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European Association of Urology



Letter to the Editor

Re: Per-Uno Malmström, Richard J. Sylvester, David E. Crawford, et al. An Individual Patient Data Meta-Analysis of the Long-Term Outcome of Randomised Studies Comparing Intravesical Mitomycin C versus Bacillus Calmette-Guérin for Non-Muscle-Invasive Bladder Cancer. *Eur Urol* 2009;56:247–56

We compliment the authors on this important contribution to our understanding of the role of mitomycin C (MMC) and bacillus Calmette-Guérin (BCG) in the management of non-muscle-invasive bladder cancer [1]. This work puts to rest the proposition that the superiority of BCG immunotherapy over intravesical chemotherapy, demonstrated in 15 randomized clinical trials [2–10], is due to the inclusion of patients previously treated with chemotherapy. Prior treatment with chemotherapy reduces response to subsequent chemotherapy, especially if agents with similar mechanisms of action are used, and BCG is better in this pretreated risk group. Moreover, BCG is superior even in those who have not received previous intravesical chemotherapy.

While the superiority of BCG over chemotherapy is undeniable, as illustrated by this meta-analysis [1] and others, MMC has fared better than other chemotherapies when compared with BCG. Sophisticated statistical analysis may help discern the truth, but a basic mathematical dilemma persists: Quantities equal to the same quantity are equal. In multiple randomized clinical trials, MMC has failed to demonstrate superiority over other intravesical chemotherapies, as confirmed by the European Association of Urology (EAU) guidelines. Why, then, should MMC perform better than other chemotherapies when compared with BCG? The answer may lie in the populations studied and the treatment regimens selected. BCG is relatively more effective in high-risk patients, and a single 6-wk course of BCG is suboptimal.

The four studies that found an overall 28% recurrence benefit of MMC over BCG when BCG maintenance was not used provide insight into the optimal use of these agents [1]. The study population was at relatively low risk for recurrence, as demonstrated by the overall recurrence of only 37% (554 of 1496; 42.6% BCG, 32.8% MMC) compared with 50% recurrence (43.2% BCG, 57.9% MMC) in the studies with maintenance BCG, and had a high proportion of G2

tumors. Two studies used what is reported to be an immunosuppressive schedule of BCG, namely, two 6-wk courses.

In a randomized clinical trial, Palou et al found repeated 6-wk courses of BCG to be no better than induction alone [11]. The two other studies used no maintenance BCG and compared that approach to an extended MMC schedule. These data suggest that in lower risk patients, MMC maintenance reduces recurrence by 11% (43.6% vs 31.8%) compared with suboptimal BCG immunotherapy. Cytology and fluorescence in situ hybridization may be useful in selecting lower risk patients who are candidates for MMC maintenance. Repeated instillation of MMC and other chemotherapeutic drugs in the normal rodent bladder has been demonstrated to be carcinogenic, so some caution is appropriate to avoid overuse of MMC maintenance [12–14]. The EAU guidelines suggest the restriction of maintenance therapy to a maximum of 1 yr.

Bladder cancer has been wisely described as a heterogeneous tumor, and no single treatment will be best for every patient or every cancer cell in an individual patient. Our goal is to use the best treatment for an individual patient, and we must be willing to change treatment strategies when tumors recur. It is not uncommon to see patients with high-grade tumors respond to BCG and then recur with a low-grade tumor that is refractory to BCG. Intravesical chemotherapy, using what we now know to be improved treatment techniques to maximize drug concentration (eg, 40 mg/20 ml MMC, 50 mg/25 ml doxorubicin, 30 mg/15 ml thiotepa in the United States), to completely drain the bladder, to dehydrate the patient, and to alkalinize the urine is clearly beneficial [15]. When low-grade tumors are controlled in such patients, maintenance BCG can be resumed to prevent eventual recurrence and progression of high-grade, high-risk disease. Future studies should compare current optimal chemotherapy, which was not available at the time these studies were done, with current optimal BCG.

We are concerned that readers may incorrectly conclude from this study [1] that BCG maintenance does not reduce disease progression. While no statistically significant reduction in progression or bladder cancer mortality was found in this analysis comparing suboptimal BCG with

maintenance MMC, bladder cancer deaths were 9.3% in the MMC group and 5.6% in the BCG group; 71.8% of the MMC group was alive versus 79.7% of the BCG group, and cystectomy was done in 15% of the MMC patients compared with 8.6% of the BCG-treated patients. Moreover, in randomized clinical trials comparing the current optimal 3-wk maintenance schedule with induction BCG alone or epirubicin chemotherapy, statistically significant reduction in recurrence, disease worsening, metastasis, overall mortality, and cancer-specific mortality has been documented.

These data clearly demonstrate that 3-wk maintenance BCG is currently the most effective treatment for high-risk bladder cancer. Efforts to improve the treatment of these patients should be compared with this current gold standard, but demonstrating statistically significant improvement will be difficult. Previous studies, for example, have found high-dose vitamins and interferon to improve the efficacy of BCG. Our efforts to improve the 3-wk BCG maintenance schedule with vitamins and interferon using one-third dose BCG during maintenance and omitting the 30-mo course were unsuccessful. Careful statistical analysis of existing studies, as done by the authors [1], and careful consideration of the biology will permit design of studies to advance our treatment of bladder cancer incrementally.

Conflicts of interest: The authors have nothing to disclose.

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October 29, 2009
Published online on November 10, 2009