Review Article: Oncology: Genitourinary Cancer

Therapeutic management of Bacillus Calmette–Guerin refractory patients: a narrative review

Judith Stangl-Kremser[1], Kilian M. Gust[1], Shahrokh F. Shariat[1,2,3,4,5,6]

[1]Department of Urology, Medical University of Vienna, Vienna, Austria; [2]Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria; [3]Department of Urology, Weill Cornell Medical College, New York, NY, USA; [4]Department of Urology, University of Texas Southwestern Medical Center, Dallas, Texas, USA; [5]Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia; [6]Department of Urology, Motol Hospital, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic

Contributions: (I) Conception and design: J Stangl-Kremser, SF Shariat; (II) Administrative support: J Stangl-Kremser; (III) Provision of study materials or patients: J Stangl-Kremser, KM Gust; (IV) Collection and assembly of data: J Stangl-Kremser; (V) Data analysis and interpretation: J Stangl-Kremser, KM Gust; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Shahrokh F. Shariat. Department of Urology and Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. Email: shahrokh.shariat@meduniwien.ac.at.

Abstract: High risk bladder cancer (BC) patients who fail Bacillus Calmette–Guerin (BCG) therapy suffer from a challenging disease due to its molecular and clinical heterogeneity. The course of the disease depends on the risk profile. Currently, radical cystectomy is the recommended standard of care for patients with non-muscle invasive BC who fail BCG failure. However, radical cystectomy carries significant morbidity with which some patients might even be overtreated. Therefore, effective alternative treatments are needed. Despite the facilitation of research and regulatory processes, the research in this patient population has not yet brought about a change in management. Indeed, there is no accepted effective and safe alternative, yet, to radical cystectomy for these patients. Numerous bladder-sparing strategies are currently investigated in patients experiencing BCG failure, including hyperthermia, gene-, targeted- and immunotherapy; one or more of these strategies could potentially change the standard therapeutic approach in the near future. In this review, novel treatments and currently available oncological data on these therapies are reported.

Keywords: Bacillus Calmette–Guerin (BCG); bladder-sparing; failure; non–muscle-invasive bladder cancer

Received: 09 December 2019; Accepted: 10 January 2020; Published: 25 March 2020.

doi: 10.21037/amj.2020.01.03

View this article at: http://dx.doi.org/10.21037/amj.2020.01.03

Background

Introduction

Bladder cancer (BC) is the 10th most common malignant disease worldwide (1). According to worldwide cancer statistics from the Global Cancer Observatory, there are approximately 550,000 incident cases per year and 200,000 deaths per year (1). The course of the disease varies as there are differences in the oncological natural histories depending from the aggressiveness of the cancer cells in conjunction with the host protoplasma. Hence, localized BC can be clinically divided into three disease entities: low grade non-muscle invasive BC (NMIBC), high grade NMIBC and BC invading the detrusor muscle and/or beyond (≥pT2) (2,3). Within the non-muscle invasive disease phenotype: NMIBC, papillary tumours embedded into the mucosa or invading the lamina propria are classified as stage Ta or T1, respectively (2,3). Even though flat, high-grade tumours, confined to the mucosa of the bladder wall, are classified as carcinoma in situ (CIS) (4). NMIBC accounts for 80% of all BCs in the developed countries and is mostly curable (2,3,5). In intermediate- and high-risk disease, the standard treatment of NMIBC is transurethral resection of the bladder (TURB) to remove the tumour cells, followed by adjuvant intravesical therapy. Bacillus Calmette–Guerin (BCG), initially isolated and

described as an antituberculosis vaccine, has demonstrated to have significant antitumor effects and is therefore considered as standard therapy (2,6,7) reducing recurrence and progression of disease (2,8-10) in these patients. Besides the EORTC risk scoring system, the Club Urológico Espanol de Tratamiento Oncológico (CUETO) scoring model can be used to predict the short- and long-term risk of recurrence and progression of NMIBC in BCG-treated patients (2,6,8,11,12).

Although having the same terminology, NMIBC is a heterogenous disease with varied oncological course (2,12). Some patients never suffer from disease recurrence, others have frequent recurrences and others again tend to experience disease progression to muscle invasive BC with a high demise rate (2,3,13). Therefore, postoperative urooncological follow-up care with regular cystoscopies and urinary cytologies is crucial in NMIBC patients (14). After being treated, approximately 75% of the patients with NMIBC experience tumour recurrence and up to 20% experience disease progression within a 5-year follow up period (2) Approximately half of patients with high risk NMIBC experience disease progression after having undergone adjuvant BCG treatment (2,6,15). Worse survival has been reported for patients with primary NMIBC developing disease progression compared to BC patients presenting with *de novo* muscle invasive BC (16,17).

Despite the fact that the BCG-mechanism is not completely understood, the intravesical instillation is thought to activate the innate immune system (18,19). The classic treatment protocol includes 6x contiguous instillations once a week, followed by maintenance therapy at 3, 6, 12, 18, 24, 26 and 30 months (2). Subsequent BCG instillations boost the innate immune response (20). In order to standardise treatment and to identify those who need adjunctive therapy, the European Association of Urology (EAU) Guidelines Panel recommends the use of a risk stratification (2). The risk group stratification for patients NMIBC is based on established prognostic factors and data from the European Organisation for Research and Treatment of Cancer (EORTC) risk tables of the Genito-Urinary Cancer Group (6,8) and is publicly accessible online at the EAU website (https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/) (21).

BCG failure and standard treatment

There are several categories defined for patients who did not have sustainable response to intravesical BCG. In the EAU Guidelines, the definition BCG failure includes the development of muscle invasive BC during follow-up, BCG refractory-, BCG relapsing- and BCG unresponsive tumours (2). In patients with BCG failure, there is evidence that patients with BCG relapsing tumour have better survival outcomes than BCG refractory patients (22). Recently, the term "BCG-unresponsive" was introduced into the nomenclature to define a subgroup of patients at higher risk of recurrence and progression of BC; thus, for whom further BCG is not indicated. For these patients, radical cystectomy (RC) is the standard option. However, patients could also be considered for being enrolled in single-arm prospective phase II studies (23).

In this review, we focus on the therapeutic management of BCG failure patients. To date, preemptive RC is recommended in patients failing BCG therapy (2). The aim of this review is to provide the current evidence regarding the therapeutic management of patients failing BCG and elucidate on treatment alternatives to RC as well on future perspectives. Important criteria, making bladder-sparing treatment strategies viable and serious alternatives to RC, have been reported (24).

Methods

To identify relevant published data, we used the PubMed/Medline search engine to conduct an online literature search using the terms '(Bacille-Calmette-Guerin OR Bacille Calmette Guerin OR BCG) AND (non-responder OR non response OR non-response OR non-responder OR refractory OR resistant OR unresponsive OR failure) AND (bladder cancer OR urothelial cancer OR urothelial bladder cancer) AND (management OR therapy OR treatment OR therapeutic)'. Only articles in English language were retrieved. The authors reviewed the extant articles with the intention to include the relevant data in this review. A manual search from authors' bibliographies were also used, when felt to be expedient. In order to identify ongoing trials of interest that not yet published, we accessed the clinicaltrials.gov online databank and provide the NCT number when appropriate. The search term 'non-muscle-invasive bladder cancer AND BCG refractory' was used. Studies retrieved were screened and included if the study patients were diagnosed with BCG failure.

Discussion

The challenges of the management of NMIBC needs to

be discussed with the patients to allow a shared decision-making process. The potential benefit of RC must be weighed against its risks (2). To date, alternative bladder-sparing treatment strategies to RC are considered as oncologically inferior (24,25). The definite treatment for BCG failure can and sometimes must be adopted to the physical condition, the life expectance and the desires of the patients; also, different aspects of quality of life need to be discussed (26). Some patients are not willing to undergo radical surgery, fear the high risk for complications; or are not fit for an extensive surgery. Moreover, some patients are overtreated with RC; but this group still needs to be identified. Inclusion in a clinical trial allows to assess the efficacy of alternative bladder-sparing treatments in the scenario of BCG unresponsive disease.

Herein, we want to provide the current evidence regarding the therapeutic management of BCG failure patients and report treatment alternatives to RC as well as future perspectives. The search for an effective valid alternative therapy to RC still is an unmet need. New alternative treatment approaches to RC are under investigation and could potentially revolutionize the treatment approaches in BCG failure patients. Once being diagnosed with BCG failure disease in the follow-ups, further response to BCG therapy is unlikely (2) and goes along with an increased risk of disease progression (27,28).

Intravesical chemotherapy

Chemotherapeutical agents are potential alternatives to RC in BCG failure patients (26). The only FDA approved salvage option, is valrubicin, which was first proposed in 1981 (29). The complete response rate after 3 months varies between 41–46% (30-32), 18–21% after 6 months and 16.4% after 12 months (33-35). Nevertheless, these data suggest valrubicin being a suboptimal salvage therapy, as a meaningful oncological benefit has been defined as disease-free rate of at least 50% at 6 months and >30% after 1 year (23). Other tested substances are gemcitabine, which has a 12-month disease free survival rate of 10–28% (36-38) and a 24-month disease free survival rate of 21% (38). Another option has been docetaxel, which has resulted in a disease-free rate of 50% after 1 year and 22% after 4 years (39,40). Another again option is abraxane, an albumin-bound paclitaxel, with a complete response rate of 36% after 1 year and 25% after 3 years of treatment (41). Taken together, these treatments have some activity after BCG, but the treatment response is suboptimal to designate them as acceptable alternatives to RC (42).

Combinations of treatment approaches

Chemotherapeutics have also been studied in combinations: The sequential use of gemcitabine and docetaxel led to 54% disease free rate after 1 year and 34% after 2 years; the regimen was well tolerated (43). Similar recurrence free survival rates were reported for the combination of gemcitabine and mitomycin C (48% and 38% after 1 and 2 years, respectively). Also, the combination chemotherapy using gemcitabine and mitomycin C appeared to be a useful treatment for patients with high-grade NMIBC with prior BCG failure (44). However, the results of these studies are based on retrospective designs and therefore, drug combinations are not yet indicated in patients with BCG failure.

Moreover, many studies included patients who cannot really be considered as BCG failure due to inadequate treatment with BCG and/or are not really meeting BCG unresponsive criteria (24).

Chemoradiation is another treatment approach that has been attempted in patients with BCG failure. While this can be considered as bladder-sparing, the criteria for success and side effects of trimodal therapy make it an inadequate alternative to RC for patients with high-risk NMIBC failing BCG. There is currently a phase II trial (NCT00981656) that aims at assessing the efficacy of radiation therapy given together with chemotherapy (cisplatin or fluorouracil and mitomycin C) in these patients (45).

Immune checkpoint inhibitors

The immune checkpoint inhibitor atezolizumab, either in combination or without BCG, was recently tested in a single-arm phase Ib/II clinical trial (NCT02844816) in patients with BCG-unresponsive high-risk NMIBC. The investigators conduct this study in order to estimate the response after 25 weeks for those with a CIS component in their BC. The event-free survival at 18 months will also be evaluated. The expected accrual end is foreseen in April 2021 (46). Further studies with nivolumab ± the experimental medication BMS-986205 or BCG (CheckMate 9UT, NCT03519256), or durvalumab (NCT02901548) are currently recruiting (47,48).

The only immune checkpoint inhibitor study that has brought preliminary results so far is the KEYNOTE-057 phase II trial (NCT02625961). The anti-PD-1 antibody

pembrolizumab was tested in patients unresponsive to BCG who are considered ineligible for or have refused to undergo RC. Pembrolizumab showed antitumoural activity with a complete response rate of 41.2%, which was the primary endpoint of the study. The median duration of the complete response was clinically meaningful with 16.2 months. The secondary endpoint of the KEYNOTE-057 phase II trial was disease free survival estimates of 57.4%, 50.7% and 41.3% at ≥12 months, ≥15 months and ≥18 months, respectively (49). Pembrolizumab is thus the only one to date to meet the criteria set forth for bladder-sparing strategy in high-risk BCG-unresponsive NMIBC (24). A phase III study evaluating safety and efficacy of pembrolizumab in combination with BCG after BCG induction is currently recruiting (KEYNOTE-676, NCT03711032) (50).

Mycobacterium phlei cell wall-nucleic acid complex

An emerging immunotherapeutic agent derived from *Mycobacterium phlei*, the *Mycobacterium phlei* cell wall-nucleic acid complex (MCNA), which has been used in 129 patients who failed BCG therapy. A recent phase III trial reported a recurrence free survival rate of 25% after 12 months and 19% after 2 years, respectively (51). While interesting and safe, the efficacy of MCNA seems too low for approval and/or selective use. External validation of these findings is pending. To date, MCNA is not approved for second-line treatment for patients who experienced BCG failure.

Device-assisted therapy

Electromotive intravesical administration of chemotherapeutical agents represents a therapy approach that is currently investigated in patients failing BCG therapy. The underlying mechanism is based on iontophoresis which allows the chemotherapeutics to penetrate deeper into tissue layers of the human bladder (52).

The most promising approach is the radiofrequency-induced thermo-chemotherapy effect (RITE), which has been studied most with the Synergo® system (Medical Enterprises, Amstelveen, The Netherlands). Nair *et al.* conducted a prospective comparison by matching long-term disease specific outcomes for high-risk NMIBC treated with RITE and RC (n=96 and n=47, respectively). Preliminary results showed a 5-year disease-free survival of 74.6% *vs.* 85.2% and overall survival of 61.9% *vs.* 68.4% for the RITE and RC cohorts, respectively; after a median follow-up time of 40 months (IQR, 4–92 months) (53). Further studies revealed a 2-year recurrence rate varying between 41–56% in the BCG-failure population (25). Progression was seen in 3–4% of these patients (54-57). Some working groups shared their 10-year experience. Analysis of long-term follow-up data revealed that more than the half of patients remained BC-free after 10 years (55,56). Most reported adverse events were self-limiting and reversible (58-60).

Another approach is the hyperthermic intravesical chemotherapy (HIVEC™) applied by the COMBAT BRS® (Combat Medical, Wheathampstead, UK) which is based on conductive heating of the intravesical chemotherapy. Two studies reported on adjuvant HIVEC™ treatment. After a mean follow-up of 11.2 months, the recurrence rate was 27.3% while 9.1% of the patients presented a progression to muscle-invasive BC (61). The 2-year cumulative incidence of recurrence after TURB was 12.5% (62).

Gene therapy

The intravesical administration of Adstiladrin® (Instiladrin), which is rAd-IFN combined with the excipient Syn3, leads to transduction of the adenovirus into the bladder epithel. After incorporation in the DNA, upregulated synthesis and expression of IFN alpha2b protein follows (63). In BC cell lines, IFN alpha exposure lead to an increase of infiltrating T-cell markers and immune checkpoint molecules (64). In a phase I trial, 43% of patients experienced a complete response at 3 months (65). After 12 months, the complete response rate was about 29% in the phase II trial (NCT01687244). Therein, 40 patients were evaluated; 14 patients experienced complete response; 2 had recurrence of BC at 21 and 28 months, respectively; and 1 patient died due to an upper urinary tract tumour at 17 months (66). Intravesical rAd-IFNα/Syn3 was well tolerated; no dose limiting toxicity was detected (66). In the phase III trial, 151 patients were enrolled, 36 patients (24%) showed a complete response, and >30% had no recurrence after 12 months. Although these results are promising, a longer follow-up is needed (NCT02773849) (67).

Early phase clinical studies were done with CG0070 (68), an investigational oncolytic virus (NCT02365818) (69,70). CG0070 is oncolytic adenovirus that targets BC cells at their defective retinoblastoma pathway. In a recently published interim analysis of the phase II trial, the overall rate of complete response was 30% at 12 months. In the subgroup of BCG-refractory patients 48% (n=25) had a 12-month complete response. Overall toxicity was low (70).

Another ongoing trial (NCT02015104) tests if the poxviral cancer vaccine (PANVAC™) plus BCG is better than BCG therapy alone (71). PANVAC™ expresses transgenes for tumour antigens, such as mucin 1, as well as co-stimulatory molecules to stimulate the antitumour T-cell response (72).

Targeted therapies

NCT01259063 was a dose-finding study that also tests the safety of gemcitabine applied to the bladder directly combined with different oral doses of everolimus in a phase I/II trial in BCG pretreated patients. Of the 19 patients who were evaluable for response, 3 (16%) were disease free at 1 year. Notably, a high percentage of study participants (52.6%) had severe adverse events with this targeted therapy approach (73).

VB4-845 (vicinium) is an experimental agent that contains a pseudomonal exotoxin, conjugated to a structure that targets the epithelial cell adhesion molecule. NCT02449239 is a phase III trial evaluating the 24 months disease-free response rate. Results are pending as the estimated study completion is in November 2021 (74).

Conclusions

To date, RC remains the recommended standard treatment for BCG failure in NMIBC patients. There is no accepted effective and safe alternative yet to RC for these patients. Salvage approaches with bladder-sparing alternatives is reserved for patients ineligible for or refusing RC. Numerous promising bladder-sparing alternatives are currently investigated, including hyperthermia, gene-, targeted- and immunotherapy, which could potentially change the standard therapeutic approach in the future. The threshold for acceptance of these alternatives needs still to be clearly agreed upon by a consensus group of key stakeholders.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Marco Moschini) for the Series "Bladder Cancer" published in *AME Medical Journal*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.com/article/view/10.21037/amj.2020.01.03/coif). The series "Bladder Cancer" was commissioned by the editorial office without any funding or sponsorship. KM Gust reports receipt of honoraria or consultation fees: Cepheid, Ferring, Janssen, Roche, and MSD; participation in a company sponsored speaker's bureau: Astellas, Astra Zeneca, BMS, Ipsen, Janssen, MSD, and Roche. Meeting/traveling expenses: Allergan, Astellas, Astra Zeneca, Bayer, BMS, Janssen, MSD, Novartis, Pfizer, Pierre Fabre, and Roche. S.F. Shariat reports advisory board of/and or speaker for Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lissy, MSD, Olympus, Pfizer, Pierre Fabre, Roche, Sanochemia, Sanofi and Wolff. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. International Agency for Research on Cancer, WHO. Cancer today. [cited 2019 Oct 10]. Available online: http://gco.iarc.fr/today/home
2. Babjuk M, Böhle A, Burger M, et al. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol 2017;71:447-61.
3. Abdollah F, Gandaglia G, Thuret R, et al. Incidence, survival and mortality rates of stage-specific bladder cancer in United States: a trend analysis. Cancer Epidemiol 2013;37:219-25.
4. Shariat SF, Kim J, Raptidis G, et al. Association of p53 and p21 expression with clinical outcome in patients with carcinoma in situ of the urinary bladder. Urology 2003;61:1140-5.

5. Rink M, Babjuk M, Catto JWF, et al. Hexyl aminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: a critical review of the current literature. Eur Urol 2013;64:624-38.
6. Xylinas E, Kent M, Kluth L, et al. Accuracy of the EORTC risk tables and of the CUETO scoring model to predict outcomes in non-muscle-invasive urothelial carcinoma of the bladder. Br J Cancer 2013;109:1460-6.
7. Kluth LA, Black PC, Bochner BH, et al. Prognostic and Prediction Tools in Bladder Cancer: A Comprehensive Review of the Literature. Eur Urol 2015;68:238-53.
8. Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466-465; discussion 475-7.
9. Malmström P-U, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. Eur Urol 2009;56:247-56.
10. Böhle A, Bock PR. Intravesical bacille Calmette-Guérin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology 2004;63:682–6; discussion 686-7.
11. Fernandez-Gomez J, Solsona E, Unda M, et al. Prognostic factors in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guérin: multivariate analysis of data from four randomized CUETO trials. Eur Urol 2008;53:992-1001.
12. Babjuk M. BCG is the standard treatment of T1HG bladder cancer. Eur Urol Suppl 2017;16:92-3.
13. Rink M, Chun FK, Dahlem R, et al. Prognostic role and HER2 expression of circulating tumor cells in peripheral blood of patients prior to radical cystectomy: a prospective study. Eur Urol 2012;61:810-7.
14. Karakiewicz PI, Benayoun S, Zippe C, et al. Institutional variability in the accuracy of urinary cytology for predicting recurrence of transitional cell carcinoma of the bladder. BJU Int 2006;97:997-1001.
15. Martin FM, Kamat AM. Definition and management of patients with bladder cancer who fail BCG therapy. Expert Rev Anticancer Ther 2009;9:815-20.
16. Moschini M, Sharma V, Dell'oglio P, et al. Comparing long-term outcomes of primary and progressive carcinoma invading bladder muscle after radical cystectomy. BJU Int 2016;117:604-10.
17. Svatek RS, Shariat SF, Novara G, et al. Discrepancy between clinical and pathological stage: external validation of the impact on prognosis in an international radical cystectomy cohort. BJU Int 2011;107:898-904.
18. Ratliff TL, Palmer JO, McGarr JA, et al. Intravesical Bacillus Calmette-Guérin Therapy for Murine Bladder Tumors: Initiation of the Response by Fibronectin-mediated Attachment of Bacillus Calmette-Guérin. Cancer Res 1987;47:1762-6.
19. Kavoussi LR, Brown EJ, Ritchey JK, et al. Fibronectin-mediated Calmette-Guerin bacillus attachment to murine bladder mucosa. Requirement for the expression of an antitumor response. J Clin Invest 1990;85:62-7.
20. Bisiaux A, Thiounn N, Timsit MO, et al. Molecular analyte profiling of the early events and tissue conditioning following intravesical bacillus calmette-guerin therapy in patients with superficial bladder cancer. J Urol 2009;181:1571-80.
21. Babjuk M, Burger V, Compérat E, et al. EAU Guidelines: Non-muscle-invasive Bladder Cancer. Uroweb. [cited 2019 Dec 6]. Available online: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/#6
22. Herr HW, Milan TN, Dalbagni G. BCG-refractory vs. BCG-relapsing non-muscle-invasive bladder cancer: a prospective cohort outcomes study. Urol Oncol 2015;33:108.e1-4.
23. Kamat AM, Sylvester RJ, Böhle A, et al. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. J Clin Oncol 2016;34:1935-44.
24. Shariat SF, Enikeev DV, Mostafaei H. Six essential conditions for bladder-sparing strategies in bacillus Calmette-Guérin unresponsive bladder cancer. Immunotherapy 2019;11:1083-6.
25. Hassler MR, Shariat SF, Soria F. Salvage therapeutic strategies for bacillus Calmette-Guerin failure. Curr Opin Urol 2019;29:239-46.
26. Moschini M, Zamboni S, Mattei A, et al. Bacillus Calmette-Guérin unresponsiveness in non-muscle-invasive bladder cancer patients: what the urologists should know. Minerva Urol Nefrol 2019;71:17-30.
27. Solsona E, Iborra I, Dumont R, et al. The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. J Urol 2000;164:685-9.
28. Lerner SP, Tangen CM, Sucharew H, et al. 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 2009;27:155-9.
29. Blum RH, Garnick MB, Israel M, et al. Preclinical rationale and phase I clinical trial of the adriamycin analog, AD 32. Recent Results Cancer Res 1981;76:7-15.
30. Greenberg RE, Bahnson RR, Wood D, et al. Initial report on intravesical administration of N-trifluoroacetyladriamycin-14-valerate (AD 32) to patients with refractory superficial transitional cell carcinoma of the urinary bladder. Urology 1997;49:471-5.
31. Newling DW, Hetherington J, Sundaram SK, et al. The use of valrubicin for the chemoresection of superficial bladder cancer -- a marker lesion study. Eur Urol 2001;39:643-7.
32. Ignatoff JM, Chen YH, Greenberg RE, et al. Phase II study of intravesical therapy with AD32 in patients with papillary urothelial carcinoma or carcinoma in situ (CIS) refractory to prior therapy with bacillus Calmette-Guerin (E3897): a trial of the Eastern Cooperative Oncology Group. Urol Oncol 2009;27:496-501.
33. Steinberg G, Bahnson R, Brosman S, et al. Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. J Urol 2000;163:761-7.
34. Dinney CPN, Greenberg RE, Steinberg GD. Intravesical valrubicin in patients with bladder carcinoma in situ and contraindication to or failure after bacillus Calmette-Guérin. Urol Oncol 2013;31:1635-42.
35. Cookson MS, Chang SS, Lihou C, et al. Use of intravesical valrubicin in clinical practice for treatment of nonmuscle-invasive bladder cancer, including carcinoma in situ of the bladder. Ther Adv Urol 2014;6:181-91.
36. Dalbagni G, Russo P, Sheinfeld J, et al. Phase I trial of intravesical gemcitabine in bacillus Calmette-Guérin-refractory transitional-cell carcinoma of the bladder. J Clin Oncol 2002;20:3193-8.
37. Dalbagni G, Russo P, Bochner B, et al. Phase II trial of intravesical gemcitabine in bacille Calmette-Guérin-refractory transitional cell carcinoma of the bladder. J Clin Oncol 2006;24:2729-34.
38. Skinner EC, Goldman B, Sakr WA, et al. 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 2013;190:1200-4.
39. Laudano MA, Barlow LJ, Murphy AM, et al. Long-term clinical outcomes of a phase I trial of intravesical docetaxel in the management of non-muscle-invasive bladder cancer refractory to standard intravesical therapy. Urology 2010;75:134-7.
40. Barlow LJ, McKiernan JM, Benson MC. Long-term survival outcomes with intravesical docetaxel for recurrent nonmuscle invasive bladder cancer after previous bacillus Calmette-Guérin therapy. J Urol 2013;189:834-9.
41. McKiernan JM, Holder DD, Ghandour RA, et al. Phase II trial of intravesical nanoparticle albumin bound paclitaxel for the treatment of nonmuscle invasive urothelial carcinoma of the bladder after bacillus Calmette-Guérin treatment failure. J Urol 2014;192:1633-8.
42. Kamat AM, Colombel M, Sundi D et al. BCG-unresponsive non-muscle-invasive bladder cancer: recommendations from the IBCG. Nat Rev Urol 2017;14:244-55.
43. Velaer KN, Steinberg RL, Thomas LJ et al. Experience with Sequential Intravesical Gemcitabine and Docetaxel as Salvage Therapy for Non-Muscle Invasive Bladder Cancer. Curr Urol Rep 2016;17:38.
44. Lightfoot AJ, Breyer BN, Rosevear HM et al. Multi-institutional analysis of sequential intravesical gemcitabine and mitomycin C chemotherapy for non-muscle invasive bladder cancer. Urol Oncol 2014;32:35.e15-9.
45. Radiation Therapy and Chemotherapy in Treating Patients With Stage I Bladder Cancer - Full Text View - ClinicalTrials.gov. [cited 2019 Nov 11]. Available online: https://clinicaltrials.gov/ct2/show/NCT00981656
46. Atezolizumab in Treating Patients With Recurrent BCG-Unresponsive Non-muscle Invasive Bladder Cancer - Full Text View - ClinicalTrials.gov. [cited 2019 Nov 27]. Available online: https://clinicaltrials.gov/ct2/show/NCT02844816
47. 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 - Full Text View - ClinicalTrials.gov. [cited 2019 Nov 27]. Available online: https://clinicaltrials.gov/ct2/show/NCT03519256
48. Phase 2 Durvalumab (Medi4736) for Bacillus Calmette-Guérin (BCG) Refactory Urothelial Carcinoma in Situ of the Bladder - Full Text View - ClinicalTrials.gov. [cited 2019 Nov 27]. Available online: https://clinicaltrials.gov/ct2/show/NCT02901548
49. Study of Pembrolizumab (MK-3475) in Participants With High Risk Non-muscle Invasive Bladder Cancer (MK-3475-057/KEYNOTE-057) - Full Text View -

ClinicalTrials.gov. [cited 2019 Nov 11]. Available online: https://clinicaltrials.gov/ct2/show/NCT02625961
50. Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Bacillus Calmette-Guerin (BCG) in High-Risk Non-Muscle Invasive Bladder Cancer (HR NMIBC) (MK-3475-676/KEYNOTE-676) - Full Text View - ClinicalTrials.gov. [cited 2019 Nov 27]. Available online: https://clinicaltrials.gov/ct2/show/NCT03711032
51. Morales A, Herr H, Steinberg G, et al. 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 2015;193:1135-43.
52. Di Stasi SM, Giannantoni A, Massoud R, et al. Electromotive versus passive diffusion of mitomycin C into human bladder wall: concentration-depth profiles studies. Cancer Res 1999;59:4912-8.
53. Nair R, Pai A, Kaul A, et al. 1109 Challenging the gold standard: A comparison of long-term disease specific outcomes for high-risk non-muscle invasive bladder cancer treated with mitomycin hyperthermia and radical cystectomy. Eur Urol Suppl 2014;13:e1109.
54. Nativ O, Witjes JA, Hendricksen K et al. Combined thermo-chemotherapy for recurrent bladder cancer after bacillus Calmette-Guerin. J Urol 2009;182:1313-7.
55. Arends TJH, van der Heijden AG, Witjes JA. Combined chemohyperthermia: 10-year single center experience in 160 patients with nonmuscle invasive bladder cancer. J Urol 2014;192:708-13.
56. Moskovitz B, Halachmi S, Moskovitz M, et al. 10-year single-center experience of combined intravesical chemohyperthermia for nonmuscle invasive bladder cancer. Future Oncol 2012;8:1041-9.
57. Tan WS, Panchal A, Buckley L, et al. 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 2019;75:63-71.
58. Colombo R, Salonia A, Leib Z, et al. Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). BJU Int 2011;107:912-8.
59. León-Mata J, Domínguez JL, Redorta JP, et al. Analysis of tolerance and security of chemo hyperthermia with Mitomycin C for the treatment of non-muscle invasive bladder cancer. Arch Esp Urol 2018;71:426-37.
60. Colombo R, van Valenberg H, Moschini M, et al. A. Radiofrequency-induced thermo-chemotherapy effect (RITE) for non muscle invasive bladder cancer treatment: current role and perspectives. Urologia 2016;83:7-17.
61. Marquette T, Walz J, Rybikowski S, et al. Safety of Hyperthermic IntraVEsical Chemotherapy (HIVEC) for BCG Unresponsive Non-Muscle Invasive Bladder Cancer Patients. Prog Urol 2020;30:35-40.
62. Sousa A, Piñeiro I, Rodríguez S, et al. Recirculant hyperthermic IntraVEsical chemotherapy (HIVEC) in intermediate-high-risk non-muscle-invasive bladder cancer. Int J Hyperthermia 2016;32:374-80.
63. Yamashita M, Rosser CJ, Zhou JH, et al. Syn3 provides high levels of intravesical adenoviral-mediated gene transfer for gene therapy of genetically altered urothelium and superficial bladder cancer. Cancer Gene Ther 2002;9:687-91.
64. Sundi Debasish, Choi Woonyoung, Lee IL, et al. Mp83-12 in vitro effects of interferon alpha in bladder cancer: immune checkpoint expression and microrna and mrna genomic profiling. J Urol 2016;195:e1085.
65. Dinney CPN, Fisher MB, Navai N, et al. Phase I trial of intravesical recombinant adenovirus mediated interferon-α2b formulated in Syn3 for Bacillus Calmette-Guérin failures in nonmuscle invasive bladder cancer. J Urol 2013;190:850-6.
66. Intravesical Administration of rAd-IFN/Syn3 in Patients With BCG-Refractory or Relapsed Bladder Cancer - Full Text View - ClinicalTrials.gov. [cited 2019 Dec 4]. Available online: https://clinicaltrials.gov/ct2/show/NCT01687244
67. A Study to Evaluate INSTILADRIN® in Patients With High-Grade, Bacillus Calmette-Guerin (BCG) Unresponsive NMIBC - Full Text View - ClinicalTrials.gov. [cited 2019 Dec 4]. Available online: https://clinicaltrials.gov/ct2/show/NCT02773849
68. Burke JM, Lamm DL, Meng MV, et al. A first in human phase 1 study of CG0070, a GM-CSF expressing oncolytic adenovirus, for the treatment of nonmuscle invasive bladder cancer. J Urol 2012;188:2391-7.
69. Safety and Efficacy of CG0070 Oncolytic Virus Regimen for High Grade NMIBC After BCG Failure - Full Text View - ClinicalTrials.gov. [cited 2019 Nov 11]. Available online: https://clinicaltrials.gov/ct2/show/NCT02365818
70. Packiam VT, Lamm DL, Barocas DA, et al. An open label, single-arm, phase II multicenter study of the safety and

efficacy of CG0070 oncolytic vector regimen in patients with BCG-unresponsive non-muscle-invasive bladder cancer: Interim results. Urol Oncol 2018;36:440-7.
71. 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 - Full Text View - ClinicalTrials.gov. [cited 2019 Nov 11]. Available online: https://clinicaltrials.gov/ct2/show/NCT02015104
72. Gulley JL, Arlen PM, Tsang KY, et al. A Pilot Study to Evaluate the Safety and Clinical Outcomes of Vaccination with Recombinant CEA-MUC-1-TRICOM (PANVAC) Poxviral-based Vaccines in Patients with Metastatic Carcinoma. Clin Cancer Res 2008;14:3060-9.
73. RAD001 and Intravesical Gemcitabine in BCG-Refractory Primary or Secondary Carcinoma In Situ of the Bladder - Full Text View - ClinicalTrials.gov. [cited 2019 Nov 11]. Available online: https://clinicaltrials.gov/ct2/show/NCT01259063
74. Vicinium Treatment for Subjects With Non-muscle Invasive Bladder Cancer Previously Treated With BCG - Full Text View - ClinicalTrials.gov. [cited 2019 Nov 11]. Available online: https://clinicaltrials.gov/ct2/show/NCT02449239

doi: 10.21037/amj.2020.01.03
Cite this article as: Stangl-Kremser J, Gust KM, Shariat SF. Therapeutic management of Bacillus Calmette–Guerin refractory patients: a narrative review. AME Med J 2020;5:9.

