INTRAVESICAL ADJUVANT CHEMOTHERAPY FOR SUPERFICIAL TRANSITIONAL CELL BLADDER CARCINOMA: RESULTS OF 2 EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER RANDOMIZED TRIALS WITH MITOMYCIN C AND DOXORUBICIN COMPARING EARLY VERSUS DELAYED INSTILLATIONS AND SHORT-TERM VERSUS LONG-TERM TREATMENT

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ABSTRACT

The European Organization for Research and Treatment of Cancer genitourinary group has completed 2 parallel prospective randomized studies, one with 30 mg. mitomycin C and the other with 50 mg. doxorubicin as adjuvant intravesical treatment after transurethral resection of superficial transitional cell bladder carcinoma. These studies were designed to compare early (the day of resection) versus delayed (between 7 and 15 days after resection) instillations and short-term (6 months) versus long-term (12 months) treatment. The results indicate that in regard to recurrence rate patients having a delayed and short-term treatment do worse than those having early instillations (for 6 or 12 months) or those having prolonged treatment (either immediate or delayed). With an average followup of 4 years survival, progression beyond T1 disease, development of distant metastases and appearance of a second primary were not influenced by the therapeutic regimen. A multivariate analysis of prognostic factors is presented, which indicates that after adjustment for these factors, patients in the delay, no maintenance arm have a significantly higher recurrence rate than the other patients.

KEY WORDS: bladder neoplasms; carcinoma, transitional cell; chemotherapy, adjuvant

Administration of adjuvant intravesical chemotherapy or immunotherapy is a common practice today for the prophylaxis of recurrent superficial bladder cancer. Among the different agents used for this purpose, thiotepa, mitomycin C and doxorubicin have been shown to be active.1 Regimens based on these adjuvant treatments have often been established on an empirical basis, and are a compromise between potential toxic effects and aimed benefits. Many questions still remain unanswered in relation to the scheme of instillation. When is the ideal time to start the treatment? What is the ideal dosage at each instillation? What is the optimal duration of the treatment? What is the ideal interval between 2 instillations?2

In 1983 the genitourinary group of the European Organization for Research and Treatment of Cancer (EORTC) started 2 parallel trials, one with mitomycin C (protocol 30831) and one with doxorubicin (protocol 30832) to try to answer 2 questions: 1) what is the best time for initiation of adjuvant intravesical treatment and 2) how long should the drug be administered for prophylactic purpose after complete transurethral resection of superficial bladder cancer? The final results of these 2 studies are reported.

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MATERIALS AND METHODS

Objectives of the study. These 2 randomized clinical trials were designed to compare immediate instillations versus delayed instillations and short-term versus long-term treatment of mitomycin C (30831) or doxorubicin (30832) given intravesically after transurethral resection of superficial transitional cell carcinoma of the bladder with respect to duration of disease-free interval, recurrence rate including evaluation of the number of recurrent tumors, percentage of patients with an increase in the T category greater than T1, percentage in whom distant metastases develop, percentage in whom a second primary tumor develops and duration of survival.

Patient selection. Criteria for patient selection were similar to those used by the EORTC genitourinary group in previous superficial bladder cancer trials.3 All patients with completely resectable, stage Ta or T1 (0 or A), papillary transitional cell carcinoma of the bladder (single or multiple, primary or recurrent) were eligible for the 2 trials. Due to the early treatment pathological evaluation was not available at randomization and if tumors were not Ta or T1 patients were ineligible. Previous intravesical treatment with cytotoxic drugs was allowed (except for mitomycin C in 30831 and doxorubicin in 30832) provided there was at least a 3-month interval between the start of protocol treatment.

Criteria for exclusion were the presence of another cancer, previous treatment with local or systemic chemotherapy within 3 months of randomization, previous treatment with mitomycin C (30831) or with doxorubicin (30832), local ra-
intravesical adjuvant chemotherapy for bladder carcinoma

dioterapy within 12 months of randomization, patient general condition such that survival of 3 years was unlikely, expected difficulties of followup, blood urea or creatinine level increased more than 50% above the upper normal limit, white blood count less than 3,000/mm. and/or platelet count less than 100,000/mm. and untreated urinary tract infection.

Design of the trial. After transurethral resection, patients were centrally randomized at the EORTC data center to receive early or delayed instillations with stratification by institution. The choice of the drug was initially optional but each center had to adhere to its initial choice for the entire period of the study.

Protocol 30831: After endoscopic examination or immediately after transurethral resection patients were randomly assigned to receive early (on day 0) or delayed (between 7 and 15 days after transurethral resection) instillations of 30 mg. mitomycin C. The drug was instilled into the bladder in 50 ml. saline and retained for at least 1 hour. Instillations were given every week for 4 weeks and then every month for 5 months (a total of 9 instillations). After 6 months of treatment patients were randomized a second time between maintenance treatment, which consisted of 6 further instillations (1 every month for 6 months, total 15 instillations) or no maintenance (discontinue adjuvant treatment after the 9 initial instillations). Followup cystoscopy was performed every 3 months and if there was recurrence during treatment, the lesions were resected and the treatment was continued without any change to fulfill the initial regimen. Hemoglobin, white blood count and platelets, blood urea, creatinine, urinalysis and urine cytology had to be determined at each followup cystoscopy.

Protocol 30832: Patients were randomly assigned to receive early (day 0) or delayed (between days 7 and 15 after transurethral resection) instillations of 50 mg. doxorubicin. The remaining design of the protocol was identical to 30831.

Followup. All patients were to be followed until the second recurrence after randomization. Recurrences were detected by cystoscopy repeated every 3 months during year 1, every 4 months during year 2 and every 6 months thereafter (provided there was no recurrence in the meantime), and findings had to be confirmed by biopsy. After the second recurrence or if progression in stage to greater than T1 was documented, the patient was followed only for progression and survival, with further treatment at the urologist's discretion.

Criteria of evaluation. The disease-free interval (time to first recurrence) was defined as the total time between randomization at entry and the date of the first positive biopsy. Patients without recurrence were censored at the date of the last cystoscopic examination. The recurrence rate in a group of patients was defined as the total number of positive cystoscopies divided by the number of years of followup in that group (followup began at the initial randomization and ended at the last cystoscopy). All recurrences were histologically documented and initial biopsies were reviewed by a referee pathologist. The grading system recommended by the International Union Against Cancer (grades 1 to 3) was used and the staging was based on the tumor, nodes and metastasis system (Geneva, 1982). The duration of survival and percentage of patients with local or distant progression or a second primary tumor were also evaluated.

Statistical methods. The time to first recurrence and duration of survival were estimated using the Kaplan-Meier product limit estimate and compared using the log rank test. For ordered variables with more than 2 categories a log rank test for trend was used. In order to account for the number and frequency of recurrences that were noted, the recurrence rate was also calculated and compared using a nonparametric permutation test. The relative prognostic importance of various factors on the recurrence rate was studied in a multivariate linear logistic regression model taking as an end point the number of positive cystoscopies divided by the total number of cystoscopies.

RESULTS

Clinical material. From August 1983 until January 1986, 965 patients were entered in these 2 studies, including 517 in protocol 30831 and 448 in protocol 30832. A total of 483 patients was randomized to early treatment and 482 to delayed treatment. A total of 625 patients was randomized a second time, including 312 to maintenance and 313 to no maintenance. There were 113 patients (60 in 30831 and 53 in 30832) ineligible for the study because of incorrect T category or cell type (86), distant metastases or second malignancy (6), previous treatment with mitomycin C or doxorubicin (6) and miscellaneous reasons (15). Of the 852 remaining patients no information was available for 18 in protocol 30832, thus leaving 834 patients for whom at least information on entry on study was available, including 457 entered by 28 institutions in protocol 30831 and 377 entered by 20 institutions in protocol 30832. Table 1 provides the distribution of the 834 eligible patients by treatment group. Of the patients 215 were not randomized a second time (after 6 months) because of intercurrent death, progression or second recurrence (60), loss to followup (64), toxicity (20), treatment refusal (18), protocol violation or other reasons (53).

Patient characteristics at entry on study. Characteristics at entry on study for the 834 eligible patients are given by protocol in table 2. While the patient characteristics were well balanced in the different treatment groups, table 2 shows that patients entered in protocol 30831 generally tended to have a worse prognosis than those entered in 30832. There was a higher percentage of recurrent cases (72% versus 37%) and recurrent cases with a prior recurrence rate of greater than 1 recurrence per year (41% versus 16%). Patients in 30831 also tended to have more tumors at entry on study (32% versus 16% had more than 3 tumors at entry) but they also had a slightly higher incidence of Ta tumors (63% versus 51%).

Toxicity. Local toxicity (cystitis) was a minor problem in both studies. In 30831 bacterial and chemical cystitis necessitated delay or discontinuation of mitomycin C in 26 of 449 patients (6%). The incidence of chemical cystitis requiring an arrest of treatment was higher in the early instillation scheme (3%) than in the delayed scheme (0%). In 30832 bacterial and/or chemical cystitis requiring a delay or discontinuation of treatment occurred in 34 of 368 patients (9%). The incidence of chemical cystitis requiring discontinuation of treatment was higher in the early instillation scheme (2.2%) than in the delayed scheme (0.5%).

Systemic toxicity was never life threatening. In 30831 allergic reactions were reported by 31 of 449 patients (7%), including 19 (4.2%) in whom these reactions were mild and did not require any alteration of instillation treatment, while in 8 (1.8%) the severity of the reaction required discontinuation of the instillations. In 30832 systemic toxicity was reported in 26 of 368 patients (7.1%) requiring discontinua-

<table>
<thead>
<tr>
<th>Protocol Treatment</th>
<th>30831 Mitomycin C</th>
<th>30832 Doxorubicin</th>
<th>Total Mitomycin C + Doxorubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>First randomization:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>228</td>
<td>188</td>
<td>417</td>
</tr>
<tr>
<td>Delayed</td>
<td>229</td>
<td>188</td>
<td>417</td>
</tr>
<tr>
<td>Totals</td>
<td>457</td>
<td>377</td>
<td>834</td>
</tr>
<tr>
<td>Second randomization:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No maintenance</td>
<td>171</td>
<td>143</td>
<td>314</td>
</tr>
<tr>
<td>Maintenance</td>
<td>165</td>
<td>140</td>
<td>305</td>
</tr>
<tr>
<td>Not randomized</td>
<td>121</td>
<td>94</td>
<td>215</td>
</tr>
<tr>
<td>Totals</td>
<td>457</td>
<td>377</td>
<td>834</td>
</tr>
</tbody>
</table>
Of the 834 eligible patients no followup for recurrence was available for 82. Thus, the efficacy analyses for time to first recurrence, recurrence rate and tumor invasion (greater than T1) are based on the 752 eligible patients for whom followup cystoscopy was available. Analyses of distant metastases, second primaries and survival are based on the 824 patients for whom followup of any type was available.

**Disease-free interval (time to first recurrence).** Based on an average followup of 2.75 years 161 of 374 patients (43%) on early treatment had at least 1 recurrence compared to 187 of 378 (49%) on delayed treatment. Comparison of the time to first recurrence based on a 2 sided log rank test was not significant (p = 0.18). Followup data after the second randomization were available for 617 of the 619 patients randomized a second time there was no significant difference in the percentage with tumor invasion.

**Tumor invasion.** Based on a maximum followup of 6.5 years and an average followup of 4 years of 374 patients (11%) on early treatment compared to 38 of 378 (10%) on delayed treatment had an increase in T category to greater than T1 during followup. Concerning maintenance treatment, 25 of 314 patients (8%) not receiving maintenance and 26 of 303 (9%) on maintenance had tumor invasion.

**Distant metastases.** Of 412 patients on early treatment 24 (6%) compared to 17 of 412 (4%) on delayed treatment had distant metastases during followup. Concerning maintenance treatment, 13 of 314 patients (4%) not receiving maintenance and 12 of 304 (4%) on maintenance had distant metastases.

**Second primaries.** In 28 of 412 patients (7%) on early treatment and 25 of 412 (6%) on delayed treatment second primary tumors developed during followup. In 21 of 314 patients (7%) not receiving maintenance compared to 15 of 304 (5%) on maintenance second primaries developed.

**Survival.** Of 824 eligible patients with followup 164 (20%) died, including 74 (9%) of cardiovascular disease and 48 (6%) of malignant disease. Of 412 patients on early treatment 78 (19%) compared to 86 of 412 (21%) on delayed treatment died. The difference in the duration of survival is not statistically significant (p = 0.60). Of 314 patients not receiving maintenance 63 (20%) and of 304 patients on maintenance 53 (17%) died. The difference in the duration of survival is not statistically significant (p = 0.41).

Table 5 presents the percentage of patients in whom metastases developed, who presented with a second primary tumor and who died according to the different cross classifications of the different groups. For the patients who were randomized a second time there was no significant difference among the 4 groups. Figure 2 presents the duration of survival by treatment group. For the patients who were randomized a second time there was no significant difference in the duration of survival.

**Adjustment for prognostic factors.** The prognostic importance of the following factors was studied: number of tumors—1, 2 to 3, greater than 3; previous recurrence rate—primary, recurrence less than 1 per year, recurrence 1 or more per year; T category—Ta, T1; size of largest tumor diameter—less than 3 cm., 3 cm. or more; tumor status—primary, recurrent; grade—1, 2 to 3; protocol—30831 (mitomycin C), 30832 (doxorubicin); age—less than 50 years, 50 or older; sex—male, female; first randomization—early treatment, delayed treatment; second randomization—no maintenance, maintenance; and treatment interaction—delayed, no maintenance, other.

The prognostic importance of these factors on the recurrence rate was studied in a univariate analysis using the permutation test and then in a multivariate linear logistic regression model taking as an end point the number of positive cystoscopies divided by the total number of cystoscopies. Univariate analyses showed the first 7 variables to be of prognostic importance (p < 0.01). The multivariate model retained the first 4 variables as being the most significant...
INTRAVESICAL ADJUVANT CHEMOTHERAPY FOR BLADDER CARCINOMA

Probability

TIME TO FIRST RECURRENCE

Fig. 1. Time to first recurrence according to different cross classifications of treatment groups. E-NM, early treatment, no maintenance. E-M, early treatment, maintenance. D-NM, delayed treatment, no maintenance. D-M, delayed treatment, maintenance.

Table 3. Recurrence rate by treatment group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. Pts.</th>
<th>Recurrence Rate/Yr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early treatment, no maintenance</td>
<td>160</td>
<td>0.23</td>
</tr>
<tr>
<td>Early treatment, maintenance</td>
<td>150</td>
<td>0.25</td>
</tr>
<tr>
<td>Delayed treatment, no maintenance</td>
<td>154</td>
<td>0.33</td>
</tr>
<tr>
<td>Delayed treatment, maintenance</td>
<td>153</td>
<td>0.22</td>
</tr>
<tr>
<td>Early treatment only</td>
<td>64</td>
<td>1.20</td>
</tr>
<tr>
<td>Delayed treatment only</td>
<td>71</td>
<td>1.71</td>
</tr>
</tbody>
</table>

Early treatment, no maintenance versus delayed treatment, no maintenance \( p = 0.01 \); early treatment, maintenance versus delayed treatment, no maintenance \( p = 0.09 \) and delayed treatment, maintenance versus delayed treatment, no maintenance \( p = 0.01 \).

Table 4. Invasion (greater than T1) by treatment group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. Pts.</th>
<th>No. Invasion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early treatment, no maintenance</td>
<td>160</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Early treatment, maintenance</td>
<td>150</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Delayed treatment, no maintenance</td>
<td>154</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Delayed treatment, maintenance</td>
<td>153</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Early treatment only</td>
<td>64</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Delayed treatment only</td>
<td>71</td>
<td>18 (28)</td>
</tr>
</tbody>
</table>

For patients who were randomized a second time inclusion of a treatment interaction term (delay, no maintenance versus other) significantly improved the model \( (p = 0.001) \). Thus, after adjustment of the prognostic factors patients in the delay, no maintenance arm had a significantly higher recurrence rate than the other patients.

Considering the 4 most important prognostic factors, risk groups were formed based on the number of poor prognostic factors (more than 1 tumor, recurrence, T1, 3 cm. or more) a patient possessed. Patients were divided into 4 risk groups with differing prognoses as shown in Table 6. While the same trends were seen with each of the 4 risk groups, the greatest treatment benefit appeared in patients with just 1 poor factor (the best prognosis group with no poor factor had too few
INTRAVESICAL ADJUVANT CHEMOTHERAPY FOR BLADDER CARCINOMA

Probability

DURATION OF SURVIVAL

30831/32

Fig. 2. Duration of survival by treatment groups. E-NM, early treatment, no maintenance. E-M, early treatment, maintenance. D-NM, delayed treatment, no maintenance. D-M, delayed treatment, maintenance.

Table 6. Risk groups based on poor prognostic factors

<table>
<thead>
<tr>
<th>No. Poor Factors</th>
<th>No. Pts.</th>
<th>Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>129</td>
<td>0.09</td>
</tr>
<tr>
<td>1</td>
<td>281</td>
<td>0.20</td>
</tr>
<tr>
<td>2</td>
<td>269</td>
<td>0.36</td>
</tr>
<tr>
<td>3 or 4</td>
<td>171</td>
<td>0.63</td>
</tr>
</tbody>
</table>

There are different possible explanations for recurrence of the tumors. Incomplete resection can leave tumors or parts of tumors that are at the origin of regrowth. In EORTC protocol 30790, 75% of the early recurrences were at the same site as the previous tumors. Implantation of floating neoplastic cells was a concept first advanced in 1903 by Albarran and Imbert, and it was demonstrated through an animal experiment performed by Soloway et al. It is also supported by the results of some clinical trials that indicate that a single instillation of a cytostatic agent at the time of transurethral resection is able to reduce the recurrence rate compared to resection alone. In patients with papillary disease hyperplasia, atypia or dysplasia may be discovered in apparently normal areas of the bladder and recurrences are more frequent in these cases than in those without urothelial abnormalities.

If implantation and incomplete resection are responsible for some true recurrences, an early (and intensive) regimen...
of instillations after transurethral resection should be recommended to destroy the floating cells (or the residual papillary tumors). If urothelial instability is the major cause of subsequent tumors, a long-term intravesical treatment is advised to destroy the abnormal cells that appear in different areas of the bladder.\textsuperscript{12,16,23-25}

The literature provides some data about the value of early and/or long-term instillations but there are few prospective randomized trials comparing the time of first instillation and the duration of treatment. Some studies favor immediate treatment after transurethral resection.\textsuperscript{12,26-29} The results of a Medical Research Council study comparing early thiotepa, delayed thiotepa and no treatment showed a 5\% lower incidence of recurrence in the control group than in the treatment groups.\textsuperscript{30} There are no studies on early intravesical treatment with BCG; an interval of 15 to 30 days between transurethral resection and start of treatment is recommended with this drug to avoid resorption and possible important systemic toxicity. In regard to maintenance, the results of the literature are also somewhat contradictory, not only for chemotherapeutic agents\textsuperscript{11,31,32} but also for BCG.\textsuperscript{33-35}

In these 2 EORTC genitourinary group trials, including 834 eligible patients, the global analysis shows that the disease free-interval was not influenced by the time of the first instillation nor was the recurrence rate, although there was a trend in favor of early treatment. However, when the influence of the time of the first instillation was analyzed separately for each protocol, the results were slightly different. In protocol 30831 (mitomycin C), with relatively poor prognostic factors, early were not better than delayed instillations, while in protocol 30832 (doxorubicin), with better prognostic factors, early instillations provided better results than delayed treatment.

An analysis of the duration of the treatment did not show any benefit for maintenance compared to nonmaintenance treatment. Based on 617 patients with an average followup of 36 months, there was no difference in the recurrence rate, which remained true when the influence of the duration of the treatment was analyzed separately in trials 30831 and 30832. When both trials were combined the analysis of the results indicated that patients receiving early treatment (with or without maintenance) and those receiving delayed treatment with maintenance tended to have less recurrences than those receiving delayed and short-term treatment.

Like other trials with at least as long a followup, these protocols could not show that progression of the disease or survival was influenced by the treatment regimen. Since progression in stage may logically be related to more aggressive recurrences, there is no clear explanation why adjuvant treatment, which is able to reduce the recurrence rate, is not able to reduce the incidence of progression. A probable explanation is that the number of patients with progression in any 1 trial is too small to detect differences of reasonable magnitude. This finding emphasizes the need for large meta-analyses, which have been undertaken by the EORTC genitourinary group. When the results were adjusted for prognostic factors, a multivariate analysis showed that treatment effect was highly significant and that patients in the delay,
no maintenance arm had a significantly higher recurrence rate than the other patients (p = 0.001).

CONCLUSIONS

These 2 EORTC genitourinary group phase III trials indicate in regard to recurrence rate that early treatment after transurethral resection seems to be slightly superior to delayed treatment (mainly in the good prognostic tumors) and it appears to be really effective in the no maintenance group. Also, maintenance alone has no benefit except in the delayed treatment group. These differences are at the limit of the statistical confidence but they become much stronger when the results are adjusted for prognostic factors. Results of early, maintenance; early, no maintenance and delayed, maintenance are not different but they are significantly superior to those of delayed, no maintenance treatment. This finding indicates that when intravesical adjuvant chemotherapy but not BCG is considered, if early treatment is elected, it is not necessary to prolong it but if the first instillation is not performed within 24 hours of transurethral resection it is wiser to maintain the treatment for a longer period. These 2 studies could not show that progression in stage or survival was influenced by the treatment regimen but this is probably related to the low percentage of patients with superficial disease who have progression towards infiltrative disease. This finding stresses the need for large meta-analyses. For this reason, patients entered in these studies are still being followed for progression and survival.

REFERENCES


