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Hyperthermia combined with intra-thoracic chemotherapy and radiotherapy for malignant pleural mesothelioma

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Abstract

Background: Prognosis for patients with malignant pleural mesothelioma (MPM) remains poor and such patients require intensive treatment. Few studies have examined hyperthermia for MPM. The present study investigated the feasibility of hyperthermia combined with weekly chemo-radiotherapy for patients with MPM and estimated the efficacy of this regimen.

Methods: A total of 11 patients (median patient age was 67 and all had pleural effusion) with MPM were enrolled in this study. The treatment regimen comprised of weekly thermo-radiotherapy with intra-thoracic chemotherapy 2–5 times at initiation of treatment. Hyperthermia was performed once per week for ~60 min. Hemithorax external radiotherapy was administered once weekly on the same day as hyperthermia and just before thermochemotherapy. Median total radiation dose was 6 Gy (range, 2–10 Gy). Chemotherapy was administered into the thoracic cavity through a tube. Chemotherapeutic agents administered were CDDP for seven patients, carboplatinum (CBDCA) for three patients and both CDDP and CBDCA for one patient. Dose of CDDP was 50 mg/body and dose of CBDCA was 200–300 mg m^{-2}. Response rate and median survival time (MST) and palliative effect were investigated.

Results: Complete response was not achieved in any of the 11 patients. Partial response was achieved in three of 11 patients (27.3%), SD in six patients (54.5%) and PD in two patients (18.2%). There was no correlational relationship between thermal parameters and response. MST was 27.1 months. Pleural fluid decreased in all patients after therapy, while all patients displayed improved performance status and could be discharged from hospital. Patients with partial response had a relatively longer survival time than SD or PD. All patients underwent the complete course of treatment and only one of 11 patients developed grade 4 thrombocytopenia.

Conclusion: It was therefore concluded that hyperthermia combined with intra-thoracic chemotherapy using cisplatinum or carboplatinum may be tolerable. This approach appears effective and more acceptable for patients with MPM with pleural effusion than other multi-modality therapy.

Keywords: *Malignant pleural mesothelioma hyperthermia, thermo-chemo-radiotherapy, intra-thoracic chemotherapy*

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Introduction

Malignant pleural mesothelioma (MPM) is a rare disease that is usually caused by exposure to asbestos. Although most countries have quite strict rules about asbestos now, due to the long latency of MPM and the fact that the exposure was increasing until a certain time ago, the numbers of patients with MPM has been predicted to increase over the next few decades [1]. Depending on the health of the individual, time of diagnosis and other factors, survival time is ~4–12 months from onset of symptoms [2]. Treatment for mesothelioma can involve surgical resection of the tumour, chemotherapy, radiotherapy or a combination of these approaches. However, the roles of surgery, radiotherapy and chemotherapy in the treatment of mesothelioma remain undetermined [3]. New chemotherapeutic agents are currently being tested in clinical trials and appear somewhat promising [4, 5]. Treatments using some combination of surgery, radiotherapy and chemotherapy, known as multi-modality therapy, are now being studied and may provide the most promising option for some patients. However, the majority of patients presenting with MPM are not candidates for radical surgical resection due to unresectable, locally advanced disease or comorbidity. Even with strictly selected patients, surgery is associated with relatively high risks, with mortality for pleurectomy and decortication reportedly ~2% [6] and mortality for extra-pleural pneumonectomy ranging from 6–30% [7].

Ratto et al. [8] demonstrated that hyperthermic intra-thoracic perfusion with cisplatinum (CDDP) offers pharmacokinetic advantages with limited systemic toxicity. DeBree et al. [9] reported the feasibility and toxicity of cytoreductive surgery combined with hyperthermic intra-thoracic chemotherapy for patients with MPM. In that study, most patients underwent surgical resection. However, thermo-chemo-radiotherapy for unresectable MPM has not been reported. This study reports herein the use of thermo-chemo-radiotherapy to treat 11 patients with MPM without surgical resection.

Materials and methods

Patients

A total of 11 patients (seven men, four women) with MPM were enrolled in this study between March 1995 and March 2005. Median patient age was relatively old, ~67 years (range, 48–85 years) at initiation of treatment. Patient characteristics are shown in Table I.

Hyperthermia

Hyperthermia was produced using a radiofrequency capacitive heating apparatus (Thermotron RF8; yamamoto Vinita Co. Ltd, Osaka, Japan). Hyperthermia was produced once per week for ~60 min (median, 3.5 times). Electrodes were placed on the front and back of the patient and were 25–30 cm in diameter (Figure 1). Overlay bolus was used to reduce the edge effect. Thermometry was performed by inserting thermocouples directly into the tumour for two patients, into the chest wall for six patients, into effusion itself for one patient or onto the skin for two patients. Since skin temperature is not an accurate indicator of tumour temperature, these two patients were excluded from thermal parameter analysis.

Radiotherapy

All patients received hemithorax external radiotherapy using a 10-MV linear accelerator (Mevatron; Toshiba medical Co. Ltd, Tokyo, Japan). In principle, MPMs are disseminated

Table I. Patient and treatment characteristics.

No.	Age	Sex	PS before	Stage	Side	RT (Gy/fr)	Chemo	HT	T_{max}
1	64	M	2	T3N1M0	R	2/1	Cb	2	44.2 t
2	54	F	1	T1N0M0	R	8/4	C	4	43.2 w
3	48	M	1	T2N2M0	L	10/5	Cb	5	42.3 w
4	77	F	1	T1N0M0	R	6/3	C	3	43.7 w
5	67	M	1	T1N0M0	L	10/5	C/Cb	5	40.1 s
6	76	F	1	T3N1M0	L	6/3	C	3	43.0 w
7	85	M	2	T3N2M0	L	3/3	Cb	3	42.8 i
8	51	M	2	T3N2M0	R	10/5	C	5	41.2 t
9	57	M	1	T3N0M0	R	6/3	C	3	42.7 w
10	71	M	0	T1N0M0	R	6/3	C	3	39.5 w
11	73	F	0	T2N0M0	R	4/2	C	2	35.4 s

RT: radiotherapy; Chemo: chemotherapeutic agents; HT: hyperthermia; M: male; F: female; C: CDDP; Cb: CBDCA; T_{max}: maximum temperature; t: tumour; w: chest wall; s: skin; i: intra-thoracic; fr: fraction.
Median patient age was 65.7 years (range, 48–85 years) at initiation of treatment. Every patient underwent 2–5 courses of hyper-chemo-radiotherapy (median, 3.5 courses) without surgical treatment. T_{max} for the last two patients was not high, as thermocouples were placed near the skin surface and were thus susceptible to cold circulation water.

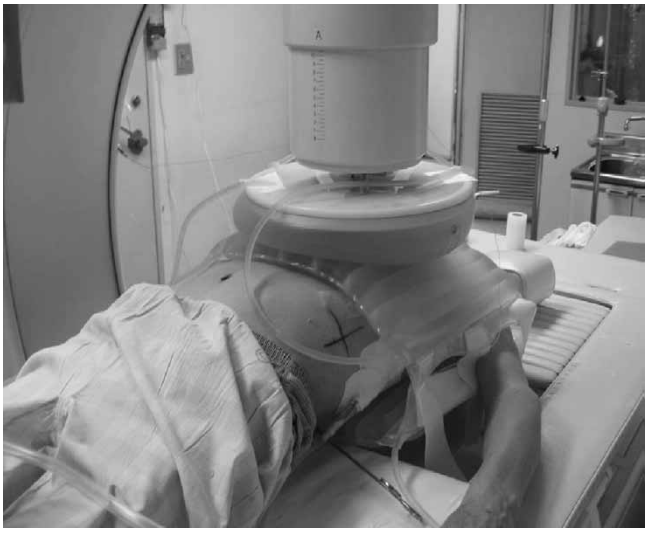

Figure 1. A patient receiving hyperthermia treatment. This patient is undergoing hyperthermia treatment. The catheter in the left chest is used for infusion of cisplatinum or carboplatinum.

to the cavity, so the field should cover the entire hemithorax. As lung tissue is radiosensitive, radiotherapy was administered once weekly on the same day as hyperthermia and just before thermochemotherapy. Median total radiation dose was 6.5 Gy (range, 2–10 Gy) and median fraction size was 1–2 Gy.

Chemotherapy

Chemotherapy was administered into the thoracic cavity through a tube. Chemotherapeutic agents administered were CDDP for seven patients, carboplatinum (CBDCA) for

three patients and both CDDP and CBDCA for one patient. Dose of CDDP was 50 mg/body and dose of CBDCA was 200–300 mg m^{-2}.

Data analysis

Clinical tumour response was evaluated by measuring the tumour under computed tomography (CT). Complete response (CR) was defined as complete absence of disease. Partial response (PR) was defined as a $\geq$50% reduction from baseline of the sum of the products of perpendicular diameters for bidimensionally measurable disease or a $\geq$30% decrease in sum of the greatest diameters of unidimensionally measurable lesions. Progressive disease (PD) was defined as a $\geq$50% increase from baseline of the sum of the products of perpendicular diameters of bidimensionally measurable lesions. Stable disease (SD) represented disease that did not qualify for CR, PR or PD. Analysis of overall survival was conducted using the Kaplan–Meier method.

Results

Table II summarizes treatment results. Complete response was not achieved in any of the 11 patients. PR was achieved in three of 11 patients (27.3%), SD in six patients (54.5%) and PD in two patients (18.2%). Survival period ranged from 4.1–68.0 months.

As for thermal parameters, the average of T_{max} for PR cases, SD cases and PD case were $43.2 \pm 0.95^{\circ}$C, $42.2 \pm 1.86^{\circ}$C and $42.0 \pm 1.13^{\circ}$C, respectively. There was no correlational relationship between T_{max} and the response.

Pleural fluid decreased in all patients after therapy, while all patients displayed improved performance status and pain relief and could be discharged from hospital. Complications comprised grade 4 thrombocytopenia in one patient. A blood transfusion was administered and no severe cardiac or pulmonary toxicity was observed.

As of June 2005, a total of eight of the 11 patients were dead from respiratory failure due to intra-throracic recurrence and intractable pleural effusion. Four patients survived more than 2 years. Among them three were PR and one was SD. Two patients were PD and lived no more than 7 months. Median survival time (MST) was 27.1 months (Figure 2).

Table II. Treatment results.

No.	Age	Sex	Response	PS (after)	Discharge	Time/status
1	64	M	PR	1	yes	68.0 dead
2	54	F	PR	0	yes	27.4 dead
3	48	M	PR	0	yes	27.1 dead
4	77	F	SD	0	yes	38.1 alive
5	67	M	SD	0	yes	7.6 dead
6	76	F	SD	0	yes	6.5 dead
7	85	M	PD	1	yes	6.5 dead
8	51	M	PD	1	yes	4.1 dead
9	57	M	SD	0	yes	14.3 dead
10	71	M	SD	0	yes	17.1 alive
11	73	F	SD	0	yes	12.8 alive

All patients were discharged after hyper-chemo-radiotherapy due to pleural fluid control. PR was achieved in three of 11 patients (27.3%), SD in six patients (54.5%) and PD in two patients (18.2%). As of 11 June 2005, eight of 11 patients were dead due to primary disease and three patients were still alive. Survival time ranged from 4.1–68.0 months.

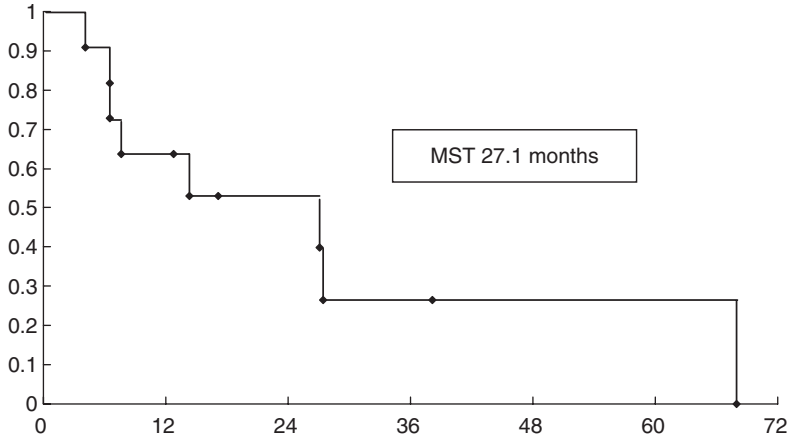

Figure 2. Overall survival. Overall survival for 11 patients with MPM. Median survival time (MST) was 27.1 months.

Discussion

Despite many years of clinical research, no effective therapies have yet been identified for MPM. Untreated, prognosis is poor, with a median survival of <1 year [10]. MPM may be treated using surgery, radiotherapy, chemotherapy or a combination of these approaches. In most patients, treatment remains palliative with symptom relief and moderate gains in survival. Some research has demonstrated that surgery can only offer symptom relief, with MST remaining poor at 8–11 months [11–13].

Most monotherapies have been tested for MPM (Table III). In general, single-agent response rates are <20% and no survival benefit for single-agent chemotherapy has been suggested by cohort studies. CDDP has demonstrated overall response rates of 14% and 36% when administrated at doses $100\,mg\,m^{-2}$ every 21 days or $80\,mg\,m^{-2}$ weekly, respectively [17, 18]. CBDCA, a better tolerated and easier-to-deliver analogue of CDDP, demonstrated response rates similar to CDDP when used with a conventional regimen [19]. Some new agents, such as paclitaxel and gemcitabine, also display low response rates and therefore do not appear to represent effective monotherapies for MPM [22, 24]. Pemetratexed is a novel multi-targeted anti-folate that has been studied as a monotherapy in a phase II study, with a response rate ~16% [26]. Single-agent chemotherapy is thus not recommended for treatment of MPM.

Combination chemotherapeutic regimens have been extensively evaluated in MPM (Table IV) [27]. The majority of these regimens have been adriamycin- or platinum-based. With few exceptions, however, most response rates have been a little higher than monotherapies and have remained <30% and MST has remained within 7–14.8 months.

While often attempted with curative intent, neither surgical management nor chemotherapy appears to offer significant improvements in survival. Efforts have therefore been focused on multi-modal approaches. Sugarbaker et al. [28] conducted a large study evaluating multi-modalities against MPM. A single cohort of patients underwent EPP (extrapleural pneumonectomy) and adjusted chemotherapy with cyclophosphamide/doxorubicin and/or CDDP and/or CBDCA/paclitaxel. That study demonstrated total MST as 19 months and a sub-set of patients with good prognostic parameters (i.e. epithelial histology, no nodal

Table III. Single-agent chemotherapy for MPM.

Reference	Patients	Drug	RR (%)
Lerner et al. [14]	51	Doxorubicin	14
Magri et al. [15]	21	Epirubicin	5
Bajorin et al. [16]	19	Mitomycin C	21
Zidar et al. [17]	35	Cisplatinum (21d)	14
Planting et al. [18]	14	Cisplatinum (7d)	36
Raghavan et al. [19]	31	Carboplatinum	16
Harvey et al. [20]	20	5-Fluorouracil	4
Solheim et al. [21]	60	Methotrexate	37
Van Meerbeeck et al. [22]	25	Paclitaxel	0
Steele et al. [23]	29	Vinorabine	24
Van Meerbeek et al. [24]	27	Gemcitabine	7
Anderson et al. [25]	26	Ifosfamide	4
Scagliotti et al. [26]	64	Pemetrexed	16

Most single agents have been tested for MPM. In general, monotherapy response rates are <20% and single-agent chemotherapy is thus not recommended for treatment of MPM.

Table IV. Combination chemotherapy for MPM.

Drug	Patients	Response rate	MST (months)
ADM + CTX	36	11	8
ADM + CDDP	59	19	8.8
ADM + CDDP + MMC	24	21	11
CDDP + CPT-11	15	27	7
CDDP + MMC	35	26	7.7
CDDP + Vp-16	25	24	9.5
CDDP + GEM	21	48	10
CDDP + pemetrexed	456	41	12.1
CBPDA + pemetrexed	27	32	14.8

ADM: adriamycin; CTX: cyclophosphamide; MMC: mitomycin C; CPT-11: irinotecon; Vp-16: etoposide; GEM: gemcitabine.
Combination chemotherapy regimens have been extensively evaluated in MPM. However, most response rates to these regimens are little higher than monotherapy and still <30% and MST remains in the range of 7–14.8 months.

involvement and clear resection margins) achieved an MST of 51 months and 2- and 5-year survival rates of 68% and 46%, respectively. Other approaches to multi-modal therapy have been tried. Yoshino et al. [29] selected 11 patients with resectable MPM who underwent hemithorax radiotherapy with gemcitabine/vinorelbine/cisaplatinum, achieving an MST of ~22 months. Weder et al. [30] investigated patients who underwent neoadjuvant chemotherapy using CDDP and gemcitabine followed by extra-pleural pneumonectomy with or without radiotherapy in patients with potentially resectable MPM. The response rate was 32% and MST was 23 months.

In the present study, hyperthermia was used for 11 patients instead of surgical management. This approach seems more practical, as the majority of patients have no opportunity to be operated on due to wide unresectable lesions when diagnosed. On the other hand, although systemic intravenous administration of the drug may be more effective

in establishing diffuse dose intensity in malignant cells than local administration in patients with bulky tumours, especially with lymph-node metastases, it is not always suitable for every patient because of the toxicity of drug, especially to old patients. Also in such cases with bulky tumours local radiotherapy might be indicated. In the absence of surgical risk and with reduced invasiveness and toxicity of drug, this is more acceptable to the older patients. The regimen seemed tolerable and no severe complications were observed except for one case. All patients gained therapeutic benefits after initial therapy and were able to be discharged because of pain relief and control of pleural effusion. The stage of two patients with PD was T3N2M0, which was relatively advanced compared to other patients. It seems that local administration may be less effective in patients with bulky tumours, especially with lymph-node metastases. However, this regimen may be more tolerable to the older patients, especially without good performance status. And the patient survival was in accordance with the response rate which had a close relationship with stage of MPM. Response rate was 27.3% and MST was 27.1 months, comparable with the multi-modal approach mentioned above. This result was attributable to the fact that hyperthermia involves two biological interactions with radiation: a radiosensitizing effect [31]; and a direct cytotoxic effect on tumour cells [32]. When the target lesion is heated to $\sim 42^{\circ}$C, the cancer-killing effects of radiation or anti-cancer agents are enchanced [33]. Intra-cavitary chemotherapy has the additional advantage of allowing high local doses with limited systemic toxicity [34]. Hyperthermia also improves the efficacy and penetration depth of chemotherapy [35]. This therapy is thus considered an effective approach to treat MPM with pleural effusion.

As for thermal parameters, one could not have any positive correlational relationship between $T_{\max}$ and response. This is partly because of the possible heterogeneity of temperature distributions in diffuse MPM and partly because of the limited number of cases. Since one will continue to treat MPM patients in this way, any relationship would be acquired in the future.

In summary, the therapeutic effects and survival benefits described herein demonstrate the feasibility of thermo-chemo-radiotherapy for MPM with pleural effusion. The efficacy of thermo-chemo-radiotherapy remains to be confirmed in further studies involving a larger subject population.

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