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Comprehensive treatment of malignant mesothelioma patients after the failure of systemic chemotherapy ☆

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ABSTRACT

Malignant mesothelioma (MM) is an aggressive neoplasm usually arising from the mesothelial surfaces of the pleural or peritoneal cavity. Currently, no standard therapy is available. The most commonly used therapy is cytoreductive surgery combined with systematic chemotherapy, but the median overall survival (OS) is less than 12 months; moreover, treatments are lacking for patients in whom chemotherapy has failed and/or who cannot withstand surgery. We investigated multiple minimally invasive therapies (cryosurgery, photodynamic therapy and intracavity chemotherapy) for the treatment of MM patients in whom systemic chemotherapy had failed. Twenty-seven patients were divided into comprehensive (combination of the three therapies) and palliative (intracavity chemotherapy only) treatment groups. The OS of patients who received comprehensive treatment was significantly longer than that of those who received palliative treatment (median OS: 64 vs. 9 months, $P < 0.001$). This interesting result was not associated with treatment timing, but was closely associated with repeated treatments.

Introduction

Malignant mesothelioma (MM) is an uncommon tumor arising from the mesothelial cells lining the pleura, peritoneum, pericardium or tunica vaginalis testis [16,21]. The incidence of the disease has been rising worldwide since 1970, due to widespread exposure to asbestos during past decades [21]. The most common types of MM are pleural (MPM) and diffuse peritoneal (DMPM); both are traditionally regarded as rapidly lethal malignancies with limited and ineffective therapeutic options. As the disease progresses, the nodules become confluent to form plaques or masses, or uniformly cover the pleural or peritoneal surfaces [2,28]. Most patients (80%) are diagnosed in the late stage (IIIb/IV) and are not candidates for surgical cure. Systemic therapy (pemetrexed and cisplatin) has been the treatment option for these patients, but poor performance status and the low chemo- and radiosensitivity of this tumor result in a poor prognosis (median overall survival (OS) is only 12 months) [5,9,13,14,28]. Increasingly, researchers believe that a multidisciplinary approach is needed to improve the management of MM [28]. Interestingly, the results of comprehensive treatment (cytoreductive surgery (CRS) combined with intracavity chemotherapy) compare favorably with those of conventional chemotherapy. Median survival was 31–34 months in early trials [10,15,17] and up to 92–100 months in recent series [4,6], though it is unclear whether such dissimilarities in survival depend on differences among the series in terms of their inclusion criteria, the aggressiveness of surgical and comprehensive treatment, or the severity of the disease.

Minimally invasive therapy involves less surgical trauma and has fewer side effects. Treatments including argon–helium cryosurgery, microwaves, radiofrequency, endoscopy, photodynamic therapy, interventional embolism and intracavity chemotherapy are especially suitable for patients who are unable or refuse to undergo surgery. In this study, intracavity chemotherapy, cryosurgery and photodynamic therapy were integrated for the treatment of MM patients after failure of systemic chemotherapy. OS was the main evaluation index. The influence of treatment timing and repeated treatment on OS was also assessed.

Material and methods

Ethics

The study protocol received ethical approval from the Regional Ethics Committee of Guangzhou Fuda Cancer Hospital. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

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Patient selection

This was a retrospective study of patients treated for MPM or DMPM in our cancer hospital from September, 2003 to January, 2012. Twenty-seven patients had tumors that were considered unresectable after comprehensive evaluation before hospitalization. These were multidisciplinary decisions made by a radiologist, a gastrointestinal (or cardiothoracic) surgeon and an oncologist in our hospital. Diagnoses were principally based on computed tomography (CT) and thoracoscope (or laparoscope; EXERAII; Olympus, Japan)-guided needle biopsy to obtain a definitive histologic diagnosis. An 18-gauge Tru-cut (Baxter, Deerfield, IL, USA) biopsy needle was used percutaneously to obtain one or two cores of tissue from the solid tumor. Patients received their final treatments in our hospital and almost 10 years of follow-up data were reviewed.

Patients were deemed unsuitable for surgery and systemic chemotherapy for the following reasons: (1) multifocal disease; (2) unresectable primary tumor; (3) patient refused surgery and chemotherapy, or sought further treatment after chemotherapy; (4) severe complications (e.g. hypertension, hydrothorax, ascites); or (5) advanced age. The inclusion criteria were as follows: (1) Karnofsky performance status (KPS) score $\geqslant 70$; (2) platelet count $\geqslant 80 \times 10^9$/L, white blood cell count $\geqslant 3 \times 10^9$/L, neutrophil granulocyte count $\geqslant 2 \times 10^9$/L, hemoglobin $\geqslant 90$ g/L; (3) prothrombin time international normalized ratio $\geqslant 1.5$; (4) largest primary or metastatic tumor diameter <6 cm as measured on preoperative CT; (5) without level 3 hypertension, severe coronary disease, myelosuppression, brain metastases, respiratory system disease, and acute or chronic infection; and (6) basic normal liver function and puncture release hydrothorax or ascites <1 L. Patients with primary or metastatic tumors of diameter $\geqslant 6$ cm were treated by other methods [1,25] and were not enrolled in this study. For the selection of treatment methods, the personal wishes of the patient were fully respected.

Cryosurgical and photodynamic therapies

According to the patients' own wishes, 15 patients (five with MPM and 10 with DMPM) were given comprehensive treatment and 12 (four with MPM and eight with DMPM) received intracavity chemotherapy only (palliative treatment group).

In the comprehensive treatment group, cryosurgery was performed under double row helical CT (Somatom Emotion Duo; Siemens, Germany); photodynamic therapy was performed with the aid of thoracoscopy and laparoscopy. Before treatment, all patients underwent general anesthesia. All ablation surgical procedures were performed by H.B.L. and assistants (B.L. and F.M.); intracavity chemotherapy was administrated by B.L.

Based on the location of the MM, cryoprobes were inserted percutaneously via the intercostal or abdominal muscle. For tumors >3 cm in longest diameter, more than two 1.7 mm cryoprobes (CRYO-42; Endocare, Irvine, CA, USA) were used. Under CT or color ultrasound (ALOKA SSD-5500SA; Aloka, Japan) guidance, a two-cycle freeze/thaw procedure was used with an argon gas-based cryosurgical unit (Endocare, USA) [23,24]. During the procedure, the operator tried to ensure that the edge of the ice ball extended about 1 cm beyond the edge of the tumor. Porfimer sodium (Photofrin, 2 mg/kg; Canadian Pharmaceutical Industries Ltd) was added to dextrose solution and administrated intravenously. After 48–72 h, cylindrical fibers were protruding through the intercostal or abdominal muscles, and the tumor area was irradiated with a photodynamic dose of 200–250 J/cm^2. During this procedure, the operator tried to ensure that the 7-mm fiberoptic semiconductor laser treatment instrument (PDT-630; Ceralas D, BioLitec, Germany) was in the center of the endoscope tube, and that the area of irradiation extended more than 1 cm from the tumor's edge. After 72 h, we cleared the necrotic tissue under endoscopy and irradiated the tumor again; the photodynamic dose and exposure time depended on the endoscopy findings; the dose generally ranged from one-half of to the same as the first dose. The patients strictly avoided exposure to light for l week after treatment.

In the comprehensive treatment group, an argon–helium cryosurgical system was used for the ablation of tumor masses and photodynamic therapy was applied for the ablation of tumor plaques. If necessary, the two therapies were performed simultaneously. If the diameter of the tumor mass or plaque was $\geqslant 2$ cm, two or more cryoprobes or fibreoptical instruments were used for complete ablation. Metastases to other areas (e.g. liver, thoracic wall) were ablated intraoperatively.

Intracavity chemotherapy

In both groups, hyperthermal perfusion chemotherapy was administered four times, once every 3 days. For each administration, 60–200 mg cisplatin was dissolved in normal saline (2000–3000 ml, kept 42–43 °C) and perfused into the thoracic or abdominal cavity for about 1 h. The dose given was positively correlated with the number of pleural or peritoneal tumors.

Evaluation and statistical analysis

Complications were recorded and classified in accordance with the Common Terminology Criteria of Adverse Events v4.0. Local tumor control and OS were also evaluated. Radiographic local tumor control was assessed using image-guided tumor ablation criteria [8]. Thoracic or abdominal ultrasonography was performed both 1 day and 1 week after the minimally invasive treatment. Follow-up dynamic CT was performed at 1 month and then at 3–4 month intervals. The revised Response Evaluation Criteria in Solid Tumors v1.1 were used to assess the response of the thoracic and abdominal tumors [3]. Three diagnostic radiologists (X.P., Q.Z. and J.T.) with 17, 20 and 13 years of clinical experience, respectively, reviewed CT scans for every case to determine whether progression or recurrence had occurred. Diagnoses were made independently, though the radiologists discussed cases over which they disagreed. OS was calculated from the date on which patients were first diagnosed with MM and compared using the Kaplan–Meier test with log-rank analysis. Significant differences were indicated by $P < 0.05$, $P < 0.01$ and $P < 0.001$. All analyses were conducted using GraphPad software (San Diego, CA, USA).

Results

Clinical data

Comprehensive treatment was administered to 18 patients (38–79 years of age, median age: 59 years; 13 males, five females). Twelve patients had MPM and six had DMPM. Ten patients were from China and eight from other countries. All patients had initially been treated with systemic chemotherapy in our hospital (five patients) or another center (13 patients), and came to our hospital 1–46 months later for further treatment. Liver metastases (eight lesions) were found in five patients, lung metastases (16 lesions) in 10 patients and other metastases (11 lesions) in three patients. Chest/abdominal pain (14 patients) and hydrothorax/ascites (12 patients) were common complaints.

Palliative treatment was given to nine patients (47–77 years of age, median age: 63 years; eight males, one female). Six patients had MPM and three had DMPM. Four patients were from China and five from other countries. All patients were initially treated

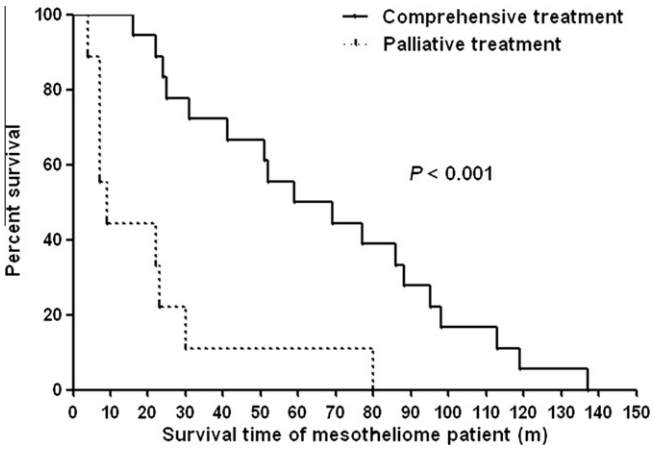

Fig. 1. Overall survival (OS) after comprehensive or palliative treatment. All 27 patients had late stage malignant mesothelioma (MM) and died before July, 2012. There were 18 patients in the comprehensive treatment group and nine in the palliative treatment group. OS rates were measured from the date of diagnosis of MM in our hospital or another center.

with systemic chemotherapy in our hospital (two patients) or another center (seven patients), and came to our hospital 1–30 months later for further treatment. Liver metastases (three lesions) were found in two patients, lung metastases (nine lesions) in five patients and other metastases (six lesions) in two patients. These patients had complaints similar to those of the comprehensive treatment group.

Perioperative outcomes

All percutaneous ablations of primary and metastatic MM with ultrasound or CT monitoring were performed successfully. There were no severe complications (e.g. renal toxicity, neurotoxicity, bone marrow suppression), but some common adverse effects were observed postoperatively in the comprehensive treatment group. Pneumothorax occurred in four patients (33%) on the first day after ablation, seven patients (39%) suffered slight wound hemorrhage in the chest or abdominal wall, and seven patients (39%) had chest pain; all returned to normal within 8–13 days without any treatment. Abdominal distension and abdominal pain occurred after seven sessions in three patients (17%) on the first day post-cryoablation, but this disappeared within the following 5 days. Eight patients (44%) complained of a poor appetite after the procedure and were found to have hydrothorax or ascites on ultrasonography; this improved over the following 3–5 days without any treatment. No adverse effects have yet been found in the palliative treatment group. There were no treatment-related deaths or conversions to systemic chemotherapy. Within 1 week after the first comprehensive treatment, 14 patients (78%) experienced $\geqslant$50% reduction in pain score and 12 (67%) experienced $\geqslant$20 increase in KPS score. Within 1 week after the first palliative treatment, six patients (67%) experienced $\geqslant$50% reduction in pain score and five (56%) experienced $\geqslant$20 increase in KPS score.

Influence of treatment type, timing and repeats on OS

Up to the date of the last follow-up for each patient, the median OS for all patients was 41 months (25% percentile: 22 months; 75% percentile: 86 months). The median OS of the patients who received comprehensive treatment was 64 months; that with palliative treatment was 9 months. The OS of the comprehensive treatment group was significantly longer than that of the palliative treatment group according to the log-rank test ($P < 0.001$; Fig. 1).

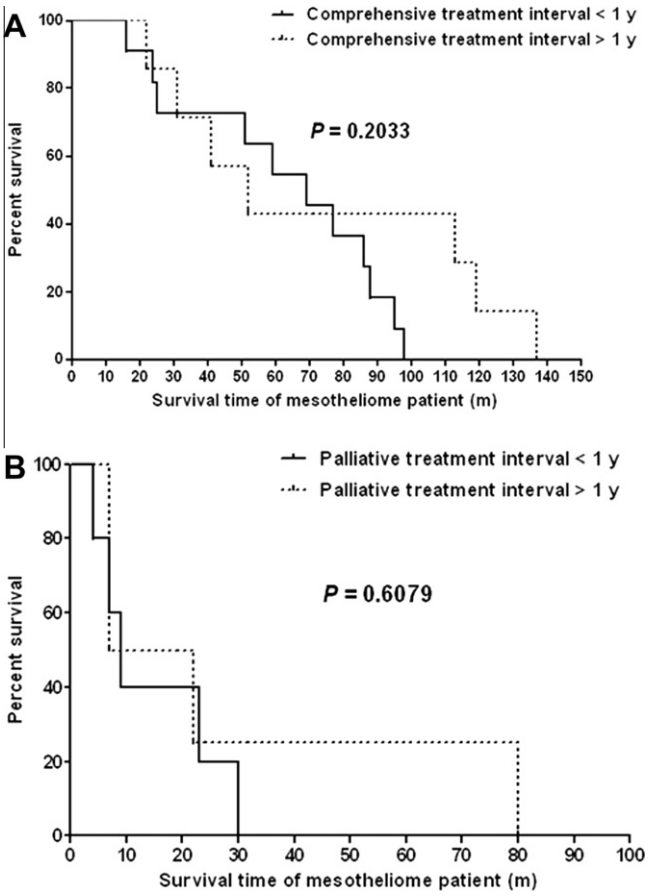

Fig. 2. Overall survival with treatment interval of less or more than 1 year. (A) Comparison between patients in the comprehensive treatment group; 11 patients received treatment <1 year and seven >1 year after systemic chemotherapy. (B) Comparison between patients in the palliative treatment group; five patients received treatment <1 year and four >1 year after systemic chemotherapy.

In the comprehensive group, 11 patients received treatment <1 year after systemic chemotherapy and seven after >1 year; in the palliative group, five patients received treatment <1 year after systemic chemotherapy and four after >1 year. An influence of treatment timing on OS was detected. In the comprehensive group, the median OS of patients who received timely treatment was 69 months; that with delayed treatment was 52 months ($P = 0.2033$; Fig. 2A). In the palliative group, the median OS after timely treatment was 9 months; that after delayed treatment was 14.5 months ($P = 0.6079$; Fig. 2B). Thus, there was no obvious correlation between OS and treatment interval in either group.

Based on the progression of the disease, tumor recurrence and individual patients' wishes, 16 patients (59%) received repeated treatment on reexamination. In the comprehensive treatment group, the median OS of patients who underwent multiple treatments was 81.5 months; that of patients who underwent a single treatment was 38 months ($P = 0.0403$; Fig. 3A). In the palliative treatment group, the median OS of patients who underwent multiple treatments was 26.5 months; that of patients who underwent a single treatment was 7 months ($P = 0.037$; Fig. 3B). In both groups, therefore, the OS of patients who received multiple treatments was longer than that of those who received a single treatment.

Discussion

In the past, treatment of DMPM often followed the recommendations for MPM. In a meta-analysis assessing all trials of systemic

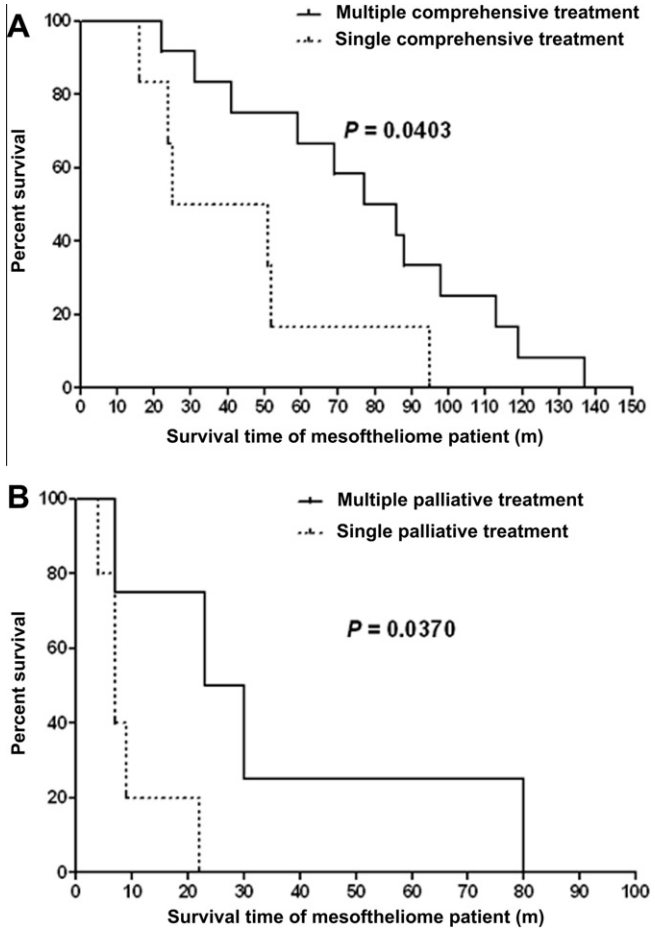

Fig. 3. Overall survival with repeated treatment. (A) Comparison between patients in the comprehensive treatment group; 12 received multiple comprehensive treatments (seven patients twice, four patients three times and one patient four times) and six underwent a single comprehensive treatment. (B) Comparison between patients in the palliative treatment group; four patients underwent multiple palliative treatments (four patients three times) and five underwent a single palliative treatment.

chemotherapy for MM from 1995 to 2002, cisplatin was found to be the most active single agent and cisplatin + doxorubicin the most active combination [7]. There has been much clinical research on combination chemotherapy for unresectable MPM, including cisplatin + pemetrexed, cisplatin + raltitrexed, pemetrexed + gemcitabine, cisplatin + gemcitabine and cisplatin + vinorelbine, with OS rates of 10–16.8 months [9]. Targeted agents such as gefitinib, erlotinib, sorafenib and sunitinib have also been used in many clinical trials, with OS rates of 5.9–15.6 months [9]. For patients with DMPM, several highly specialized centers reported improved survival by means of an innovative local–regional approach in 2003 [20]. This treatment strategy combined aggressive CRS with perioperative intraperitoneal chemotherapy (PIC) to eradicate microscopic residual disease, and extended the median OS to 67 months following the initial treatment. Similar reports were published in 2007 (a review of 240 DMPM patients from six tertiary institutions treated with CRS + PIC; median OS after initial treatment was 34–92 months [27]) and in 2009 (a registry study of 401 DMPM patients from eight international centers; median OS after initial treatment was 53 months [26]). The longest reported median OS of DMPM patients to date is that published by Elias et al. in 2007; in their study, the prognosis was improved to 92–100 months [4]. Compared with traditional debulking surgery, CRS is a new concept involving peritonectomy procedures and multivisceral resections to remove all visible tumor and create an optimal environment for PIC [19]. Local–regional drug administration results in higher intraperitoneal concentrations and minimal systemic toxicity [18]. The intraoperative period allows optimal distribution of drug throughout the abdominal cavity before the development of postoperative adhesions [12], and mild hyperthermia has both intrinsic and synergistic effects with platinum compounds [22]. CRS + PIC thus represents a rational basis for comprehensive treatment.

Although no staging system is currently available to support the choice of treatment and prognostic assessment in DMPM, there is substantial agreement among different research groups that incomplete CRS is correlated with poor prognosis, presumably due to limited penetration into residual tumor [11]. Our hospital specializes in comprehensive cancer treatment, using cryoablation as the main technology. Most MM patients who come to our hospital are from overseas and have poor health status or refuse to undergo thoracic or abdominal surgery. Since 2003, we have used comprehensive CRS + PIC therapy for patients with MPM and DMPM in whom systemic chemotherapy has failed, with techniques including cryosurgery, photodynamic therapy and intracavity chemotherapy. In the present study, patients who received palliative treatment (intracavity chemotherapy) only were designated as the control group, to compare differences in prognosis.

Nine years of follow-up demonstrated the advantages of comprehensive treatment (Fig. 1), which can extend the median OS of MM patients to 64 months. The median OS of MM patients who received palliative treatment was only 9 months. The results of comprehensive treatment were similar to our former results with initial CRS + PIC, but the results in the palliative treatment group were even worse than those of systemic chemotherapy only. Although the combined application of minimally invasive techniques can reduce surgical trauma and promote the recovery of physical fitness, we believe that, in some patients, the optimal time for treatment might have been missed, thereby reducing the overall therapeutic effect. To investigate this, we considered the time interval between systemic chemotherapy and subsequent treatment. However, even when the interval was as long as 1 year, we could find no meaningful evidence of any effect of timing on therapeutic efficacy (Fig. 2). That is, if had received systemic chemotherapy, the patients may probably lose better treatment opportunities.

Patients treated in our hospital are scheduled to return for examination and further treatment on a regular basis. As the study progressed, we found that the OS of patients who received repeated treatments differed significantly from that of those who never returned. The median OS of patients who received two or more comprehensive treatments may be as long as 81.5 months, whereas that of patients who received a single comprehensive treatment was only 38 months. In the palliative treatment group, the respective findings were 26.5 and 7 months (Fig. 3). These results may indicate that: (1) initial systemic chemotherapy followed by repeated minimally invasive treatments has an effect similar to that of initial CRS + PIC – that is, when considering the advantages of minimally invasive therapies, the need for reexamination and retreatment for new metastases must be taken into account; (2) even a single comprehensive treatment can double the OS of MM patients after failure of chemotherapy; (3) repeated palliative treatments are still important after systemic chemotherapy and can also double the OS; and (4) a single palliative treatment has no benefit in terms of median OS.

At present, some newly diagnosed MM patients in our hospital have begun to abandon systemic chemotherapy and progress directly to comprehensive treatment with minimally invasive techniques. Given the small number of treatments delivered thus far and the newness of this project, there are currently insufficient data for analysis. However, according to the evidence available at

present for the clinical treatment of MM, initial treatment with CRS + PIC therapy still achieves the longest OS.

This study investigated therapy for late stage MM patients in whom systemic chemotherapy had failed and who had poor health status, using multiple and single comprehensive and palliative treatments. Further experimental data are needed to assess the therapeutic effects of CRS + PIC in the treatment of newly diagnosed patients.

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