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Platinum Priority – Editorial and Rebuttal from Authors

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Is Intravesical Bacillus Calmette-Guérin Better than Mitomycin for Intermediate-Risk Bladder Cancer?

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The role of intravesical therapy is to prevent recurrences and progression of bladder cancer. Among patients who present with superficial disease, recurrence rates range from 67% to 73%, and progression rates from 20% to 30% [1]. There is some controversy about the best agent to be used for intravesical therapy. Although studies have shown that bacillus Calmette-Guérin (BCG) is superior to mitomycin C (MMC) in the management of carcinoma in situ (CIS) and high-risk disease, the role of intravesical chemotherapy is still debated in the management of intermediate-risk bladder cancer. The optimal agent should be more effective with lesser morbidity.

The efficacy of BCG intravesical immunotherapy has been compared to that of MMC. Although results have been mixed, most studies have shown equivalent or superior results for BCG. The results from three large meta-analyses help to put the BCG versus MMC question in proper perspective. Using 11 clinical trials involving approximately 2800 patients in aggregate, Bohle et al reported an overall statistical superiority of BCG over MMC in reducing tumor recurrence rate by an odds ratio of 0.56 (38.6% for BCG vs 46.4% for MMC) [2]. Importantly, only studies using BCG maintenance contributed to this advantage (odds ratio: 0.43). The trade-off, though, was a 1.8-fold increase in associated cystitis for BCG (53.8% vs 39.2%). With regard to superficial transitional cell carcinoma progression, the results are less clear. Sylvester et al could not demonstrate a statistically significant advantage of BCG versus MMC for progression (overall 14% difference favoring BCG) [3]. However, Bohle et al, using a larger database including non-English literature, did find a statistically significant reduction in risk of progression for BCG compared to maintenance MMC (odds ratio: 0.66) [4].

In the current study, Malmström et al [5] performed a meta-analysis with individual patient data. They concluded that BCG with maintenance was more effective than intravesical MMC in preventing recurrences, while there were no significant differences regarding progression.

However, most studies evaluating different chemotherapeutic agents have lacked standardization in the dose and concentration, but these factors can be critical. Thiotepa has been shown to be an effective prophylactic agent, and, yet, a large Medical Research Council trial did not show a decrease in recurrence rate [6]. In this trial, the patients received 30 mg of thiotepa diluted in 50 ml, a dose similar to other studies but in a much lower concentration, suggesting that, unlike systemic chemotherapy, response to intravesical chemotherapy is proportional to the concentration rather than to the total dose of the drug. In a pharmacokinetics study of thiotepa, Masters at al suggested that systemic exposure depends on the total dose and that tumor exposure depends on the concentration [7]. It is, therefore, possible to increase the efficacy of the drug by decreasing the volume of the diluent without increasing the systemic toxicity. Similarly, Gao et indicated that tumor uptake of MMC was proportional to the drug concentration [8]. An international consortium study by Au et al showed the importance of optimized MMC drug delivery regimen in 230 patients receiving six weekly instillations of an optimized or standard regimen [9]. The optimized regimen consisted of a 40-mg dose of MMC, pharmacokinetic manipulations to increase drug concentration by decreasing urine volume, and urine alkalinization to improve stabilization of the drug. The second group received a standard 20-mg dose without pharmacokinetic manipulations or urine alkalinization. Interruption of

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treatment schedules did not differ between the groups. Patients in the optimized arm had a significantly longer median time to recurrence and a greater recurrence-free fraction at 5 yr than patients in the standard arm. Thus, this study demonstrated the improved efficacy of the optimized MMC treatment.

Improved results have also been shown for other methods of administration. For example, electromotive administration of MMC was superior to the passive method of administration and similar to BCG [10].

In summary, although most studies have shown the superiority of intravesical BCG over MMC, the optimized delivery of MMC, which has been shown to be superior to the standard delivery, has not been adequately evaluated in a head-to-head comparison with BCG. Because these studies comparing BCG with MMC did not routinely incorporate more recent modifications optimizing MMC efficacy, the conclusion that BCG is superior may no longer be applicable. At this time, MMC should be considered a viable option for patients with papillary tumors at low to intermediate risk of progression, particularly because of the lower morbidity associated with MMC [11]. However, prospective clinical trials confirming this possibility are still lacking.

Conflicts of interest: The author has nothing to disclose.

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Platinum Priority

Rebuttal from Authors re: Guido Dalbagni. Is Intravesical Bacillus Calmette-Guérin Better than Mitomycin for Intermediate-Risk Bladder Cancer? Eur Urol 2009; 56:257–8

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We would like to thank Dr. Dalbagni [1] for the comments in his editorial, with which we largely agree.

Clinical guidelines for patient management require a high level of evidence, with randomized clinical trials being the gold standard. However, individual trials inevitably have their shortcomings; hence, the birth of meta-analyses, which provide a quantitative synthesis of the outcome based on all available properly randomized studies. However, like individual trials, meta-analyses can also be criticized. The three previously published meta-analyses comparing bacillus Calmette-Guérin (BCG) to mitomycin C (MMC) have their limitations: They were not based on individual patient data, and two of them included nonrandomized studies [2–4]. Hence, the current meta-analysis [5] was carried out in order to overcome these deficiencies.

Unfortunately, the trials included in our meta-analysis were not conducted according to today's standards. Most patients were treated in the 1990s, and, since then, advances made in an effort to improve patient outcome (the use of fluorescence cystoscopy, an immediate instillation after transurethral resection, and optimized MMC drug delivery) may result in a decreased difference

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