INTRA-ARTERIAL CHEMOTHERAPY FOR MUSCLE-INVASIVE URINARY BLADDER CANCER

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A total of 9 patients with muscle-invasive bladder cancer (T3 or T4N0M0) were treated with a modified intra-arterial M-VEC (IA-M-VEC) regimen beginning in October 1992 to evaluate its therapeutic efficacy, and in 3 evaluable patients who subsequently underwent radical cystectomy, the possibility of bladder preservation was assessed.

The responses of the 8 evaluable patients were rated as complete response (CRs) in 3, partial response (PRs) in 3 and no change (NCs) in 2. The objective response rate (PR+CR) was 75%. An obvious down-staging (T3→pT1b) was confirmed in 2 of the 3 evaluable patients, suggesting the possibility of bladder preservation. Otherwise similar changes to hemorrhagic cystitis with minimal muscular fibrosis were conspicuous in the normal bladder wall. These pathological findings corresponded with those obtained by dynamic single photon emission computed tomography (D-SPECT) using ^{99m}TC-macroaggregate albumin (^{99m}TC-MAA). Besides a buttock-to-perianal erosion with neuralgia on the injection side, mild to moderate sensory disturbance of the sacral plexus was observed.

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Key words : Intra-arterial chemotherapy (IAC), M-VEC regimen, Muscle-invasive urinary bladder cancer, Dynamic single photon emission computed tomography (D-SPECT)

INTRODUCTION

Intravenous M-VAC treatment (methotrexate, vinblastine, adriamycin and cisplatin) has proved to be an effective option as adjuvant or neo-adjuvant chemotherapy against advanced urothelial cancer, with good patient's compliance[1]. Later, intra-arterial chemotherapy (IAC) was developed for patients with muscle-invasive urinary bladder cancer to have a higher concentration of chemotherapeutic agents in the tumor with concomitant reduction of the resultant toxicity, and excellent efficacy has been reported[2–9]

However, the role of IAC for the erradication of possible existing micrometastases is still unresolved. In our unpublished data on the concentrations of cisplatin and epirubicin (1, 2 and 4-hr level), a comparable intravenous level was detected compared with those in IV-M-VAC, expecting the effiicacy on micrometastases. A total of nine patients with advanced bladder cancer (T3 or T4N0M0) were treated with a modified IA-M-VEC regimen beginning in October 1992 to evaluate its therapeutic effiicacy, and in three evaluable patients who subsequently underwent radical cystectomy, the possibility of bladder preservation was assessed.

MATERIALS AND METHODS

Patients' characteristics

A total of nine patients with advanced muscle-invasive urinary bladder cancer (T3 or T4N0M0) were treated with a modified IA-M-VEC regimen

Table 1A. Characteristics of 5 patients* with advanced bladder cancer treated with an intra-arterial M-VEC regimen

Patient	Age (years)	Sex (M/F)	PS	History	Histology	Stage	Prior therapy	Number of courses (M-VEC)	Number of maintenance courses (CDDP)	Complication
1	76	M	1	Primary	TCC, G3	T3N0M0		2	6	CHF
2	73	F	2	Recurrent	TCC, G2	T4N0M0	TUR (3) M-VEC (iv, 2) BCG instillation (6)	1		
3	69	M	3	Recurrent	TCC, G2	T3N0M0	BCG instillation (6) Radiation (4,000 rad)	2		Schizophrenia
4	59	M	1	Primary	TCC, G3	T4N0M0		3 (CDDP 80 mg)	3	ASO
5	70	M	2	Primary	TCC, G3	T3N0M0		2		Hepatitis Ileus (5)

* Radical cystectomy was not performed due to complications or for other reasons.

Table 1B. Characteristics of 4 eligible patients who underwent radical cystectomy in a neo-adjuvant setting

Patient	Age (years)	Sex (M/F)	PS	History	Histology	Stage	Number of courses (M-VEC)	Number of post-operative courses (i, v-VEC)	Metastasis
6	65	M	1	Primary	TCC, G3	T3N0M0	1*	2	(−)
7	63	M	1	Primary	TCC, G3	T4N0M0	2	2	lung** (8M)
8	49	F	1	Primary	TCC, G2	T3N0M0	2		(−)
9	59	M	1	Primary	TCC, G2	T3N0M0	2		(−)

* Radical cystectomy was performed after the 1st course due to the appearance of buttock-to-perianal erosion.
** The patient died of lung metastasis after 8 months.

beginning in October 1992 in our department (Table 1A, B). In five of them (Patient 1–5) radical cystectomy was not performed due to complications or for other reasons (Table 1A). The subjects consisted of four males and one female. The mean age of the patients was 69.4 years, ranging from 59 to 76 years. The performance status (PS) was above 2 in all except one patient. The tumors in three patients were primary, and those in two patients were recurrent.

The tumors were clinically classified as stage T3 in three patients and stage T4 in two patients according to the category of the Japanese Urological Association & the Japanese Society of Pathology (2nd edition). As for the tumor grade, differentiation of transitional cell carcinoma (TCC) was grade 2 in two patients and grade 3 in three patients. As prior therapy, two patients had undergone transurethral resection (TUR) of a vesical tumor or radiation, followed by intravesical BCG instillation. The mean number of IA-M-VEC courses was 2.0, ranging from 1 to 3 and the mean number of maintenance courses of cisplatin was 3.7, ranging from 2 to 6. Complications, such as arteriosclerosis obliterans (ASO), congestive heart failure (CHF), schizophrenia, hepatitis or ileus were found in four patients. On the other hand, the remaining four eligible patients (Patient 6–9) underwent radical cystectomy voluntarily in a neoadjuvant setting (Table 1B). The number of IA-M-VEC courses was 2 in all patients except the one, who was forced to undergo radical cystectomy after the 1st course due to the appearance of buttock-to-perianal erosion. The number of postoperative intravenous M-VEC (IV-M-VEC) courses was 2 in two patients.

Method of IAC (Fig. 1).

While conducting pelvic arteriography, CDDP 25 mg was infused into the internal iliac artery on the opposite side, where less blood supply was found, followed by embolization with a steel coil. The superior gluteal artery on the injection side was also embolized with a steel coil (if necessary, together with an inferior gluteal artery), and a vascular catheter placed in the internal iliac artery was attached to a reservoir (Tokibo) which was subcutaneously implanted in the iliac fossa or the inside of the femur.

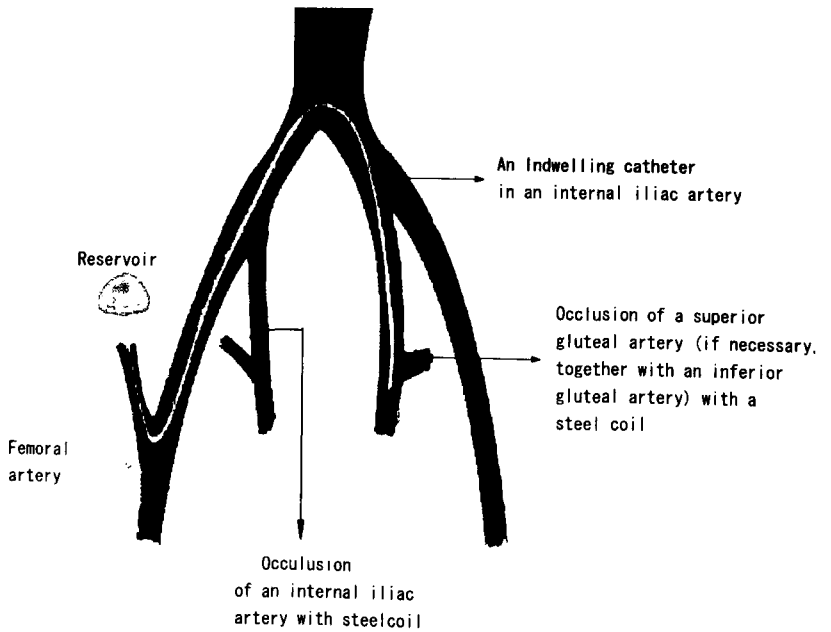

Fig. 1. Scheme of reservior implantation in the iliac fossa or the thigh.

IA-M-VEC regimen

The following chemotherapeutic multi-agents for IA-M-VEC treatment were used: 40 mg of methotrexate (days 1, 8, 15), 4 mg of vinblastine (days 2, 8, 15), 40 mg of epirubicin (day 2) and 100 mg of cisplatin (day 2) infused slowly via an injection port. This regimen was administered once every three weeks for at least two courses. Three or four weeks later, the patients (Patient 1–5) were clinically evaluated by cystoscopy followed by biopsy, USG and CT. Concomitantly, tegafur-uracil 300 mg given orally. As a maintenance regimen, CDDP 25 mg was infused once each month via the port to patients with clinical CR as ambulatory care, and this was continued for at least 6 months. In patients with a response below PR, radical cystectomy was undertaken or additional doses were administered.

D-SPECT

To examine the effiiciency of drug delivery to tumors, we conducted digital subtraction angiography (DSA) of the correspondent hypogastric artery via the port, followed by D-SPECT using ^{99m}Tc-MAA.

RESULTS

Overall response rate (Table 2)

The clinical responses of the eight evaluable patients consisted of three CRs, three PRs and two NCs. The objective response rate (PR+CR) was 75%.

The median duration of response and follow-up for the complete responders was 16 months ranging from 8 to 21 months and 21 months ranging from 11 to 28 months. One patient achieved a CR after the first course, and another patient is suffering from a relapsing tumor after the 19-month CR duration. The remaining patient is now on the first maintenance course of cisplatin.

The median duration of follow-up for the partial responders was 10.7 months ranging from 8 to 13 months. All of the patients underwent radical cystectomy, and of these three, one died of lung metastasis after 8 months.

The median duration of follow-up for the patients with no change was 9.5 months ranging from 7 to 12 months, and both patients died of lung metastasis.

Table 2. Summary of results of intra-arterial M-VEC treatment of 8 evaluable patients with advanced bladder cancer

Response	Number of patients	Duration of response (months)	Duration of follow-up (months)
CR	3*	(8, 19, 21)	(11, 24, 28)
PR	3**		(8, 11, 13)
NC	2***		(7, 12)

* One patient achieved a CR after the 1st course, and another patient is suffering from a relapsing tumor after the 19-months CR duration. The remaining patient is now on the first maintenance course of cisplatin. ** All of the patients underwent radical cystectomy, and of these three one died of lung metastasis after 8 months. *** Both patients died of lung metastasis after 7 and 12 months.

Pathological findings

An obvious down-staging (T3→pT1b) was confirmed in two of the three evaluable patients which was correspondent to grade 2B according to the Ohboshi-Shimasato's classification. Pathologically, besides the granulomatous changes with accumulation of foamy histiocytes in tumor, similar changes to hemorrhagic cystitis, such as exfoliation or erosion of mucosa with minimal muscular fibrosis were conspicuous in the normal bladder wall.

DSA and D-SPECT (Fig. 2, 3)

DSA of the left hypogastric artery showed a hypervascularity in tumor lesions of the two patients with an obvious down-staging (Fig. 2A, 3A). Similarly D-SPECT-images (sagittal & coronal) revealed an intensive accumulation of ^{99m}Tc-MAA in the tumor-bearing sites (Fig. 2B, 3B), but in Patient 9 with a flush of glans, a moderate pooling in the pudendal area was also observed. The accumulation-gradient of ^{99m}Tc-MAA in the three patients (Patient 7–9) corresponded with the grade of pathological changes of surgical specimens, that is, the necrotic changes followed by granulomatous proliferation were dominant in tumor lesions with a high accumulation-rate.

Adverse effects

Mild to moderate hematological toxicities were observed. Anemia with an Hb level below 10 g/dl was found in eight patients during the two courses. Leukopenia with a WBC count below 4,000/mm, was also seen in three patients during the 1st course and in five patients during the 2nd course. Granulocyte colony-stimulating factor (G-CSF) was intermittently administered to four patients. Only mild gastrointestinal toxicity, such as anorexia, nausea and vomiting, was observed in most of the patients during the two courses. Mild to moderate hair loss was seen during the two courses, but this later was decreased. Transient buttock flush was noted in one patient during the 1st course but later disappeared. Moderate buttock-to-operianal erosion followed by neuralgia was observed in one patient after the 1st IA-M-VEC course, and cystectomy was necessary. A flush of glans was also found in one patient after the 1st course. Mild to moderate sensory disturbance of the sacral plexus was seen in three patients early during the 1st course. One of them, who achieved a CR after the 1st course, complained of persistent

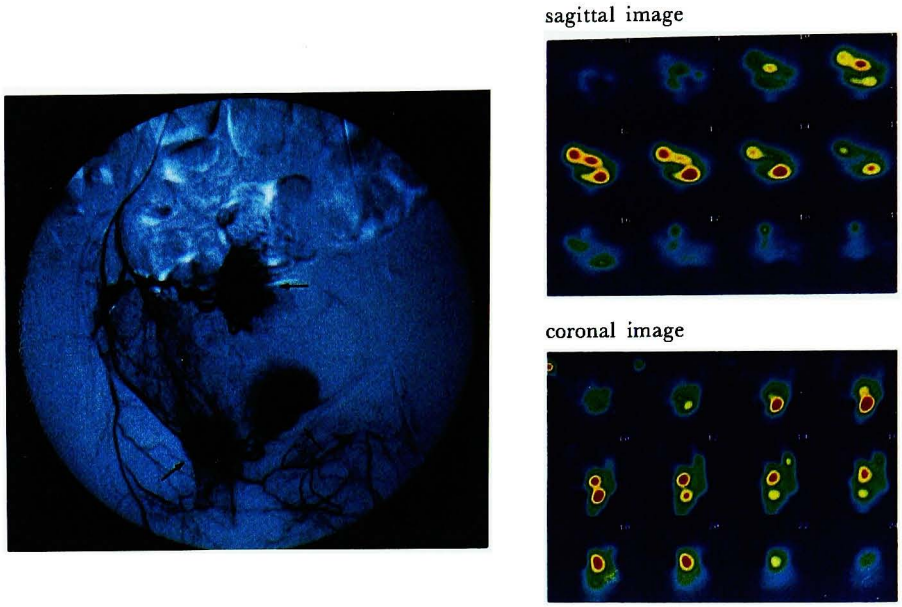

Fig. 2. Patient 8: (A) DSA of the left hypogastric artery showed a hypervascularity in tumor lesions (arrow). (B) SPECT images (sagittal & coronal) revealed an intensive accumulation of ^{99m}TC-MAA in tumor-bearing sites (red area).

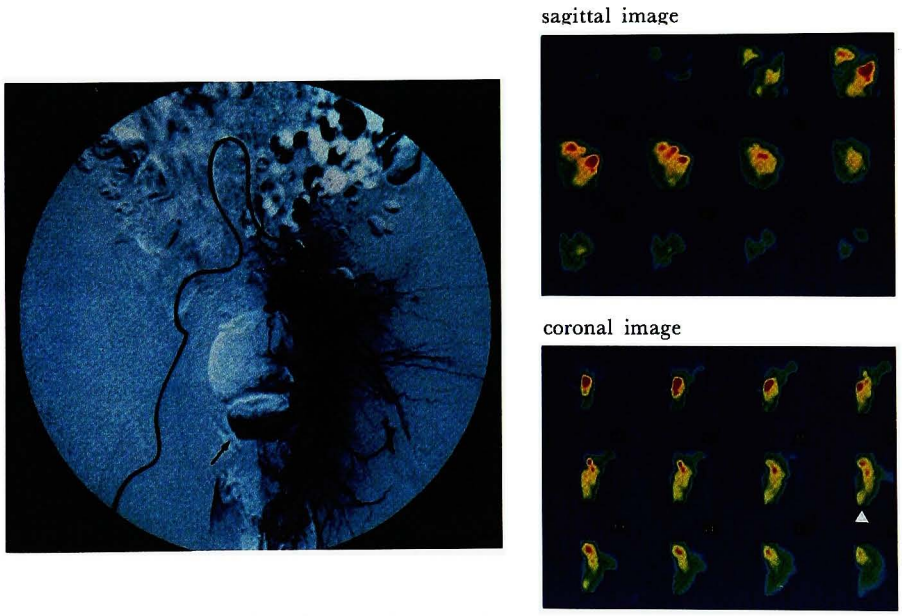

Fig. 3. Patient 9 with a flush of glans: (A) A hypervascularity in tumor lesions in shown (arrow). (B) Except for a high accumulation of ^{99m}TC-MAA in tumor-bearing sites (red area), a moderate pooling in the pudendal area was observed (arrowhead).

neuralgia followed by intermittent gait disturbance despite conservative therapy and refused further maintenance therapy. A fever of unknown origin (above 38°C) and an atrophic bladder were detected in one patient. Moderate renal toxicity with a serum creatinin level above 2 mg/dl occurred in one patient even though the dose of cisplatin was decreased. No complications related to the long-term catheterization were seen.

DISCUSSION

As for the therapeutic effect of IAC[4], the reported objective response rates (CR+PR) have mostly been over 80%, ranging from 36 to 97%, with a 5-year actual survival rate of about 70%. In a neo-adjuvant setting, the post-operative histological findings showed a pathological CR rate of about 25%. Bladder preservation was possible in 19 to 90% of patients, with the follow-up duration being 12 to 84

months. In our patients, an objective response rate of 75% was observed, and an obvious down-staging (T3→pT1b) was found in two of the three evaluable patients, suggesting the possibility of bladder preservation, if followed by complete erradication with transurethral resection (TUR). However, some concern still remains as to the necessity of maintenance chemotherapy after remission inclusive of drug selection, administration route (intravenous or intra-arterial) and duration. In the one patient, who was assessed preoperatively after the two courses as T2 and died of lung metastasis after 8 months, a huge intravesical tumor-mass was completely necrotic, but a small tumor-nest remained deep in the muscular layer (pT3b). It was difficult to make a precise staging-diagnosis pre-operatively after the IAC. SPECT using ^{99m}Tc-MAA which is trapped in capillaries was a useful tool for not only examining the effiiciency of drug delivery rate to tumors, but also predicting some pathological changes of surgical specimens.

As for adverse effects[4,10], sensory disturbance of the sacral plexus with or without sciatic neuralgia, has been of great concern. The occurrence rate of the severe type has been 2 to 13%, and buttock-to-perianal erosion or ulcers have been observed at a 3 to 7% frequency. In our patients, four patients experienced mild to moderate sciatic neuralgia, and one patient was suffering from a moderate buttock-to-perianal erosion.

These findings suggest that IA-M-VEC treatment might be an optimal choice with the possibility of bladder preservation for those patients with localized invasive urinary bladder cancer, who refuse radical cystectomy due to complications or for other reasons.

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和文抄録

浸潤性膀胱癌に対する動注化学療法

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局所浸潤性膀胱癌（T3-4，N0M0）を有する9例に対して，骨盤内血流改変術を伴うリザーバーを用いたM-VEC動注療法（methotrexate 40 mg，vinblastine 4 mg，epirubicin 40 mg，cisplatin 100 mg）を施行し，CR 3例，PR 3例，NC 2例で全体の奏効率は75％であった．PRの3例は根治的膀胱全摘除術を施行したが，2例にdown-staging（T3→pT1b）が認められた．病理組織学的には，腫瘍以外の正常膀胱壁には軽度の筋層の線維化を伴った出血性膀胱炎に類似した変化が著しく，組織学的変化の程度は，dynamic single photon emission computed tomography（D-SPECT）によりえられた^{99m}Tc-macroaggregate albumin（^{99m}Tc-MAA）の集積勾配の強さに一致していた．一方，膀胱以外の臀部や陰部領域に対する薬剤の分布状態もD-SPECTにより明瞭に抽出されており，局所的な副作用の発現をある程度，予測しえた．

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