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Prospective, randomized trial to evaluate high- versus low-dose interferon-α2b versus conventional chemotherapy in prevention of the recurrence of superficial transitional cell carcinoma of the urinary bladder

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Forty-four patients with superficial bladder cancer were randomized to receive 10 MU (14 patients) or 100 MU (14 patients) of interferon (IFN)-α2b or 1.3 g ethoglucid (16 patients) instilled into the bladder once weekly for 10 weeks and then monthly for 1 year. Efficacy (evaluated in 34 patients who completed the course of treatment), based on recurrence rate and time to first recurrence, was similar in the three groups. No systemic toxicity of treatment was seen. Severe chemocystitis occurred in some patients who received ethoglucid (three had to discontinue treatment), while no local toxicity was seen with IFN-α2b treatment.

Key words: Ethoglucid, interferon-α2b, superficial bladder cancer

Introduction

It has been recognized for many years that bladder cancer is closely associated with modulation of the immune system and that reactivity to surface antigens, such as those of the ABO blood group and the T group, is often lost with the development of the disease.[1–3] These observations, in addition to the fact that the bladder mucosa is easily accessible for direct topical application of drugs, have led to the development of immunotherapeutic methods of treating bladder cancer. *Bacillus Calmette-Guérin* (BCG) is an established therapy for superficial bladder cancer, and experimental and clinical findings have shown that circulating levels of interferon (IFN) are increased with BCG therapy.[4] However, it is not yet certain if the cytotoxic, cytostatic or immunomodulatory activities of BCG treatment are due to the increased circulating IFN levels.[5] The effects of both recombinant and non-recombinant IFN, used in different modes of application, have been studied in superficial bladder cancer.[6–9] It has been shown that antiproliferative effects of IFN on human bladder carcinoma cell lines are dependent upon the dose used and the exposure time.[10,11]

Encouraged by the results of phase I–II studies, which have suggested that IFN might be useful in the treatment of superficial bladder cancer, a controlled, randomized phase III trial was designed to compare the prophylactic efficacy of high-dose IFN-α2b versus low-dose IFN-α2b versus the chemotherapeutic agent ethoglucid (each administered topically). The aim of the study was to define the therapeutic efficacy of topical IFN-α2b.

Materials and methods

Patient selection and treatment groups

A total of 44 patients were admitted to the study and were randomized to one of three treatment groups. Group 1 was to receive low-dose (10 MU) IFN-α2b; Group 2 high-dose (100 MU) IFN-α2b and Group 3 ethoglucid (1.13 g). Details ofnumber and age of patients in each group are given in Table 1.

Inclusion criteria for the study required patients to have histologically documented primary grade 1 or 2 transitional cell carcinoma (TCC) of the bladder of stage T_a, T_1 or T_{is} or if they had recurrent grade 1 tumor, stage T_a, T_1. All visible tumor was removed by transurethral resection and multiple random biopsies taken. Table 2 shows the initial number (single or multiple), grade and category of tumor(s) for patients from each treatment group and also the number of cases of primary and recurrent disease.

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Table 1. Total number, number of male and female patients, median age and age range of patients

	Group 1 (low-dose IFN)	Group 2 (high-dose IFN)	Group 3 (ethoglucid)
Total patients	13	11	10
Male	10	6	6
Female	3	5	4
Median age (years)	68.1	67.6	72.6
Age range (years)	52–84	44–85	61–89

Table 2. Number, grade category of tumor(s) in Groups 1, 2 and 3, and the incidence of primary and recurrent disease

	Group 1 (low-dose IFN)	Group 2 (high-dose IFN)	Group 3 (ethoglucid)
Primary tumor	6	4	5
Recurrent disease	7	7	5
Number of tumors			
Single	7	4	5
Multiple	6	7	5
Grade of tumor			
1	10	8	7
2	2	2	2
3	1	1	1
Category of tumor			
T_a	1	0	1
T_1	11	10	8
T_{is}	1	1	1

Exclusion criteria included prior intravesical or systemic chemotherapy or immunotherapy, pelvic irradiation within the previous 3 months and a documented history of other malignancies except for non-metastatic skin cancer.

Experimental procedure

Treatment was started within 36 h after complete resection of all visible tumor. IFN-α2b (10 or 100 MU), reconstituted in 30 ml sterile pyrogen-free water, was instilled into the bladder by catheterization once weekly for 10 weeks and then monthly for 1 year. Ethoglucid (1.13 g) was dissolved in 100 ml sterile pyrogen-free water and also instilled into the bladder once weekly for 10 weeks and then monthly for 1 year. Cystoscopy and cytology were used to establish disease status in all patients prior to the initiation of therapy and then before the 3, 6, 9 and 12 month treatments.

Results

All 44 patients initially enroled for the study were evaluated for toxicity of treatment. However, only 34 patients were available for evaluation of response to treatment. Table 3 gives details of 'drop-outs' in each of the treatment groups.

Evaluation of efficacy

The recurrence rate, defined as the quotient of the number of recurrent tumors multiplied by 100, was calculated as a measure of the efficacy of the treatments. The median recurrence rate for all patients was 4.11; for Group 1, 4.84; for Group 2, 3.85; and Group 3, 3.49. The median time to first recurrence for Groups 1, 2 and 3 was 22.23, 22.36 and 21.76 months, respectively. Recurrence rates and times to first recurrence were analyzed by the χ^2 test, which showed no statistically significant differences (at $p < 0.05$).

Table 3. Data on 'drop-out' and follow up

	Group 1 (low-dose IFN)	Group 2 (high-dose IFN)	Group 3 (ethoglucid)
Patients available for evaluation of response ($n = 34$)	13	11	10
'Drop-out' rate ($n = 10$)	1	3	6
Reason for 'drop out'			
Other malignancy	1[a]	—	—
Death (unrelated to treatment)	—	1 (stroke)	1 (myocardial infarction)
Non-compliance (unspecified)	—	2	2
Non-compliance (due to chemocystitis)	—	—	3
Mean follow-up period in months (range)	34.9 (8–52)	37.7 (3–52)	27.2 (6–52)

[a] Patient developed non-Hodgkin lymphoma.

Evaluation of toxicity

No systemic toxicity was reported in any of the treatment groups. Local toxicity, such as chemocystitis and dysuric symptoms, occurred only in the ethoglucid-treated group (Group 3) and for three of the patients the severity of the chemocystitis was such that they had to withdraw from treatment.

Discussion

As with topical chemotherapy, the mechanism(s) by which topically applied IFN exerts its therapeutic effect has not been clearly identified and there are experimental data reporting both direct and indirect mechanisms. IFNs have been shown to affect malignant cells directly by cytotoxic, cytostatic, antiproliferative or differentiating effects, including changing the phenotype and metabolism of the cells, or inhibiting important cellular genes such as oncogenes. They also have indirect influence on cells of the immune system, such as natural killer (NK) cells, T cells and macrophages. Results from clinical trials of IFNs in the treatment of human cancers imply that the direct effects on tumor cellsare primarily responsible for the antitumor activity.[12,13]

The study reported here showed that topically applied IFN-α2b (10 and 100 MU per dose) was an effective treatment for prevention of recurrence of superficial bladder cancer. While the efficacy of IFN-α2b was comparable to that of ethoglucid, in this study treatment with IFN-α2b did not cause any local toxicity, while some patients who received ethoglucid experienced chemocystitis which was so severe that treatment had to be discontinued. However, the cost of treatment with IFN was at least 10-fold greater than with ethoglucid, which has to be taken into account if it is to be considered as a routine method of treatment for this disease. In future trials, with larger patient populations, it would be desirable to identify those patients with superficial bladder cancer who would be most likely to benefit from topical IFN treatment, based on the stage and grade of tumor present at initial examination. The most effective treatment schedule would then be determined. There is evidence to suggest that IFN may be more effective if the tumor is only a few layers in thickness because its activity is dependent on penetration of the drug and also that it may be more active against less well-differentiated tumors. This has also been shown using IFN for intraperitoneal treatment of ovarian tumor implants.[14] Combination therapy with IFN plus other cytotoxic or immunomodulatory drugs may further enhance efficacy.

Conclusion

In this study, topically applied IFN-α2b (both 10 and 100 MU) was shown to be of comparable efficacy to ethoglucid in the treatment of superficial bladder cancer. Unlike ethoglucid, which produced severe chemocystitis in some patients, IFN-α2b did not cause any systemic or local adverse effects.

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