

Use of methotrexate, vinblastine, Adriamycin, and cisplatin in combination with radiation and hyperthermia as neo-adjuvant therapy for bladder cancer*

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Summary. In an attempt to improve the poor prognosis of invasive and/or high-grade bladder cancer after total cystectomy, we tried a combination of regional irradiation with hyperthermia (RH) therapy and systemic M-VAC (methotrexate, vinblastine, Adriamycin, and cisplatin) chemotherapy followed by surgery. The short-term results of these treatments were evaluated. A total of 17 patients received the combination of RH and M-VAC therapy between January 1989 and July 1990, and 12 then underwent total cystectomy. Of the 17 patients, 14 were evaluable for tumor response. The objective response rate was 64% (9/14), with 4 patients achieving a complete remission that was confirmed by histological examination. Nausea and vomiting were inevitable, and 71% (12/17) of the patients developed leukopenia. However, these side effects were not serious. Considering the previous results obtained using RH therapy in the absence of chemotherapy for this disease, no significant difference in the tumor response was detected between the RH only group and the RH plus M-VAC group. The long-term results cannot yet be evaluated, but we will continue to follow these patients in the future so as to clarify the usefulness of M-VAC therapy as preoperative therapy.

Introduction

The prognosis of high-grade or high-stage bladder cancer patients after total cystectomy is not satisfactory. Local recurrence and distant metastasis after surgery are two main reasons for therapeutic failure in these patients

[9, 14]. In attempts to improve the poor prognosis of these patients, several therapeutic modalities as preoperative therapy have been described. Preoperative radiation is one of them; it has been reported to play some role in controlling local lesions before surgery [12, 15]. The combination of regional hyperthermia with radiation (RH) as well as chemotherapy has been expected to introduce better therapeutic efficacy than either radiation or chemotherapy alone in the treatment of bladder cancer [3, 5]. On the other hand M-VAC therapy (methotrexate, vinblastine, Adriamycin, and cisplatin), which was developed for the treatment of metastatic transitional cell carcinoma and has been demonstrated to be an effective chemotherapy regimen, can also be effective as preoperative treatment [1, 13].

We tried to combine these three therapeutic modalities, i.e., radiation, hyperthermia and M-VAC chemotherapy, as preoperative neo-adjuvant therapy for high-grade, high-stage bladder cancers. The objectives of this study were to evaluate the initial response and the toxicity of preoperative RH plus M-VAC therapy and to compare the effects with those obtained using RH therapy alone.

Patients and methods

Through 1988, a total of 18 patients received RH as preoperative therapy as the Department of Urology, Yokohama City University Hospital. Between January 1989 and July 1990, 17 patients received RH plus M-VAC therapy as preoperative neo-adjuvant treatment. The background characteristics of the patients in both groups are shown in Table 1. All patients had moderately to poorly differentiated transitional-cell carcinoma of the bladder.

The current neo-adjuvant therapy for high-grade or high-stage bladder cancer used at our institute is shown in Fig. 1. Patients who were scheduled to undergo total cystectomy received 40 Gy (4 Gy \times 10 times, twice a week) of pelvic irradiation (Linac) and regional hyperthermia delivered with an 8-MHz radio-frequency apparatus. Each patient received ten treatments of hyperthermia on the same days of radiation therapy. A single course of M-VAC therapy, as first reported by Sternberg et al. [13], was given to the patients at 1 week after the initial RH therapy; at 3 or 4 weeks after completion of the preoperative therapy and after confirmation of complete recovery of the general condition and laboratory data of the patients, radical cystectomy and urinary diversion

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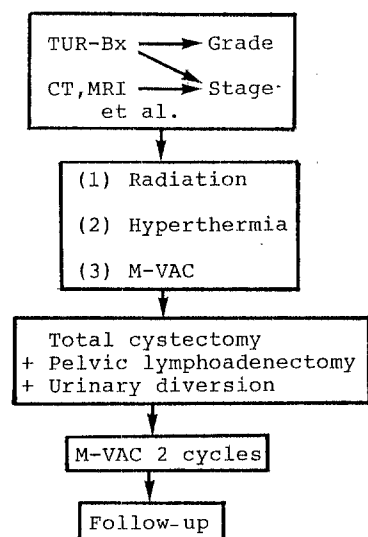


Fig. 1. Current neo-adjuvant therapy for high-grade and/or invasive bladder cancer

Table 1. Patients' characteristics

	RH only group	RH + M-VAC group
Number of patients	18	17
Age (years):		
Range	41–76	37–73
Mean	64	62
Sex:		
M	10	14
F	8	3
Tumor grade:		
Grade 2	8	4
Grade 3	10	13
Tumor stage:		
Ta–T1	6	1
T2	7	9
T3–T4	5	7

Table 2. Quantity of radiation and hyperthermia

	RH only group	RH + M-VAC group
Radiation:		
Field (cm ²):		
Range	48–144	48–168
Mean	85	87
Dose (Gy)	40	40
Hyperthermia:		
Treatments:		
Range	7–10	1–10
Mean	8.7	8
Maximal temperature (°C):		
Range	40.6–47.1	39.8–44.6
Mean	43.9	42.5

Table 3. Initial response of tumors to RH only as compared with RH + M-VAC therapy

	Number of cases	Tumor response				Response rate (CR+PR)
		CR	PR	NC	ne	
RH only group	17	4	5	5	3	9/14 (64%)
RH + M-VAC group	18	4	7	3	4	11/14 (79%)

ne, not evaluated

Table 4. Side effects encountered

	RH only group	RH + M-VAC group
Number of patients	18	17
Tenesmus and pollakisuria	12/18 (67%)	12/17 (71%)
Diarrhea	3/18 (17%)	1/17 (6%)
Fatty necrosis	3/18 (17%)	3/17 (18%)
Nausea and vomiting	0/18 (0)	17/17 (100%)
Leukopenia	3/18 (17%)	12/17 (71%)
Anemia	0/18 (0)	5/17 (30%)
Liver dysfunction	1/18 (5%)	1/17 (6%)

were performed. Usually, two courses of M-VAC therapy were given postoperatively.

Table 2 presents the data on the radiation fields and bladder temperatures in the RH plus M-VAC group as compared with the RH group. The mean radiation field was 87 cm², and all patients received 40 Gy within 5 weeks. No significant difference existed between these two groups. The bladder temperature was monitored by a thermosensor that was attached to a balloon catheter during the hyperthermia treatment. The temperature in the bladder cavity is also shown in Table 2. The bladder cavity was scheduled to be adjusted to 42°C. No significant difference was found between the two groups.

A complete remission (CR) was defined as the total disappearance of all tumor tissues as assessed by histological examination of specimens obtained during total cystectomy. A partial remission (PR) was defined as a decrease of at least 50% in the total tumor volume as determined by radiographic imaging, including computerized tomographic (CT) scans and magnetic resonance imaging (MRI). No change (NC) was defined as a decrease of <50% in the total tumor volume as assessed by the same methods used for a PR.

Results

Table 3 presents the results of the initial response to RH therapy in the presence or absence of M-VAC therapy at the time of surgery. Of the 14 evaluable patients in the RH plus M-VAC group, 4 achieved a CR and 5 showed a PR, in for an objective response (CR + PR) rate of 64%. Of the 14 evaluable patients in the RH group, 4 achieved a CR and

7 showed a PR, for an objective response rate of 79%. No significant difference in the initial response rate was observed between the two groups.

The side effects of these treatment are shown in Table 4. Pollakisuria and tenesmus were commonly encountered in both groups, but they were tolerable. Fatty necrosis, regarded as a side effect of hyperthermia, was observed in 3 of the 17 patients (18%) in the RH plus M-VAC group and in 3 of the 18 patients (17%) in the RH group. Inevitable side effects in the RH plus M-VAC group were nausea and vomiting, and 12 of the 17 patients (71%) in this group also developed leukopenia. However, all of these side effects were reversible and tolerable. Fatal toxicity was not observed in either of the two groups.

Discussion

In our previous report on the clinical observation of patients with high-grade bladder cancer, even those with superficial tumors had a poor prognosis after transurethral resection or partial cystectomy [10]. Total cystectomy is thought to be required for the treatment of these lesions. However, the survival of patients with high-grade and/or high-stage bladder cancer after total cystectomy remains unsatisfactory. Local recurrence and distant metastasis commonly lead to death. In the present trial, we used RH plus M-VAC therapy with the goal of eliminating local lesions and micrometastases.

For local tumor control, preoperative irradiation has been investigated [12, 15]. In an attempt to improve the initial response of bladder cancer to this modality, we used hyperthermia treatment delivery with a capacitive-type radio-frequency apparatus together with local irradiation. In our previous study, radiation and hyperthermia by intravesical irrigation with warmed saline and bleomycin achieved good local control of superficial bladder cancer [7]. In another trial using hyperthermia treatment delivered with a radio-frequency device in combination with radiation, we achieved good local control of deep lesions of the bladder as well as superficial tumors [8]. Thus, in the present study we used a radio-frequency device to achieve hyperthermia in the bladder.

M-VAC chemotherapy has been used to treat measurable metastatic disease and advanced local tumors, with encouraging results [11, 13]. This regimen has been widely applied as neo-adjuvant therapy for invasive bladder cancer [1, 4]. On the other hand, several lines of experimental evidence suggest that the ability of anticancer drugs such as Adriamycin or cisplatin to permeate through the cancer cell membrane is increased by hyperthermia [2], and hyperthermia therapy inhibits the repair of drug-induced DNA damage [6]. On the basis of these findings, Adriamycin and cisplatin are thought to be the best candidates for combination with hyperthermia. Therefore, RH plus M-VAC therapy is expected to provide better local control and killing of metastatic cancer cell foci.

However, in the present study, only the short-term initial response could be evaluated, and no significant differ-

ence was found between the RH plus M-VAC regimen and the regimen of RH therapy alone. Hereafter, two cycles of M-VAC therapy should be attempted preoperatively. All side effects encountered in this study were reversible and tolerable, and no delay in the scheduled cystectomy was ever required. The long-term results cannot yet be evaluated, but we will continue to follow these patients carefully in the future in an attempt to clarify further the usefulness of M-VAC therapy as preoperative treatment for bladder cancer.

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