原 著

Effects of Combined Treatment with Local Hyperthermia and Intravesical Instillation of Hydroxypropylcellulose-doxorubicin on Recurrent Bladder Cancer

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Abstract : Combined therapy with intravesical instillation of hydroxypropylcellulose-doxorubicin and local hyperthermia was performed in 11 patients with recurrent and multiple bladder carcinomas. The stage of the cancer before treatment was T1 in 4 cases, carcinoma in situ in 2 cases and T2 in 5 cases. Among the 11 cases, 7 cases had severe complications such as cardiac disease and pulmonary emphysema. Hydroxypropylcellulose-doxorubicin was instilled into the bladder, and then local hyperthermia was applied by means of capacitive heating using Thermotron RF-8. Therapeutic effect was as follows: complete response in 6 cases, partial response in 4 cases, and no response in 1 case. All 11 cases are alive as of this report with a survival duration ranging from 8 to 45 months. Adverse effects seen were induration of subcutaneous fatty tissue in 5 cases and first degree burns in 2 cases. There was no systemic adverse effect in the 11 patients treated.

Key words : Bladder carcinoma, hyperthermia, hydroxypropylcellulose-doxorubicin.

Introduction

There has been no effective modality to treat cancer of the urinary bladder, particularly recurrent and multiple cancers. This is particularly true when severe complications are present or when the patients have already received radiation therapy or systemic chemotherapy. In such cases, total cystectomy or aggressive chemotherapy using methotrexate, vinblastin, doxorubicin and Cisplatin (M-VAC) are difficult to perform. We have been treating such difficult cases with local hyperthermic therapy together with local application of chemotherapeutic drugs and have observed favorable results¹⁾²⁾.

We have previously described the development of a membrane adhesive anti-cancer drug, hydroxypropylcellulose-doxorubicin (HPC-doxorubicin)³⁾. In the present report, we describe

our encouraging results that instillation of HPC-doxorubicin into the urinary bladder and local hyperthermia treatment of the bladder is an effective means to treat recurrent bladder tumors.

Subjects and Methods

The subjects in the present study were 11 patients with a urinary bladder cancer who were referred to the Department of Urology, Nagoya City University School of Medicine during the period of 1987–1990. There were 8 male and 3 female patients. The age distribution of the patients ranged between 45 and 85 years. All cases were recurrent cancer of the urinary bladder with a history of previous therapy: 6 patients had transurethral resection (TUR), 2 partial cystectomy, 2 radiation therapy and 1 a combination of TUR, radiation and chemotherapy. Stage (TNM) and grade of the cancer before hyperthermia are shown in Table 1. All 11 patients had multiple tumors or carcinomas in situ.

Table 1. Patient characteristics.

Case	Age (y. o)	Sex	Stage	Grade	Previous Treatment
1.	55	M	TisNOMO	TCC grade 1	partial cystectomy
2.	45	F	TisNOMO	TCC grade 3	TUR
3.	57	M	T1NOMO	TCC grade 3	TUR
4.	73	F	T1NOMO	TCC grade 1	radiation
5.	72	M	T1NOMO	TCC grade 2	TUR
6.	85	M	T1NOMO	TCC grade 2	partial cystectomy
7.	72	F	T2NOMO	TCC grade 2	radiation
8.	52	M	T2NOMO	TCC grade 2	TUR
9.	73	M	T2NOMO	TCC grade 2	TUR
10.	68	M	T2NOMO	TCC grade 2	TUR, radiation, CDDP, doxorubicin
11.	55	M	T2NOMO	TCC grade 2	TUR

Table 2. Disease as complications in patients with bladder carcinoma.

Complication	No. of Case(s)
Heart disease	6
Pulmonary emphysema	1
None (Refusal of total cystectomy)	4

Complications were observed in 7 out of 11 patients: myocardial infarction or other cardiac symptoms in 6 patients, and pulmonary emphysema in one patient. No complications were observed in the remaining 4 cases. The patients refused total cystectomy because of the inconveni-

ence to their daily lives resulting from the alteration of the urinary tract (Table 2).

HPC-doxorubicin at 20 mg/20 ml was instilled into the urinary bladder through the urethra, and hyperthermia was then given immediately with a Thermotron RF-8, a capacitive hyperthermia unit using 8 MHz-RF (Yamamoto Vinyter Co., Osaka, Japan) (Fig. 1). The characteristics of this machine have been reported elsewhere¹⁾²⁾⁴⁾. The RF was applied with a

Fig. 1. Combined treatment with hyperthermia and intravesical instillation of HPC-doxorubicin is illustrated.

pair of 30 cm diameter electrodes coupled to the posterior and anterior surface of the pelvis. The temperature in the urinary bladder was determined using a thermosensor (thermocouple) inserted into the bladder cavity through the urethra. A vinyl bolus containing physiological saline was placed between the electrode and the body surface. In order to prevent the heating of the skin and subcutaneous tissues, the saline solution was cooled to 5°C by circulation through a heat exchanger. Hyperthermia lasting 60 min. per session was given once or twice a week. One patient received chemo-hyperthermia only twice while the other 10 cases received the therapy 3–9 times (Table 3). Cystoscopy, cold punch biopsy, urine cytology, CT and IVU were performed before and after the treatment. HPC-doxorubicin was excreted spontaneously with urine after the instillation.

The therapeutic results were judged according to the following criteria: complete disappearance of evaluable abnormality; complete response (CR); more than 50% reduction in

Table 3. Clinical results of combined treatment with hyperthermia and intravesical instillation of HPC-doxorubicin.

Case	No. Times	Effective Time (min)	Clinical Result	Prognosis (mo)
1.	4	40	PR	alive (37)
2.	5	30	CR	alive (38)
3.	2	10	CR	alive (38)
4.	5	40	CR	alive (31)
5.	3	30	NC	alive (10)
6.	3	30	CR	alive (10)
7.	6	0	CR	alive (36)
8.	9	30	PR	alive (45)
9.	3	40	PR	alive (29)
10.	8	20	CR	alive (22)
11.	5	30	PR	alive (8)

evaluable abnormality, partial response (PR); 25–50% reduction in evaluable abnormality, minor response (MR); less than 25% reduction or increase in the evaluable abnormality; no change (NC); and more than 25% increase, progressive disease (PD). Criteria for the post-treatment effects on carcinoma in situ have been described as follows: the complete response (CR) represents no tumor cells found pathohistologically in the multiple cold cup biopsy and yielded negative result on the weekly performed urine cytology. The partial response (PR) represents no tumor cells found in the biopsy, but suspicious carcinoma cells observed in the urine cytology. The no change (NC) represents positive results in both the pathohistological findings and urine cytology. The progressive disease (PD) represents a confirmation of grade ups in the both findings.

Heating

When the pelvic area was capacitively heated with 600–900 watts of RF, the intravesical temperature increased higher than 42°C in 10 cases. In one case whose subcutaneous fatty tissue was thicker than 8 cm, the intravesical temperature could not be raised above 42°C. In our institute, the temperature higher than 42°C is regarded as effective temperature and the duration of heating at temperature higher than 42°C are referred to as effective time. The shortest effective time per session was 10 min. and the longest effective time was 40 min. in the present study (Table 3). In the 11 cases, no adverse effects of heating were observed except hardening of the subcutaneous fatty layer in 5 cases and first degree burns in 2 cases.

Clinical Result

The clinical results of treatment are shown in Table 3. The overall results were CR in 6 cases, PR in 4 cases and NC in 1 case. The 4 PR cases which received TUR or total cystectomy are alive and tumor-free. Thus 4 PR and 6 PR out of a total of 11 patients treated are tumor-free as of this report. The duration of freedom from tumors is 8–45 months and the survival duration is 8–45 months in the 11 cases.

Among 6 cases of T1, CR was observed in 4 cases, PR in 1 case and NC in 1 case. One PR case had a residual tumor which could be removed by TUR and the patient has been tumor-free for the past 39 months. The NC case had severe complications from cardiac disease so that surgical operation of the urinary bladder was impossible. The tumor was subsequently treated with radiation therapy followed by intra-cystic administration of anticancer agent.

Out of 5 cases with T2 infiltrated cancer of the urinary bladder, 2 were CR and 3 were PR. All 3 PR cases agreed to receive total cystectomy. In one of the 3 PR cases, reconstruction of the neobladder was made using the ileocecal procedure. In another (female), a ureterosigmoidostomy was performed. The remaining one case was a 73 years-old so that ileal conduit was selected. These 3 cases are tumor-free as of this report. All 5 T2 pa-

tients are alive at the present time.

Discussion

Total cystectomy or systemic chemotherapy using M-VAC are often the choice of treatment for recurrent and multiple bladder tumors. However, when the patients have severe complications, such as cardiac or pulmonary disease, these treatments are usually difficult to perform. The 11 subjects treated in the present study were such patients. We treated these patients with intravesical instillation of HPC-doxorubicin, which is a membrane adhesive anti-cancer drug developed by us³⁾, in combination with 8 MHz radiofrequency hyperthermia.

The adhesive property of HPC-doxorubicin on the intravesical membrane was previously investigated by using an experimental animal model³⁾. HPC-doxorubicin was found to remain significantly longer in the urinary bladder than the conventional water soluble doxorubicin. Such an adhesive type of drug has already been used clinically for superficial cancer of the urinary bladder and found to be effective with smaller doses of drugs and fewer numbers of administration as compared with those for the conventional water soluble doxorubicin preparation⁵⁾.

It is now a well known fact that hyperthermia potentiates the effects of a number of chemotherapeutic drugs including doxorubicin⁶⁾. We also have observed the synergistic effect of HPC-doxorubicin and hyperthermia on the T24 bladder cancer cells in vitro⁷⁾. These results encouraged us to initiate the present study in which recurrent and multiple cancers of the urinary bladder were treated with HPC-doxorubicin in combination with hyperthermia.

Thermotron RF-8, which was developed in Japan for the therapeutic purpose of heating deep as well as superficial malignant tumors, was used for the hyperthermic treatment. Encouraging results have been obtained for the treatment of pulmonary, hepatic, pancreatic, and bladder cancers with hyperthermia alone using Thermotron RF-8 or in combination with radiation or chemotherapy⁴⁾. In the present study, we could raise the intravesical temperature higher than 42°C in 10 out of 11 cases. We failed to raise the intravesical temperature to 42°C in 1 case whose subcutaneous fatty tissue was 8 cm thick. One patient only received hyperthermia twice because of a transportation problem. Nevertheless, the tumor in this patient responded completely to the treatment. The adverse effects of hyperthermia observed were induration of subcutaneous fatty tissue and first degree heat burns. However, these side effects were judged to be insignificant.

Overall, satisfactory clinical responses were obtained for the recurrent and multiple cancers: among the 11 cases, 6 patients showed complete response (CR), 4 partial response (PR) and 1 no change (NC). Among 4 patients showing PR, 3 cases received total cystectomy and 1 case had TUR. These CR and PR patients are currently alive in a tumor-free state. The patient showing NC had severe cardiac complications. A total cystectomy was impossible and the tumor was subsequently treated with radiation therapy.

The present study demonstrated that local hyperthermia in combination with intravesical instillation of chemotherapeutic drugs may be useful for the treatment of bladder cancer. The follow-up period for the present study is still less than 5 years with the longest survival period being 45 months. Although it is still too early to make a final conclusion based on the study using only 11 patients, we are encouraged with our results. Investigations are in progress reveal whether another chemotherapeutic agent other than doxorubicin may be combined with hyperthermia to attain a more effective method of treatment.

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再発性膀胱癌に対する hydroxypropylcellulose-doxorubicin の 膀胱内注入とハイパーサーミアの 併用効果

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要 旨： 再発性で多発性の膀胱癌 11 例に対して、hydroxypropylcellulose-doxorubicin (HPC-doxorubicin) の膀胱内注入に局所ハイパーサーミアを併用して治療した。

治療前の stage は、T1 が 4 例、carcinoma in situ が 2 例、T2 が 5 例である。11 例中 7 例に心疾患や肺気腫などの重篤な合併症がみられた。治療方法としては、まず HPC-doxorubicin 20mg/20ml をあらかじめ膀胱内に注入しておき、ついで 8MHz-RF 波による局所ハイパーサーミアをおこなった。治療結果は完全寛解 (complete response) が 6 例に、部分寛解 (partial response) が 4 例に、効果なし (no response) が 1 例であった。11 例全例が現在まで生存している。その生存期間は 8～45 ヶ月である。この治療による副作用としては、5 例に皮下脂肪の硬結と 2 例に軽度の火傷を認めたのみで、重篤なものはみられなかった。以上よりこの治療法は再発性膀胱癌に対して有用な治療法であると考えられた。

Key words： 膀胱癌，ハイパーサーミア，hydroxypropylcellulose-doxorubicin