European Urology

European Urology 45 (2004) 600–605

Effect of Prophylactic Treatment with Intravesical Epirubicin on Recurrence of Superficial Bladder Cancer—The 6th Trial of the Japanese Urological Cancer Research Group (JUCRG): A Randomized Trial of Intravesical Epirubicin at Dose of 20 mg/40 ml, 30 mg/40 ml, 40 mg/40 ml

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Accepted 8 December 2003

Published online 11 January 2004

Abstract

Objectives: We compared the prophylactic efficacy and safety of epirubicin (EPI) in primary superficial bladder cancer.

Methods: The major inclusion criteria were primary superficial bladder tumour (Ta, T1, G1, G2) and new cases of primary multiple tumours, or recurrent cases. The major exclusion criteria were Tis or G3 tumours. Group A received 17 doses of EPI 20 mg/40 ml over a period of 12 months for a total dose of 340 mg. In contrast, Group B received 12 doses of EPI 30 mg/40 ml over a period of 7 months, while Group C received 9 doses of EPI 40 mg/40 ml over a period of 4 months, both for a total dose of 360 mg. This study enrolled a total of 622 patients diagnosed as having primary superficial bladder cancer during the period from June 1994 through November 1996 at the 118 institutions. Follow-up of the patients was conducted through October 1999.

Results: The relationship between the EPI concentration and the recurrence-free rate was evaluated by Tarone's test, and it was found that the recurrence-free rate became significantly higher as the drug concentration increased ($p = 0.0375$). In the safety evaluation, with regard to adverse drug reactions, pollakiuria and pain on urination occurred at significantly higher incidences as the concentration of the EPI solution increased.

Conclusions: The greatest effect of intravesical instillation of EPI after TUR-BT was shown by the regimen using the highest concentration of the drug solution which was administered during a short period of time.

Keywords: Epirubicin; Intravesical instillation; Superficial bladder cancer; Prophylaxis

1. Background

Superficial bladder cancer accounts for 60–70% of all bladder cancer cases in Japan, and almost all of those patients are treated by transurethral resection of the bladder (TUR-BT) [1–3]. However, when treatment consists of only TUR-BT, recurrence in the bladder is observed in 60–70% of the patients [4], and the disease progresses to invasive cancer in some patients. There are numerous reports of trials of intravesical instillation of anticancer agents with the objective of lowering this recurrence rate. The principal anticancer agents that have been tested include mitomycin, doxorubicin, epirubicin (EPI), etc. In recent years, BCG has also

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doi:10.1016/j.eururo.2003.12.010

been widely used. Nevertheless, there is still no established regimen.

The fifth randomized clinical trial of the Japanese Urological Cancer Research Group (JUCRG) [5] found doxorubicin and epirubicin to show equivalent prophylactic efficacy, but blood tests revealed that EPI caused slightly fewer drug adverse reactions than doxorubicin. For this reason, it was decided to use EPI in the present sixth trial, which was designed as a randomized study. By this time, however, the optimal concentration of EPI was not known, and we conducted a study on different concentrations and regimen intensities on a large scale.

2. Objective

For the present study, an EPI regimen, which was found to be useful in terms of the recurrence-free period in the fifth Japanese trial, was used as the control group. The total EPI dose was kept constant, while the drug concentration was increased and the number of doses and the duration of treatment were reduced in two other groups to increase the dose intensity. The endpoints in the study was the recurrence free period and rate. The second endpoint was the safety of the three regimens.

3. Patients and methods

The regimen which had shown the highest prophylactic efficacy in the previous five trials was used as the control group (Group A) in the present trial. For comparison, two other groups (Group B and Group C) were administered approximately the same total EPI dose as the control, but in a smaller number of higher individual doses instilled over a shorter period of time. Diagrams in Fig. 1 show those three regimens. That is, Group A received 17 doses of EPI 20 mg/40 ml over a period of 12 months for a total dose of 340 mg.

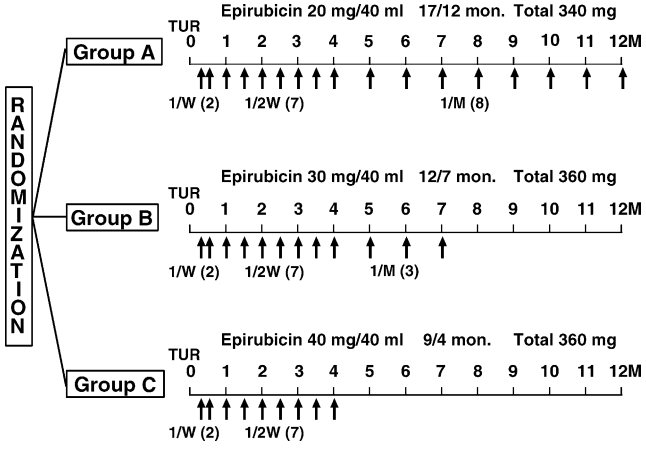

Fig. 1. Regimen adopted in the sixth JUCRG study.

In contrast, Group B received 12 doses of EPI 30 mg/40 ml over a period of 7 months for a total dose of 360 mg, while Group C received 9 doses of EPI 40 mg/40 ml over a period of 4 months for a total dose of 360 mg. The instilled volume at the time of each treatment was thus the same in all three groups.

This study enrolled a total of 622 patients who had been diagnosed as having primary superficial bladder cancer during the period from June 1994 through November 1996 at the 118 institutions (Table 1) participating in this trial. All patients granted informed consent and were randomly allocated to the three treatment groups. The following are the patient inclusion criteria and the exclusion criteria.

Patient inclusion criteria were

1. any primary or recurrent Ta or T1, G1 or G2 transitional cell carcinoma of the bladder;
2. patients who underwent curative resection by TUR-BT;
3. any age, gender and PS;
4. informed consent was obtained from patients before entry onto the study.

Patient exclusion criteria were

1. patients with Tis or G3 tumours;
2. patients with primary and solitary tumour;
3. patients with any other severe illness.

The enrollment was performed by telephone or facsimile contact with the Patient Registration Center. Random allocation to the treatment groups was done by the central enrollment method. At the time of allocation, the patients were assigned to the three groups in a ratio of 1:1:1 using a dynamic randomization method which took into consideration the status of recurrence (i.e., primary and single; recurrent and single; recurrent and multiple), stage, grade, tumour diameter and institution.

Table 2 describes the details of the method of administration of the EPI regimens to the three groups. All patients had given informed consent prior to undergoing TUR-BT and again prior to inclusion in the present EPI trial. Enrollment was performed after the patient was diagnosed as having bladder cancer (transitional cell carcinoma) on the basis of histopathological examination of the resected tissue.

Bladder instillations were started after approximately 1 week of the TUR-BT. The assigned EPI solution was instilled into the bladder in accordance with the administration method described below. In principle, the drug solution was to be retained in the bladder for 1 hour. The patient was instructed to change of body position for the EPI solution to make good contact with the whole bladder mucosa. Follow-up of the patients was conducted through October 1999. Observation period of all enrolled cases was 12 days in shortest, 1909 days in longest and the median was 1288 days.

The patients were examined by cystoscopy every 3 months after the TUR-BT to determine whether or not there had been recurrence of the bladder cancer. In addition, in principle, concomitant administration was prohibited in the case of drugs which might influence the assessment of the inhibitory effect of the administered EPI regimens on recurrence of the bladder cancer. When coadministration of a drug was unavoidable, the details of that treatment were described on the case card. The patients went off-study at first recurrence or severe toxicity.

3.1. Statistical analysis

Comparison of the efficacy of the EPI regimens in the three treatment groups was carried out by Tarone's method [6] (i.e., for