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A RANDOMIZED STUDY OF INTRAVESICAL MITOMYCIN C, BACILLUS CALMETTE-GUERIN TICE AND BACILLUS CALMETTE-GUERIN RIVM TREATMENT IN pTa-pT1 PAPILLARY CARCINOMA AND CARCINOMA IN SITU OF THE BLADDER

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ABSTRACT

Results of a randomized prospective study are reported in which mitomycin C, Tice bacillus Calmette-Guerin (BCG) and RIVM-BCG were compared in 437 patients with primary or recurrent pTa and pT1 bladder tumors, including carcinoma in situ. The follow-up (or time in study) varied from 2 to 81 months (mean 36 months). After complete transurethral resection of all visible tumors the patients were treated with 30 mg. mitomycin C once a week for 4 consecutive weeks and thereafter every month for a total of 6 months, and $5 \times 10^{8}$ colony-forming units Tice BCG or RIVM-BCG once a week for 6 consecutive weeks. For papillary tumors mitomycin C and RIVM-BCG treatments were equally effective ($p = 0.53$), and mitomycin C was more effective than Tice BCG therapy ($p = 0.01$).

Key Words: bladder neoplasms, drug therapy, immunotherapy, BCG vaccine

In pTa and pT1 bladder cancer intravesical chemotherapy and immunotherapy are used as adjuvant treatment after transurethral resection. Both therapies can reduce the high rate of recurrences in papillary tumors as well as eradicate carcinoma in situ.

Response rates of different studies comparing chemotherapeutic agents versus bacillus Calmette-Guerin (BCG) after transurethral resection in patients with pTa, pT1 and carcinoma in situ bladder tumors suggest that BCG is superior to thiopeta, doxorubicin or mitomycin C. Mitomycin C was selected as a chemotherapeutic agent in our study because of its proved efficacy in regard to prevention of tumor recurrence and high response rate in patients with carcinoma in situ.

In 1988 we reported the results of a prospective trial in which mitomycin C was compared with RIVM-BCG, and no statistically significant differences in toxicity and efficacy were noted between the 2 arms. Because of the lack of superiority of RIVM-BCG over mitomycin C, the efficacy of RIVM-BCG was questioned. BCG is a biological product, consisting of living bacteria, subcellular debris and adjuvant compounds. Considerable differences in the various strains and even lots of the same strain can be present. Most of the BCG strains, for example Tice BCG, are grown as a surface pellicle, ground in a ball mill, resuspended and freeze-dried. However, RIVM-BCG is grown in a homogeneously dispersed culture and lyophilized in a solution containing glucose and polysorbate 80.

It has been suggested that those strains with the best ability to bind to fibronectin could be the strains with the most potent antitumor efficacy. The glycoprotein fibronectin has an important role in the attachment of BCG to the bladder wall, which has been demonstrated in mice. At least in the mouse model BCG strains grown as a surface culture (Tice) showed a better attachment to the bladder wall than homogeneously dispersed cultured BCG (RIVM).

These observations led to the necessity to compare the 2 different BCG strains to each other and to a well known chemotherapeutic drug.

The first objective of our 3-arm prospective, controlled and randomized trial was to compare the efficacy of mitomycin C chemotherapy with that of BCG immunotherapy, using 2 different substrains in patients with primary or recurrent pTa, pT1 and carcinoma in situ bladder tumors. The parameters compared were duration of disease-free interval and the rate of progression to a higher stage (T category) of disease. The second objective was to compare the incidence and severity of side effects of the treatments. Primary end point of the study was the time to recurrence of bladder tumors, which was considered treatment failure.

MATERIALS AND METHODS

From April 1987 to December 1990, 469 patients entered the study from 27 institutions of the Dutch Southeast Cooperative Urological Group. All patients had histologically proved papillary pTa-pT1 transitional cell carcinoma of the bladder with or without concomitant or primary carcinoma in situ. Pathological classification was done according to the tumor, node and metastasis system, and grading was done according to the method of Koss. The highest stage and grade of all tumor specimens in individual cases were used to characterize each case. All specimens of tumor and bladder biopsies were reviewed by a single pathologist. The toxicity, local and systemic side effects, has been reported elsewhere. Briefly, side effects were classified as local, systemic or allergic. Local toxicity was defined as the occurrence of culture proved bacterial cystitis (not BCG related), drug-induced cystitis (mitomycin C or BCG related) or other local side effects, such as hematuria, prostatitis and epididymitis. The severity of side effects was scored by classifying them as requiring no delay, delay or cessation of instillation therapy.

Treatment. Intravesical chemotherapy consisted of 30 mg. mitomycin C in 50 ml. saline instilled once a week for 1 month (week 1 to 4) and thereafter once a month for a total of 6 months. If superficial tumor recurred or carcinoma in situ persisted at 3 months the treatment schedule was not changed after complete transurethral resection (or biopsy), and if disease recurred or persisted after 6 months 3 additional monthly mitomycin C instillations were given.

Intravesical immunotherapy was performed with Tice BCG, with a dosage consisting of 50 ml of saline containing $5 \times 10^{8}$ colony-forming units. The BCG administration was given once a week for 6 weeks, followed by 30 mg. mitomycin C once a week for 4 consecutive weeks. After that every month for a total of 6 months.
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BCG or with RIVM-BCG. BCG was administered (5 × 10^6 colony-forming units in 50 ml. saline) once a week for 6 consecutive weeks. If superficial tumor recurred or carcinoma in situ persisted at 3 or 6 months a second 6-week course with BCG instillations was given after complete transurethral resection or biopsy. In all other cases of recurrences, irrespective of the treatment arm, the patient went off study and treatment was left to the discretion of the urologist.

Followup and treatment response. Followup cystoscopy was performed at 3-month intervals during the first 2 years after transurethral resection, and thereafter at 4 and 6-month intervals. Cytology was done at each cystoscopy. For papillary tumors the efficacy of the therapy was evaluated by determining the disease-free period after randomization. The response to therapy in patients with carcinoma in situ was scored as no response or a complete response. Complete response was defined as the complete disappearance of carcinoma in situ, documented by normal urine cytology, cystoscopic examination and bladder biopsies.

Statistical analysis. To detect a difference of 50% in the median duration of the disease-free interval between mitomycin C and the best (smallest hazard rate) of the BCG treatments (assuming the time to recurrence follows an exponential distribution), 90 eligible and evaluable patients were needed, for a total of 414 evaluable patients. For randomized treatment 65% of the patients will have at least 1 recurrence during the study, 138 evaluable patients per treatment arm (error probabilities (mean 36 months).

Patient and tumor characteristics. Tumor characteristics were equally distributed among the 3 treatment arms (table 1). Of the 437 eligible patients 50 had carcinoma in situ, 254 had pTa tumors and 133 had pT1 tumors (table 1). Of the patients with carcinoma in situ 12 received mitomycin C, 23 Tice BCG and 15 RIVM-BCG. After complete transurethral resection patients with pTa or pT1 papillary tumors were treated with mitomycin C (136), Tice BCG (117) and RIVM-BCG (134). Of the patients with carcinoma in situ 25 had pure flat multifocal carcinoma in situ and 25 also had papillary tumors (concomitant carcinoma in situ). Of all patients 84 had pTa grade 1 tumors, including 43 with a solitary tumor and 41 with multiple (2 to 8) tumors.

Of study patients. A total of 230 patients (74 treated with mitomycin C, 76 Tice BCG and 80 RIVM-BCG) went off study because of recurrence at or after 9 months (122), protocol violation (36), progression in tumor stage to T2 or higher (23), adverse effects (14), intercurrent death (10), treatment refusal (7), lost to followup (3) and other reasons (15). A detailed differentiation of reasons for off study is shown in table 2.

Efficacy of treatment. For stages pTa and pT1 papillary tumors the time to first recurrence was recorded. Recurrence was noted during the study in 58 of 136 patients (43%) treated with mitomycin C, 75 of 117 (64%) treated with Tice BCG and 62 of 134 (46%) treated with RIVM-BCG. The estimated percentages of disease-free patients in the 3 treatment arms are shown in table 3. The analysis of efficacy in the patients with papillary tumors shows a statistically significant difference among the treatment arms (p = 0.04). The mitomycin C and RIVM-BCG treatments were equally effective (p = 0.53) but mitomycin C was more effective than Tice BCG (p = 0.01, see figure). For carcinoma in situ the complete response was analyzed as parameter of efficacy. In all 50 patients with carcinoma in situ the complete response was 68% for a duration of 2 to 49 months (mean 19). Complete response was 67% (8 of 12 patients) for mitomycin C, 74% (17 of 23) for Tice BCG and 60% (9 of 15) for RIVM-BCG. These differences between sample percentages the chi-square test was used. All statistical computations were done using statistical analysis system procedures.

RESULTS

Eligibility. Of the 469 patients who entered the study 17 (6%) were ineligible because of no malignancy after pathological review, 9, tumor stage greater than pT1 after pathological review and prior intravesical chemotheraphy, and they were excluded from subsequent analysis. Another 15 patients (3%) were also excluded from subsequent analysis because of first instillation more than 4 weeks after transurethral resection, no instillations started due to hematuria (2), refusal (2), medication problems (2), death (1), myocardial infarction (1) before the instillation procedure and other reasons (3). Ultimately 437 patients were eligible for analysis. Followup (time in study) of these patients varied from 2 to 81 months (mean 36 months).

Patient and tumor characteristics. Tumor characteristics were equally distributed among the 3 treatment arms (table 1). Of the 437 eligible patients 50 had carcinoma in situ, 254 had pTa tumors and 133 had pT1 tumors (table 1). Of the patients with carcinoma in situ 12 received mitomycin C, 23 Tice BCG and 15 RIVM-BCG. After complete transurethral resection patients with pTa or pT1 papillary tumors were treated with mitomycin C (136), Tice BCG (117) and RIVM-BCG (134). Of the patients with carcinoma in situ 25 had pure flat multifocal carcinoma in situ and 25 also had papillary tumors (concomitant carcinoma in situ). Of all patients 84 had pTa grade 1 tumors, including 43 with a solitary tumor and 41 with multiple (2 to 8) tumors.

Table 2. Reasons off study differentiated by treatment arm

<table>
<thead>
<tr>
<th></th>
<th>Mitomycin C</th>
<th>Tice BCG</th>
<th>RIVM-BCG</th>
<th>Total</th>
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<td>No Ca</td>
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<tr>
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<td>3</td>
<td>39</td>
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<tr>
<td>Totals</td>
<td>65</td>
<td>9</td>
<td>62</td>
<td>14</td>
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</table>
results do not allow any conclusion to be drawn because the numbers of patients randomized are too small.

**Progression in tumor stage.** Progression in stage (pT2 or higher) at recurrence (patients who went off study) was observed in 8 (6%) of the mitomycin C group, 7 (5%) of the Tice BCG group and 8 (6%) treated with the RIVM-BCG.

**Toxicity.** The number and severity of adverse effects were recorded during the instillation period (6 months for mitomycin C, 6 weeks for BCG) and are listed in Table 4. Between the BCG groups no statistical difference in number and severity was found. Drug-induced cystitis, other local side effects and systemic side effects were significantly less frequent in the mitomycin C group. Three of 148 patients (2%) had to stop mitomycin C treatment, 5 of 140 (4%) stopped Tice BCG and 11 of 149 (7%) stopped RIVM-BCG. No life threatening adverse effects or treatment related deaths were recorded.

**DISCUSSION**

The primary objective in this study was to compare the efficacy of mitomycin C chemotherapy with that of BCG immunotherapy, using 2 different strains, in patients with pTa, pT1 and carcinoma in situ bladder cancer. The efficacy in patients with papillary tumors was related to the percentage disease-free period after transurethral resection of all visible tumors. When all patients with papillary tumors (grades 1, 2 and 3, and stages pTa and pT1) were analyzed together a statistically significant difference was seen in efficacy among the 3 treatment schemes in favor of mitomycin C and RIVM-BCG treated patients compared to Tice BCG treated patients.

Because of statistical reasons, definitive results of this study should be withheld until at least 50% of the patients in each of the 3 arms have shown recurrent tumor. However, after 3 years of followup only the Tice BCG group has a slight decrease from 42% disease-free at 3 years to 36% after 4 and 5 years, respectively (Table 2). The disease-free percentage for mitomycin C decreases only from 59% at 3 years to 57% at 5 years and for RIVM-BCG it decreases only from 55 to 54% at 3 and 5 years, respectively. Since in superficial bladder studies most recurrences are observed in the first 2 years after randomization, it is hard to estimate how many years are needed to obtain less than 50% disease-free in all 3 arms (see figure).

Only a few studies have presented a 5-year followup of patients with superficial bladder cancer treated with mitomycin C or BCG. Lamm reported the estimated 5-year recurrence rates of 78% for mitomycin C treated patients and 48% for BCG treated patients. This means that 22% of patients treated with mitomycin C and 52% of those treated with BCG were tumor-free after 5 years. Our results are comparable for BCG patients. The percentage of patients free of tumor after 5 years was 54% of RIVM-BCG, 36% of Tice BCG and 57% of mitomycin C treated patients. Although intravesical chemotherapy delays the time to first recurrence, it is unknown whether chemotherapy influences progression and survival. Recent studies suggest that the time to progression is prolonged with intravesical immunotherapy in patients with superficial bladder cancer. The progression rate in our study was low at 6%, 5% and 4% for mitomycin C, Tice BCG and RIVM-BCG, respectively. Our data do not indicate that the progression rate to muscle-invasive disease was different in any of the treatment arms, which may explain the relatively low number of grade 3 and T1 tumors as well as the low number of carcinoma in situ patients. Most of the patients had intermediate risk tumors. Tumor grade did not signifi-
Our study included 84 patients with pTa grade 1 tumors. These low stage, low grade tumors have a low risk for recurrence or progression if they are solitary. Of the 84 pTa grade 1 cases 43 had a solitary tumor and 41 had multiple primary or recurrent tumors. However, multiple pTa grade 1 tumors have an intermediate risk for recurrences, which indicates that in our study only 43 of all eligible patients (9.8%) had a recurrence or progression if they are solitary. Of the 84 pTa grade 1 tumors with low risk for recurrence or progression this also means that 90.2% of the patients may have had at least potential benefit of adjuvant intravesical therapy after transurethral resection. Therefore, the significance of the results is not particularly diluted by inclusion of the 10% of patients at low risk.

Comparing a 6-week BCG schedule to 6 months of mitomycin C therapy, our data do not provide evidence that BCG offers better response in the treatment of patients with pTa and pT1 bladder tumors than mitomycin C. In patients with primary or concomitant carcinoma in situ, immunotherapy with BCG also was not superior to chemotherapy with mitomycin C. However, the efficacy results in patients with carcinoma in situ do not allow any conclusion to be drawn because too few patients with carcinoma in situ were entered in this study.

This study does not address the issue of whether a 6-week course of BCG is less effective than BCG maintenance therapy. However, it remains useful to look at the response rates in different studies in which 6-week courses, repeated 6-week courses or maintenance therapy has been used.4,19,20 Comparisons with other reported studies must be interpreted with caution because of multiple variable factors, such as different doses, instillation schedules, selected patient groups and so forth.

In Southwest Oncology Group study 8795 a randomized comparison of Tice BCG and mitomycin C was performed in 469 patients.21 Of 377 evaluable patients 37 tumor recurrences were documented in the 190 BCG treated patients (19.4%) versus 61 recurrences in the 187 mitomycin C treated patients (32.6%) (p = 0.0052). The highly significant advantage of BCG over mitomycin C prompted early closure of the trial. However, in the Southwest Oncology Group trial at least 3 major differences can be noted compared to our study. In study 8795 only patients with rapidly recurring tumors (high risk) were enrolled, they were treated by maintenance therapy and the 20 mg. dose of mitomycin C was low.

Mr. Wim Lemmens assisted with the data processing. Dr. Ewout Schaalma reviewed the histological slides and Dr. Rinie van Gils Gielien evaluated the carcinoma in situ patients.

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**EDITORIAL COMMENT**

The primary goal of intravesical therapy is to eradicate existing
disease (treatment) and/or to prevent recurrent disease (prophylax-
sis). Few contemporary trials evaluate the former subset, since it is
believed to be unethical to leave a “marker lesion” to evaluate the
definitive effect of intravesical therapy. The exception to this is
carcinoma in situ, which is often diffuse and not amenable to
complete surgical resection. Therefore, clinical trials such as that
reported by the Dutch Southeast Cooperative Urological Group, which
include carcinoma in situ should evaluate and report each compo-
nent, that is one as treatment of carcinoma in situ and the other as
prophylaxis.

The goal of prophylaxis is obvious, namely to prevent recurrence
and progression of the disease. Ample evidence exists that intravesi-
cal chemotherapy and immunotherapy are capable of preventing
recurrences. Studies suggest that there exists a salutary effect in
reducing the progression rate (reference 17 in article). However, no
study has convincingly demonstrated that intravesical therapy im-
proves survival, although a recent Southwest Oncology Group pro-
tocol would suggest this. Therefore, the primary end point examined
in a superficial bladder trial is time to recurrence, which is influ-
enced by the risk of recurrence and the length of followup. The
inclusion of patients at significant risk for recurrence helps to assure
the validity of any comparisons. For example, a trial could be under-
taken, which shows that intravesical BCG shows no advantage over
an oral placebo. Obviously all that would need to done would be to
include patients at low risk of recurrence and progression, namely
those with the first TA grade 1 solitary tumor. In order to compare
patients with substantial risk of recurrence patients should have
histologically proved, completely resected stage TA or T1 transi-
tional cell carcinoma and be judged to be at increased risk for tumor
recurrence by virtue of 2 occurrences of the tumor within 56 weeks,
stage T1 tumor within 16 weeks of registration, or 3 or more tumors
presenting simultaneously within 16 weeks. Patients presenting
with stages TA and T1 with concurrent carcinoma in situ are also
eligible and, as mentioned, are considered in the treatment rather
than prophylaxis group. Therefore, the target population represents
a group who have not received the drug being evaluated and have at
least an 80 to 90% chance of recurrence within 12 to 24 months.
These are the criteria used in Southwest Oncology Group studies.

The current clinical trial evaluates 2 different strains of the im-
munotherapeutic agent BCG and compares them to a widely ac-
cepted intravesical chemotherapeutic drug, mitomycin C. Patients
entered were those deemed at risk of recurrence with completely
resected papillary pTa and pT1 transitional cell carcinoma of the
bladder with or without concurrent carcinoma in situ. Primary car-
cinoma in situ was also studied. The statistical design is such to
detect a 50% difference in the median duration of disease-free inter-
val between mitomycin C and the 2 intravesical immunotherapy
BCG treatment arms. Patients in the study needed at least a 65%
risk of recurrence during the study, and the study is powered at 80%
chance of detecting the aforementioned differences. The authors
state that their study only includes 43 patients (9.8%) who were at
low risk for recurrence or progression. Total of 254 cases (65.6%)
was pTa grade 1 but 34 were pT1 grade 1, which I would
consider a low risk for recurrence. Of the patients 34% had lamina
propria invasion (pT1 grades 1 to 3). However, only 88 of the 387
papillary tumors were recurrent. Unfortunately, only 50 patients
were accrued who had carcinoma in situ, including 12 in the mito-
mycin C, 23 in the Tice BCG and 15 in the RIVM-BCG arm. These are
too few patients to draw any conclusions regarding the efficacy of any
of these drugs in the treatment of carcinoma in situ.

Treatment schedules vary considerably from that which is com-
monly practiced in the United States. Thirty mg. mitomycin C and 50
ml. saline were instilled once a week for 4 weeks and then once a
month for 6 months. In patients who had a recurrence at 3 months
the tumor was resected and the treatment was continued. However,
if a tumor was noted at 6 months 3 additional monthly treatments
were given. In comparing the results to Southwest Oncology Group
trials and most other large intravesical trials in the United States, it
is important to remember that cases with tumors at 3 or 6 months
are considered treatment failures (reference 4 in article).
In this study the envelope of treatment was extended and the case was not
considered a failure at 3 or 6 months. The administration of both
strains of BCG was accomplished on a 6-week basis, followed by another
6-week course at 3 and 6 months if recurrence was noted. This
initial 6-week treatment was standard at the institution of the study
but a recent Southwest Oncology Group protocol would favor
maintenance therapy for 6 weeks. There were no life threatening
toxicities in any of the treatment arms. In Southwest Oncology
Group studies we have reported 2 deaths from BCG. The authors
report a decreased incidence of local side effects as well as systemic
effects in the mitomycin C arm.

In a recently completed Southwest Oncology Group trial compar-
ing Tice BCG to mitomycin C, BCG significantly improved time to
recurrence (reference 21 in article). However, the dose of mitomycin
C as well as the administration schedule are different in this Dutch
trial. The current study emphasizes the continued role of intravesi-
cal chemotherapy, particularly with mitomycin C, to prevent recur-
rences of superficial bladder cancer. BCG immunotherapy is not the
gold standard for prophylaxis of superficial bladder cancer. However,
it seems to be the agent of choice when treating carcinoma in situ.

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