



Collaborative Review – Bladder Cancer

The Role of Bacillus Calmette-Guérin in the Treatment of Non-Muscle-Invasive Bladder Cancer

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Abstract

Context: Bacillus Calmette-Guérin (BCG) remains the most effective intravesical treatment for non-muscle-invasive bladder cancer (NMIBC), but the clinical development of BCG has been accompanied by controversy. Recent publications have called into question a number of aspects related to its use.

Objective: To review the current clinical role of BCG in NMIBC, focusing on efficacy and tolerability as primary objectives and on strategies to predict response and decrease toxicity as secondary objectives.

Evidence acquisition: We performed a systematic literature search of published articles in PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases for the period from 1976 to November 2008. The following “free text” combination was used in the first instance: “BCG and intravesical and bladder cancer.” Further free text searches were performed by separately adding the following keywords to the combination “BCG and intravesical”: *survival, progression, recurrence, maintenance, dosing, toxicity, tolerability, side effects, prognostic factors*.

Evidence synthesis: BCG is the most effective intravesical agent for preventing NMIBC recurrence, but its role in disease progression remains controversial. In intermediate-risk NMIBC, the superiority of BCG over chemotherapy is well established for disease recurrence but not for progression and needs to be balanced against higher toxicity. With regard to high-risk NMIBC, there is sufficient evidence to show that BCG is the most effective treatment of carcinoma in situ for ablation, disease-free interval, and progression, but the impact of BCG on the natural history of T1G3 tumors relies on a low level of evidence. Maintenance remains crucial for efficacy. The dose can be safely and effectively reduced to decrease its toxicity, which is slightly greater than chemotherapy.

Conclusions: BCG should still be viewed as the most effective intravesical agent, but its role in the progression of papillary tumors needs to be clarified. BCG remains an alternative to intravesical chemotherapy in intermediate-risk NMIBC, and it is recommended as the standard of care for high-risk NMIBC.

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1. Introduction

After more than 30 yr of research, bacillus Calmette-Guérin (BCG) remains the most effective intravesical treatment in non-muscle-invasive bladder cancer (NMIBC). The key element of BCG antitumor activity resides in its ability to switch on a robust cellular immune response, although the precise mechanism of action is not yet fully understood. The complex immunologic cascade starts with the initial adherence of mycobacteria to the urothelial lining and proceeds through the secretion of cytokines from urothelial cells, a process that attracts a large array of inflammatory cells (neutrophils, monocytes) [1]. This cascade has provided a rationale for the use of BCG. Urinary cytokine patterns and the intensity of bladder wall infiltration with immunocompetent cells have helped to define the treatment schedule and the concept of maintenance. Nonetheless, the clinical development of BCG has been, and still is, accompanied by controversy, from the initial cautiousness generated by the fear of lethal complications to the recognition of BCG as the most effective intravesical agent to date. Recent publications, however, have called into question a number of aspects related to its use.

The purpose of this review is to conduct a critical analysis of the available literature to provide answers to a number of controversial questions. Issues include the comparison of efficacy and tolerability of BCG with chemotherapeutic agents, the optimization of BCG dose and regimen of administration, and factors predicting BCG's clinical success. The optimization of the dose and regimen with a view to reducing toxicity and the identification of predictors of response are addressed as secondary objectives.

2. Evidence acquisition

A literature search was conducted according to current methodological recommendations for systematic reviews [2]. The search was focused on the primary outcome measures of survival, progression, recurrence, and toxicity after intravesical BCG in NMIBC and on secondary outcome measures including predictors of response and methods to reduce toxicity.

The PubMed, Embase, and Cochrane Central Register of Controlled Trials databases were searched for the period from 1976 to November 2008, using the following “free text” combination in the first instance: “BCG and intravesical and bladder cancer.” Further free text searches were performed by separately adding the following keywords to the combination “BCG and intravesical”: *survival, progression, recurrence, maintenance, dosing, toxicity, tolerability, side effects, prognostic factors*.

Identified articles were examined by two authors (PG and MO), and the most relevant articles were selected according to their level of evidence, as defined by the Oxford Center for Evidence-based Medicine [3]. When meta-analyses were available, individual papers were not cited unless they contained relevant concepts not addressed in the meta-analysis itself. The initial list of selected papers

was further enriched by individual suggestions from a panel of international expert opinion leaders in the topic who acted as coauthors of the present review (RS, JAW, AB, P-UM, MO'D).

3. Evidence synthesis

3.1. Mode of bacillus Calmette-Guérin administration

3.1.1. Strain

By the time the original Pasteur strain vaccine obtained by Calmette and Guérin after 231 passages in subcultures could be lyophilized for storage, many additional passages had been made. These passages resulted in a number of additional strains with phenotypes that were different from the original but that retained the same antigenic potency [4]. Some were named after the location of origin. The current view is that different strains do not differ in efficacy, although only a few comparative studies exist. A meta-analysis published in 2002 [5] suggested that there were no large differences in efficacy between the Pasteur, Frappier, Connaught, Tice, and RIVM strains. Thus, any of the commercially available strains currently can be proposed for intravesical use.

3.1.2. Dose

The first intravesical BCG dose was empirically determined to be 120 mg (Frappier strain), based on the observation that the same dose was well tolerated by intradermal scarification [6]. Since then, several attempts have been made to find a lower dose that is as effective and has less toxicity. As shown in Table 1, there is clear evidence that a half dose of the Pasteur BCG strain (75 mg) and a one-third dose of the Connaught (30 mg) and Danish (40 mg) strains are less toxic but are as effective as their respective full doses. In contrast, a one-sixth dose of the Connaught strain is significantly less effective than a one-third dose, despite the same toxicity level [7]. It seems that a three-fold decrease in dose of intravesical BCG is as effective against progression as the standard dose, even in patients with high-risk T1G3 and carcinoma in situ (CIS), with significantly less toxicity [8]. The habit of measuring BCG dose in milligrams rather than in number of bacilli is inaccurate and could potentially affect the immunogenic effectiveness of BCG.

3.1.3. Timing of the first instillation

BCG induction instillations usually start a minimum of 2 wk after transurethral resection (TUR) to allow healing of the urothelium and to decrease the risk of systemic side effects; nevertheless, in some studies, BCG was initiated as early as 7 d after TUR [9,10].

3.1.4. Induction course

The six weekly instillations were empirically chosen by Morales et al because the Frappier strain was packed in six separate vials and adverse events lasted <1 wk [6]. Bassi et al tested a modified induction course with an instillation interval of 2 wk and showed a reduction in

Table 1 – Low-dose bacillus Calmette-Guérin (BCG) efficacy and toxicity: Comparison of recent studies

Authors	BCG dosage and strains	Cases	Mean follow-up	Major findings
Pagano et al. [65]	BCG Pasteur strain, 75 mg vs 150 mg	183	NA	Reducing the dose resulted in decreased toxicity without affecting BCG efficacy.
Losa et al. [64]	BCG Pasteur strain, 75 mg	70	74 mo	After induction and maintenance, 71.4% of patients were disease free, 17.1% had recurrence, and 11.4% had progression. The drug was well tolerated with few side effects (mainly cystitis-like symptoms [25.7%], hematuria [8.5%], fever [11.4%]). No patients stopped treatment because of severe toxicity.
Mack et al. [67]	BCG Connaught strain, 30 mg	44	NA	The ablative effect of 30 mg BCG on a marker lesion appears to be similar to the effect of full-dose BCG. Patients had local side effects (dysuria [54%], hematuria [39%]) but no BCG-induced infection or sepsis.
Martinez-Pinero et al. [68]	BCG Connaught strain, 81 mg vs 27 mg	500	69 mo	Toxicity was significantly less frequent or severe with reduced dose, with similar results for recurrence and progression. However, patients with multifocal tumors fared better with the standard dose, and there was a trend toward better recurrence rates in high-risk tumors.
Martinez-Pinero et al. [8]	BCG Connaught strain, 81 mg vs 27 mg	155	61 mo	Three-fold decreased dose of intravesical BCG is as effective as the standard dose against progression in patients with high-risk stages T1G3 and Tis superficial bladder carcinoma but with significantly less toxicity.
Agrawal et al. [69]	BCG modified Danish strain 1331, 40 mg vs 80 mg vs 120 mg	152	36 mo	No difference in efficacy of BCG in dosage 40 mg, 80 mg, and 120 mg. Toxicity is decreased if the dose is reduced to 80 mg or 40 mg.
Ojea et al. [7]	BCG Connaught strain 27 mg vs 13.5 mg vs MMC 30 mg	430	52 mo	One-third of the standard dose, BCG 27 mg, is more effective than MMC, and it is the minimum effective dose as adjuvant treatment for intermediate-risk superficial bladder tumors. One-sixth of the standard dose, BCG 13.5 mg, is less effective than BCG 27 mg, and toxicity levels are similar.

MMC = mitomycin C.

side effects [11]. Alternatively, some authors tried to reduce the number of instillations on the basis of Zlotta et al, who showed that in most patients, the maximal peripheral immune response was already observed after four weekly instillations, although patients who were not previously immunized against mycobacterial antigens required six instillations to achieve maximum stimulation [12]. More recently, De Boer et al reported that in the mouse model, a schedule consisting of only two BCG instillations, administered in weeks 1 and 6, showed the same level of Th1 cytokines compared to six weekly instillations, with a positive effect on the Th1–Th2 ratio; the immune reaction seems to be dependent on the time interval between the two instillations [13]. Until further studies establish the feasibility of these schedule modifications in humans, the six weekly instillation regimen is considered to be the standard induction course.

3.1.5. Repeat induction course

Repeating the BCG induction course has been suggested in two situations. The first is BCG recurrence, defined as disease recurrence while off treatment after a period of being disease free. In this case, a second course of BCG is often successful, particularly in those cases with a longer disease-free interval after the first course [14]. The second situation applies to CIS that persists after an initial induction course. Forty percent to 60% of patients who do not respond to the initial induction course respond to a

second cycle of six weekly instillations [9,15,16]. Patients whose disease persists beyond that time have a poor prognosis and are considered to have *BCG refractory disease* [17]. There is no evidence that a repeat induction course improves the clinical outcome of T1G3 high-risk NMIBC. In case of positive urine cytology with negative biopsy mapping of the bladder, it is mandatory to exclude presence of CIS in the urethra or in the upper urinary tract.

3.1.6. Dwell time and dilution

The standard duration of BCG retention, defined as *dwell time*, is 1–2 h, as originally proposed by Morales et al. [6]. There is no evidence of a significant difference between 1 h and 2 h of dwell time in terms of either adhesion of BCG to the bladder wall or patient tolerability. Reducing the dwell time to ≤ 30 min could be an alternative to dose reduction in patients with pronounced BCG side effects after instillation [18].

3.1.7. Maintenance bacillus Calmette-Guérin: The longer, the better?

Maintenance has been advocated as a crucial factor for BCG efficacy. A maintenance regimen consisting of three weekly instillations at 3 mo, 6 mo, and then every 6 mo up to 3 yr was compared to induction BCG alone in 384 high-risk NMIBC patients in Southwest Oncology Group (SWOG) trial 8507 [12]. With a median follow-up of 90 mo, maintenance BCG doubled disease-free survival and significantly reduced

the time to disease worsening. The choice of the three weekly instillations was based on experimental evidence showing that urinary cytokine levels peak 3 wk following the initial induction course [19]. The observation that lymphocytic infiltration and delayed cutaneous hypersensitivity response weaken after 6 mo provided evidence for the interval of maintenance cycles [20], while the 3-yr duration was chosen for convenience. Only 16% of the 243 maintenance patients received all eight scheduled maintenance courses during 3 yr [12]. Other maintenance schedules have been described in the literature. The Club Urológico Español De Tratamiento Oncológico (CUETO) group used short-term BCG maintenance (once every 2 wk, six instillations) [21]. Pansadoro et al. [22] administered three cycles of BCG as maintenance, with the first cycle every 2 wk for six instillations, the second cycle monthly for six instillations, and the third cycle every 3 mo for six instillations. New studies would be required to assess any differences in efficacy between these various maintenance schemes.

The key role of maintenance in the efficacy of BCG has been further emphasized in recent meta-analyses of randomized controlled trials (RCTs). As shown in Tables 2 and 3, maintenance is a prerequisite for superiority of BCG over mitomycin C (MMC). In the meta-analyses by Malmstrom et al. [23] and Bohle et al. [24], BCG was superior to MMC in the prevention of recurrences only in the trials with maintenance BCG. Bohle et al found that a minimum of 12 instillations during 1 yr were necessary to achieve superiority over MMC. A meta-analysis of progression demonstrated the need for maintenance BCG by using indirect comparisons: The relative effect of BCG on progression was greater in the presence of maintenance than in its absence [5].

Recently, the benefit of maintenance BCG has been questioned. After a critical analysis of the current evidence, Herr [25] claimed that maintenance BCG does not appear to be superior to the initial induction BCG treatment in preventing or delaying tumor progression, and prolonged BCG treatment adds toxicity. The controversial role of BCG in the progression of NMIBC (see section 3.2.2) calls into question the use of long-term maintenance; however, based on the overall body of evidence, BCG maintenance is still considered to be necessary for BCG to be effective. While the optimal maintenance scheme has yet to be determined, the 3-yr scheme outlined by Lamm et al. [9] remains the only schedule supported by randomized trials.

3.1.8. *Bacillus Calmette-Guérin combination therapies*

Several BCG-combination therapies have been explored to improve BCG efficacy (Table 4), both in primary high-risk NMIBC and in BCG failures.

3.2. *Bacillus Calmette-Guérin efficacy*

3.2.1. *Recurrence*

BCG is currently considered the most effective intravesical agent for preventing recurrence in NMIBC. This evidence has been generated by RCTs comparing BCG to chemotherapy, with most of the trials having been included in

published meta-analyses. As shown in Table 2, five meta-analyses of controlled studies have concluded that BCG is superior to chemotherapy [23,24,26–28], with four of the five specifically comparing BCG with MMC. Although four of the meta-analyses did not use individual patient data and several included nonrandomized studies, a recent meta-analysis without these limitations demonstrated the superiority of BCG to MMC in preventing recurrence, both in previously treated and previously untreated patients, but only when maintenance BCG was given [23], confirming results reported in previous meta-analyses. MMC was administered using some form of maintenance beyond the six- or eight-induction instillations in all but one of the studies. A comparison of maintenance schedules for BCG and MMC was reported in an American Urological Association (AUA) guidelines panel subanalysis [26], in which maintenance BCG was still shown to be superior, even when MMC was given with maintenance. The recurrence-free interval when BCG was given at one-third dose was also significantly longer than with MMC [7]. In contrast, when both drugs are administered without maintenance, no difference in efficacy can be demonstrated. This conclusion is supported by a cross-study comparison of arms in randomized trials provided by the AUA guidelines panel [26] and by a recent RCT [29]. Both Friedrich et al. [29] and Malmstrom et al, in their recent meta-analysis [23], found that maintenance MMC was superior to nonmaintenance BCG.

3.2.2. *Progression*

The main limitations of the available literature for assessing the relative efficacy of BCG on progression are heterogeneity in patient risk, a relatively short follow-up period, and the limited number of events that are observed in the individual studies, along with a nonuniform definition of disease progression in these trials. The assumption of *progressive disease* as “any increase” in stage or grade [27] is certainly too vague compared with the more reliable definition of “increase to stage T2 or higher” [5].

Several meta-analyses have concluded that BCG, but not intravesical chemotherapy, delays bladder cancer progression. The largest meta-analysis showed that maintenance BCG reduced the risk of progression when compared with all other conservative treatment strategies combined and also when compared with chemotherapies other than MMC [5]. No conclusion could be drawn in the subgroup of studies comparing BCG and MMC [5]. Among five previous meta-analyses comparing BCG and MMC for disease progression (Table 5), only one concluded the superiority of BCG over MMC when maintenance BCG was used [30]; however, this meta-analysis also included several nonrandomized studies. The four other meta-analyses could not detect a difference, regardless of the use of maintenance [5,26,27,31]. More recently, an individual patient data meta-analysis in 1880 patients, three-quarters of whom were intermediate risk, could not detect a significant benefit of BCG compared with MMC for tumor progression [23]. Thus, the ability of BCG to prevent disease progression remains controversial.

Table 2 – Comparative meta-analyses of bacillus Calmette-Guérin (BCG) and intravesical chemotherapy related to non-muscle-invasive bladder cancer (NMIBC) for disease recurrence

Author	Type of study	Disease category	No., treatment: dose/maintenance*	Main outcome	Comment
Shelley et al. [27]	Meta-analysis of six RCTs comparing BCG and MMC, selected based on the allocation of concealment method of randomization (Cochrane Collaboration Handbook)	Intermediate- or high-risk NMIBC	834 BCG: different strains, low-full doses 693 MMC: 20, 30, or 40 mg	Parmar 1998 method ln(hour) – 0.0221 (variance: 0.00512) (<3% difference in probability of progression in favor of BCG)	No significant difference between BCG and MMC
Bohle et al. [24]	Meta-analysis of 11 studies comparing BCG and MMC; four were quality B (two of four were retrospective)	Ta, T1, any grade	1421 BCG, 1328 MMC	Median follow-up: 26 mo OR: 0.56, significantly in favor of BCG OR: 0.42, significantly in favor of BCG in the six studies in which maintenance was used No significant difference when BCG maintenance is not used (OR: 0.91) OR: 0.88, significantly in favor of BCG	BCG significantly superior over MMC only when maintenance is used
Han and Pan [28]	Subgroup analysis of 10 trials comparing BCG to chemotherapy (from a meta-analysis of 25 trials comparing BCG and different non-BCG arms); RCT and controlled observational cohort studies included	Ta, T1, any grade, or CIS	378 BCG, 398 different chemotherapeutic agents		BCG superior to MMC Notably, a significant proportion of the trials considered had a fairly low number of patients and were clearly not RCTs
Hall et al. [26]	Meta-analysis of RCTs	All risk-level disease	MMC maintenance vs BCG induction (<i>n</i> = 1066 patients from three studies) BCG maintenance vs MMC maintenance (<i>n</i> = 594 patients from two studies)	–7% (CI: –15–0) recurrence rate with MMC –17% (CI: –26 to –7) recurrence rate with BCG	MMC with maintenance significantly better than BCG without maintenance BCG with maintenance significantly better than MMC with maintenance
Malmstrom et al. [23]	Individual patient data meta-analysis of nine RCTs	Intermediate- and high-risk NMIBC	BCG (<i>n</i> = 1437) MMC (<i>n</i> = 1383)	Median follow up: 4.4 yr No difference in time to first recurrence between BCG and MMC 32% (<i>p</i> < 0.0001) reduction in risk of recurrence with maintenance BCG 28% (<i>p</i> = 0.006) increase in risk of recurrence with no maintenance BCG	BCG significantly better than MMC only with maintenance MMC significantly better than nonmaintenance BCG

CI = confidence interval; CIS = carcinoma in situ; MMC = mitomycin C; OR = odds ratio; RCT = randomized controlled trial.
* Maintenance is defined as any instillation beyond the induction course.

Table 3 – Relevant studies and meta-analyses addressing the efficacy of bacillus Calmette-Guérin (BCG) in high-risk non-muscle-invasive bladder cancer (NMIBC)

Author	Type of study	Comparisons	Type of high-risk patient	End points	No. of patients	Treatment dose/maintenance*	Main outcome	Comment
Patard et al. [34]	Retrospective, case control	TUR alone vs TUR plus BCG	T1G3	Progression, recurrence, survival	30 (TUR alone) 50 (TUR plus BCG)	75–150 mg Pasteur times 6 wk, 13 patients had maintenance	Median follow-up: 63 mo Progression and CSS [§] : 22% and 90%, respectively, with BCG vs 46.7% and 70%, respectively, with TUR alone	TUR plus BCG may improve survival over TUR alone.
Shahin et al. [35]	Retrospective, case control	TUR alone vs TUR plus BCG	T1G3 with or without CIS (12%)	Recurrence, progression, survival	92 (TUR alone) 61 (TUR plus BCG)	NA	Median follow-up: 5.3 yr Recurrence: 70% BCG vs 75% TUR alone Progression: 33% BCG vs 36% with TUR TTP: 38 mo with BCG vs 28 mo without BCG CSS [§] : 77% BCG, 79% without BCG	BCG delays recurrence and progression. No influence on overall survival and CSS.
Shelley et al. [27]	Subanalysis of three of six RCTs selected for a meta-analysis	BCG vs MMC	Patients with intermediate- or high-risk NMIBC at high risk of recurrence**	Recurrence	828	BCG: different strains, low-full doses MMC: 20, 30, or 40 mg	Parmar 1998 method ln(hours) minus 0.3714 (variance: 0.0122), indicating a 31% reduction in the risk of recurrence with BCG	Favor BCG for the reduction of recurrence; progression not evaluable.
Sylvester et al. [42]	Meta-analysis of nine RCTs	BCG vs chemotherapy	Primary, secondary, or concurrent CIS	CR*** rate, recurrence, progression, survival	345 (BCG) 355 (chemotherapy)	BCG: different strains, 75% maintenance Chemotherapy: four agents (50% MMC), 95% maintenance	Median follow up: 3.6 yr OR: 0.53 ($p = 0.0002$), for CR OR: 0.47 ($p = 0.008$), for recurrence in favor of BCG OR: 0.74 ($p = 0.2$), favoring BCG for progression	BCG significantly better than chemotherapy for CR and recurrence. Superiority over MMC significant only when maintenance BCG used. Insufficient power to state superiority of BCG in progression and survival.

Table 3 (Continued)

Author	Type of study	Comparisons	Type of high-risk patient	End points	No. of patients	Treatment dose/maintenance*	Main outcome	Comment
Gardmark et al. [38]	RCTs	BCG vs MMC	Ta G1-3 or T1 G1-2, with at least three tumor events in the previous 18 mo or any T1G3 and CIS	Progression (increased in stage from Ta to T1 and from T1 to T2), CSS	130 (BCG) 131 (MMC)	BCG: 120 mg Danish strain with 2 yr maintenance MMC: 40 mg with 2 yr maintenance	Median follow-up survivors: 123 mo Progression: 23% with MMC and 19% with BCG	No significant difference in progression, overall survival and CSS between BCG and MMC
Hall et al. [26]	Meta-analysis of RCTs	BCG vs MMC	No G1 tumors or any T1 or any CIS	Progression	79 (MMC maintenance) 260 (BCG induction) 341 (BCG maintenance)		Recurrence: 62% with MMC maintenance, 32% with BCG induction, 34% with BCG maintenance Progression: 10% with MMC maintenance, 14% with BCG induction, 14% with BCG maintenance	BCG better on recurrence, no significant difference in progression
Thalmann et al. [37]	Retrospective, case control	BCG vs early cystectomy	T1G3	Progression, CSS [§]	92 (BCG) 29 (immediate cystectomy)	NA	Median follow-up: 3.9 yr for cystectomy, 6.9 yr for BCG 5-yr CSS: 80% with BCG and 69% with cystectomy	No apparent survival benefit of early cystectomy but selection bias toward higher risk for cystectomy
Denzinger et al. [36]	Retrospective, case control (patients choose treatment)	BCG plus delayed cystectomy vs early cystectomy	T1G3 with more than two risk factors (CIS 46%, multiple tumors 45%, >3 cm 75%)	CSS	51 (BCG) 53 (early cystectomy)	No maintenance	Median follow-up: 5.4 yr 10-yr CSS: 78% in early cystectomy vs 51% in BCG plus delayed cystectomy	Early cystectomy provides significantly better survival than BCG in T1G3 with two or more risk factors

CIS = carcinoma in situ; CR = complete response; CSS = cancer-specific survival; MMC = mitomycin C; NA = not applicable; TTP = time to progression; TUR = transurethral resection.

* Maintenance is defined as any instillation beyond the induction course.

** Definition of *high risk* in the three studies subanalyzed by Shelley et al. [27]: (1) CIS or Ta-T1 G1-3 with two previous recurrences; (2) any T1 or any CIS or Ta with two recurrences within 1 yr and/or two to three tumors at 4-mo cystoscopy; (3) any T1G3 and CIS or Ta G1-3/T1G1-2 with more than three recurrences in 18 mo.

*** Complete response is defined as negative cytology, cystoscopy, and biopsies.

Table 4 – Combination bacillus Calmette-Guérin (BCG) therapies

Authors	Type of study	Patient characteristics	Cases	Median follow-up	Major findings
BCG plus IFN-α intravesical therapy					
Joudi et al. [45] Gallagher et al. [80]	Multicenter phase 2 trial	Ta, T1, CIS; BCG-naïve and BCG-refractory	1003	24 mo	59% recurrence-free rate for BCG naïve, 45% recurrence-free rate for BCG refractory
O'Donnell et al. [81]	Multicenter phase 2 trial	Ta, T1, CIS; BCG-naïve and BCG-refractory	490	24 mo	57% recurrence-free rate for BCG naïve, 42% recurrence-free rate for BCG refractory
Lam et al. [82]	Prospective study	Ta, T1, CIS; BCG-naïve and BCG-refractory	32	22 mo	75% recurrence-free rate for BCG naïve, 60% recurrence-free rate for BCG refractory
Punnen et al. [83]	Retrospective review	Superficial TCC; BCG-refractory	12	12 mo	50% recurrence-free rate
O'Donnell et al. [84]	Prospective study	Superficial TCC; BCG-refractory	40	30 mo	63% and 53% recurrence-free rates at 12 and 24 mo
Luciani et al. [85]	Retrospective review	T1, Tis; BCG-refractory	14	28.5 mo	64% recurrence-free rate (35.7% with an additional course of BCG plus IFN- α)
BCG plus epirubicin intravesical therapy					
Bilen et al. [86]	Prospective study	High-risk NMIBC, BCG-naïve	41	18 mo	BCG and epirubicin group: 89% recurrence-free rate, 95% progression-free rate BCG alone group: 81% recurrence-free rate, 90% progression-free rate
Tozawa et al. [87]	Prospective study	Superficial TCC, pTa, pT1	24	24 mo	BCG and epirubicin group: 74% recurrence-free rate, 86% adverse reactions BCG alone group: 68% recurrence-free rate, 58% adverse reactions
Cai et al. [88]	Prospective study (but underpowered)	High-risk NMIBC	161	15 mo	BCG and early single dose epirubicin group: 57.5% recurrence-free rate BCG alone group: 50.6% recurrence-free rate
BCG plus MMC intravesical therapy					
Witjes et al. [89]	Prospective study	Intermediate- and high-risk NMIBC and CIS	182	32 mo	MMC and BCG group: 61% recurrence-free rate, 94% progression-free rate MMC alone group: 54% recurrence-free rate, 96% progression-free rate
Kaasinen et al. [90]	Prospective study	Frequently recurring Ta or T1 NMIBC	205	30.7 mo	MMC plus BCG group: 73% and 67% recurrence-free rates at 2 and 5 yr, respectively
Kaasinen et al. [91]	Prospective study	Primary, secondary or concomitant CIS	304	56 mo	MMC plus BCG group: 40.7% recurrence-free rate
Di Stasi et al. [92]	Prospective study	pT1 NMIBC at high risk for recurrence and moderate to high risk for progression	212	88 mo	BCG alone group: 53.8% recurrence-free rate BCG alone group: 42% recurrence-free rate, 88% progression-free rate BCG plus electromotive MMC group: 58% recurrence-free rate, 91% progression-free rate
CIS = carcinoma in situ; IFN- α = interferon α ; MMC = mitomycin C; NMIBC = non-muscle-invasive bladder cancer.					

3.2.3. *Bacillus Calmette-Guérin in low- and intermediate-risk non-muscle-invasive bladder cancer*

BCG is generally not advocated for low-risk NMIBC in view of the extremely favorable prognosis of these patients and BCG's toxicity. The guidelines of both the European Association of Urology (EAU) [32] and the AUA [26] classify NMIBC risk factors with minimal differences. Recently, risk tables have been developed to predict recurrence and progression [33]. European and American guidelines propose BCG as a valid alternative to intravesical chemotherapy for NMIBC at "intermediate risk" of recurrence and progression. In intermediate-risk patients, who have a 50% risk of recurrence and a 10% risk of progression, maintenance BCG reduces the recurrence rate compared to MMC; however, it cannot be concluded that BCG also lowers the progression rate.

3.2.4. *Bacillus Calmette-Guérin in high-risk non-muscle-invasive bladder cancer*

Both AUA [26] and EAU [32] guidelines recommend BCG with maintenance (ie, for at least 1 yr) for NMIBC at high risk of progression (stage T1, high-grade papillary tumors, and CIS), implying BCG's superiority over chemotherapy for these patients and, at least, its noninferiority versus early cystectomy. The most relevant studies and meta-analyses comparing BCG to different treatment options in high-risk NMIBC (TUR plus BCG, TUR alone, TUR plus chemotherapy, and TUR plus cystectomy) are reported in Table 3. Unfortunately, seven of the eight publications have at least one of the following limitations: they are based on nonrandomized, retrospective analyses [34–37]; they include a control arm of TUR alone [34,35]; or they include a mixture of intermediate- and high-risk patients [26–28].

Table 5 – Comparative meta-analyses of bacillus Calmette-Guérin (BCG) and intravesical chemotherapy on non-muscle-invasive bladder cancer (NMIBC) for disease progression

Author	Type of study	Definition of progression	Disease category	Treatment, dose/maintenance*	Main outcome	Comment
Sylvester et al. [5]	Meta-analysis of 24 RCTs comparing BCG to TUR alone or with chemotherapy or immunotherapy	Any occurrence of T2 or higher, “disease worsening” (ie, cystectomy), or death from any cause	Ta and T1 (<i>n</i> = 3967), CIS (<i>n</i> = 896)	BCG: five different strains, <i>n</i> = 2658 Control group: <i>n</i> = 2205	Median follow-up: 2.5 yr Progression rate: 9.8% with BCG and 13.8% in the control group (27% reduction in the odds of progression with BCG) OR: 0.63, favoring BCG when BCG is administered with maintenance OR: 1.28, (no difference with control group) when BCG administered without maintenance	BCG reduces the risk of progression when maintenance is used. No significant difference between BCG and MMC.
Shelley et al. [26]	Two of six RCTs in a meta-analysis with sufficient data for progression	An increased level of tumor stage and/or grade	Intermediate- or high-risk NMIBC	BCG: Tyce or RIMV (<i>n</i> = 362) MMC: 20 or 30 mg (<i>n</i> = 359)	Parmar 1998 method ln(hours) plus 0.044 (variance: 0.039) (no difference)	No significant difference between BCG and MMC.
Huncharek and Kupelnick [30]	Meta-analysis of eight RCTs comparing BCG and chemotherapy, selected for a minimum of 2 yr follow-up and a minimum of 20 patients per arm	NA	Ta, T1, with or without CIS	Chemotherapy (<i>n</i> = 1165) [MMC: 20–40 mg used in 4 of 9 arms] BCG (<i>n</i> = 1262): different strains, doses, and schedules	Median follow-up range: 30–86 mo Chemotherapy vs BCG—OR: 1.24, favoring BCG but not statistically significant MMC vs BCG—OR: 1.04, no difference MMC vs BCG (patients previously untreated with chemotherapy)—OR: 0.75, favoring MMC but not statistically significant MMC vs BCG (patients previously treated with chemotherapy)—OR: 1.49, significantly favoring BCG	No significant difference between BCG and MMC. BCG better (significantly) only in trials enrolling patients previously treated with chemotherapy. MMC better (not significantly) in patients not previously treated with chemotherapy.
Bohle and Bock [29]	Meta-analysis of nine studies comparing BCG and MMC; two of nine were retrospective observational cohort studies	Progression to a higher tumor stage, development of metastasis, or “disease worsening”	Ta, T1, any grade; trials with CIS alone excluded	MMC (<i>n</i> = 1133) BCG (<i>n</i> = 1277)	Median follow-up: 26 mo Progression rate: 7.67% with BCG and 9.44% with MMC OR: 0.77, not significantly in favor of BCG (<i>p</i> = 0.081) OR: 0.66, significantly favoring BCG only in the BCG maintenance subgroup OR: 1.16, not significantly favoring MMC in the non-BCG maintenance group	Statistically significant superiority of BCG only in the subgroup of BCG maintenance.
Hall et al. [25]	Meta-analysis of RCTs	NA	All risk-level disease	(1) MMC maintenance vs BCG induction (1066 patients from three studies) (2) BCG maintenance vs MMC maintenance (594 patients from two studies)	(1) 0% (CI, –5 to 5) difference in progression rate between MMC and BCG (2) –5% (CI, –11 to 1) progression with BCG	No significant difference between BCG and MMC either with or without maintenance.

Table 5 (Continued)

Author	Type of study	Definition of progression	Disease category	Treatment, dose/maintenance	Main outcome	Comment
Malmstrom et al. [22]	Individual patient data meta-analysis of seven RCTs	Any occurrence of T2 or higher	Intermediate- and high-risk NMIBC	1880 patients BCG (n = 1050) MMC (n = 830)	Median follow-up: 4.8 yr Overall progression rate: 12%; overall mortality: 24%, 30% of those due to bladder cancer	No significant difference in progression and survival rate between BCG and MMC.

CI = confidence interval; CIS = carcinoma in situ; MMC = mitomycin C; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; TUR = transurethral resection.
* Maintenance is defined as any further instillation beyond the induction course.

The clinical benefit of BCG after TUR versus TUR alone in T1G3 tumors has been studied in only a few nonrandomized series [34,35]. Thus, conclusions of a survival advantage [34] or a significant delay in progression [35] with BCG cannot be considered very meaningful. In contrast, non-comparative series of T1G3 tumors treated with BCG have shown that up to 90% of patients are alive at 5 yr with only a minority (5–20%) needing cystectomy [39–41]. Retrospective data comparing BCG and early cystectomy suggest a significant survival benefit for early cystectomy when T1G3 is associated with two or more risk factors, namely multifocal disease, concomitant CIS, and a tumor diameter >3 cm [36,37].

With one exception [42], the available meta-analyses are of little help in assessing the comparative efficacy of BCG and chemotherapy in high-risk NMIBC; these meta-analyses included only a minority of high-risk patients, thus preventing the possibility of a subgroup analysis. In three studies comparing BCG and MMC in so-called high-risk patients, BCG with maintenance was superior to MMC with regard to recurrence, while progression was not affected by BCG [26,27,38]. However, in these publications, the definition of high-risk NMIBC also included “highly recurrent” intermediate-risk NMIBC, thereby limiting the ability to extend the results to NMIBC at high risk of progression.

Based on a meta-analysis of nine RCTs comparing intravesical BCG to intravesical chemotherapy for CIS [42], maintenance BCG was found to be the most effective intravesical therapy. It reduced both the short- and long-term risks of treatment failure as compared to both MMC and chemotherapy overall. The power to detect differences in progression and in disease-specific survival was too low to draw conclusions for these end points in this meta-analysis. Updated results from similar RCTs could provide more meaningful treatment information on progression.

In conclusion, maintenance BCG is currently the most effective intravesical agent for CIS, with the caveat that sufficient long-term follow-up is not yet available to evaluate survival. BCG, but not chemotherapy, has been shown to reduce the overall risk of progression to muscle-invasive disease, both in patients with papillary tumors and in patients with CIS [5]. Consequently, maintenance BCG is also recommended in high-risk papillary tumors, even though separate randomized trials have not been carried out in this specific subgroup of patients. Likewise, there are no randomized trials comparing BCG to cystectomy. Patients undergoing conservative management of high-risk NMIBC with BCG should be followed closely and considered for cystectomy at the first sign of BCG failure.

3.3. Factors affecting or predicting bacillus Calmette-Guérin efficacy

Because patients failing BCG and undergoing radical surgery seem to have a worse prognosis than those submitted to immediate cystectomy [43], the identification of prognostic markers of BCG response is of the utmost clinical importance [21].

Table 6 – Prognostic markers of recurrence and progression in non-muscle-invasive bladder cancer (NMIBC) treated with bacillus Calmette-Guérin (BCG)

Author	Type of marker (cut-off)	No., type of patients	Follow-up	Treatment dose; maintenance	Main outcome	Comment
Traditional tumor prognostic variables						
Takashi et al. [70]	Host and tumor characteristics	146, Ta/T1/CIS	64.7 mo (median)	BCG: Tokyo 172 strain, 40 or 80 mg; induction only	Multivariate analysis showed that a history of bladder cancer was the only significant factor affecting recurrence ($p = 0.004$), while concomitant CIS was the only significant factor for disease progression ($p = 0.005$); patient age ($p = 0.0006$), history of bladder cancer ($p = 0.02$), and concomitant CIS ($p = 0.021$) were significantly associated with patient survival.	Patient age, history of bladder cancer, and concomitant CIS predict disease-free survival in NMIBC after BCG therapy. History of bladder cancer also correlates with recurrence, while concomitant CIS is also a predictor of progression.
Andius et al. [58]		236, Ta/T1 (CIS excluded)	44 mo (median)	BCG: Danish 1331 or OncoTice strain; induction plus maintenance	Multivariate analysis revealed that first cystoscopy findings ($p < 0.001$), tumor grade ($p = 0.003$), and six or fewer initial instillations ($p = 0.002$) had prognostic importance for the time to progression. Age, number of tumors, and BCG strains had no influence on time to recurrence and progression.	A negative first cystoscopy after BCG treatment is a very important prognostic sign. Patients treated with fewer than six induction instillations had a greater risk of tumor progression.
Andius et al. [71]		173, CIS	72 mo (median)	BCG: Danish 1331 or OncoTice strain; induction plus maintenance (57 patients)	No pretreatment variables, including T1G3, had prognostic value in terms of time to progression. A multivariate analysis revealed that first cystoscopy findings had prognostic importance for time to progression ($p < 0.001$), time to local failure ($p < 0.0001$), and time to death ($p = 0.0002$). Age was important to time to recurrence ($p = 0.0014$).	The authors were not able to predict which patients would respond favorably to BCG in this selected population of patients with CIS.
Lopez-Beltran et al. [72]		51, T1G3	63.8 mo (mean)	BCG: Tice-strain; induction only	Tumor size was associated with disease-free survival ($p < 0.0001$) and overall survival ($p < 0.0296$) in the univariate analysis. Age at diagnosis, gender, and concomitant CIS did not give any significant result.	Between traditional prognostic tumor variables, only tumor size had a predictive role in T1G3 NMIBC treated with BCG.
Fernandez-Gomez et al. [21]		1062, high- and intermediate-risk NMIBC	69 mo (median)	BCG: standard and low-dose regimens of BCG were given to the patients	In multivariate analysis, female gender ($p = 0.0006$), recurrent tumors ($p < 0.0001$), multiplicity ($p = 0.011$), and associated Tis ($p = 0.0239$) were significant independent predictors of recurrence; age ($p = 0.052$), recurrent tumors ($p = 0.068$), high-grade ($p < 0.0001$), stage T1 ($p = 0.0076$), and recurrence at first cystoscopy ($p < 0.0001$) were significant independent predictors of progression.	History of recurrence, T1, high grade, and early recurrence were the most important prognostic factors in patients receiving BCG immunotherapy.
Molecular tumor characteristics						
Lebret et al. [73]	Ki67 (>20%)	35, T1G3	57.3 mo (median)	BCG: 75 mg Pasteur strain; induction only	With a Ki67 threshold of 20%, there was a statistically significant difference ($p < 0.05$) between responder and nonresponder patients. Patients with <20% of nuclear activity positively responded to BCG.	Ki67 could be a useful predictive marker of response to BCG therapy in a high-risk selected population of T1G3 NMIBC patients.

Table 6 (Continued)

Author	Type of marker (cut-off)	No., type of patients	Follow-up	Treatment dose; maintenance	Main outcome	Comment
Peyromaure et al. [74]	p53 (>20%)	29, T1G3	36.7 mo (median)	BCG: 75 mg Pasteur strain; induction plus eventual repeat induction	The log-rank test showed no statistical difference between p53-positive and p53-negative groups for either recurrence ($p = 0.62$) or progression ($p = 0.36$).	P53 overexpression has no predictive value for recurrence and progression in T1G3 NMIBC treated with BCG.
Lopez-Beltran et al. [72]	p53 (>6%) Ki67 (>13%) p21 (>15%) p27 ($\leq 40\%$) Cyclin D1 (>15%) Cyclin D3 (>15)	51, T1G3	63.8 mo (mean)	BCG: Tice-strain; induction only	P27 downregulation ($p < 0.001$) and cyclin D3 overexpression ($p = 0.02$) were independent predictors of disease-free survival, while overexpression of p53 ($p = 0.039$), cyclin D1 ($p < 0.001$), and cyclin D3 ($p = 0.001$) were predictors of progression-free survival; cyclin D3 ($p < 0.005$) was a predictor of overall survival.	Downregulation of p27 and overexpression of p53, cyclin D1, and cyclin D3 might be relevant predictors of survival in the selected, high-risk T1G3 NMIBC population previously treated with BCG.
Saint et al. [75]	p53 (>20%)	102, Ta/T1/CIS	40 mo (median)	BCG: 150 mg Immun F (induction only) or 81 mg Connaught Immucyst (induction plus maintenance)	Times to recurrence ($p = 0.03$), progression ($p < 0.0001$), and cancer death ($p = 0.0003$) were shorter among patients with p53 overexpression. In multivariate analysis, p53 overexpression was an independent predictor of recurrence ($p = 0.0003$).	Pretreatment p53 overexpression is associated with high risk of recurrence, progression, and cancer death after BCG therapy.
Esuvaranathan et al. [76]	p53 pRb	80, high risk NMIBC	54 mo (mean)	BCG: Connaught strain; induction plus maintenance in different regimens (81 mg [$n = 33$], 27 mg [$n = 20$], 27 mg plus IFN- α [$n = 27$])	PRb underexpression was significantly associated with BCG nonresponse and recurrence ($p = 0.047$) after BCG plus IFN- α . There was no statistical difference in patient outcomes according to pretreatment p53 expression or its combination with pRb.	PRb underexpression may be predictive of nonresponse and recurrence after BCG plus IFN- α . P53 expression or its combination with pRb is not associated with post-BCG clinical outcome.
Cormio et al. [77]	pRb (0% or $\geq 50\%$)	27, T1G3	60 mo (mean)	BCG: 75 mg Pasteur strain; induction plus maintenance	There was a statistically significant difference in recurrence-free ($p = 0.037$) and progression-free ($p = 0.018$) survival between patients with altered pRb expression (no expression, 0%, or overexpression $\geq 50\%$) and normal pRb expression.	Altered (0% or $\geq 50\%$) pRb expression predicted recurrence and progression in a homogenous population of T1G3 NMIBC patients after BCG treatment.
Markers of immune response						
Thalmann et al. [78]	IL-8 IL-18	28, Ta/T1/CIS	66 mo (median)	BCG: 81 mg Connaught Immucyst or 120 mg Pasteur	Patients secreting more than 4000 ng IL-8 into the urine after BCG have a significantly higher chance of remaining disease free ($p < 0.05$), and those with elevated IL-18 expression have significantly longer disease-free survival ($p < 0.05$).	IL-8 and IL-18 expression in the urine, respectively, during the first 6 h and 12 h after the first BCG instillation correlates with disease-free survival.
Kumar et al. [79]	IL-8	26, Ta/T	24 mo (median)	BCG: 40 mg or 120 mg modified Danish 1331	IL-8 levels are significantly higher in responders than in nonresponders. In all patients who remained disease free, IL-8 levels were >400 pg/ml.	IL-8 expression in the urine during the first 4 h after the first BCG instillation strongly correlates with the possibility of future recurrence or progression.
Bilen et al. [54]	PPD skin test	61, Intermediate- or high-risk NMIBC	18 mo (median)	BCG: 81 mg Connaught Immucyst	The number of recurrences and of recurrence-free intervals after BCG therapy did not differ significantly between PPD-positive and PPD-negative groups.	PPD skin test reactivity does not seem to be a predictive marker of response to BCG therapy.

CIS = carcinoma in situ; IFN- α = interferon α ; IL = interleukin; PPD = purified protein derivative.

Table 7 – Incidence and severity of bacillus Calmette-Guérin (BCG) side effects according to the most representative series. Categories are shown according to the American Urological Association (AUA) 2007 guidelines [26], International Bladder Cancer Group (IBCG) recommendations for the management of side effects [61] are also reported

Author	Study design	Side effect (AUA category)	Incidence	Severity	IBCG treatment recommendations
Local side effects					
Hall et al. [26]	BCG induction only	LUTS	59% minimal overlap 38% maximal overlap [§]	NA	Continue BCG. Consider postponement of intravesical therapy and subsequent dose reductions if cystitis persist >48 h. Treatment with NSAIDs, useful fluoroquinolones.
Hall et al. [26]	BCG induction plus BCG maintenance		71% minimal overlap 57% maximal overlap [§]	NA	
Morgia et al. [62]	BCG induction plus BCG maintenance		52.2% irritation	NA	
Van der Meijden et al. [10]	BCG induction plus BCG maintenance		97.5% bacterial plus BCG-induced cystitis	NA	
Saint et al. [50] [*]	BCG maintenance only		46.7% 38% 7%	Class 1 Class 2 Class 3	
Vegt et al. [63]	BCG induction plus BCG maintenance		53% frequency 39.5% chemical cystitis 22.4% bacterial cystitis	NA	
Koga et al. [49] [#]	BCG induction		35.8% 37.4% 3.3% 5.7%	Grade 1 Grade 2 Grade 3 Grade 4	
Losa et al. [64]	BCG induction (75 mg) plus BCG maintenance		25.7% cystitis-like symptoms	NA	
Hall et al. [26]	BCG induction only	Hematuria	29%	NA	Suspend BCG until urine clears.
Van der Meijden et al. [10]	BCG induction plus BCG maintenance		34.5%	NA	
Losa et al. [64]	BCG induction (75 mg) plus BCG maintenance		8.5%	Mild	
Vegt et al. [63]	BCG induction plus BCG maintenance		34%	NA	
Hall et al. [26]	BCG induction only	Bladder contracture	1%	NA	Suspend BCG until symptoms have resolved.
Hall et al. [26]	BCG induction plus BCG maintenance		3%	NA	
Hall et al. [26]	BCG induction only	Epididymitis/prostatitis/urethral infections	4%	NA	Suspend BCG. Treatment with high-dose fluoroquinolones or isoniazid and rifampicin.
Hall et al. [26]	BCG induction plus BCG maintenance		4%	NA	
Losa et al. [64]	BCG induction (75 mg) plus BCG maintenance		0.7%	NA	
Vegt et al. [63]	BCG induction plus BCG maintenance		26.9%	NA	

Table 7 (Continued)

Author	Study design	Side effect (AUA category)	Incidence	Severity	IBCG treatment recommendations
Van der Meijden et al. [10]	BCG induction plus BCG maintenance	Skin rash	3.3%	NA	Grades 1 and 2 (WHO): Consider suspension of BCG.
Koga et al. [49] [#]	BCG induction		0.8%	Grade 1	Grades 3 and 4 (WHO): Cessation of BCG.
Vegt et al. [63]	BCG induction plus BCG maintenance		2%	NA	Treatment with NSAIDs and antihistamines.
Systemic side effects					
Hall et al. [26]	BCG induction only	Fever/chills/flu-like symptoms	26% minimal overlap 19% maximal overlap	NA	Continue BCG; in case of persistent high-grade fever (>38.5 °C for >48 h), permanent discontinuation of BCG. Prompt treatment with two or more antimicrobial agents (fluoroquinolones, isoniazid, rifampicin).
Hall et al. [26]	BCG induction plus BCG maintenance		30% minimal overlap 22% maximal overlap	NA	
Van der Meijden et al. [10]	BCG induction plus BCG maintenance		14.8% fever ≥39 °C 23.2% malaise	NA	
Saint et al. [50]	BCG induction only		11% 2%	Low-grade fever Moderate-grade fever	
Losa et al. [64]	BCG induction (75 mg) plus BCG maintenance		11.4% fever up to 38.5 °C 0.7% fever >39 °C	NA	
Vegt et al. [63]	BCG induction plus BCG maintenance		11% fever >39% 17% malaise, chills	NA	
Koga et al. [49] [#]	BCG induction		17.9% 17.9% 1.6% 2.4%	Grade 1 Grade 2 Grade 3 Grade 4	
Van der Meijden et al. [10]	BCG induction plus BCG maintenance	Lung complications	0.2% lung infection	NA	Cessation of BCG.
Hall et al. [26]	BCG induction only	Systemic infection	1%	NA	Cessation of BCG. For severe infection, treatment with high-dose fluoroquinolones; isoniazid, rifampicin, and ethambutol daily for 6 mo; high-dose corticosteroids as long as symptoms persist.
Hall et al. [26]	BCG induction plus BCG maintenance		7%	NA	
Losa et al. [64]	BCG induction (75 mg) plus BCG maintenance		0.7%	NA	
Van der Meijden et al. [10]	BCG induction plus BCG maintenance		0% BCG sepsis	NA	

AE = adverse event; LUTS = lower urinary tract symptoms; NA = not applicable; NSAIDs = nonsteroidal anti-inflammatory drugs; WHO = World Health Organization.

[§] *Maximal overlap* estimates the side-effect rate in case different symptoms of the same category may have occurred simultaneously in the same patients; *minimal overlap* reports side effects taking into account the opposite scenario, in which all AEs of the same category presented separately in different patients within the same series.

^{*} Saint et al. [50] developed a four-class rating scale based on the WHO's adverse reaction terminology and the National Cancer Institute's terminology and a review of published reports on AEs to BCG.

[#] Koga et al. [49] classified the AEs according to the grading reported by Bassi [66].

3.3.1. Age

Aging progressively weakens the immune system [44], on which the therapeutic efficacy of BCG depends; therefore, older patients could be less responsive to intravesical immunotherapy. A retrospective analysis performed in 1106 patients showed that patients >80 yr had a poor response to BCG plus interferon. In multivariate analysis, age remained an independent risk factor for BCG failure [45]. A more recent study found no difference in the first response to BCG or in cancer-free survival at 24 mo among age groups by decade; however, after 5 yr, only 27% of patients >70 yr were cancer free compared with 37% of patients <70 yr ($p = 0.005$) [46]. Age >70 yr was a significant factor predicting tumor recurrence compared to other age groups. It was concluded that age has a measurable, although small, impact on the overall outcome of high-risk NMIBC. Further studies should be carried out to confirm these findings.

3.3.2. Prognostic markers

Table 6 shows an overview of the most relevant clinical, molecular, and immunologic prognostic markers that have been assessed as potential predictors of BCG response. Current evidence does not support the use of molecular markers as predictors of BCG response in clinical practice, while traditional variables predicting NMIBC behavior have retained their prognostic importance in patients treated with 5–6 mo of BCG [21].

3.4. Is tolerability an important limitation in the use of bacillus Calmette-Guérin?

Although BCG therapy is generally considered safe, it has potential local and systemic side effects that may either lead to treatment cessation in up to 30% of patients or lead to a delay or reduction in the number of instillations in 55–83% of patients [10]. Adverse events (AEs) following intravesical BCG therapy have been associated with strain virulence, allergic reactions, and nosocomial urinary tract infections [47].

A number of limitations arise when attempting to review the available literature regarding the incidence, severity, and management of AEs (Table 7). The first limitation is due to the number of different descriptors across different studies when reporting AEs, which are likely to be similar. A typical example is represented by the AE defined as “LUTS” (ie, lower urinary tract symptoms), which can be reported with synonyms (eg, “cystitis-like symptoms”) or split into different symptoms (eg, “urgency,” “frequency”) [48,49] that may occur individually at different rates in a given study. In an attempt to provide the most realistic estimation of AEs, the AUA guidelines panel for NMIBC [26] combined AEs into several broad categories. Rates of occurrence of each AE category have been reported as “maximal overlap” and “minimal overlap.” Maximal overlap indicates a situation in which different symptoms of the same category occurred simultaneously in the same patients; minimal overlap indicates the opposite scenario, in which all AEs of the same category are presented separately in different patients within the same series (Table 7).

A second drawback often encountered when attempting to review AEs of BCG is a lack of information on severity. The use of standardized terminology and toxicity scales, such as the World Health Organization grading scale or the National Cancer Institute’s Common Toxicity Criteria for Adverse Events (CTCAE) [50], was seldom encountered in our search.

Table 7 lists BCG side effects, their incidence, and their management. The most common local side effects are drug-induced cystitis, characterized by irritative voiding symptoms with negative urine cultures, and hematuria, which usually subsides within 48 h without the need to discontinue BCG instillations [48,50].

The role of BCG in the occurrence of a contracted bladder is not clear because multiple TURs and previous chemotherapy may contribute to this rare complication [51]. More severe local side effects due to BCG infection include symptomatic granulomatous prostatitis and epididymo-orchitis, which require permanent BCG discontinuation [47,48,52].

The most common systemic side effects consist of flu-like symptoms, such as malaise and fever <38.5 °C (<101.3 °F). Fever typically resolves within 2 d with antipyretics (nonsteroidal anti-inflammatory drugs) and fluids. High, persistent fever is less common but may be a sign of progressive BCG infection or sepsis in case of further BCG instillations. In such cases, intravesical therapy should be withheld until resolution of symptoms, and prompt treatment with antimicrobial agents, such as fluoroquinolones, isoniazid, and rifampicin, should be considered while a diagnostic evaluation, including cultures, is conducted [48,50].

Although rare, major systemic BCG reactions may occur due to active BCG infection and the accompanying immune response, which typically consists of systemic granulomatous illnesses generally associated with high-grade fever and may progress to multiple organ failure. Life-threatening AEs, such as BCG sepsis, are due to systemic absorption of BCG [48]. Onset may occur several months or even years after the last instillation. The reason for this phenomenon might be long-term presence of BCG in the body.

Toxic deaths during BCG have been a source of major concern for the widespread use of BCG, but a review of the literature reveals very few reports of BCG-related deaths in the last 10 yr [9,53]. The most recent case reported was a 92-yr-old patient who died from BCG sepsis [53]. Although severe systemic complications of BCG are rare, it would be useful to identify a test to be done prior to initiation of BCG therapy to exclude patients who are at risk for such AEs. The old tuberculosis tine test should no longer be performed due to its poor reliability; however, hypersensitivity reaction against the purified protein derivative, applied by the Mantoux method, could at least alert the physician to severe complications [54].

The risk of increased toxicity during maintenance has been questioned. According to the results of a European Organization for Research and Treatment of Cancer (EORTC) phase 3 trial [10], local side effects of BCG do not increase during maintenance and systemic side effects are more frequent during the first 6 mo of treatment. However, a

significant proportion of patients (84% [9], 67.3% [10]), 86% [50] in the three most representative series) failed to complete the 3-yr maintenance course for various reasons. The high drop-out rate of patients on long-term maintenance courses is often related to patient choice or to treatment failure rather than to toxicity, but true BCG toxicity may be underestimated.

Particular caution should be exercised with elderly patients; with aging, the immune system becomes progressively weaker [44], and the risk of BCG infection might be increased. Maintenance BCG in patients >80 yr of age should be considered on a case-by-case basis [53].

3.4.1. *Is bacillus Calmette-Guérin significantly more toxic than intravesical chemotherapy?*

Intravesical chemotherapy is generally better tolerated than BCG and is not affected by the small but actual risk of BCG sepsis and death. Recent reports and reviews have shown that local and systemic side effects are slightly more frequent with BCG than with MMC, except for allergy and skin reactions, which are more common with MMC [7,24,26,27,29]. A meta-analysis by Shelley et al showed that 30% of patients receiving MMC developed local toxicity compared to 44% receiving BCG, with respective values of 12% and 19% for systemic side effects, although the difference was not statistically significant [27]. A significantly higher withdrawal rate of patients treated with BCG compared with MMC could not be demonstrated [24]. Similar findings were reported in a randomized study that compared BCG to doxorubicin: Fever, pain on urination, and hematuria were more common with BCG, whereas allergic reactions such as rubor or itching were more frequent on doxorubicin. Further studies would be useful to evaluate whether the difference in toxicity between BCG and chemotherapeutic agents actually affects the patient drop-out rate and patients' quality of life.

3.4.2. *Bacillus Calmette-Guérin contraindications*

Several clinical conditions are potential contraindications to intravesical BCG. These conditions include TUR within the previous 2 wk, traumatic catheterization, hematuria, urethral stenosis, active tuberculosis, prior BCG sepsis, and immunosuppression; however, there is no consensus in the literature about recommendations. With regards to patients with vesicoureteral reflux, increased toxicity has not been reported in literature.

3.5. *Can bacillus Calmette-Guérin toxicity be effectively reduced?*

Many attempts have been made to reduce BCG toxicity without compromising its efficacy. Measures that may prevent or decrease BCG-associated AEs include concomitant use of isoniazid or ofloxacin, dose reductions, decrease of dwell time of BCG, and addition of other immune modulators.

3.5.1. *Isoniazid*

Although the tuberculostatic agent isoniazid has been frequently used for prophylaxis of BCG-associated AEs,

randomized trials failed to demonstrate a role in the reduction of BCG side effects [55]; thus, its use is not recommended.

3.5.2. *Ofloxacin*

A recent randomized, prospective, double-blind, multicenter study assessed the effectiveness of short-term ofloxacin, a fluoroquinolone with tuberculostatic properties, in enhancing BCG tolerability [56]. In this study, 115 patients were randomized to treatment with intravesical BCG (81 mg, Connaught strain, six plus three instillations) plus ofloxacin (200 mg) or plus placebo. Prophylactic ofloxacin significantly decreased the incidence of grade ≥ 2 BCG-associated AEs during the final 3 wk of BCG induction [56]. Ofloxacin did not appear to impair the efficacy of BCG up to 24 mo after treatment and, compliance with BCG treatment was improved [57]. These promising findings were statistically significant. Nonetheless, because the trial was underpowered, further confirmation in large randomized trials is needed.

3.5.3. *Dose and/or schedule modification*

Dose reduction, as shown in Table 1, can be applied with a reduction in side effects without compromising clinical efficacy. Another option to reduce BCG side effects consists of modifying the treatment schedule, as previously discussed in section 3.1. In a study from 2004, the dwell time was reduced to ≤ 30 min in 51 patients who had experienced pronounced side effects after BCG instillations; the result was significant improvement in chills, fever, and dysuria but no change in frequency and hematuria [58]. The long-term outcome of these patients is not available, and the effect of dwell time warrants further investigation.

3.5.4. *Is bacillus Calmette-Guérin contraindicated in immunocompromised patients?*

Immunocompromised patients are at increased risk of systemic infection; thus, intravesical BCG is not recommended in these patients because of the theoretical risk of severe morbidity and sepsis [59]. Nonetheless, retrospective evidence has shown that intravesical BCG is safe and effective in patients with concomitant lymphoma, chronic lymphocytic leukemia, or steroid treatment [60] as well as in renal transplant patients [59].

3.5.5. *Is bacillus Calmette-Guérin efficacy linked to side effects?*

It has been suggested that BCG effectiveness may be related to BCG-associated side effects. An EORTC trial has shown that although a correlation between BCG toxicity and efficacy exists, side effects are not responsible for an improved outcome and cannot be considered as a prognostic factor for subsequent recurrence [60].

4. Conclusions

Although it is clear that an immunocompetent host is mandatory for BCG to exert its action, factors of BCG failure remain largely unknown and unpredictable. Maintenance BCG is currently the most effective intravesical agent. The

efficacy of maintenance BCG is primarily related to a significant reduction in tumor recurrence. Although BCG reduces the risk of progression in high-risk patients, its effect on progression in intermediate-risk patients has not been proven. Consequently, BCG's use in intermediate-risk NMIBC is called into question, given BCG's increased toxicity over chemotherapy. Further work is needed to better understand the mode of action of BCG, to refine the treatment schedule, and to more accurately identify the patients most likely to benefit from BCG. Until then, the current American and European recommendations on BCG use remain valid.

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Acquisition of data: Gontero, Bohle, Malmstrom, O'Donnell, Oderda, Sylvester, Witjes.

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