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TOPIC PAPER

Treatment options for BCG failures

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Introduction

Scope of the problem

Despite the significant activity of bacillus Calmette-Guerin (BCG) on superficial bladder cancer, most patients eventually relapse. Even in the case of carcinoma in situ (CIS), where BCG is the undisputed superior intravesical agent, after up to 2 cycles of BCG therapy only 46.7% of all patients are disease free at 3.6 years median follow-up [1]. In countries where BCG is used as the predominant first line agent even for papillary disease it is expected that the BCG failure population accumulates in the prevalence pool, accounting for at least an estimated 50,000 cases in the United States alone.

Need for clear definitions of BCG failure

Herr and Dalbagni aptly noted that comparisons between therapies for BCG failure patients have been hampered by the lack of standard definitions for BCG failure and BCG-refractory transitional cell carcinoma (TCC) [2]. Some series have defined BCG failure after a single induction course of BCG [3, 4], others after two courses [5]. In addition, the methods of reporting the results have been inconsistent. Most studies have included all patients who received one or more courses of BCG [6–8]. Investigators have often combined patients with persistent disease (non-responders) and patients with recurrent disease after an initial response [3–5] and a few studies have combined patients who were non-responders to BCG and patients who could not complete BCG therapy because of toxicity (BCG intolerant) [5, 6]. Finally, most studies did not indicate the disease-free interval after the last BCG course. These inconsistencies have led to comparisons of outcome in a very heterogeneous population.

In the most general sense any recurrent disease after initiation of BCG therapy can be referred to as "BCG failure." However, to provide more uniformity in reporting, the following alternative descriptive terms for specific types of BCG failure should be used whenever possible:

BCG refractory

Failure to achieve a disease-free state by 6 months after initial BCG therapy with either maintenance or re-treatment at 3 months due to either persistent or rapidly recurrent disease. Also includes any progression in stage, grade, or disease extent by 3 months after first cycle of BCG, i.e., non-improving or worsening disease despite BCG.

BCG resistant

Recurrence or persistence of disease at 3 months after induction cycle but of lesser degree, stage or grade which subsequently is no longer present at 6 months from BCG re-treatment ± TUR, i.e., disease improves then resolves with further BCG.

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BCG relapsing

Recurrence of disease after achieving a disease-free status by 6 months, i.e., disease resolves after BCG then returns. Relapse is further defined by time of recurrence: early (within 12 months); intermediate (12–24 months); late (>24 months). Caution: relapsing disease while on active maintenance (within 3 months) may qualify as *BCG refractory*.

BCG intolerant

Disease recurrence after a less than adequate course of therapy is applied due to a serious adverse event or symptomatic intolerance that mandates discontinuation of further BCG, i.e., recurrent disease in setting of inadequate BCG treatment from drug toxicity.

Treatment options

BCG regimen adjustment

Several changes in the regimen of BCG administration have been explored to lessen the negative impact of BCG-related side effects for previous BCG intolerant patients. These changes include decreasing the dose of BCG to one-third or less [9], spacing the intervals between successive treatment to 2 weeks instead of 1 week [10], and decreasing the dwell time for BCG to as little as 30 min [11]. In most cases the incidence of significant side effects can be decreased 30–50% by any one of these manipulations. A combination of changes may be necessary for particularly difficult cases. Additional actions to improve or control symptomatology include administration of a fluoroquinolone antibiotic at 6 and 12 h after each BCG dose [12] or the use of NSAID or Cox-2 inhibitor drugs that may also potentiate favorable BCG immune responses [13]. The previous held belief that pain is necessary to achieve therapeutic BCG antitumor activity has been debunked by a recent large multicenter study [14].

Repeat BCG treatment

Possibly appropriate for both BCG resistant and BCG relapsing disease, the success of a second course of BCG has not been extensively reported and only a few published studies have specifically addressed this issue [15–19] (Table 1). Overall, about 35% of patients failing the first course of BCG achieve durable success with another BCG cycle. However, further courses of BCG are not recommended because of the reduced chance of success (<20%) coupled with the increased likelihood of tumor progression [21, 22]. Unfortunately there is insufficient data to assess the effectiveness of repeated BCG in refractory patients or those with recurrent T1 disease.

Standard intravesical chemotherapy

Of the various standard intravesical chemotherapeutic agents (thiotepa, adriamycin, and mitomycin), there is only minimal reported experience with their use in patients failing prior BCG. Malmstrom et al. reported a 19% 3-year disease-free rate amongst intermediate-high risk patients treated with mitomycin who had failed a prior first induction cycle of BCG [23]. Similarly, there is little data on the newer anthracycline derivative valrubicin, despite the fact that it was approved by the US FDA for BCG refractory patients with CIS. Of 90 valrubicin-treated patients with CIS ± papillary TCC who had failed at least 2 cycles of prior intravesical therapy, most commonly BCG, only 21% had a complete response at 6 months and 8% by 24 months [24]. An additional 16% of patients had reduction to stage Ta disease, the long-term significance of which is unknown. Notably, all five patients with stage T1 disease (previously resected) plus CIS failed to achieve a complete response at all. Given these poor results, it appears that conventional intravesical chemotherapy has little to offer patients failing BCG, especially with stage T1 or CIS disease.

Table 1 Reported durable (>2 years) disease-free rates for second course of full-dose BCG

Patient population	Number	Outcome	Author
Papillary TCC + CIS	15	4/15 (27%)	Merz et al. [15]
Superficial TCC	28	10/28 (36%)	Bretton et al. [16]
Superficial TCC	66	22/66 (41%)	Nadler et al. [17]
Superficial TCC	31	11/31 (35%)	Yamada et al. [18]
CIS	17	4/17 (24%)	Ovesen et al. [19]
Stage T1, grade 3	37	19/37 (51)	Brake et al. [20]
Stage T1, grade 3	22	6/22 (27%)	Pansadoro and De Paula [21]
Aggregate results	216	76/157 (35%)	

Interferon-alpha immunotherapy

The long-term (>2 year) success rate of IFN-α monotherapy of BCG failure patients (CIS and/or papillary TCC) is generally under 15% [25]. Furthermore, in a study of IFN-α monotherapy for primary stage T1 disease, IFN-α was found to be no better than water placebo at 43 months' follow-up, suggesting it has no role for recurrent stage T1 disease [26].

Combination BCG plus IFN-α

Several single institutional studies have demonstrated that the combination of low-dose BCG plus IFN-α may be useful as a salvage regimen in BCG failures [7, 8, 27, 28]. With follow-up ranging from 12 to 30 months, disease-free rates were in the range of 50–60% even in patients with recurrent T1 disease. Furthermore, no patient having an expedient cystectomy after BCG + IFN failure had unresectable or metastatic disease [7, 8, 29]. Results from a much larger group of 467 BCG failure patients in a multi-institutional study have revealed an overall 45% freedom from disease rate at 24-month median follow-up [30]. Importantly, among BCG failures, multivariate analysis has revealed that the response likelihood is based on both number of prior BCG (but not chemotherapy) failures as well as the relapse interval between BCG failures [31]. Over half of the patients failing one cycle of prior BCG are disease-free at 2 years, with 45% disease-free at 3 years (Fig. 1). The results are especially good for CIS single BCG failures with a 3-year complete-response rate of 54%, essentially identical to the 56% found in CIS patients receiving BCG plus interferon the first time. However, after two prior BCG failures, salvage therapy with low-dose BCG plus interferon remains limited, especially for CIS patients (2-year complete-response only 24%) versus papillary patients (35%) [32]. The situation is modified greatly by the interval from prior BCG failure whereby refractory (<6-month relapse) patients do much worse, but patients relapsing >12 months have 2-year disease-free rates approaching 60%. Other negative prognostic factors found to be important in multivariate analysis included age >80, stage T1 disease, >5 tumors, and tumor size >5 cm. Unfortunately, these studies to date were not made with direct comparison to BCG without the addition of IFN. Still, considering the magnitude and durability of the response, this therapy should be considered for BCG resistant and BCG relapsing patients. It should not be advocated for true BCG refractory disease, especially in patients with high-grade stage T1 disease or CIS.

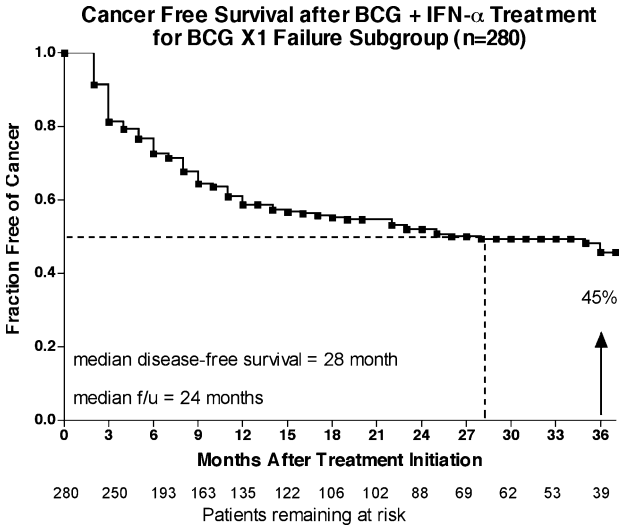

Fig. 1 Cancer free survival after BCG + IFN-α treatment for BCG X1 failure subgroup ($n = 280$)

Technological advances in standard intravesical chemotherapeutic drug delivery

Better delivery of standard intravesical chemotherapeutic agents has the potential to improve outcome in high-risk patients and is just beginning to be applied to BCG failure patients. Currently there are two competing technologies undergoing clinical trials that may result in resurgence in the use of intravesical chemotherapy after BCG failure.

Local microwave hyperthermia in conjunction with mitomycin C [(MMC) 20 mg/50 cc] was compared in a multicenter randomized trial to intravesical MMC alone in 83 patients [33]. Hyperthermia was delivered at a temperature of 42°C for at least 40 min. At a minimum follow-up of 24 months, there was a statistically significant reduction in recurrences between the two groups: 17.1% for chemothermotherapy versus 57.5% for chemotherapy alone. This modality has also been used in treating patients with high-grade superficial bladder cancer (Ta T1 G3) as a prophylactic (40 mg MMC) or ablative (80 mg MMC) protocol [34]. In 24 patients administered the prophylactic protocol, 62.5% were recurrence-free after a mean follow-up of 35.3 months. The ablative protocol was administered to 28 patients with complete ablation of the tumor in 75% and a recurrence-free rate of 80.9% at a mean follow-up of 20 months. An preliminary report of this technology in intermediate and higher-risk patients, 45% of which were prior BCG failures, revealed a 75% disease-free rate at 2 years [35].

Electromotive intravesical mitomycin C (eMMC) has been proposed to improve drug delivery across

biological membranes with increased accumulation in bladder tissue. In a trial involving patients with CIS, three groups were randomized to 40 mg eMMC instillation with 20 mA electric current for 30 min, 40 mg passive MMC with a dwell time of 60 min or 81 mg BCG with a dwell time of 120 min [36]. Patients were scheduled for an initial six weekly treatments, a further 6 weekly treatments for non-responders and a follow-up of ten monthly treatments for responders. There was a statistically significant superior complete response rate at 6 months for eMMC (58%) compared to passive MMC (31%). The response rate of eMMC approached that of BCG (64%). Peak plasma MMC was significantly higher following eMMC than after passive MMC (43 ng/ml vs. 8 ng/ml), supporting the hypothesis that electromotive MMC increases tissue levels.

New intravesical chemotherapeutic drugs

Recently, two newer cytotoxic chemotherapeutic drugs, gemcitabine and docetaxel, with known systemic activity against advanced bladder cancer, have been tried in the intravesical route (Platinum derivatives have also been tried but were generally too irritating and associated with occasional fatal anaphylaxis [37]). As non-vesicants (agents that do not cause contact tissue injury), both gemcitabine and docetaxel have been generally well tolerated with minimal induction of cystitis and little systemic absorption. The exception has been in multiply previously treated patients where gemcitabine intolerance was seen in 8 of 64 (13%) patients, necessitating withdrawal [38]. Activity against marker lesions and primary and previous refractory tumors has been demonstrated in multiple phases I and II trials with gemcitabine [39]. Several early reports have demonstrated modestly high levels of complete responses (30–50%) in patients with otherwise BCG refractory disease [40–42]. However, in the largest and most dose-intensive regimen with the longest follow-up, the 1-year complete-response rate was only 21%, suggesting that single-agent gemcitabine will not likely meet its role as a universal salvage drug. Yet limited results have been reported for docetaxel. In 18 patients, most of whom had failed other therapies, six patients were disease-free at a 14-month median follow-up (33%) [43, 44]. Docetaxel was very well tolerated.

Combination drug strategies

While multi-agent chemotherapy has become the norm in almost all cases of systemic chemotherapy, previous attempts to use combined or alternating older chemotherapy drugs, such as adriamycin and mitomycin intravesically, were frustrated by severe cystitis despite some evidence of enhanced activity [45]. However, combinations of drugs in which one or both are non-vesicants may be better received. One such combination of immediate sequential gemcitabine followed by mitomycin reported a near 50% recurrence-free rate in 27 BCG refractory patients at 18 months compared to 20% with gemcitabine alone in 12 similar patients [46]. Further study with yet other combinations of the non-vesicants, gemcitabine and docetaxel, appear to be justified.

Other alternatives

External beam radiation therapy with or without systemic chemotherapy is rarely appropriate for the treatment of superficial bladder cancer because it may cause significant morbidity while displaying limited efficacy. CIS is particularly resistant and low-grade disease responds more poorly than higher-grade disease. Some benefit may be derived for patients with stage T1 G3 tumors with radiochemotherapy following a complete TURBT with a 5-year reported survival of 76% [47]. Photodynamic therapy using hematoporphyrin derivatives can achieve a high initial complete response rate especially against CIS but generalized cutaneous photosensitivity remains limiting [48]. Moreover, severe local irritative symptoms persisting for months are not uncommon as well as occasional severe loss in bladder capacity. Newer, better-tolerated photoporphorins are under development but such therapy is still only available at very few select centers [49].

BCG failure and cystectomy

The American Urological Association's Bladder Cancer Clinical Guidelines Panel concluded that cystectomy or further intravesical therapy may be considered for CIS or high grade T1 cancer that persists or recurs after initial intravesical treatment [50]. This same opinion was echoed by two independent panels of international consultants on bladder tumors [51, 52]. It has been shown that after BCG failure, each additional course of BCG carries a 7% actuarial risk of progression [22]. Reports from various BCG treatment series involving aggressive superficial TCC report a median time to progression averaging 24 months with rare occurrences before 6 months [52]. Another study showed that tumor response at 6 months was the single most important point for predicting ultimate failure

and progression [53]. This corresponds to the use of up to two series of 6-week induction treatments with BCG. Thus, recurrent aggressive disease 6 months after diagnosis or disease persisting after two courses of BCG therapy is a strong indication to consider radical therapy.

Patients who fail BCG and wish to have conservative treatment for their recurrent disease should be stratified according to their risk of progression. Those with T1 high-grade disease and CIS are at high risk of progression and should be cautioned on the risk of progression while second-line therapy is contemplated. Patients with Ta low-grade disease are at low risk of progression and may have second-line therapy without compromising their survival. Patients with Ta high-grade disease have a similar progression risk as those with T1 tumors [54]. There are also certain other features that convey a greater risk of ultimate failure: multifocal disease, failure to ever achieve a complete response (refractory disease), and prostatic urethral involvement [55, 56]. In these cases, failure to respond to even a single course of BCG may justify early radical therapy. Reliable prognostic tumor markers that identify patients at risk of progression after BCG failure are still lacking [57].

While all conservative treatments for BCG failure patients remain investigational and uncertain, cystectomy remains the treatment of choice. However, some patients are not candidates for radical surgery due to comorbid medical illness and others refuse to consider the change in their lifestyle that the surgery entails despite being counseled about the risks. It is for this group of patients that the urologist will exhaust all possibilities to avoid radical surgery. Furthermore, radical cystectomy is associated with 28% morbidity and 2.5% mortality [58]. This, among other reasons, could explain why a survey of 105 practicing US urologists on treatment preferences of superficial bladder cancer showed that only 19% would treat high grade Ta-T1 disease that has failed BCG twice with radical therapy [59]. For those who are good surgical candidates, the timing of cystectomy is an important consideration. A non-randomized study has shown that patients with high-risk superficial bladder cancer failing BCG therapy have improved survival with an earlier rather than a delayed cystectomy [60]. Unfortunately, there have been no prospective randomized trials comparing cystectomy to second-line intravesical therapy for high-risk superficial bladder cancer patients. Thus, while alternative therapy continues to be actively developed, cystectomy remains the standard of care for high-risk patients with BCG failure.

Conclusions

Patients failing BCG are becoming an ever-increasing problem. Failures due to BCG intolerance can often be managed by several regimen adjustments to maintain tolerance. For single course BCG failures or late relapsers, the addition of interferon to BCG has proven very effective. However, patients with high-risk superficial bladder cancer refractory to BCG are also at high risk for progression and must be counseled accordingly. For those who are good surgical candidates, cystectomy remains the treatment of choice and should not be delayed. New treatment modalities are evolving and may be considered for select intermediate risk patients or those who either cannot or will not consider a cystectomy. Technological advances in chemotherapy drug delivery with microwave or electromotive adjuncts are showing promise. Likewise, the new intravesical drugs gemcitabine and docetaxel are demonstrating activity from phases I and II trials with further encouraging data emerging from combination strategies.

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