Cancer Chemother Pharmacol (1986) 16: 176–177

Cancer Chemotherapy and Pharmacology

Intravesical chemotherapy with 4'-epi-Adriamycin in patients with superficial bladder tumors

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Summary. We evaluated the effects of 4'-epi-Adriamycin (EPI), a derivative of Adriamycin (ADR), in intravesical instillation chemotherapy. The patients received two courses of three daily instillations of 50–80 mg EPI dissolved in 30 ml physiological saline on 3 consecutive days, with an interval of 4 days between courses. Full evaluation was possible in 33 of 35 patients with superficial bladder tumors treated with EPI. Complete response was observed in 4 cases and partial response in 14 cases, giving a response rate of 55%. Side effects such as pollakiuria and pain on micturition occurred in 9 cases. EPI appears to be an effective agent for intravesical instillation chemotherapy in patients with superficial bladder tumors.

Introduction

4'-epi-Adriamycin (EPI) is a derivative of Adriamycin (ADR) developed by the Farmitalia Carlo Erba Research Institute; it has been reported to yield similar antitumor effects to those of ADR but with a lower incidence of side effects [1–5].

The authors administered ADR by intravesical instillation for the treatment of superficial bladder tumors and concluded that it was one of the most effective drugs for use by this route [6, 7]. However, side effects, such as irritative effects on the bladder, were observed in 30%–50% of cases. The present investigation was performed in the hope that EPI would be similar to ADR in therapeutic effectiveness, but with fewer and milder side effects.

Materials and methods

Materials. The test sample consisted of 35 patients with superficial bladder tumors (Ta or Tl) being treated at the Department of Urology, Okayama University Medical School. Of these patients, 33 were male and 2 were female; their ages ranged from 39 to 81 years. Twenty patients had presented for the first time, and the remaining 15, with recurrences. Lesions were solitary in 8 and multiple in 27. In terms of pathological grade, there were 10 cases of G1, 16 of G2, 4 of G3, and 5 of GX tumors.

Method of instillation. The same method of instillation was used as has been described in previous reports on ADR [6, 7]; 50–80 mg was dissolved in 30 ml physiological saline and instilled once per day for 3 consecutive days, followed by 4 days' rest and then by another series of 3 daily instillations, giving a total of six instillations. Each instillation lasted for 2 h, the position of the body being changed every 15 min.

Evaluation criteria. Effectiveness was evaluated by cystoscopy, ultrasonic tomography and/or computed tomography results before and 2 weeks after completion of treatment. Total absence of tumor according to all methods of examination was considered to consitute a complete response (CR) and regression by more than 50% but less than 100%, a partial response (PR). The course of treatment could not be completed in 5 of 35 patients because of side effects (2 receiving 60 mg, 3 receiving 70 mg). Of these, 2 patients in whom treatment was stopped after two instillations (60 mg) and three instillations (70 mg) were not included in the evaluation of therapeutic effectiveness. The other 3 cases (1 with 4 and 2 with 5 instillations) were included in the evaluation.

Results

CR was obtained in 4 of the 33 cases and PR in 14, giving an overall response rate of 55% (18/33). Since PR cases were subsequently treated by transurethral resection (TUR), the duration of response duration is not known. Of the 4 patients who achieved CR, 2 are disease-free at 21 and 25 months, 1 developed recurrence at 3 months and the remaining patient was lost to follow-up. Concerning effectiveness in terms of dosage level, neither of the cases receiving 50 mg (1600 μg/ml) experienced any effect, while in the 60 mg (2000 μg/ml) group effectiveness was 56% (5/9), in the 70 mg (2300 μg/ml) it was 55% (11/20), and in the 80 mg (2600 μg/ml) group it was effective in both. Pollakiuria and pain on micturition were observed in 9 of the 35 cases (26%). As shown in Table 1, no side effects (0/2) were seen in the 50 mg group, while the incidence of side effects was (2/10) in the 60-mg group, 29% (6/21) in the 70-mg group, and 50% (1/2) in the 80-mg group. Apart from irritative effects on the bladder, no systemic side effects were revealed by clinical examinations.

Effectiveness was seen in 8 of 20 patients (40%) being treated for the first time and in 10 of 13 patients (77%) with recurrences; in 4 of 8 cases with solitary lesions (50%) and in 14 of 25 cases with multiple lesions (56%); while in G1,

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Table 1. Clinical response and side effect

Dose[a]		50 mg	60 mg	70 mg	80 mg	Total
Response	CR		2	2		4[c]
	PR		3	9	2	14[d]
	NC	2	4	9		15
	Total	2	9[b]	20[b]	2	33[b]
Response rate (%)		0/2 (0%)	5/9 (56%)	11/20 (55%)	2/2 (100%)	18/33 (55%)
Side effect		0/2 (0%)	2/10 (20%)	6/21 (29%)	1/2 (50%)	9/35 (26%)

[a] Drug was dissolved in 30 ml physiological saline
[b] Two patients were not evaluated
[c] Two disease-free at 21 and 25 months; one recurrence at 3 months, one lost to follow-up
[d] Response duration figures unavailable as TUR subsequently performed

Table 2. Relationship between response and patient characteristics

Response		CR	PR	NC	Total	Response rate (%)
Male		4	13	15	32	53
Female			1		1	100
Primary			8	12	20	40
Recurrent[a]		4	6	3	13	77
Solitary		1	3	4	8	50
Multiple		3	11	11	25	56
Pathological grade	G1		4	5	9	44
	G2	2	6	7	15	53
	G3		2	2	4	50
	GX	2	2	1	5	80

[a] Other instillation chemotherapy had been performed in 4 of 13 cases (pepleomycin 2 cases, carboquone 1 case, Adriamycin 1 case). PR was achieved in the carboquone case, but other cases showed no effect

G2, and G3 cases effectiveness was 44% (4/9), 53% (8/15), and 50% (2/4), respectively (Table 2).

Discussion

Intravesical instillation of anticancer agents is one of the most effective methods of treating superficial bladder tumors. ADR is considered suitable for this type of treatment because (a) it is effective for transitional cell carcinoma; (b) it has dose-dependent effects and can yield results with a short period of contact; and (c) transference into the blood is low. However, it also has dose-dependent irritative effects on normal bladder mucosa [6, 7].

EPI is a derivative of ADR, which has been reported to have antitumor effects similar to those of ADR but with a lower incidence of side effects [3–5]. We examined its in vitro effectiveness in a human bladder cancer cell line, T24. The LD_{50} in terms of plating efficiency for 2 h exposure was 0.04 μg/ml for ADR and 0.06 μg/ml for EPI. Pathologic changes in normal bladder mucosa and transfer to blood, urine, and several organs were investigated intravesically in beagles with surgically altered urinary tracts. Since the results with EPI were similar to those obtained with ADR, a clinical study with EPI was carried out [8].

The overall effectiveness in this series of 35 cases was 55%, with 4 CRs and 14 PRs. The results with EPI were therefore approximately the same as those with ADR, which we reported as 32% in the 1000 μg/ml group, 66% in the 1600 μg/ml group, and 60% in the 2000 μg/ml group [6]. The incidences of side effects in the same three ADR groups were 29%, 20% and 45%, respectively. While the effects of the two drugs appeared similar in the basic study, in the clinical study it was seen that the incidence of side effects was lower and their degree milder in cases treated with EPI than in the ADR group. Clarification of the divergence of basic and clinical results remains to be elucidated by further research.

In conclusion, EPI appears to be an effective agent for intravesical instillation in cases of superficial bladder tumors. A randomized study is presently being performed to clarify the questions of optimal dosage and methods.

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Received October 22, 1984/Accepted July 10, 1985