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Update on intravesical agents for non-muscle-invasive bladder cancer

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Abstract

Major controversies still exist with regard to the indication, type and regimen of intravesical therapy for non-muscle-invasive bladder cancer. Other areas of controversy are the criteria for response/failure of treatment and for decisions regarding secondary intravesical therapy versus radical cystectomy. In this article, we analyze the different intravesical therapeutic strategies and compare their safety and efficacy. Well-designed clinical trials have found that the addition of bacillus Calmette–Guerin (BCG) to transurethral resection (TUR) decreases the risk for both disease recurrence and progression. These encouraging results are sustained even in patients with recurrent or aggressive disease, including patients whose prior intravesical chemotherapy has failed. Most investigators believe that the efficacy of BCG therapy can be maximized with maintenance therapy. Mitomycin C (MMC), the most commonly used intravesical chemotherapy to date, decreases the risk of disease recurrence but not disease progression when used after TUR compared with TUR alone. The oncologic efficacy of intravesical MMC can be optimized by increasing its concentration in addition to alkalinizing and reducing urine production. For patients at high risk of disease progression, BCG with maintenance therapy should be the preferred primary intravesical therapeutic strategy. However, MMC can be considered as a viable alternative for patients with papillary tumors (no carcinoma *in situ*) that are at low or intermediate risk of disease progression. Combination intravesical therapy may be more successful than single-agent strategies. Intravesical therapy failures indicate the need to include radical cystectomy as an option in the management decision.

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Worldwide, urothelial bladder cancer (UBC) represents a frequent urologic malignancy, and is mainly diagnosed as non-muscle invasive [1]. At presentation, approximately 30% of patients have muscle-invasive UBC (clinical T2 or higher) [2]. Both the natural history of non-muscle-invasive UBC and its treatment strategies are highly variable. Although some patients never experience disease recurrence, others experience disease progression and eventually die of their disease [3–7]. In the absence of intravesical treatment, a patient with non-muscle-invasive UBC has a 47% probability of disease recurrence within 5 years of diagnosis and a 9% probability of progression to muscle-invasive disease [8].

There are few evidence- and risk-based tools to help in the decision-making for patients with non-muscle-invasive UBC. Factors predictive of outcome include clinical and pathologic features and molecular markers, such as cytology, NMP22® (Matritech, MA, USA) and UroVysion™ (Vysis, Inc., IL, USA) fluorescence *in situ* hybridization [4–7,9]. While management of clinical Ta low-grade UBC is relatively noncontroversial, the best management of patients with high-grade clinical Ta carcinoma *in situ* (CIS) or clinical T1 UBC is not yet agreed upon. The development and testing of effective intravesical therapies for non-muscle-invasive UBC are still evolving. Indeed, major controversies still exist with regard to the indication, type and regimen of intravesical therapy. Other areas of controversy are the criteria for response/failure of treatment and for decisions regarding secondary intravesical therapy versus radical cystectomy. In this article, we analyze the different intravesical therapeutic strategies and compare their safety and efficacy.

Intravesical bacillus Calmette–Guerin immunotherapy

Dose & strain

After bacillus Calmette–Guerin (BCG) was isolated and described as an antituberculosis vaccine, *in vivo* and *in vitro* studies demonstrated significant antitumor effects against several malignant cell lines [10–14]. In 1976, Morales *et al.* reported the first successful clinical study, where they evaluated nine patients with recurrent UBC treated with intravesical BCG once a week for 6 weeks (6-weekly), achieving a complete response in seven patients (78%) [15]. In the following years, other studies verified the efficacy of the Morales regimen against UBC in larger, well-designed trials [16–19]. These studies have led to an increasing interest in intravesical BCG therapy for non-muscle-invasive UBC. Currently, multiple substrains of BCG, such as Pasteur Armand-Frappier, Tice, RIVM and Glaxo Tokyo, are in use for intravesical immunotherapy throughout the world. Several trials have compared strains with different dosages and regimens, finding comparable clinical results [20]. A meta-analysis published in 2002 suggested no large differences in efficacy between Pasteur Armand-Frappier, Connaught, Tice and RIVM strains [21]. Thus, any of the commercially available strains are appropriate for intravesical use. It seems that a threefold decrease in dose of intravesical BCG is as effective against disease progression as

the standard dose, even in patients with high-risk T1 grade III and CIS, with significantly less toxicity [22]. The habit of measuring BCG dosages in milligrams, rather than in number of bacilli, is inaccurate and could potentially affect the immunogenic effectiveness of BCG.

The 6-weekly instillations were empirically chosen by Morales because the Armand-Frappier strain was packed in six separate vials and adverse events lasted less than 1 week [15]. Bassi *et al.* tested a modified induction course with an instillation interval of 2 weeks, demonstrating a reduction of side effects [22]. Instead, some authors tried to reduce the number of instillations on the basis of a study by Zlotta *et al.*, who demonstrated that, in most patients, the maximal peripheral immune response was already observed after 4 weekly instillations [23]. These authors found that patients not previously immunized against mycobacterial antigens required six instillations to achieve maximum stimulation [23]. 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 with 6-weekly instillations, with a positive effect on the Th1:Th2 ratio: the immune reaction seems to be dependent upon the time interval between the two instillations [24]. Until further studies establish the feasibility of these schedule modifications in humans, the 6-weekly instillation regimen is considered to be the standard induction course.

Efficacy

Several well-designed clinical trials have directly compared transurethral resection (TUR) alone with TUR followed by induction BCG. BCG induction instillations usually start a minimum of 2 weeks after TUR in order to allow the healing of the urothelium and decrease the risk of systemic side effects. Nevertheless, in some studies, it was initiated as early as 7 days after TUR. Studies have unanimously demonstrated a statistically significant reduction of approximately 32% in UBC recurrence rates [16,25–28]. The median time from TUR to first recurrence was prolonged from between 1 and 2 years with TUR alone to between 2 and 4 years with TUR plus intravesical BCG. It has been demonstrated that the use of BCG was associated with a relative risk for UBC recurrence of 0.39 [29,30]. These encouraging results were sustained even in patients with recurrent or aggressive disease, including patients whose prior intravesical chemotherapy had failed [16,31].

While reducing and/or delaying disease recurrence is an important end point for the management of patients with non-muscle-invasive UBC, an even more important end point is preventing progression to higher stage disease. Addition of intravesical BCG to TUR lowers the progression rate by a statistically and clinically significant margin. A large meta-analysis involving 4863 patients from 24 clinical trials revealed a 27% reduction (9.8 vs 13.8%) in the odds of disease progression at a mean follow-up of 2.5 years for patients treated with TUR plus BCG (induction and maintenance) compared with those treated with TUR alone [21]. More recently, a meta-analysis of 25 trials including 4767 patients confirmed these results with an odds ratio (OR) of 0.61 for tumor recurrence with TUR plus BCG versus TUR alone [32]. Finally, combinations of BCG with other intravesical therapies have demonstrated some early promise; for example, the combination of BCG and interferon has demonstrated some potential benefit, with recurrence-free rates of 59 and 45% in BCG-naïve and -failure patients, respectively, within a 2-year median follow-up [33].

As with any treatment, optimal response depends on patient selection. Residual tumor after an incomplete TUR will result in treatment failure. Predictors of decreased response are clinical stage T1, multifocality, large tumor size, prior BCG failure, short time to previous BCG failure and, most importantly, accurate staging using re-resection; however, none of these characteristics is an exclusion criterion. A repeat TUR within approximately 6 weeks of initial TUR will improve selection by reclassifying approximately 30% of understaged patients and eliminating the residual tumor in another 50% [34].

Maintenance therapy

Two early randomized studies compared no maintenance versus maintenance with either one dose of BCG every 3 months or one dose monthly for 2 years. Neither trial demonstrated a statistical advantage to maintenance therapy [35,36]. Furthermore, patients in both trials had additional local toxicity attributable to BCG maintenance. Palou *et al.*, in a large randomized Spanish trial, reported an 11% overall benefit to routine 6-week courses every 6 months for 2 years in patients with no evidence of disease 6 months after TUR and induction BCG, but this difference did not reach statistical significance [37].

Despite the negative results of these early trials, the South-West Oncology Group (SWOG) 8507 trial, which was specifically designed to answer the maintenance question, indicated the utility of BCG maintenance [38]. Patients were randomized to no maintenance versus maintenance that consisted of using miniseries of 3 weekly treatments administered at 3 and 6 months, then every 6 months for 3 years. Over a 1-year follow-up, there was a statistically significant difference in favor of maintenance therapy. Among the 233 patients with CIS, a complete response occurred in 84% with maintenance BCG therapy versus 68% of patients without ($p = 0.004$). Among 254 patients with papillary disease and complete resection at the time of randomization, 87% of the patients in the maintenance arm were disease-free at 2 years compared with 57% without maintenance. A differential recurrence-free survival rate of at least 20% persisted for up to 5 years. For patients with CIS or papillary disease, median recurrence-free survival was approximately doubled in the maintenance arm from 36 to 77 months. Treatment with maintenance BCG lowered even the progression rate by a statistically significant margin of 6%. However, a quarter of patients on maintenance therapy experienced grade 3 toxicity and less than half completed more than three cycles, with only 16% completing all seven planned cycles. Since the maintenance group as a whole benefited even without most patients completing a full 3 years of therapy, maximum benefit may have been achieved earlier.

Additional indirect support for BCG maintenance has come from large meta-analyses of prior clinical trials. As noted previously, Sylvester *et al.* found that only trials employing maintenance therapy contributed to the observed benefit of BCG compared with mitomycin C (MMC) [21]. Similarly, Böhle *et al.* found that a statistically significant improvement in tumor recurrence favoring BCG over MMC was apparent only in trials using at least 1 year of BCG maintenance [39].

Malmström *et al.* recently published a meta-analysis of nine trials and 2820 patients [40]. Compared with patients receiving MMC, patients receiving BCG with maintenance therapy had a 32% reduction in risk of recurrence, while patients receiving BCG without

maintenance had a 28% risk reduction. Disease progression did not differ significantly for either BCG treatment or MMC.

With few exceptions, most investigators believe that the efficacy of BCG therapy can be maximized with maintenance therapy [41]. Indeed, in a European Organisation for Research and Treatment of Cancer (EORTC) meta-analysis, Sylvester *et al.* reported that only trials involving maintenance therapy demonstrated a significant decrease in disease progression for BCG plus TUR compared with TUR only (OR: 0.63) [21]. Even in patients with CIS only, maintenance therapy with BCG results in the highest reduction of disease recurrence and progression rates [42]. Therefore, based on these and other studies, the European Association of Urology (EAU) and American Urological Association (AUA) uniformly recommend at least 1 year of maintenance therapy for all high-risk patients receiving BCG. The optimal maintenance schedule remains undecided. The SWOG program is the most widely applied schedule, with a 3-week miniseries given at scheduled intervals of 3, 6, 12, 18, 24, 30 and 36 months [38].

The key role of maintenance in the efficacy of BCG has been further emphasized in recent meta-analyses of randomized controlled trials. Maintenance has been suggested to be a prerequisite for the superiority of BCG over MMC. In the meta-analyses by Böhle [39] and Malmstrom [40], BCG was superior to MMC in the prevention of disease recurrence only in trials with maintenance BCG. Böhle found that a minimum of 12 instillations during 1 year were necessary to achieve superiority over MMC. Similarly, BCG is superior to MMC for disease progression only if maintenance therapy is used. However, after a critical analysis of the current evidence, Herr suggested 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 [41]. The controversial role of BCG in the progression of disease thus brings 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-year scheme of Lamm *et al.* remains the only schedule supported by a randomized trial [38].

Toxicity

The toxicities of BCG therapy vary from local urinary symptoms to severe inflammatory responses. Most patients develop self-limited cystitis that may increase in intensity with later treatments [43,44]. A progressively increasing symptomatology with each BCG cycle should prompt a delay, a lower dose or interruption of BCG instillations, which may preclude long-term complications related to the immunotherapy [45]. Although BCG therapy is generally considered safe, it has potential to induce local and systemic side effects that may lead to either treatment cessation in up to 30% of patients or to a delay or reduction in the number of instillations in 55–83% of patients [46]. The tolerability of BCG can be improved by dose reduction to a third of the standard dosage, which is associated with a 30–50% reduction in toxicity with near equivalent efficacy [22].

Side effects following intravesical BCG therapy have been associated with strain virulence, allergic reactions and nosocomial urinary tract infections [47]. The most common local side

effects of BCG are drug-induced cystitis, characterized by irritative voiding symptoms with negative urine cultures, and hematuria, which usually subside within 48 h without the need to discontinue BCG instillations [48]. The role of BCG in the occurrence of a contracted bladder is not clear, since multiple TURs and previous chemotherapy may contribute to this rare complication [49]. More severe local side effects owing to BCG infection include symptomatic granulomatous prostatitis and epididymo-orchitis, which require permanent BCG discontinuation [47,48]. The most common systemic side effects consist of influenza-like symptoms, such as malaise and fever below 38.5°C. Fever typically resolves within 2 days with antipyretics (NSAIDs) and fluids. High persistent fever is less common but it may be a sign of progressive BCG infection or sepsis in cases of further BCG instillations. Therefore, intravesical therapy should be withheld until the resolution of symptoms and prompt treatment with antimicrobial agents, such as fluoro-quinolones, isoniazid and rifampicin, should be considered while a diagnostic evaluation, including cultures, is conducted [48]. Although rare, major systemic BCG reactions may occur owing to active BCG infection and the accompanying immune response: basically, they consist of systemic granulomatous illnesses that are generally associated with high-grade fever and may progress to multiple organ failure. Life-threatening side effects, such as BCG sepsis, are due to systemic absorption of BCG. Their onset may still 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.

The old tuberculosis tine test should no longer be performed due to its poor reliability; on the other hand, hypersensitivity reaction against the purified protein derivative, applied by the Mantoux method, could at least alert the physician to severe complications [50]. The risk of increased toxicity during maintenance has been questioned: according to the results of an EORTC Phase III trial [46], the local side effects of BCG do not increase during maintenance and systemic side effects are more frequent during the first 6 months of treatment. However, a significant proportion of patients failed to complete the 3-year maintenance course for various reasons. The high dropout rate of patients on long-term maintenance courses is often related to patient choice or to treatment failure rather than to toxicity; however, the true BCG toxicity may be underestimated. Particular caution should be exercised in elderly patients: with aging, the immune system becomes progressively weaker [51] and might increase the risk of BCG infection. Therefore, maintenance BCG in patients over 80 years of age should be considered on a case-by-case basis [52].

Intravesical chemotherapy

Several antineoplastic agents have been tested for the treatment of non-muscle-invasive UBC. MMC is the most commonly used intravesical chemotherapy to date. Alternative agents are gemcitabine, doxorubicin, docetaxel and epirubicin (not approved for clinical use in North America).

Mitomycin C

Mitomycin C is an antitumor antibiotic that acts by inhibiting DNA synthesis. A review of nine randomized trials (n = 1774) revealed that only five were able to demonstrate a

statistically significant benefit to using intravesical MMC after TUR compared with TUR alone. The average recurrence rate was 54% in the TUR-alone group versus 38% in the TUR-plus-MMC group [53]. Dysuria and frequency were the most common side effects, occurring in 41% of the patients [54]. Response rates have varied widely across studies, due in part to differences in MMC preparation and protocol. Gao *et al.* demonstrated that tumor uptake and, consequently, oncologic efficacy of intravesical MMC was proportional to the drug concentration [55]. In an attempt to optimize MMC delivery, a multi-institutional Phase III trial was carried out, which randomized patients to the standard regimen versus the optimized regimen (MMC 40 mg in 20 ml of sterile water, manipulations to reduce urine production and alkalization of urine). The recurrence rate at 5 years was decreased from 75% for the standard regimen to 49% for the optimized regimen. Moreover, the median time to recurrence was delayed from 12 to 29 months [56]. Huncharek *et al.* performed a meta-analysis of 11 randomized trials comparing patients treated with intravesical chemotherapy after TUR versus TUR alone; the study focused on primary TUR, excluding patients with recurrent disease [57]. The authors reported that the addition of chemotherapy to TUR decreased the risk of tumor recurrence at 1 year by 44%. Patients receiving chemotherapy for 2 years demonstrated the greatest decrease in recurrence rates. In a follow-up meta-analysis of eight chemotherapy studies focusing on patients with recurrent tumors, Huncharek *et al.* found a 38% reduction in the risk of disease recurrence at 1 year; this rate improved with prolonged treatment beyond 2 years [58]. In these studies, doxorubicin appeared to be less effective than MMC.

While MMC has been found to decrease the risk for disease recurrence by approximately 14%, the more important question for the management of patients with non-muscle-invasive UBC is whether MMC reduces tumor progression and mortality. A meta-analysis of 22 prospective randomized trials including 3899 patients did not find any decrease in the risk of tumor progression with the addition of MMC to TUR compared with TUR alone [59]. Similarly, the addition of MMC to TUR did not improve survival in an analysis of four EORTC and two Medical Research Council randomized trials including 2535 patients with Ta and T1 UBC [8].

Although earlier reports suggested that the beneficial effects of adjuvant intravesical chemotherapy are temporary, several studies have since demonstrated durable effects. A trial comparing one and five instillations of MMC after TUR versus TUR alone demonstrated a decrease in the recurrence rate after a median follow-up of 7 years [28,57]. Similarly, a Phase III trial comparing a standard versus an optimized dose of MMC demonstrated a decreased recurrence rate at 5 years for the optimized dose [12]. However, the role of maintenance chemotherapy and sequential chemo-immunotherapy remains unclear.

Finally, although single instillations are not the focus of this review, ample evidence demonstrates that the immediate single postoperative instillation of chemotherapy reduces the recurrence rate when compared with TUR alone. The results are best in patients with a single small tumor that was entirely resected [60]. After a meta-analysis of several randomized studies, Sylvester *et al.* concluded that one immediate intravesical instillation of chemotherapy results in a 39% reduction of the risk of a recurrence in patients with Ta and T1 bladder cancer [60].

In their meta-analysis of seven trials, Sylvester *et al.* evaluated the treatment of 1476 patients, of whom 748 underwent TUR alone and 728 TUR in combination with an immediate chemotherapeutic instillation administered within 24 h after TUR. The results of all chemotherapeutic agents – epirubicin, MMC and doxorubicin – were comparable, with the exception of thiotepa that proved to be of no additional benefit. The hypothesis for this effect was twofold. One might be chemoresection of the tumor that may be left behind after incomplete TUR and the second was destruction of circulating tumor cells that could implant at the site of resection. The side effects of the treatment are mild and consist of dysuria, frequency and macroscopic hematuria in 10% of patients. Systemic side effects, consisting of allergic skin reactions, are observed in only 1–3% of patients. However, not all studies indicate a benefit of an immediate early instillation. The approximation that only one out of 8.5 patients undergoing early treatment experience no recurrence of symptoms [60] is an underestimation, since patients were excluded from the analysis if they had no malignant lesion or appeared to have a muscle-invasive lesion on histopathologic investigation. However, in daily practice, some of these patients do receive their instillation, thus making the approximation even higher. In addition, little is known regarding the kinds of recurrences that are actually prevented as a result of single instillation. Furthermore, treatment of disease recurrence in the operating room under general anesthesia is more expensive than in-office treatment with biopsy and fulguration.

Gemcitabine

Gemcitabine is a pyrimidine analog of deoxycytidine and acts as an inhibitor to ribonucleotide reductase; inhibition of DNA synthesis may result in alterations of deoxynucleotide pools and interference with DNA chain elongation. Its cytotoxicity is dose dependent and increases with time of exposure. It is one of the only active chemotherapeutic agents in urothelial cancer. It can induce a complete response in patients with metastatic bladder cancer and is well tolerated, with a proven safety profile.

Recently, Dalbagni *et al.* tested the efficacy of intravesical gemcitabine in patients with BCG-refractory, high-risk, non-muscle-invasive bladder cancer in Phase I and II prospective trials. In the Phase I study, intravesical gemcitabine administered twice a week was tolerable [61]. Eligible patients received two courses of intravesical gemcitabine twice-weekly for a period of 3 weeks with an interruption period of 1 week. Two additional courses were used when disease recurrence occurred. The levels of gemcitabine were undetectable at the first three dose levels (500, 1000 and 1500 mg). In a Phase II trial, 30 patients with non-muscle-invasive bladder cancer, for whom intravesical BCG therapy had failed, received two courses of intravesical gemcitabine twice-weekly at a dose of 2000 mg/100 ml for 3 consecutive weeks [62]. Of the 30 patients, 15 (50%; 95% CI: 32–68%) achieved a complete response, while 12 experienced disease recurrence with a median recurrence-free survival time of 3.6 months (95% CI: 2.9–11.0 months). Recurrence-free survival rates at 1 year for patients with a complete response was 21% (95% CI: 0–43%). The median follow-up for patients who did not experience disease progression or treatment with radical cystectomy was 19 months (range: 2–35 months). A total of 11 patients (37%) underwent radical cystectomy subsequent to gemcitabine therapy [62]. Other studies used a less intensive weekly schedule [63]. However, most patients experienced disease recurrence within 1 year.

Combination therapy with other agents may be more successful than intravesical gemcitabine therapy [64].

Docetaxel

Docetaxel, a chemotherapeutic agent used in systemic therapy, has also demonstrated a potential benefit in non-muscle-invasive bladder cancer. McKiernan *et al.* demonstrated its safety and tolerability in a Phase I trial including 18 patients [65]. In the long-term clinical outcomes of the Phase I study (median follow-up of 48.3 months), four patients (22%) had a complete response but 11 out of 18 patients (61%) required further treatment owing to disease recurrence [66]. No late toxicities were described. This treatment strategy requires additional data before inclusion in daily clinical practice.

Comparison of intravesical mitomycin C & bacillus Calmette–Guerin

We will focus on the comparison between BCG and MMC since several studies have demonstrated the superiority of BCG to other chemotherapeutic agents [67]. A multitude of studies have compared BCG with MMC. While some have found no significant differences between BCG and MMC, others have shown a greater reduction in recurrence and progression rates with BCG. This discrepancy may be attributable in part to differences in study design, patient selection, tumor biology, regimen and dosages. None of these studies used the optimal MMC regimen discussed previously. Nevertheless, in patients with CIS, the verdict is largely in favor of BCG over MMC, regardless of whether the regimen included maintenance therapy.

Bacillus Calmette–Guerin was superior to MMC with regard to time to recurrence in two large meta-analyses. In a meta-analysis involving 2749 patients with intermediate- to high-risk tumors, Böhle *et al.* found a significant superiority of BCG over MMC, with 61% of the patients in the BCG group and 53% in the MMC group being recurrence-free after a median follow-up of 29 months (OR: 0.56 in favor of BCG) [39]. Interestingly, the recurrence-free advantage of BCG was only observed in those studies that used BCG maintenance (OR: 0.43 for BCG with maintenance vs MMC). However, the trade-off was a 1.8-fold increased risk of cystitis in patients treated with BCG (53.8 vs 39.2%). Shelley *et al.* found no significant difference in the efficacy between BCG and MMC therapy in their overall meta-analysis of 1901 patients [68]; however, they reported a highly significant reduction in disease recurrence in favor of BCG in a subgroup analysis involving patients with highly recurrent disease. Böhle *et al.* concluded that at least 12 BCG instillations or 1 year's duration of therapy were needed to achieve the significant superiority of BCG over MMC.

A comparison between maintenance schedules of BCG and MMC was reported in an AUA Guidelines Panel subanalysis where maintenance BCG was again demonstrated to be superior, even when MMC was given with maintenance therapy [69]. The recurrence-free interval when BCG was administered at a third of the dose was also significantly longer compared with MMC [70]. By 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 [69] and by a recent randomized controlled trial by Friedrich *et al.* [71]. Both

Friedrich *et al.* and a recent meta-analysis found that maintenance MMC was superior to nonmaintenance BCG [40,70,71].

With regard to disease progression, the results for BCG versus MMC are less clear. The largest meta-analysis demonstrated 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. Sylvester *et al.* demonstrated a statistically significant advantage of BCG over MMC for disease progression (OR: 0.73) [21]. No conclusion could be drawn in the subgroup of studies comparing BCG with MMC. In addition, Böhle *et al.*, using a large database, found a statistically significant reduction in the OR of disease progression for patients treated with BCG compared with those treated with maintenance MMC (OR: 0.66) [69,72]. Among five previous meta-analyses comparing BCG with MMC for disease progression, only one concluded the superiority of BCG over MMC when maintenance BCG was used [72,73]; however, this meta-analysis also included several nonrandomized studies. The four other meta-analyses could not detect a difference, with or without the use of maintenance therapy [21,68,69,73]. More recently, an individual patient data meta-analysis of 1880 patients, three-quarters of whom were of intermediate risk, did not detect a significant benefit of BCG compared with MMC for tumor progression [40].

Intravesical chemotherapy is generally better tolerated than BCG and is not affected by the small but present risk of BCG sepsis and death. Recent reports and reviews have demonstrated 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. A meta-analysis by Shelley *et al.* found that 30% of patients receiving MMC developed local toxicity compared with 44% with BCG, with respective values of 12 and 19% for systemic side effects, although the difference was not statistically significant [68]. A significantly higher withdrawal rate of patients treated with BCG compared with MMC was not demonstrated [72]. Similar findings were reported in a randomized study that compared BCG with doxorubicin: fever, pain on urination and hematuria were more common when receiving BCG, whereas allergic reactions such as rubor or itching were more frequent when receiving doxorubicin. Further studies would be useful in order to evaluate whether the difference in toxicity between BCG and chemotherapeutic agents actually affects the patient dropout rate and their quality of life.

Given the nonconclusive evidence, MMC should be considered a viable alternative for patients with papillary tumors at low or intermediate risk for disease progression. Nevertheless, we lack level-I evidence for this assumption, as there are no prospective clinical trials of optimized MMC [68]. The clinical management decision in UBC involves the assessment of individual risk for recurrence and progression [3]. In low-risk patients, a single immediate instillation of chemotherapy is recommended [60]. However, in the Ta low-grade group, other possible options comprise no adjuvant therapy or an induction course of chemotherapy, while for high-grade or T1 disease, BCG is the preferred option. Either BCG or MMC is recommended for patients with an increased risk of disease recurrence but a low risk of disease progression [69].

In a prospective multicenter study, Huland *et al.* found no significant difference in recurrence rates among patients treated or without maintenance MMC or doxorubicin [74]. Two EORTC prospective randomized trials comparing early versus delayed and short-term versus long-term (6 vs 12 months) treatment with MMC and doxorubicin found no significant difference in the disease-free interval between any of these groups. However, the recurrence rate was worse among patients with delayed treatment and no maintenance [75]. This was further confirmed by a randomized trial of maintenance versus no maintenance after early instillation of epirubicin, which demonstrated no difference in disease recurrence [76]. By contrast, Koga *et al.* reported a higher efficacy for a long-term versus short-term instillation of epirubicin [77]. In a prospective randomized trial, the patients received their first treatment within 24 h of TUR, followed by epirubicin for 3 or 12 months. The 3-year recurrence rate was 36% in the 3-month group versus 15% in the 12-month group. Similarly, Conrad *et al.* found that 3 years of monthly MMC maintenance was superior to no maintenance (recurrence: 14 vs 31%) in Ta G2/3 and T1 G1–3 tumors at a median follow-up of 2.9 years [78]. In a meta-analysis of 11 randomized trials, Huncharek *et al.* suggested that chemotherapy for 2 years had the greatest effect on decreasing the rate of recurrence [57]. Given these mixed results, the role of maintenance chemotherapy is not yet clear. Further prospective randomized trials are needed before recommendations can be made based on high-level evidence.

More recently, a multi-institutional randomized Phase IV trial compared short- and long-term prophylaxis with MMC versus short-term immunoprophylaxis with BCG in 495 patients [71]. In intermediate- and high-risk non-muscle-invasive UBC patients, long-term MMC significantly reduced the risk of tumor recurrence without increasing adverse events, with 3-year recurrence-free rates of 86.1% for long-term MMC, and 65.5 and 68.6% for short-term BCG and MMC, respectively.

Future perspective

The guidelines and consensus panels on non-muscle-invasive UBC (the AUA National Comprehensive Cancer Network [NCCN] and the EAU) did not agree on the optimal maintenance schedule and duration and, therefore, do not make any recommendations. However, the best available data support the use of a 6-week induction course of BCG, followed by a maintenance course for at least 1 year, when compared with standard MMC treatment [39,72]. Nonetheless, there are no studies evaluating optimized MMC regimens in a maintenance schedule in this setting [69]. Moreover, despite published data supporting the use of maintenance BCG for non-muscle-invasive UBC, the issue remains unclear, since other randomized trials analyzing induction alone found evidence of comparable benefits in reducing the progression rate [79]. Moreover, most of the cases of BCG intolerance occur during maintenance therapy, contributing to the reluctance of urologists to use this regimen [46].

Intravesical therapy failures indicate the need to include radical cystectomy as an option in the management decision, since only half of the patients will respond to conservative treatment when recurrence is detected at 3 months after a BCG course [80]. In this setting, no strong evidence supports the use of chemotherapy as a first option, unless the patient has

shown evident signs of BCG intolerance. Ultimately, the risk of BCG toxicity should always be considered when recommending immunotherapy, and individual assessment is crucial when selecting the most appropriate therapy for patients at higher risk for recurrence and progression.

Apart from defining the best regimen with the available drugs, efforts to increase efficacy have included several promising attempts to introduce new agents to intravesical therapy, to combine them with established agents or to modify current regimens. Future potential means to improve BCG efficacy can be envisioned, based on mechanistic considerations. One attractive mechanism is enhancing the Th1 regulatory cytokine cascade. Toward this goal, the activity of inhibitory mediators such as IL-10 and prostaglandin E2 can be decreased by IFN- γ and nonsteroidal anti-inflammatory drugs, respectively. Addition of stimulatory cofactors, such as IFN- γ , IL-2 and GM-CSF, have similarly been demonstrated to increase the Th1-inducing effects of BCG [81]. Identifying BCG resistance mechanisms remains a high priority. A novel possibility for boosting BCG antitumor activity is enhancing effector processes via death domain receptors/apoptosis signaling, which is suspected of being operative during BCG therapy. While some drugs, such as COX-2 inhibitors, have been found to promote these effects, novel inhibitors of apoptosis inhibitors (e.g., survivin and XIAP) have the potential for being even more beneficial. Finally, there is the prospect of genetically modifying the properties of BCG to express tumor-associated antigens, thereby creating a more specific cancer vaccine.

Several novel compounds have been proposed for the management of non-muscle-invasive bladder cancer, such as a mycobacterial cell wall–DNA complex. Patients receiving 4 and 8 mg achieved complete response rates of 27.3 and 46.4%, respectively [82]. Although recent studies have been reported for several other compounds, there has been no published evidence to date that supports their clinical use.

Factors of BCG or chemotherapy failure remain largely unknown and unpredictable. The efficacy of maintenance BCG and MMC is related to a significant reduction in tumor recurrence. While BCG reduces the risk of disease progression in high-risk patients, its effect on progression in intermediate-risk patients has not been proven, thus calling into question its use in intermediate-risk non-muscle-invasive bladder cancer given its increased toxicity compared with chemotherapy. Further work is still required in order to better understand the mode of action of BCG and different chemotherapeutic agents, refine the treatment schedule and more accurately identify the patients most likely to benefit from BCG or chemotherapy.

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Executive summary

- The differences in efficacy between most bacillus Calmette–Guerin (BCG) strains are minimal.
- Until further studies establish the feasibility of these schedule modifications in humans, the BCG instillation regimen once a week for 6 weeks is considered to be the standard induction course.
- While there are convincing data demonstrating that intravesical BCG therapy reduces and/or delays disease recurrence in patients with non-muscle-invasive urothelial bladder cancer, its effect on prevention of progression to higher-stage disease remains controversial. A large meta-analysis involving 4863 patients from 24 clinical trials revealed a 27% reduction (9.8 vs 13.8%) in the odds of disease progression at a mean follow-up of 2.5 years for patients treated with transurethral resection (TUR) plus BCG (induction and maintenance) compared with those treated with TUR alone.
- Predictors of decreased response to intravesical therapy include clinical stage T1, tumor multifocality, large tumor size, prior intravesical therapy failure, short time to previous intravesical therapy failure and, most importantly, accurate staging using re-resection; however, none of these characteristics is an exclusion criterion.
- A repeat TUR within 2–6 weeks of initial TUR will improve selection by reclassifying approximately 30% of understaged patients and eliminating the residual tumor in another 50%.
- Patients receiving BCG with maintenance have a lower risk of disease progression compared with patients receiving chemotherapy without maintenance: although disease recurrence rates do not differ significantly between them. However, in an individual patient data meta-analysis of 1880 patients, three-quarters of whom were intermediate risk, a significant benefit of BCG compared with mitomycin C (MMC) was not detected for tumor progression.
- With few exceptions, most investigators believe that the efficacy of BCG therapy can be maximized with maintenance therapy. The European Association of Urology and American Urological Association uniformly recommend at least 1 year of maintenance therapy for all high-risk patients receiving BCG.
- The optimal BCG maintenance schedule remains undecided. The South-West Oncology Group program is the most widely applied schedule, with a 3-week miniseries given at scheduled intervals of 3, 6, 12, 18, 24, 30 and 36 months.
- While MMC has been found to decrease the risk of disease recurrence by approximately 14%, it does not decrease the risk of tumor progression when compared with TUR alone.

- Intravesical emcitabine and ocetaxol are safe and tolerable. A Phase II prospective study of gemcitabine in BCG-refractory patients has demonstrated a 50% complete response rate, with 21% of patients remaining disease-free at 1 year.
- For patients at a high risk for disease progression, BCG with maintenance therapy should be the preferred strategy. However, given the inconclusive evidence, MMC can be considered as a viable alternative for patients with papillary tumors (no carcinoma *in situ*) at low or intermediate risk of disease progression. Nevertheless, we lack level-I evidence for this assumption, as there are no prospective clinical trials of optimized MMC.
- A single dose of immediate chemotherapeutic instillation given within 24 h after TUR reduces the risk of disease recurrence by approximately 30–40%. The results of all chemotherapeutic agents (epirubicin, MMC and doxorubicin) were comparable, with the exception of thiotepa, which proved to be of no additional benefit.
- Intravesical chemotherapy is generally better tolerated than BCG and is not affected by the small but present, risk of BCG sepsis and death.
- Combination intravesical therapy with other agents may be more successful than single-agent strategies.
- Intravesical therapy failures indicate the need to include radical cystectomy as an option in the management decision, since only half of the patients will respond to conservative treatment when recurrence is detected at 3 months after a BCG course.