Commentary

Intravesical bacillus Calmette-Guerin for bladder cancer: What is known? What is not? What is next?

It is 36 years since Morales described the use of intravesical bacillus Calmette-Guerin (BCG) for non-muscle invasive bladder cancer (NMIBC).[1] During this period, thousands of patients were treated, hundreds of studies were performed as well as multiple dose and schedule modifications were tried. However, many questions regarding its use are still unanswered.

BCG remains the most effective intravesical therapy for NMIBC. BCG, but not chemotherapy, has been shown to reduce the overall risk of progression to muscle invasive disease, both in patients with high risk papillary tumors and in patients with carcinoma *in situ* (CIS).[2]

The precise mechanism of BCG action is not yet fully understood. Furthermore, the optimum dose is not yet known, and the optimum time to evaluate the response at 3 or 6 months is still debatable. The first intravesical BCG dose was empirically determined to be 120 mg (Frappier strain) based on the observation that the same dose was tolerated by intradermal scarification.[1] Several attempts have been made to find a lower dose that is as effective and less toxic than the standard dose.[3]

Similarly, the 6 weekly instillations of the induction course were empirically chosen by Morales *et al*. because the Frappier strain was packed in 6 separate vials and adverse events lasted less than 1 week.[1] Modifications including 2 weekly instillations, weekly instillation for 4 weeks, or a schedule of 2 instillations in weeks 1 and 6 have been suggested.[4-6]

The key role of maintenance in the efficacy has been emphasized in Southwest Oncology Group (SWAG) trial 8507 and in recent meta-analyses of randomized controlled trials.[2,7] BCG was superior to mitomycin C (MMC) in the prevention of recurrences only in the trials with maintenance BCG. Recently, the benefit of maintenance BCG has been strongly questioned by Herr *et al*.[8]

A number of limitations arise when attempting to review the available literature regarding incidence, severity, and management of BCG adverse events. First, different descriptions of the same adverse event are mentioned in different studies. The typical

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example is the adverse event defined by lower urinary tract symptoms (LUTS), which can be reported also as cystitis-like symptoms or split into urgency frequency, dysuria, etc., A second drawback is lack of a grading system for the severity of these adverse events.

The most common local side effects are drug-induced cystitis and a self-limited hematuria, which usually subsides in 48 hours.[9] Intravesical chemotherapy is generally better tolerated than BCG and is not affected by the small but actual risk of BCG sepsis and death.[3] A meta-analysis by Shelley *et al*. showed that 30% of patients receiving MMC developed local toxicity compared to 44% receiving BCG, with respect values of 12% and 19% for systemic side effects. However, the difference was not statistically significant.[10] Moreover, a significantly higher withdrawal rate of patients treated with BCG compared with MMC could not be demonstrated. Similar findings were reported in a randomized study that compared BCG to doxorubicin. Fever, pain on urination, and hematuria were more common with BCG, whereas allergic reactions such as rubor or itching were more frequent on doxorubicin.[3]

A long term follow-up is essential for any study about BCG role and effectiveness. Being in a dynamic field, by the time the study is performed and long term follow-up results are executed; many advances took place and introduced to the Urology armamentarium. For example, many of the available studies are lacking second TURB-T for high risk patients, immediate post TURB-T instillation, and fluorescent cystoscopy/TURB-T. Consequently, involved patients were undertreated according to today's standards and recurrence, and progression rates are higher than in current practice.

Thirty-sex years of BCG immunotherapy have passed with a lot of success, yet with an ample room for improvement. A deep insight into the mechanisms of BCG action to maximize its benefits at the least untoward effects and a thorough search in molecular and immunological markers that can predict patients with likelihood of BCG failure or with propensity for progression of their bladder cancer are two important aspects of research that will further enhance our knowledge regarding BCG.

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