Original Contribution

Intrathoracic Thermochemoradiotherapy for the Treatment of Locally- Advanced Malignant Pleural Mesothelioma

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Abstracts : Malignant pleural mesothelioma (MPM) is considered to carry very poor prognoses and reported surgical results revealed median survival time to be less than one year for UICC-stage I to III. Instead of surgery, we performed thermoradiotherapy combined with chemotherapy using platinum compounds into the pleural cavity for the treatment of this disease. We experienced 8 cases of UICC-stage I to III MPM and 3 of them got good response and survival time of more than 2 years, respectively (median survival time was 14.1 months). This treatment method might be well tolerated by the patient with good quality and quantity of life. Furthermore, the amount of the pleural effusion was controlled in most patients. As radical aggressive treatment carries considerable risk of mortality and morbidity, this organ-conserving trimodal therapy might be an alternative treatment modality.

Key Words : chemothermotherapy, hyperthermia, malignant pleural mesothelioma

Introduction

Malignant pleural mesothelioma (MPM) is considered to carry very poor prognoses and reported surgical results revealed median survival time to be less than one year for UICC-stage I to III¹⁻⁵⁾. However, it is considered that the only curative treatment is complete surgical resection which can be life threatening. Instead of surgery, we performed thermoradiotherapy combined with chemotherapy into the pleural cavity for the treatment of this disease⁶⁾. Since 1995, we have experienced 8 cases and some of them obtained good response and favorable prognosis. In this paper, we presented our preliminary results and discussed about the problems.

Table I patient's characteristics

No	age	sex	side	PS	UICC-TNM	UICC-stage
1	64	M	R	2	T3N1M0	III
2	54	F	R	1	T1N0M0	I
3	48	M	L	1	T2N2M0	III
4	77	F	R	1	T1N0M0	I
5	67	M	L	1	T1N0M0	I
6	76	F	L	1	T3N1M0	III
7	85	M	L	2	T3N2M0	III
8	51	M	R	2	T3N2M0	III
med	65.5					

R : right , L : left

Table II treatment protocol

Eligibility criteria

Age between 20 and 85

PS 0-3

No concurrent chemo-and/or radiotherapy

WBC $\geq$ 2,500, Plt $\geq$ 100,000

No severe hepatic nor renal dysfunction

No severe infection nor heart disease that precludes this treatment

Treatment Schedule

Concurrent thermo-radio-and intrathoracic chemotherapy once a week

Radiotherapy for hemithorax 2Gy/fr by 10MV photon beam
through AP-PA technique just before chemotherapy

Chemotherapy CDDP/CBDCA

CDDP 50mg/body, or CBDCA 450mg/body
infuse just before hyperthermia treatment

Hyperthermia (RF Capacitive heating)

AP-PA technique, duration 45-60min.

Patient & Method of Treatment*Patient characteristics*

From 1995 to 2002, there were 8 patients with UICC-stage I to III MPM who were treated with thermoradiotherapy combined with chemotherapy into the pleural cavity at Tokyo Metropolitan Komagome Hospital. Among this 8 patients, three were reported previously ⁶⁾. Patient characteristics are shown in table 1.

Patient's age ranged from 48 to 85 years (median 65.5). There were 5 males and 3 females. There were 4 left-sided tumors and 4 right-sided tumors. The Zubrod performance status at the beginning of radiotherapy was 1 in 5 cases and 2 in 3 cases. All patients were diagnosed histologically as malignant pleural mesothelioma. Pretreatment UICC-stage I was in 3 cases, stage III in 5 cases.

Method of Treatment

Our treatment protocol is listed in Table 2. We mentioned the protocol in detail in the previous paper ⁶⁾.

We administered thermochemo-radiotherapy once weekly until pleural effusion almost vanished. We did not give any further adjuvant treatment until disease progression.

Hyperthermia

Hyperthermia was given using RF-capacitive heating apparatus (Thermotron RF-8). Hyperthermia was given once per week for about 60 minutes (median 3.5 times). The electrodes were placed in front and back of the patient. The used electrodes ranged from 25cm to 30cm in diameter. Overlay bolus was used to reduce the edge effect. Thermometry was performed by inserting thermocouples directly into the tumor for 2 patients, into chest wall for 4 patients, effusion itself for 1 patient or put on the patient's skin for 1 patient.

Chemotherapy

Chemotherapy was administered into thoracic space through the Trocker tube. Chemotherapeutic agents administered were Cisplatinum (CDDP) for 4 patients, Carboplatinum (CBDCA) for 3 patients, both CDDP and CBDCA for 1 patient. The dose of CDDP was 50 mg / body, and the dose of CBDCA was 450 mg / body.

Radiotherapy

Radiotherapy was administered with 10MV photon beams generated by a linear accelerator. In principle, MPMs are disseminated to the entire pleural cavity, so the field should cover the entire hemithorax. Because lung tissue is radiosensitive, radiotherapy was administered once weekly on the very day of hyperthermia and just before thermochemotherapy. The total radiation dose ranged from 2 to 10Gy and the fraction size was 1 or 2 Gy (median 7Gy/3.5fr).

Data analysis

We analyzed this data in June 2003. The response of treatment was assessed by CT. The criteria of response was based on those of Vogelzang and the colleagues⁷⁾. A complete response (CR) was defined as complete absence of disease. A partial response (PR) was defined as $\geq 50\%$ reduction from baseline of the sum of the products of perpendicular diameters of bidimensionally measurable disease or $\geq 30\%$ decrease in the sum of the greatest diameters of unidimensionally measurable lesions. A progressive disease (PD) was defined as $\geq 50\%$ increase from baseline of the sum of the products of perpendicular diameters of bidimensionally measurable disease or $\geq 25\%$ increase in the sum of the greatest diameters of unidimensionally measurable lesions. A stable disease (SD) was disease that did not qualify for CR, PR, nor PD. Analysis of overall survival was calculated using the Kaplan- Meier method.

Results

The results are shown in table 3. Three cases could reach PR, another 3 was SD, and 2 was PD. Survival period ranged from 4.1 to 68.0 months, and the median survival time was 14.1 months (Fig1). Survival time is closely related to the response. All 3 PR cases survived more than 2 years whereas no patient whose response was SD or PD survived 2 years.

After this treatment, we could decrease the amount of their pleural effusion in 6 of 8 patients and their performance status was improved, and all cases could discharge from the hospital.

As for complications, we experienced grade 4 thrombocytopenia in 1 case. We needed blood transfusion to the patient. No severe cardiac nor pulmonary toxicity has been observed.

Of all 8 patients, 7 patients died of respiratory disorder caused by intrathoracic recurrence and intractable pleural effusion. There were no patients who recurred either at biopsied site or at the site of Trocker tube was put. Three patients survived more than 2 years.

Table III treatment results

No.	RT (Gy/fr)	HT	chemo	Tmax	response	Survival period (months)
1	2/1	2	Cb	44.2 t	PR	68.0 / D
2	8/4	4	C	43.2 w	PR	27.4 / D
3	10/5	5	Cb	42.3 w	PR	27.1 / D
4	6/3	3	C	43.7 w	SD	14.1 / A
5	10/5	5	C/Cb	40.1 s	SD	7.6 / D
6	6/3	3	C	43.0 w	SD	6.5 / D
7	3/3	3	Cb	42.8 i	PD	6.5 / D
8	10/5	5	C	41.2 t	PD	4.1 / D
median	7.0/3.5	3.5				14.1

RT : radiotherapy, HT : hyperthermia, chemo : chemotherapeutic agents,
Tmax : maximum temperature, t : tumor, w : chest wall, s : skin, i : intrathoracic
C : CDDP, Cb : CBDCA
D : dead, A : alive

Fig. 1. Overall survival of all eight patients

Discussion

The annual incidence and mortality rate of MPM were around 1 per 100,000 populations in the United States⁸⁾. In Japan, they were certainly less than those of USA. Because of the rarity of the disease and its dismal prognosis, the standard treatment has not fully been established. But the incidence has been increasing gradually in recent years. Therefore, it is necessary to improve the treatment results.

As for the treatment of MPM, only possibly curative treatment is considered to be panpleuropneumonectomy¹⁻⁵⁾, the MSTs of which are around 1 year, whereas radiation therapy^{9) 10)} or chemotherapy¹¹⁾ is used only palliatively with dismal treatment results with the MST of around only several months. Recently, combined modality treatment approach has improved the treatment results¹²⁾. However, aggressive treatment will have high risk of morbidity and mortality, thus it is not entirely safe to say it is the standard treatment^{12) 13)}.

In recent years, chemotherapy might be administered intrathoracically instead of intravenously to increase the drug concentration¹⁴⁾. Furthermore, hyperthermia might be added to promote the depth dose of the chemotherapeutic agents¹⁵⁾. We reported a case of extremely good response⁶⁾, which suggested the thermal enhancement of chemotherapeutic agent (CBDCA) because of the bulk of the tumor and the response would not have been acquired with chemotherapy alone. van Ruth *et al.* reported the enhancing effect of hyperthermia¹⁶⁾. Hyperthermia might be combined with chemotherapy for this kind of disease with otherwise dismal prognosis.

Regarding intrathoracic thermochemotherapy combined with surgery there have been other reports¹⁷⁻¹⁹⁾. In their cases there were a few hospital deaths but their median survival time and 5-year survival rate calculated from their data were 17 months and 7%, respectively, which were quite similar to our survival curve. The meaning of surgical debulking needs to be tested because we treated relatively old patients.

Hyperthermia has been expected to have another usefulness of enhancing the inflammatory reactions caused by chemotherapeutic reaction, which results in the adhesion of pleural space. In fact, pleural effusion stopped in the majority of our cases and all cases could discharge from the hospital.

Although our median survival time was 14.1 months, 3 cases (37.5%) survived more than 2 years, 1 case (12.5%) survived more than 5 years, no patients died within 1 month and all patients could discharge from the hospital. Therefore, our treatment approach might well be an alternative approach for aggressive surgery though the number of patients is small.

Moreover, we will not give any further adjuvant treatment until disease progression. Therefore our approach is quite cost-effective and might be recommended for the future.

Concerning radiation therapy, we have been giving radiotherapy expecting that it will enhance the effect of chemotherapy and hyperthermia. Because of the radiosensitivity of the normal lung tissue, we restrict the radiation dose under 10 Gy in one course of the treatment. We need to test the efficacy of such low dose of radiation in a prospective trial.

For the future, we will have to analyze the prognostic factors and further optimize the treatment.

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当科における悪性胸膜中皮腫に対する 温熱化学放射線療法の治療成績

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要 旨：悪性胸膜中皮腫は非常に予後不良の疾患とされ、Butchart 分類の II 期以上での手術成績は 1 年以下と報告されている。我々は手術療法の代わりに、プラチナ系抗癌剤胸腔内投与を併用した温熱放射線療法を施行している。我々は悪性胸膜中皮腫 8 例 (UICC-TNM 分類 I 期 3 例, III 期 5 例) を経験し、うち 3 例に生存期間 2 年以上という良好な結果を得た (生存期間の中央値 14.1 ヶ月)。この治療方法は患者にとって耐容し得るものでありかつ胸水を制御でき、良好な QOL を維持できるものと思われる。侵襲的な治療法は治療関連死や合併症を起こす危険をはらむため、臓器温存的なこの 3 者併用療法は、その代替療法となる可能性がある。