INTRAVESICAL BACILLUS CALMETTE-GUERIN VERSUS MITOMYCIN C FOR SUPERFICIAL BLADDER CANCER: A FORMAL META-ANALYSIS OF COMPARATIVE STUDIES ON RECURRENCE AND TOXICITY

A. BOHLE,* D. JOCHAM† AND P. R. BOCK‡

From the Department of Urology, Medical University of Lübeck, Lübeck, Germany, and IFAG Basel AG, Institute for Medical Research and Biostatistics, Basel, Switzerland

ABSTRACT

Purpose: We compare the therapeutic efficacy and toxicity of intravesical bacillus Calmette-Guérin (BCG) with mitomycin C on recurrence of stages Ta and T1 bladder carcinoma.

Materials and Methods: Combined published and unpublished data from comparative studies on BCG versus mitomycin C for superficial bladder carcinoma considering possible confounding factors were analyzed. Odds ratio (OR) and its 95% CI were used as primary effect size estimate. Toxicity data were evaluated descriptively.

Results: In 11 eligible clinical trials 1,421 patients were treated with BCG and 1,328 were treated with mitomycin C. Within the overall median followup time of 26 months 38.6% of the patients in the BCG group and 46.4% of those in the mitomycin C group had tumor recurrence. In 7 of 11 studies BCG was significantly superior to mitomycin C, whereas in 4 of 5 studies no significant difference was found. In 1 study mitomycin C was significantly superior to BCG. An overall statistically significant superiority of BCG versus mitomycin C efficacy in reducing tumor recurrence was detected (OR 0.56, 95% CI 0.38 to 0.84, p = 0.005). In the subgroup treated with BCG maintenance all 6 individual studies showed a significant advantage of BCG over mitomycin C (OR 0.43, 95% CI 0.35 to 0.53, p < 0.001). In 4 of 5 studies with reported data on toxicity BCG associated cystitis was significantly more frequent than in the mitomycin C group (53.8% versus 39.2%). The combined cystitis OR was 1.81 (95% CI 1.48 to 2.23, p < 0.001). The OR for cystitis in the BCG maintenance group did not significantly differ from that in the nonmaintenance therapy group.

Conclusions: The results suggest superiority of BCG over mitomycin C for prevention of tumor recurrences in the combined data and particularly in the BCG maintenance treatment subgroup, irrespective of the actual (intermediate or high) tumor risk status. The toxicity with BCG is higher but does not differ between BCG maintenance and nonmaintenance groups.

KEY WORDS: bladder neoplasms; administration, intravesical; mitomycin; meta-analysis; recurrence

The primary treatment of bladder cancer is transurethral resection but up to 70% of superficial tumors recur. Adjuvant intravesical instillation against tumor recurrences with chemotherapy or immunotherapy is well established. Among the chemotherapeutic agents mitomycin C was effective compared with transurethral resection in some but not all studies. The most important immunotherapeutic agent against bladder cancer recurrences is bacillus Calmette-Guerin (BCG). In randomized clinical trials comparing adjuvant BCG with transurethral resection only BCG showed a superior efficacy against tumor recurrences. However, in direct comparative studies of BCG versus mitomycin C the results remain controversial with proved BCG superiority in some but not all studies. We analyzed combined published and unpublished data from comparative clinical trials and cohort studies on BCG versus mitomycin C considering possible confounding factors such as maintenance therapy and tumor risk profile of the patients.

Accepted for publication July 5, 2002.

Supported by an educational grant from Aventis Pasteur Ltd., Lyon, France.

Financial interest and/or other relationship with Aventis Pasteur, Ltd.

Editor’s Note: This article is the third of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 334 and 335.

METHODS

Selection criteria. For the methods of data extraction, statistical analysis and reporting, the rules and principles of the Cochrane Collaboration Reviews were applied as far as possible and feasible. All available published and unpublished data on treatment results in patients with histologically confirmed stage Ta or T1 of any grade bladder carcinoma were selected for analysis provided the data source was a controlled clinical trial or a controlled observational cohort study, the study design included the comparison of the efficacy of intravesically administered BCG and mitomycin C, and the treatment doses and regimen as well as followup duration were reported. Carcinoma in situ was not considered in this meta-analysis because in only 4 of 11 studies the outcomes in patients with carcinoma in situ were documented and the number of available patients in the eligible studies was too small for any inference.

The primary end point criterion of this meta-analysis was the frequency of tumor recurrence within the followup time period of the studies. Recurrence was defined as reappearance of the tumor of the same or lower, stage and grade as the primary tumor. The risk groups were defined according to the European Association of Urology (EAU) guidelines. Because in most studies patients with different risk profiles were included without stratification, we used the most prevalent risk profile of the patients in a study for allocation of
the particular study to the appropriate, namely intermediate or high risk, group (table 1). A low risk group was not included in this analysis because patients with predominantly low risk tumors were not documented in any of the eligible studies. The secondary end point criterion was the frequency of treatment associated toxicity.

Search strategy. An electronic search of MEDLINE, EMBASE, Cancerlit, Current Contents and Cochrane Library data bases from 1985 to 2000 was performed. Hand searches were made from 1993 to 2000 of the annual meeting proceedings of American Urological Association, EAU, International Society of Urology, American Society of Clinical Oncology, and the German, French and Italian urological associations. Unpublished data and additional information were requested from the individual authors by personal contact. Reports of any language were eligible for the searches. Duplicate references as well as repeated references to the same data sets were removed. The only exception were follow-up publications of the same original data when later publications were considered for analysis only in case of substantial new information.

Review methods. Two independent reviewers (A. B. and P. B.) extracted and interpreted the data according to the analysis protocol. For dichotomous outcomes the odds ratio (OR) and relative risk (RR) with its 95% CI were used. The OR (Cochran-Mantel-Haenszel and Peto methods) was used as a primary (confirmatory) effect size estimate and test criterion, while the RR was used as a secondary (exploratory) criterion for reevaluation of all data sets in a sensitivity analysis. In the course of data combination (pooling) heterogeneity was evaluated by Cochran-Q and Breslow-Day tests. The fixed effect model and random effect model were applied. The hypotheses tests were based on the 95% CI and p values were used only for illustration. In case of a potential risk of bias in the overall results due to included studies that violated some of the eligibility criteria, a sensitivity analysis was performed by evaluating the results with and without the suspected studies.

The dose effect relationship was evaluated from the log OR for tumor recurrence and the number of administered BCG doses using linear regression models. Potential confounding effects of BCG strain, BCG dose, mitomycin C dose, number of mitomycin C instillations, risk group, follow-up duration and year of publication were investigated by stratified meta-analysis as well as standard nonparametric (Wilcoxon-Mann-Whitney-test, Kruskal-Wallis-ANOVA, Spearman correlation) statistical methods, using in case of a when possible stratification were requested from the individual authors by personal contact. Reports of any language were eligible for the searches. Duplicate references as well as repeated references to the same data sets were removed. The only exception were follow-up publications of the same original data when later publications were considered for analysis only in case of substantial new information.

Results

The size of the 11 included trials ranged between 61 and 464 patients (total 2,749). Together 1,421 patients were treated with BCG compared to 1,328 treated with mitomycin C. Of the 11 studies 9 were prospective clinical trials (8 randomized studies) and 2 were retrospective (observational) cohort studies with concurrent groups (table 1). Overall median followup was 26 months and mean followup ± SD was 28.6 ± 16 months (range 11.5 to 50.4). Mean followup duration was not significantly different between the combined treatment groups, maintenance-subgroups and the risk subgroups strata.

Tumor recurrence. All Studies Combined: Within the followup period 548 of 1,421 (38.56%) BCG treated patients and 616 of 1,328 (46.39%) mitomycin C treated patients had tumor recurrence. Among the 11 studies analyzed BCG was significantly superior to mitomycin C in 7, no significant difference was found in 3 and mitomycin C was significantly superior to (Tice strain) BCG in 1. For the confirmatory test the resulting random model combined OR was 0.56 (95% CI 0.38 to 0.84, p = 0.005, fig. 1). The combined RR (random model) was 0.75 (95% CI 0.61 to 0.94, p = 0.010, not shown). The results indicated a statistically significant superiority of BCG versus mitomycin C for tumor recurrence. After exclusion of 1 partially eligible study the overall results of the 10 remaining studies were still consistent with the conclusion of a significant superiority of BCG over mitomycin C efficacy in reducing tumor recurrence (not shown).

Stratification by the Presence of BCG Maintenance Therapy: In 6 of the 11 studies analyzed the patients received BCG maintenance therapy for at least 1 year, whereas in 5 studies maintenance was of short duration (less than 6 months) or there was no maintenance therapy at all. The presence or absence of BCG maintenance therapy was the major cause of heterogeneity between the studies. In the BCG maintenance subgroup all 6 studies demonstrated a significant superiority of BCG versus mitomycin C with a combined OR of 0.42 (95% CI 0.30 to 0.58, p < 0.001, fig. 2). The RR was 0.64 (95% CI 0.52 to 0.79, p < 0.001) (not shown). These results indicate a statistically significant superiority of BCG versus mitomycin C efficacy on tumor recurrence in the BCG maintenance subgroup.

Among the 5 studies without BCG maintenance BCG demonstrated significant superiority over mitomycin C in 1, significant superiority of mitomycin C to BCG in 1 and no significant difference between the 2 drugs in 3. The no maintenance subgroup showed a combined random effect model OR of 0.91 (95% CI 0.56 to 1.49, p = 0.71, fig. 2). The RR was

Table 1. Characteristics of studies

<table>
<thead>
<tr>
<th>References</th>
<th>No. Evaluable Pts.</th>
<th>BCG Maintenance (1 or more yrs.)</th>
<th>Study Quality*</th>
<th>Predominant Risk Group†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayed et al21</td>
<td>270</td>
<td>Yes</td>
<td>B</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Debruyne et al10</td>
<td>325</td>
<td>No</td>
<td>A</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Jauhainen et al22</td>
<td>321</td>
<td>No</td>
<td>A</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Krag et al19</td>
<td>214</td>
<td>No</td>
<td>A</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Lamm et al12</td>
<td>363</td>
<td>Yes</td>
<td>A</td>
<td>High</td>
</tr>
<tr>
<td>Lundholm et al13</td>
<td>250</td>
<td>Yes</td>
<td>A</td>
<td>High</td>
</tr>
<tr>
<td>Millán-Rodríguez et al10</td>
<td>464</td>
<td>Yes</td>
<td>B</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Nogueira et al12</td>
<td>210</td>
<td>No</td>
<td>A</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Pagano et al25</td>
<td>114</td>
<td>Yes</td>
<td>B</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Vegt et al28</td>
<td>387</td>
<td>No</td>
<td>A</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Lee et al26</td>
<td>61</td>
<td>No</td>
<td>B</td>
<td>High</td>
</tr>
</tbody>
</table>

* Adapted from original definition of Cochrane Reviews as A—prospective, randomized, controlled clinical trials and B—observational cohort studies or prospective, controlled clinical trials with missing randomization information.
These results did not show any significant difference between BCG and mitomycin C efficacy on tumor recurrence in the absence of BCG maintenance therapy.

**Combined Stratification by BCG Maintenance Therapy and Risk Group:** Among the 11 analyzed studies 3 with BCG maintenance and a predominantly high risk patient population, and 3 studies with BCG maintenance and a predominantly intermediate risk patient population showed a similar significant and relevant superiority of BCG over mitomycin C in prevention of tumor recurrence. No significant difference between the treatment groups was found in the subgroups without maintenance for the high risk (1 study) or the intermediate (4) subgroups.

The 2 risk subgroups (intermediate, and high risk) with BCG maintenance therapy were statistically homogeneous with a combined OR of 0.51 (95% CI 0.37 to 0.69, p = 0.032) in the high risk subgroup, and OR 0.37 (95% CI 0.27 to 0.50, p < 0.001) in the intermediate risk subgroup (fig. 3). The subgroup without maintenance (all 4 studies with intermediate risk populations) showed no significant difference between the treatments with a combined OR of 1.02 (95% CI 0.63 to 1.67, p = 0.927) and RR 1.01 (95% CI 0.75 to 1.37, p = 0.934). These results indicate a statistically significant superiority of BCG with maintenance therapy versus mitomycin C in reducing tumor recurrences irrespective of the 2 predominant tumor risk profiles of the study populations analyzed. However, without maintenance therapy there was no significant difference between the treatments in any risk group.

**Dose Response Relationship:** There was a significant relationship between the number of administered BCG doses and the log OR on the efficacy of BCG versus mitomycin C in reducing tumor recurrences. The optimal simple model was a linear regression with goodness of fit r² = 0.356, p = 0.033, that is 36% of the log OR variance can be explained by the linear function of the number of BCG instillations. According to this model at least 12 BCG administrations were needed for its relevant superiority over mitomycin C (OR approximately 0.6 or log OR = −0.22). This finding was in agreement with the BCG superiority found in studies of BCG maintenance therapy which all had a log odds ratio of less than −0.22.

**Potential Confounding Effects on Treatment Efficacy Concerning Tumor Recurrence:** The results from studies using different BCG strains, that is Pasteur (3 studies), Connaught (4), Tice (1), RIVM (1), RIVM plus Tice (1) and Danish SSI-1331 (1), differed significantly (Kruskal-Wallis-ANOVA p = 0.023) mainly due to lower relative efficacy of BCG versus mitomycin C (higher OR) in 2 studies without BCG maintenance using BCG strain RIVM, or RIVM plus Tice, respectively. The latter study delivered much weaker efficacy results for BCG compared to mitomycin C than any other study included in our analysis.

The BCG dose (normal or low) did not influence significantly the treatment results (Kruskal-Wallis-ANOVA p = 0.927).
The predominant risk group (intermediate versus high) had no significant independent effect on the treatment results (Kruskal-Wallis-ANOVA $p = 0.679$). In the 11 studies mitomycin C dose was 20, 30 or 40 mg. The results did not significantly change by the administered dose (Kruskal-Wallis-ANOVA $p = 0.321$) or by the number of mitomycin C instillations (Spearman $r = 0.13$, $p = 0.744$). Also, neither follow-up duration or year of publication significantly correlated with the treatment results (Spearman $r = 0.106$, $p = 0.757$ and $r = 0.198$, $p = 0.556$, respectively). Again, BCG maintenance therapy remained the only independent factor associated with significant superiority of BCG versus mitomycin C for tumor recurrence ($p = 0.041$).

Carcinoma in situ: While a meta-analysis of carcinoma in situ was not intended in this study, nevertheless 4 of the 11 eligible studies contained information about carcinoma in situ with 10 to 42 cases per treatment group. The pooled data showed a nonsignificant trend to better results in the BCG group with OR 0.60 (95% CI 0.35–1.04). However, the overall number of cases was not sufficient for a conclusive formal meta-analysis.

Comparative Analysis of Toxicity: Data on toxicity were documented in 5 studies of 901 BCG treated patients and 776 mitomycin C treated patients (table 2). Only 2 studies reported details on all relevant adverse reactions.12, 13 Among the local symptoms in all 5 studies cystitis was the most common local adverse reaction reported in both treatment groups. In 4 of the 5 studies BCG associated cystitis was significantly more frequent than in the mitomycin C group. The overall cystitis rate was 53.8% and 39.2% for BCG and mitomycin C, respectively, and the combined cystitis OR was 1.81 (95% CI 1.48 to 2.23, $p < 0.001$). No significant difference in cystitis incidence and OR was observed between patients with or without BCG maintenance therapy (ANOVA $p = 0.841$, fig. 4). Generally, symptoms of local and systemic toxicity were more frequent in the BCG group, except for...
variety of chemotherapeutic agents. In a recent meta-analysis performed an analysis of randomized clinical trials for a Medical Research Council and the European Organization for Research and Treatment of Cancer. The EAU guidelines on bladder cancer recommended BCG recurrence without further guidance on preference. Similarly, mitomycin C was recommended for prevention of tumor recurrence. When stratified by BCG maintenance regimen OR for cystitis does not differ significantly between subgroups with or without BCG maintenance regimen. Lower, upper and upper 95% CI of OR, p value (2-sided). Ntotal, total sample size n/N, number of events per number of cases in treatment group. Fixed, fixed effect model. Random, random effect model. Lines indicate 95% CI, squares OR estimates, whereas square size is proportional to sample size, and rhombs meta-analytically pooled OR estimates ≥95% CI. MMC, mitomycin C.

**DISCUSSION**

Many individual trials have only a low power to detect medically plausible differences between 2 treatment regimens, especially if both regimens are of valid efficacy. A possible way to overcome this problem is to perform a combined analysis of available material using meta-analysis technique, which is a formal statistical methodology used to combine the results of separate but similar studies in a quantitative manner, so that the statistical power of the tests used to compare treatments is increased by using all of the evidence from a larger number of controlled trials rather than only one. Particularly consistent and strict meta-analytical techniques were developed, validated and applied by the Cochrane Collaboration as the “Cochrane Reviews” to establish and support the evidence based medicine framework.

Meta-analytical techniques were also used to draw conclusions on the benefits of different therapeutic options for the adjuvant treatment of superficial bladder cancer. In 1994 data from 23 controlled clinical trials were analyzed and confirmed that the average net benefit from intravesical chemotherapy compared to transurethral resection alone was 14% at 1 to 3 years. These findings were supported by the Medical Research Council and the European Organization for Research and Treatment of Cancer (EORTC) when they performed an analysis of randomized clinical trials for a variety of chemotherapeutic agents. In a recent meta-analysis of randomized clinical trials adjuvant intravesical chemotherapy in comparison with transurethral resection of the bladder only led to a reduction of recurrences between 12.6% and 23.8%, while BCG instillation therapy reduced the tumor recurrence rate by 47% (95% CI 39.5% to 56.0%). A previous Cochrane collaboration meta-analysis on the efficacy of adjuvant BCG proved that BCG immunotherapy was significantly more effective in reducing the number of tumor recurrences at 12 months and delaying the time to recurrence compared to transurethral resection of the bladder alone. The American Urological Association recently reported guidelines derived from English articles for the treatment of Ta and T1 bladder cancer. Intravesical BCG or mitomycin C was recommended for prevention of tumor recurrence without further guidance on preference. Similarly, the EAU guidelines on bladder cancer recommended BCG instead of intravesical chemotherapy only for highly recurrent or multiple tumors and in cases of intermediate to high risk tumors when prevention of progression was a major concern. Our meta-analysis showed superiority of BCG over mitomycin C for tumor recurrence prevention in the overall combined data and particularly in the BCG maintenance treatment subgroup, irrespective of the actual (intermediate or high) risk status. On average, at least 12 BCG instillations were needed to achieve significant superiority over mitomycin C.

This different outcome can be attributed to several details. In contrast to the aforementioned meta-analyses, no language restrictions were made and a more profound search was performed. With this background we believe that our study completely reflects the present knowledge on the efficacy of BCG in comparison to mitomycin C and offers more relevant conclusions for daily urological practice. The results further make a clear case for the benefits of BCG maintenance therapy. It should be emphasized that the role of maintenance therapy in the literature is controversial.

While for intravesical chemotherapy the early postoperative start of instillations appears to be an important factor with virtually all studies indicating a decrease in the likelihood of subsequent tumors, a 6-week induction course alone was regarded suboptimal for BCG by some but not by others. Our meta-analysis suggests that BCG maintenance therapy is superior to an induction course only. However, a note of caution must be added as BCG maintenance therapy may be associated with an increased risk of side effects. For instance, only 16% of the maintenance cases in a recent study received all 8 maintenance courses during 3 years. However, in our meta-analysis the OR for cystitis was not significantly different between studies with and without BCG maintenance therapy. Generally, more adverse reactions were reported in BCG treated patients than in the mitomycin C group. BCG is clinically known for inflammatory cystitis, occurring mostly after instillation 2 or 3 for 1 or 2 days and becoming more intense throughout the treatment cycle. Another common symptom of BCG therapy is febrile episodes of short duration. However, in a multivariate analysis fever (greater than 37.5°C) after BCG instillation proved to be an important positive prognostic factor regarding the risk of tumor recurrence (Cox model p = 0.009).

**CONCLUSIONS**

The evidence from this formal meta-analysis suggests that adjuvant intravesical BCG and, particularly maintenance BCG, treatment for at least 1 year and 12 instillations is effective and superior to intravesical mitomycin C chemotherapy for the pro-
low recurrence and risk of high risk bladder carcinoma. This intervention is associated with local and systemic side effects but the majority are manageable. Evidence for increased BCG toxicity during maintenance therapy was not found. Adjuvant intravesical BCG therapy with maintenance should be offered to eligible patients with intermediate and high risk tumors.

REFERENCES


