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Intravesical Ethoglucid (Epodyl^{R}) for Treatment of Noninvasive Bladder Cancer (Stage Ta)

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ABSTRACT

Widespread, well differentiated (grade I) bladder tumours confined to the mucosa (stage Ta) were treated with regular intravesical instillations of ethoglucid (Epodyl^{R}) in 24 patients. The therapeutic schedule could be followed in all but one patient, in whom side effects necessitated cessation of treatment. Complete response was obtained in 75 % of the patients, and during continued prophylactic therapy 90 % remained tumour-free. After termination of the treatment,however, new tumours appeared in 60–80 % of the patients.

INTRODUCTION

Superficial bladder tumours (stage Ta and T1) have always been regarded with some distrust because of the high recurrence rate after endoscopic resection or fulguration. Moreover, tumours developing after resection have sometimes been of higher stage or grade. Consequently, the evolution of antitumour chemotherapeutic drugs for intravesical use aroused expectations of more permanent cure of superficial bladder tumours as an alternative to conventional endoscopic resection or as prophylactic adjuvant to transurethral treatment. During the past 25 years several cytotoxic agents have come into use. Numerous studies have been done to determine which patients should receive chemotherapy, when to initiate treatment, and what agent, dose, treatment schedule and duration of treatment are most appropriate for superficial bladder tumours. Definitive answers to these questions are still awaited.

Thiotepa seems to have been the first agent utilized for this purpose. Although highly effective in some cases of highly differentiated bladder tumour, this drug has never achieved popularity, mainly because of its serious side effects, the chief of which is myelosuppression due to absorption through the bladder mucosa.

Ethoglucid (Epodyl^{R}), introduced in 1971 by Riddle & Wallace (9), is another drug used for topical chemotherapy. It is an alkylating antineoplastic

agent with higher molecular weight than thiotepa. Systemic side effects are uncommon, presumably because none or very little of the drug is absorbed from the bladder. Although new drugs such as adriamycin (Doxorubicin hydrochloride) and mitomycin C have well established efficacy against superficial bladder cancer, Epodyl is still extensively used in many centres, especially in Europe, as standard treatment of superficial tumours of the bladder.

The aim of this study was to determine the therapeutic effect of intravesical Epodyl on superficial papillary cancer of the bladder, without invasion into the lamina propria (stage Ta) and of low malignancy grade (grade 1).

MATERIAL AND METHODS

The series comprised 24 patients, 21 men (mean age 66, range 33-85 years) and three women (aged 68, 76 and 81). All presented with extensive bladder tumours. In 12 cases these tumours were recurrences after frequent transurethral resection and/or fulguration for papilloma. The other 12 patients had not previously received treatment.

In all the patients surgical biopsy was taken for pathologic classification of the tumour, which otherwise was left intact.

To make the series as homogeneous as possible, only patients with tumours classified as stage Ta (UICC), grade I (WHO) were included in the study. For treatment with Epodyl (ICI, UK), the Riddle-Wallace (9) schedule was used. A solution of 1 ml Epodyl in 100 ml distilled water was instilled with a glass syringe into the empty bladder, and the solution was retained for one hour. The schedule for instillations was as follows:

Once weekly for 3 months,
then
fortnightly for 3 months,
then
monthly for 1 year,
then
monthly to every third month.

The treatment was given on an out-patient basis. Cystoscopic checks were made every third month.

RESULTS

The results are surveyed in Fig. 1. Complete regression (CR) was obtained

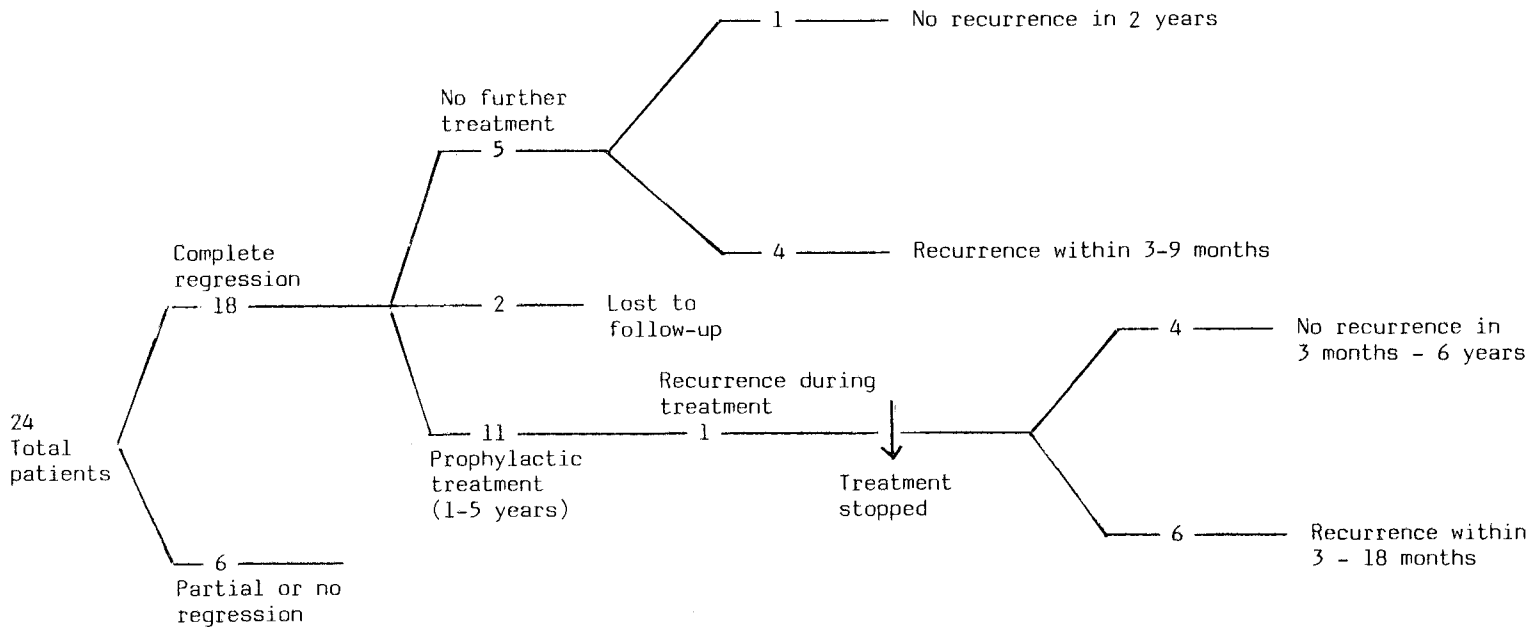

Fig. 1. Flow diagram presenting the results of intravesical Epodyl treatment of superficial bladder tumours (grade I, stage Ta)

in 18 of the 24 patients after 3 to 6 months of therapy. Eleven of the 18 received further prophylactic treatment for periods ranging from 1 to 5 years, and during these periods 10 of the patients remained free from tumour. After the treatment was stopped, however, six had recurrence, all within 18 months. Four patients have remained tumour-free during follow-up for periods of 3 months to 6 years. One patient showed recurrence of tumour while undergoing prophylactic treatment.

Five of the 18 patients with CR were not subsequently given prophylactic treatment. In four of them there was recurrence of tumour after 3 to 9 months, while one has remained tumour-free during two years of observation. In 6 of the 24 patients the Epodyl instillations did not result in CR.

Two of the 18 patients with CR failed to attend for follow-up investigation.

Local side effects in the form of frequency of micturition and dysuria were experienced by 10 (40 %) of the patients, but necessitated discontinuation of treatment only in one. There were no systemic side effects.

All the patients with recurrence of tumour have received further treatment, with intensified transurethral resection and/or additional chemotherapy.

DISCUSSION

In this series of patients, intravesical instillations of Epodyl for widespread, noninvasive (stage Ta), highly differentiated (grade I) bladder cancer initially gave complete eradication of tumour in 75 % of the cases. When the curative treatment was not superseded by prophylactic chemotherapy, however, new tumours appeared in 80 % of the patients within 3 to 9 months. When prophylaxis was given, 90 % of the patients remained tumour-free during the treatment period. After termination of the prophylaxis, 60 % of these patients also sooner or later showed new tumours.

Comparison of our results with those of other investigators is not easy, since such studies commonly do not describe in detail how many of the so-called superficial tumours were, in fact, in stage Ta or T1, how many were papillary tumours or primary carcinoma in situ and how many patients had been given Epodyl as treatment with curative intent or as prophylaxis following transurethral tumour resection. Moreover, figures for response rate have sometimes included both complete and partial regression of tumour.

In some series reported in the literature, however, superficial bladder tumours were managed essentially as in our patients, with intravesical instillations of Epodyl given as therapy and not simply as complement to endoscopic procedures. In comparison with such series, our figures for complete

tumour regression equal or exceed those stated for Epodyl treatment (1,9,10, 11,12), equal those for mitomycin C (4), and are clearly superior to results with thiotepa (3,7,14) and adriamycin (2,5).

Our series comprised only patients with precisely defined pathologic stage of tumour, Ta. This may explain the more favourable response rate among our patients than in other series, which included Tis, a tumour with prognosis often much worse than for other superficial tumours.

The observation that new tumours so often arise after termination of initial transurethral resection and/or intravesical chemotherapy that has eliminated existing tumours supports the theory postulated by Soloway (13) and others, viz. that the later lesions are not "recurrences" but are indeed new, possibly produced by carcinogens or other, still obscure aetiologic factors.

Local side effects occurred in 40 % of our patients, especially during the first phase of treatment, when the instillations had to be fairly frequent. But only in one case were the side effects so severe as to necessitate discontinuation of the treatment. In the other patients frequency and dysuria were transient, and after some adjustment of dosage and treatment schedule the instillations could be continued. Our results in this respect contrast favourably with earlier reported observations that Epodyl treatment had to be stopped because of serious side effects in 5 to 25 % of cases (8).

Much attention has been given to the risk that tumours may develop as a complication of chemotherapy (6). In our study, however, the histologic appearance of new tumours appearing during or after the prophylactic treatment did not differ from that in the initial tumours, although in some cases treatment had been given for up to 5 $\frac{1}{2}$ years.

In conclusion, our study showed that patients with superficial bladder tumours of stage Ta, grade I are suitable for intravesical chemotherapy. Compared with other chemotherapeutic agents, Epodyl has proved favourable for this purpose. The advantages of Epodyl are its documented effectiveness, relative lack of side effects and fairly low cost.

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