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SESSION III

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Single instillation of hydroxypropylcellulose-doxorubicin as treatment for superficial bladder carcinoma

Abstract A single instillation of hydroxypropylcellulose (HPC)-doxorubicin (20 mg/20 ml) was performed in 20 patients with superficial bladder carcinoma. The therapeutic effect was assessed by cystoscopy at 14–30 days after the instillation, and the residual tumor tissue was resected by transurethral resection (TUR) when possible. The results obtained for the therapeutic effect were as follows: a complete response (CR), in 7 cases (35%); a reduction in size of more than 50% (partial response, PR), in 6 cases (30%); and a reduction of less than 25% in size (no change, NC), in 7 cases (35%). Combined intravesical instillation of HPC-doxorubicin and local hyperthermia using a Thermotron RF-8 was performed in 11 patients with recurrent superficial bladder carcinoma. The total number of treatment courses ranged from three to five per patient. The results obtained for the effect of this combined treatment were as follows: a CR, in 6 cases (54.5%); a PR, in 3 cases (27.3%); and NC, in 2 cases (18.2%). Therefore, the combination of intravesical instillation of HPC-doxorubicin and local hyperthermia was more effective against superficial bladder carcinoma than the single instillation of the chemotherapeutic agent alone.

Key words Superficial bladder carcinoma · Intravesical instillation · HPC- doxorubicin · Local hyperthermia

Introduction

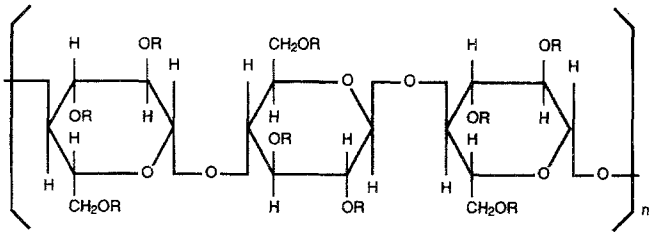
Intravesical instillation of anticancer agents such as mitomycin C, doxorubicin, and bacillus Calmette-Guérin (BCG) is widely used for the treatment of superficial bladder carcinomas. However, these drugs are water-soluble and thus do not remain within the urinary bladder for long. Hence, their contact time with tumors is short, and frequent administration is required. Taking account of this, we have developed a drug preparation that adheres to the bladder mucosa such that the drug-retention time within the bladder is prolonged [3].

Patients and methods

The base of the preparation is hydroxypropylcellulose (HPC), which is used in food processing and film-coating of medicines, compounded with the anticancer drug doxorubicin (Fig. 1). An electron microscopic photograph of HPC-doxorubicin is shown in Fig. 2; molecules of doxorubicin are seen to be conjugated with HPC.

Two treatment methods were performed in 31 patients with superficial bladder carcinoma as diagnosed by the Department of Urology, Nagoya City University Hospital, from 1987 to 1992. One treatment method consisted of a single instillation of HPC-doxorubicin and was applied to 20 cases of superficial bladder carcinoma comprising 5 Ta cases and 15 T1a cases. Tumor grading showed 5 cases of transitional-cell carcinoma (TCC), grade 1; 11 cases of TCC, grade 2; and 4 cases of TCC, grade 3 (Table 1). A single intravesical instillation of HPC-

Fig. 1 Chemical structure of hydroxypropylcellulose (HPC)



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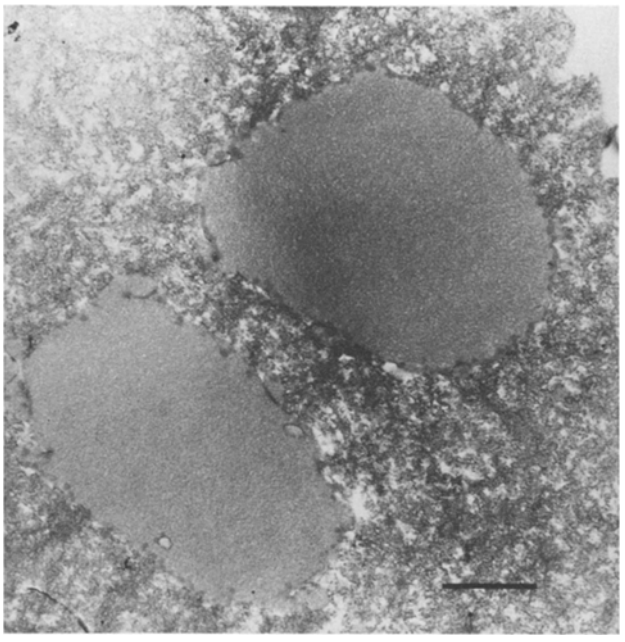


Fig. 2 An electron microscopic photograph of HPC-doxorubicin. Two molecules of doxorubicin are conjugated with HPC

doxorubicin (20 mg/20 ml) was performed in each case through a catheter. After more than 14 days, the therapeutic effect was assessed by cystoscopy, and then transurethral resection (TUR) was performed (Fig. 3).

Table 1 Background characteristics of patients treated with a single intravesical instillation of HPC-doxorubicin

	Tumor grade			Pathological stage	
	G1	G2	G3	Ta	T1a
Number of cases	5	11	4	5	15

Table 2 Background characteristics of patients treated with the combination of intravesical instillation of HPC-doxorubicin and local hyperthermia

	Tumor grade			Pathological stage		
	G1	G2	G3	Ta	T1a	T1b
Number of cases	3	4	4	3	3	5

Table 3 Therapeutic effects of the intravesical instillation of HPC-doxorubicin

	CR	PR	NC
Number of cases	7 (35%)	6 (30%)	7 (35%)

Table 4 Therapeutic effects of the combination of intravesical instillation of HPC-doxorubicin with local hyperthermia

	CR	PR	NC
Number of cases	6 (54.5%)	3 (27.3%)	2 (18.2%)

Fig. 3 Treatment method I for the single intravesical instillation of HPC-doxorubicin and assessment of the effect

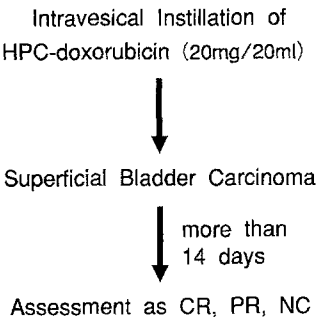
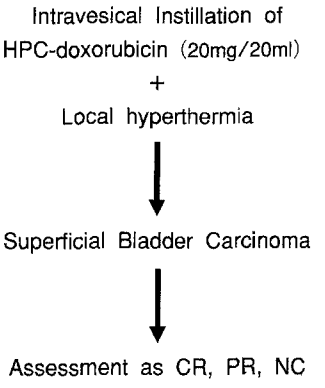


Fig. 4 Treatment method II for the combination of intravesical instillation of HPC-doxorubicin with local hyperthermia treatment



The therapeutic effect was assessed using the following criteria: complete response (CR), complete disappearance of the tumor; partial response (PR), a reduction of more than 50% in tumor size; minor response (MR), a reduction of 25%–50% in tumor size; no change (NC), a reduction of less than 25% or an increase in tumor size; and progressive disease (PD), an increase of greater than 25% in size (Fig. 3).

As the second treatment, intravesical instillation of HPC-doxorubicin was combined with local hyperthermia using a Thermotron RF-8. This combination was performed in 11 patients with superficial bladder carcinoma. The pathological stage was Ta in 3 cases, T1a in 3 cases and T1b in 5 cases, and the tumor grade was TCC, grade 1, in 3 cases; TCC, grade 2, in 4 cases; and TCC, grade 3, in 4 cases (Table 2). Intravesical instillation of HPC-doxorubicin (20 mg/20 ml) was performed just before 60 min of local hyperthermia using a Thermotron RF-8 to achieve an intravesical temperature of more than 42° C as one treatment. The total number of treatment courses of combined intravesical instillation and local hyperthermia per patient ranged from three to five (Fig. 4). The therapeutic effect of this combined treatment was assessed using the criteria described above.

Results

The assessment of the therapeutic effect of the single intravesical instillation treatment showed 7 CRs (35%). This was diagnosed by cold-cup biopsy, which was performed at the site where the tumor had been present, and confirmed the absence of tumor cells. A PR was found in 6 patients (30%), whereas the remaining 7 patients (35%) showed NC. There was no case of progressive disease (Table 3).

The combined intravesical instillation and hyperthermia treatment achieved a CR in 6 of the 11 patients (54.5%) and a PR in 3 patients (27.3%), whereas 2 patients (18.2%) showed NC (Table 4).

The side effects of the treatments were symptoms of bladder irritation such as pain on urination, pollakisuria, and dysuria in 5 (25%) of the 20 patients treated with HPC-doxorubicin alone and in 3 (27%) of the 11 receiving the combination treatment, but these adverse effects were not severe.

Discussion

Intravesical instillation of anticancer drugs into the urinary bladder is performed for treatment of superficial bladder carcinoma to achieve direct contact with the tumors in situ and to prevent tumor recurrence after TUR. The conventional formulation of the instilled drug is water-soluble, which makes repeated doses necessary. Moreover, since judgment of the therapeutic effect cannot be made until after the completion of each course of instillation, selection of the most appropriate drug might be considerably delayed.

As evidenced by the present results, these short-comings can be overcome by administration of a mucous-membrane-adhesive preparation form using HPC [4].

One positive feature of the HPC-doxorubicin used in this study is that a dose amounting to only about one-half to one-third of that required for the conventional water-soluble doxorubicin preparation gives an equivalent effect within a considerably shortened time span.

The combination of intravesical instillation of HPC-doxorubicin and local hyperthermia gave a good response rate of 81.8%. These results indicated that the combined treatment was more effective than the single instillation alone. Intravesical instillation of other drugs, such as bleomycin and mitomycin C, has also been combined with local hyperthermia for the treatment of bladder cancer, and good therapeutic effects have been reported [1, 2].

The incidence of side effects was 25% for the single intravesical instillation of HPC-doxorubicin and 27% for the combination treatment, but no systemic side effect was observed.

The single intravesical instillation of HPC-doxorubicin enabled us to judge the efficacy of doxorubicin in these patients with bladder carcinoma, but the combination of intravesical instillation of HPC-doxorubicin with local hyperthermia was more effective than the single instillation alone.

References

1. Matsui K, Takebayashi S, Watai K, Kakehi M, Kubota Y, Yao M, Shin T (1991) Combination radiotherapy of urinary bladder carcinoma with chemohyperthermia. Int J Hyperthermia 7: 19
2. Rigatti P, Lev A, Colomobo R (1991) Combined intravesical chemotherapy with mitomycin C and local bladder microwave-induced hyperthermia as a preoperative therapy for superficial bladder tumors. A preliminary clinical study. Eur Urol 20: 204
3. Ueda K, Masui Y, Okamura T, Ohtaguro K, Inoue K (1988) Studies of anticancer drugs adhering to bladder mucosa for the treatment of bladder cancer. Jpn J Urol 79: 44
4. Ueda K, Sakagami H, Ohtaguro K, Masui Y (1992) Studies on the retention of the mucous-membrane-adhesive anticancer agent hydroxypropylcellulose doxorubicin. Eur Urol 21: 250