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European Association of Urology



Words of Wisdom

Re: Long-Term Follow-up of T1 High-Grade Bladder Cancer After Intravesical Bacille Calmette-Guérin (BCG) Treatment

Kakiashvili DM, van Rhijn BW, Trottier G, et al

BJU Int 2011;107:540–6

Re: Editorial Comment

Wood DP

J Urol 2011;186:1809–10

Expert's summary:

The authors report the long-term results of bacillus Calmette-Guérin (BCG) intravesical therapy in 136 patients with primary high-grade (HG) T1 transitional cell carcinoma (TCC) of the bladder who were recruited retrospectively in two urologic centers in Canada and Europe. An experienced uropathologist reviewed all of the slides, ensuring that muscle was present in the specimen and thus confirming the exact tumor stage and grade. Recurrence rate and disease progression determination were the main objectives. After transurethral resection (TUR), all of the patients received an induction course of BCG (six instillations) and were followed with cytology and cystoscopy. After a mean follow-up of 6.5 yr, 47 patients (35%) recurred and 42 (30.9%) progressed to greater than category T1 in a median time of 2.1 yr. Twenty-two patients who progressed died from bladder cancer (BCa): 52.3% of progressing patients and 16% of all patients. Carcinoma in situ (CIS) was the only independent predictor of recurrence in multivariate analysis ($p = 0.011$). No independent predictors were found for progression.

The authors concluded that conservative treatment with BCG is a valid option in primary T1 HG TCC of the bladder. Nevertheless, the aggressive nature of T1 HG BCa is evident in the fact that 30% progressed. Caution should be exercised when relying on the long-term effects of BCG, and close follow-up of these patients should not be neglected. Wood commented on the article and concluded that until we have better methods to determine the aggressiveness of T1 HG TCC of the bladder or better monitoring methods for recurrence and progression, immediate cystectomy should be considered.

Expert's comments:

I am a little surprised that Wood did not comment on the BCG schedule that was utilized in the study. In fact, patients received only the BCG induction course, which implies one

instillation a week for 6 wk. This schedule is not considered standard treatment for these tumors by the majority of urologists and by the most recognized guidelines [1]. It has been shown clearly that in high-risk HG TCC of the bladder, BCG with maintenance (1–3 yr) is by far the best possible treatment and is able to reduce recurrence and progression rate [2]. Moreover, it has been reported recently in the prospective, randomized European Organization for Research and Treatment of Cancer (EORTC) study 30911 that BCG with maintenance improves overall survival and disease-specific survival [3]. It is therefore possible that the high progression and mortality rates reported in this study could be due to the BCG schedule without maintenance.

Maintenance BCG for 1–3 yr should be recommended as standard treatment for patients with T1 HG TCC of the bladder. The editorial ends with a proposal to consider immediate radical cystectomy for these patients. I fully agree with this suggestion. I think urologists should perform many more immediate radical cystectomies for HG T1 than they do currently.

We frequently hear during uro-oncologic meetings or read, as in this article, that we do not have enough data (prospective, randomized studies) or reliable prognostic factors for suggesting immediate radical treatment to our patients with T1 HG BCa and that we need further studies. Is this completely true, or are urologists trying to preserve bladders, even in risky situations, due to lack of surgical experience or the fear of possible complications or deaths? If so, is this approach justified? All of the presentations or articles on treatment of T1 HG TCC conclude saying “Prospective randomized studies are needed” or “Further studies are a must.” However, we know that prospective, randomized studies comparing TUR followed by BCG to immediate radical cystectomy are impossible to perform and that important organizations like the EORTC have failed in trying to perform them. Therefore, what should we do?

I think we should carefully evaluate and use the data that we have available. We know that multiplicity, the presence of CIS and lymphovascular invasion (LVI), tumor in the prostatic urethra, micropapillary type, and diameter >3 cm are very important negative characteristics in T1 HG TCC of the bladder. Part of this information has been reported in the guidelines [1]. The presence of these adverse prognostic factors should suggest immediate, aggressive surgical treatment. If an immediate radical cystectomy is

performed in T1 cases, cancer-specific survival is >90% but the patient loses a functioning bladder with a possible complication rate of approximately 40% and with a mortality rate of 0–3%. In addition, using a conservative approach with BCG after TUR, about 70% of patients with T1 HG cancer can retain the bladder with no tumor progression [1]. These data probably induce urologists to suggest that their patients undergo instillation therapy, maintaining the bladder.

A 30% progression rate with a 16% mortality rate, as reported in the study, is a high price to pay because BCG treatment, especially maintenance, may determine local and/or systemic side effects with a consistent worsening of patients' quality of life. In addition, repeated urethroscopies may provoke urethral stenoses, and multiple TURs may result in a reduced bladder capacity and, finally, in a contracted bladder. In these cases, radical cystectomy is indicated and should be proposed.

In conclusion, in the absence of randomized studies comparing TUR followed by BCG versus immediate radical cystectomy in T1 HG TCC of the bladder, we should use the robust and reliable data that we have. When adverse prognostic factors such as multiplicity, concomitant CIS and/or LVI, tumor in the prostatic urethra, diameter >3 cm, and micropapillary type are present, an immediate radical cystectomy should be proposed to the patient. In the absence of adverse prognostic factors, conservative treatment with BCG should be suggested. When radical surgery is indicated, high-volume surgeons and highly specialized

centers performing >40 radical cystectomies per year should be chosen to minimize mortality and side effects. These centers should be considered centers of excellence for BCG treatment.

Conflicts of interest: The author has nothing to disclose.

References

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Maurizio A. Brausi

Department of Urology Ausl Modena, Via G. Molinari, 1,
41012 Carpi-Modena, Italy

E-mail address: brausi@interfree.it

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Re: Markers Predicting Response to Bacillus Calmette-Guérin Immunotherapy in High-Risk Bladder Cancer Patients: A Systematic Review

Zuiverloon TCM, Nieuweboer AJM, Vékony H, Kirkels WJ, Bangma CH, Zwarthoff EC

Eur Urol 2012;61:128–45

Expert's summary:

It was with great interest that we read the article by Zuiverloon et al that was recently published in *European Urology*. Bacillus Calmette-Guérin (BCG) intravesical instillations are standard treatment for high-grade non-muscle-invasive bladder cancer, but no markers are available to predict BCG response. In this interesting study, the authors have nicely aggregated the literature and discussed a broad spectrum of possibilities for markers predicting BCG response in high-risk bladder cancer patients. The authors have clearly debated and correlated the links between BCG response prediction and various factors (eg, recurrence, progression, survival, molecular marker, prognosis, tumor protein p53, Ki-67, retinoblastoma 1, fibronectin, immunotherapy, cytokine, interleukin [IL], natural killer, macrophage). The authors concluded that IL-2 levels are currently the most promising predictive markers of BCG response. They suggested that future studies need to apply more advance techniques such as microRNA profiling and genomewide sequencing in the search for new biomarkers.

Expert's comments:

These data are extremely fascinating. With consideration of all the other factors, we discuss in our report that inflammatory markers are one of the crucial and critical regulatory segments in this process. The association of cytokine gene variants and their role with respect to BCG response in bladder cancer is a very critical junction to explore in the near future [1]. The current report supports our previous paper very well, and on the basis of existing current literature, we can clinch the major role of cytokines in the evolution of markers predicting BCG response. For instance, after the cell processes with BCG, a complex is formed and recognized by CD4⁺ T cells, leading mainly to a Th-1 response and production of IL-2, IL-12, interferon, tumor necrosis factor (TNF) recruitment, and activation of natural killer cells and cytotoxic T lymphocytes, initiating an immense immune reaction and abolition of tumor cells [2]. In contrast, a less promising Th-2 response is induced together with production of IL-4, IL-5, IL-6, and IL-10. With respect to that, there are few interesting studies that indicated the influence of various cytokine gene variants (eg, IL-8, TNF) with prediction of BCG response in bladder carcinoma [3].

These examples suggest an unblemished association between the critical role of various pro- and anti-inflammatory cytokines with respect to their levels as well as gene variants for BCG response prediction in systemic bladder carcinogenesis. Additional large-scale studies will be needed