special article

Alternative Therapies to *Bacillus* Calmette-Guérin Shortage for Nonmuscle Invasive Bladder Cancer in Brazil and Other Underdeveloped Countries: Management Considerations

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abstract

Bacillus Calmette-Guérin (BCG) plays a cornerstone role in the management of nonmuscle invasive urothelial carcinoma of the bladder. However, there has been a worldwide intermittent BCG shortage in recent years that may affect the care of patients with bladder cancer and pose difficult clinical decisions to urologists and clinical oncologists. This literature review aims to clarify alternatives to BCG during a shortage and propose measures to replace BCG, mainly in Brazil and probably in other low- and middle-income countries, where not all studied and commonly suggested treatments are available.

INTRODUCTION

Bladder Cancer Scenario

In 2017, an estimated 81,190 new patients with bladder cancer were diagnosed in the United States. The incidence in men is four times higher than in women, accounting for an estimated 62,380 new patients, ranking as the fourth most common malignancy and responsible for 7% of all cancers in men. There were an estimated 12,520 deaths in men, corresponding to the eighth leading cause of cancer-specific death.[1]

In Brazil, there were an estimated 6,690 and 2,970 new patients with bladder cancer in men and women, respectively, in 2018. The incidence rate estimates are 6.43 and 2.63 per 100,000 for men and women, respectively, corresponding to the seventh and fourteenth most common cancers.[2] However, it is important to point out that these numbers are probably higher because new patients with bladder cancer are under-reported in several regions in Brazil, which may also be seen in other low- and middle-income countries (LMICs).

Approximately 50% to 60% of bladder cancers are nonmuscle invasive urothelial cancers of the bladder (NMIUCB). These include stages Ta (noninvasive papillary tumor), T1 (tumor invades subepithelial connective tissue [lamina propria]) and Tis (carcinoma in situ [CIS] flat tumor), without lymph node involvement.[3] NMIUCB can also be divided according to histologic grading: (1) papillary urothelial neoplasm of low malignant potential, (2) low-grade papillary urothelial cancer, and (3) high-grade papillary urothelial cancer. All in situ carcinomas should be considered high grade.[4]

Bladder cancer overall survival (OS) rate varies significantly according to the disease stage. Patients with NMIUCB have a much better prognosis, with a 5-year OS rate of 70%, compared with 5% in patients with metastatic disease.[1] Transurethral resection (TUR) is the surgical gold standard treatment of NMIUCB. For decades, intravesical *Bacillus* Calmette-Guérin (BCG) therapy has been the standard treatment for recurrence prevention after TUR in most patients with NMIUCB.

Bacillus Calmette-Guérin

Although the exact mechanism of action of BCG therapy is not fully understood, it is well known that a strong cellular immune reaction occurs in the urothelium, starting with the adherence of the mycobacteria. Subsequently, cytokine production stimulates the influx of inflammatory cells (monocytes and neutrophils).[5]

Intravesical BCG therapy is indicated according to clinical and pathologic characteristics: multicentric tumors, tumor size, T1 stage, grade, recurrence history, associated CIS, and unfavorable location. Patients can be stratified to low, intermediate, and high risk of recurrence according to those features (Table 1).[6]

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TABLE 1. NMIUCB Risk of Recurrence Stratification

Risk Group	Clinical and Pathologic Features
Low	First occurrence AND
	Single lesion AND
	Stage Ta or PUNLMP AND
	Low-grade tumor AND
	Tumor size < 3 cm AND
	Favorable location AND
	Absence of CIS
Intermediate	Not low risk and not high risk
High	Stage T1 OR
	High grade OR
	Presence of CIS OR
	Unfavorable location OR
	Recurrent tumor, with multiple lesions, tumor size > 3 cm, but with a low grade

Abbreviation: CIS, carcinoma in situ; NMIUCB, nonmuscle invasive urothelial carcinoma of the bladder; PUNLMP, papillary urothelial neoplasm of low malignant potential.

Usually, after TUR of bladder tumor (TURBT), patients in the low-risk group do not need intravesical BCG. It is usually recommended that patients in the high-risk group receive an induction course of intravesical once-per-week BCG for 6 weeks, followed by maintenance therapy for 1 to 3 years (three cycles of instillations once per week in months 3, 6, 12, 18, 24, 30, and 36 after induction).[7] Treatment of patients in the intermediate-risk group remains controversial. According to guidelines published by the Brazilian Society of Urology and American Urological Association,[8] these patients should follow the same scheme proposed for high-risk patients. However, the European Association of Urology[7] and National Comprehensive Cancer Network[9] guidelines suggest induction therapy with once-per-week BCG for 6 weeks, followed by maintenance therapy for 1 year (three cycles of instillations once per week in months 3, 6, and 12 after induction).

BCG Supply in Brazil

There is only one laboratory (Fundacao Ataulpho Paiva) that manufactures and supplies BCG for intravesical therapy in Brazil. The strain produced in Brazil is Moreau Rio de Janeiro, and it is available in 40-mg lyophilized powder formulation vials containing 2.0×10^6 cfu/mg of BCG. According to the package insert, two vials should be reconstituted with 50 mL of saline and administered through intravesical instillation. However, there have been several periods of manufacturing shortages, negatively affecting the treatment of several patients with NMIUCB.

In the last decade, several other countries also suffered from a shortage in BCG supply, and there were some published recommendations for how to cope with this.[10] However, typically, these recommendations could not be extrapolated to all countries because of local limitations, especially in LMICs. Table 2 lists several countries, the BCG strain, and whether the strain is in short supply.

Certain chemotherapy options may not be available in some countries, such as mitomycin-C in Brazil. Also, although BCG is usually easily manipulated by a physician and/or nurse, chemotherapy agents must be prepared by specialized oncologic pharmacies that are not usually present in many places. Another issue is that in many countries, chemotherapy drugs must be prescribed exclusively by clinical oncologists who have not necessarily been involved in the initial phase of the treatment. These factors could delay treatment or, worse, result in additional costs that would make the intravesical instillations unfeasible. Therefore, we sought to review and discuss alternative approaches to BCG therapy for NMIUCB in Brazil that could potentially be used in other LMICs.

ALTERNATIVE THERAPIES TO BCG DURING A SHORTAGE

Importing BCG

Calmette and Guérin cultivated and developed the Pasteur strain. Since then, several other strains, with different phenotypes, were developed and have started to be used. There is evidence suggesting that different strains might present the same antigenic profile and efficacy.[11] Few studies have directly compared the different strains, but a 2002 meta-analysis suggested that there is no significant difference among the most commonly used strains, such as Pasteur, Frappier, Connaught, Tice, and RIVM.[12] However, a prospective randomized trial suggested that the efficacy results might vary. Patients receiving the BCG Connaught strain had a significant improvement in 5-year recurrence-free survival compared with those receiving the Tice strain

TABLE 2. BCG Strains Around the World

Country	BCG Strain	Current Availability
Brazil	Moreau	±
Hong Kong	Tokyo	+
	Connaught	–
Italy	Tice	+
Mexico	Danish	+
	Tice	±
Russia	Tice	±
Singapore	Tokyo	+
Spain	Medac	+
	Tice	±
United Kingdom	Tice	+
	Connaught	–
United States	Tice	+

NOTE. +, drug is available; –, drug is not available; ±, there is certain difficulty finding the drug.

Abbreviation: BCG, *Bacillus* Calmette-Guérin.

(74% *v* 48%; $P = .0108$).[13] Nevertheless, a reasonable option to overcome the shortage of BCG supply in Brazil is to import other strains, especially for those patients with high-risk features. However, there are also limitations related to the higher cost of import taxes and shipment, as well as the longer time needed for this (usually 2 to 3 weeks). Each vial in Brazil has an approximate cost of 65.00 euros, whereas the RIVM strain from Germany (BCG-Medac, Hamburg, Germany) and Tice strain from the United States (Onco-Tice, Merck, Whitehouse Station, NJ) are much more expensive, costing approximately 340.00 euros per vial, plus shipping costs and taxes totaling approximately 720.00 euros.

Reduction of the Dose and/or Duration of Induction and Maintenance Courses

There are several schedules of induction and maintenance reported in the literature for NMIUCB. The ideal number of instillations for induction, frequency, and duration of maintenance is not fully understood.

Since 1976, the induction cycle of BCG therapy was empirically defined as six instillations (intravescial) once per week.[14] Depending on the protocol used, the maintenance phase might vary from 18 weeks (10 cycles) to 3 years (27 cycles). The most widely accepted and used maintenance protocol was proposed by SWOG, recommending a once-per-week BCG instillation for 3 weeks in months 3, 6, 12, 18, 24, 30, and 36. This protocol has shown that the addition of 3 years of maintenance was associated with improved 3-year recurrence-free survival compared with induction only (76.8 *v* 35.7 months, respectively; $P < .001$), improved progression-free survival (not estimable *v* 111.5 months, respectively; $P = .04$), and increased 5-year OS (83% *v* 78%, respectively; $P = .08$).[15] When there is a supply shortage, it is probably valid to split the vials for different patients, with partial/reduced doses and reduction in the number of vials for each patient, to increase the number of patients treated.

Number of instillations during induction. There are no high-quality clinical trials evaluating the number of induction sessions. Nevertheless, one trial evaluated the lymphocyte count increase in peripheral blood after induction cycles. The investigators observed a maximum immune response after the fourth instillation, with the fifth and sixth dose being necessary only for those patients who were not previously exposed to *Mycobacterium* antigens (ie, BCG vaccination).[16] Therefore, in Brazil, where BCG vaccination is compulsory for newborns, it might be sufficient to give four induction instillations. Nevertheless, this strategy would need to be tested in clinical trials designed in the Brazilian population.

Number of instillations during maintenance cycles and length of maintenance. A prospective randomized trial evaluating recurrence of multifocal NMIUCB showed a significant improvement in the 2-year recurrence-free survival for those patients receiving induction and maintenance cycles compared with only induction (84.6% *v* 65.4%, respectively). The improvement was significant, even for those patients who received fewer maintenance cycles (for only 1.5 years; three once-per-week doses for consecutive weeks in months 3, 6, 12, and 18).[17]

There is no immunologic evidence supporting other maintenance schedules that do not contain three instillations once per week every 6 months. Evidence suggests that cytokine peak levels occur 3 weeks after the first instillation,[18] and the lymphocyte infiltration decreases after 6 months.[19]

A common alternative maintenance schedule administers a single maintenance once-per-month dose for 1 year after the induction phase. However, a prospective randomized clinical trial failed to show any improvement over the induction phase alone (3-year recurrence-free survival of 77.6% *v* 74.2%, respectively).[20] Even after extending the single maintenance once per month cycles for 2 years, the recurrence and progression rates were not statistically different compared with induction alone.[21]

Another clinical trial attempted to reduce the number of instillations in the maintenance cycles. These authors compared induction alone with induction followed by maintenance with single instillations every 3 months for 3 years. However, the 5-year recurrence-free survival was not statistically different for induction followed by alternative maintenance and induction alone (38.5% and 33.5%, respectively; $P = .2$). Five-year progression-free survival rates were also similar for both groups (19.5% and 16%, respectively; $P = .3$). OS and cancer-specific survival were also similar. Therefore, there is no indication for single instillations in the maintenance phase.[22]

Dose of BCG and decreased instillations. To compare BCG doses, we would need to compare the number of bacilli per instillation. However, the doses are usually reported in milligrams per vial only, and the number of bacilli per milligram varies significantly for different strains. This could lead to a significant bias when comparing different strains.

The initial dose of BCG was empirically determined to be 120 mg with the Frappier strain.[14] Other studies attempted to evaluate a reduced dose to decrease the potential adverse effects. A phase III trial compared two different doses of the Pasteur strain (75 mg *v* 150 mg) and showed a decrease in the adverse events with the same efficacy with the reduced dose of 75 mg.[23] The Danish strain was also compared in three doses (120 mg, 80 mg, and 40 mg), and again, there was no difference in efficacy, but there was less toxicity with the reduced doses.[24]

Regarding the Connaught strain, two initial prospective studies did not observe any improved efficacy with the full doses (81 mg *v* 27 mg) in the majority of patients. The first study included 500 patients with Ta, T1, or Tis that were randomly assigned to receive the standard dose (81 mg) or one third of the dose (27 mg), with six instillations once per

week (induction) followed by six additional instillations every 2 weeks (maintenance). The recurrence rate was 31% and 28% for patients receiving 27 mg and 81 mg, respectively. However, for those patients with multifocal disease, the standard dose presented a significant improvement in efficacy, and there was also a beneficial trend for those patients with high-risk tumors. Regarding the disease progression rate, patients treated with the standard or the reduced dose had similar overall incidence rates of 11.5% and 13.3%, respectively. However, when evaluating the subgroup of patients with multifocal disease, the standard dose had improved efficacy.[25] The second study included 151 patients with only high-grade T1 and/or Tis and suggested that the reduced dose (27 mg) was as effective as the standard dose (81 mg). These authors observed a 5-year recurrence rate of 39% and 45% for patients treated with the standard and reduced dose, respectively, and a progression rate of 24.7% and 26%, respectively. No statistically significant difference between groups was observed.[26]

Greater dose reductions were also tested, but they were associated with worse outcomes. Using the Connaught strain, 27 mg was compared with 13.5 mg in patients with intermediate-risk disease. Significantly more recurrences were observed with 13.5 mg, and the toxicity profile was similar.[27] Therefore, the Society for Immunotherapy for Cancer[28] issued a consensus statement that considered it reasonable to use reduced doses (one third of the standard) for induction and maintenance, especially in those areas with BCG shortage problems.

However, the best available evidence is from a large prospective phase III randomized controlled trial that included 1,355 patients with a high-grade pT1 tumor or any-grade multifocal pTa-pT1. All patients received the Tice strain (full dose was considered 5×10^8 cfu). Patients were randomly assigned to four groups receiving (1) one third of the full dose for 1 year (n = 341); (2) full dose for 1 year (n = 339); (3) one third of the full dose for 3 years (n = 337); and (4) full dose for 3 years (n = 338). The 5-year disease-free survival rates were 54.5%, 58.8%, 62.6%, and 64.2%, respectively. Patients treated with one third of the full dose for 1 year had more recurrences compared with patients treated with the full dose for 3 years. For those patients with intermediate-risk disease, there was no additional improvement in efficacy with 3 years of the full dose compared with 1 year. Therefore, it is recommended that patients with intermediate-risk disease be treated with the full dose for 1 year. However, for those patients with high-risk disease, the authors observed decreased incidence rates of recurrence, but similar rates of progression and survival. Therefore, the risk-benefit ratio and costs should be evaluated and discussed for patients with high-risk disease to determine the need for the additional 2 years of maintenance.[29]

Therefore, in places where BCG supply falls short, it would be acceptable to stop the maintenance phase for those patients completing at least 1 year of treatment, especially for the intermediate-risk group, but it could also be discussed and considered for the high-risk group. Nevertheless, standard monitoring with regular cystoscopies should be further emphasized.

Radical Cystectomy

There are several reasons to consider radical cystectomy in some patients with NMIUCB, including treatment failure with BCG therapy and disease progression. However, in places with BCG supply problems, radical cystectomy could also be an alternative, and it should be considered and discussed carefully.

Overall, radical cystectomy is the best method for accurately staging bladder cancer. In fact, it is important to point out that up to 27% to 51% of patients with NMIUCB can be upstaged to muscle-invasive disease after radical cystectomy.[30] Also, some patients with high-risk NMIUCB can have up to a 78% recurrence risk and 45% progression in 5 years. In particular, those patients with high-grade T1 associated with CIS, large tumors (> 3 cm) and/or multifocal and/or recurrent high-grade disease, variant histology (ie, micropapillary), and lymphovascular invasion are those with the highest recurrence risk. In such patients, radical cystectomy should be included in the treatment discussion. Furthermore, it is important to point out that patients who have disease progression to muscle-invasive disease usually have a poorer outcome compared with those with de novo muscle-invasive disease.[31] A retrospective study comparing BCG followed by radical cystectomy with radical cystectomy upfront for patients with high-risk T1 disease showed shorter 10-year cancer-specific survival for those initially treated with BCG (51% and 78%, respectively).[32] Also, patients with NMIUCB treated with radical cystectomy had a greater than 80% chance of being recurrence free at 5 years.[33] Therefore, the risks and benefits of radical cystectomy, including mortality, morbidity, and quality of life, should be discussed with patients.

Other Drugs

Chemotherapeutic agents have also been evaluated in NMIUCB after TURBT. The rationale to administer intravesical chemotherapy 24 hours after TURBT is to prevent tumor cell implantation, thus reducing recurrence. A meta-analysis showed that chemotherapy administration just after TURBT with mitomycin-C, epirubicin, thiotepa, or pirarubicin was able to improve the risk of recurrence by 35% at 5 years, but there was no effect on the risk of progression.[34] However, there was no benefit for those patients with European Organisation for Research and Treatment of Cancer recurrence score greater than 5 and in those with more than one recurrence per year, as in most intermediate-risk and practically all high-risk patients (precisely those who would need to receive BCG therapy).

For patients with intermediate-risk disease, particularly those with multifocal tumors, repeated intravesical chemotherapy instillations (post-TURBT immediate instillation) might decrease the recurrence risk. However, the frequency or duration of subsequent instillations is not well established.[35] In a prospective study, the maintenance of intravesical instillations of mitomycin-C (40 mg) every 3 months for 1 year was superior to a single instillation post-TURBT. The 7-year recurrence rate was reduced from 48.3% to 36.3%.[36]

In the high-risk group of patients, BCG therapy is significantly superior to mitomycin-C regarding the recurrence rate, but with a similar progression risk.[37] For these patients, hyperthermic intravesical chemotherapy has been studied, with some promising data. A small, underpowered randomized study showed that microwave-induced hyperthermic mitomycin-C (six instillations once per week followed by six maintenance sessions at 6-week intervals for 1 year) was superior to BCG (induction and maintenance for 1 year), with greater 2-year recurrence-free survival (81.8% *v* 64.8%, respectively).[38]

A meta-analysis suggested the importance of maintenance therapy with BCG. BCG induction and maintenance had a 32% lower recurrence rate ($P < .001$) compared with mitomycin-C induction and maintenance. However, BCG induction was inferior only to mitomycin-C induction and maintenance, with a 28% higher recurrence rate ($P = .006$). Therefore, in areas with a BCG shortage, induction and maintenance therapy with intravesical mitomycin-C should be considered.[39] However, unfortunately, mitomycin-C is also not widely available in Brazil, and patients and health care providers need to import it, thus increasing treatment costs that are usually not reimbursed by the health care system.

Intravesical epirubicin, which is more widely available, was also compared with BCG in patients with intermediate- and high-risk disease. Intravesical BCG therapy was still significantly superior compared with intravesical epirubicin, with improved time to first recurrence, as well as improved time to distant metastasis, cancer-specific survival, and OS.[40] Another study also showed a significantly lower recurrence rate in favor of those patients treated with standard BCG (27%), compared with epirubicin combined with interferon alfa-2b (38%), but no difference in the risk of progression.[41]

Another promising therapy is intravesical gemcitabine. A recently published study showed a reduction in the 4-year recurrence risk from 47% (placebo) to 35% (gemcitabine) in low-risk patients with NMIUCB.[42] In a retrospective study including different risk groups, with a follow-up of 15 months, there was a trend toward improved disease-free survival with gemcitabine compared with BCG therapy (both with six instillations once per week for induction, followed by maintenance according to risk group) and with fewer adverse events (7% *v* 44%, respectively).[43] A small prospective study compared BCG and gemcitabine in treatment-naive high-risk patients with NMIUCB but with no CIS; recurrence rates (30% and 25%, respectively) and progressive disease rates (2.5% and 2.5%, respectively) were similar.[44] However, in another series with high-risk

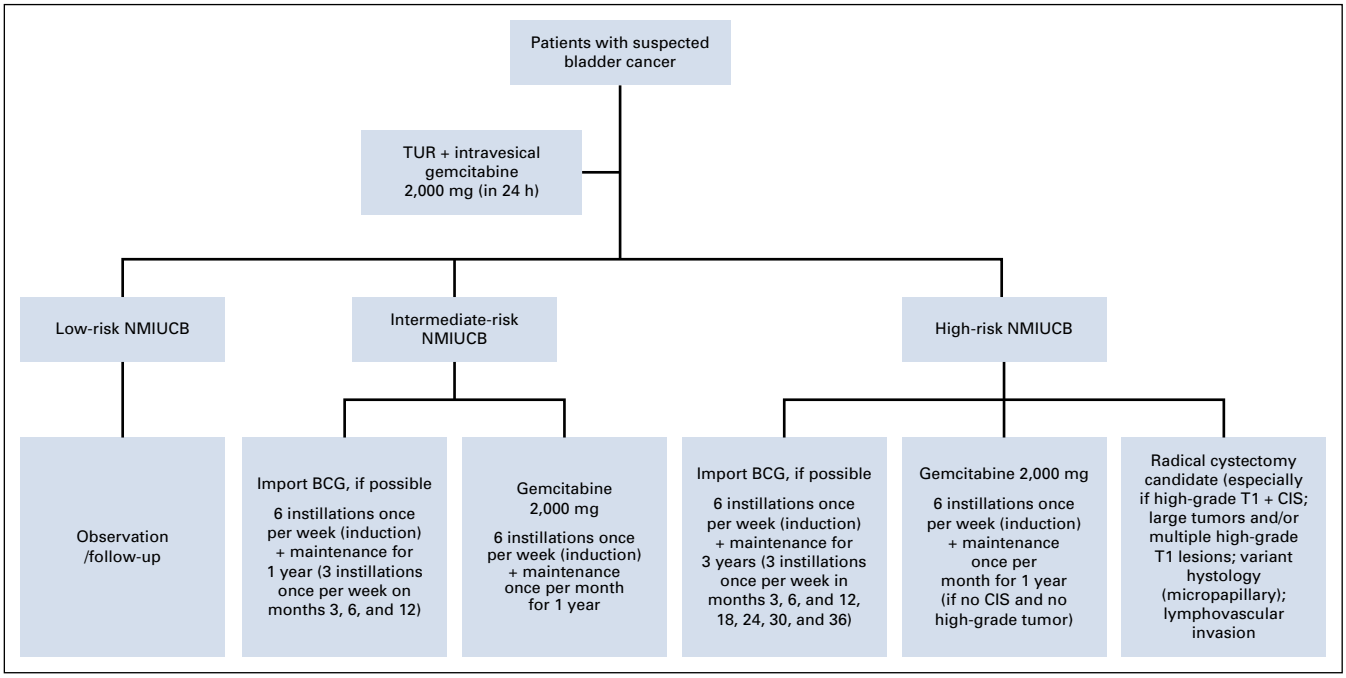

FIG 1. Proposed flowchart of alternatives to *Bacillus* Calmette-Guérin (BCG) during a supply shortage in recently diagnosed patients with nonmuscle invasive urothelial carcinoma of the bladder (NMIUCB). CIS, carcinoma in situ; TUR, transurethral resection.

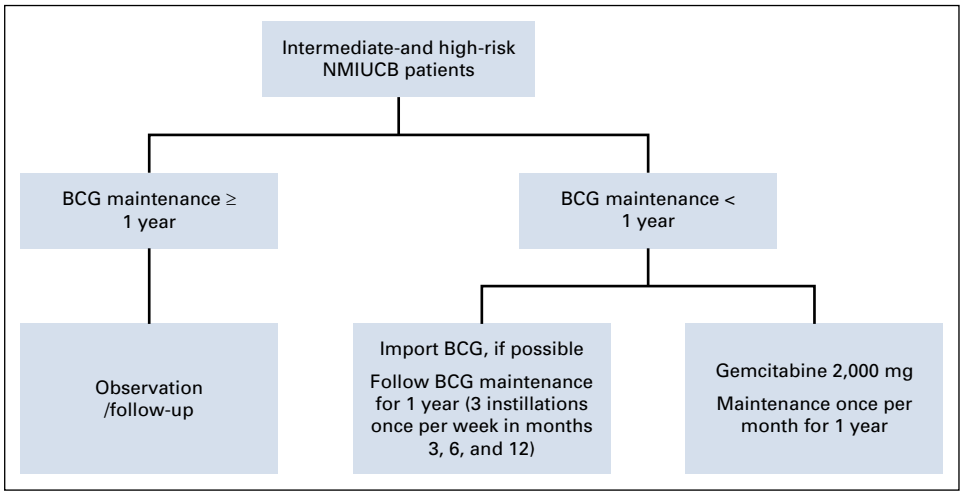

FIG 2. Proposed flowchart for patients with nonmuscle invasive urothelial carcinoma of the bladder (NMIUCB) who have already started therapy with *Bacillus* Calmette-Guérin (BCG) but face BCG supply shortage during therapy.

patients, with high-grade tumors and/or CIS, the recurrence rate was significantly higher in the gemcitabine group compared with BCG (53.1% and 28.1%, respectively), and the time to recurrence was also worse with gemcitabine (25.5 and 39.4 months, respectively).[45] However, high-risk patients who failed previous BCG therapy and received subsequent gemcitabine had a better outcome (fewer recurrences) compared with those retreated with BCG, with a lower recurrence rate (52.5 and 87.5%, respectively) and longer recurrence-free interval (3.9 and 3.1 months, respectively), but with similar progression rates (33% and 37.5%, respectively) and no difference in toxicity profile.[46]

Therefore, in areas with BCG supply problems, especially for intermediate-risk and some high-risk patients with no CIS, gemcitabine can be considered, mainly when mitomycin-C is unavailable. The intravesical gemcitabine recommended dose is 2,000 mg (diluted in 50 mL of distilled water), administered every week for 6 weeks, followed by once-per-month intravesical instillations for 1 year.

TREATMENT OPTIONS SUMMARY

If a patient has been diagnosed with NMIUCB during a BCG shortage period, management will depend on the risk stratification (Fig 1). Patients with low-risk NMIUCB must undergo regular observation and follow-up. Intermediate-risk patients have the option of importing BCG and then following the 6-week induction and maintenance for the 1-year recommendation. Full-dose schemes should be preferred, but a dose reduction of up to one third is acceptable. In this scenario, two to three patients per BCG

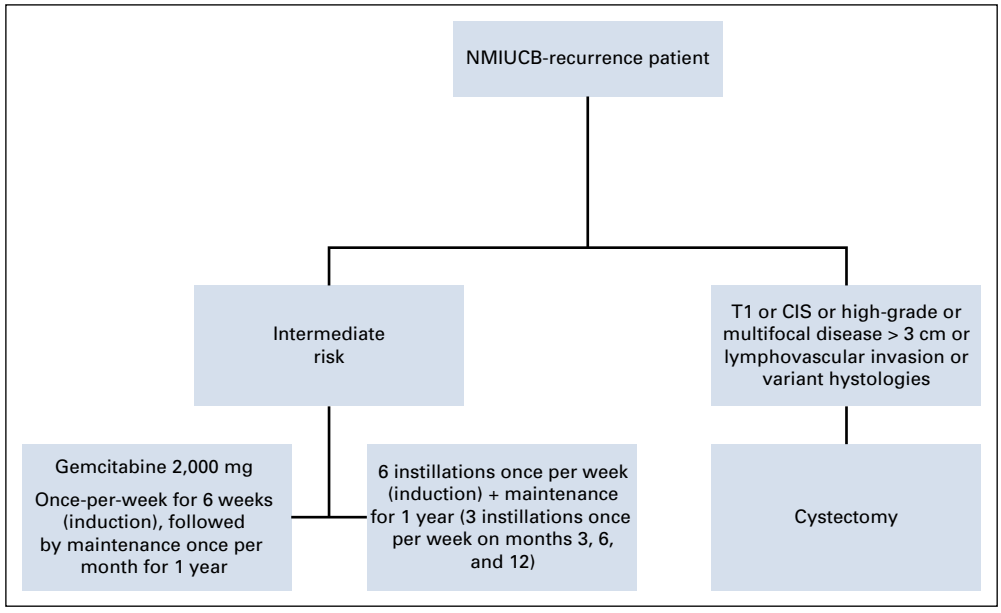

FIG 3. Proposed flowchart for patients with nonmuscle invasive urothelial carcinoma of the bladder (NMIUCB) with recurrent disease and no availability of *Bacillus* Calmette-Guérin therapy. CIS, carcinoma in situ.

vial should be treated simultaneously to keep safety precautions and avoid waste. If BCG supply is reestablished, the local strain may substitute for the international one. Another option for intermediate-risk patients is, if available in the particular region, beginning gemcitabine for 6 weeks followed by maintenance once per month for 1 year. Although BCG importation and gemcitabine are acceptable, good surgical candidates among high-risk patients should be encouraged to pursue upfront radical cystectomy, mainly in the presence of adverse features, such as high-grade T1, CIS, lymphovascular invasion, and prostatic urethra involvement of variant histologies.

For those intermediate- and high-risk patients in whom BCG therapy has already been started but experience a shortage during treatment (Fig 2), observation is a reasonable option if they have received at least 1 year of therapy, mainly in intermediate-risk patients. However, if maintenance therapy has been given for less than 1 year, a switch to once-per-month gemcitabine for 1 year or an attempt to import BCG and at least finish the 3-, 6-, and 12-month courses is recommended. The dose reduction strategy could also be used in this situation, even more so if it could lead to the possibility of finalizing the 3-year maintenance in the high-risk group. As for patients with newly diagnosed NMIUCB, these recommendations could also be applied in the case of recurrent disease (Fig 3).

In conclusion, BCG supply problems have been occurring in Brazil, as well as in other parts of the world, in the past few years. Until new options (ie, immune checkpoint inhibitors [ClinicalTrials.gov: NCT02844816]) are available in daily practice or new strategies are described [ClinicalTrials.gov: NCT03091660]), BCG therapy remains the standard of care for patients with NMIUCB. This review describes how to optimize the use of BCG regarding schedule and dosage, as well as all the alternative treatments that may be considered in the scenario of a BCG shortage, focusing on the situation in Brazil, which could eventually be extrapolated to other LMICs. Efforts with local regulatory agencies and manufacturers should be made to improve the logistics and supply of BCG in a more efficient and consistent manner.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2018. CA Cancer J Clin 68:7-30, 2018
2. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA): Estimativa 2018: Incidência de Câncer no Brasil. https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-incidencia-de-cancer-no-brasil-2018.pdf
3. Sobin LH, Gospodarowicz MK, Wittekind C (eds): TNM Classification of Malignant Tumors (ed 7), Hoboken, NJ, Wiley-Blackwell, 2009

4. Soukup V, Čapoun O, Cohen D, et al: Prognostic performance and reproducibility of the 1973 and 2004/2016 World Health Organization grading classification systems in non-muscle-invasive bladder cancer: A European Association of Urology Non-Muscle Invasive Bladder Cancer Guidelines Panel systematic review. Eur Urol 72:801-813, 2017
5. Gontero P, Bohle A, Malmstrom PU, et al: The role of Bacillus Calmette-Guérin in the treatment of non-muscle-invasive bladder cancer. Eur Urol 57:410-429, 2010
6. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al: Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. Eur Urol 49:466-465, 2006;discussion 475-477
7. Guidelines EAU: Edn. presented at the EAU Annual Congress Copenhagen 2018. ISBN 978-94-92671-01-1
8. Sociedade Brasileira de Urologia: Diretrizes Guia de Bolso, 2017 http://portaldaurologia.org.br/medicos/wp-content/uploads/2017/08/guideline_AUA_SBU-ilovepdf-compressed.pdf
9. National Comprehensive Cancer Network: Bladder cancer (version 3.2019). https://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf
10. Abufaraj M, Mostafid H, Shariat SF, et al: What to do during Bacillus Calmette-Guérin shortage? Valid strategies based on evidence. Curr Opin Urol 28:570-576, 2018
11. Herr HW, Morales A: History of Bacillus Calmette-Guerin and bladder cancer: An immunotherapy success story. J Urol 179:53-56, 2008
12. Sylvester RJ, van der MEIJDEN AP, Lamm DL: Intravesical Bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. J Urol 168:1964-1970, 2002
13. Rentsch CA, Birkhäuser FD, Biot C, et al: Bacillus Calmette-Guérin strain differences have an impact on clinical outcome in bladder cancer immunotherapy. Eur Urol 66:677-688, 2014
14. Morales A, Eidinger D, Bruce AW: Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol 116:180-183, 1976
15. Lamm DL, Blumenstein BA, Crissman JD, et al: Maintenance Bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: A randomized Southwest Oncology Group Study. J Urol 163:1124-1129, 2000
16. Zlotta AR, van Vooren JP, Huygen K, et al: What is the optimal regimen for BCG intravesical therapy? Are six weekly instillations necessary? Eur Urol 37:470-477, 2000
17. Hinotsu S, Akaza H, Naito S, et al: Maintenance therapy with Bacillus Calmette-Guérin Connaught strain clearly prolongs recurrence-free survival following transurethral resection of bladder tumour for non-muscle-invasive bladder cancer. BJU Int 108:187-195, 2011
18. De Boer EC, De Jong WH, Steerenberg PA, et al: Induction of urinary interleukin-1 (IL-1), IL-2, IL-6, and tumour necrosis factor during intravesical immunotherapy with Bacillus Calmette-Guérin in superficial bladder cancer. Cancer Immunol Immunother 34:306-312, 1992
19. Winters WD, Lamm DL: Antibody responses to Bacillus Calmette-Guérin during immunotherapy in bladder cancer patients. Cancer Res 41:2672-2676, 1981
20. Akaza H, Hinotsu S, Aso Y, et al: Bacillus Calmette-Guérin treatment of existing papillary bladder cancer and carcinoma in situ of the bladder. Four-year results. Cancer 75:552-559, 1995
21. Badalament RA, Herr HW, Wong GY, et al: A prospective randomized trial of maintenance versus nonmaintenance intravesical Bacillus Calmette-Guérin therapy of superficial bladder cancer. J Clin Oncol 5:441-449, 1987
22. Martínez-Piñeiro L, Portillo JA, Fernández JM, et al: Maintenance therapy with 3-monthly Bacillus Calmette-Guerin for 3 years is not superior to standard induction therapy in high-risk non-muscle-invasive urothelial bladder carcinoma: Final results of randomised CUETO study 98013. Eur Urol 68:256-262, 2015
23. Pagano F, Bassi P, Piazza N, et al: Improving the efficacy of BCG immunotherapy by dose reduction. Eur Urol 27:19-22, 1995 (suppl 1)
24. Agrawal MS, Agrawal M, Bansal S, et al: The safety and efficacy of different doses of Bacillus Calmette Guérin in superficial bladder transitional cell carcinoma. Urology 70:1075-1078, 2007
25. Martínez-Piñeiro JA, Flores N, Isorna S, et al: Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guérin with a reduced dose of 27 mg in superficial bladder cancer. BJU Int 89:671-680, 2002
26. Martínez-Piñeiro JA, Martínez-Piñeiro L, Solsona E, et al: Has a 3-fold decreased dose of Bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. J Urol 174:1242-1247, 2005
27. Ojea A, Nogueira JL, Solsona E, et al: A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: Low-dose Bacillus Calmette-Guerin (27 mg) versus very low-dose Bacillus Calmette-Guerin (13.5 mg) versus mitomycin C. Eur Urol 52:1398-1406, 2007
28. Kamat AM, Bellmunt J, Galsky MD, et al: Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma. J Immunother Cancer 5:68, 2017 [Erratum: J Immunother 5:80, 2017]
29. Oddens J, Brausi M, Sylvester R, et al: Final results of an EORTC-GU cancers group randomized study of maintenance Bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: One-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol 63:462-472, 2013
30. Fritsche HM, Burger M, Svatek RS, et al: Characteristics and outcomes of patients with clinical T1 grade 3 urothelial carcinoma treated with radical cystectomy: Results from an international cohort. Eur Urol 57:300-309, 2010 [Erratum: Eur Urol 57:300-309, 2010]
31. Moschini M, Sharma V, Dell'oglio P, et al: Comparing long-term outcomes of primary and progressive carcinoma invading bladder muscle after radical cystectomy. BJU Int 117:604-610, 2016
32. Denzinger S, Fritsche HM, Otto W, et al: Early versus deferred cystectomy for initial high-risk pT1G3 urothelial carcinoma of the bladder: Do risk factors define feasibility of bladder-sparing approach? Eur Urol 53:146-152, 2008
33. Hautmann RE, de Petriconi RC, Pfeiffer C, et al: Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: Long-term results in 1100 patients. Eur Urol 61:1039-1047, 2012
34. Sylvester RJ, Oosterlinck W, Holmang S, et al: Systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy after transurethral resection with transurethral resection alone in patients with stage pTa-pT1 urothelial carcinoma of the bladder: Which patients benefit from the instillation? Eur Urol 69:231-244, 2016
35. Sylvester RJ, Oosterlinck W, Witjes JA: The schedule and duration of intravesical chemotherapy in patients with non-muscle-invasive bladder cancer: A systematic review of the published results of randomized clinical trials. Eur Urol 53:709-719, 2008
36. Tolley DA, Parmar MK, Grigor KM, et al: The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: A further report with 7 years of follow up. J Urol 155:1233-1238, 1996
37. Shelley MD, Wilt TJ, Court J, et al: Intravesical Bacillus Calmette-Guérin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: A meta-analysis of randomized trials. BJU Int 93:485-490, 2004
38. Arends TJ, Nativ O, Maffezzini M, et al: Results of a randomised controlled trial comparing intravesical chemohyperthermia with mitomycin c versus Bacillus Calmette-Guérin for adjuvant treatment of patients with intermediate- and high-risk non-muscle-invasive bladder cancer. Eur Urol 69:1046-1052, 2016

39. Malmström PU, Sylvester RJ, Crawford DE, et al: An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus Bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. Eur Urol 56:247-256, 2009
40. Sylvester RJ, Brausi MA, Kirkels WJ, et al: Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, Bacillus Calmette-Guérin, and Bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol 57:766-773, 2010
41. Duchek M, Johansson R, Jahnson S, et al: Bacillus Calmette-Guérin is superior to a combination of epirubicin and interferon-alpha2b in the intravesical treatment of patients with stage T1 urinary bladder cancer. A prospective, randomized, Nordic study. Eur Urol 57:25-31, 2010
42. Messing EM, Tangen CM, Lerner SP, et al: Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence: SWOG S0337 randomized clinical trial. JAMA 319:1880-1888, 2018
43. Prasanna T, Craft P, Balasingam G, et al: Intravesical gemcitabine versus intravesical Bacillus Calmette-Guérin for the treatment of non-muscle invasive bladder cancer: An evaluation of efficacy and toxicity. Front Oncol 7:260, 2017
44. Bendary L, Khalil S, Shahin A, et al: Intravesical gemcitabine versus Bacillus Calmette-Guerin (BCG) in treatment of non-muscle invasive bladder cancer: Short term comparative study. Conference Proc Am Urol Assoc 185:e664-e665, 2011
45. Porena M, Del Zingaro M, Lazzeri M, et al: Bacillus Calmette-Guérin versus gemcitabine for intravesical therapy in high-risk superficial bladder cancer: A randomised prospective study. Urol Int 84:23-27, 2010
46. Di Lorenzo G, Perdonà S, Damiano R, et al: Gemcitabine versus bacille Calmette-Guérin after initial bacille Calmette-Guérin failure in non-muscle-invasive bladder cancer: A multicenter prospective randomized trial. Cancer 116:1893-1900, 2010
47. Food and Drug Administration: NCT02844816: Phase II trial of atezolizumab in BCG-unresponsive non-muscle invasive bladder cancer. http://fdaaa.trialstracker.net/trial/NCT02844816/
48. Food and Drug Administration: NCT03091660: S1602, A phase III randomized trial to evaluate the influence of BCG strain differences and T cell priming with intradermal BCG before intravesical therapy for BCG-naive high-grade non-muscle invasive bladder cancer. http://fdaaa.trialstracker.net/trial/NCT03091660/