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Intravesical mitoxantrone for superficial bladder tumors

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Thirty-five patients (33 males, median age 58) with stage Tα (21 patients) or T_1, grade 1 (17 patients) or grade 2 superficial bladder carcinoma, were treated with transurethral resection (TUR) followed by intravesical prophylactic therapy with 10 mg mitoxantrone administered weekly for 6 weeks and then monthly for 10 months. Twenty-five patients were newly diagnosed and 10 had relapsed after previous therapy. Diagnosis was confirmed with cytology and biopsy. The aim of the study was to evaluate the prophylactic effect (relapse rate, disease free interval) and toxicity of intravesical mitoxantrone in superficial bladder carcinoma. Relapses were established with biopsy. After a mean period of 12 months follow-up (median 8.3 months), 63% of patients in the whole group, 72% in the newly diagnosed group and 40% in the group of previously relapsed patients remained relapse free. These rates compare very favorably with the most effective prophylactic agents available. At the end of the follow-up period the median disease-free survival for the whole group was not reached. Therapy was well tolerated with no systemic toxicity and 14 patients reporting grade 1–2 local toxicity. In no patient was treatment discontinued due to toxicity. Mitoxantrone is an effective and safe agent for the post-TUR adjuvant intravesical therapy.

Key words: Bladder carcinoma, intravesical, mitoxantrone.

Introduction

The treatment of superficial bladder cancer aims at the eradication of the existing disease and at the prevention of recurrences, some of which may invade deeper into the muscle layers.[1] Depending mainly on the tumor stage, grade, size and number of lesions, the majority of the tumors will recur. Between 5 and 50% of these recurrences are of a higher grade or stage.[2] The mainstay of the treatment of superficial bladder cancer is transurethral resection (TUR) of the lesions followed by prophylactic or adjuvant intravesical therapy. TUR is essential not only for the removal of the lesions but also for the accurate diagnosis and staging of the disease.[3]

The objective of post-TUR prophylactic intravesical therapy is to reduce or delay tumor recurrence, to eradicate any residual disease or carcinoma *in situ*, to prevent deeper invasion, to reduce the need for cystectomy and to maintain a good quality of life.[4] The results achieved coupled with the toxicity involved do not justify the use of systemic therapy for the superficial disease.[5] Agents commonly used for intravesical prophylactic therapy are thiotepa, mitomycin C, doxorubicin and immunotherapy, either with BCG or interferon-α. Thiotepa is a low molecular weight agent and systemic absorption may lead to myelosuppression. Mitomycin C and doxorubicin can cause chemical cystitis. BCG is the most effective among the other prophylactic agents, but the frequency and severity of local and systemic side effects, varying with the strain, may be potentially worse than with the chemotherapeutic agents.[2]

Intravesically placed effective chemotherapeutic agents should be minimally absorbed through the bladder mucosa and should cause a minimum amount of local toxicity. A major determinant for bladder absorption is the molecular weight of the compounds. Mitoxantrone is a high molecular weight anthracenedione derivative, with extensive binding to tissues, with a steep dose–response curve and better local tolerance compared with anthracyclines.[6,7] In a phase I study, systemic absorption and toxicity were negligible after intravesical application of 5–10.5 mg mitoxantrone in patients with relapsing bladder tumors.[8] Furthermore, in *in vitro* studies on transitional cell bladder cancer cell lines, mitoxantrone was classified as one of the most cytotoxic agents tested.[9]

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The aim of the present study was to evaluate mitoxantrone in the adjuvant therapy of both newly diagnosed or relapsed patients submitted to TUR for superficial bladder cancer.

Material and methods

Thirty-five patients (33 males) with a median age of 58 years (mean 55.9, range 28–75 years) and stage $T\alpha/T_1$, grade 1/2, superficial transitional cell bladder carcinoma were included in the study. Diagnosis was confirmed with cytology and biopsy. Patients with invasive disease or any other concomitant cancers were excluded. The mitoxantrone dose chosen was based on previous phase I safety and pharmacokinetic studies.[8] Ten patients had a recurrent disease (one in second relapse) and 25 were newly diagnosed. Regarding the stage and the histology, 21 patients had $T\alpha$, 14 patients T_1, 17 patients grade 1 and 18 patients grade 2 disease. Nineteen patients had one lesion and 16 multiple lesions.

All of the patients were initially treated by TUR or fulguration. Two weeks after TUR and after postoperative irritative symptoms and any infection ceased, intravesical therapy was started. Mitoxantrone (10 mg) was dissolved in 50 ml saline and inserted into the bladder. After 2 h the drug was discharged from the bladder by urination. Mitoxantrone was given at weekly intervals for 6 doses and then monthly for 10 months. Cystoscopy was performed 4 and 12 weeks after the initiation of the adjuvant therapy, and then every 3 months. Biopsy material was obtained during cytoscopy and whenever indicated. Recurrence was established only by histological examination of the biopsy material.

The side-effects were recorded at every drug administration. Complete blood counts were performed before, every 4 weeks or whenever it was indicated. Antispasmodic medications were applied to the patient with cystitis. Toxicity was evaluated based on the WHO criteria. Local bladder toxicity was rated as grade 1: dysuria requiring no therapy and/or microscopic hematuria; grade 2: dysuria requiring therapy and/or gross hematuria; grade 3: bladder spasms lasting more than 24 h, bladder spasms not controllable by medical treatment, dysuria or other evidence of bladder irritation persisting for more than 1 week or hematuria leading to reduction of hemoglobin levels.

The aims and possible toxicity associated with the therapy were explained and informed consent was obtained from all patients.

Results

The mean duration of follow-up for the 35 patients was 12 months (median 8.3 months, range 1.9–25.7 months) and the total observation period was 419.3 months. During this period 13 patients relapsed—seven in the group of 25 patients with newly diagnosed disease (relapse rate 28%) and six in the group of 10 patients with relapsed disease (relapse rate 60%). Consequently 72% of the patients in the group with newly diagnosed disease and 40% in the group with previously relapsed disease remained relapse-free after a mean follow-up of 12 months. If both groups are taken together the total relapse rate after an average of 12 months was 37%. The difference in the relapse rate between the newly diagnosed and the previously relapsed patients, computed with the χ^2, 2×2 contingency table, with the application of a correction for continuity,[10] was statistically significant at the 5% level only when percents were applied ($\chi^2 = 19.5$ d.f. $= 1$ $p < 0.001$) but not when the actual numbers were calculated ($\chi^2 = 1.91$ d.f. $= 1$ $p < 0.2$). This shows that differences on actual numbers would be statistically significant if more patients were enrolled. The relapse rate per 100 patient months of follow up[11] was 2.1 in the newly diagnosed group, 6.9 in the patients with relapsing disease and 3.1 in the whole group.

Relapse rates were also compared in patients with single versus multiple lesions, grade 1 versus grade 2 and stage $T\alpha$ versus stage T_1 tumors (Table 1). No difference was statistically significant at the 5% level (χ^2 test with correction for continuity). When the whole group was taken together, after a median duration of follow-up of 8.3 months (maximum 25.7 months) the median disease-free interval (DFI) was not reached. However the median DFI for the newly diagnosed patients, compared with the patients with previous disease, was much longer: not reached after 840 days in the newly diagnosed group versus 210 days in the previously relapsed patients.

The treatment proved to be safe—complete blood counts and blood biochemistry analyses revealed no bone marrow suppression, hepatotoxicity or renal toxicity in any patient. Regarding local toxicity, 10 patients complained of grade 1 and 4 of grade 2 bladder toxicity. Cystic complaints appeared only once in each patient and in no case was treatment discontinued. No severe cystitis was encountered. Treatment was discontinued only in one patient due to non therapy related heart failure.

Table 1. Relapse rates in patients with single versus multiple, Tα versus T_1 and grade 1 versus grade 2 tumors

	Lesions		Stage		Grade	
	single	multiple	Tα	T_1	1	2
Number of patients	19	16	21	14	17	18
Total observation period (months)	232.7	186.6	227.7	191.6	218.0	201.3
Median follow-up (months)	8.3	10.7	8.1	14.2	13.3	7.9
Mean follow-up (months)	12.2	11.7	10.8	13.7	12.8	11.2
Number of relapses	5	8	8	5	5	8
Relapse rate (%)	26.3	50.0	38.1	35.7	29.4	44.4
Relapse rate per 100 patient months	2.15	4.29	3.51	2.61	2.29	3.97
χ^2	1.19		0.04		0.32	
p value	<0.3		<0.9		<0.7	

Discussion

The benefit of prophylactic intravesical therapy over the control group, treated with TUR alone, has been repeatedly proven.[12,13] In previously run prophylactic intravesical therapy studies, with sufficiently high numbers of patients, the average percentage of patients without tumor recurrence after at least 1 year follow-up was 56% for thiotepa, 69% for doxorubicin, 58% for mitomycin C and 72% for immunotherapy with BCG.[12] In the present study the percentage of newly diagnosed patients with no recurrence, after a mean duration of 1 year follow-up (median 8.3 months), was 72% and when all patients are taken together 63%. This compares very favorably with the results achieved with all previously used chemotherapeutic agents, including BCG, and ranks mitoxantrone among the most effective agents. These clinical results confirm the results of previous *in vitro* studies.[9]

Prophylactic treatment schedules for intravesical chemotherapy have been different. The EORTC GU Group recommends an intensive 4–6 weeks of treatment followed by monthly prophylaxis for 6 months to 1 year.[13] Other investigators also reconfirm the recommendation of 4–8 weekly doses followed by monthly administrations.[1] Initiation of prophylaxis immediately after TUR is more toxic compared with the initiation after 1 or 2 weeks.[12] Our dosage schedule was based on these results. Dosage variations aim at the reduction of local toxicity maintaining the same results. In a $T\alpha/T_1$, grade 1/2 superficial bladder cancer study, in patients with multiple relapses, Tyrrell *et al.*[14] used a different chemoprophylactic dosage schedule of mitoxantrone with four 20 mg doses administered 1 month apart. Cystitis was reported in 11 (out of 36) patients (30.5%) and three patients interrupted therapy due to local toxicity. In the same study,[14] 43.3% of these high risk patients remained disease free for 1 year or more and 23.3% suffered only one or two small recurrences. In our study with 10 mg administered initially weekly and then monthly, 14 out of 35 patients (40%) complained of some degree of local toxicity. However, the majority (28.5%) was grade 1 cystic complaints with none interrupting the treatment due to side-effects. Using weekly intravesical doses of 5–13.5 mg mitoxantrone, Sharifi *et al.*[15] concluded that up to 10.5 mg weekly is well tolerated without major local side-effects. In the same study, four patients refractory to BCG showed an average response duration of 5 months after treatment with mitoxantrone.

Conclusion

In conclusion, mitoxantrone administered prophylactically after TUR, in $T\alpha/T_1$, grade 1/2, newly diagnosed or relapsing superficial bladder cancer patients, proved at least as effective and better tolerated than other chemotherapeutic agents. The lack of systemic side effects in our study reconfirms the negligble absorption of the high molecular weight mitoxantrone from the bladder.

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