SPECIAL ARTICLE

Treatment of non muscle invasive bladder tumor related to the problem of bacillus Calmette-Guerin availability. Consensus of a Spanish expert’s panel

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Received 10 April 2013; accepted 11 April 2013
Available online 26 October 2013

Abstract

Context: Since June 2012, there has been a worldwide lack of availability of the Connaught strain. In December 2012, a group of experts met in the Spanish Association of Urology to analyze this situation and propose alternatives.

Objective: To present the work performed by said committee and the resulting recommendations.

Acquisition of evidence: An update has been made of the principal existing evidence in the treatment of middle and high risk tumors. Special mention has been made regarding the those related with the use of BCG and their possible alternative due to the different availability of BCG.

Evidence synthesis: In tumors with high risk of progression, immediate cystectomy should be considered when BCG is not available, with dose reduction or alternating with chemotherapy as methods to economize on the use of BCG when availability is reduced. In tumors having a medium risk of progression, chemotherapy can be used, although when it is associated to a high risk of relapse, BCG would be indicated if available with the mentioned savings guidelines. BCG requires maintenance to maintain its effectiveness, it being necessary to optimize the application of endovesical chemotherapy and to use systems that increase its penetration into the bladder wall (EMDA) if they are available.

KEYWORDS
Bladder cancer; Intravesical therapy; Bacillus Calmette-Guerin; Maintenance; Cystectomy


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2173-5786/$ - see front matter © 2013 AEU. Published by Elsevier España, S.L. All rights reserved.
Conclusions: Due to the scarcity of BCG, it has been necessary to agree on a series of recommendations that have been published on the web page of the Spanish Association of Urology.
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Introduction

Intravesical bacillus Calmette-Guérin (BCG) is still, after more than 30 years, the most effective adjuvant therapy after transurethral resection (TUR) for high-and medium-risk non-muscle-invasive bladder cancer (NMIBC), especially when used with maintenance therapy.

In April 2012, after a Food and Drug Administration (FDA) inspection of the world’s largest manufacturing facility for BCG (Connaught strain), the production of this strain was stopped until 2013. In Spain, the situation is similar to that of other countries, with varying availability of other BCG strains (RIVM, Tice, etc.) in health centers, even leading to a total shortage of treatment.

Therefore, a group of experts met in December 2012 and, considering the existing evidence on BCG treatment and the recommendations made by other international agencies and scientific societies, they developed a report with a series of recommendations which try to adjust to this different availability of BCG. There is limited scientific evidence supporting it (level 4), as usual in the case of scientific evidence from expert interpretation, and it is only valid as long as the problem with BCG persists. The aim of the present article is to provide an overview of the work done by that committee and to present the recommendations given in view of this scarcity of BCG.

Evidence synthesis. Treatment for high-and medium-risk non-muscle-invasive bladder cancer

Transurethral resection. Postoperative instillation

A good-quality TUR is the fundamental treatment for non-muscle-invasive bladder cancer (NMIBC), with re-TUR being indicated in certain cases, depending on the information and findings provided by the first TUR. Among its indications, the following stand out: absence of the detrusor muscle in initial TUR, suspicion of not having performed a complete TUR procedure due to the extension or multiplicity of the neoplasia, pathologist’s doubts on the stage and/or due to inappropriate storage of the sample, extension, etc.

The use of postoperative instillation of chemotherapy has been based on a meta-analysis which compared TUR and TUR followed by postoperative instillation, although most tumors in the included series were low-risk tumors (stage T1a, low grade, etc.). Postoperative instillation is recommended for these malignancies with a high level of evidence (1A), its effectiveness having been demonstrated with mitomycin (MMC) and epirubicin. Nevertheless, when there is suspicion of high-risk tumor (sessile or multiple tumors, Tis, recurrent high-risk tumors, etc.), where intravesical therapy is probably going to be used, postoperative instillation is not clearly
recommended, although it may have a certain beneficial effect which might be useful considering the unavailability of BCG.

**Adjuvant intravesical therapy**

The differentiated classification of recurrence and progression according to the EORTC scoring system has provided a better prognostic definition. Although it has been confirmed that, when BCG is used, risks are lower than those estimated in the above-mentioned tables, with the CUETO scoring model being more effective in these cases, they enable an appropriate separation of well-differentiated prognostic groups. Thus, the EORTC tables are the basis for therapeutic strategies of the European Association of Urology (EAU) guidelines. Thus, on the basis of the EAU classification of risk of progression, different treatments after TUR have been established.

In the case of tumors with low risk of progression, and when the risk of recurrence is low (LG Ta-unique G1 < 3 cm, non-recurrent) no adjuvant therapy is required, with postoperative instillation and/or check-ups after TUR being sufficient. However, when there is an intermediate risk of recurrence (the same as the above tumors, but classified as G2 tumors according to the WHO-1973 grading system) intravesical chemotherapy (CT) would be indicated with the recommendations quoted below.

In the case of tumors at an intermediate risk of progression (absence of G3 or of carcinoma in situ), when the risk of recurrence is also intermediate (Ta1G1-2 with an additional factor: recurrence or ≥ 3 cm or non extreme multifocality < 8 tumors), intravesical CT, which has shown a decrease of the recurrence rate when compared with TUR alone, is recommended, although it does not affect progression. There are no established protocols or duration. A 3-4-month intensive chemotherapy regimen (in terms of frequency or concentration) seems to be optimal if postoperative instillation was used, whereas it should be extended to 1 year without postoperative instillation (NE: 1b). In this way, when postoperative instillation is used, a treatment scheme with MMC (40 mg/40 cc saline) per week or with MMC (40 mg/20 cc saline) every 15 days, since its concentration is increased, may be considered during the first phase. Both of them should be followed by monthly maintenance for 4–6 months, which would be extended to 1 year in those cases where there was no postoperative instillation.

In tumors at an intermediate risk of progression and with a high risk of recurrence (Ta1G1-2, either with extreme multifocality, or with 2 additional factors: recurrence or ≥ 3 cm or non extreme multifocality < 8 tumors), BCG with maintenance (≥1 year) is superior to chemotherapy with maintenance for recurrence, with no significant benefits on the progression rate when compared with chemotherapy, although it is lower with BCG (4%). Intravesical CT with maintenance (6–12 months) has also been suggested in cases of intolerance or when there are problems with BCG.

In tumors at a high risk of progression (high grade, Tis and T1G1-2 tumors either with 3 additional factors such as recurrence, size or multiplicity < 8 tumors, or with extreme multiplicity along with an additional factor such as recurrence or ≥ 3 cm) BCG treatment is a priority. There seems to be an equivalence in effectiveness of the different strains, though there are few studies on this issue, most of them conducted only with induction. Some recent works have experimentally shown the superiority of the Connaught strain when compared with the Tice strain in the production of cytokines and when inhibiting the growth of cultured cancer cells.

There is no optimal established schedule for BCG. Treatment is started at least 2 weeks after TUR with an induction cycle which includes 6 weekly instillations, the effectiveness and biological substrate thereof seem to be proven. Although there is no evidence that any maintenance scheme is superior, Lamms BCG protocol with weekly mini-cycles, which seem to appropriately increase the levels of urinary cytokines, is emphasized. Thus, it would be used in cycles of 3 weekly instillations at months 3 and 6 and then each 6 months. The drop-out rate was 84% in the 3-year study conducted by Lamms, but it was reduced to 15% with 1-year maintenance therapy. An intercalated combination of chemotherapy and BCG does not appear to be more effective than BCG monotherapy, but it has been suggested as an alternative in order to reduce the side effects of BCG maintenance therapy. While it is superior to CT alone in case of recurrence, there are no significant differences in progression.

Dose reduction measures have been proposed in order to reduce side effects. In this situation of scarcity, this may also be a possible BCG-saving alternative. Several studies in this regard have been published, including some studies conducted by the Spanish group CUETO on T1G3 tumors. The authors concluded that with one-third of the dose (Connaught BCG) the results were similar in terms of progression, with fewer side effects when using a lower dose.

Dose reduction was recommended especially in maintenance therapy, with less convincing results in the case of multiple tumors where a full dose should be administered. On the other hand, the recent EORTC 30962 study analyzed the duration (1 year versus 3 years) and BCG dosage (Tice strain), one-third vs. full-dose BCG in a group of patients, 40% of them being high-risk patients. No differences were found among groups for progression, survival or toxicity. As far as recurrence is concerned, full-dose BCG for 1 year had a similar effectiveness to 3-year treatment in intermediate-risk patients. However, in high-risk patients, that 1-year dosage was less effective when compared with 3-year treatment. Besides, the authors found a difference larger than 10% in the recurrence rate when one-third dose BCG was given for a year than when full-dose BCG was used for 3 years.

BCG maintenance therapy, when it is used for at least a year and/or with more than 12 instillations, reduces the risk of recurrence with respect to CT usage, but that does not seem so clear in terms of progression. Although many of the studies on BCG maintenance therapy mix intermediate-risk and high-risk tumours, some meta-analyses show a decrease in the risk of progression (37%) when compared with no-treatment groups or groups with intravesical chemotherapy. A 27% reduction in the risk of progression to muscle-invasive tumor, which increased up to 37% when maintenance therapy was used, was demonstrated. Nevertheless, it is doubtful that this will have an impact on long-term survival in the case of high-risk tumors, since
some studies only show 30% of disease-free patients with a healthy bladder under long-term follow-up. \(^{29}\)

In some cases it is not possible to use intravesical BCG (intolerance, patient refusal, etc.), with few alternative treatment possibilities. Notable among these is immediate cystectomy. Due to the high rates of supra-stratification (49.7\%) and of cancer-specific mortality (35\%) found in these tumors at the time of cystectomy, \(^{30}\) in certain cases (young patients in good general condition and/or a high risk of progression) cystectomy is indicated after TUR, without BCG therapy. In this way, cystectomy would be indicated in high-grade T1 tumors with additional risk factors \(^{31}\) such as hydronephrosis, affected prostatic urethra, or in case of 2 or more of the following factors: T1b stage, associated Tis, tumor >3 cm, multifocality or high-grade T1 at reTUR. \(^{32}\)

Chemotherapy is relatively effective for less aggressive, high-risk tumors, reducing the recurrence rate with respect to TUR alone. 48\% of isolated Tis can respond to treatment, according to the few retrospective analyses available on this issue. \(^{33}\) However, almost half of the Tis tumors treated with chemotherapy will recur. Besides, BCG seems to be superior to CT in controlling the progression of Tis, \(^{34}\) and a combination of BCG and sequential MMC does not improve the results obtained with BCG alone. \(^{21}\) Several systems have been developed to enhance MMC absorption into the urinary bladder wall, although they are not available in many health centers. One of those systems is thermo-CT (Synergö\(^{\text{®}}\)) which seems to be effective in patients with T1G3 tumors, \(^{34}\) although there are few trials of this product versus BCG and few studies on thermo-CT with maintenance. In a recent review, Lammers et al. suggested that it might be an option for high-risk tumors when use of BCG is contraindicated or when it is not possible to perform a radical cystectomy, although the heterogeneity of data makes it difficult to draw definite conclusions. \(^{35}\) There are few existing studies which compare ionophoresis (EMDA) with BCG. In one of those studies, EMDA/MMC with maintenance therapy (6 weekly doses followed by monthly maintenance for 10 months in both treatments) showed similar results to those of BCG for recurrent high-risk NMIBC. \(^{36}\)

**Recommendations of the committee of experts related to the problem of bacillus Calmette-Guerin availability (Table 1)**

Due to the situation created by the shortage of BCG – Connaught strain, different agencies and urological scientific societies have published several recommendations applicable to intermediate- and high-risk NMIBC. Among the published recommendations, we could highlight those made by the French Association of Urology, according to the EORTC risk scores for progression, or those made by the European Association of Urology (EAU), which in August 2012 published the recommendations of those members who develop the EAU guidelines related to this situation of BCG shortage.

The EAU committee recommends a good quality TUR (with reTUR) and notes that BCG must be used with maintenance therapy, without mentioning a possible dose reduction. In Ta-1 tumors at an intermediate risk of progression and intermediate or high risk of recurrence, the EAU recommends intravesical chemotherapy. In those tumors at a high risk of progression, they insist on the fact that BCG is a priority, with the possibility of exchanging strains if treatment with the Connaught strain was initiated in this situation of scarcity. In the absence of BCG, an immediate cystectomy may be indicated in certain cases (young patients in good general condition and risk factors for progression). On the other hand, passive chemotherapy may reduce recurrence in TaT1 tumors in those patients with no factors affecting progression (there may be a response even in the case of isolated Tis) and the use of systems to enhance mitomycin absorption into the urinary bladder wall (thermo-CT and iontophoresis) may increase its effectiveness.

The Spanish Drug Agency (Agencia Española del Medicamento) published some recommendations for BCG shortage in July 2012. In the case of intermediate-risk tumors they recommend to consider the use of mitomycin or doxorubicin and they confirm that BCG is a priority in high-grade TaT1 tumors, with or without Tis. They also recommend that, during this period of BCG shortage, instillations should be limited just to the induction period and dose reductions should be assessed individually.

After having considered the evidence on intravesical therapy and the possible alternatives regarding these problems of BCG availability, the committee of experts from the EAU proposed a series of recommendations (NE: 4) in December 2012, to be taken into account just while this situation persists. These recommendations were reflected in a table form which is included on the EAU website (Table 1). Since the availability of BCG in urological services differs, it is important to figure out how many patients may require BCG therapy (intermediate and high risk) over a period of time at each health center, and the amount that is available at the hospital pharmacy over that period. It must be noted that BCG shortage might last at least until the end of 2013, and that there may also be an increase in the production of other strains over this period of time. If it is not possible to fulfill all the needs regarding BCG, it is also advisable to reserve this treatment mainly for those tumors at a high risk of progression. In addition, indications for reTUR must be strictly taken into account and indications for postoperative chemotherapy must be extended to all cases (unless contraindicated) to try to delay recurrence. Thus, a set of recommendations has been proposed depending on the risk group (EORTC tables) the classification of risk groups provided by the EAU and on the availability of BCG.

**Tumors at intermediate risk of progression** (progression scores of 2–6 according to the European Organization for Research and Treatment of Cancer risk tables) \(^{37}\)

In this kind of tumors the estimated risk of progression is 6\% (5–8\%). \(^{37}\) Thus, the main objective of the treatment is to decrease recurrence rates.

Therefore, when the risk of recurrence is also intermediate (Ta-1G1-2 with one of the following additional factors: recurrent tumor, \(\geq 3 \text{ cm} \), non-extreme multifocality), with a low score according to the EORTC tables (1–4) and a 40\% risk of recurrence (42–49\%), therapy is based on intravesical CT with mitomycin (first-line) or epirubicin (second-line). The recommended dose of mitomycin (MMC) is 40 mg (in
### Treatment of non muscle invasive bladder tumor

**Table 1** Summary of recommendations given the limited availability of BCG. We must extreme ReTUR indications and extend the use of postoperative chemotherapy (IPOP). Rigorous control and reassessment of early cystectomy is required before initial treatment failure.

<table>
<thead>
<tr>
<th>BCG availability</th>
<th>Tumor classification (tables of the EORTC)/risks (EAU)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Average risk of progression</td>
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<tr>
<td></td>
<td>Risk of progression (5 years): 6% (5–8%)</td>
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<tr>
<td></td>
<td>Score for progression: 2–6</td>
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<tr>
<td>Partial</td>
<td>Average risk of relapse: Score for relapse: 1–4</td>
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<td></td>
<td>Score for relapse 5 at: 40% (42–49%)</td>
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<td></td>
<td>Ta-1G1-2 + 1 factor</td>
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<tr>
<td></td>
<td>- Relapsing</td>
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<td></td>
<td>- ≥3 cm</td>
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<td></td>
<td>- Multifocal (&lt;8 t)</td>
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<td></td>
<td>BCGb Induction (total dose or 1/3) + maintenance (total dose or 1/3) for one year</td>
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<tr>
<td></td>
<td>Options1: 1st BCG induction (total dose) + maintenance (total dose or 1/3)b for one year</td>
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<tr>
<td></td>
<td>3rd alternating MMC and BCGb,c</td>
</tr>
<tr>
<td></td>
<td>Options: 1st EMDAd 2nd CTa for 12 months</td>
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<tr>
<td></td>
<td>Options1: 1st immediate cystectomy (T1G3 with one risk factor)</td>
</tr>
<tr>
<td></td>
<td>3rd CTa for 12 months</td>
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</tbody>
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**Notes:**
- Adjuvant CT with MMC or epirubicin: We recommend an intensive regimen starting with 6–8 weekly instillations and then a monthly maintenance. It is recommended not to drink liquids 8 h before and 1 g of bicarbonate the previous night, in the morning and 30' after each instillation of MMC. In patients in whom the CT previously had not been previously effective and given the lack of availability of BCG, other drugs could be considered if they were available (gemcitabine, valrubicin, etc.).
- In the case that there is no BCG available for all patients with tumors of medium and high risk of progression, it would be reserved for higher-risk tumors.
- Alternating MMC and BCG: 6 instillations of MMC (40 mg in 100 cc of saline), followed by 10 monthly instillations in which MMC and BCG are alternated (complete dose).
- EMDA with maintenance: 6 weekly instillations of MMC (40 mg in 100 cc of double distilled water for 30' at 20 mA) and then a monthly instillation for 10 months.
- Risk factors in T1G3: hydronephrosis (HD), involvement of the prostatic urethra (PU), T1b, Tis, broad T1G3 in reTUR, multifocality, tumor > 3 cm.
- Essential ReTUR and response control at 3 months.
- Patients for bladder preservation at high risk (without BCG): general malaise or patient refusal to undergo cystectomy.

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40 cc of saline) and that of epirubicin is 50 mg (in 50 cc of saline). If the patient had previously received postoperative instillation, it would be administered in 6–8 weekly doses and subsequent maintenance therapy for 4–6 months (one instillation per month). If the patient had not previously received postoperative instillation, after those 6–8 weekly doses, maintenance therapy would be used for a year (one instillation per month).

When these tumors have a score of 5–9 according to the EORTC table for the prediction of recurrence (Ta-1G1-2 with extreme multifocality; Ta-1G1-2 with 2 additional factors: recurrent ≥3 cm, non-extreme multifocality), which
corresponds to malignancies at an intermediate or high risk of recurrence (63%; 58–65%), the recommended treatment depends on the availability of BCG. If there is no availability of it, intravesical CT with MMC (first-line) or epirubicin (second-line) is recommended, with the doses and regimens mentioned above. When there is partial availability, the use of BCG with maintenance therapy for a year is advisable, giving a one-third dose or a full dose depending on availability. Induction without maintenance has lower effectiveness in terms of recurrence than CT in intermediate-risk tumours. Maintenance therapy would consist of 3 weekly BCG instillations at months 3, 6 and 12 at the end of induction therapy. However, if estimates showed that the available amount of BCG is not enough to complete treatments for tumors at a high risk of progression, those at an intermediate risk of progression would be treated with CT, just as if there were no BCG available.

**Tumors at a high risk of recurrence and/or progression (progression scores > 7 according to the European Organization for Research and Treatment of Cancer risk tables)**

The main objective in this group is to decrease progression and recurrence rates, with close control and early cystectomy after initial treatment failure. As mentioned in the preceding section, in the event of a limited number of BCG doses, they should be reserved for these tumors.

When there is high risk of recurrence with non-extreme progression scores according to the EORTC (7–13), which corresponds to T1G1-2 tumors with 3 additional factors (recurrence, ≥3 cm, multiplicity ≥8) or T1G1-2 tumors with extreme multiplicity and other associated factor (recurrent or ≥3 cm), with a risk of progression of 17% (14–20%) at 5 years, the recommended treatment depends on the availability of BCG.

When there is no availability, the first option would be to use EMDA/MMC with maintenance therapy according to the schedule provided by di Stasi, at a dose of 40 mg of MMC in 100 cc of distilled water for 30’ (20 mA). 6 weekly MMC instillations are given and subsequent maintenance therapy with one instillation per month for 10 months. If this technique is not available, passive CT (MMC or epirubicin) is recommended, with maintenance therapy for 12 months (one instillation per month), after an intensive regimen, as mentioned before.

When the amount of BCG is limited, several alternatives are recommended depending on their availability. Foremost among them is BCG with induction (full dose) and maintenance therapy with one-third dose for a year. BCG alone with induction at a full dose could be used, since Herr has found similar progression rates without maintenance, although the recurrence rate is significantly higher. Other possibility is BCG with alternating MMC according to the schedule provided by Rintala, which achieves higher effectiveness than chemotherapy and similar effectiveness to that of BCG in terms of progression. Treatment consists of 6 MMC instillations (40 mg in 40 cc of saline), followed by 10 instillations per month, alternating MMC at the same dose and BCG (full dose). Some patients might require immediate cystectomy, in spite of not being high-risk tumors (unresectability due to multiplicity, large size, etc.).

High-grade tumors (G3/Tis) are considered to be at a high risk of progression, with a 5-year estimated probability of progression of 45% (35–55%), corresponding to progression scores > 13 according to the EORTC tables. If there was no BCG available, an immediate cystectomy would be indicated in cases at a high risk of progression, such as high grade-T1 with only one associated factor (hydronephrosis, affected prostate urethra, T1b, Tis, wide T1G3 in reTUR, multifocality, tumor > 3 cm). Bladder preservation in this group is only possible in very specific cases (patients in poor condition for cystectomy or refusal to perform it), which require strict follow-up and possible further radical treatment. The use of EMDA/MMC with maintenance therapy might be attempted in these patients, according to the above-mentioned schedule provided by di Stasi, or passive CT (MMC/epirubicin) with maintenance therapy for a year if EMDA is not available. In those cases where MMC was not effective, CT might be used along with new drugs (gemcitabine, valrubicin, etc.) if available at health centers.

If BCG is available, but limited, an estimation of usage possibilities and the number of patients who may require treatment should be carried out. Thus, the spectrum would range from BCG with induction at a full dose with one-third-dose maintenance therapy for a year, to BCG with alternating MMC, according to the above-mentioned schedule by Rintala, to immediate cystectomy. The latter would be used in tumors at a very high risk of progression, such as high-grade T1 with hydronephrosis and/or affected prostate urethra or high-grade T1 with 2 associated factors (T1b, Tis, wide T1G3 in reTUR, multifocality, tumor > 3 cm), since with only one associated factor they could still be treated with BCG if available. Naturally, early cystectomy would also be indicated as a first option in case of refractoriness to BCG.

**Conflict of interest**

The authors declare that the Inbisa Laboratory collaborated in organizing and coordinating this work.

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Treatment of non muscle invasive bladder tumor


