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Pre-operative Intra-arterial Chemotherapy for Bladder Cancer

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Summary. Thirteen partients with carcinoma of the bladder have been treated by arterial infusion of doxorubicin hydrochloride pre-operatively. Teflon catheters 0.25 mm in diameter were inserted by the Seldinger technique and the tips were placed in the aorta between the origin of the inferior mesenteric artery and the aortic bifurcation. The doses administered ranged from 80 mgs to 250 mgs with an average of 125 mgs. A response rate of 69% was seen. In 3 cases tumours disappeared; in a further 6 patients some tumour regression was apparent. One patient died from cardiac insufficiency. Although this method of treatment remains to be fully evaluated, preliminary results suggest that it may be an effective pre-operative treatment.

Key words: Transitional cell carcinoma, Intra-arterial infusion, Doxorubicin, Pre-operative treatment.

INTRODUCTION

We set out to develop new methods of chemotherapy for bladder tumours which might be used in combination with surgery.

Bladder chemotherapy may be administered either by direct instillation into the bladder or by arterial perfusion. We have previously reported our preliminary experience with doxorubicin hydrochloride applied intra-vesically (9).

Arterial infusion is not a new procedure in anticancer chemotherapy. Klopp and his associates (4) reported the effectiveness of the method in 1950. Since Watkins (16) developed a portable continuous injection pump, the technique has been popular in anticancer chemotherapy for various kinds of malignancies (14). Many studies on bladder tumours treated by the arterial-infusion system have been reported. Nitrogen mustard, MMC, 5-FU and cyclophosphamide were the most common agents used. In spite of their acceptable results, this method has not played an important role in chemotherapeutic procedures so far. The reasons for this lack of popularity are the technical difficulty of catheter insertion and of keeping the catheter patent, and also side effects which include the toxic effects of the agents used together with necrosis of normal tissue in the region of perfusion.

Considerable efforts have been made to prevent these sequential and toxic effects. Administration of vit. B6, steroid hormones, combination use of proteolytic enzymes such as urokinase, and development of new operative techniques have been applied, but none of them seemed satisfactory. A further limitation is that the administered agents cannot be retained by the target sites but are distributed through the systemic circulation.

An ideal agent for arterial infusion should meet these conditions:

1. The agents should have selective tissue affinity or be taken up by cancer cells and kill the cancer cells but not normal cells.
2. There should be no effect on the circulation and no effect on blood cell elements such as erythrocytes, leucocytes, lymphocytes, platelets.
3. The agent should have a time dependent action.

MMC, 5-FU and cyclophosphamide do not meet these conditions since they do not have strong selective tissue affinities, and they are distributed to the entire circulatory system leading to complications such as bone marrow depression, alopecia, mucositis and skin necrosis. Doxorubicin hydrochloride seems to partially meet these conditions. It has a strong tissue affinity (1, 5), and has both a time dependent action together with a concentration dependent action (12, 13).

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The efficacy of doxorubicin hydrochloride given by continuous intra-arterial infusion as a pre-operative chemotherapeutic treatment was studied and the results are reported.

PATIENTS AND METHODS

Thirteen patients were studied.

One patient had a renal pelvic tumour and multiple tumours in the bladder which proved to be transitional cell carcinoma grade 2; two were cases with recurrent bladder tumours and the remaining 10 patients had primary bladder carcinoma. The patients ranged in age from 61 to 78 years, with an average of 70 years. All the patients had transitional cell carcinoma proved by biopsies or surgical specimens. Bimanual examinations under anaesthesia were performed in all the cases.

Clinical staging was done according to the classification proposed by Jewett and Strong (3) with the modifications of Marshall (6). Teflon catheters (0.25 mm in inner diameter) were inserted by Seldinger's method (11). Pelvic angiograms were taken using KIFA green straight catheters to confirm the position of the inferior mesenteric artery and the aortic bifurcation. The teflon catheters were inserted into the aorta using the KIFA green catheter as a guide. The tip of the teflon catheter was placed in between the inferior mesenteric artery and the bifurcation to cause the agent to be distributed into the entire pelvic cavity and to avoid the agent distributing into the mesenteric artery. The catheters had been placed 5 to 13 days prior to operation depending on the general condition of the patient and the average was 8 days. Total doses ranged from 80 to 250 mg Sharp[1] PIP - 21 type infusion pumps were used.

In some cases where we thought large amounts of the agent were needed, a rapid infusion technique was used combined with urokinase in a dose of 6000 units/20 mg doxorubicin hydrochloride to keep the catheter patent and to improve the distribution of the agent into cancer nests.

The catheter was fixed to the skin of the thigh with silk sutures. The initial puncture point, where the KIFA catheter was inserted, was closed and the teflon catheter was pulled out at least 7 cm away from the initial point through a subcutaneous tunnel, and was fixed to the skin with silk ligatures. The bleeding from the initial point could be controlled by compression for 10 to 15 min. The operated groin was covered with an elastic bandage during the infusion. The schematic illustration of the fixation technique is shown in Fig. 1.

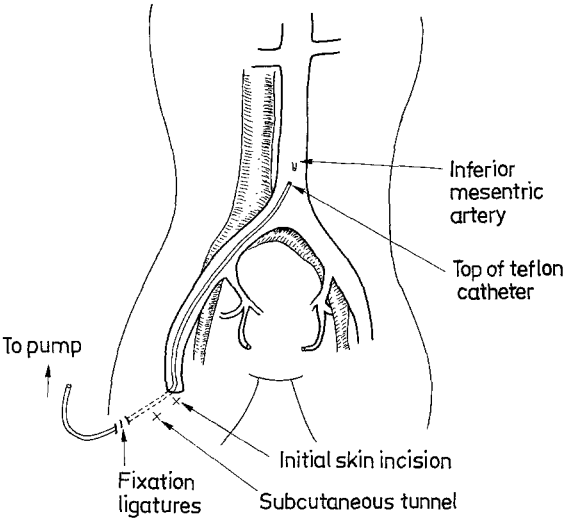


Fig. 1. Schematic illustration of catheter insertion technique

It was not necessary to confine the patients to bed during treatment. They could walk freely during the infusions.

RESULTS

The results are summarised in Table 1.

The overall response rate was 69%. In 3 cases tumours disappeared. Destructive changes were noted in 3 cases (Fig. 2), and significant shrinkages and/or partial destructive changes were noted in 3 cases. In 4 cases no significant change was seen endoscopically or pathologically. Cases 1 and 2 developed liver abscesses and died from sepsis and intracranial bleeding respectively. The details are shown in the case reports. Case 10 (grade 3, stage C) died on the 4th post-operative day due to cardiac insufficiency. Myocardial toxicity of doxorubicin hydrochloride was the most likely cause. Other toxic effects observed during the study were mild bladder irritability, alopecia, stomatitis and mild bone marrow depression. Mild alopecia was seen in 2 cases and stomatitis was observed in 2 cases.

Bone marrow depression was also noted in 2 cases (Cases 2 and 6). Bleeding, embolism, phlebitis in the lower extremities, necrosis or abscess in the buttocks were not seen.

In Case 1 total nephro-ureterectomy and partial cystectomy were performed and in Case 2 only urinary diversion was performed because cystectomy was impossible. Total cystectomy and ileal conduit were done in 10 cases. Partial cystectomy was done in Case 9. There was no TUR-Bt case.

[1] Sharp Electronic Co., Ltd., Tokyo, Japan

Table 1. The result of the study

Case no.	Sex	Age	Total dosage	Cystoscopic findings	Pathological findings (by Koss)	
1. T.O.	M	70	100 mg	Disappearance	gr. II. (Renal pelvic tumor multiple growth)	Laparotomy & Autopsy *
2. I.H.	M	70	120 mg	Disappearance	gr. II. Stage D_2	Urinary diversion * & Autopsy
3. E.Y.	M	72	120 mg	Disappearance	gr. II (Proved previous TUR-biopsy) Stage B_1	Total cystectomy and urinary diversion
4. S.O.	M	78	115 mg	Destruction	gr. II. Stage B_1	Total cystectomy & urinary diversion
5. S.W.	M	76	80 mg	Destruction	gr. I ▲→gr. III ▲▲ Stage D_2	Transitional cell carcinoma infiltrating to the ileal wall.
6. S.T.	M	67	200 mg	Destruction	gr. II. Stage C	Total cystectomy & urinary diversion
7. S.M.	M	67	170 mg	Shrinkage & partial destruction	gr. III. Stage C	Total cystectomy & urinary diversion
8. M.N.	M	68	80 mg	Shrinkage & necrotic tendency	gr. II. Stage C	Total cystectomy & urinary diversion
9. K.S.	M	77	100 mg	Partial destruction	gr. II. Stage B_1	Partial cystectomy
10. J.M.	M	65	250 mg	not significant	gr. III. Stage C	Total cystectomy & urinary diversion**
11. S.O.	F	71	80 mg	not significant	gr. I. Stage B_1	Total cystectomy & urinary diversion
12. R.K.	M	61	120 mg	not significant	gr. I.~ II Stage B_1	Total cystectomy & urinary diversion
13. S.I.	M	72	110 mg	not significant	gr. I ▲→gr. II ▲▲ Stage C	Total cystectomy & urinary diversion

* Cases expired not related with primary disease
** Case expired due to cardiac insufficiency
▲ Initial histological grade based on specimens by TUR-Bt
▲▲ Histological grade based on specimens by total cystectomy

CASE REPORTS

Case 1. A 69-year-old male was referred to the clinic complaining of haematuria and pyrexia. On palpation, two large masses were found in the right upper quadrant and flank. One was a swollen liver and under it a large hard tumour was palpated and it extended to 1.5 Q.F.B. up to the right iliac crest. The right kidney was not visualized on an IVP and angiographic studies suggested renal cell carcinoma with a possibility of transitional cell carcinoma of the renal pelvis. At cystoscopy the bladder was normal. The kidney was exposed through an oblique flank incision. Frozen section disclosed transitional cell carcinoma. Nephro-ureterectomy and partial cystectomy were performed. His post-operative course was uneventful, but 13 months later he was re-hospitalized due to a hard mass in the right flank and macroscopic haematuria. Endoscopically multicentric growth of tumours were found in the bladder. Arterial infusion of doxorubicin hydrochloride was performed. The total dosage was 100 mg. Thirty-two days after the termination of the infusion a laparotomy was performed; the tumour in the retroperitoneal cavity could not be resected, but the bladder itself was free of tumour.

This patient died from a liver abscess followed by sepsis, and several cancer nests were found in the subepitherial layer at post-mortem. The mass in the right retroperitoneal cavity was found to be recurrent transitional cell carcinoma enclosed by fibrous tissue.

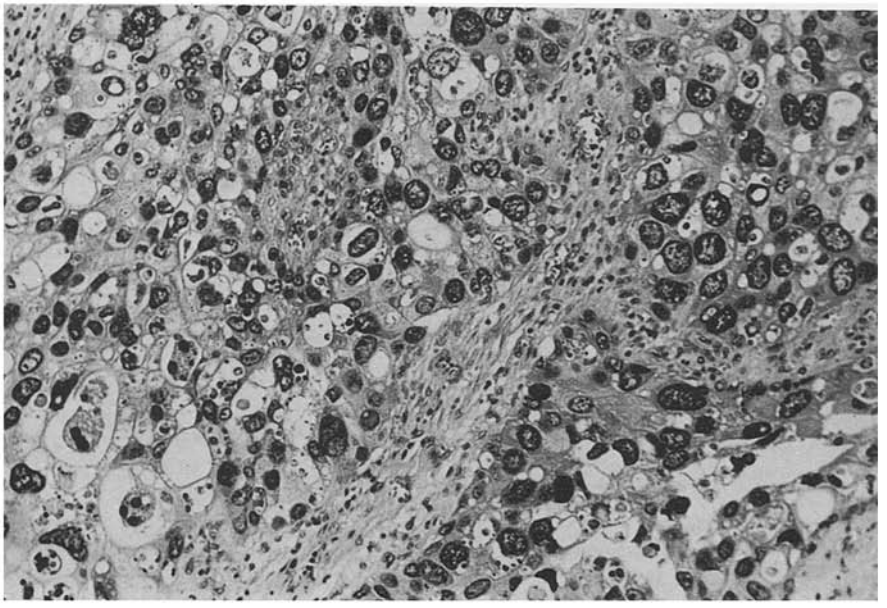


Fig. 2. Pathological findings of Case 6. Necrobiotic change of the cancer cells is dominant

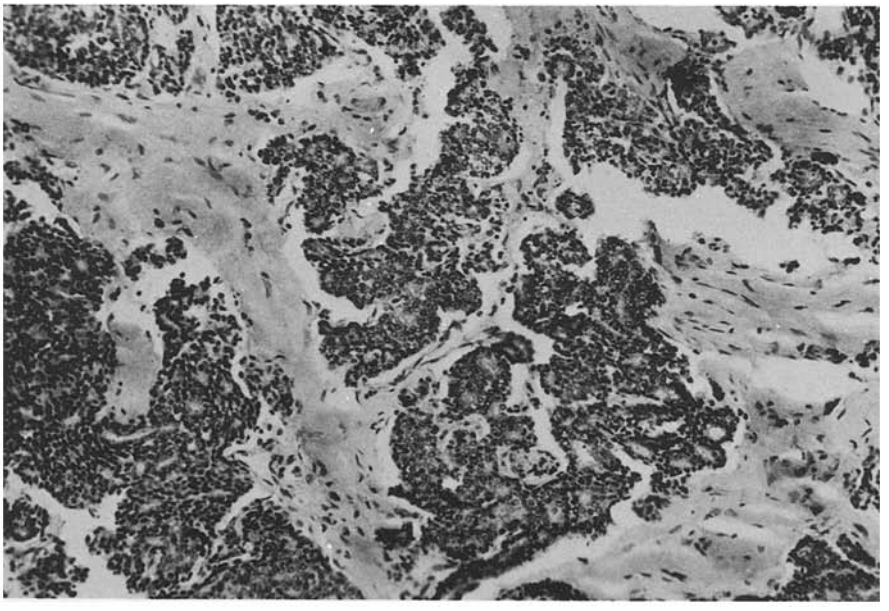


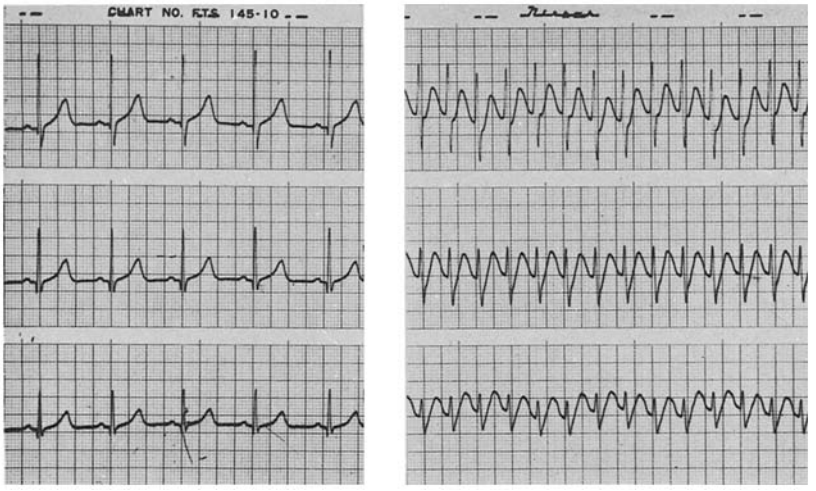
Fig. 3. Metastatic cancer nests found in the lumbar vertebrae (Case 2)

Table 2. Blood chemistry of Case 10

	Pre-operative	1th post op. day	4th post op. day (died)
GOT	13 (Karmen U.)	16	112
GPT	12 (Karmen U.)	10	31
LDH	263 (W. U.)	263	771
CPK	30 (I. U.)	167	97
Na	136.2 (mEq/l)	137.8	148.4
K	4.5 (mEq/l)	4.3	5.7
BUN	24.4 (mg/dl)	24.4	60.7
Creatinine	1.2 (mg/dl)	1.2	3.0
Urine volume	1800 (ml)	2350	1400

Case 2. 70-year-old male. Sixteen months prior to his death urinary diversion was done for transitional cell carcinoma proved by TUR-Biopsy. The bladder was not resectable. Radiation therapy was performed after the operation. The grade and stage were based on the TUR-Biopsy and operative findings. Seven months after his discharge he again entered the hospital because of the recurrence in the bladder.

Endoscopic study disclosed invasive tumour and 120 mg doxorubicin hydrochloride was administered through continuous arterial infusion. The bladder cavity shrank significantly and no tumour was seen endoscopically. He died suddenly of intracranial bleeding and at post-mortem no cancer nest was found in the bladder wall, but



Pre op. ECG. (Case 10)

4th post op. day ECG. (Case 10)

Fig. 4. ECG findings in Case 10

metastatic tumour nests were found in the 4th and 5th lumbar vertebrae (Fig. 3).

No specific change due to radiation therapy was found in the pelvic cavity.

Case 10. A 65-year-old male was referred to the clinic complaining of macroscopic haematuria for 20 days.

Cystoscopy revealed an invasive tumour covering almost the entire bladder wall. The right ureteric orifice could not be identified. After infusion therapy (total doses: 250 mg - duration: 13 days) total cystectomy and ileal conduit were performed. The kidney and ureter showed moderate hydrotic changes but no evidence of malignancy was found in them. No metastatic lesion was found in the liver or paraaortic lymphonodes. The operation was uneventful.

In this case continuous infusion had been conducted just before the operation to determine the tissue, arterial and venous serum concentrations of the agent. Five pieces were taken from the various parts of the wall and tissue concentrations ranged from 1.79 to 0.50 μg/gr with an average of 0.96μg/gr. Arterial and venous serum concentrations were 0.19 and 0.17 μg/ml respectively. Until heart failure was noticed on the 4th post-operative day his condition had been acceptable.

Anti-arythmic agents such as procain amide hydrochlodride, xylocain, digoxin were administered but despite all efforts he died. The blood chemistry is summarised in Table 2 and ECGs are also shown in Fig. 4. Autopsy could not be performed, so that the cause of death could not be confirmed, but the myocardial toxicity of doxorubicin hydrochloride was the most probable cause taking the chemical data and ECG findings into consideration.

Pathological study of the operative specimens disclosed transitional cell carcinoma, grade 3 stage C. No significant oncocytic effect was seen histopathologically.

DISCUSSION

It has been emphasised that pre-operative radiation is beneficial in the management of patients with invasive bladder cancer. By reducing the radiation dose from 6000 R to 4500 or 5000 R the risk of serious complications is decreased, but some delay in wound healing, post-operative infections, haematuria and marked bladder irritative symptoms are still troublesome problems (5). Despite recent advancements in chemotherapy for bladder cancer, pre-operative chemotherapy has not been considered feasible and chemotherapy still has been confined to post-operative adjuvant treatment in advanced cases. We have focused on continuous intra-arterial infusion. Many reports have been published and most of the investigators performed selective intra-arterial infusion system. Regional perfusion seems more effective compared with a non-selective one. Nevin (10), Iguchi (2), Nakamura (8) and Uyama (15) used semi-selective catheterisation system: a catheter was inserted into the internal iliac artery which was ligated after the insertion. Some recommend ligation of the superior gluteal artery to prevent necrosis in the buttocks.

Our aims were: 1. the procedure should be effective, simple, and easy; 2. no hazardous complication should occur; 3. the patients should be comfortable during the procedure. At least, we should avoid restricting patients to bed during the infusion; 4. toxic effects of the agents used

should be reduced; 5. no unfavourable effects in operative procedures should occur. According to Matsumoto (7), the best method of treatment of malignancies in the pelvic cavity is to place the catheter tip in between the inferior mesenteric artery and the aortic bifurcation; agents circulating in the inferior mesenteric artery may cause necrosis of the rectum and sigmoid colon. The fact that the bladder does not show necrotic changes after bilateral ligation of the internal iliac arteries means the blood supply to the bladder does not depend on the internal iliac arteries completely and that blood is supplied through various routes. Thus, the anticancer agents should be distributed to the entire pelvic cavity. To do this, the catheter should be located in the lower part of the aorta in the advanced or multiple growth cases. Based on the principle of the blood supply to the bladder, to limit the agent's distribution unilaterally seemed meaningless. So we decided it was not necessary to perform selective or semiselective catheterisation in our cases. The other problem is what kinds of agents should be chosen. The concentration dependent agents can be divided into two subgroups, one has no time dependent action (type A), and the other has time dependent action (type B). In type A agents, the clinical effects are mostly dependent on the concentration in the serum or in the cancer nests, but in type B agents, although they are concentration dependent agents, it is expected that they will kill the cancer nest with relatively low concentration with their long term action and long contact period. Generally, in contrast, short time action agents need high concentrations in the serum or in cancer nests and it is expected that good clinical effects will be obtained by keeping a certain concentration for a long period in type B agetns (12, 13). Doxorubicin hydrochloride belongs to type B and has long time action; moreover, it has strong tissue affinity and it is easily accumulated in the cancer nests as shown. Thus, continuous or frequent periodic administration seem suitable modes of administration. Though we have been careful of the toxic effects, one patient died of myocardial damage; alopecia and mild bone marrow depression were seen in the series and more effort must be made to avoid these complications. We had relatively good results in the study, but we do not think it is possible to eliminate cancer cells completely from the patients or to expect long term survivals with the chemotherapeutic treatment only.

Although we could expect some effects like destructive changes or disappearance at endoscopy from this method, in the tissues excised at cystectomy or autopsy tumour nests were found histologically. So, once we judged there was some indication for total cystectomy or partial cystectomy based on endoscopic study and other observations at the time of diagnosis, total cystectomy or partial cystectomy was done regardless of the chemotherapeutic effects. Our series is limited in number and follow up is limited in time so that it is difficult to evaluate the method precisely but it seems that it may be useful a pre-operative procedure.

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