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Treatment of carcinoma in situ of the bladder with doxorubicin (Adriamycin)

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Summary. *Fifty-five patients with carcinoma in situ of the bladder have been treated with intravesical Adriamycin, the longest follow-up being over 2.5 years. Side-effects were negligible. Primary carcinoma in situ shows the highest overall response rate, with over 80%, followed by secondary carcinoma in situ with no tumours, with 67%; in the presence of active tumour only 25% of patients treated showed any real improvement. Adriamycin is recommended for the conservative management of primary carcinoma in situ.*

Introduction

Carcinoma in situ of the bladder has been defined as a flat, urothelial neoplasm confined to the epithelial layer, consisting of cells of high cytological grade (G3) [5]. This definition is histologically accurate, but the clinical disease is probably more widespread than is generally appreciated. The lesion, which may be widespread, consists of flat areas of epithelium with cells showing anaplastic features and a variable pattern of growth. Many published studies of this condition have been performed retrospectively on cystectomy specimens or at autopsy, and although the condition has a sinister reputation, in many patients with carcinoma in situ it may be a long time before carcinoma actually develops and becomes invasive. Some urologists advise total cystectomy, while others adopt a 'wait and see' attitude until such time as a tumour actually appears. Any treatment that can keep the disease under control and at the same time allow a patient to retain his bladder should be considered; the series now described consists of 55 patients who have been treated with intravesical doxorubicin (Adriamycin). The criterion of entry into the study was histological evidence of carcinoma in situ with malignant exfoliative urine cytology.

What evidence is there that intravesical Adriamycin has any effect in carcinoma in situ? Cytological examination of the urine following intravesical therapy shows marked pyknosis or disruption of the nucleus, eosinophilic staining of the cytoplasm, and disruption of the cell membrane, while the nucleus becomes paler and less hyperchromatic. The nucleus is usually pushed to one side of the cell and eventually extruded, and intracellular phagocytosis appears to take place. These features can be observed after two treatments and are constantly reproducible. The initial cells that are killed are large, hyperchromatic, malignant cells, but as the treatment continues the damaged cells become smaller and rounder, and have obviously come from the basal cell layers. The appearance of the bladder at cystoscopy before treatment is variable; the bladder mucosa may look relatively normal, but in other cases widespread areas of pink mucosa may be observed. Following treatment the cystoscopic appearance of the bladder improves considerably and, in time, becomes more normal. Evidence of severe damage to the epithelial lining of the bladder may also be seen on biopsy and the basement layers become so eroded that it is difficult to see any epithelial lining in the histological sections.

Materials and methods

In all patients, in addition to the usual history, which included a detailed occupational background, a complete blood count and serum electrolyte profile were performed. Intravenous pyelography, urine culture, and cytological examination of the urine were carried out in early morning specimens which were spun down, stained, and graded using the Papanicolaou technique. Cystoscopy was then performed under a general anaesthetic and multiple biopsies of the bladder mucosa obtained, which were examined histologically to confirm carcinoma in situ.

Informed consent was obtained from the patients, who were treated on an out-patient basis. The bladder was emptied by a small urethral catheter (size 14 Fr), and 50 mg Adriamycin dissolved in 50 ml sterile saline was introduced into the bladder, after which the catheter was removed. The patients were then placed in different positions, e.g., prone, supine, head down etc., every 20 min for a period of 2 h before they were allowed to empty their bladders. No patient had this treatment within 21 days of either a transurethral resection of tumour or multiple mucosal biopsies. They were not asked to dehydrate themselves, but they were advised not to drink excessively on the morning of treatment, so that they could retain the Adriamycin for the 2-h period. This treatment was repeated at weekly intervals for 6 weeks so that a total of 300 mg Adriamycin was given to each patient.

There were 55 patients in the series, who were divided into 17 cases of primary carcinoma in situ, 22 cases of secondary carcinoma in situ with a previous history of localised tumour that had been successfully resected, and finally, 16 patients who in addition to carcinoma in situ had tumour present in some other part of the bladder, which was resected before any intravesical treatment was initiated. There were 52 males and three females in the series, 32 of whom had almost certainly been exposed to industrial carcinogens, e.g., naphthylamine and benzidine.

Table 1. Cytological response to Adriamycin

Initial condition	Improvement at				Overall success rate
	1 month	3 months	1 year	2 years	
I Ca in situ	15/17 88%	15/17 88%	8/9 88%	3/5 60%	82%
II Ca in situ with previous tumour	20/22 91%	19/22 88%	12/14 88%	5/7 70%	67%
II Ca in situ plus tumour	9/16 57%	6/16 37%	6/14 43%	3/3 100%	38%

Each patient was assessed cytologically after three and six instillations of the drug, then at 1 month, 2 months, and 3 months, and thereafter at 3-monthly intervals. Regular cystoscopies were performed at 3-monthly intervals and further biopsies taken of the bladder wall.

Results

Primary carcinoma in situ

Cytologically, the condition had improved in 15 out of 17 after the course of treatment, becoming benign in 10 cases; in two the condition was unchanged. These results were maintained at 3 months, when two more had a benign cytological picture. One patient's condition deteriorated at 3 months and review cystoscopy showed a raised carcinoma in situ requiring alternative treatment. The condition of one patient was unchanged at his first assessment and remained the same for 2.5 years. At 1 year, eight of the nine patients whose condition had been benign at 3 months remained in an improved state, and at 2 years three of the five maintained their improvement without further treatment. One patient deteriorated at 2 years, so that in summary the overall results showed a marked improvement in 14 of 17 patients on cytological assessment.

At cystoscopy 3 months after treatment, 15 of the bladders were normal in appearance, but one deteriorated with a raised carcinoma in situ and one was unchanged. At 1 year, eight of nine patients maintained their improvement, the other patient developing a small T_1 tumour. At 2 years all five patients were improved, with four of the bladders looking quite normal (see Tables 1 and 2). The failure rate in this group was 12%.

Secondary carcinoma in situ with a previous history of T_1 tumours

There were 22 patients in this group, 20 of whom improved cytologically after treatment, while two were unchanged. At 3 months, 19 had maintained their improvement and three had deteriorated. At 1 year, 12 of 14 remained satisfactory and a further two had deteriorated. In two years five of seven remained satisfactory with two relatively unchanged, so that altogether in this group seven of 22 had deteriorated.

At cystoscopy at 3 months, 19 of the 22 patients showed marked improvement, two being unchanged and the other having developed a T_1 tumour. At 1 year 10 of 14 maintained their improvement, but a further patient developed a T_1 tumour, two had developed invasive carcinoma, and the other remained unchanged. At 2 years, five of seven patients maintained their improvement but a further two had developed T_1 tumours. In summary, then of 22 patients who were adequately assessed, four developed T_1 tumours and two developed invasive carcinoma, which gives an overall failure rate of 37% (see Table 1 and 2).

Table 2. Cystoscopic response to Adriamycin

Initial condition	Improvement at			Overall success rate
	4 months	1 year	2 years	
I Ca in situ	15/17 88%	8/9 88%	5/5 100%	88%
II Ca in situ with previous tumours	19/22 88%	10/14 71%	5/7 71%	67%
II Ca in situ plus tumour	11/16 68%	7/14 50%	2/3 66%	25%

Secondary carcinoma in situ associated with T_1 tumours

In this group all the patients had their T_1 tumours resected and 3 weeks later had a course of intravesical Adriamycin. Cytologically nine of the 16 had improved at 1 month, but in seven the condition was unaltered. At 3 months six maintained their improvement but another three deteriorated and at 1 year six of 14 remained improved. At 2 years all three patients maintained their improvement. Thus 10 patients had not significantly improved, giving a failure rate of 10 out of 16 (62%).

At cystoscopy 11 of 16 showed improvement at 3 months, but 4 had developed T_1 tumours. At 1 year seven of 14 maintained their improvement, but in two the appearance of the bladder mucosa had deteriorated, four had developed T_1 tumours and one, an invasive carcinoma. At 2 years, two out of the three bladders had maintained improvement but one remained unchanged, so that in this group, nine of the 16 patients had developed tumours, one was unchanged, and in two the bladder mucosa had become redder; that is to say, 12 of 16 did not really respond, giving a failure rate of 75% (see Table 1 and 2).

Adverse reactions

Three patients of the 55 could not tolerate the Adriamycin regimen as frequency, dysuria, and bladder spasm meant they were unable to retain the Adriamycin for the 2-h period. Two patients had proven urinary tract infections which responded to suitable antibiotics. There was no evidence of any systemic upset.

Discussion

In patients who did not show a satisfactory response to their 6 weeks of treatment, further courses of Adriamycin were given. One patient had 18 treatments in all, but extra Adriamycin did not seem to confer any benefit. The impression gained is that if

a patient is going to respond he will do so after six treatments, although it should be pointed out that there is often a delay before the urine becomes completely clear cytologically, as dead malignant cells often exfoliate in the urine 9–12 months after the last treatment.

The literature on carcinoma in situ contains many unexplained observations, but previous reports do suggest that carcinoma in situ is a precursor of invasive carcinoma. One series [3] showed that in patients who had a cystectomy for extensive carcinoma in situ, 25% had microfoci of invasive carcinoma when the bladder was examined following surgery. When carcinoma in situ is present in a patient who has previously undergone resection of a bladder cancer, the likelihood of developing an invasive tumour is 42% [2] and if carcinoma in situ is shown to be in close proximity to other T_1 tumours the incidence of invasive carcinoma rises to 83% [1]. When the results obtained in the present series are compared with these figures a considerable benefit seems to have been obtained, but only a longer follow-up will give the final answer. It seems reasonable that total cystectomy should always be deferred until such patients as these have had a course of intravesical therapy.

In conclusion, Adriamycin undoubtedly causes massive malignant cell death in carcinoma in situ of the bladder, and it consistently improves the appearance of the bladder mucosa at cystoscopy. Experience suggests that 300 mg Adriamycin intravesically is quite adequate in the treatment of primary carcinoma in situ, since if a good response has not been obtained this is unlikely to be altered by increasing the dose or giving the drug more frequently. It has recently been suggested [4] that in patients who show a good initial response further Adriamycin may be necessary 2–3 years after the original treatment. It seems from the figures that intravesical Adriamycin has an important role in the active management of primary carcinoma in situ, as substantial regression of the disease occurs (82%); but these patients must be kept under close clinical supervision so that early deterioration may be noted and more radical therapy instituted. Where secondary carcinoma in situ has been diagnosed in the absence of active tumours the response is still good (63%), but in association with active malignant disease the response is much poorer (25%). Larger studies with a longer follow-up are urgently needed before a definitive assessment can be made.

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