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ORIGINAL ARTICLE

Preliminary results of M-VAC chemotherapy combined with mild hyperthermia, a new therapeutic strategy for advanced or metastatic transitional cell carcinoma of the urothelium

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Abstract
Objective We evaluated the efficacy and safety of M-VAC chemotherapy combined with mild hyperthermia, a new therapeutic strategy for advanced metastatic transitional cell carcinoma of the urothelium.
Subjects and methods The subjects were 12 patients diagnosed with advanced metastatic transitional cell carcinoma of the urothelium. For mild hyperthermia, the patients' oral temperature was elevated to about 38°C by heating for 20 min and retaining the heat for 20 min with a far-infrared heater. The antitumor effect was evaluated according to the RECIST, while adverse drug reactions were assessed based on the NCI-CTC.
Results The antitumor effect was rated as partial remission (PR) in 10 of the 12 patients and stable disease in 2 patients, with an efficacy rate of 83% (10/12). All 10 patients who had achieved PR received three courses of treatment. Of the 12 patients, 5 died during the observation period, with survival for 9–23 months (mean: 15.6 months). Adverse drug reactions included myelosuppression in all patients (Grade 3 in 4 patients, Grade 4 in 8), and gastrointestinal toxicity, such as nausea or vomiting, which was mild (Grade 0 in 2 patients, Grade 1 in 8, Grade 2 in 1, Grade 3 in 1).
Conclusions The results of the present study suggest that M-VAC chemotherapy combined with mild hyperthermia, which potentiates the anticancer effect and reduces adverse drug reactions such as gastrointestinal symptoms, is a useful and safe method for the treatment of advanced transitional cell carcinoma of the urothelium.

Keywords Mild hyperthermia · M-VAC chemotherapy · Heat-shock protein (HSP) · Transitional cell carcinoma · Urothelial cancer

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Introduction

At present, surgical resection is established as the standard treatment for nonmetastatic invasive transitional cell carcinoma of the urothelium. However, the outcome of surgery depends largely on the pathologic stage of the disease and the presence or absence of lymph node metastasis at the time of surgery. It has been reported that in patients with invasion confined to the muscularis, the 5-year cause specific disease-free survival is as high as about 70%, while the rate is 30–40% in patients with a tumor invading the surrounding adipose tissue (pT3 or higher), and is about 20% in patients with lymph node metastases [1–3]. It has also been reported that many postoperative recurrences are distant metastases, and local recurrence occurs in about 10% of cases [4]. To improve the results of treatment of invasive transitional cell carcinoma of the urothelium, it is therefore more important to eradicate micrometastases that

cannot be detected by imaging than to perform radical local treatment. In addition, surgical resection is not sufficient for the treatment of invasive transitional cell carcinoma of the urothelium with extramural extension or lymph node metastases, and additional treatment is required.

Unresectable or metastatic advanced transitional cell carcinoma of the urothelium is generally treated with combination chemotherapy with various anticancer drugs. The typical chemotherapy regimen is methotrexate, vinblastin, doxorubicin, and cisplatin (M-VAC) therapy. Since the report of a response rate of 72% and a complete remission (CR) rate of 36% published by Sternberg et al. [5, 6], this regimen had been the gold standard. Subsequent studies, however, showed that this therapy produced low response rates with a short duration of response, hardly offering long-term survival, and that dose reduction of these highly toxic drugs might be required since this therapy is indicated for many elderly patients. These issues often become problematic with regard to dose intensity [7, 8].

The results of clinical studies of combination chemotherapy with gemcitabine and cisplatin have recently been reported. The results are far from satisfactory, with a response rate of 49.4% and a 5-year survival rate of 13.0% [9, 10]. In a study of combination therapy of gemcitabine and carboplatin, the efficacy rate was also found to be lower than that achieved with a combination of gemcitabine and cisplatin [11]. Considering these findings, there is undoubtedly an urgent need for a new regimen or method of administration that involves lower toxicity of anticancer drugs and a greater antitumor effect for the treatment of unresectable or metastatic advanced transitional cell carcinoma of the urothelium.

Mild hyperthermia therapy, in which the whole body is heated for 30 min with a heater to increase the oral temperature by 1–2°C, has been reported to induce heat-shock proteins (HSPs), increase biophylaxis and immunocompetence, prevent stress and fatigue, and reduce depression, anxiety, fear, and the like [12–17].

We investigated whether a combination of M-VAC chemotherapy and mild hyperthermia, a new therapeutic strategy for advanced metastatic transitional cell carcinoma of the urothelium, could potentiate the antitumor effect and reduce adverse drug reactions.

Subjects and methods

The subjects were 12 patients who were diagnosed with advanced metastatic transitional cell carcinoma of the urothelium between February 2005 and April 2008 and received M-VAC chemotherapy combined with mild hyperthermia at Aichi Medical University Hospital. The patients were observed for 7–40 months (mean: 17.8 months). The last observation was performed on October 31, 2008. The patients' ages ranged from 55 to 71 years, with a mean age of 60.8 years. All the patients were men. The baseline patient characteristics are shown in Table 1. A far-infrared heater (Fujika, Ltd., Tokyo, Japan) was used to induce mild hyperthermia. As it had been confirmed that HPS 70 increases one to 3 days after heating with this equipment, patients were heated for 30 min and kept warm for 20 min 2 days before and on each day of administration of anticancer drugs, to increase the patients' oral temperature to about 38°C. The doses and the treatment schedule are presented in Fig. 1. Antitumor effect was evaluated based on the response evaluation criteria in solid tumors [18] after the patient had received two courses of M-VAC chemotherapy combined with mild hyperthermia. Patients who had achieved a partial

Table 1 Characteristics of 12 patients

Case	Age (years)	Sex	KPS (%)	Primary lesion	Pathology	Metastatic site	Prior therapy
1	58	M	80	Ureter	TCC	RPLN	NUx
2	60	M	70	Bladder	TCC	Multiple LN	Cx
3	71	M	70	Bladder	TCC	Lung	TUR-Bt
4	62	M	60	Ureter	TCC	RPLN, bone	NUx
5	57	M	90	Ureter	TCC	Pelvic LN	NUx
6	56	M	60	Bladder	TCC	Multiple LN, liver, bone	Cx
7	62	M	80	Renal pelvis	TCC	RPLN	NUx
8	55	M	80	Bladder	TCC	RPLN	Cx
9	58	M	80	Bladder	TCC	Pelvic LN	Cx
10	62	M	90	Bladder	TCC	Pelvic LN, RPLN	NUx, Cx
11	57	M	70	Ureter	TCC	Lung, pelvic LN	Nux
12	71	M	90	Bladder	TCC	Pelvic LN, RPLN	TUR-Bt

RPLN Retroperitoneal lymph node; *NUx* Nephroureterectomy; *Cx* Total cystectomy; *TUR-Bt* Transurethral resection-bladder tumor; *KPS* Karnofsky performance scale

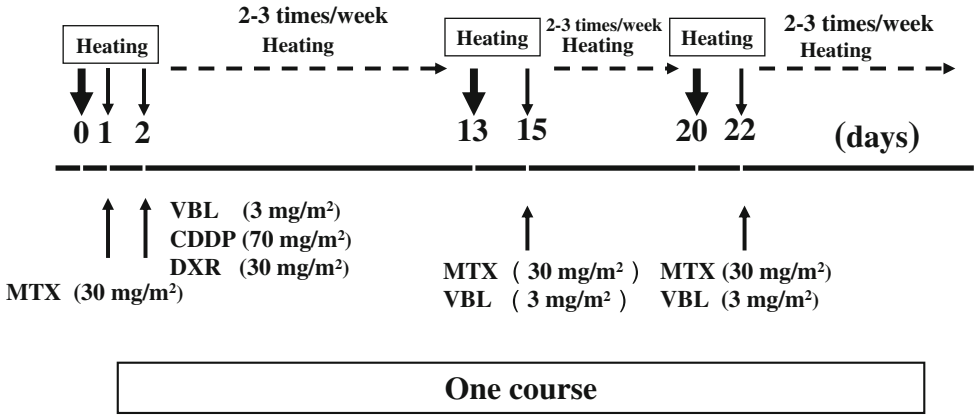

Fig. 1 *Treatment schedule of M-VAC chemotherapy combined with mild hyperthermia.* The patient's whole body was heated by a far-infrared heater. The patient's oral temperature was 38°C or higher 2 days before administration of drugs, and around 37.5°C on each day of administration and other days. Geranylgeranyl acetone, inducer of HSP 70, was administered when heating was not feasible. In M-VAC chemotherapy, anticancer drugs are administered on days 1, 2, 15, and 22. Mild hyperthermia is performed 2 days before each administration of anticancer drugs to increase the patient's temperature to 38°C or more. In addition, mild hyperthermia is performed two to three times per week during the intervening period to increase the patient's temperature to 37.5–38°C to enhance immunity

remission (PR) or better response received three courses of treatment. Adverse drug reactions were evaluated according to the Common Toxicity Criteria established by the National Cancer Institute [19].

This clinical study was approved (No. 383) by the Institutional Review Board of Aichi Medical University School of Medicine. All patients received sufficient explanation and gave informed consent to participate in the study before receiving M-VAC chemotherapy combined with mild hyperthermia.

Results

The antitumor effect was evaluated as PR in 10 of the 12 patients and stable disease (SD) in two patients, with an efficacy rate of 83% (10/12). There were no patients with complete remission (CR) or progressive disease (PD). The two patients with SD only received two courses of M-VAC chemotherapy, while all of the 10 patients with PR received three courses. Five of the twelve patients died during the observation period, with a survival time of 9–23 months (mean survival time: 15.6 months). This therapy involved severe toxicity as an adverse drug reaction; all patients experienced myelosuppression (Grade 3 in 4 patients, Grade 4 in 8). However, gastrointestinal toxicity, such as nausea or vomiting, was mild (Grade 0 in 2 patients, Grade 1 in 8, Grade 2 in 1, Grade 3 in 1). Two patients with bone metastases experienced pain relief. High dose intensity was maintained in each course, with an average relative dose intensity of 83–100% (Table 2). None of the patients experienced any adverse events in relation to mild hyperthermia.

Discussion

There is a need for a new regimen or method of administration that involves lower toxicity of anticancer drugs and a stronger antitumor effect for the treatment of unresectable or metastatic advanced transitional cell carcinoma of the urothelium. We previously studied the expression of the human epidermal growth factor receptor 2 in patients with invasive bladder cancer with the aim of developing tailor-made treatment, but failed to identify a relationship between its expression and the outcome [20, 21]. Ciardiello et al. [22] also studied the effect of molecular targeting drugs using Iressa, but could not demonstrate its usefulness. The recently reported results of clinical studies of combined chemotherapy with gemcitabine and cisplatin were far from satisfactory, with a response rate of 49.4% and a 5-year survival rate of 13.0% [9, 10]. Another study showed that combination therapy of gemcitabine and carboplatin produced a lower efficacy rate than combination therapy of gemcitabine and cisplatin [11]. In our present study, which was conducted in a smaller number of patients for a shorter period, M-VAC chemotherapy combined with mild hyperthermia showed a high efficacy rate with PR rate of 83% (10/12), although no patient achieved CR, but no patient had PD during the treatment period. Five of the twelve patients died during the observation period; however, their mean survival time was 15.6 months, which was slightly longer than those reported by other researchers [9, 10].

We presume that one of the advantages of concomitant use of mild hyperthermia is the induction of HSPs, which have been reported to have the following effects: biophylaxis; enhancement of immunocompetence caused by an increase in NK, $CD4^+$, $CD8^+$, and CTL cells; prevention of

Table 2 Results

Case	Nausea/ vomiting	Myelosuppression	Effect (tumor regression rate %)	Average RDI (%)	Hyperthermia (times)	Outcome
1	Grade 0	Grade 4	PR (90%)	(1) 83, (2) 83, (3) 100	24	Dead (16 months)
2	Grade 0	Grade 3	PR (90%)	(1) 100, (2) 100, (3) 100	87	Alive (40 months)
3	Grade 1	Grade 3	PR (50%)	(1) 100, (2) 100, (3) 83	58	Dead (16 months)
4	Grade 1	Grade 3	PR (60%)	(1) 100, (2) 100, (3) 100	28	Dead (16 months)
5	Grade 1	Grade 3	SD (20%)	(1) 83, (2) 83	11	Alive (29 months)
6	Grade 1	Grade 4	PR (90%)	(1) 100, (2) 100, (3) 100	41	Alive (17 months)
7	Grade 1	Grade 4	PR (50%)	(1) 83, (2) 100, (3) 100	37	Alive (19 months)
8	Grade 1	Grade 4	SD (0%)	(1) 83, (2) 83	29	Dead (14 months)
9	Grade 3	Grade 4	PR (45%)	(1) 100, (2) 100, (3) 100	40	Alive (14 months)
10	Grade 2	Grade 4	PR (44%)	(1) 100, (2) 100, (3) 100	42	Dead (9 months)
11	Grade 1	Grade 4	PR (84%)	(1) 84, (2) 100, (3) 84	41	Alive (9 months)
12	Grade 1	Grade 4	PR (60%)	(1) 84, (2) 84, (3) 84	37	Alive (7 months)

Observation period, 7–40 months (mean 17.8 months)

RDI, Relative dose intensity; PR, 10/12, Efficacy rate: 83%

(1), (2), (3): Chemotherapy course

stress and fatigue; and reduction of depression, anxiety, fear, and the like [12–17]. Among the HSPs, HSP 70 is the molecular chaperone most commonly induced by thermal stress. We presume that an increase in HSP 70 contributed to a reduction of gastrointestinal adverse reactions and potentiation of the antitumor effect, although the therapy involved severe myelosuppression. We are now measuring the blood HSP 70 concentration with enzyme-linked immunosorbent assay before and after mild hyperthermia, and have already confirmed that the blood HSP 70 concentration was increased on day 2 of heating [23]. At present, the mechanism by which HSP expression is involved in the high efficacy rate remains unclear. It seems very important to elucidate this mechanism because it may lead to potentiation of the antitumor effect and extensive use of chemotherapy combined with mild hyperthermia, not only for the treatment of transitional cell carcinoma of the urothelium but also for the treatment of other diseases.

Another advantage of mild hyperthermia seems to be an increase in the uptake of anticancer drugs into tumor cells, caused by an increase in blood flow in tumor tissue, which was demonstrated in an in vivo experiment performed in C3H/He mice by Ono et al. [24]. We presume that this increase in the uptake of anticancer drugs into tumor cells potentiates the antitumor effect.

None of the patients experienced adverse events in relation to the far-infrared heater used for mild hyperthermia during the study, showing that this equipment is safe to use.

The results of the present study suggest that M-VAC chemotherapy combined with mild hyperthermia, which potentiated the anticancer effect and reduced adverse drug reactions on gastrointestinal symptom such as nausea or vomiting, is useful for the treatment of advanced transitional cell carcinoma of the urothelium. However, four patients who had achieved PR died during the observation period, and one recurrence occurred some time after chemotherapy. We thus think it necessary to establish chemotherapy combined with mild hyperthermia as maintenance therapy, which can prolong the duration of remission.

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