INTRAVESICAL BACILLE CALMETTE-GUERIN VERSUS MITOMYCIN C IN SUPERFICIAL BLADDER CANCER: FORMAL META-ANALYSIS OF COMPARATIVE STUDIES ON TUMOR PROGRESSION

A. BÖHLE AND P. R. BOCK

ABSTRACT

Objectives. To compare the therapeutic efficacy of intravesical bacille Calmette-Guérin (BCG) with mitomycin C (MMC) on progression of Stage Ta and T1 bladder carcinoma.

Methods. Combined published and unpublished data from comparative studies on BCG versus MMC in superficial bladder carcinoma were analyzed, considering possible confounding factors. Odds ratios (ORs) and 95% confidence intervals (CIs) were used as the primary effect size estimate. Tumor progression was defined as progression to a higher tumor stage or the development of metastatic disease.

Results. In nine eligible clinical trials, 1277 patients were treated with BCG and 1133 with MMC. Within the overall median follow-up of 26 months, 7.67% of the patients in the BCG group and 9.44% of the patients in the MMC group developed tumor progression. In all nine individual studies and in the combined results, no statistically significant difference in the ORs for progression between the BCG and MMC-treated groups was found (combined OR = 0.77; 95% CI 0.57 to 1.03; P = 0.081). In the subgroup with BCG maintenance, the combined result of the five individual studies showed a statistically significant superiority of BCG over MMC (OR = 0.66; 95% CI 0.47 to 0.94; P = 0.02). In the four studies without BCG maintenance, the combined result indicated no statistically significant difference between the two treatments (OR = 1.16; 95% CI 0.65 to 2.07; P = 0.612). Potential confounders, such as tumor risk status, duration of follow-up, BCG strain, BCG and MMC treatment regimen, and year of publication did not significantly influence these results.

Conclusions. The results demonstrated statistically significant superiority for BCG compared with MMC for the prevention of tumor progression only if BCG maintenance therapy was provided.

TABLE I. Characteristics of eligible studies

<table>
<thead>
<tr>
<th>Investigator, Year</th>
<th>Patients (MMC/BCG)</th>
<th>BCG Maintenance (≥1 yr)</th>
<th>Study Quality* (A/B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayed et al., 16 1998</td>
<td>109/43</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td>Debruyn et al., 17 1992</td>
<td>158/167</td>
<td>No</td>
<td>A</td>
</tr>
<tr>
<td>Jauhiainen et al., 18 1989</td>
<td>45/46</td>
<td>Yes</td>
<td>A</td>
</tr>
<tr>
<td>Krege et al., 19 1996</td>
<td>102/112</td>
<td>No</td>
<td>A</td>
</tr>
<tr>
<td>Lamm et al., 9 1995</td>
<td>182/181</td>
<td>Yes</td>
<td>A</td>
</tr>
<tr>
<td>Malmström et al., 20 1999</td>
<td>125/125</td>
<td>Yes</td>
<td>A</td>
</tr>
<tr>
<td>Millén-Rodriguez et al., 21 2000</td>
<td>207/211</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td>Nogueira et al., 22 2000</td>
<td>98/112</td>
<td>No</td>
<td>A</td>
</tr>
<tr>
<td>Vegt et al., 23 1995</td>
<td>251/136</td>
<td>No</td>
<td>A</td>
</tr>
</tbody>
</table>

Key: MMC = mitomycin C; BCG = bacille Calmette-Guerin

* Study quality assessment adapted from original definition for Cochrane Reviews as A, prospective, randomized, controlled, clinical trials; and B, observational cohort studies or prospective, controlled clinical trials with missing information about randomization.

MATERIAL AND METHODS

For the methods of data extraction, statistical analysis, and reporting, the rules and principles of the Cochrane Collaboration Reviews’ were those published in a previous report on the relative effects of BCG and MMC, against superficial bladder cancer recurrence applied as far as was possible and feasible.

SELECTION CRITERIA

All available published and unpublished data on the treatment results in patients with histologically confirmed Stage Ta or T1, any grade, bladder carcinoma were selected for analysis, provided all the following data were available: (a) the data source was a controlled clinical trial or a controlled observational cohort study; (b) the study design included the comparison of the efficacy on tumor progression of intravesically administered BCG and MMC; and (c) the treatment doses and regimen, as well as the follow-up duration, were reported. To control for potential confounding effects, including BCG strain, the most prevalent risk profile of the patients in a study was used.5

The primary endpoint criterion of this meta-analysis was the frequency of tumor progression within the follow-up period of the studies. Tumor progression was defined as progression to a higher tumor stage or the development of metastatic disease. If more precise information was not available, “disease worsening” was also accepted as progression.

SEARCH STRATEGY

An electronic search of Medline, Embase, Cancerlit, Current Contents, and the Cochrane Library databases from 1985 to 2001 was performed. Hand searches were made in publications from 1993 to 2001 of the annual meeting proceedings of the American Urological Association, European Association of Urology, International Society of Urology, American Society for Clinical Oncology, and the German, French, and Italian urologic 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.

METHODS OF REVIEW

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 with its 95% confidence intervals (CIs) were used. The OR (Cochran-Mantel-Haenszel method) was used as a primary (confirmatory) effect size estimate and test criterion, and relative risk was used as a secondary (exploratory) criterion for the re-evaluation of all data sets in a sensitivity analysis. In the course of data combination (pooling), the heterogeneity was evaluated by the Cochran-Q and Breslow-Day tests. Both the fixed effect model and the random effect model were applied. The hypotheses tests were based on the 95% CI. P values were used only for illustration. In the case of a potential risk of bias in the overall results owing to included studies that violated some of the eligibility criteria, a sensitivity analysis was performed by evaluating the results with and without the suspect studies. Potential confounding effects, including BCG strain, BCG dose, BCG treatment regimen, MMC dose, number of MMC instillations, risk group, follow-up duration, and year of publication, were investigated by stratified meta-analysis, as well as by standard nonparametric (Wilcoxon-Mann-Whitney test, Kruskal-Wallis analysis of variance, Spearman’s correlation) statistical methods, using exact tests. The following software was used for analysis: Review Manager, Comprehensive Meta-Analysis, SPSS, Excel 2000, StatXact, StatsDirect, EasyMA, and Testimate.

RESULTS

In nine eligible clinical trials with a total of 2410 patients, the sample size range of the included trials was 91 to 418 patients. In total, 1277 patients were treated with BCG and compared with 1133 patients treated with MMC. Seven of these studies were prospective clinical trials and two were retrospective observational cohort studies with concurrent groups (Table I). The overall median follow-up was 26 months (mean 28.6 ± 16 SD, range...
11.5 to 50.4). The mean follow-up duration was not significantly different between the combined treatment groups, maintenance subgroups, or risk subgroups.

**ALL STUDIES COMBINED**

Within the follow-up period, 98 (7.67%) of 1277 BCG-treated patients and 107 (9.44%) of 1133 MMC-treated patients developed tumor progression. In all nine individual studies and in the combined analysis, no statistically significant difference in the progression rate between the two treatment groups was found. The fixed model combined OR was 0.77 (95% CI 0.57 to 1.03, \( P = 0.081 \); Fig. 1). The relative risk was 0.79 (95% CI 0.61 to 1.03, \( P = 0.081 \); data not shown). Thus, the overall results of the nine included studies were consistent with the conclusion of no statistically significant difference between BCG and MMC efficacy on tumor progression in the overall pooled data.

**STRATIFICATION BY BCG MAINTENANCE THERAPY**

In five of the nine studies analyzed, the patients received BCG maintenance therapy for at least 1 year. In the other four studies, only short (6 months or less) or no maintenance therapy was given. The presence or absence of BCG maintenance therapy was the major cause of heterogeneity among the studies.

In the BCG maintenance subgroup, the combined fixed effect OR was 0.66 (95% CI 0.47 to 0.94, \( P = 0.020 \); Fig. 2). The relative risk was 0.70 (95% CI 0.52 to 0.94, \( P = 0.0195 \); data not shown). These results indicated the statistically significant superiority of BCG versus MMC efficacy on tumor progression in the BCG maintenance subgroup. The no-maintenance subgroup showed a combined fixed effect model OR of 1.16 (95% CI 0.65 to 2.07, \( P = 0.61 \); Fig. 2). The relative risk was 1.15 (95% CI 0.67 to 2.00, \( P = 0.61 \); data not shown). These results did not show any statistically significant differences between BCG and MMC efficacy on tumor progression in the absence of BCG maintenance therapy.

**POTENTIAL CONFOUNDING EFFECTS ON TREATMENT EFFICACY AGAINST TUMOR PROGRESSION**

The stratified meta-analysis and exact nonparametric statistical tests did not show any statistically significant confounding effects on the results when stratified by BCG strain (Connaught, Pasteur, Tice, and Danish SSI 1331), BCG dose (normal versus low dose), predominant risk group (intermediate versus high), MMC dose (20, 30, or 40 mg), number of MMC instillations, follow-up duration, or year of publication. Thus, BCG maintenance therapy remained the single independent factor associated with the statistically significant superiority of BCG versus MMC against tumor progression.

In contrast to our recent meta-analysis on recurrence, a subanalysis of risk groups (intermediate versus high) was not meaningful, because the number of studies was too small and all the studies with a predominantly high-risk population also used BCG maintenance therapy.

**COMMENT**

Published reports have a paucity of valid data on the effect of intravesical therapy on the progression of superficial bladder cancer probably because of the relatively small numbers of high-risk patients entered into clinical trials. Furthermore, many individual trials had low power to detect medically plausible differences between two treatment regi-
mens, especially if both regimens were of valid efficacy. One way to overcome these problems is to perform a combined analysis of available material using meta-analysis techniques. Particularly consistent and strict meta-analytical techniques have been developed, validated, and applied by the Cochrane Collaboration to establish and support the framework of evidence-based medicine. Meta-analytical techniques with regard to progression have been used by other groups. The Medical Research Council and the European Organization for the Research and Treatment of Cancer performed a combined data analysis of randomized clinical trials for a variety of chemotherapeutic agents. They found no effect on progression using chemotherapy. In a recent meta-analysis of randomized clinical trials, adjuvant intravesical chemotherapy compared with transurethral resection of the bladder only led to a reduction in the recurrence rate of between 12.6% and 23.8%; BCG instillation therapy reduced the tumor recurrence rate by 47% (95% CI 39.5% to 56.0%). A previous Cochrane Collaboration meta-analysis proved that BCG immunotherapy was significantly more effective in reducing the number of patients with tumor recurrence at 12 months compared with transurethral resection of the bladder alone. In recent guidelines from the American Urological Association, the use of intravesical BCG or MMC was mentioned for prevention of tumor progression. However, no data supported the use of the latter. The European Association of Urology Guidelines on Bladder Cancer recommended BCG instead of intravesical chemotherapy only in highly recurrent or multiple tumors and in the case of intermediate to high-risk tumors when the prevention of progression was of major concern. Our meta-analysis demonstrated superiority of BCG treatment compared with MMC against tumor progression only in the BCG maintenance treatment subgroup.

The results further made a clear case for the benefits of BCG maintenance therapy that was also independently supported by the results of three recent reports. Our data confirmed those in a recent publication on a related topic by Sylvester and coworkers that stated that the effect of BCG on progression was limited to trials with some form of BCG maintenance. In contrast to our data, their results in the subgroup comparing BCG and MMC were not significantly different statistically.

This difference, however, can easily be attributed to the incorporation of only six studies into their subgroup analysis, three with and three without BCG maintenance.

CONCLUSIONS

The evidence from this formal meta-analysis suggests that adjuvant intravesical BCG with maintenance treatment is effective and is superior to intravesical MMC chemotherapy for the prophylaxis of tumor progression in superficial bladder cancer. To patients with a risk of progression, adjuvant intravesical BCG therapy with maintenance should be offered as the treatment of choice.

<table>
<thead>
<tr>
<th>Maintenance</th>
<th>Citation</th>
<th>Effect Lower</th>
<th>Upper</th>
<th>PValue</th>
<th>NTot BCG n/N</th>
<th>MMC n/N</th>
<th>0.01</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>DeBruyne, 1992</td>
<td>3.267</td>
<td>6.6</td>
<td>0.15</td>
<td>325/8158</td>
<td>2/167</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>Krege, 1999</td>
<td>2.30</td>
<td>7.78</td>
<td>0.18</td>
<td>214/8/102</td>
<td>4/112</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>Noguiera, 2000</td>
<td>0.16</td>
<td>1.28</td>
<td>0.05</td>
<td>210/1/86</td>
<td>7/112</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>Vegh-combined, 1995</td>
<td>1.02</td>
<td>2.46</td>
<td>0.97</td>
<td>387/15/251</td>
<td>8/136</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed</td>
<td>no (4)</td>
<td>1.16</td>
<td>6.6</td>
<td>0.27</td>
<td>1136/30/809</td>
<td>21/527</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random</td>
<td>no (4)</td>
<td>1.23</td>
<td>4.32</td>
<td>0.68</td>
<td>1136/30/809</td>
<td>21/527</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>Ayed, 1998</td>
<td>0.47</td>
<td>1.21</td>
<td>0.11</td>
<td>152/12/109</td>
<td>9/43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>Jauhainen, 1989</td>
<td>0.50</td>
<td>5.72</td>
<td>0.57</td>
<td>91/1/45</td>
<td>2/46</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>Lamm, 1995</td>
<td>0.62</td>
<td>1.23</td>
<td>0.17</td>
<td>363/15/82</td>
<td>23/181</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>Malmström, 1999</td>
<td>0.69</td>
<td>1.31</td>
<td>0.26</td>
<td>250/20/125</td>
<td>27/125</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>Millin, 2000</td>
<td>0.80</td>
<td>1.48</td>
<td>0.47</td>
<td>418/20/207</td>
<td>25/211</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed</td>
<td>yes (5)</td>
<td>0.66</td>
<td>0.47</td>
<td>0.94</td>
<td>1274/68/668</td>
<td>86/606</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random</td>
<td>yes (5)</td>
<td>0.66</td>
<td>0.47</td>
<td>0.93</td>
<td>1274/68/668</td>
<td>86/606</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed</td>
<td>Combined (9)</td>
<td>0.77</td>
<td>1.03</td>
<td>0.08</td>
<td>2410/99/1277</td>
<td>107/1133</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random</td>
<td>Combined (9)</td>
<td>0.78</td>
<td>1.13</td>
<td>0.19</td>
<td>2410/99/1277</td>
<td>107/1133</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 2. Tumor progression (all studies with maintenance) with OR as effect size. Maintenance = BCG maintenance regimen; Lower, Upper = lower and upper 95% CIs of ORs; 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% CIs, squares indicate OR estimates (square size proportional to sample size). Rhombs indicate meta-analytically pooled OR estimates ± 95% CI. P values were two-sided.
REFERENCES


EDITORIAL COMMENT

Is BCG better than MMC in preventing progressive disease in patients with superficial bladder cancer? The jury is still out.

Many patients with superficial bladder cancer can be treated relatively conservatively, perhaps by transurethral resection (TUR) alone or in combination with simple, nontoxic intravesical chemotherapy. However, a small proportion of patients have disease that has a high risk of progression to invasive or metastatic disease. In these patients, it is entirely reasonable to ask whether more aggressive early treatment, such as BCG can prevent disease progression. Several randomized trials have demonstrated that intravesical BCG reduces superficial recurrences in patients with superficial bladder cancer.1 The data on whether BCG reduces invasive recurrence or metastatic disease is less clear, mainly because individual randomized trials have been too small to confirm or refute any realistic benefits reliably. In an effort to increase the statistical power, two meta-analyses have been performed.

In this article the authors considered nine studies that compared intravesical BCG with intravesical MMC, involving a total of 2410 patients. The meta-analysis by Sylvester et al.2 considered 24 randomized trials comparing TUR plus intravesical BCG with either TUR alone or TUR plus treatment other than BCG, involving a total of 4863 patients.

On a cursory reading, these two meta-analyses appear to provide good evidence that adjuvant BCG plus maintenance BCG is better than MMC in preventing progression. However, a closer reading suggests we should be more circumspect, because, although there are a number of good methodologic aspects of both meta-analyses, a number of problems and difficulties exist with both that prevent reaching such a definitive conclusion. First, it should be noted that the two meta-analyses should not be regarded as providing independent information, because a number of the same trials were included in both. Both meta-analyses claimed to find an effect only in the trials in which BCG maintenance was used. However, the meta-analysis by Sylvester et al.2 did not present an analysis of trials comparing BCG plus BCG maintenance with MMC (presumably because there were such a small number of such trials). Thus, the positive subgroup result observed in favor of