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TOPIC PAPER

BCG-unresponsive high-grade non-muscle invasive bladder cancer: what does the practicing urologist need to know?

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Abstract

Purpose Bacille Calmette-Guérin (BCG) is a well-established treatment for preventing or delaying tumour recurrence following high-grade nonmuscle invasive bladder cancer (NMIBC) resection. However, many patients will experience recurrence or progression during or following BCG. This scenario has been one of the most challenging in urologic oncology for several decades since BCG implementation. Finally, significant progress has occurred lately. The aim of this review was to summarize for the practising urologist the current treatment options available in 2020 or expected to be ready for routine use in the near future for patients with high-risk NMIBC who experience BCG failure.

Methods Narrative review using data through the end of 2020.

Results First, the definition of BCG unresponsive disease which is critical in counseling and managing patients has finally reached a consensus. Second, some promising options other than radical cystectomy are finally available and many other should be in a near future. The options can be categorized as chemotherapy, device-assisted therapy, check-point inhibitors, new intravesical and systemic agents and sequential combinations of these newer modalities with conventional therapy.

Conclusions Considering the options that are currently under scrutiny, many of which in phase III trials, clinicians should have at their disposal several new treatment options in the next five years.

Keywords NMIBC · BCG · BCG failure

Introduction

Bacille Calmette–Guérin (BCG) remains commonly used in non-muscle invasive bladder cancer (NMIBC) with intermediate and high-risk papillary tumors and those with carcinoma in situ (CIS) following a number of studies showing its efficacy [1]. The recent worldwide shortage of BCG confirmed that it had no comparable alternative yet. Other agents have been used, but until now none has surpassed the effectiveness of BCG which has been consistently confirmed in the literature [2] with heterogeneous outcomes however. The conflicting results can be explained by different patient characteristics, duration of follow-up, methodology, statistical power and definitions of BCG failure. To improve this issue, the FDA has issued a document based on expert consensus guidelines that defines BCG-unresponsive disease and indicated that single-arm clinical trials for CIS-containing BCG-unresponsive NMIBC with CRR and duration of response (DoR) as the primary endpoints would be accepted to support a marketing application. BCG-unresponsive patients with only resected papillary disease should be tested using a randomized controlled trial design [3].

For optimal efficacy, long-term maintenance therapy following the induction phase is recommended following several metaanalysis [1]. Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high-risk NMIBC [4]. A recent systematic review of the therapeutic efficacy of bladder-preserving treatments for NMIBC following intravesical BCG has been published by Li and coworkers, covering all the available information until 2019 [5]. The aim of this narrative review was to summarize for the practicing urologist the options that are already available end of 2020 or expected to be ready for routine use in the near future.

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What is the risk of progression following recurrence in patients treated with BCG?

Although this risk is unanimously viewed as significant [4, 6, 7], it is difficult to determine. Previous studies have noted erratic rates of stage progression after BCG therapy failure and tend to lump together all patients owing to the lack of a standard classification system for BCG failure until recently [3]. In a study by Shirakawa et al. [8] patients with BCG failure were divided into four groups, which were based mainly on the responsiveness to BCG therapy and duration until tumor recurrence: BCG-refractory (presence of the disease at 6-month follow-up after BCG therapy, or any progression in stage, grade, or disease extent at 3-month follow-up), BCG-resistant (disappearance of disease at 6-month follow-up despite presence of disease that was of a lesser degree, stage, or grade 3 months after induction BCG therapy), BCG-relapsing (recurrence after disease-free status at 6-month follow-up), and BCG-intolerant (recurrence after administering inadequate BCG therapy because of BCG toxicity). Patients in the BCG-refractory group had a higher risk for subsequent stage progression and disease-specific death over a long duration compared with patients in the other BCG failure groups.

When should we consider that BCG is not working?

Approximately, one-third of the NMIBC patients will not respond to BCG. Among those who demonstrate an initial response, more than 50% will experience recurrence or progression during long-term follow-up. [9]. Several categories of BCG failures, mostly defined as any disease occurrence following adequate therapy (at least 5 instillations for the induction cycle and at least 2 for each maintenance cycle) with the exception of BCG intolerance, have been defined in the European Association of Urology Guidelines [7]:

- BCG intolerance: severe side effects that prevent further BCG instillation
- Muscle invasive bladder cancer (MIBC) detection during follow-up
- BCG-refractory tumor i.e., one of the following situations:
    - HG tumor appears during BCG maintenance therapy
    - T1 high grade (HG) is present at 3 months
    - Ta HG is present at 3 months and/or at 6 months, after either re-induction or first course of maintenance
    - Pure CIS is present at 3 months and persists at 6 months after either re-induction or first course of maintenance.
- BCG-relapsing tumor: recurrence of HG tumor after maintenance.
- BCG-unresponsive tumor: comprises BCG-refractory and early BCG-relapsing tumor, i.e., within 6 months for HG papillary tumors and within 12 months for CIS.

This last category is the largest among patients with NMIBC in whom further BCG therapy is not recommended. It constitutes a challenge for the practicing urologist. The optimal management of these patients is still controversial [5, 10].

Cystectomy remains the standard option for patients with BCG-unresponsive NMIBC following adequate BCG treatment

No established and effective intravesical therapies are available for patients whose tumors recur after BCG, representing a clinically important unmet need. Radical cystectomy (RC) provides cancer eradication in a significant number of HG NMIBC cases [11]. In the series of Stein and coworkers [12], the 10-year recurrence-free survival for patients with lymph node-negative tumors was 86% for T0, 89% for Tis, 74% for Ta, and 78% for T1 tumors. Several studies since have shown the advantage of performing early cystectomy in high-risk NMIBC patients, particularly in the case of BCG failure. It remains the standard of care in the case of BCG-unresponsive patients following adequate BCG treatment [6, 7].

However many patients are elderly, have significant comorbidities with a diminished performance status, and/or are unwilling to undergo radical extirpative surgery.

What are the non-extirpative treatment options?

Changing from BCG to the following options can yield responses in selected cases with BCG-unresponsive disease. In the EAU Guidelines [7], it is stated that treatments other than RC must be considered oncologically inferior in this setting (LE: 3).

Further BCG therapy or related agents Patients with BCG-unresponsive NMIBC are unlikely to respond to

further BCG therapy. However, there are still lines of research using modified protocols:

– *BCG plus interferon-alpha* The US national Phase II multicenter trial for BCG plus interferon-alpha (IFN-alpha) intravesical therapy for NMIBC showed that those with disease recurrence more than 1 year after BCG treatment had response rates similar to those of BCG naive patients [13]. The contribution of IFN-alpha in the outcomes is unknown as there were no BCG-only arm. The same conclusions were drawn in a study focusing on CIS-only patients [14]. However, BCG plus IFN-alpha in general did not demonstrate a significant benefit versus BCG alone in the long term. A systematic Cochrane review evaluated intravesical BCG versus intravesical BCG with IFN-alpha for treating NMIBC [15]. They found low-quality evidence suggesting:

  - No clear differences in recurrence or progression with BCG plus IFN-α
  - Increased time-to-recurrence when BCG is alternated with IFN-α.

  Additional high-quality, adequately powered well-conducted trials are needed to provide a more solid conclusion.

– *MCNA (Mycobacterium phlei cell wall-nucleic acid complex)* In 2015, Morales and coworkers published the results of a study evaluating the efficacy and safety of intravesical MCNA after failed treatment with BCG [16]. They found that this agent achieved significant activity, especially in patients with papillary only tumors and those with BCG relapse. A durable response was seen, in patients with a response at 1 year. MCNA was well tolerated and few adverse events led to treatment discontinuation. The same group published in 2017 [17] a re-analysis of the oncologic outcomes according to the new definition of BCG-unresponsive NMIBC. They concluded that MCNA had the potential to render 26.5% of patients with CIS and 61.2% of patients with papillary tumors disease-free for at least 1 year with an intact bladder. However, this agent was denied FDA approval in 2016 as long as the results were not confirmed by a phase 3 trial.

Cytotoxic intravesical chemotherapy Intravesical chemotherapy after BCG failure has been attempted with several agents, either alone or in combination with each other or with BCG. Although FDA-approved, intravesical thiotepa is not used anymore due to its lack of efficacy [18].

– *Gemcitabine* A Cochrane systematic review in 2012 aimed to evaluate the effectiveness and toxicity of intravesical gemcitabine in preventing tumor recurrence and progression in NMIBC [19]. Compared to intravesical BCG therapy, gemcitabine had similar effects in intermediate risk patients, was less effective in high-risk patient and superior in BCG-refractory patients. However, each randomized trial identified represents a different clinical setting in NMIBC and therefore the evidence base is limited. Di Lorenzo and coworkers published in 2010 the results of a randomized phase 2 trial that had enrolled 80 patients and compared gemcitabine versus BCG after initial BCG failure in NMIBC [20]. They found that 52.5% of the patients treated with gemcitabine developed disease recurrence versus 87.5% of those treated with BCG ($p=0.002$). There was no significant difference in mean time to the first recurrence. They concluded that gemcitabine might represent a second-line treatment option after BCG failure in HR NMIBC patients. The results of this study confirmed those of a previous smaller phase II trial (30 eligible patients) from Dalbagni and coworkers [21]. However as durable responses were uncommon in these studies, the SWOG cooperative group performed a prospective non-comparative study to evaluate the potential role of gemcitabine induction plus maintenance therapy in patients with NMIBC who have experienced recurrence after BCG. Again this small study (47 evaluable patients of whom 89% had high-risk disease) confirmed good results at 3 months with 47% of the patients free of disease but the figures dropped at 1 and 2 years at 28% and 21% respectively although patients had maintenance therapy [22].
– *Docetaxel* In 2009, the results of a retrospective single-institution experience, evaluating the use of intravesical Docetaxel for the treatment of NMIBC refractory to BCG in 33 patients, was published [23]. Docetaxel was well tolerated. With a median follow-up of 29 months, 1- and 2-year recurrence-free survival rates were and 45 and 32%, respectively. The authors concluded that Docetaxel was a promising agent for the management of BCG-refractory NMIBC. The same group reported long-term survival outcomes in 2013 [24]. Median follow-up was 39.1 months. Of the 54 patients, 32 (59%) had a complete initial response after induction therapy, including 18 who received additional monthly maintenance treatments. Median time-to-recurrence in

initial responders treated with or without docetaxel maintenance was 39.3 vs 19.0 months. One and 3-year recurrence-free survival rates for the entire cohort were 40% and 25%, respectively. The authors concluded that intravesical docetaxel appeared to be a promising agent with significant efficacy and durability for BCG-refractory NMIBC and that adding maintenance treatment may increase the duration of recurrence-free survival. However, no other paper was published since then and it seems that the focus has shifted to a combination of Gemcitabine and Docetaxel.

– *Sequential gemcitabine and docetaxel* Intravesical gemcitabine and docetaxel therapy seems to be a promising option. A recent retrospective multi-institution evaluation has concluded that it is well tolerated and effective, providing a durable response in patients with recurrent NMIBC after BCG therapy [25]. The 2-year recurrence-free survival rate was 46%, and high-grade recurrence-free survival rate was 52%. Ten patients (3.6%) had disease progression on transurethral resection. Forty-three patients (15.6%) went on to cystectomy of whom 11 (4.0%) had progression to muscle invasion. These outcomes confirmed those of previous retrospective studies [26, 27]. However, further evaluations are still needed as no prospective study has been performed yet.
– *Device-assisted instillations of mitomycin C (MMC)* Standard MMC does not seem an appropriate treatment option following BCG failures as BCG has been shown to be superior to MMC in intermediate and high-risk NMIBC [28] and gemcitabine was shown to be superior to MMC in a head-to-head RCT for BCG failure [29]. Methods to enhance its efficacy were devised in the hope of obtaining a valid alternative to BCG.

  • *Thermo-chemotherapy* Hyperthermia is known to potentiate the effect of various chemotherapeutic agents and this strategy of chemohyperthermia has been used for intravesical chemotherapy. Two different concepts have been described and are currently used. The most extensively studied uses RITE which stands for radiofrequency-induced thermo-chemotherapy (Synergo® system), which uses an intravesical microwave applicator located in the catheter to heat the bladder wall. The treatment aims to achieve a bladder wall temperature > 41 °C while circulating a solution of MMC. An RCT of BCG-naïve NMIBC reported a significantly higher 24-mo recurrence-free survival (RFS) in RITE-treated patients than in those treated with BCG in per-protocol analysis [30]. The only phase III RCT (HYMN trial) comparing RITE with control in patients with recurrence of NMIBC following failure of induction/maintenance BCG was published recently [31]. A total of 104 patients were randomized (48 RITE vs 56 control). Median follow-up for the 31 patients without a DFS event was 36 mo. There was no significant difference in DFS between treatment arms or in 3-month CR rate in CIS patients. DFS was significantly lower in RITE than in control in CIS with/without papillary patients. The authors concluded that RITE may be a second-line therapy for non-CIS recurrence following BCG failure; however, confirmatory trials were needed. No difference in adverse events between each treatment modality was observed (one or more adverse events occurred in 42 RITE patients vs 42 control patients). Most adverse events were grade 1–2. No difference in HRQoL was observed between the two treatment arms.

    Another technique based on the recirculation of heated chemotherapy called HIVEC (for Hyperthermic Intra-VEsical Chemotherapy) is also an interesting path under scrutiny. Independent retrospective studies have already shown a significant activity in BCG-unresponsive NMIBC patients [32, 33]. These data should, however, be confirmed by prospective studies that are not yet available end of 2020.
  • *ElectroMotive drug administration (EMDA)* EMDA® uses a 15–20 mA electrical current applied for 20–30 min via an anterior abdominal wall pad to induce a directional and accelerated movement of the ionized MMC toward the tissue (iontophoresis). The efficacy of EMDA was reported in 2003 by di Stasi and coworkers [34]. Patients with multifocal Tis with or without T1 tumors were randomized into three equal groups of 36 each who underwent electromotive MMC instillation, passive MMC or BCG. EMDA provided a superior response rate compared with passive MMC and matched those induced by BCG. Side effects were significantly more prominent in the BCG arm. There were no statistical differences between the 2 MMC arms, although there was a trend toward increasing numbers and side effect severity in the electromotive MMC group. The same group has published since the results of additional trials confirming the efficacy and acceptable toxicity of EMDA. However, its specific role in the BCG-unresponsive setting needs to be elucidated. Racioppi and coworkers published in 2018

the results of a prospective, single-center, single-arm phase II study evaluating a first-line salvage treatment with EMDA®-MMC in 26 patients with high-grade NMIBC "unresponsive" to BCG [35]. At the end of a 3-year follow-up, disease-free rates of patients with TaG3, T1G3, Cis and TaT1G3 + Cis were 75, 71.4, 50 and 25%, respectively. These interesting results warrant obviously further comparative studies.

– Other intravesical chemotherapy agents

- *Paclitaxel* Long-term follow-up results of a phase II trial of salvage intravesical nanoparticle albumin-bound (nab)-paclitaxel for patients with recurrent NMIBC after previous intravesical BCG therapy were published in 2017 [36]. With a median follow-up of 41 months, 18% of this cohort treated with nab-paclitaxel was disease free. Cystectomy-free survival was 61% and bladder cancer-specific mortality was 9%. The authors concluded that nab-paclitaxel was a reasonable treatment option in this high-risk population. However, routine use of this agent awaits an independent validation.
- *Valrubicin* Dinney and coworkers published in 2013 the results of 2 trials evaluating intravesical valrubicin in patients with bladder CIS and contraindication to or failure BCG [37]. Both studies demonstrated a consistent degree of efficacy even in highly pretreated patients. Intravesical valrubicin (Valstar) is currently the only FDA-approved agent for this particular indication although it provided inadequate cancer control, demonstrating a 12-month CRR of only 13%. Since 2013, no other study evaluating the efficacy of intravesical valrubicin in NMIBC was published.

Immunotherapy (checkpoint inhibitors) Immune checkpoint blockade is rapidly gaining interest in many solid tumors, including bladder cancer. Inhibitors of programmed cell death protein (PD1) and PD1 ligand (PD-L1) represent a major breakthrough in the treatment of patients with metastatic bladder cancer. These agents interrupt a negative regulatory signal that suppresses tumor cell kill by activated T cells, thereby triggering an antitumour response. High mutational load makes NMIBC an ideal target for immunotherapy although they have been reported to express lower levels of PD1 than MIBC but BCG infection can induce PD-L1 expression in regulatory T cells [38]. Furthermore, PD-L1 is enhanced on tumor tissue after BCG treatment in BCG-resistant patients, making combination or sequential CKI therapy a promising option [39]. However, efficacy of checkpoint inhibitors in HG NMIBC that have failed BCG is yet unclear. In the KEYNOTE-057 study, NMIBC patients who failed BCG received pembrolizumab every 3 weeks. The results of the study showed that almost 40% of patients with pembrolizumab had a complete tumor response. In addition, no patients progressed from T2 disease in the group treated with pembrolizumab, and only 8.7% of patients had stage progression. These results have led to an FDA approval in January 2020. A systematic review of publications related to immunotherapy for the treatment of patients with NMIBC who have recurrent or progressive disease despite receiving intravesical BCG therapy was published in December 2019 [40]. This review confirmed that there was a clear biological and clinical rationale for the continued evaluation of immune-based therapies in the setting of BCG-unresponsive NMIBC. Yet, most of the results are from early phase trials and although they support additional studies to assess the benefits of immune checkpoint inhibitors and other immunotherapy-based regimens, they cannot justify yet their use in clinical routine. However, this is expected to change in the near future.

– *Intravesical immunotherapy* Nearly, all the ongoing studies use systemic immunotherapy. Intravesical immune therapy is currently poorly assessed. Intravesical administration of anti-PD-1 was shown to have comparable anti-tumor activity to that of systemic anti-PD-1 in a mouse model [41]. Currently, at least two small single-group assignment studies are recruiting patients to evaluate the tolerance and efficacy of intravesical administration of Pembrolizumab (NCT 02808143) and Durvalumab (NCT03759496) in patients with high-grade NMIBC possibly BCG-refractory (Table 1).
– Systemic immunotherapy

  Pembrolizumab was investigated in KEYNOTE-057 (NCT NCT02625961), a multicenter, single-arm trial that enrolled 148 patients with high-risk NMIBC, 96 of whom had BCG-unresponsive CIS with or without papillary tumors. Patients received pembrolizumab 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression. The CR rate in the 96 patients with high-risk BCG-unresponsive NMIBC with CIS was 41% (95% CI: 31, 51) and median response duration was 16.2 months (0.0+, 30.4+). Forty-six percent (46%) of responding patients experienced a complete response lasting at least 12 months [42].

Several phase 2 trials are ongoing [43] assessing various agents in BCG-unresponsive patients (Table 1):

Table 1 Ongoing trials evaluating checkpoint inhibitors in patients with high-grade non-muscle invasive bladder cancer (HG NMIBC) who have failed BCG therapy [43]

Trial no	Study title	Primary outcomes	Status
NCT 02,808,143	(Intravesical) Pembrolizumab and BCG solution in treating patients with recurrent NMIBC	To determine the maximum tolerated dose of pembrolizumab when administered intravesically in combination with BCG in patients with HR or BCG-refractory NMIBC	Active, not recruiting
NCT 03,759,496	Intravesical Administration of Durvalumab (MEDI4736) to patients with HR NMIBC. A phase II study with correlative	–Maximum tolerated dose of Durvalumab given intravesically to patients with BCG-refractory NMIBC –Possibility of a rate of high-grade relapse free after the initiation of durvalumab –Efficacy of intravesical administration of Durvalumab in patients with BCG-refractory NMIBC	Recruiting
NCT 02,844,816	Atezolizumab in treating patients with recurrent BCG-unresponsive NMIBC	Estimate complete response at 25 weeks after registration for those with a CIS component and to evaluate event-free survival at 18 months in patients with BCG-unresponsive HR NMIBC treated with atezolizumab	Active, not recruiting
NCT 03,317,158	ADAPT-BLADDER: modern immunotherapy in BCG-relapsing urothelial carcinoma of the bladder	–Phase 1: determine the recommended phase 2 dose from BCG-unresponsive NMIBC patients treated with durvalumab plus BCG, durvalumab plus radiation –Phase 2: determine the 6-month relapse-free survival rates of BCG-relapsing or persistent NMIBC subjects treated with durvalumab plus BCG, durvalumab plus radiation, BCG monotherapy	Recruiting
NCT 03,519,256	A study of nivolumab or nivolumab plus experimental medication BMS-986205 with or without BCG in BCG unresponsive NMIBC (CheckMate 9UT)	In patients with pathologically demonstrated BCG-unresponsive CIS with or without papillary component -HR NMIBC, proportion of CIS participants with complete response (CR), per Pathology Review Committee (PRC) –Duration of complete response, per PRC, in CIS participants with CR	Recruiting
NCT 04,149,574	A phase 3, randomized, double-blind trial of nivolumab in combination with intravesical BCG versus standard of care BCG alone in participants with HR NMIBC that is persistent or recurrent after treatment with BCG (CheckMate 7G8)	Event-free survival [time frame: approximately 3 years]	Recruiting

- Atezolizumab: SWOG S1605, (NCT02844816)
- Durvalumab Adapt-Bladder, (NCT03317158)
- Nivolumab +—BMS-986205 (NCT03519256) and CheckMate 7G8 (NCT 04,149,574)

Other targeted therapies

– *Vicinium (Oportuzumab Monatox, VB4-845)* Vicinium is a fusion protein consisting of an Epithelial Cell Adhesion Molecule (EpCAM)-specific antibody fragment fused to Pseudomonas Exotoxin A, a potent inhibitor of protein synthesis. In Phase 1 and 2 studies, intravesical Vicinium demonstrated good safety profile and meaningful clinical activity in BCG-unresponsive high-grade NMIBC [44]. Since then, the single-arm multicenter registrational phase III VISTA trial (NCT02449239) has been completed. This trial accrued BCG-unresponsive NMIBC patients defined as refractory or relapsing within 6 months ($n=126$) and relapsing within 6–11 months (n = 7) after adequate BCG therapy. During induction, Vicinium was instilled for 2 h twice weekly for 6 weeks, then weekly for 6 weeks. Disease-free patients at 3 months received maintenance every 2 weeks for up to 2 years. Response was defined as negative cytology along with normal cystoscopy or absence of high-grade disease on biopsy. Outcomes have been communicated at the 2020 AUA congress [45]. As of May 29th, 2019, the CR rate of the evaluable CIS patients ($n=89$) at 3 months was 40%. Of the 3-month CIS responders, 52% remained disease-free for 12 months. The recurrence-free rates of the evaluable papillary patients (n = 38) at 3, 12 and 24 months were 71, 50 and 37%, respectively. Overall, the rate of RC was 10% (6 of 63) for the 3-month responders. Vicinium was well tolerated with 52% of patients experiencing treatment-related AEs, the majority being grade 1–2. The authors concluded that Vicinium was well tolerated, demonstrated clinically meaningful anti-tumor activity and may delay and/or prevent RC. Fine analysis of the results requires, however, the paper publication. Of interest, a phase I single-arm study of the combination of Durvalumab (MEDI4736) and Vicinium in subjects with high-grade NMIBC previously treated with BCG is currently recruiting (NCT03258593).

– *Adstiladrin® (Nadofaragene firadenovec (rAd-IFNα2b/Syn3))*

Adstiladrin® (Nadofaragene firadenovec (rAd-IFNα2b/Syn3)) Adstiladrin® is a non-replicating adenovirus vector harboring the human IFN alpha2b gene. When combined with the excipient Syn3, intravesical administration of the rAd-IFN results in transduction of the virus into the epithelial cell lining in the bladder. The IFN alpha2b gene is incorporated into the cellular DNA resulting in the synthesis and expression of large amounts of IFN alpha2b protein. Adstiladrin® is being developed for the treatment of high-risk NMIBC unresponsive to BCG. It was shown to be biologically active and inhibits IFNα-resistant bladder cancer cells in vitro and tumor growth in vivo. Adstiladrin® was well tolerated in Phase I studies [46]. A Phase II trial showed that the agent was effective and confirmed that it was well tolerated [47]. The latter trial was an open label, parallel arm US multicenter trial conducted from 2012 to 2015. Eligible patients ($n=40$) were randomized 1:1 to receive intravesical Adstiladrin® at two different dosages of viral particles. There were 14 patients (35%) that were high-grade recurrence free after 12 months. There were no grade 4 or 5 adverse events. The most common drug related adverse events were micturition urgency ($n=16$), dysuria ($n=16$), and fatigue ($n=13$). Following these promising results, a phase III single-arm multicenter registrational trial (NCT02773849) was completed. Nadofaragene was administered once every 3 months for up to four doses in the initial 12 months, with additional dosing at the investigator's discretion. As of August 10th, 2020 the results were not yet published but they were presented at the 2020 ASCO meeting [48]. A total of 157 pts (safety population, $n=157$; efficacy population, $n=151$) were enrolled. Among pts with CIS ($n=103$), 55 (53.4%) (95% CI 43.3–63.3) achieved CR by month 3 after treatment. Of these 55 CIS CR pts, 25 (45.5%) remained free of high-grade recurrence at month 12. For pts with HG Ta/T1 alone, 21 (43.8%) were free from recurrence at 12 months. Most AEs were transient: instillation site discharge 33.1%; fatigue 23.6%; bladder spasm 19.7%; micturition urgency 17.8%; hematuria 16.6%. There were 2 Gr4 AEs (sepsis and anaphylactic reaction, neither related to study drug).

– *CG0070* CG0070 is a replication-competent oncolytic adenovirus that targets bladder tumor cells through their defective retinoblastoma pathway. Preliminary reports of intravesical CG0070 have shown promising activity in patients with high-grade NMIBC who previously did not respond to BCG. The 18 month follow-up results of a phase II single-arm multicenter trial (NCT02365818) evaluating the safety and efficacy of CG0070 have been presented at the AUA meeting in 2019 [49]. This trial has accrued 67 patients with high-grade Ta, T1, or CIS ± Ta/T1 who were unable to achieve disease-free state at 6 months after adequate BCG (BCG-refractory) or developed recurrence after CR to BCG (BCG-relapsed). On

analysis of 57 evaluable patients, the overall 18-month CR rate was 23%. Among stage subsets, 18-month CR was 19% for pure CIS or CIS-containing tumors and 36% for pure papillary tumors. All treatment-related AEs were Grade 1–3. Eventually, in this high-risk BCG-unresponsive NMIBC population, intravesical CG0070 yielded overall 44% and 23% complete response rates at 6, and 18 months, respectively. Rb and checkpoint biomarker analysis are ongoing as they may predict which patients have durable response to this agent.

- Other agents under scrutiny

  Several other agents are potential candidates for high-risk NMIBC BCG-refractory/intolerant patients. We have cited below some promising agents but obviously the list is not exhaustive.

- *Erdafitinib* A randomized phase 2 study of Erdafitinib versus investigator choice of intravesical chemotherapy in high-risk NMIBC and FGFR mutations or fusions subjects who received BCG and recurred (NCT04172675) is currently recruiting.
- *Intravesical photodynamic therapy (PDT)* PDT is currently evaluated in a single-group assignment phase II study in BCG-refractory/intolerant NMIBC patients (NCT03945162). Study completion is estimated in May 2022 with an accrual target of 125 participants.
- Inodiftagene Vixteplasmid (BC-819) is a targeted gene therapy made up of recombinant DNA plasmid containing regulatory sequences from the H19 gene driving expression of diphtheria toxin A chain gene found only in malignant cells. A single-arm phase 2 Study (NCT03719300) in patients with NMIBC whose disease is unresponsive to BCG has been terminated in September 2020 due to COVID-19 Pandemic according to the ClinicalTrials.gov website [43].

- All in all, what are the options to consider end of 2020 for the management of HG NMIBC that have failed BCG therapy?

  Unfortunately, in routine practice little has changed since the collaborative review published in European Urology in 2012 [10]: cystectomy remains the option to consider and no non-extirpative management has yet proven a similar efficacy. However, since this review, substantial progress was made giving hope for an immediate or a near future change:

- BCG failure should follow the definition that is now standardized [3, 7] avoiding the misclassifications that were common previously, leading to inappropriate management.
- Until the end of 2020, the only FDA-approved treatments for BCG-unresponsive high-risk NMIBC were intravesical valrubicin (VALSTAR®) and pembrolizumab (KEYTRUDA®). However, this has brought little change in everyday practice as valrubicin efficacy has been questioned by many experts as the registration trial was not convincing and Pembrolizumab, although approved in 2020 by the FDA, remains a costly, difficult to access therapy with a role yet to be determined in Europe.

However, many agents are in the pipe-line, hopefully ready to be used soon in a routine setting. This includes in particular agents that have successfully completed a phase III study (Vicinium and Adstiladrin®) or a phase II study (CG0070). Results of ongoing studies evaluating other promising agents provide also hope although in the longer term. These include checkpoint inhibitors agents currently evaluated in the specific situation of HG NMIBC that have failed BCG (Table 1). Many of these studies are presently recruiting: participating in one of these trials represents an appropriate management option to discuss with our patients.

Conclusion

Until January 2021, the only FDA-approved treatments for BCG-unresponsive high-risk NMIBC were intravesical thiotepa, which is not used anymore due to its lack of efficacy, intravesical valrubicin, whose efficacy is questionable, and pembrolizumab not yet approved by the EMEA. Thus, in routine practice little has changed since the collaborative review published in European Urology in 2012 [10]. However, the definition of BCG-unresponsive disease, that is critical in managing patients, is better defined and has gained a near consensus. An effective alternative to radical cystectomy, that remains the optimal treatment option in this setting, remains an important unmet clinical need. Yet, considering the options that are currently under scrutiny, some of them having already completed phase III trials, one can reasonably expect that clinicians will have at their disposal new agents and treatment options in the next 2 years. As for today, clinical trials represent one of the most valid options if the patient is unwilling or unable to undergo a radical cystectomy.

Compliance with ethical standards

Conflicts of interest Jacques Irani: Investigator in study NCT03519256 (evaluating Nivolumab + —BMS-986205), Investigator in study NCT04172675 (evaluating Erdafitinib); Cédric Lebacle: Investigator in study NCT03519256 (evaluating Nivolumab + —BMS-986205), Investigator in study NCT04172675 (evaluating Erdafitinib); Yohann Loriot: Investigator in study NCT03519256 (evaluating Nivolumab + —BMS-986205), Investigator in study NCT04172675 (evaluating Erdafitinib).

References

1. Malmstrom PU et al (2009) An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus Bacillus Calmette–Guerin for non-muscle-invasive bladder cancer. Eur Urol 56:247
2. Chou R, Selph S, Buckley DI, Fu R, Griffin JC, Grusing S, Gore JL (2017) Intravesical therapy for the treatment of nonmuscle invasive bladder cancer: a systematic review and meta-analysis. J Urol 197(5):1189–1199
3. Administration UFD (2018) II. Development program. In: UDoHaH rie (eds) BCG-unresponsive nonmuscle invasive bladder cancer: developing drugs and biologics for treatment guidance for industry, Office of Communications, Division of Drug Information, Silver Spring, pp 1–10
4. Lerner SP et al (2009) Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high risk non-muscle invasive bladder cancer. Urol Oncol 27:155
5. Li R, Sundi D, Zhang J et al (2020) Systematic review of the therapeutic efficacy of bladder-preserving treatments for non-muscle-invasive bladder cancer following intravesical Bacillus Calmette–Guérin. Eur Urol 78:387–399
6. Kamat AM, Colombel M, Sundi D et al (2017) BCG-unresponsive non-muscle-invasive bladder cancer: recommendations from the IBCG. Nat Rev Urol 14:244–255
7. European Urology Guidelines. https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/. Accessed 15 Dec 2020
8. Shirakawa H, Kikuchi E, Tanaka N et al (2012) Prognostic significance of Bacillus Calmette–Guérin failure classification in non-muscle-invasive bladder cancer. BJU Int 110:E216–E221
9. Cookson MS, Herr HW, Zhang ZF et al (1997) The treated natural history of high risk superficial bladder cancer: 15-year outcome. J Urol 158:62–67
10. Yates DR, Brausi MA, Catto JW et al (2012) Treatment options available for Bacillus Calmette–Guérin failure in non–muscle-invasive bladder cancer. Eur Urol 62:1088–1096
11. Herr HW, Sogani PC (2001) Does early cystectomy improve the survival of patients with high-risk superficial bladder tumors? J Urol 166:1296–1299
12. Stein JP, Lieskovsky G, Cote R et al (2001) Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1054 patients. J Clin Oncol 19:666–675
13. Gallagher BL et al (2008) Impact of previous Bacille Calmette–Guerin failure pattern on subsequent response to Bacille Calmette–Guerin plus interferon intravesical therapy. Urology 71:297
14. Rosevear HM et al (2011) Factors affecting response to Bacillus Calmette–Guerin plus interferon for urothelial carcinoma in situ. J Urol 186:817
15. Shepherd AR, Shepherd E, Brook NR (2017) Intravesical BCG with IFN-alpha versus intravesical BCG for treating NMIBC. Cochrane Database Syst Rev 3:CD012112
16. Morales A, Herr H, Steinberg G, Given R, Cohen Z, Amrhein J, Kamat A (2015) Efficacy and safety of MCNA in patients with nonmuscle invasive bladder cancer at high risk for recurrence and progression after failed treatment with Bacillus Calmette–Guérin. J Urol 193(4):1135–1143
17 Li R, Amrhein J, Cohen Z, Champagne M, Kamat A (2017) Efficacy of mycobacterium phlei cell wall-nucleic acid complex (MCNA) in BCG-unresponsive patients. Bladder Cancer 3(1):65–71
18. Martínez-Piñeiro JA et al (1990) Bacillus Calmette–Guerin versus doxorubicin versus thiotepa: a randomized prospective study in 202 patients with superficial bladder cancer. J Urol 143:502–506
19 Jones G, Cleves A, Wilt TJ, Mason M, Kynaston HG, Shelley M (2012) Intravesical gemcitabine for non-muscle invasive bladder cancer. Cochrane Database Syst Rev 1:CD009294
20. Di Lorenzo G, Perdonà S, Damiano R, Faiella A, Cantiello F, Pignata S, Ascierto P, Simeone E, De Sio M, Autorino R (2010) Gemcitabine versus bacille Calmette–Guerin after initial Bacille Calmette–Guerin failure in non-muscle-invasive bladder cancer: a multicenter prospective randomized trial. Cancer 116:1893
21. Dalbagni G, Russo P, Bochner B, Ben-Pora L, Sheinfeld J, Sogani P, Donat MS, Herr HW, Bajorin D (2006) Phase II trial of intravesical gemcitabine in Bacille Calmette–Guerin-refractory transitional cell carcinoma of the bladder. J Clin Oncol 24:2729
22. Skinner EC, Goldman B, Sakr WA, Petrylak DP, Lenz H-J, Lee CT, Wilson SS, Benson M, Lerner SP, Tangen CM, Thompson IM (2013) SWOG S0353: phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical Bacillus Calmette–Guérin. J Urol 190(4):1200–1204
23. Barlow LJ, McKiernan JM, Benson MC (2009) The novel use of intravesical docetaxel for the treatment of non-muscle invasive bladder cancer refractory to BCG therapy: a single institution experience. World J Urol 27(3):331–335
24. Barlow LJ, McKiernan JM, Benson MC (2013) Long-term survival outcomes with intravesical docetaxel for recurrent nonmuscle invasive bladder cancer after previous Bacillus Calmette–Guérin Therapy. J Urol 189(3):834–839
25. Steinberg RL, Thomas LJ, Brooks N et al (2020) Multi-institution evaluation of sequential gemcitabine and docetaxel as rescue therapy for nonmuscle invasive bladder cancer. J Urol 203(5):902–909
26. Milbar N, Kates M, Meera R et al (2017) Oncological outcomes of sequential intravesical gemcitabine and docetaxel in patients with non-muscle invasive bladder cancer. Bladder Cancer 3(4):293–303
27. Daniels MJ, Barry E, Milbar N, Schoenberg M, Bivalacqua TJ, Sankin A, Kates M (2020) An evaluation of monthly maintenance therapy among patients receiving intravesical combination gemcitabine/docetaxel for nonmuscle-invasive bladder cancer. Urol Oncol 38(2):40.e17-40.e24
28. Bohle A, Jocham D, Bock PR (2003) Intravesical Bacillus Calmette–Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 169:90–95
29. Addeo R, Caraglia M, Bellini S et al (2010) Randomized phase III trial on gemcitabine versus mytomicin in recurrent superficial bladder cancer: evaluation of efficacy and tolerance. J Clin Oncol 28(4):543–548
30. Arends TJ, Nativ O, Maffezzini M et al (2016) Results of a randomized controlled trial comparing intravesical chemohyperthermia with mitomycin C versus Bacillus Calmette–Guérin for adjuvant treatment of patients with intermediate-and high-risk non–muscle invasive bladder cancer. Eur Urol 69:1046–1052

31. Tan WS, Panchal A, Buckley L et al (2019) Radiofrequency-induced thermo-chemotherapy effect versus a second course of Bacillus Calmette–Guérin or Institutional Standard in patients with recurrence of non-muscle-invasive bladder cancer following induction or maintenance Bacillus Calmette–Guérin Therapy (HYMN): a phase III, open-label randomised controlled trial. Eur Urol 75(1):63–71
32. de Jong J, Hendricksen K, Rosier M, Mostafid H, Boormans JL (2018) Hyperthermic intravesical chemotherapy for BCG unresponsive non-muscle invasive bladder cancer patients. Bladder Cancer 4(4):395–401
33. Marquette T, Walz J, Rybikowski S (2020) Safety of Hyperthermic IntraVEsical Chemotherapy (HIVEC) for BCG unresponsive non-muscle invasive bladder cancer patients. Prog Urol 30(1):35–40
34. Di Stasi SM, Giannantoni A, Stephen RL et al (2003) Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. J Urol 170:777–782
35. Racioppi M, Di Gianfrancesco L, Ragonese M et al (2018) ElectroMotive Drug Administration (EMDA) of mitomycin C as first-line salvage therapy in high risk "BCG Failure" non muscle invasive bladder cancer: 3 years follow-up outcomes. BMC Cancer 18(1):1224
36. Robins DJ, Sui W, Matulay JT et al (2017) Long-term survival outcomes with intravesical nanoparticle albumin-bound paclitaxel for recurrent non-muscle-invasive bladder cancer after previous Bacillus Calmette–Guérin therapy. Clin Trial Urol 103:149–153
37. Dinney CP, Greenberg RE, Steinberg GD (2013) Intravesical valrubicin in patients with bladder carcinoma in situ and contraindication to or failure after Bacillus Calmette–Guérin. Urol Oncol 31:1635–1642
38. Copland A, Sparrow A, Hart P, Diogo GR, Paul M, Azuma M, Reljic R (2019) Bacillus Calmette–Guérin induces PD-L1 expression on antigen-presenting cells via autocrine and paracrine interleukin-STAT3 circuits. Sci Rep 9:3655
39. Hashizume A, Umemoto S, Yokose T, Nakamura Y, Yoshihara M, Shoji K, Wada S, Miyagi Y, Kishida T, Sasada T (2018) Enhanced expression of PD-L1 in non-muscle-invasive bladder cancer after treatment with Bacillus Calmette–Guerin. Oncotarget 9(75):34066–34078
40. Meng MV, Gschwend JE, Shore N et al (2019) Emerging immunotherapy options for Bacillus Calmette–Guérin unresponsive nonmuscle invasive bladder cancer. J Urol 202(6):1111–1119
41. Rajkumar A, Wang J, Neuzil KE, Kirschner AN, Chang SS (2020) Intravesical anti-PD-1 immune checkpoint inhibition in urothelial bladder cancer in a mouse model. J Clin Oncol 38(6_suppl):537–537
42. Balar AV, Kamat AM, Kulkarni GS et al (2020) Pembrolizumab for the treatment of patients with Bacillus Calmette–Guérin (BCG) unresponsive, high-risk (HR) non–muscle-invasive bladder cancer (NMIBC): Over two years follow-up of KEYNOTE-057. J Clin Oncol 38(15):5041–5041. https://doi.org/10.1200/JCO.2020.38.15_suppl.5041
43. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/home. Accessed 30 Jan 2021
44. Kowalski M, Guindon J, Brazas L et al (2012) A phase II study of oportuzumab monatox: an immunotoxin therapy for patients with noninvasive urothelial carcinoma in situ previously treated with Bacillus Calmette–Guérin. J Urol 188(5):1712–1718
45. Shore N, Beach M, O'Donnell M et al (2020) Phase 3 results of Vicinium in BCG-unresponsive non-muscle invasive bladder cancer. J Urol 203(4S, Supplement):PD03-02 e72
46. Navai N, Benedict W, Zhang G et al (2016) Phase 1b trial to evaluate tissue response to a second dose of intravesical recombinant adenoviral interferon α2b formulated in Syn3 for BCG failures in non-muscle invasive bladder cancer. Ann Surg Oncol 23:4110–4114
47. Shore ND, Boorjian SA, Canter DJ et al (2017) Intravesical rAd–IFNa/Syn3 for patients with high-grade, Bacillus Calmette–Guerin—refractory or relapsed non–muscle-invasive bladder cancer: a phase II randomized study. J Clin Oncol 35:3410–3416
48 Boorjian SA, Dinney CPN (2020) Safety and efficacy of intravesical nadofaragene firadenovec for patients with high-grade, BCG unresponsive nonmuscle invasive bladder cancer (NMIBC): Results from a phase III trial. J Clin Oncol 38(6_suppl):442–442
49. Packiam VT, Barocas DA, Chamie K et al (2019) CG0070, an oncolytic adenovirus, for BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC): 18 month follow-up from a multicenter phase II trial. J Urol 201(Supplement 4):e617