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Intravesical Mitoxantrone in Superficial Bladder Tumours (Ta–T1)

Vincenzo Serretta, Gaspare Corselli, Carlo Pavone and Michele Pavone-Macaluso

36 patients with histologically proven grade G1–G2, Ta–T1 transitional cell carcinoma of the bladder were introduced, after transurethral resection (TUR), into a study of intravesical chemoprophylaxis with mitoxantrone (20 mg diluted in 50 ml). After a mean follow-up of 23 months, 16 (50%) patients showed a superficial recurrence with a mean recurrence rate of 0.56 per year. In 19 patients with recurring tumours the mean recurrence rate decreased from 1.65 to 0.58 per year. 9 patients (25.7%) suffered from a chemical cystitis that in 2 cases (5.7%) required treatment interruption.
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INTRODUCTION

ALTHOUGH INTRAVESICAL treatment with BCG doxorubicin, epirubicin, ethoglucide, thiotepa or mitomycin C has been shown to reduce recurrence rate of superficial (Ta, T1) bladder tumours, a substantial number of patients will continue to show recurrent lesions and some may undergo tumour progression and death. As discussed in previous papers [1, 2] there is an urgent need for more information on new modalities of treatment and to test new anticancer drugs for their potential intravesical use.

Correspondence to V. Serretta.
V. Serretta is at Via Malaspina 136, 90145 Palermo, Italy; V. Serretta is at the Civic Hospital, Dept. Of Urology, Ospedale Civico, Divisione di Urologia, Via C. Lazzaro 90129 Palermo; and G. Corselli, C. Pavone and M. Pavone-Macaluso are at the Institute of Urology, University of Palermo, Italy.
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Mitoxantrone is an anthraquinone derivative, related to daunorubicin, doxorubicin and epirubicin. It differs from these in that it has a more intense and broader antitumour activity *in vitro*. It acts on neoplastic cells at phase G0, being able to interact not only with DNA but also with mRNA [3, 4].

A recent phase I study of intravesical chemotherapy suggested some activity of mitoxantrone on vesical transitional cell tumours and indicated that 10 mg (diluted in 30 ml of saline solution) was the highest tolerable dose [5]. Since the antitumour activity of mitoxantrone was proven to be dose-related *in vitro*, we initiated a pilot study to test the tolerability and the efficacy of mitoxantrone at a higher dose than previously reported and adopting a different retention time.

MATERIALS AND METHODS

36 patients with histologically proven grade G1–G2, Ta–T1 transitional cell carcinoma of the bladder, removed by trans-

Table 1. Characteristics of the 32 evaluable patients

Stage	Number	(%)		Number	(%)
G1	7	(21.8)	Single	11	(34.3%)
G2	25	(78.2)	Multiple	21	(65.7%)
Ta	26	(81.3)	Primary	13	(40.6%)
T1	6	(18.7)	*Recurrent	19	(59.4%)

* Mean recurrence rate 1.65 per year.

Table 2. Results

No. of entered patients	36
No. evaluable for toxicity	35
No. evaluable for efficacy	32
Mean follow-up (months)	23.2
Patients with recurrence (%)	50
Mean recurrence rate (per year)	
All patients	0.56
Recurring patients (19)	0.58
Chemical cystitis (%)	25.7

urethral resection (TUR), extended at the underlying muscular layer were subsequently introduced into a prospective pilot study. Patients whose tumours were primary, single, of G1 grade and Ta category and patients with G3 grade tumours and/or Tis were excluded.

Abnormal haematological, renal or hepatic function, previous systemic chemotherapy or pelvic radiotherapy, intravesical chemotherapy or immunotherapy in the last 3 months, other tumours except cutaneous basalioma or persistent urinary tract infection, were criteria of exclusion.

At 14–21 days post-TUR, mitoxantrone was given intravesically at the dose of 20 mg diluted in 50 ml of normal saline solution and maintained in the bladder for 1 h. Fluid intake was restricted during the preceding night. The treatment schedule consisted of four weekly administrations repeated monthly for the next 11 months, according to the standard schedule adopted in the studies of intravesical chemoprophylaxis by the Urological Group of the EORTC (European Organization for Research on Treatment of Cancer).

All patients were submitted to routine laboratory tests to monitor haematological, renal and hepatic function before each administration and to urine cytology, cystoscopy and biopsy of all suspicious vesical lesions every 3 months. Multiple biopsies of apparently normal mucosa were taken in case of positive cytology and negative cystoscopy. In cases of bacterial cystitis, confirmed by urine analysis and culture, or in case of chemical cystitis of moderate or severe intensity, the instillation was postponed, and appropriate therapy given, until clinical recovery and urine normalisation. If administration was delayed longer than 14 days, patients were considered to be off-study.

The characteristics of the patients are given in Table 1.

More than 50% of the patients had recurrent tumours, in spite of intravesical chemoprophylaxis (epirubicin or mitomycin C), with a mean recurrence rate of 1.65 per year. The mean interval of time free from recurrence was 7.2 months.

RESULTS

Of the 36 entered patients, 1 refused the treatment after the second instillation and 3 patients refused control cystoscopies during and after the treatment. At a mean follow-up period of 23 months (range 13–31) 32 patients were evaluable with respect to efficacy and 35 for toxicity assessment.

16 (50%) patients showed a superficial recurrence with a mean recurrence rate of 0.56 per year. Among the 19 patients with recurring tumours the mean recurrence rate decreased from 1.65 to 0.58 per year (Table 2). The mean recurrence-free interval increased from 7.2 to 19 months. No patients showed progression in T-category. Small papillary lesions, less than 10 mm in diameter, totally necrosed and still adherent to the vesical walls were detected at follow-up cystoscopies in 7 patients, at 3, 6 and 12 months from start of treatment. Biopsy always revealed extensive necrosis. Urine cytology was negative in all cases and patients were free of lesions at the subsequent cystoscopies.

No systemic toxicity was evident. 2 (5.7%) patients presented a chemical dermatitis localised at the penis glans and foreskin that did not require treatment interruption. 9 patients (25.7%) suffered from a chemical cystitis that in 2 cases (5.7%) required permanent treatment withdrawal.

DISCUSSION

The preliminary results of our study suggest the tolerability and a possible efficacy of mitoxantrone in the intravesical chemoprophylaxis of superficial bladder tumours. Since the patients introduced in this study were at medium or high risk for recurrence, the decrease of the recurrence rate after treatment in previously relapsing patients points to the efficacy of the drug. A relevant aspect emerging from our experience is the contrast on tolerability between our data and those reported by Stewart *et al.* [5]. In the above mentioned study, although the drug was administered at a lower dose and concentration (10 mg diluted in 30 ml) than in the present study, mitoxantrone caused a higher incidence of severe chemical cystitis requiring definitive interruption of the treatment. This fact was probably due to the shorter retention time of the drug in the bladder in our study (1 and 2 h, respectively).

We feel that large phase III studies, supported by the results of pilot phase II studies on a marker lesion or on Tis, are needed to assess the value of our preliminary data.

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