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High-dose versus low-dose intravesical interferon-α2b in the treatment of carcinoma *in situ*: a randomized, controlled study

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Eighty-seven patients with carcinoma *in situ* of the bladder were randomized to receive either 10 MU (low dose, 38 patients) or 100 MU (high dose, 47 patients) of recombinant interferon-α2b intravesically once weekly for 12 weeks and then monthly for up to 1 year. The 100 MU dose produced a significantly greater incidence of complete responses than the 10 MU dose (43 and 5%, respectively), $p < 0.0001$. Adverse effects of treatment were infrequent except for mild-to-moderate flu-like symptoms, which occurred in 8% and 17% of patients from the low- and high-dose groups, respectively.

Key words: Carcinoma *in situ*, intravesical interferon-α2b

Introduction

Bladder cancer is a frequent malignant tumor of the urinary tract, with a rate of occurrence in males of almost three times that in females.[1] Most bladder tumors arise within the bladder urothelium and may be either superficial or invasive.[2] Superficial transitional cell carcinoma (TCC), including papilloma, papillary tumors and carcinoma *in situ* (CIS), constitutes approximately 90% of all bladder tumors with squamous cell cancer and adenocarcinoma accounting for about 8 and 2%, respectively.[3] CIS is of higher histologic grade and is more likely to develop into invasive disease than papillary TCC, the most common form of bladder cancer.[4,5] A small focus of CIS may surround or be situated adjacent to the base of papillary tumor but more commonly there is extensive superficial urothelial involvement, with or without papillary tumors.[5] Multifocal CIS will progress to invasive disease in 40–50% of patients, if untreated.[5–9]

Intravesical chemotherapy and immunotherapy is commonly used in the treatment of superficial bladder cancer because recurrence of tumors is frequent even after complete surgical resection. Chemotherapeutic agents including thiotepa, doxorubicin, ethoglucid and mitomycin are all beneficial when used intravesically. The main drawback to their use is the local and/or systemic toxicity which often occurs. Intravesical immunotherapy with *Bacillus Calmette–Guérin* (BCG) has given response rates ranging from 36 to 73% in patients with CIS,[6,7,9] however, local toxicity and cystitis occur in the majority of patients. Thus, new, less toxic treatments with antiproliferative activity in bladder cancer are being investigated.

The antiproliferative effect of the interferons in cell lines derived from human bladder carcinoma led to the investigation of interferon (IFN)-α2b as a potential treatment for superficial bladder cancer, including CIS. Early results from studies in patients with superficial bladder tumors demonstrated that intravesical therapy with IFN-α2b was highly effective, with complete responses observed in 32% of patients.[8] Determination of the optimum dosage regimen was not an objective of these studies, however, significant biologic activity was demonstrated even at the lowest dose (50 MU) and no dose-limiting systemic or local toxicity was noted (highest dose 1000 MU).[8] The randomized, controlled study reported here was designed to compare the activity of low dose (10 MU) and high dose (100 MU) IFN-α2b, administered intravesically, in patients with CIS. A more complete account of this work is published elsewhere.[10]

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Materials and methods

Patients

Inclusion/exclusion criteria. All patients were required to have biopsy-documented CIS of the bladder with positive post-biopsy cytology results. If positive post-biopsy cytology was not documented, patients could still be eligible for inclusion if (a) positive cytology results were obtained within 1 month before entry into the study and (b) the biopsy revealed multiple tumor sites in the bladder despite persistently negative cytology results performed before entry. Patients were excluded if they showed evidence of invasion into the bladder muscle or other malignancy (except non-melanomatous skin cancer).

Classification. Patients were assigned to one of four categories according to clinical stage (O or A) and the presence or absence of irritative bladder symptoms, and were then randomly allocated to treatment with 10 or 100 MU of IFN-α2b.

Experimental procedure

The investigators and site pharmacists were blinded as to the dosages of recombinant IFN-α2b (10 or 100 MU per unit dose). Treatment was started within 1 month of a documented positive cytology test and the drug was then administered once weekly for 12 weeks and then monthly for 1 year. The drug (reconstituted in 30 ml of sterile, pyrogen-free water) was administered into the bladder by catheterization and retained for 2 h. Patients were instructed to rotate positions every 15 min, to ensure as far as possible that the entire mucosal surface of the bladder was adequately and evenly exposed; at the end of the 2 h retention time the drug was expelled by voiding.

Evaluation of response

Patients were evaluated 3, 6, 9 and 12 months after the first dose, using bladder wash cytology and cystoscopy/biopsy to follow response. At the end of the treatment schedule all patients who showed a complete response were then evaluated every 3 months for at least 2 years to follow response rate of progression. All other patients were also followed for the same length of time to determine survival and the need for surgery.

Table 1. Objective response criteria used to define response to treatment

Definition	Criteria
Complete response	Complete resolution of CIS. Negative bladder biopsy. Benign cytology. No TCC tumors present.
Partial response	
type 1	Negative bladder biopsy and cytology for CIS. TCC present (grade 1 or 2, stage T_a or 0).
type 2	Negative bladder biopsy for CIS. Positive cytology. No disease documented in upper tracts or prostatic urethra.
type 3	Negative bladder biopsy for CIS. Positive cytology. Disease documented in upper tracts or prostatic urethra.
No response	Categories *not* defined by complete response, partial response or progressive disease, e.g. persistent CIS of the bladder without documented significant progression of disease—with or without TCC (stage T_a, grade 1 or 2).
Progressive disease	Progression to a higher stage, recurrence or occurrence TCC at grade 3 or 4, recurrence or occurrence of stage T_1 TCC, unresectable TCC and documented significant progression of CIS in the bladder.

Response to treatment was evaluated with specific objective criteria and defined as complete response, partial response (type 1, 2 or 3), no response or progressive disease as shown in Table 1.

Evaluation of toxicity

Patient reports, observations by the investigator or local and systemic reactions occurring during the treatment period or prior to the first follow-up visit were used to assess the toxicity of the treatments. All adverse effects were judged by the investigator as being probably, possibly or not related to treatment, and were graded according to World Health Organization guidelines for acute and subacute toxicity. Particular attention was paid to occurrence of flu-like symptoms, which are commonly associated with systemic IFN treatment.

Statistical analysis

The Mann–Whitney *U*-test was used to compare the two treatment groups for age, performance status,

severity of bladder inflammation, prior bladder tumors and urinary symptoms (urgency, frequency, dysuria and pain). Differences between the treatment groups for previous therapy, extent of CIS and presence of TCC were determined using the χ^2 test. Fisher's 2 × 2 exact test was used to compare the occurrence of hematuria. Complete response and complete plus partial response formed the basis of data for best response rates, which were compared using Fisher's exact test. Response was also evaluated using the Mann–Whitney *U*-test.

Results

Of the 87 patients enroled and evaluated for safety, one did not have CIS and in another CIS was not confirmed, leaving 85 patients to be evaluated for efficacy (38 randomized to low dose and 47 to high dose). The age of patients ranged from 46 to 89 years, with a median of 67 years. Baseline demographics were similar for the two patient groups. Median duration of treatment for low-dose patients was 6.3 (range 0–12 months) and for the high-dose patients was 5.6 months (range 0–15.7 months).

Efficacy

Figure 1 illustrates the best objective response rates for both low- and high-dose groups. It can be seen that complete response to treatment was achieved more frequently in the high-dose group (20 out of 47 patients) than in the low-dose group (two out of 38 patients), this difference is statistically significant at $p < 0.0001$. No type 1 partial responses were seen and the overall response to treatment (complete plus partial type 2) was found in significantly more patients from the high-dose group than from the low-dose group ($p = 0.003$).

Figure 2 shows the current duration of complete responses. Two patients from the high-dose group continued to respond after 24 months and five

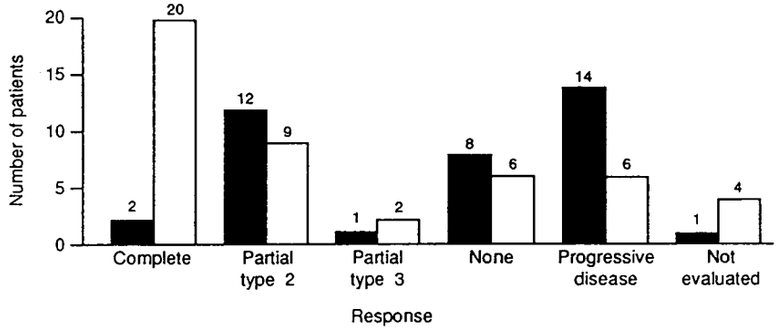

Figure 1. Best objective response rates achieved following treatment with low-dose (10 MU, ■) or high-dose (100 MU, □) IFN-α2b.

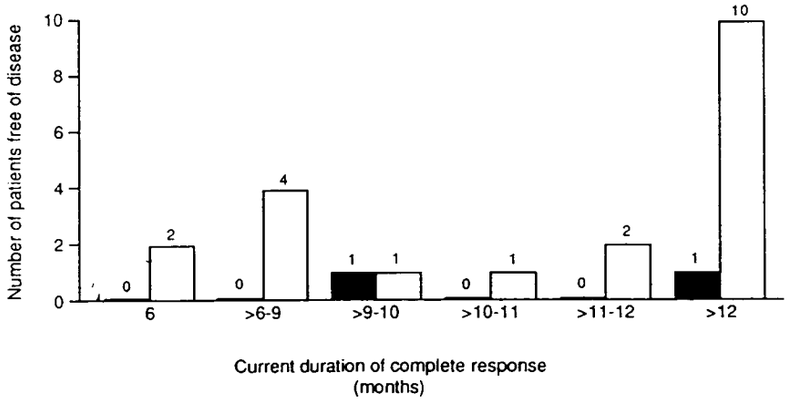

Figure 2. Current duration of complete response following treatment with low-dose (10 MU, ■) or high-dose (100 MU, □) IFN-α2b.

patients who achieved partial response (type 2) subsequently experienced a complete response.

Retrospective analysis of patients' baseline clinical characteristics revealed tumor stage to be the strongest predictor of clinical outcome, with lower stage cancer (stage 0) patients showing a greater response. Of 22 patients who showed a complete response 20 were reported to have stage 0 disease at initial examination. The ability of a patient to respond to IFN-α2b treatment was not significantly influenced by duration of disease, the presence or absence of irritative bladder symptoms, performance status or previous exposure to chemotherapy. Two complete responses (both high dose) and four partial responses (three high dose) were seen in patients who had experienced a relapse of the disease after earlier BCG treatment. Currently seven patients from each group have undergone cystectomy.

Safety

No patient discontinued treatment as a result of adverse, treatment-related effects. The most commonly reported adverse experiences reported in both groups were mild-to-moderate flu-like symptoms, which occurred in 8% (three out of 38) of patients from the low-dose group and 14% (8 out of 47) from the high-dose group.

Discussion

All patients in this trial of intravesical IFN-α2b therapy had histologically documented CIS and many had multifocal disease (65%), had previously received chemotherapy or BCG treatment (54%), or had prior (74%) or concurrent (14%) papillary lesions. Since each of these factors adversely influences prognosis, the patients were at considerable risk for subsequent development of invasive disease. The optimal clinical outcome is complete resolution of CIS with no TCC tumors present, classified in this trial as complete response. However, partial responses, with negative biopsy but positive cytology, are indicative of some biologic activity, and in this study continued treatment when partial response was seen initially resulted eventually in complete response in five patients, which is consistent with delayed antitumor effects reported in other studies of IFN.[8] Although responses were seen with both the 10 and 100 MU doses, the higher dose was associated with a significantly greater occurrence of complete response (43 compared with 5% in low-dose groups). However, the duration of complete response was similar in the two dose groups, suggesting that once a response has been achieved, a dose of 10 MU may maintain that response as effectively as a dose of 100 MU. More than 50% of the responses, in this study, have been maintained for more than 6 months after the start of treatment. However, the average follow up was only 6 months and in an earlier study five out of 10 complete responses were maintained for 18–37 months.[8]

Intravesically administered BCG is now widely used for the treatment of superficial bladder cancer in spite of considerable variation in results of trials of its use for this condition, and the high incidence of local irritation and cystitis and also occasional systemic effects which occur.[6] In addition, the optimal dose, dosing schedule, duration of treatment and strain of BCG to be used have not been clearly determined. In six out of the nine patients in the present trial who had relapsed after BCG therapy, a response to IFN-α2b was seen, with complete response occurring in two of these patients. Thus, it appears that cross-resistance between the two agents is not a problem and their concurrent, cyclical or serial use in future studies should be considered. The safety profile of intravesical IFN-α2b in comparison with other intravesical agents is good, as illustrated in a preliminary dose-ranging study which was unable to document a dose-limiting toxicity even at 1000 MU per dose.[8] The results of the trial reported here confirm the lack of toxicity of IFN-α2b.

Conclusion

The results of this study confirm that IFN-α2b is an effective and safe treatment for CIS of the bladder and show that complete remission was induced more frequently with a dose of 100 MU than with a dose of 10 MU. It is proposed that IFN-α2b is a safer choice for treatment of CIS of the bladder than more toxic chemotherapeutic and immunotherapeutic treatments.

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