Actas Urol Esp. 2014;38(5):280–284

Actas Urológicas Españolas

www.elsevier.es/actasuro

ORIGINAL ARTICLE

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

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Received 8 October 2013; accepted 23 October 2013
Available online 4 April 2014

KEYWORDS
Non-muscle invasive bladder cancer;
Bacillus Calmette-Guérin;
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

☆ Please cite this article as: Portillo JA, Madero R, Solsona E, Fernandez JM, Martínez-Piñeiro L, Palou J, et al. Influencia del número real de instilaciones de Bacilo de Calmette-Guérin aplicadas en el pronóstico de los tumores vesicales no músculo-infiltrantes. Actas Urol Esp. 2014;38:280–284.

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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.

PALABRAS CLAVE
Carcinoma de células transicionales no músculo-infiltrantes;
Bacilo de Calmette-Guérin;
Dosis;
Número de instilaciones

Influencia del número real de instilaciones de Bacilo de Calmette-Guérin aplicadas en el pronóstico de los tumores vesicales no músculo-infiltrantes

Resumen
Objetivos: Analizar si el número real de instilaciones de BCG aplicadas en los tumores vesicales no músculo-infiltrantes tiene alguna influencia en su pronóstico, así como otras variables clínicas y del tumor: edad, sexo, diferentes protocolos, dosis de BCG, primario o recurrente, G3 o Cis.
Pacientes y métodos: De 1.491 pacientes incluidos en la base de datos del grupo CUETO se analizaron 324 tumores de alto grado (15 TaG3, 184 T1G3, 125 Cis). Tras la inducción de 6 instilaciones de BCG post-RTU fueron programados para recibir una instilación cada 2 semanas (3–6 veces), total 9–12 instilaciones. Un tercio de dosis (27 mg) en 112 casos y dosis total (81 mg) en 212 casos. Seguimiento medio: 59,6 meses. Análisis estadístico: Kaplan–Meier, regresión de Cox uni y multivariado.
Resultados: Con el análisis de Kaplan–Meier y regresión de Cox multivariado se obtuvo mayor riesgo de recidiva ($p = 0{,}032$) y progresión ($p = 0{,}013$), y peor supervivencia cáncer-específica ($p = 0{,}005$) si < de 12 instilaciones. Dosis de 27 mg ($p = 0{,}008$) y el ser mujer ($p < 0{,}001$) fueron factores independientes predictivos de mayor recidiva, pero no de mayor progresión ni de peor supervivencia cáncer-específica. El resto de las características estudiadas no fueron estadísticamente significativas.
Conclusiones: Con los resultados obtenidos parece que el número de instilaciones aplicadas tiene alguna influencia sobre el pronóstico, quedando por determinar cuál es el mínimo de instilaciones a partir del cual el paciente se puede beneficiar y su tiempo de aplicación. Dosis de 27 mg y el ser mujer son factores predictivos para mayor recidiva.

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[1] and the 2012 International Consultation on Urologic Diseases[2] 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