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Phase I–II evaluation of intravesical novantrone (mitoxantrone) in superficial bladder cancer

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The objective of this study was to determine the safety and efficacy of intravesical novantrone in refractory superficial bladder cancer. The eligibility criteria included proven carcinoma *in situ* or superficial transitional cell carcinoma of the bladder at stage Ta or T1 that was proven refractory to or in relapse after the use of at least one other standard anti-cancer agent. The patient was to have received no prior radiotherapy or intravesical therapy for at least 4 weeks prior to entry. Patients also did not suffer significant cardiac dysfunction, such as angina, congestive heart failure, or uncompensated cardiomyopathy. All patients were given 4–6 doses of intravesical novantrone at the same dose level at weekly dosing interval. Patients were required to retain the drugs in the bladder for 2 h. Baseline study included history/physical, hematology, blood chemistry, cystoscopy, bladder barbotage, urine cytology, cystometrogram to assess the bladder capacity, and finally, chest X-ray, EKG, and MUGA scan, if indicated. Weekly assessment involved toxicity notation, blood chemistry, hematology and urinalysis. Monthly assessment included physical examination, toxicity notation, hematology, urinalysis and blood chemistry. Within 4 weeks of completion of the last dose, patients underwent repeat cystoscopy to assess disease status. Patients who responded to the 4–6 week induction phase were entered in a monthly dose regimen for up to 5 months. A total of 23 patients were enrolled: 22 males and 1 female. One patient dropped out before receiving medication because of a protocol violation for entry criteria. Twenty-two patients were eligible for assessment of safety and 20 were eligible for assessment of efficacy. Prior therapy for all patients included a total of 29 courses of intravesical chemotherapy and eight courses of BCG. These patients had either tumor recurrence or relapse to previous treatment. Twelve patients had papillary carcinoma, stage T1–Ta and grade I–II, and eight had carcinoma *in situ*. Twenty-two patients received an escalating weekly dose ranging from 5 to 13.5 mg. Patients could be entered more than once. Four patients received monthly maintenance doses for up to 5 months. The results indicate that the drug dose level up to 10.5 mg weekly dose was tolerated without major side effects on the bladder. At doses of 12 and 13.5 mg the patients developed mild to severe bladder irritative symptoms, with significant reduction in bladder capacity. Two patients were dropped from the study because of the severe bladder symptoms. Both were receiving 13.5 mg weekly doses at the second and third week of treatment.

The average time to tumor recurrence for five responders with TIS and 12 responders in stage Ta–T1 and grade I–II, was similar and slightly longer in patients who failed previous treatment with BCG. Intravesical novantrone appeared to hold promise as a therapy for superficial bladder cancer. Further randomized comparative study is needed.

Key words: Novantrone, mitoxantrone, bladder cancer.

Introduction and background

Bladder cancer is the fifth most common cancer in men in Western countries with an annual incidence of 16–20 cases per 100 000 population.[1,2] In the United States more than 45 000 are detected each year.[1] Peak prevalence of bladder cancer occurs in the 60- to 70-year-old age group, and the data suggest that both incidence and prevalence are rising.[3] The death rate for bladder cancer is about 11 000 annually.[1] More than 99% of bladder tumors are carcinomas, and more than 90% of these exhibit transitional cell histology. Approximately 70% of bladder tumors are papillary; the rest are either nodular or mixed pattern. Transitional cell carcinoma of the bladder includes a heterogenous group of tumor cells. They have a broad spectrum of different biological potential, ranging from superficial well-differentiated papilloma to poorly differentiated invasive carcinoma with a high

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potential of metastasis. In general, most patients present with tumors which are well-differentiated and superficial. About 10–15% of these patients will subsequently develop invasive or metastatic cancer.[4] Approximately 70% of patients having superficial transitional carcinoma of the bladder have one or more tumor recurrences if treated with endoscopic resection alone,[5] and about 25% of patients will recur with the higher grade tumor. It is generally believed that most recurrences are actually new tumors arising from dysplastic urotheliums, but some of them may be recurrences resulting from inadequate treatment or from tumor implantations.[6] The main task of urologists dealing with superficial bladder tumor is to minimize recurrence rate and, if possible, identify those patients who will progress to invasion and/or metastasis. Approximately 70–80% of bladder cancer patients have a low grade superficial tumor at the time of clinical presentation. The great majority of these patients can be treated by transurethral resection or fulguration of the tumor. Only a small portion (10–15%) of the patients ultimately develop invasive bladder cancer.

The aim of laboratory and clinical investigations in recent years has been the development of intravesical therapeutic treatment of superficial bladder cancer. These investigations should lead to development of treatment that prevents or delays recurrence, eradicates the unresectable superficial tumor, and prevents the development of invasive bladder carcinoma. In general, intravesical chemotherapy or immunotherapy is used to prevent tumor recurrence in the high risk patient. These risk factors include patients with a high grade tumor, recurrent tumors, multiple tumors, tumors associated with urothelial atypia or carcinoma *in situ*.

Those patients who have a subsequent recurrence following intravesical therapy with one agent may be treated with a different agent with some hope for a favorable response. Thiotepa has been the most commonly used anti-cancer drug for intravesical treatment or prophylaxis of superficial bladder cancer. Response rate varies between 24 and 100%, depending on the degree of tumor bulk and response criteria.[7,8] One of the major side effects of this drug is occasional severe leukopenia that may occur following intravesical treatment as a result of variable systemic absorption. Other drugs for treatment of superficial bladder cancer include chemotherapeutic agents, such as doxorubicin and mitomycin-C, and finally, immunotherapy using interferon or BCG. In contrast to thiotepa, doxorubicin and mitomycin-C have relatively low systemic absorption. In general, similar results have been achieved with all of the agents used for intravesical chemotherapy. When these agents were used for the therapy of residual papillary tumors, the complete response rates ranged from 33 to 57%.[8–10] When they were used for therapy of carcinoma *in situ*, complete regression was reported in 55–66%. Finally, when intravesical therapy is used for prophylaxis, tumor recurrence rate is reduced to 30–44%, compared with 70% in control group.[11] There is no evidence suggesting that intravesical chemotherapy reduces or prevents the incidence of subsequent invasive tumor, or has any effect on survival.

Mitoxantrone (novantrone) is known to exhibit a steep dose–response relationship against bladder cancer cells grown in tissue culture.[12] It also shows a steep dose–survival curve against several types of epithelial malignancy.[13] Furthermore, because of its relatively high molecular weight and extremely good solubility characteristics, a high concentration can be achieved in a small volume of fluid. All of these qualities make it a reasonable drug to be tested against bladder cancer.

In an animal study done at Lederle Laboratories Division, American Cyanamid Company, the toxicity of novantrone and adriamycin was evaluated when given intravesically to beagle dogs. Intravesical administration of 5 mg novantrone for 2 h showed diffuse and moderate thickening of the bladder wall with mild, acute and chronic cystitis accompanied by superficial mucosal erosion and edema. When the dose was increased to 20 mg the changes were similar and involved thickness of the bladder wall, as well as acute changes comparable with pyelonephritis. A similar dose of adriamycin caused similar bladder changes in this model. A clinical study in Canada of novantrone with 22 patients who failed other intravesical chemotherapy has shown a dose of 10 mg to be well-tolerated.[14] The results from this study suggested that some patients experienced a marked prolongation of their tumor-free interval as a result of treatment with mitoxantrone. Out of 18 patients who were studied for pharmacokinetics, only one had evidence of mitoxantrone in his plasma and he had a peak plasma level of 4.7 ng/ml after his sixth dose of mitoxantrone. This particular patient developed a severe reaction to a mitoxantrone dose of 10 mg with a necrotic-looking urothelium at cystoscopy. The average amount of mitoxantrone recovered in the urine post-treatment was 75%. On the basis of this information, phase I–II evaluation of novantrone in superficial bladder

cancer was designed in order to determine the maximum tolerated dose and the safety of this agent in bladder cancer patients. In phase II of this study, the efficacy and safety of novantrone for treatment of superficial bladder cancer was determined.

Methods

This was an open, non-randomized, non-comparative trial. Patients had to have pathologically proven carcinoma *in situ* or superficial bladder cancer. Their disease had been proven refractory to or relapsed following exposure to at least one other standard intravesical agent.

All candidates should have an expected survival of at least 2 months with relatively normal hematologic and biochemical parameters. Patients must have a Karnofsky Performance Status of ≤ 2. Presence of measurable disease was not required in phase I of the study but was preferable in phase II. The exclusion criteria included previous exposure to radiotherapy, patients with cardiac dysfunction, and a history of other malignancy except basal cell carcinoma of the skin. Pregnant patients were excluded. Patients had to give a written informed consent indicating that they understood the investigational nature of this treatment. The initial dose was 5 mg, which was then increased to 6 mg, and thereafter increased in 1.5 mg increments until the maximum tolerated dose was reached. Treatment was given at weekly intervals for 6 weeks. In phase II of the study, weekly treatments were followed by maintenance treatment given once a month for 5 months. Mitoxantrone was dissolved in 30 ml of normal saline. The drug was introduced into the patient's bladder via foley catheter. Following installation of the drug into the bladder, the catheter was removed or plugged and the patient was instructed to keep the solution in the bladder for 2 h. In some cases, ditropan was given to decrease premature evacuation of the drug from the bladder as a result of bladder spasm. After 2 h, the drug was evacuated by a catheter. Treatment was repeated weekly for a total of six treatments. Treatment was stopped prematurely if toxicity was excessive and was delayed if the patient had marked irritative symptoms at the time that their weekly treatment was scheduled. A complete blood count, differential platelet count and biochemical evaluation were done prior to each course of therapy; urine cytology, urinalysis and urine culture were also repeated periodically. The patient underwent recheck cystoscopy 4 weeks after completion of their sixth course of intravesical mitoxantrone and then approximately once every 3 months thereafter. For the assessment of clinical response, complete remission was defined as disappearance of all clinical evidence of tumor for a minimum of 4 weeks. In addition, cytology of bladder washing must have been consistently negative. Persistence of existing lesions, appearance of new lesions, or carcinoma *in situ*, or positive cytology on bladder washing or voided urine, were all considered failure of therapy.

Results

Twenty-three patients were enrolled by three investigators into the study, 22 male and 1 female, with a median age of 67 years (range 56–70 years). Median weight for these patients was 81 kg (range 36–108 kg). Five patients were enrolled for more than one dose level. The duration of the disease was 0–10.6 years with a median of 2 years. Doses of 5–13.5 mg were given to patients in different patient groups (generally three patients per group). Four patients received monthly treatment for 3–5 months after the initial weekly × 6 induction phase. The patients previously had received a total of 29 courses of different intervesical chemotherapy, such as thiotepa, adriamycin, mitomycin-C. Eight courses of intravesical BCG had been used for some of these patients, after which their tumors had become refractory. One patient was considered non-evaluable for protocol violations at study entry due to eligibility criteria, and two patients were dropped from efficacy analysis because treatment was terminated after only 2 and 3 weekly treatments. They were counted for toxicity analysis. Patients' classification by stage and grade of lesions for evaluable patients is listed in Table 1. In order to determine the maximum tolerated dose and dose-limiting toxicity of novantrone, different doses of novantrone were used for different treatment groups. The safety and efficacy parameters were also monitored and these results are outlined in Table 1. Weekly and monthly clinical evaluation during the course of therapy indicated that the most common adverse event was genito-urinary symptoms, such as dysuria, urinary frequency, bladder spasm, hematuria. Bladder capacity was monitored on all these patients before and after treatment. The above-mentioned genito-urinary toxicity symptoms were very minimal at the dose of 9 mg or below, and in this group maximum delay of the next

Table 1. Patient classification and results of treatment with intravesical novantrone®

No. of patients	Tumor stage	Tumor grade	Novantrone weekly dose (mg)	Total no. RX	Time to recurrence (mos)	Bladder toxicity	
						Symptoms[a]	Bladder capacity
3	Ta 2 TIS 1	I–II	5	25	3.3	None	Normal
3	T1 1 TIS 2	I	6	18	3.7	None	Normal
3	Ta 2 TIS 1	I–II	7.5	18	3.7	Mild	Normal
2	Ta 1 T1 1	I I	9	12	2.5	Mild	Normal
3	Ta 1 TIS 2	I	10.5	18	2.5[c]	Mild	Significant reduction
4	T1 3 TIS 1	I–II	12	21	3[c]	Mild/severe	Significant reduction
4[b]	Ta 1 T1 1 TIS 2	I II	13–13.5	16	3[c]	Mild/severe	Significant reduction

[a] Dysurea, urgency, frequency, bladder spasm, hematuria.
[b] Two patients dropped due to side effects.
[c] One failure.

treatment for the reason of side effects was only 1 week. Bladder capacity was not affected. At 10.5 mg weekly dose the symptoms of bladder toxicity were mild and also the changes in bladder capacity were negligible. At doses of 12 and 13.5 mg, genito-urinary complaints were moderate to severe and the effect on bladder capacity was significant, in some cases more than a 50% decrease was noted. In one patient who received the 12 mg dose, the symptoms were so severe that the patient was hospitalized for systemic dehydration and anorexia, hematuria, nausea, vomiting, diarrhea, bladder spasm and tremendous irritability of the lower urinary tract. The patient developed urgency incontinence. Cystoscopy following treatment in this patient revealed severe chemical cystitis with necrotic epithelium, severe congestion and edema. Repeated biopsies for malignancy were negative. Urge incontinence lasted for nearly 6 months, at which time the patient gained continence and developed a reasonable bladder capacity. He has remained in complete remission for the past 13 months.

Hematology, serum chemistry and urinalysis were done at baseline and at various times during the study. Of the 20 patients, none had a clinically significant laboratory value change during the course of therapy except transient microhematuria and pyuria.

The small number of patients and the short follow-up precluded a formal evaluation of efficacy. However, assessment of the patient's clinical response even for this short time provides a preliminary indication of efficacy. All the patients were cystoscoped at baseline a few weeks post-induction, and prior to first monthly therapy. Cytology of bladder washing and voided urine, and bladder biopsy were performed at the same time. Time to treatment failure was evaluated using the information from repeated cystoscopies and cytology and biopsies. At the first evidence of recurrent disease, as evidenced by cystoscopy, positive cytology or biopsy, patients were considered in relapse and taken off the study. Twenty patients were evaluable for clinical response assessment. Three of eight patients with TIS failed to respond to therapy. The average time to progression for responders was 3.6 months, while in 12 remaining patients with stage Ta, T1 and grade I–II, average time to progression was 3 months. Mean time to tumor recurrence for these responders was an average of 3 months in different treatment groups, with some remaining in complete response. The response rates in different treatment groups are comparable. Of interest, there were four patients refractory to BCG, all with papillary lesion stage Ta–T1 and grade I–II. They showed an average duration response of 5 months after treatment with novantrone. In four patients who received monthly novantrone maintenance doses for 3–5 months, time to recurrence was the same. The average time to recurrence in all groups was 3.1 months. Due to the small number of patients and the short follow-up, a meaningful clinical response assessment is not possible.

Discussion

Overall, novantrone seems to have molecular characteristics of a good intravesical agent and is well tolerated at doses of ≤9 mg. At this dose, bladder adverse effects such as dysuria and urinary frequency are minimal and there is no significant effect on bladder capacity. These minor initial symptoms are comparable to those seen with other intravesical agents commonly used. We suggest a 9 mg weekly dose to be used as a starting dose. Severe irritative symptoms for this dose reported in the Canadian study in one patient indicates the need for close follow-up and monitoring, particularly when the dose is increased to 12–13 mg/week. Bladder irritative symptoms at the higher doses (≥10.5 mg) were moderate to severe and the effect on bladder capacity was significant. At this dose novantrone can cause bladder mucosal necrosis, ulceration, or hematuria, which may take a long time (several months) to heal. If the patient develops moderate bladder irritability, one should withhold therapy for 1–2 weeks until recovery. The effect on bladder capacity at large doses may be long-lasting and patients usually improve only after several weeks. In one patient it took several months to improve bladder capacity and 30% loss of bladder capacity was permanent.

In regard to efficacy, the 5-month response in four BCG-treated patients was promising. Overall, follow-up was too short and a meaningful analysis was not possible. In view of the above-mentioned observation, a randomized comparative study using ≤9 mg dose is needed in order to assess efficacy of this agent.

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