incidence estimates in the BCG group (p=0.005). There was a weak trend for fewer progressions (p=0.1) and cancer-specific deaths (p=0.2) in the cumulative incidence analysis, as 4 patients versus 10 patients progressed and 4 patients versus 9 patients died from the disease in the BCG group versus the MMC group, respectively. No difference existed in the overall mortality. The study population, however, was too small for conclusive evidence about progression or survival.

Conclusions: An intensive intravesical BCG immunotherapy results in a sustained and significant long-term reduction in recurrence in frequently recurrent bladder carcinoma. The relatively low progression rate during the long follow-up suggests that it may be difficult to show significant differences in overall mortality with a substantially larger but otherwise similar study population.

Trial Registration: Registration was not considered to be necessary at this stage of the follow-up because the study was initiated as early as 1984 and the last randomisation took place in July 1987, that is, long before the current requirements concerning study registrations were implemented.

Editorial Comment

These data show the long-term results of a comparative trial that was initiated in 1984 in patients with intermediate risk bladder cancer. The present publication with roughly 20 years of overall follow-up focuses on the durability of the response and the possible impact of instillation therapy on progression and mortality. The recurrence rate before therapy was 2.54 and 1.99 in the BCG and the MMC arms, respectively, showing more rapidly recurrent patients in the BCG arm. The results are impressive; even with this extremely long follow-up and as few as 45 patients in the MMC arm and 44 patients in the BCG arm there was a statistically sound advantage of BCG therapy with regard to recurrence. Furthermore, this advantage was sustained over time with the probability of recurrence in the BCG arm vs. MMC was 50 vs. 70% after 5 years, 57 vs. 80% after 10 years and 59 vs. 80% after 15 years of follow-up, respectively (p = 0.005). Due to the low numbers of patients, data on progression and mortality should be regarded with caution and lack significance. Still, fewer patients had progression (4 vs. 10 pts.) and died of bladder cancer in the BCG arm than in the MMC trial arm. In retrospective, one might criticize the suboptimal monthly maintenance regimen in the BCG arm and the quite low concentration of MMC used in this trial. Still, these data support other results on the sustained long-term efficacy of BCG.

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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

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Background: Patients with non-muscle-invasive bladder cancer with an intermediate or high risk need adjuvant intravesical therapy after surgery. Based largely on meta-analyses of previously published results, guidelines

recommend using either bacillus Calmette-Guérin (BCG) or mitomycin C (MMC) in these patients. Individual patient data (IPD) meta-analyses, however, are the gold standard.

Objective: To compare the efficacy of BCG and MMC based on an IPD meta-analysis of randomised trials.

Design, Setting, and Participants: Trials were searched through Medline and review articles. The relevant trial investigators were contacted to provide IPD.

Measurements: The drugs were compared with respect to time to recurrence, progression, and overall and cancer-specific death.

Results and Limitations: Nine trials that included 2820 patients were identified, and IPD were obtained from all of them. Patient characteristics were 71% primary, 54% Ta, 43% T1, 25% G1, 58% G2, and 16% G3, and 7% had prior intravesical chemotherapy. Based on a median follow-up of 4.4 yr, 43% recurred. Overall, there was no difference in the time to first recurrence (p=0.09) between BCG and MMC. In the trials with BCG maintenance, a 32% reduction in risk of recurrence on BCG compared to MMC was found (p<0.0001), while there was a 28% risk increase (p=0.006) for BCG in the trials without maintenance. BCG with maintenance was more effective than MMC in both patients previously treated and those not previously treated with chemotherapy. In the subset of 1880 patients for whom data on progression, survival, and cause of death were available, 12% progressed and 24% died, and, of those, 30% of the deaths were due to bladder cancer. No statistically significant differences were found for these long-term end points.

Conclusions: For prophylaxis of recurrence, maintenance BCG is required to demonstrate superiority to MMC. Prior intravesical chemotherapy was not a confounder. There were no statistically significant differences regarding progression, overall survival, and cancer-specific survival between the two treatments.

Editorial Comment

Randomized comparative clinical trials (RCT) allow us to come closer to the "truth" in therapy. Data from meta-analyses, which comprise several of such RCTs, are regarded even more meaningful as they may compensate for flaws of single trials, e.g. lack of sufficient numbers of patients or "events" (e.g. tumor recurrence, progression or death). Thus, meta-analyses may have enough "power" to detect differences between treatment groups that had not been detectable in the included trials alone. The problem is that meta-analyses usually refer to the published data of individual trials which themselves are a surrogate of the "truth" within hundreds of individual patient data. The authors of the present meta-analysis tried to omit this particular flaw by going back into the primary data of the different trials and performing the meta-analytic calculations on this special set of data. Thus, the authors managed to share with us a deeper look into the truth of superficial bladder cancer therapy and answered some questions that had been raised in the meantime.

First, and to my opinion most importantly, the importance of BCG maintenance therapy was confirmed which resulted in a 32% reduction in recurrence in comparison to MMC.

Second, the issue of previous chemotherapy biasing the results in favor of BCG can be neglected. There was no such influence detectable.

Third, the issue of BCG effectiveness in intermediate risk patients is answered. BCG with maintenance therapy is superior to chemotherapy in this analysis comprising (as the authors state themselves) 74% intermediate risk patients.

Forth, the data on progression and death supporting the superiority of maintenance BCG did not approach the level of statistic significance due to the low numbers of "events" (namely, progression and death of disease) in this intermediate risk group cohort of patients.

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