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How Should I Manage a Patient with Tumor Recurrence Despite Adequate Bacille Calmette-Guérin?

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Abstract

Intravesical immunotherapy with bacille Calmette-Guérin (BCG) vaccine is the main treatment for non-muscle-invasive bladder cancer (NMIBC), with proven effects on reducing recurrence, progression, and death from NMIBC. However, it is not effective in all patients, and recurrence after adequate BCG therapy can frequently lead to progression to more life-threatening disease. This point-counterpoint review considers how to treat a healthy 60-yr-old patient with T1 high-grade NMIBC fitting the new definition of BCG-unresponsive disease, that is, persistent high-grade disease at 6–12 mo, despite an adequate course of induction and maintenance with BCG.

Patient summary: When T1 high-grade non-muscle-invasive bladder cancer is persistent or recurs shortly after a full course of bacille Calmette-Guérin (BCG) plus maintenance, further BCG is not likely to work; this meets the new definition of a "BCG unresponsive" disease. For this situation, the safest (curative) option is removal of the bladder. If that is not an accepted alternative, then a clinical trial or combination intravesical chemotherapy or hyperchemotherapy may be another option.

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1. Case presentation

The patient is a healthy 60-yr-old man who presented with gross hematuria. Cystoscopy showed an accessible tumor on the right wall, and transurethral resection of the bladder tumor (TURBT) with blue light revealed a T1 high-grade, pure urothelial carcinoma with muscle present but not involved. This was confirmed in a second opinion from another pathologist. A planned repeat TURBT at 4 wk revealed a small focus of cancer in situ (CIS), with no papillary involvement. Imaging was negative for upper tract or metastatic disease.

After an informed discussion, the patient elected to receive 6-wk induction of intravesical bacille Calmette-Guérin (BCG), which was tolerated fairly well. His 3-mo cystoscopy and cytology were negative.

Induction was followed by 3-wk maintenance with BCG. At the 6th-month evaluation, a small (0.5 cm) lesion was noted at the dome, distant from the original tumor. TURBT showed CIS plus a Ta high-grade tumor. The rest of the

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bladder and prostate were essentially negative, and the results of random biopsies were negative as well.

This patient fits the new definition of BCG-unresponsive disease by virtue of having persistent high-grade disease at 6 mo, despite induction and maintenance with BCG.

So the question is, what do you do now?

2. Option A: Conservative treatment in high-risk BCG-unresponsive non-muscle-invasive bladder cancer

This clinical case pertains to a high-risk non-muscle-invasive bladder cancer (NMIBC) (originally a solitary T1G3 with CIS) that recurred as a solitary high-grade Ta with a concomitant small focus of CIS after adequate exposure to BCG (six plus three instillations) and during maintenance BCG (Fig. 1) [1].

According to the most existing guidelines (including 2017 European Association of Urology [EAU] guidelines [2,3]), this clinical scenario is a condition that is best treated with radical surgery. This also fits the recent definition of BCG-unresponsive disease by the Food and Drug Administration (FDA) [4] and the International Bladder Cancer Group (IBCG) [1]. For discussion purposes, according to an international consensus on staging of T1 disease [5], this case, where NMIBC presents as a lower-stage disease after an initial partial response, can also be called BCG resistant.

The currently available conservative therapies (immunotherapies, chemotherapies, device-assisted therapies, or combinations) must be considered oncologically inferior to radical surgery, since they are associated with a significant risk of disease progression. As such, they are recommended only in patients unfit for or who refuse radical surgery [2,3]. In this case, the patient was apparently young and fit, and not unusually, such patients are asking their clinician to help them weigh the "oncological benefit" versus potential detriments of the possible treatment alternatives.

2.1. *Can the prognosis of this patient be determined?*

A patient such as this is usually considered at a high risk of disease progression, but can the magnitude of this risk be estimated in this individual patient? Both European Organisation for Research and Treatment of Cancer EORTC [6] and CUETO [7] risk tables work for predicting progression in individual patients with primary or recurrent NMIBC receiving predominantly chemotherapy (EORTC) or BCG (CUETO), respectively, but neither risk calculator applies to a BCG-unresponsive disease.

The risk of a missed muscle-invasive bladder cancer (MIBC) would be low in this patient, since the high risk of discovering MIBC in T1G3 undergoing radical cystectomy (up to 50% in the series of Fritsche et al. [8]) does not apply to this scenario due to recurrence with Ta disease. In 87 Ta high-grade NMIBC cases undergoing repeat transurethral resection (TUR), the rate of persistent disease was 41%, but none had MIBC [9].

In addition, this patient received a good quality photodynamic diagnosis-guided TUR; this method was recently found to significantly reduce the recurrence rate over good-quality white-light TUR, and the effect was even more marked in high-risk disease [10].

The SWOG trial [11] randomized patients at a high risk of progression to receive BCG with or without maintenance. Patients failing to achieve a complete response (CR) to BCG had a significantly higher risk of 5-yr death compared with

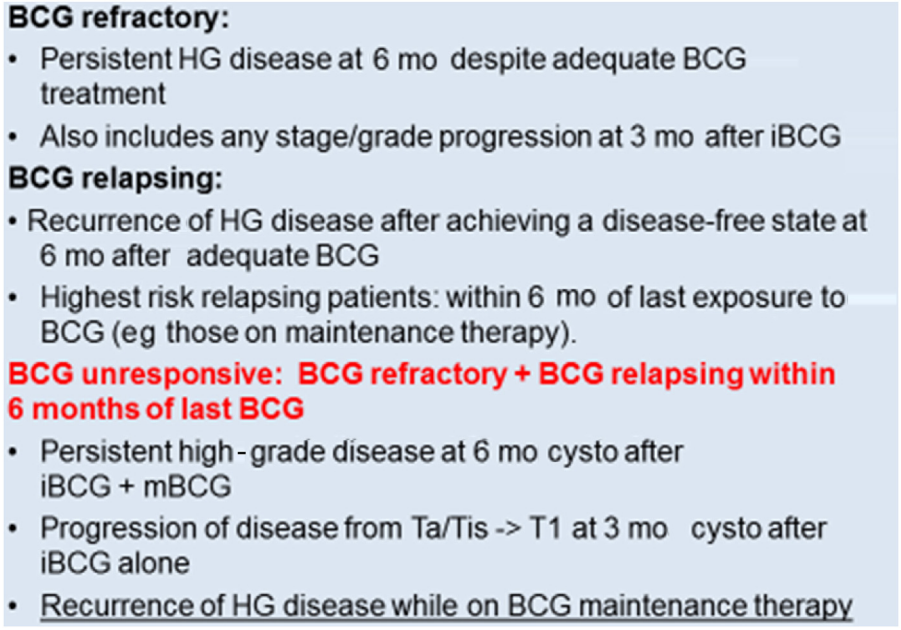

Fig. 1 – Definition of BCG-unresponsive NMIBC. BCG = bacille Calmette-Guérin; HG = high grade; iBCG = intravesical BCG; mBCG = maintenance BCG; NMIBC = non-muscle-invasive bladder cancer.
Adapted from Kamat et al. [1].

BCG responders (77% vs 62%), with a hazard ratio of 0.6 (67% increased risk of death). This study confirms the higher risk of cancer-specific death for BCG-failure disease and supports the need for an effective early treatment for this clinical condition.

2.2. Is early cystectomy the best available treatment for high-risk BCG-unresponsive NMIBC?

No randomized study has specifically addressed this question. In a retrospective series of T1G3 patients, Hautmann et al. [12] compared the results of immediate cystectomy in 175 BCG-naïve patients versus delayed cystectomy in 99 BCG-failure patients, and showed a 9% 5-yr cancer-specific survival (CSS) advantage in favor of immediate cystectomy. While the delayed cystectomy arm of this study provides a good estimate of the outcomes of BCG failures receiving delayed surgery (75% at 5 yr and 64% at 10 yr), it does not demonstrate that this is an ideally effective treatment. Notably, CSS continues to decrease beyond 5 yr from cystectomy, suggesting that cystectomy is far from an ideal treatment.

2.3. Are current conservative therapies inferior to cystectomy?

Chemohyperthermia with mitomycin C using a radio-frequency-emitting catheter has been tested in retrospective series and also in one small randomized controlled trial (RCT) for BCG-failure NMIBC. In a review of 111 patients with BCG failure, Nativ et al. [13] reported a recurrence-free rate of 85% at 1 yr and 56% at 2 yr, with an average time to recurrence of 16 mo. Progression rate at a median follow-up of 16 mo was only 3%.

Initial reports of intravesical gemcitabine in NMIBC showed promise in both BCG-naive and BCG-failure patients. In the only RCT published so far [14], high-risk BCG-failure NMIBC patients had a recurrence rate of 52.5% (21/40) following intravesical gemcitabine, compared with 87.5% (35/40) for rechallenge with intravesical BCG. Progression rates were similar between groups: gemcitabine 33% and BCG 37.5% ($p = 0.12$) [14]. Notably, the patients were not true BCG unresponsive according to the new definitions.

Taxanes are another group of systemically administered chemotherapies that have been tested after failure of BCG; a few small studies, mainly using docetaxel, have failed to report significant results: recurrence rates up to 70% after an average initial complete response rate (CRR) of 50% at 6 wk to 43 mo of follow-up were reported. Notably, when a progression rate was reported, it was relatively low (5%) [15].

More recent studies have combined intravesical chemotherapy with improved results far superior to anything we have seen to date [16]. However, large-scale studies have not been conducted.

In conclusion, while the oncological efficacy of these second-line therapies remains limited in terms of response rate and durability of response, the progression rate (with the exception of one study) at an average follow-up of 2 yr is usually low (5%). This suggests that there may be a 2-yr period during which conservative therapies can safely be attempted in BCG-failure disease, since the majority of patients will recur without progression, thus leaving a good opportunity for delayed cystectomy still to be effective. However, it must be noted that these have not been tested in a true BCG-unresponsive patient to date.

2.4. Investigational immunological drugs (checkpoint inhibitors): a new avenue in BCG-unresponsive disease?

The undisputed efficacy of BCG in primary high-risk NMIBC makes the search for alternative immunotherapeutic routes in patients who are BCG nonresponsive attractive. Rechallenges with combinations of traditional immunotherapies (BCG + interferon) have shown an acceptable initial response rate (50%), but raise concerns in terms of durability of response [17].

Molecules that act as PD-1 and PD-L1 inhibitors have shown 26% objective responses in metastatic bladder cancer with a good tolerability profile [18]. These drugs may represent a promising avenue in BCG failures; clinical trials investigating the role of pembrolizumab (two trials addressing response rate and maximal tolerated dose), atezolizumab (one trial addressing cancer response rate), and durvalumab (one trial addressing safety) in BCG-unresponsive disease are underway. In early reports [19], a single agent pembrolizumab demonstrated 38% initial CRRs in patients with BCG-unresponsive CIS.

3. Option B: Radical cystectomy in high-risk BCG-unresponsive NMIBC

Currently, the best approach to BCG response failure in the treatment of high-grade NMIBC is to differentiate patients according to risk category, time of relapse, and the type of BCG course (ie, with or without BCG maintenance) [20].

According to the recent EAU guideline update [2,3], patients with high-grade NMIBC at 3 mo or with CIS present at 3 and 6 mo after at least a complete induction course of BCG are considered to be the group with the worst prognosis among BCG failures. As noted earlier, when a patient has persistent or recurrent disease according to the BCG-unresponsive definition, this confers the highest risk to the patient.

The best treatment options for this very-high-risk group represent a challenge. As a recent review reminds [21], since no established and effective intravesical therapies are available for tumors that recur after BCG, radical cystectomy remains the standard treatment for patients who are truly unresponsive to BCG. According to the EAU guidelines [2,3], conservative treatment alternatives are “oncologically inferior” to radical cystectomy, since BCG failures are unlikely to respond to further BCG therapy. In only a few selected cases (eg, low-grade recurrent tumors), bladder preservation strategies (immunotherapy, computed tomography, and device-assisted therapies) can be considered acceptable; current evidence is that the oncological safety of any other conservative treatment is at best debatable [22].

3.1. Why not delay cystectomy?

Patients who failed to respond to the first BCG course have a very high risk of progression to muscle-invasive disease (MIBC) with a subsequent fatal outcome. In 2004, Schrier et al. [23] reported 3-yr CSS of 35% in patients who progress to MIBC after NMIBC, compared with 67% in patients with primary NMIBC. These results highlight the importance of evaluating BCG-failure patients carefully, since a delayed cystectomy may lead to worsening of survival.

A randomized clinical trial [10] in 2009 confirmed a better prognosis for patients with primary tumors at baseline. The population was divided into four groups according to age, presence or absence of a CR to BCG, and administration or not of prior intravesical therapy for patients without a CR. The no-CR groups had a risk of death from bladder cancer that was three to five times the risk in younger CR patients. Moreover, among the no-CR patients, those with a history of repeated intravesical treatments had a higher risk of a worsening prognosis (83% vs 63% for patients without repeat treatments and 33% for those with a CR).

Support for bladder-sparing treatment has been reported by a retrospective comparison of recurrent NMIBC patients who were treated with radical cystectomy or additional intravesical therapies [24]. A delayed cystectomy in this population seemed not to affect the mortality rate, with no statistically significant differences in the 5-yr CSS. However, this study may have been affected by a number of selection biases, since no information was reported regarding pathological characteristics at the first diagnosis or type of subsequent recurrences. Most of the patients treated with radical cystectomy at the first recurrence had a higher incidence of T1 disease confirmed by precystectomy pathological TUR specimens. In the face of the missing information, it is possible that patients treated with an early cystectomy may have had a more aggressive primary tumor.

In 2010, Tilki et al. [25] tried to address the prognostic value of CIS refractory to intravesical therapy. Surprisingly, BCG-refractory CIS was upstaged upon inspection of the radical cystectomy specimens in >50% of the cases; approximately 25% revealed MIBC and 5.8% of the patients had metastases to regional lymph nodes. CSS in this group of patients was 85%; lymph-node density metastases and lymphatic vessel invasion were identified as the most important predictors of mortality.

Further support for the importance of performing radical cystectomy to prevent progression to MIBC in high-risk NMIBC was provided by a retrospective study published in 2005 [26]. Of 62 BCG-failure patients treated with cystectomy, the 5-yr CSS reached 90% in those who were not upstaged at cystectomy.

3.2. Are there any circumstances when delay of cystectomy is correct?

There are patients who experience recurrence of low-grade tumors after being treated for high-grade NMIBC. These patients do well and the risk of progression is really low, so another conservative approach might be offered [27].

It is known also that in surgically high-risk patients with comorbidities, the possibility of complications and the risk of dying in the postoperative period are increased. Clearly, the pros and cons of going ahead with radical surgery must be carefully explained to and evaluated with the patient [28].

If the patient is worried about the short- and long-term sequelae and possible impairment of the quality of life, other treatments can be considered or the patient can be entered into a clinical trial.

4. Discussion of treatment options

BCG-unresponsive disease is an NMIBC category at a very high risk of progression and consequently of cancer-related adverse events, including death. The US FDA defines BCG-unresponsive disease as follows: “Persistent high-grade disease or recurrence within 6 mo (or 12 mo for CIS) of receiving at least two courses of intravesical BCG (at least five of six induction doses and at least two of three maintenance doses); or T1 high-grade disease at the first evaluation following induction BCG alone (at least five of six induction doses).” Based on the available data, current guidelines from the EAU, American Urological Association, IBCG, and other agencies recommend a radical cystectomy. This is because not only does the “gold standard” of radical surgery offer the best chance of CSS, but importantly, delaying extirpative surgery can mean that the window of opportunity for curing the disease gets lost.

Second-line conservative therapies have so far been disappointing in terms of both initial response rates and 1- and 2-yr recurrences. That being said, most of the available studies report low rates (5%) of progression at 2 yr, leaving a decent window of opportunity for assessing new conservative strategies in an informed patient. Hence, regulatory bodies have allowed single-arm studies in patients who refuse or are not eligible for radical cystectomy. Based on this, several trials have emerged in this area of BCG-unresponsive disease; these are summarized in the study by Li et al. [16].

Clearly, while the US FDA’s guidelines will improve the quality of trial design, many cystectomy-ineligible patients with BCG-unresponsive disease today are unwilling to participate in these ongoing trials. For these patients, alternative intravesical agents need to be considered. Unfortunately, valrubicin, which is the only agent approved for recurrent CIS after intravesical BCG treatment, has a dismal 8% CRR at 30-mo follow-up [29]. Alternative options with higher response rates include other intravesical chemotherapies, including gemcitabine, docetaxel, and sequential or combination therapy; for example: combination treatment with gemcitabine and docetaxel has yielded 1- and 2-yr CRRs of 49–54% and 34%, respectively [30]. Of course, when data finally emerge from ongoing trials of checkpoint inhibitors and chemohyperthermia, as well as gene therapy and antibody-drug conjugates, more options will be available for our patients.

5. Summary and treatment recommendation

Patients with BCG-unresponsive disease are extremely unlikely to benefit from further therapy with BCG and represent a unique population for study of new therapies. For the current patient, we must recognize this and encourage him to participate in a clinical trial unless he agrees to undergo a radical cystectomy, which must be offered, as it is the only treatment to date that has proven effects on reducing the risk of progression and death after failure of BCG. However, if he refuses a radical cystectomy and is not able to participate in clinical trials, then the currently available data would support the use of combination chemotherapy or chemohyperthermia in this patient.

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Acquisition of data: Kamat.
Analysis and interpretation of data: Kamat.
Drafting of the manuscript: Kamat.
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