Management of BCG Failures in Superficial Bladder Cancer: A Review

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1. Introduction

Intravesical bacillus Calmette-Guérin (BCG) is standard therapy for adjuvant treatment in patients with high-risk superficial bladder cancer. In the European Association of Urology (EAU) guideline on bladder cancer, BCG is considered more effective than intravesical chemotherapy and therefore it is advocated in intermediate-risk patients in whom intravesical chemotherapy failed and as the first treatment choice in high-risk patients [1]. In patients with carcinoma in situ (CIS) even maintenance BCG is advocated [1,2]. BCG is superior in reducing the recurrence rate [3]. BCG is also considered to prevent or delay progression as was clearly demonstrated is several meta-analyses, such as the biggest by Sylvester et al. [4]. Last, but not least, intravesical BCG is even found to be the only factor in a
multivariate analysis to improve survival in patients with T1G3 tumors, although this was compared to transurethral resection (TUR) alone retrospectively [5]. However, not all patients benefit from intravesical BCG. What can be the reasons for failing BCG?

2. BCG failure

First, there can be BCG intolerance, meaning that a patient cannot tolerate BCG or (usually) its side effects. If this occurs during the first six instillations, it is not strictly a BCG failure, because BCG therapy was insufficient. Although intravesical BCG has more severe and more frequent side effects as compared to intravesical chemotherapy, the number of patients stopping BCG instillations during the induction course is limited. In a study by the European Organization for Research and Treatment of Cancer (EORTC), in which 487 patients were planned for 36 mo of BCG therapy, 99 (20.3%) patients stopped BCG due to local (n = 72) and/or systemic (n = 46) side effects [6]. However, only 18 and 20, respectively, did so during the induction course. Local toxicity remained constant during maintenance therapy. Systemic toxicity was predominantly seen in the first 6 mo of therapy (36 of 46 patients). Adding antituberculous drugs to BCG instillations does not reduce toxicity [7]. BCG toxicity was not actually correlated with an improved outcome [8]. In summary, BCG intolerance is inevitable and occurs in approximately 20% of patients during maintenance therapy. Fewer than 5% of patients never completed the induction course, meaning they never had sufficient BCG therapy. In these patients, certainly those who never completed the induction course, intravesical therapy with another drug at the time of a recurrence seems appropriate.

There are also patients with recurrences after initial complete resection of papillary tumors and BCG therapy or disappearance of CIS due to BCG. In general, at the first recurrence a new induction course is given. With longer follow-up, recurrences are more frequent. Reviewing studies with a minimal follow-up of 1 yr, between 0% and 42% of patients failed BCG due to side effects or recurrences [9]. In a meta-analysis of 1421 patients treated with BCG, 38.6% had a recurrence after a median follow-up of 26 mo [3]. Pansadoro et al followed 81 pT1GIII patients, treated with at least two cycles of six BCG instillations, for a median of 76 mo [10]. The recurrence rate was 33% with a median time to recurrence of 20 mo. Twelve of the 27 patients with recurrence had progression and 5 patients died of the disease. However, 56 patients (69%) were alive with a functioning bladder. In the same EORTC study mentioned above, an additional 80 (16.4%) patients stopped BCG therapy during treatment due to a second recurrence (n = 54) or progression (n = 26) [6]. In summary, between 20% and 40% of patients apparently fail after BCG with recurring tumors, depending on the follow-up time and their initial risk profile.

Finally, there is a group of patients resistant to BCG used as treatment, predominantly in case of CIS. In general, patients with CIS are considered BCG refractory or failures when biopsies and cytology do not normalize after one initial course of six weekly instillations and at least a second course of three or six instillations after 3 mo, because that second course can produce an additional 10–20% complete responders [1]. Herr and Dalbagni came to similar conclusions for high-risk superficial tumors [11]. Because maintenance BCG did not decrease tumor recurrence beyond 6 mo of induction BCG, they concluded that 6 mo was the minimum treatment period to identify high-risk tumors as truly BCG refractory. In a recent meta-analysis the results of BCG in patients with CIS was studied [12]. Of 298 patients treated with BCG, 203 (68.1%) had a complete response and 46.7% remained so after a median follow-up of 3.6 yr. In summary, BCG induces a 70% initial complete response rate, which remains so in 50% of patients.

3. Prediction and fate of BCG failure

Can we predict BCG failures? We cannot predict nor treat patients who have side effects, although patients with a positive purified protein derivative (PPD) skin reaction before intravesical BCG tend to have more systemic side effects [13]. Interestingly, in this small study, patients with symptomatic side effects had a trend of longer recurrence-free survival. Those patients with recurrence or resistance also cannot be predicted accurately. Although host, tumor, and immunologic parameters can help, no single prognostic factor predicts response [14]. Several factors, however, warrant close follow-up of a patient with high-risk disease during and after BCG.

3.1. Clinical risk factors

Clinical risk factors are the basis for the recent EORTC risk tables [15]. Prediction of tumor recur-
rence (tumor number, size, and prior recurrence rate) and progression (tumor stage, grade, and CIS) in individual patients with stage Ta and T1 bladder tumors is fairly accurate and clinically useful. A disadvantage is that most of the studies included are from before the BCG maintenance era and before the standard second TUR in high-risk patients. Moreover, approximately 20% of the patients did not receive any additional intravesical treatment, and <10% received an immediate instillation. Still, these tables are of great practical value and are easy to use. Another important clinical prognostic factor is the tumor status 3 mo after the initial TUR [1,16]. Lockyer et al., for example, found progression and cancer death in 21 and 14 patients in case of a positive cystoscopy (n = 35) after BCG [16]. In case of a negative cystoscopy (n = 77), these numbers were 9 and 4. Finally, the prognostic significance of lamina propria invasion (pT1 subclassification) remains significant and, probably, is underestimated. Orsola et al. recently again demonstrated that deep invasion in T1 bladder tumors was a significant negative prognostic factor [17]. Although recurrence rates were independent of the depth of lamina propria invasion, progression rates were 34% (16 of 47) and 8% (3 of 38, p = 0.016) with and without deep invasion, respectively. BCG treatment (67 cases) improved outcome only marginally. Especially in case of associated CIS the risk of progression in these patients was significantly higher, also in BCG-treated patients. On multivariate analysis, deep lamina propria invasion and presence of CIS remains two independent prognostic factors, increasing the hazards ratio of progression to 4.47 and 3.19, respectively. Orsola et al. also underlined that pT1 substaging was technically feasible in 87% of cases.

3.2. Fibronectin and cytokine profiles

The role of fibronectin, involved in the attachment of BCG to the bladder wall, to predict the response to BCG therapy remains to be proven [18].

Probably most promising are urinary cytokine profiles. Saint et al. found that undetectable urinary interleukin 2 (IL-2) during the first 6 mo of BCG therapy correlated with time to recurrence and progression (p = 0.01) [19]. In these first 6 mo, a favorable IL-2 reaction gradually changed to an IL-10 profile. This cytokine profile might be used to adapt maintenance therapy on an individual basis. Watanabe and colleagues also reported prognostic value of several urinary cytokines [20]. In a multivariate analysis urinary IL-2 at the eighth BCG instillation appeared to predict treatment outcome and recurrence. Thalmann et al. indicated the value of urinary IL-8 expression during the first 6 h after BCG instillation to predict a favorable response [21]. Unfortunately, none of these urinary cytokines is currently used in clinical practice.

3.3. Tumor markers

The role of tumor markers remains controversial. The p53 status is a well-known risk factor for tumor recurrence and progression, but its value to predict a BCG response is limited. Saint et al. recently reported data on 102 patients with high-risk superficial bladder cancer treated with BCG for the first time [22]. In a multivariate analysis, pretreatment p53 nuclear overexpression was an independent predictor of recurrence (RR = 0.15). In summary, BCG failure cannot be predicted accurately on an individual basis, but risk groups that should be followed closely can be identified, even with clinical and histologic parameters.

3.4. Fate of patients

Last, but not least, the fate of patients failing intravesical therapy and showing progression into muscle-invasive disease is surprisingly bad. Schrier et al. found a 3-yr bladder cancer-specific survival of 37% for patients who progressed from superficial to muscle-invasive tumors, as compared to 67% for patients with invasive tumors without a history of superficial cancer, matched for stage and grade [23]. Sylvester et al. reported similar figures looking at the patients showing progression after BCG treatments; the bladder cancer-specific death rate was 64% in 2.5 yr after progression from a superficial tumor [4]. Recently, a Spanish group found similar figures [24]. Of 62 failures, treated with cystectomy, 17 patients appeared to have stage pT2 or higher. The 5-yr disease-specific survival of these progressive patients was 38%, significantly lower than nonprogressive patients (90%, p = 0.006). In summary, the window of opportunity is these patients is limited. This indicates the need for meticulous follow-up, good or repeated TUR, and effective treatments in patients in whom BCG fails. What are potential treatment alternatives for these patients?

4. Chemotherapy after BCG failure

Only few attempts were made to treat BCG failures with conventional intravesical chemotherapy. The Swedish-Norwegian bladder cancer group compared mitomycin C (MMC) and BCG in superficial
bladder cancer patients and treatment failures were allowed to cross over [25]. Twenty-one patients with BCG failure changed to MMC therapy, but only four remained recurrence free with a median follow-up period of 64 mo.

Recently, some interesting new drugs have been studied. Valrubicin, an anthracycline, is the only drug approved by the US Federal Drug Administration for patients with CIS failing intravesical therapy, among which is BCG. This was based on a relatively small phase 2 study with 90 patients [26]. After a 1-yr follow-up only 21% showed a complete response and only 8% were disease free at 2 yr. A marker lesion study in refractory patients confirmed some potential of valrubicin, with 18 of 39 (46%) patients free of disease after 3 mo [27]. However, for several reasons, valrubicin is not used currently.

Gemcitabine, considered standard in systemic therapy for advanced bladder cancer, is also studied for its potential in intravesical use. Although most reports are small phase 1 studies without long-term data, intravesical gemcitabine appears safe. The marker lesion response varies, with a highest response rate reported of 56% [28]. The first phase 1 study in patients refractory to BCG and treated with gemcitabine reported on 18 patients refusing cystectomy [29]. Four dose levels of gemcitabine were given intravesically for 1 h twice a week. Patients received two courses of six instillations. Only one patient (highest dose level of 2000 mg in 100 ml) experienced grade 3 toxicity. Eleven patients had negative biopsies after treatment, of whom seven also had negative cytology. In a recent phase 2 study, 2000 mg gemcitabine in 50 ml was used in BCG-refractory patients; 18 of 24 intermediate-risk and 7 of 16 high-risk patients remained recurrence free, confirming the potential of gemcitabine in these patients [30].

A very high, histologically confirmed marker lesion response of 67.4% was noted in a recent phase 2 study with six intravesical instillations of 4 mg apaziquone (EO9, EOquin) [31]. An ongoing study will reveal its potential in BCG refractory patients.

In summary, intravesical chemotherapy after BCG failure has some promise but still remains highly investigational.

5. **Immunotherapy after BCG failure**

Intravesical keyhole-limpet hemocyanin (KLH), a nonspecific immunomodulator, has shown efficacy in Ta and T1 bladder cancer and CIS. However, there are no reports on the use of KLH in BCG-refractory patients.

Intravesical instillations with mycobacterium cell wall complex have been done; the use in BCG failures requires studies.

Bropirimine is an oral immunomodulator, which was also reported to be active against CIS of the bladder and upper urinary tract, even after previous BCG therapy. One phase 2 trial specifically addressed the efficacy of bropirimine in BCG-resistant CIS of the bladder [32]. Of 65 evaluable patients, 21 had a complete response, including 14 of 47 BCG-resistant and 7 of 18 BCG-intolerant patients. Median response duration was >12 mo and only four patients progressed to invasive disease or metastasis during or immediately after therapy with bropirimine. Although bropirimine was considered an alternative to cystectomy for some CIS patients after BCG, no further evaluation of the drug has been done.

Of the group of cytokines, interferon-α (IFN-α) is studied most. Side effects are minimal. Efficacy is dose dependent but apparently less than intravesical chemotherapy or BCG. The combination of IFN-α and BCG for BCG failures has been the subject of a large multicenter phase 2 trial [33]. In all, 231 patients failing BCG were treated with a 6-wk induction course of low-dose BCG plus 50 million units IFN and three additional similar treatments at 3, 9, and 15 mo after induction. With a median follow-up of 24 mo, 48% remained tumor free compared to 60% in the BCG-naïve group treated with normal dose BCG. A recent subgroup analysis indicated that two or more prior BCG failures or early failures indicate a poor response to therapy [34]. Progression to muscle-invasive tumor (about 5%) and metastasis (about 2.5%) were comparable in both groups. Of the BCG-failing patients, 2.6% had serious side effects compared to 5.4% in BCG-naïve patients. Although the authors concluded that this study is a benchmark for the combination of BCG and IFN as salvage therapy, they also indicated that the incremental value of IFN could not be determined. Moreover, confirmation of these phase 2 results seems appropriate.

In summary, the combination of BCG and IFN-α seems a promising second-line immunotherapy regimen after BCG failures, but results should be confirmed.

6. **Device-assisted instillations after BCG failure**

Although intravesical chemotherapy is not a standard treatment option in BCG failures, intravesical chemotherapy combined with an energy source
might be better. Examples are the combination of intravesical MMC and a current gradient between the drug and the bladder wall (electromotive drug administration [EMDA]), and the combination of intravesical MMC and bladder wall hyperthermia (Synergo).

Feasibility and safety of both techniques were compared and tested as four weekly ablative sessions prior to TUR in 29 (thermochemotherapy) and 15 (EMDA) patients [35]. Treatments were safe, and the complete response rates were 40% for EMDA and 66% for thermochemotherapy, as compared to 27.7% with four weekly MMC instillations only. In a recent study, the potential of EMDA with MMC was confirmed. In 108 high-risk patients with superficial bladder cancer passive MMC instillations were prospectively compared to MMC with EMDA, and BCG as a third arm [36]. All groups were treated with one or two 6-wk courses. The 6-mo complete response rates were 31% for MMC, 58% for MMC with EMDA, and 64% for BCG. Side effects with EMDA were more than with MMC alone, but still significantly less than with BCG. Plasma MMC concentrations were also higher after EMDA. Unfortunately, no data for MMC with EMDA in BCG failures have been reported.

The combination of intravesical hyperthermia and MMC has also been studied in recent years, both in vivo and in vitro. This so-called Synergo treatment combines heating of the bladder wall to a temperature around 42 °C with a cooled solution of MMC. Heating is done with special microwave equipment and a special catheter with thermocouples to control for temperature (changes). Randomized trials have shown superiority of thermochemotherapy over MMC alone. In grade 3 patients Gofrit et al recently showed that thermochemotherapy can be used both to prevent recurrences and as ablative treatment [37]. In the prophylactic setting 15 of 24 patients remained recurrence free after a mean follow-up of 35.3 mo. In the ablative setting 21 of 28 patients experienced a complete remission of the tumor, of whom 81% remained tumor free after a mean follow up of 20 mo. Thermochemotherapy also is reported to be successful in BCG failures [38]. In a group of 90 intermediate- and high-risk patients the 1- and 2-yr recurrence rates after 1 yr of thermochemotherapy therapy were 14.3% and 24.6%, respectively. No progression was noted. In 41 patients failing BCG treatment, the 1- and 2-yr recurrence rates were 23% and 41%, which are at least as good as the results achieved with BCG and IFN-α. In a recent update of this multicenter series with 76 eligible BCG-failing patients the 1- and 2-yr recurrence rate estimates were 17% and 38%, respectively (R. Colombo, personal communication). Remarkably, patients with a high recurrence rate before thermochemotherapy therapy fared worse than patients “only” failing BCG. Still, longer follow-up and more results will have to indicate the value of thermochemotherapy in patients in whom BCG fails.

Finally, photodynamic therapy (PDT) combines photo sensitizers that selectively bind to tumors and a powerful intravesical light source to destroy tumors. Waidelich et al used PDT after oral administration of 5-aminolevulinic acid (5-ALA) in 24 high-risk BCG-failing patients, including those with CIS [39]. They found 3 of 5 CIS patients and 4 of 19 patients with papillary tumors were recurrence free after a median of 36 mo. Hemodynamic side effects (hypotension and tachycardia) occurred in the majority of patients. These systemic side effects can be avoided with the intravesical administration of 5-ALA, as was studied in 31 patients, among whom were 10 BCG failures [40]. Treatment was done after 5-ALA administration with a mean laser light dose of 3.9 W for a mean time of 21 min. After an average follow-up of 23.7 mo, 16 patients were free of tumor recurrence, including 4 of 10 BCG-failing patients. Side effects were urinary tract infection in four patients and hematuria in seven patients. In conclusion, PDT might be a second-line treatment for patients with tumor recurrence after BCG failure. Especially if the newer generation of photo sensitizers, which at least have improved diagnostic potential, are used, these results might even be better.

In summary, PDT and especially the combination of intravesical hyperthermia and chemotherapy, are potential candidate strategies in BCG-failing patients.

7. Surgery after BCG failure

The guidelines of the EAU mention cystectomy as treatment of choice for CIS failing adequate BCG and as an option in other high-risk tumors [1]. A recent survey illustrates that radical therapy in these patients, indeed, is considered in a substantial number of high-risk patients [41]. In patients failing intravesical therapy, cystectomy even remains the treatment of choice, when patients are willing and compliant. The advantage of cystectomy in superficial tumors failing BCG is obvious. Tumor-specific survival is between 80% and 90% in 5 yr, and thereby approaches the 5-yr tumor-specific survival of 88–90% of the whole group of patients with superficial bladder cancer [42,43].
However, cystectomy for high-risk superficial disease has several problems. In the first place, a good TUR and good pathology in these high-risk patients are important but require expertise. Even if resection and pathology are state of the art, there is an approximately 10% chance of invasive disease on re-resection [44]. Therefore, re-resection should be considered in these patients. Secondly, when patients with superficial bladder tumors have a recurrence with invasive disease, a window of opportunity is apparently missed. A good illustration of the problems mentioned above is a recent publication from an experienced Spanish group [24]. Sixty-two patients failing adequate BCG treatment with a high-grade recurrence were treated with cystectomy. At final pathology, 17 patients had stage pT2 or greater in the cystectomy specimen, indicating understaging in 27%! Also, the 5-yr disease-specific survival rate of progressive patients was only 38%, significantly lower than in those patients without invasive tumor (90%, p = 0.006). The authors identified presence of tumor in the prostatic urethra before cystectomy as the only factor associated with clinical understaging (p = 0.003) and shorter survival (p < 0.0002). A third problem is an increased recurrence rate of approximately 25% in the upper urinary tract and prostatic urethra in high-risk patients who are treated successfully with cystectomy [45].

On the other hand, the price for this potential survival advantage is also obvious. Cystectomy is major surgery and not everyone is fit or willing to undergo this. Even in the best hands the mortality rate is 2–3%, and short-term and long-term morbidity occurs in approximately one third of the patients [42]. Moreover, erectile dysfunction after cystoprostatectomy in men remains a significant problem. Whether prostate-sparing techniques are the answer remains to be seen. The preservation of sexual function is much better than after nerve-sparing cystoprostatectomy. In a well-selected group of 100 patients, Valencien et al, for example, performed TUR of the prostate with frozen section of the prostatic urethra with subsequent cystectomy and ileal neo-bladder [46]. After 1-yr of follow-up 86 of 88 patients were fully daytime continent, and 84 were dry during the night with nocturia of maximal two times. Fifty of 61 presurgery potent men (82%) remained fully potent, and only 5 were impotent. However, oncologic results warrant caution. Although 5-yr cancer-specific survival was as expected, local recurrence were seen in five patients. Apparently, with sparing of the prostate and prostatic urothelium, there appears to be a 10–15% higher oncologic failure rate [47].

In summary, although cystectomy in high-risk superficial disease gives the best disease-specific survival, there is a significant chance of understaging, in which case the prognosis is worse. Even in the best-case scenario, a patient will end up with a diversion. Prostate-sparing cystectomy should still be considered investigational at this moment.

8. Conclusion

BCG failures are not one group of patients. BCG intolerance is inevitable and occurs in approximately 20% of patients during maintenance therapy. Fewer than 5% of patients never complete the induction course, meaning they never had sufficient BCG therapy. In BCG-intolerant patients, certainly those who never completed the induction course, intravesical therapy with another drug at the time of a recurrence is worth trying. Between 20% and 40% of patients, depending on follow-up time and risk profile, have a recurrence after adequate BCG therapy. When BCG is used as therapy, it induces a 70% initial complete response rate, which remains so in 50% after long follow-up. Those having a recurrence or not achieving a complete response are real failures. BCG failure cannot be predicted accurately on an individual basis. However, with clinical and histologic parameters risk groups can and should be identified, because the window of opportunity in failing patients is small; in case of tumor progression to muscle-invasive cancer the chance of survival drops dramatically.

Intravesical chemotherapy after BCG failure holds some promise but remains highly investigational. Second-line immunotherapy, the combination of BCG and IFN-α, is an effective regimen, but results should be confirmed. Device-assisted intravesical strategies, such as PDT and especially the combination of intravesical hyperthermia and chemotherapy are candidates to keep in mind for the near future. Finally, cystectomy gives the best disease-specific survival in patients failing BCG. The disadvantage is that even in the best-case patients will end up with a diversion. Although prostate-sparing techniques have better functional outcomes, oncologic results appear less, so this is still considered investigational. In all, patients in whom BCG fails are a challenge to the urologist and careful individualization of therapy in experienced hands seems warranted. New conservative possibilities should be explored, however, with the risk of being too late in a certain subgroup.
References


