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Early adjuvant Adriamycin in superficial bladder carcinoma

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Summary. *A multicenter study was performed in 110 patients with superficial transitional cell carcinoma of the bladder. Adriamycin (50 mg/50 ml) was administered intravesically within 24 h after transurethral resection of TA–T1 (O–A) bladder tumors. Instillation was repeated twice during the first week, then weely during the first month and afterwards monthly for 1 year. The tolerance was evaluated in these 110 patients, and 29 patients presented with local side-effects. In 24 of these patients chemical cystitis was severe enough for them to drop out of the study. No systemic side-effects were observed.*

Recurrence was studied in 82 evaluable patients after 1 year of follow-up and in 72 patients followed for 2–3 years (mean 32 months). Of the 82 patients studied after 1 year, 23 had primary and 59 recurrent disease. Of the 82 evaluable patients, 50 did not show any recurrence after 1 year (61%), while 32 presented with one or more recurrences (39%). Of these recurrences, 27 were T1 tumors while five progressed to more highly invasive lesions. In patients that were free of recurrence during the first year, 80% remained tumor-free during the 2- to 3-year follow-up period. Of the patients developing one or more recurrences during the first year, only 50% presented with further recurrence once the instillations were stopped. The beneficial effect of Adriamycin appears obvious and might be related to the drug itself, the early and repeated instillations after TUR, or both.

Introduction

The multifocal nature of superficial transitional cell carcinoma of the bladder and the frequent recurrences after transurethral resection indicate a need for adjuvant chemotherapy to reduce or delay the incidence of recurrent tumors. For several decades various substances have been used intravesically, e.g., silver derivatives, lead, alcohol, selenium, and phenol. The introduction of thio-TEPA by Jones and Swinney in 1961 [7] was the beginning of a new era in bladder cancer with the use of chemotherapeutic drugs for local treatment of bladder tumors. Thio-TEPA is still one of the drugs most frequently used for intravesical chemotherapy. Numerous studies have documented its relative activity in diminishing the recurrences of superficial bladder tumors, but systemic side-effects are not uncommon due to its absorption through the bladder wall [11].

Adriamycin (doxorubicin hydrochloride) proved to be an active antineoplastic drug when given IV, and it has recently been used intravesically for the treatment of bladder tumors [1, 2, 4, 9]. Intravesical administration might be effective, since studies have documented a high uptake into normal and neoplastic epithelial cells. The minimal absorption beyond the basement membrane would provide an important advantage over Thio-TEPA. Hence, the measurement of blood levels of Adriamycin following its intravesical instillation have shown that there is very litte absorption into the bloodstream and all its effects on bladder tumors and the urothelium are mediated by direct contact of the drug with tumor and urothelial cells [5, 6]. Thus, systemic absorption of Adriamycin from the bladder is very low and the risk of systemic side-effects is therefore very limited.

The high incidence of recurrences is primarily due to the multifocal nature of these tumors, but implantation of tumor cells following transurethral resection may be a contributing factor [11, 12].

The therapeutic implications of these concepts are obvious. Those who favor the idea of diffused urothelial disease advocate repeated and prolonged instillation of chemotherapeutic agents. People who a favor the tumor implantation theory advocate early instillation of drugs in the bladder to destroy any remaining floating neoplastic cells. Since at present adequate methodology is not available to prove or disprove either of these concepts, it is wiser to consider that both theories are correct: that this is a multifocal urothelial disease and that implantation of tumor cells may occur. Thus, a combined therapeutic approach seems advisable: early instillation of chemotherapeutic agents in the bladder, repeated at regular intervals for a least 1 year.

We have applied this concept in the present study, using early and prolonged adjuvant chemotherapy in patients presenting with superficial transitional cell carcinoma of the bladder after transurethral resection.

Clinical materials and methods

This multicenter study involving six university institutions was performed in 110 patients with transitional cell carcinoma of the bladder classified as stage TA–T1 according to the TNM classification (infiltration not extending beyond the lamina propria) (Jewett's stage O–A). Of the 110 patients entered in this study, 23 had primary disease while 77 had recurrent lesions.

Prior to the initiation of treatment, a full history was taken down for each patient and each was subjected to a full physical examination, chest X-ray, comprehensive blood examination, and a chemistry profile. At the time of cystoscopy and

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transurethral resection a bimanual examination was performed. All visible tumors were resected and subjected to histological examination.

Intravesical instillation was begun after all visible lesions had been cleared from the bladder by transurethral resection. Thus, in this study, intravesical chemotherapy was considered as an adjuvant prophylactic treatment. The first intravesical instillation was given within 24 h after transurethral resection. Adriamycin 50 mg was dissoveld in 50 ml physiologic saline.

The drug was instilled into the bladder through a sterile catheter and retained for 1 h, the position of the patient being changed regularly. Instillation of Adriamycin at the same dosage was repeated twice during the first week (3rd and 7th days), then weekly during the first month and subsequently monthly for 1 year. Thus, a total of 17 instillations was given during this 1-year treatment.

Control cystoscopy was performed each 3 months for the first year and then each 4 months in subsequent years of follow-up.

Results

All 110 patients were evaluable for tolerance. Of these, 29 (26.3%) presented with local side-effects, essentially chemical cystitis (dysuria, pain and/or hematuria). In 24 patients (21.8%) the side-effects were severe enough for them to drop out of the study. All of three patients who had received earlier radiotherapy to the bladder experienced severe chemical cystitis during the instillations and dropped out of the study. In no patients were systemic side-effects observed.

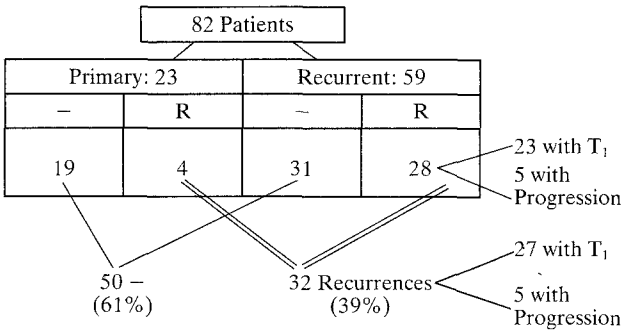
Recurrences were analyzed in 82 evaluable patients followed-up for 1 year and in 72 patients remaining in the sutdy for periods ranging between 2 and 3 years (mean 32 months). Among the 82 patients evaluable 1 year after entry in the study who received the complete course of treatment, 23 had primary disease while 59 had had recurrent lesions previously.

Of the total of 82 patients, 50 did not show any recurrence after 1 year (61%), while 32 showed one or more recurrences (39%). Among these recurrences, 27 were lesions of the same stage (TA–T1), while in five progression to more invasive lesions was seen (T2, 3 cases; T3, 2 cases). The distribution of recurrences among patients with primary and recurrent disease is shown in Table 1. Thus, after 1 year of treatment the percentage recurrence rate in patients with primary disease was 17%, while in the recurrent disease group it was 47%.

After a period of regular cystoscopic follow-up ranging from 2 to 3 years (mean 32 months) a second analysis was performed on the 72 patients remaining in the study. Among the 50 patients who did not show any recurrence during the first year three were lost to follow-up, and of the 47 patients remaining in the study for the later analysis 38 (81%) remained free of any recurrence while nine (19%) presented with a recurrence at some time during the 2–3 years of follow-up. Of the 32 patients who had a recurrence during the first year of the study while under treatment, 25 remained in the study for the later analysis (5 progressions and 2 patients lost for follow-up). Among these 25 patients, 14 (56%) presented with one or more new recurrence during this follow-up period, while 11 (44%) remained free of any recurrence during the same period (Fig. 1).

If the results for the total period of follow-up are analyzed as described in the EORTC clinical trials, the recurrence rate is

Table 1. Evaluation of recurrences (R) after 1 year



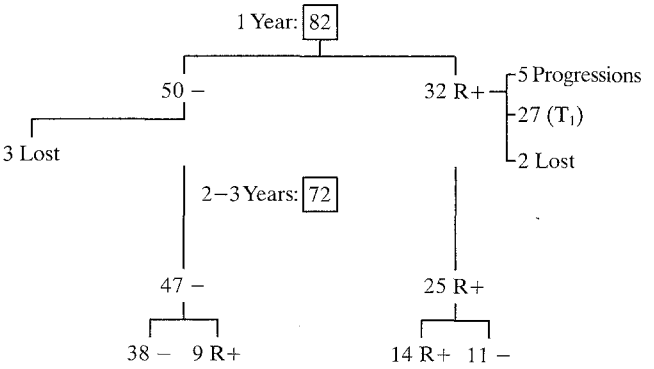


Fig 1. Evolution of patients treated for 1 year

Table 2. Recurrence rate

No. of patients	110
No. of patients followed up	82
No. of patients with recurrence	41
Percent with recurrences	50
Total no. of recurrences	52
Total months of follow-up	1,783
Recurrence rate $= \frac{\text{No. recurrences}}{\text{Months follow-up}} \times 100$	2.9

defined as the number of follow-up cystoscopies at which a recurrence is noted, divided by the total months of follow-up. This result is then multiplied by 100 to simplify the presentation [11]. In this study, the recurrence rate/100 patients months was 2.9 (Table 3).

Discussion

This study provides evidence that Adriamycin is active as an adjuvant therapy for patients with superficial transitional cell carcinoma of the bladder. A significantly lower recurrence rate was noted in patients treated with Adriamycin when the results were compared with the data given in the literature from various studies on non-treated patients [3, 8, 10, 11, 13].

The percentage of recurrence in all patients receiving early and repeated adjuvant prophylactic instillations of Adriamycin was 39% after 1 year of treatment and 51% after a 2- to 3-year follow-up period without any further treatment. This is significantly lower than in a non-treated population, where it usually ranges between 60% and 70% [3, 11, 12]. This difference is even more significant if patients with primary disease receiving Adriamycin are considered separately; the

percentage of recurrence in these patients was 17% at 1 year and 23% after 2–3 years, while it is about 60% in non-treated patients [11]. In the case of recurrent disease the corresponding were 47% after 1 year and 58% later following treatment with Adriamycin, compared with more than 80% in a non-treated group even with a shorter follow-up, the majority of these recurrences occurring during the first year [3, 11].

The recurrence rate, which takes into account the total number of recurrences during the total period of follow-up, compares very favourably with the recurrence rate observed in other studies, and in particular in the EORTC randomized trial comparing thio-TEPA, an epipodophyllotoxin, and transurethral resection alone, where the recurrence rates were, respectively, 5.41, 6.67, and 8.93 recurrences/100 patient-months [11], while the recurrence rate in patients treated with Adriamycin was 2.9. Although these groups cannot be strictly compared as they were not randomized in the same study, the total period of follow-up and all the criteria for selection of patients were comparable.

This study allowed follow-up of patients treated for 1 year with intravesical prophylactic chemotherapy and observation of their evolution once the treatment had been stopped. It clearly showed that of patients who remained free of any recurrence during the first year of treatment, 80% remained tumor-free for the next 2–3 years. Thus it seems reasonable not to prolong chemotherapy for more than 1 year in patients who are free of any recurrence during the first year. One may even question whether a year of treatment is necessary or whether it could not be reduced in patients free of recurrence after 3–6 months.

In patients presenting with one or more recurrence during the first year of treatment, once the treatment was stopped only a little over half of them developed further recurrences. This is a very interesting observation, since it would be reasonable to expect that when patients present with one or more recurrence while receiving a year's prophylactic treatment, the majority will experience recurrence once the treatment is stopped. However, this was not the case since only a little over half of them did so. This indicates the long-term beneficial effect of Adriamycin instillations in controlling urothelial degeneration. In patients with recurrent disease prolonged treatment for at least 1 year therefore seems advisable, since they certainly make up a higher-risk group.

The high cure rate observed in this study might be due to the drug itself, the regimen of very early, repeated instillations, or both.

The early and repeated instillations proposed in this schedule, which are certainly active, lead to significant local side-effects in the form of chemical cystitis. Although no systemic side-effects were observed, a less aggressive regimen should be advised in routine clinical practice. In stead of three instillations during the first week, a single instillation administered within 24 h after TUR should be the only one during the first week, to be followed by the classic schedule of weekly instillations during the first month and subsequent monthly instillations over a period to be determined according to various prognostic factors.

Since the beneficial effect of Adriamycin is obvious from this study, it should stimulate further prospective randomized studies comparing Adriamycin with other drugs and early chemotherapy versus delayed instillations.

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