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Platinum Priority – Bladder Cancer

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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

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Abstract

Background: The optimal dose and duration of intravesical bacillus Calmette-Guérin (BCG) in the treatment of non–muscle-invasive bladder cancer (NMIBC) are controversial.
Objective: To determine if a one-third dose (1/3D) is not inferior to the full dose (FD), if 1 yr of maintenance is not inferior to 3 yr of maintenance, and if 1/3D and 1 yr of maintenance are associated with less toxicity.
Design, setting, and participants: After transurethral resection, intermediate- and high-risk NMIBC patients were randomized to one of four BCG groups: 1/3D-1 yr, 1/3D-3 yr, FD-1 yr, and FD-3 yr.
Outcome measurements and statistical analysis: The trial was designed as a noninferiority study with the null hypothesis of a 10% decrease in the disease-free rate at 5 yr. Times to events were estimated using cumulative incidence functions and compared using the Cox proportional hazards regression model.
Results and limitations: In an intention-to-treat analysis of 1355 patients with a median follow-up of 7.1 yr, there were no significant differences in toxicity between 1/3D and FD. The null hypotheses of inferiority of the disease-free interval for both 1/3D and 1 yr could not be rejected. We found that 1/3D-1 yr is suboptimal compared with FD-3 yr (hazard ratio [HR]: 0.75; 95% confidence interval [CI], 0.59–0.94; $p = 0.01$). Intermediate-risk patients treated with FD do not benefit from an additional 2 yr of BCG. In high-risk patients, 3 yr is associated with a reduction in recurrence (HR: 1.61; 95% CI, 1.13–2.30; $p = 0.009$) but only when given at FD. There were no differences in progression or survival.
Conclusions: There were no differences in toxicity between 1/3D and FD. Intermediate-risk patients should be treated with FD-1 yr. In high-risk patients, FD-3 yr reduces recurrences as compared with FD-1 yr but not progressions or deaths. The benefit of the two additional years of maintenance should be weighed against its added costs and inconvenience.
Trial registration: This study was registered at ClinicalTrials.gov, number NCT00002990; http://clinicaltrials.gov/ct2/show/record/NCT00002990.

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1. Introduction

After initial transurethral resection (TUR), non–muscle-invasive bladder cancer (NMIBC) is characterized by a high risk of recurrence and, to a lesser extent, progression to muscle-invasive disease. These risks can be quantified based on a patient's tumor characteristics using the European Organization for Research and Treatment of Cancer (EORTC) risk tables or with a simplified risk group classification [1,2]. To decrease the risk of recurrence and progression, adjuvant instillations of chemotherapy or bacillus Calmette-Guérin (BCG) are given in accordance with the European Association of Urology (EAU) guidelines [3]. In intermediate- and high-risk patients, the protective effects of maintenance BCG are more pronounced compared with chemotherapy [4,5].

The initial report by Morales et al described six weekly BCG induction instillations [6]. Afterward, it was found that additional instillations of BCG reduced recurrences; however, the optimal duration of maintenance instillations remains controversial [7–9]. Based on several meta-analyses, the EAU guidelines recommend at least 1 yr of maintenance.

A major disadvantage of BCG is its toxicity, leading to interruptions and premature discontinuation of maintenance. In EORTC trial 30911, isoniazid did not reduce toxicity for patients on 3 yr of maintenance [10]. However, toxicity was reduced when two doses of ofloxacin were given shortly after each of nine BCG instillations [11].

The Club Urológico Español de Tratamiento Oncológico (CUETO) compared the effect of a reduced dose of BCG with the standard dose in intermediate- and high-risk patients [12–14]. These studies, where a short schedule <6 mo of BCG was used, suggested that a one-third dose (1/3D) is the minimum effective dose.

The current randomized phase 3 study (30962) was designed to investigate two strategies to decrease the toxicity of maintenance BCG without compromising its efficacy. The purpose was to show that 1/3D BCG is not inferior to full-dose (FD) BCG and that 1 yr of maintenance is not inferior to 3 yr of maintenance with respect to efficacy and that 1/3D and 1 yr of maintenance are associated with less toxicity.

2. Materials and methods

2.1. Inclusion and exclusion criteria

Patients with biopsy-proven, completely resected solitary pT1G3 or multiple pTa–T1, grade 1–3 (1973 World Health Organization [WHO] classification) urothelial carcinoma of the bladder were included. Excluded were patients with solitary tumors except T1G3, >10 tumors, carcinoma in situ (CIS), tumor stage T2 or higher, age >85 yr, WHO performance status 3 or 4, previous treatment with BCG, and intravesical chemotherapy during the previous 3 mo. An intravenous pyelograph was performed to rule out upper tract tumors. Informed consent was obtained in accordance with the Declaration of Helsinki and/or existing national and local regulations.

2.2. Randomization and study interventions

Within 14 d after TUR, patients were randomized to one of four treatment groups:

1. One-third dose BCG with 1-yr maintenance (1/3D-1 yr): BCG was instilled once a week for 6 wk, followed by three weekly instillations at months 3, 6, and 12.
2. Full dose BCG with 1 yr of maintenance (FD-1 yr).
3. One-third dose BCG with 3 yr of maintenance (1/3D-3 yr): BCG was instilled once a week for 6 wk, followed by three weekly instillations at months 3, 6, 12, 18, 24, 30, and 36, for a total of 27 instillations.
4. Full dose BCG with 3 yr of maintenance (FD-3 yr).

The OncoTICE strain containing 5×10^8 CFU was used. The preparation of the 1/3D was done either by dissolving one vial with 150 ml of saline and taking 50 ml or by dissolving it with 50 ml, taking 17 ml, and diluting this to 50 ml.

Patients stopped protocol treatment at the second Ta/T1 recurrence after randomization and at progression to muscle-invasive disease, appearance of CIS, carcinoma in the upper urinary tract or prostatic urethra, or distant metastases. Further treatment was at the discretion of the local investigator.

Cystoscopy and urine cytology were repeated every 3 mo during the first 3 yr and every 6 mo thereafter. Recurrence of disease was established by histology.

Local side effects (bacterial cystitis, chemical cystitis, frequency, and hematuria) and systemic side effects (fever, general malaise, lung infection, skin rash, and sepsis) were collected during induction and maintenance instillations according to a standardized format.

2.3. End points

The primary end point was the duration of the disease-free interval (DFI): the time until first recurrence including progression to muscle-invasive disease, distant metastases, and death due to bladder cancer. Secondary end points included time to progression (muscle-invasive disease, distant metastases, or death due to bladder cancer), duration of survival, and toxicity.

2.4. Statistical considerations

The trial was designed as a noninferiority study. Two comparisons were foreseen for each of the two null hypotheses:

(1) The efficacy of 1/3D is inferior to FD:
- One-third versus FD BCG with 1 yr of maintenance
- One-third versus FD BCG with 3 yr of maintenance

(2) The efficacy of 1 yr of maintenance is inferior to 3 yr of maintenance:
- One year versus 3 yr of maintenance with 1/3D BCG
- One year versus 3 yr of maintenance with FD BCG

One-sided noninferiority tests at $\alpha = 0.025$ and $\beta = 0.20$ were planned for each comparison.

Times to events were compared using the Wald test from a Cox proportional hazards regression model. The DFI and time to progression curves were estimated using cumulative incidence functions to take into account patients who died of other causes prior to the event of interest (competing risks). Duration of survival curves was estimated using the Kaplan-Meier technique.

To reject the null hypothesis of a decrease of 10% in the 5-yr disease-free (DF) rate from 50% on the control arms (FD BCG, 3 yr of maintenance) to 40% on the experimental arms (1/3D BCG, 1 yr of maintenance) with a hazard ratio (HR) of 1.32, 414 events and 644 patients were required for each of the four comparisons. Because patients were analyzed twice, a total of 1288 patients and 828 events were required, leading to 322 patients in each treatment group.

The study was reviewed in September 2011 by the EORTC Independent Data Monitoring Committee, which recommended the release of the results. Because there was no interaction between the dose