Influence of the true number of Bacillus Calmette-Guérin instillations on the prognosis of non-muscle invasive bladder tumors

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Dose;
Number of instillations

Abstract
Objectives: To analyze if the true number of BCG instillations applied in non-muscle invasive bladder tumors has any influence on their prognosis as well as other tumor and clinical characteristics: age, sex, different protocols, BCG dose, whether primary or recurrent, solitary or multiple, tumor size G3 or Cis.
Patients and methods: A total of 324 high grade NMIBC (15 TaG3, 184 T1G3, 125 Cis) out of 1491 cases included in the CUETO database were analyzed. Following 6 post transurethral resection (RTU) BCG instillations, the patients were scheduled to receive one instillation every two weeks (3–6 times), for a total of 9–12 instillations. One third of the dose (27 mg) (112 cases) or total dose of 81 mg (212 cases). Mean follow-up was 59.6 months. Statistical Analysis: Kaplan–Meier, Cox-regression (uni-multivariate).
Results: A higher level of recurrence (p = 0.032) and progression (p = .013) risk as well as worse Ca-specific survival (p = .005) were obtained if there were fewer than 12 instillations with the Kaplan–Meier and Cox-regression multivariate analysis. A 27 mg (p = .008) dosage and being a

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female ($p < .001$) were independent factors for a higher recurrence risk, but not for progression or Ca-specific survival. The remaining characteristics studied were not statistically significant.

**Conclusions:** In accordance with the results obtained, we can conclude that the number of BCG instillations applied has some influence on the outcome of high grade NMIBC. The optimum number of instillations as well as their time of application must still be determined. A dose of 27 mg and being a female are predictive factors of recurrence.

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**Background**

Non-muscle-invasive transitional cell carcinoma (NMITCC) of the bladder corresponds to approximately 70% of initial diagnoses of all bladder tumors. Its prognosis varies enormously depending on the degree, the presence or absence of Cis and the infiltration of the lamina propria.

For many years, we have known that isolated TUR is not sufficient for many of these cases, especially those with high-grade carcinoma and those at high risk. Over the years, we have therefore applied numerous endovesical chemotherapy agents (onco tiotepa, adriamycin, epirubicin, mitomycin, etc.) and immunotherapeutic agents (IT) such as BCG, with uneven results. The majority of these agents have reduced relapses, but only BCG is recognized to have an effect on reducing progression and thereby cancer-specific mortality.

Despite all that has been published so far on chemotherapy and immunotherapeutic agents, there is still no consensus on how to apply these agents, the dosage or the time of their application. There does seem to be a fair amount of agreement in terms of high-grade NMITCC. They should be treated with BCG in a maintenance regimen, but without specifying the dosage or the minimum number of instillations that will benefit the patient. Both the European Association of Urology (EAU) guidelines and the 2012 International Consultation on Urologic Diseases recommend BCG in maintenance therapy for at least 1 year, with a 1a level of evidence.

Moreover, not all patients scheduled to receive a given number of BCG instillations ultimately receive them, due to the toxicity and/or the fact that they leave the protocol once a recurrence is confirmed, among other reasons. This therefore appears to be a factor worth studying, to see whether a greater or smaller number of applied BCG instillations truly has an influence on the prognosis.

Given the broad base of existing cases since the beginning of 1990, our group (CEUTO) intended to analyze whether there was a real determining influence in terms of the prognosis of high-grade NMITCC based on the actual number of administered BCG instillations.

**Patients and methods**

The CUETO group’s database includes 1491 patients, of whom 324 had high-grade NMITCC treated exclusively with BCG (Connaught strain). The patients corresponded to 3 different protocols, whose distribution is shown in Table 1, as are the 2 doses administered (27 or 81 mg). In summary, all patients were scheduled for treatment with an
induction of 6 instillations plus an instillation every 2 weeks (3 or 6 times), for a total of 9–12 instillations. The enrollment period for the group of 3 protocols was started in 1990 and ended approximately in 2000. Mean follow-up: 59.62 months (2–126) (standard deviation 30.111); 55.6% (180 of 324 cases) had a mean follow-up of at least 5 years.

The characteristics of the patients and tumors are listed in Table 2.

Statistical analysis: Kaplan–Meier graphical distribution of times to recurrence, progression and cancer-specific survival. Univariate Cox regression to study the factors associated with recurrence, progression and cancer-specific survival and multivariate Cox regression to identify factors with an independent effect.

Table 1 Distribution of the 324 high-grade NMITCC according to protocol and BCG dose.

<table>
<thead>
<tr>
<th>Study number</th>
<th>No. of instillations</th>
<th>27 mg</th>
<th>81 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>90008</td>
<td>&lt;12</td>
<td>4</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>=12</td>
<td>35</td>
<td>47</td>
<td>82</td>
</tr>
<tr>
<td>93009</td>
<td>&lt;12</td>
<td>66</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>=12</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>95012</td>
<td>&lt;12</td>
<td>21</td>
<td>28</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>=12</td>
<td>52</td>
<td>54</td>
<td>106</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>112</td>
<td>212</td>
<td>324</td>
</tr>
</tbody>
</table>

Table 2 Distribution of the various clinical and tumor variables.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Men: 300 (92.6%)</th>
<th>Women: 24 (7.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;60 y: 85 (26.2%)</td>
<td>61–70 y: 125 (38.6%)</td>
</tr>
<tr>
<td>Tumor size</td>
<td>≤3 cm: 255 (78.9%)</td>
<td>&gt;3 cm: 69 (21.1%)</td>
</tr>
<tr>
<td>No. of tumors</td>
<td>Single: 162 (50%)</td>
<td>Multiple 162 (50%)</td>
</tr>
<tr>
<td>Presentation</td>
<td>Primary: 229 (70.7%)</td>
<td>Relapse: 95 (29.3%)</td>
</tr>
<tr>
<td>G3/CIS</td>
<td>G3: 199 (61.4%)</td>
<td>CIS: 125 (38.6%)</td>
</tr>
<tr>
<td>No. of instillations</td>
<td>&lt;12: 135 (51.7%)</td>
<td>=12: 189 (58.3%)</td>
</tr>
</tbody>
</table>

Results

The overall recurrence index was 38%, the progression index was 26.2% and the cancer-specific survival rate was 85.2%.

With the Kaplan–Meier analysis we obtained a significantly greater recurrence risk (p = .041) and progression risk (p = .014) if there were <12 instillations and poorer cancer-specific survival (p = .006) if there were <12 instillations (Figs. 1–3).

To study the clinical and tumor factors that could be associated with greater or lesser recurrence, progression or cancer-specific survival, we performed a univariate Cox regression. We confirmed a significantly greater recurrence risk (HR: 2.884, 95% CI 1.012–2.398, p = .044) and progression risk (HR: 1.870; 95% CI: 1.126–3.107, p = .016) and lower cancer-specific survival (HR: 2.483; 95% CI: 1.278–4.828, p = .007) if there were <12 instillations. Being female resulted in a significantly greater recurrence risk (HR: 2.884; 95% CI: 1.637–5.083, p < .001) but not a greater progression risk or cancer-specific mortality. The rest of the study variables (age, tumor size, number of tumors, being primary or recurrent, G3 or Cis) were not significant.
Instillations of BCG and prognosis of non-muscle-invasive bladder tumors

Figure 3 Kaplan–Meier analysis for cancer-specific survival ($p = .006$).

To identify factors with a possible independent effect, we performed a multivariate Cox regression. We once again found a significantly greater recurrence risk (HR: 1.539; 95% CI: 1.038–2.283, $p = .032$) and progression risk (HR: 1.954; 95% CI: 1.155–3.307, $p = .013$) and a lower cancer-specific survival (HR: 2.707; 95% CI: 1.344–5.451, $p = .005$) if there were <12 instillations. A 27-mg dose (HR: 1.722; 95% CI: 1.154–2.571, $p = .013$) and being a woman (HR: 2.814; 95% CI: 1.586–4.993, $p < .001$) were independent factors for increased recurrence, but they did not affect either progression or cancer-specific survival. The rest of the analyzed factors were not statistically significant.

In order to ascertain whether the results obtained with the various number of instillations was influenced by the different doses employed (27 and 81 mg), we analyzed the possible interaction between the 2 factors. The result was that the interaction was not statistically significant (HR: 1.693; 95% CI: 0.719–3.983, $p = .228$). Therefore, we can conclude that the effect of the number of instillations is independent of the various administered doses.

Discussion

The objective of reducing the recurrence risk of NMITCC can be achieved with chemotherapy agents and intravesical IT. However, if we refer to progression, especially when treating high-grade tumors, BCG has shown superiority to chemotherapy agents, especially in maintenance regimens.1,3–5

For high-grade tumors, the trend is to schedule patients to undergo at least 1 year of BCG treatment, empirically following the indications established by the EAU guidelines.1 Recently, numerous authors have attempted to follow the regimen suggested by Lamm and the Southwest Oncology Group,1 which consists of an induction of 6 instillations plus 3 applications (1 weekly for 3 weeks) at 3, 6, 12, 18, 24, 30 and 36 months, for a total of 27 instillations.

The reality is that this protocol is very difficult to follow, given that in many cases, patients cannot tolerate it due to the toxicity. According to various authors, only a third of patients who are scheduled to undergo instillations for 1 or 2 years receive the total number of instillations,6,7 mainly due to the toxicity. In addition, only 19% of patients scheduled for 3 years will receive all the installations, as indicated by Saint in 2001.6 The CUETO group reported in 2005 that only 68% of patients underwent the total number of instillations scheduled for 5–6 months,7 due to greater toxicity (both local and systemic) with 81 mg. Nevertheless, we should note the recent European Organisation for Research and Treatment of Cancer (EORTC) report, which, after treating 1355 patients, concluded that the toxicities for a third of the dosage and the total dosage were very similar.10

Not all authors agree on establishing BCG in maintenance therapy, with Herr the most critical of its application. What is more important than maintenance BCG therapy for this author is the practice of re-TUR and, if it is negative, applying BCG for a certain but as yet undefined length of time.11,12

In the various protocols started in 1990 by the CUETO group, there are a significant number of patients with high-grade tumors treated only with BCG (324 cases). In particular, we analyzed patients from 3 protocols who had G3 tumors or Cis, treated with 27 mg or 81 mg of BCG (Connaught strain). By examining patients scheduled to undergo 6 instillations in induction plus 3 or 6 instillations (depending on the protocol in which they were enrolled) over the course of 5–6 months, we analyzed whether there was a prognostic difference between those treated with a higher or lower number of instillations.

The results suggest that those who were treated with fewer instillations had poorer prognoses in terms of relapses, progression and cancer-specific survival.

These results support what has already been accepted by almost all authors: patients with high-grade NMIBC must be scheduled to undergo BCG therapy for at least 1 year, which corresponds to at least 15 instillations. In our case, the maximum number of administered instillations was 12; however we must consider that the protocols were designed in the 1990s. In recently developed protocols, we have applied the scheduled instillations to 3 years.

In terms of the BCG dose, this analysis of 324 patients has shown that 27 mg creates a significantly greater recurrence risk but not a greater progression or cancer-specific mortality risk, and this fact is independent of the number of administered instillations. In 2005, the CUETO group published a study on 155 high-risk patients that found a lower disease-free survival rate with 27 mg when compared with 81 mg, although the difference was not statistically significant, with a mean follow-up of 61 months.11 There was also an increased tendency to progression if <12 instillations were administered, but this was also not statistically significant.

The recently published EORTC study10 comparing a third of the dosage to the total dosage and 1 year versus 3 years found that for high-risk tumors, the total dosage for 3 years was more effective than for 1 year in terms of disease-free survival. The report also stated that a third of the dosage for 3 years was similar to the full dosage administered for 3 years. For intermediate risk, the total dosage for 3 years was similar to that applied for 1 year, and a third of the dosage administered for 3 years was more effective than if administered for 1 year. It is worth noting that this study of 1355 patients did not include Cis and did not specify whether there were more than 10 tumors. In addition, the study did not include solitary tumors except for T1G3 tumors.
In terms of increased risk of relapses for women, there are many articles have reported similar results but without finding a clear explanation; some of these reports even have conflicting explanations. On one hand, it appears that endogenous hormones and estrogen therapy play protective roles, with a lower risk in childless patients than in multiparous patients. On the other hand, there appears to be a delay in the diagnosis for women due to the fact that when faced with hematuria, the clinician considers an infectious disease before a tumor.\textsuperscript{14-16}

It is believed that women could have a different tumor biology and carcinogenesis, especially in muscle-infiltrating bladder tumors. In addition, women smokers have a poorer prognosis.\textsuperscript{17} In 2008, the CUETO group reported that the risk factors for increased recurrence in a series of 1062 NMIBC treated exclusively with BCG included the female gender. However, female gender was not a risk factor for greater progression.\textsuperscript{18}

The limitations of this study include the fact that the patients were recruited in the 1990s and therefore do not correspond to contemporary series (3 protocols over the course of approximately 10 years). The histological classification system employed for this study was developed in 1973, which of course did not use the International Society of Urologic Pathology classification system of 2004. The use of re-TUR was not systematic, and consideration was not given to the fact that over the years there has surely been an improvement in the TUR technique. Photodynamic diagnoses with blue light or narrow band imaging was not used. Finally, we did not analyze whether immediate post-TUR instillation was administered, which has only recently been implemented.

These limitations make a comparison with recent series highly complicated due to the nonuniformity of the various factors.

In conclusion, we can deduce that for high-grade NMIBC a minimum of 12 instillations show greater performance than when \(<12\) instillations are administered. Moreover, it appears that a 27-mg dose and being female are predictors of an increased risk of recurrence but not of progression or cancer-specific mortality.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References