single agent immunotherapy (BCG or INF)

A second course of BCG induction is certainly reasonable choice for patients with refractory or relapsing CIS or high-grade Ta disease. This remains part of international guideline recommendations [4, 5], and approximately 30–50% of patients with primary BCG failure (CIS or HG Ta) will respond to a second induction course of BCG [6, 41, 50, 51]. Response to additional courses of BCG beyond second induction are quite limited. BCG failure patients with progression to HG T1 disease should be considered for cystectomy.

Based on the immunomodulatory effects of BCG (T helper cell recruitment), additional cytokine recruitment therapy has been investigated. Intravesical interferon (INF)-α alone only provides a 12% 2-year disease free state for BCG-refractory CIS patients [52]. Therefore, much of the interest in this intravesical treatment turned towards combination therapy with BCG.

Chemohyperthermia

Hyperthermia used in combination with intravesical mitomycin (MMC) is referred to as chemohyperthermia. Enhanced MMC absorption is possible when the bladder is warmed to 42 °C, conventional MMC instillation [53]. The most common form of chemohyperthermia uses the Synergo system, in which local hyperthermia is administered via direct microwave irradiation of the urothelium by means of a 915-MHz intravesical microwave applicator [54]. The European Synergo working party reported their results of 51 patients with CIS who underwent weekly chemohyperthermia for 6–8 weeks followed by 4–6 treatments every 6–8 weeks. Complete response rate was 92% and remained 50% at 2 years [13]. Further study revealed a disease-free survival of 85% and 56% after 1 year and 2 year, respectively. Lack of a maintenance regimen led to an increased recurrence rate at 2 year (61% vs 39%), and the overall progression rate was 3% [55].

In a Phase I/II study, Soria et al. reported their experience with the Unithermia® system. At a median follow-up of 41 months, recurrence and progressions rates were 35.3% and 23.5%, respectively, with only low toxicity reported [56]. In a recent systematic review, a 59% relative reduction by chemohyperthermia was observed when compared to MMC alone, and the overall bladder preservation rate was an impressive 87.6% [57]. A phase III trial (HYMN; NCT01094964) is currently underway with the aim to compare hyperthermia plus MMC versus a second course of BCG. Although chemohyperthermia has shown promising

results, its role as second-line therapy for patients with recurrent NMIBC following BCG is incompletely defined and has access limitations in the U.S.

Combination immunotherapy (BCG + INF and IL2)

The combination of BCG + INF was initially reported as having a robust response for primary intravesical therapy. Unfortunately, the overall and long term response for BCG-refractory patients was not durable. Although 45% of patients having prior BCG exposure remained disease free at 2 years, by todays standard definitions, 34% of BCG refractory patients failed within 6 months [58]. Disease characteristic such as T stage, tumor size (> 5 cm), prior BCG therapy and multifocality were significantly associated with recurrence [58]. Although long-term studies did show some favorable results for BCG-failure patients receiving BCG + INF intravesical therapy [59], the only randomized trial comparing BCG to BCG + INF in BCG naïve patients failed to demonstrate superiority of the combination therapy [60]. The absence of superiority in BCG naïve patients and variable data reported on BCG + INF therapy for BCG failure patients has limited widespread use of this therapy for BCG failure patients.

Interlukin-2 (IL-2) is a known promoter of T helper cells and interferon release. The combination of BCG + IL-2 intravesical instillation has been investigated in animal models and show reasonable tumor response and increased urine and serum level of INF [61, 62]. However, clinical investigational data supporting this treatment are unavailable currently.

Alternative single agent chemotherapy (gemcitabine, docetaxel)

Prior randomized studies of BCG failure NMIBC patients have compared efficacy and toxicity of intravesical gemcitabine vs mitomycin and a second cycle of BCG [63, 64]. At 36-month following a 6-week course of gemcitabine, 72% of patients were recurrence free and reported less chemical cystitis compared to 61% of patients having received second line mitomycin [63]. Similarly, in a phase II study comparing gemcitabine to a second cycle of BCG, 52% of gemcitabine treated patient had disease recurrence versus 88% of patients treated with a second course of BCG [64]. It must be remembered that these patients were not BCG unresponsive as we understand the term today. For patients having failed two prior cycles of BCG instillations, a phase II SWOG study showed less robust results with a 24-month disease free survival rate of 21% and disease progression/cystectomy rate of 36%, again intravesical instillation was well tolerated [65].

Intravesical docetaxel has also shown good activity in BCG-failure NMIBC. In a small phase I trial of 18 patients with BCG failure a 6 week course of intravesical docetaxel using dose-escalation without maintenance therapy revealed a complete response of 56% and 4 year durable response of 22% [66]. An extension of this study was later published and included an additional 36 patients and monthly maintenance for 1 year.1 and 3 years recurrence free survival was 40 and 25%, respectively. Furthermore, 69% of patients avoided cystectomy at 2-year [67].

Combination chemotherapies (gemcitabine + mitomycin and gemcitabine + docetaxel)

Intravesical multi-agent chemotherapy in NMIBC is gaining popularity and proven efficacy, particularly in the BCG-failure category. The initial experience with combination of sequential MMC followed by gemcitabine in ten patients reported six patients without recurrence at a median of 14 months [68]. A multi-institutional review of 47 patients treated with sequential gemcitabine and MMC showed a 1 and 2-year RFS of 48 and 38%, respectively, and only 10 patients requiring cystectomy [69]. Another recent study of 27 patients who received a 6–8-week induction course of gemcitabine and MMC resulted in 10 patients (37%) with no evidence of disease at a median follow-up of 22 months [70].

Sequential gemcitabine and docetaxel is another avenue that has efficacy in BCG failure and unresponsive patients. A total of 45 patients (41 patients previously received BCG) were treated with a 6-week induction course of intravesical sequential gemcitabine and docetaxel followed by monthly maintenance therapy for 2 years. Response rates were 66% at 3 month surveillance, 54% at 1 year, and 34% at 2 years [71]. Additional investigators have found similar results for high-risk NMIBC patient including those with BCG-failure reporting a 1 and 2 year recurrence free survival rate of 56 and 42%, respectively [72]. In all, the evidence on intravesical gemcitabine and gemcitabine-based combinations appear to be potential alternatives for patients with NMIBC and prior BCG failure. Thus far, the optimal sequence of salvage intravesical therapies continues to evolve as more options become available.

Timeline and safety margin in treating BCG failure NMIBC

Important to any discussion of BCG-failure is highlighting the definitions of failure and the timing of initiation of salvage therapy compared to radical cystectomy. The stratification of failure shown in Table 2 should be used to guide one's approach to these patients. Patient with any definition of BCG-failure can be moved directly to cystectomy

depending on comorbidities, multifocality or extent of disease, disease timeline and willingness of the patient have surgery. However, many patients will advocate for salvage therapy.

Patients meeting criteria for BCG refractory or BCG relapsing (i.e.: not BCG unresponsive), repeat immunotherapy with BCG induction or clinical trial enrollment is an option. Patients with repeated failure thereafter, should strongly consider cystectomy or possibly consider alternative intravesical chemotherapy options. For BCG unresponsive patients, the best option is radical cystectomy or enrollment in a clinical trial. If the patient refuses radical cystectomy, combination gemcitabine/docetaxel, gemcitabine/mitomycin can be used. It is important to recognize that continued BCG (with or without IFN) is often futile [73]. Overall, definitive comparative trials of optimal intravesical therapy for BCG-failure patients do not exist. Thus the decision must be based on cooperative shard decision making between provider and patient. A treatment diagram is shown in Fig. 1 [73].

Also important to making these clinical judgments is the timing of disease recurrence/progression and the appropriate safety margin before moving to radical cystectomy. Median time to progression for high-risk urothelial carcinoma is 24 months and untreated CIS has an annual progression rate of 5%, which is likely higher given that 30–40% of initial responders to intravesical therapy will fail. At 1 year, 8% of untreated high-risk NMBIC will progress and 1% will experience disease related mortality [74]. Prior reports on early (< 2 years since intravesical BCG) versus late cystectomy (> 2 years) for high-risk NMIBC reveal a disease free survival 92 vs. 56% and 18 vs. 41% progression at cystectomy,

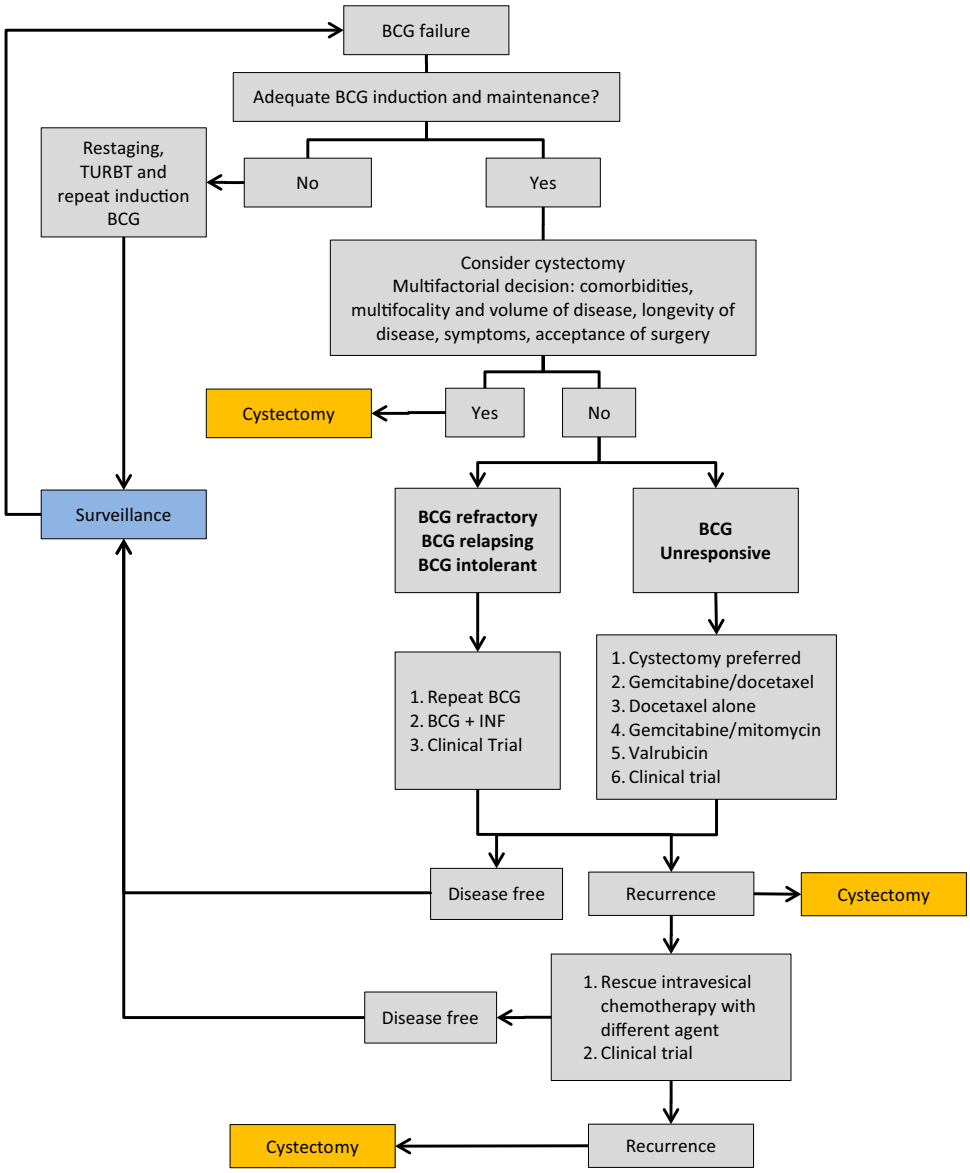

Fig. 1 NMIBC BCG failure treatment algorithm Adapted from Steinberg et al. [73]

Table 3 Novel and investigational agents

Drug	Trial ID	Institution/Sponsor	Phase	Route	Design	Status	Primary outcome
Checkpoint inhibitor trials							
Pembrolizumab	NCT02625961	Merck Sharp & Dohme Corp.	2	IV	Single arm BCG-unresponsive NMIBC not undergoing cystectomy	Recruiting	1. Complete response rate 2. Disease free survival
Atezolizumab	NCT02451423	Univ. of California, San Francisco	2	IV	Single arm Neoadjuvant therapy for BCG-refractory NMIBC or muscle invasive bladder cancer undergoing cystectomy and refusing/ineligible for neoadjuvant chemotherapy	Recruiting	1. Change in CD3 + count 2. Pathologic T0 rate
Atezolizumab	NCT02844816	National Cancer Institute	2	IV	Single arm BCG-unresponsive unfit or refusing cystectomy	Recruiting	1. Complete response rate in CIS patients 2. Event-free survival at 18 months
Durvalumab	NCT02901548	Moffitt Cancer Center	2	IV	Single arm Intravenous drug for CIS no longer responsive to BCG	Recruiting	1. Response rate at 6 months
Atezolizumab ± BCG	NCT02792192	Hoffmann-La Roche	1b/2	IV + IVes	Double arm Atezolizumab alone and Atezolizumab + BCG in BCG unresponsive NMIBC	Recruiting	1. Percentage of adverse events 2. Dose limiting toxicities and maximum tolerated dose 3. Complete response rate
Pembrolizumab + BCG	NCT02324582	Southern Illinois Univ.	1	IV + IVes	Single arm High-risk NMIBC patients will receive pembrolizumab = BCG	Recruiting	1. Safety—grade and quantity of adverse events
VPM1002BC	NCT02371447	Swiss Group for Clinical Cancer Research	1/2	IVes	Single arm Safety and efficacy of VPM1002BC (a genetically modified Mycobacterium bovis BCG) for NMIBC patients after standard BCG therapy	Active, not recruiting	1. Dose limiting toxicity 2. Recurrence-free rate in the bladder at 60 weeks
Vaccine, recombinant protein and gene therapy trials							
PANVAC ± BCG	NCT02015104	National Cancer Institute	2	SQ + IVes	Randomized BCG vs PANVAC + BCG for NMIBC patient with at least one prior BCG failure. PANVAC is a poxvirus-based vaccine known to induce immune response	Active, not recruiting	1. Improvement in disease-free survival

Table 3 (continued)

Drug	Trial ID	Institution/Sponsor	Phase	Route	Design	Status	Primary outcome
GC0070 oncolytic virus	NCT02365818	Cold Genesys, Inc.	3	IV	Single arm NMIBC BCG-failure patients who refused or are ineligible for cystectomy	Active, not recruiting	1. Durable complete response proportion (18 months) 2. Recurrence-free rate in the bladder at 60 weeks
ALT-803 + BCG	NCT02138734	Altor BioScience	1b/2	IVes + IVes	Randomized BCG + ALT-803 versus BCG alone in BCG naïve patients with high-grade NMIBC	Active, not recruiting	1. Number and severity of adverse events 2. Maximum tolerated dose 3. Time to recurrence 4. Recommended dose designation
ALT-803 + Gemcitabine	NCT01625260	Altor BioScience	1b/2	IV + IV	Single arm BCG-failure NMIBC patients who refuse or unfit for cystectomy	Active, not recruiting	1. Safety profile 2. Tolerability 3. Complete response rate
Instiladrin (rAd-INF/Syn3)	NCT02773849	FKD Therapies	3	IVes	Single arm BCG-unresponsive NMIBC patients with at least 2 prior courses of BCG	Active, not recruiting	1. Complete response in CIS patients with or without concomitant HG T1 or T1
Vivinium (VB4-845)	NCT02449239	Viventia Bio	3	IVes	Single arm BCG-failure NMIBC patients who refuse or unfit for cystectomy	Active, not recruiting	1. Complete response rate
Intravesical chemotherapy trials							
Cabazitaxel, Gemcitabine, Cisplatin	NCT02202772	Sanofi/Columbia	1	IVes	Single arm BCG-refractory NMIBC	Active, not recruiting	1. Adverse events
Nanoparticles							
ABI-009 (nab-rapamycin)	NCT02009332	Aadi, LLC	1/2	IV	Single arm BCG-refractory NMIBC	Recruiting	1. Safety and tolerability 2. Complete response rate
BCG regimen changes							
12-week course of induction BCG	NCT02281383	Memorial Sloan Kettering	2	IVes	Single arm High-risk NMIBC without prior BCG within 12 months	Recruiting	1. Disease progression

IV intravenous, *IVes* intravesical, *SQ* subcutaneous

respectively [75]. Although options exist for bladder preservation, futile intravesical therapy efforts in patient who are unlikely to respond may unnecessarily increase risk of disease mortality and/or progression.

Novel/investigational agents (Table 3)

The current landscape of NMIBC also includes several non-intravesical therapies as well. The successful use of immunotherapy in metastatic bladder cancer has led to interest in using checkpoint immunotherapy in BCG-unresponsive patients. High levels of PD-L1 tumor expression is associated with poorer survival outcomes and may be a biological plausible explanation for BCG resistance. Previous work has illustrated high-PDL1 expression in BCG-resistant tissue, suggesting PD-L1 expression may aid with tumor progression in BCG-resistant tumor lines by suppressing T cell response [76]. Several checkpoint inhibitor clinical trials are currently active, shown in Table 3.

Other emerging immunotherapeutic agents include oncolytic adenoviruses, vaccine therapy, recombinant fusion protein and gene therapy. Although precise mechanisms of actions are unique to each therapy, the concept of using an agent to enhance the natural immune-mediated killing of tumor cells remains similar. An interim analysis of a phase 2 study recently reported a 47% complete response rate at 6 months following intravesical instillation of an oncolytic adenovirus (GC0070) in BCG-unresponsive patients [77]. However, treatment durability is pending following longer-term studies. A recombinant poxvirus vaccine, known as PANVAC, induces a robust immune response. A current clinical trial is investigating the use of PANVAC in combination with BCG compared to BCG alone in BCG-unresponsive patients (NCT02015104).

Recombinant fusion protein

Recombinant fusion proteins have been developed to augment cytokine activity response that influences natural killer and T cells. Current ongoing trials in phase 1 are investigating the safety and dosage of recombinant fusion protein ALT-803 + BCG in high risk NMIBC (NCT02138734). Another phase 1 study is evaluating the combination of ALT-801 with intravesical gemcitabine in patients with BCG-unresponsive disease who cannot or will not tolerate radical cystectomy.

rAd-IFNalpha/Syn3 (Instiladrin)

rAd-INFalpha/Syn3 (Instiladrin) is another adenovirus vector has been tested as an intravesical delivery of gene therapy. Using the IFN alpha2b gene combined with recombinant adenovirus (rAd) provides a novel approach for delivering intravesical exposure to INF alpha-2b. Syn3 is a polyamide surfactant that is also incorporated into the drug formulation to increase the adenoviral transduction of the urothelium. The viral vector may provide a better response because it mimics physiologic response associated with a viral infection.

Phase 1 testing of Instiladrin is complete and phase 2 data has been recently published [15], demonstrating a 35% (14 of 40 patients) complete response at 12 months for BCG-refractory or relapsing patients. However, long-term durability was still limited with two patients experiencing recurrence at 21 and 28 months. However, the intravesical therapy was well tolerated and may be promising for patients unwilling or unfit for cystectomy. An ongoing registration trial completed enrollment in early 2018 and trial results are eagerly awaited.

Conclusion

For patients with NMIBC, a well performed TURBT is the mainstay of therapy. Peri-operative intravesical chemotherapy is the important for treatment of low-risk patients while immunotherapy remains the preferred intravesical therapy for high-risk patients. Intermediate risk patients should be risk stratified and personalized recommendations can be made. It is important to remember that effective BCG immunotherapy is highly dependent on patient selection and adequate administration of intravesical BCG with induction and maintenance therapy. BCG induction with a 6-week course followed by maintenance 3-week instillations as described by the SWOG protocol has proven reliability. In the events of recurrence after BCG, the details and timing of recurrence is critical to characterizing the type of BCG-failure which is important for determining the next course of action. For patients refusing or unfit for cystectomy and high-grade BCG-unresponsive disease, intravesical options include combination chemotherapy and clinical trials. Emerging clinical trial data are aimed at facilitating and enhancing the intravesical immune response with various delivery methods and combination intravesical chemotherapy with promising results.

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