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# Interferon-α2b instillation prophylaxis in superficial bladder cancer—a prospective, controlled three-armed trial

**U Engelmann,[CA] HJ Knopf, J Graff and the Project Group Bochum—Interferon and Superficial Bladder Cancer**

The authors are at the Department of Urology, Ruhr-Universität Bochum, Germany

**Sixty-seven patients with recurrent $pT_a$ G1–G3 to $pT_1$ G1–G3 tumors were randomized into three groups receiving either Intron A at 10 MU/instillation, Intron A at 10 MU and mitomycin C (MMC) at 20 mg/instillation or MMC at 20 mg/instillation. After a mean follow up of 6.2 months no tumor recurrence has been seen in the group receiving combined therapy, whilst four out of 22 in the interferon group and five out of 23 in the MMC group suffered a recurrence. Side effects were slight. These preliminary results suggest that a combination of the two drugs is more effective than either drug alone.**

*Key words:* Bladder cancer, interferon-α2b, mitomycin C.

## Introduction

The biologic properties of superficial bladder cancer are well known, with the potential for both recurrence and progression in grade and stage presenting a special risk that necessitates invasive treatment. Instillation prophylaxis with *Bacillus Calmette-Guérin* (BCG), or chemotherapeutic agents such as mitomycin C (MMC), ethoglucid or adriamycin, may reduce the rate of recurrence and increase the tumor-free interval.

Interferon (IFN) was described as a substance with antiviral properties in 1957 and shortly thereafter its efficacy against tumor cells was detected. At that time only very small amounts of IFN were available and thus this property could not be further investigated. However, more recent advances in genetic engineering have made it possible to produce larger quantities of IFN for which there are already a number of clinically accepted indications (Table 1).

IFNs were originally identified as a result of their antiviral properties. However, a number of distinct biologic activities are now known, including the capacity for antineoplastic activity (Table 2). In this paper we will concentrate on the use of IFN in the treatment of bladder cancer, with a specific emphasis on superficial bladder cancer. Since such investigations have only been made possible within the last 10 years, clinical results are only just emerging and thus in the near future an abundance of clinical data should become available.

## Experimental investigations

In 1985 Brouty-Boyce *et al.* detected an antiproliferative activity associated with IFN incubated with human bladder carcinoma cell lines (Table 3).[1–10] These findings were confirmed by Grups and Frohmüller,[6] who similarly described a number of human bladder carcinoma cell lines that were IFN sensitive, with the combination of IFN-α, -β and -γ apparently more efficacious than IFN-α alone. Short-term treatment with IFN-γ has been found to increase the sensitivity of bladder tumor cells to tumor necrosis factor.[1] Borden *et al.*[3] found that

**Table 1.** Clinical indications for IFN therapy

| |
|---|
| Hairy cell leukemia |
| Chronic myelogenous leukemia |
| Non-Hodgkin's lymphoma |
| Multiple myeloma |
| Mycosis fungoides |
| Kaposi's sarcoma |
| Malignant melanoma |
| Renal cell carcinoma |
| Basal cell cancer |
| Chronic hepatitis B |
| Chronic hepatitis non A, non B |
| Papillomatosis of the larynx |
| Condylomata accuminata |

[CA] Corresponding Author

**Table 2.** Biological properties of IFNs

| |
|---|
| Antiproliferative effect |
| Immunomodulation |
| Cell differentiation |
| Regulation of oncogenes |
| Antiviral potential |

both IFN and the IFN inducer bropirimine demonstrated an antiproliferative effect in *N*-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANFT)-induced bladder carcinogenesis. The antiproliferative properties of IFN, which were also confirmed by Jakse *et al.*,[8] do not seem to correlate with the number of IFN receptors on the cell surface, nor does its antineoplastic activity seem to be restricted to urothelial cell carcinoma, as demonstrated by Khaled *et al.*[9] using bilharzia-bladder carcinoma cells.

The immunomodulatory and antiproliferative activities of IFN are probably subject to complicated regulatory mechanisms, since the effectiveness of IFN-$\beta$ seems to depend on the tumor mass and its antitumor activity can be modulated by using combination therapy as shown by Hubell *et al.*[7] Frangos *et al.*[5] tried to overcome tumor cell resistance to IFN-$\alpha$ through comparison of the efficacy of free and liposome-bound IFN against human bladder carcinoma cell lines. The latter was found to be more efficacious, demonstrating stability in urine and not showing any systemic absorption.

## Instillation therapy with IFNs

Donovan *et al.*[11] compared BCG to IFN-$\alpha$2b as recurrence prophylaxis following transurethral resection in patients with carcinoma *in situ*, $T_a$ and $T_1$ bladder carcinoma (Table 4).[11–17] Prior to June 1987, 67 patients were entered in the study. The follow-up was up to 24 months, the recurrence rate (number of positive cystoscopies $\times$ 100/number of months of follow-up) was 23.3 in the control group, 13 in the BCG group and 18.4 in the IFN group. The authors concluded that there was reason for cautious optimism regarding the role of IFNs in superficial bladder cancer. Torti *et al.*[12] claimed that intravesically administered IFN-$\alpha$2b was an effective new treatment for some patients with superficial bladder cancer. Out of 19 patients, six with carcinoma *in situ* (32%) including two with severe dysplasia (11%) experienced a complete response. Even superficial tumors, that had been treated intensively before, showed a response to the regime. According to Williams a high dosage of IFN (100 MU) seemed to be considerably more effective than only 10 MU/instillation.[13] Nijima treated 51 patients with non-resected superficial bladder cancer using IFN instillation of varying dosage.[14] He concluded that frequent and longer exposure to IFN may result in better regression of superficial tumors.

Höltl *et al.*[17] compared a low and a high dosage of IFN-$\alpha$2b with epodyl (ethoglucid) therapy. Even at a high dosage, IFN showed significantly fewer side effects and the recurrence rates showed no statistically significant differences, perhaps due to the relatively small size of the groups, which contained only 14–16 patients. Glashan[15] treated 87 patients with carcinoma *in situ* for a maximum of 1 year with IFN in a prospective randomized study using either 10 or 100 MU/instillation. Forty-three

**Table 4.** Instillation therapy with IFNs

| | |
|---|---|
| Donovan *et al.*[11] | IFN versus BCG |
| Torti *et al.*[12] | IFN |
| Williams[13] | IFN low dose versus IFN high dose |
| Nijima[14] | IFN at various doses |
| Glashan[15] | IFN low dose versus IFN high dose |
| Kostakopoulos *et al.*[16] | IFN low dose |
| Hoeltl *et al.*[17] | IFN low dose versus IFN high dose versus epodyl |

**Table 3.** Experimental investigations on the efficacy of IFN in bladder carcinoma

| | | |
|---|---|---|
| Bahnson and Ratliff[1] | IFNG | Mouse bladder tumor |
| Bahnson and Ratliff[2] | IFN-$\alpha$, IFN-$\beta$, adriamycin, MMC | Mouse bladder tumor |
| Borden *et al.*[3] | IFN-$\beta$, bromopirine | FANFT-induced bladder tumor |
| Brouty–Boyce *et al.*[4] | IFN-$\alpha$ | Human bladder tumor cell lines |
| Frangos *et al.*[5] | Liposomes and IFN-$\alpha$ | Human bladder tumor cell lines |
| Grups and Frohmüller[6] | IFN-$\gamma$ | Human bladder tumor cell lines |
| Hubell *et al.*[7] | IFN-$\beta$ | Human bladder tumor xenograft |
| Jakse *et al.*[8] | IFN-$\gamma$ | Human bladder tumor cell lines |
| Khaled *et al.*[9] | IFN | Bilharzia bladder carcinoma |
| Ottesen *et al.*[10] | IFN-$\gamma$ | Human bladder tumor cell lines |

per cent of the patients receiving a high dosage and 5% of those to whom the low dosage was administered experienced a complete response. Remarkably, response was also seen in six out of nine patients in whom BCG treatment had previously failed to show an effect. Treatment safety was excellent, without any signs of local toxicity. In the same year, Kostakopoulos *et al.*[16] presented their results with 10 MU IFN-α2b as recurrence prophylaxis. Sixty-three per cent of their patients were recurrence free at the end of follow up, with no side effects noted.

## Combination of IFN with cytostatic drugs

Since 1982 there have been indications that a combination of immunomodulatory IFN with cytotoxic substances could be advantageous (Table 5).[6,18–22] The efficacy of cyclophosphamide against transitional cell carcinoma in the mouse could be enhanced additively by combining it with (poly(I)–poly(C)), an IFN inducer.[18] Synergistic effects have also been described using adriamycin, vinblastine, cisplatin and 5-fluorouracil.[19]

In 1988, Grups and Frohmüller[6] demonstrated enhancement of doxorubicin activity against human bladder carcinoma cell lines in combination with IFN. Hirabayashi *et al.*[20] found synergistic effects of MMC and IFN-α against metastasizing, chemotherapy-refractory urothelial tumors. Such additive, or synergistic, effects do not seem to be limited to the use of IFN in combination with cytostatic drugs. Sarosdy and Kierum[21] treated murine transitional cell cancer with BCG alone or with a combina-tion of 2-amino-5-iodo-6-phenyl-4($^3$H)pyrimidinone (ABPP) and BCG. The results indicated that the IFN inducer ABPP potentiated the activity of BCG.

**Table 5.** Combination therapy of IFN with cytostatic drugs

| | |
|---|---|
| Borden *et al.*[18] | IFN-inductor + cyclophosphamide |
| Bonnem[19] | IFN + adriamycin + vinblastine + cisplatin + 5-fluorouracil |
| Grups and Frohmüller[6] | IFN + adriamycin |
| Hirabayashi *et al.*[20] | IFN + MMC |
| Sarosdy and Kierum[21] | IFN-inductor + 5-fluorouracil |
| Logothetis *et al.*[22] | IFN + 5-fluorouracil |
| Project Group Bochum (1991) | IFN + MMC |

Based on these findings, a prospective, comparative, multicenter study was initiated in 1989 in order to investigate the effect of IFN alone and in combination with MMC as an instillation prophylaxis in superficial bladder cancer. MMC given alone served as a control. Patients with recurrent $pT_a$ G1–G3 to $pT_1$ G1–G3 tumors were entered in the study. Patients were enroled into the study dependent upon the tumor having been resected completely or following laser coagulation of the tumor after deep biopsies had been taken for histologic verification. The Karnofsky index had to be greater than 70%, the serum creatinine lower than 2.5 mg%, and sufficient hepatic and hematopoietic function was mandatory. Patients with adenocarcinomas and squamous cell carcinomas were excluded.

Following complete transurethral resection the patients were randomized to one of the following groups: Group 1, Intron A (IFN-α2b) 10 MU/instillation; Group 2, Intron A (IFN-α2b) 10 MU and MMC 20 mg/instillation; Group 3, MMC 20 mg/instillation. Instillation started 2 weeks after the complete transurethral resection of the tumor and was continued at monthly intervals for 1 year. Control cystoscopies and urine cytologies were performed every 8 weeks. Patients with recurrent tumors underwent transurethral resection and were excluded from further study.

Up to now 67 patients have been enroled in the study. The follow-up period ranged from 1 to 15 months with a mean of 6.2 months. The preliminary results are summarized in Table 6. So far no tumor recurrence has been seen in Group 2 (Intron A and MMC) whilst four out of 22 patients in Group 1 and five out of 23 patients in Group 3 suffered a recurrence. Recurrent tumors were $pT_a$ G1 and G2 tumors and showed no progression in stage. Recurrences were seen between 3 and 6 months after the beginning of instillation prophylaxis. In general, instillation was well tolerated. Side effects were slight and consisted mostly of dysuria and erythema. Flu-like symptoms were not reported. Due to side effects, two patients were taken off study in Group 1, none in Group 2 and one in Group 3.

These preliminary results seem to indicate that in the recurrence prophylaxis of superficial bladder cancer, a combination of MMC and IFN-α might be more efficacious than either substance alone. Side effects were not potentiated by such combination therapy as shown in Group 2, where no patient had to be taken off study due to unwanted effects. Since patient recruitment is still going on and follow-up

**Table 6.** Project Group Bochum—interferon and superficial bladder cancer—preliminary results

| | Intron A (10 MU/instillation) | Intron A (10 MU/instillation) + MMC (20 mg/instillation) | MMC (20 mg/instillation) |
|---|---|---|---|
| No. of patients | 22 | 22 | 23 |
| Mean age (years) | 68.1 | 67.6 | 64.2 |
| Side effects | 4/22 | 2/22 | 4/23 |
| Recurrences | 4/22 | none | 5/23 |

time is as yet short, definitive results are still awaited.

## Conclusion

The combination of IFN with cytostatic drugs or other immune modifiers offers the potential for more effective therapeutic regimens than are currently available. However, we do not currently fully understand the mode of action of IFN or its possible interactions with cytostatic drugs and more basic research is needed in this field, with special emphasis on drug scheduling and sequences. Carefully planned clinical trials should investigate the combination of IFN and BCG, MMC or adriamycin against both carcinoma *in situ* and recurrent superficial bladder tumors. The negligible side effects of IFN bladder instillation should enable us to use comparatively high doses in the order of 100 MU, since these seem to be more efficacious.

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