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Chemoimmunotherapy for prophylaxis of recurrence in superficial bladder cancer: interferon-α2b versus interferon-α2b with epirubicin

P Ferrari,[CA] G Castagnetti, CA Pollastri, G Ferrari, F Tavoni and D Grassi

The authors are at the Department of Urology, University of Modena, Italy.

Eighty-five patients who had undergone transurethral resection (TUR) of superficial bladder cancer were randomized to one of two treatments. Patients in Group 1 received a 10-month course of intravesical therapy with interferon (IFN)-α2b (50 MU dose), commencing 21 days after TUR once a week for 8 weeks, then once every 15 days for 4 months and then finally once a month for 4 months. Patients in Group 2 received epirubicin (80 mg) intravesically 0, 24 and 48 h after TUR, and then 21 days after TUR received IFN-α2b as for Group 1. The results confirmed the efficacy of immunoprophylaxis with IFN-α2b, and early treatment with epirubicin tended to further reduce the percentage of relapses and extended the disease-free interval.

Key words: Epirubicin, interferon-α2b, intravesical therapy, superficial bladder cancer

Introduction

Even though bladder cancer is usually localized at diagnosis, as many as 85% of patients will eventually develop recurrent tumors after initial treatment.[1] Transurethral resection (TUR) with fulguration of the tumor is the most common approach to treatment of superficial bladder cancer. However, as the probability of recurrence with TUR alone is high, intravesical chemotherapy and/or immunotherapy is routinely used to reduce both the number of recurrences and the chance of tumor cells seeding during resection and to treat undetectable areas of disease or residual lesions. This study was designed to investigate the efficacy and toxicity of intravesical therapy with interferon (IFN)-α2b with or without epirubicin for prophylaxis of recurrence of superficial bladder cancer following TUR of all visible tumor.

Materials and methods

A total of 85 patients were treated. All had undergone TUR, removing all visible tumor, followed by multiple deep cold biopsies from the tumor resection site to rule out any infiltration of the bladder wall. At this time bladder mapping, consisting of eight random biopsies from various areas of the bladder, was performed to identify areas of carcinoma *in situ*. Initial histologic tumor grading is shown in Table 1.

Patients were randomized to receive intravesical IFN-α2b, either alone or in combination with epirubicin. For patients in Group 1 (41 patients; 35 men, six women) treatment was started 21 days after TUR; 50 MU IFN-α2b was instilled into the bladder in 100 ml of sterile solution and retained for 2 h. Treatment was carried out once a week for 8 weeks, then once every 15 days for 4 months and then finally once a month for 4 months. Patients in Group 2 (44 patients; 37 men, seven women) received 80 mg of epirubicin intravesically immediately after TUR, and again 24 and 48 h later. The epirubicin was instilled as 100 ml sterile solution and was retained in the bladder for 1 h. At 21 days after TUR IFN-α2b was administered as for Group 1. Urethrocystoscopy was performed every 2 months during treatment and cytologic examinations were carried out on samples from bladder washings and voided urine. At the end of the treatment period (total time of 10 months) urethrocystoscopy with bladder mapping and intravenous urography was performed on all patients.

[CA] Corresponding Author

Table 1. Initial histologic tumor grading

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Group 1 (41 patients)	12 (29.3)	24 (58.5)	5 (12.1)
Group 2 (44 patients)	10 (22.7)	29 (65.9)	5 (11.3)

Results

Evaluation of efficacy of treatments

The median follow-up time was 19 months (range 2–32 months). During this period a total of 17 patients (20%) relapsed, 10 (24.4%) in Group 1 and seven (15.9%) in Group 2, thus early treatment with epirubicin tended to reduce the occurrence of relapse, though this difference was not statistically significant. Relapses occurring according to initial grade of tumor are shown in Table 2. No increases in grading of tumor were observed in cases of relapse and no infiltration was seen.

The number of patients in each treatment group first showing recurrence of disease at 4, 6, 8, 12 and 18 months after the end of treatment is shown in Figure 1. Fewer patients from Group 2 (epirubicin plus IFN-α2b) relapsed during the first 8 months after cessation of treatment (three patients versus six patients in Group 1) though this difference was not statistically significant. At 12 and 18 months' follow up the number of patients first showing recurrence of disease was the same in the two treatment groups. As of August 1990, 68 patients remained tumor free.

Evaluation of toxicity of treatments

The systemic side effects typically associated with IFN-α2b therapy, such as fever, arthralgia and bone pain, were not seen in any patient. Also, none of the typical side effects of epirubicin treatment, such as cardiotoxicity or leukopenia, were reported, even though high doses of the drug were used. Chemical cystitis, a local side effect, developed in seven patients from Group 1 and in six patients from Group 2, and was treated symptomatically. Bacterial cystitis was not seen. Three women from Group 1 developed eczema around the soft tissue of the urethra and vagina. IFN-α2b treatment was discontinued for 2 weeks in these women, and they received systemic and topical hydrocortisone to relieve the condition.

Discussion

Randomized trials have shown that the disease-free interval after TUR can be prolonged and the relapse rate reduced with the intravesical use of chemotherapeutic agents. Agents used intravesically should ideally be sparingly absorbed systemically, thus enabling the local lesions to be exposed to high drug concentrations, while minimizing or avoiding systemic toxicity.[2]

Transitional cell carcinoma (which constitutes over 90% of bladder cancers in the Western world) expresses cell surface antigens and during the development of malignancy the immune reaction to certain antigens can be lost.[3–7] The rationale for intravesical immunotherapy is thus based on the hypothesis that an immune stimulant, placed in contact with superficial bladder cells will stimulate a host response to tumor cells. Other possible actions of immunotherapeutic agents include direct effects on tumor cells, such as cytolysis or a

Table 2. Number and percentage of patients with initial tumor Grades 1, 2 and 3 in whom relapse occurred

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Total relapse (%)
Group 1 (41 patients)	0/12 (0)	8/24 (33.3)	2/5 (40)	10/41 (24.4)
Group 2 (44 patients)	1/10 (10)	4/29 (13.8)	2/5 (40)	7/44 (15.9)

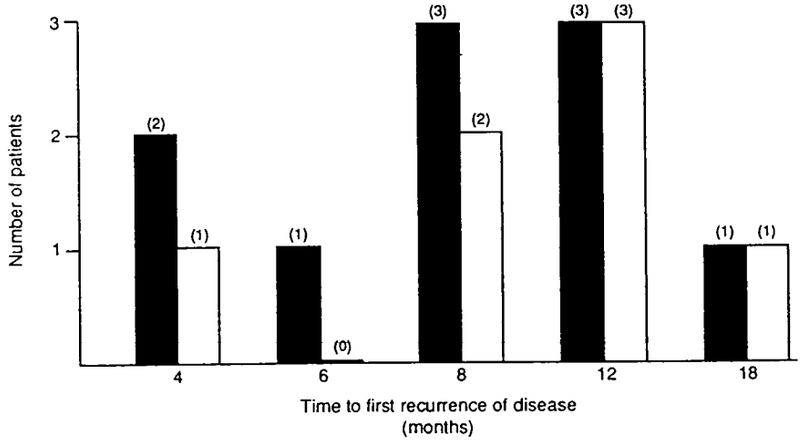

Figure 1. Recurrence of disease following treatment with IFN-α2b only (Group 1, ■) or IFN-α2b following epirubicin therapy (Group 2, □).

maturational response. Selected microbial products such as *Bacillus Calmette-Guérin* (BCG) and lymphokines, primarily interleukins and IFN, represent the two groups of immunomodulatory agents currently under investigation for intravesical treatment of superficial bladder cancer. IFNs are thought to exert their antineoplastic actions by their antiproliferative effects (inhibiting tumor cell division by depressing oncogene expression) and by immunomodulation. There have been a number of studies demonstrating the efficacy and low toxicity of intravesical IFN therapy in superficial bladder cancer.[8–10] This study has confirmed the efficacy of IFN-α2b for the prevention of recurrence of superficial bladder cancer and has shown that early treatment with intravesical epirubicin in combination may further reduce the incidence of relapse and prolong the disease-free period.

Conclusion

This study compared two intravesical treatments for the prevention of recurrence of superficial bladder cancer following TUR. The data confirm the efficacy of immunoprophylaxis with IFN-α2b. Even though there were no statistically significant differences (significance accepted at $p < 0.05$) between the percentages of relapse in the two groups, early treatment with epirubicin followed by IFN-α2b tended to further reduce the percentage of relapses and extended the disease-free interval.

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