Hyperthermic intracavitary chemotherapy in abdomen and chest
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CHAPTER FOUR

Cytoreductive surgery combined with intra-operative hyperthermic intrathoracic chemotherapy for stage I malignant pleural mesothelioma


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Intrathoracic chemotherapy for stage I malignant pleural mesothelioma

Introduction

Malignant pleural mesothelioma (MPM) has a poor prognosis with a median survival of less than one year. It is a disease usually confined to the thoracic cavity for a long time before metastasizing. Surgical resection has been considered to play an important role in the treatment of MPM. However, it is almost impossible to achieve a microscopically complete resection with surgery alone because the property of MPM to infiltrate the adjacent structures. Surgical resection alone is associated with a high recurrence rate and therefore cytoreductive surgery combined with adjuvant therapies have gained more attention in recent years. One of these therapies is intracavitary chemotherapy. It has the advantage of a high local dose with limited systemic toxicity. Hyperthermia improves the efficacy and penetration depth of chemotherapy. Recently we reported the feasibility and toxicity of cytoreductive surgery combined with Hyperthermic IntraTHOracic Chemotherapy (HITHOC). In this present study we report 20 procedures with this multimodality treatment performed in patients with limited malignant pleural mesothelioma, with a median follow-up of 14 months.

Patient and methods

Preoperative inclusion criteria

Patients with a good general condition (WHO 0-1 Performance Status) were asked to participate in this phase I/II study. A pulmonary function, measured by spirometry and a nuclear ventilation-perfusion scan, should allow for a thoracotomy and a pneumonectomy. An adequate cardiac function was necessary, defined by normal cardiac ultrasonography and a normal nuclear ejection fraction. Normal renal and liver functions were mandatory. The maximum age for inclusion was 70 years. Each patient signed a written informed consent. Disease related inclusion criteria were as follows. Proven histology of malignant pleural mesothelioma and confirmation by the Dutch Mesothelioma Panel was needed. Only stage I (TNM of IMIG classification) patients were included. CT scan of the thorax measured the volume of solid tumor (T status). All patients had a negative mediastinoscopy. CT of the thorax and upper abdomen was performed to exclude metastases and to visualize the entire diaphragm.

Surgical cytoreduction

A double lumen endotracheal tube was used. A posterolateral thoracotomy through the sixth intercostal space was performed. An extrapleural dissection between the chest wall, diaphragm and mediastinum on one side and the parietal pleura on the other side was continued until the hilar structures were free. The thickened pleural sheets were removed from the underlying healthy tissue, either visceral pleura or pulmonary parenchyma. After this decortication the viability of the lung was assessed. A pneumonectomy was performed when there
was no sufficient viability of the lung after decortication or when the lung was too much involved with tumor (decortication not possible). Extensive surgical cytoreduction was carried out with the aim to reduce residual tumor to below 2.5 mm, the thought maximum penetration depth of the used cytostatic drugs. The debulking was considered incomplete when ≥2.5 mm residual tumor was left behind.

**Score of tumor extent**

Before cytoreduction the tumor extent was scored by assessing the presence of tumor in upper visceral pleura, lower visceral pleura, upper parietal pleura, sinus/diaphragm, pericardium/mediastinum and pleural fluid. The tumor extent was again scored after the cytoreduction. We recorded opening of the pericardium and/or diaphragm and when a pneumonectomy was performed.

**Intra-operative hyperthermic intrathoracic chemotherapy**

After complete cytoreduction the perfusion system was set up (see Figure page 37). A Tenckoff inflow catheter and 3 silicone outflow catheters were placed in the thoracic cavity, usually one in the pleural cavity top, one in the posterior diaphragm sinus and one in the anterior diaphragm sinus. A temperature sensor was attached to each catheter. The thoracotomy wound was watertight closed with sutures for the period of perfusion. The catheters were connected with a fluid filter, roller pump and heat exchanger. Thereafter the closed system was filled with an isotonic dialysis fluid (Dianeal® PD1, Baxter, Uden, The Netherlands). When the temperature of 40-41°C was reached in all regions, cisplatin and doxorubicin were added to the perfusion fluid. A fixed dose cisplatin of 80mg/m² and doxorubicin starting at 20mg/m² with increments of 5mg/m² per dose step were used. A different dose method was applied for the last six patients. Cisplatin was given with a fixed dose of 40mg per liter perfusion liquid. Doxorubicin was given in three patients with a dose of 18mg per liter perfusion liquid; three other patients were given 21mg doxorubicin per liter perfusion liquid. The core temperature, measured in the pharynx was registered. If the core temperature exceeded 39°C, the temperature of the perfusion fluid was lowered to 40°C in order to maintain core temperature below 39.5°C. The duration of perfusion was 90 minutes with a flow of 1 l/min. During the perfusion the contralateral lung was ventilated separately. The ipsilateral lung was inflated at a pressure of 15 cm water with oxygen, keeping the lung semi-inflated, allowing sufficient space between parietal and visceral pleura for adequate perfusion, but limiting the possible toxicity of cytostatic drugs to the lung parenchyma. At the completion the perfusion fluid was removed, leaving drains in the pleural top and sinus. Thereafter the chest wall was closed in the regular way.

**Adjuvant radiotherapy**

Patients received external radiotherapy to the thoracotomy scar and the drainage tracts to reduce the risk on recurrence in thoracotomy wound and drainage tracts after postoperative
Intrathoracic chemotherapy for stage I malignant pleural mesothelioma

recovery and complete wound healing. Starting 6 weeks, but not later than 3 months, after the HITHOC-procedure, three times 8 Gy was administered with an interval between the fractions of 7 days.

Follow-up and recurrences

Peri-operative mortality was defined as death within 30 days after operation. Morbidity consisted of in-hospital and out-hospital complications. Chest computed tomograms were performed every three months after operation for two years and every six months thereafter. Recurrence of disease was documented by Fine Needle Aspiration or histological biopsy if possible.

Statistical analysis

Survival was determined from date of operation to date of death or date of last follow-up. Overall survival was calculated according to the Kaplan-Meier method. Statistical analysis was performed with Statistical Package for the Social Sciences software (SPSS, Chicago, Illinois, USA). Difference in survival between the pleurectomy/decortication group and the pleuropneumonectomy group was tested using the log-rank test. A p-value less than 0.05 was considered significant. The area under the curve (AUC) was calculated using the linear trapezoid rule without extrapolation to infinity (AUC$_{0-\infty}$); both samples from perfusate and blood were taken for measurements (perfusate 1-30-90 min.; blood 1-10-15-45-60-75-90 min.).

Results

Twenty procedures were performed. There were 19 males and 1 female. The median age was 57 years (range 38-67). The side of localization was ten times right and ten times left. The pathology was epithelial type (n=16) and mixed (epithelial and mesenchymal) type (n=4). Asbestos exposure was reported in 18 patients (90%). Dyspnoea and pleural fluid were present in 10 patients (50%). Cough was the first symptom in five patients. Other presenting symptoms were thoracic pain (n=4) and wheezing respiration (n=1).

Surgical procedure and intra-operative hyperthermic intrathoracic chemotherapy

Before cytoreduction, tumor presence was scored; upper visceral pleura: 17 patients (85%), lower visceral pleura: 17 patients (85%), upper parietal pleura: 18 patients (90%), sinus/diaphragm: 20 patients (100%) and pericardium/mediastinum: 19 patients (95%). Pleural fluid was found in 16 patients (80%). After cytoreduction, tumor presence was again scored: upper visceral pleura: 5 patients (25%), lower visceral pleura: 5 patients (25%), upper parietal pleura: 1 patient (5%), sinus/diaphragm: 2 patients (10%) and pericardium/mediastinum: 2 patients (10%). Fifteen patients (75%) were optimally debulked (estimated residual tumor
<2.5 mm). An example of optimal debulking is shown in Figure 1. In five patients resection was incomplete; residual tumor was mostly confined to the visceral pleura and the sinus/diaphragm.

The median duration of the operation was seven hours (range 5-8.5). A pneumonectomy was necessary in eight patients (40%). The diaphragm was opened in 13 patients (65%). The pericardium was opened in 15 patients (75%).

The median amount of perfusion liquid was 4.8 liter (range 3-7). One perfusion was aborted after 80 minutes because of hemodynamic instability. The highest core temperature before perfusion varied between 35.3 and 38.9°C. During perfusion the highest core temperature varied between 36.8 and 39.4°C, a mean rise of 0.9°C. In three procedures the temperature of the perfusion fluid had to be lowered to 40°C.

The median blood loss was 1758 ml (range 400-4615). The median number of given packed cells was 2 units (range 0-4).

The median hospital stay was 17 days (range 11-77). The median intensive care unit stay was 4 days (range 1-7). There was no mortality. Significant morbidity was noticed in 13 patients (65%). Complications are listed in Table 1. The number of complications in the pleurectomy/decortication group was comparable to the number of complications in the pleuropneumonectomy group. Complications in the pleuropneumonectomy group included pulmonary emboli (n=2) and bronchopleural fistula (n=3), indicating that the impact of a complication in the pleuropneumonectomy group seems larger than in the pleurectomy/decortication group. Well-known chemotherapy related complications as leucopenia or hair loss were not observed. A transient elevation of serum creatinine was noticed in one patient. The maximum

Figure 1. An example of optimal cytoreduction. Left upper: before cytoreduction. Left bottom: tumor particles on the pleura. Right: after cytoreduction with visible diaphragm, heart and lung.
Table 1. Complications.

<table>
<thead>
<tr>
<th>Complication type</th>
<th>No. of pat.</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaphragm rupture</td>
<td>2</td>
<td>Reconstruct diaphragm with mesh</td>
</tr>
<tr>
<td>Chylous effusion</td>
<td>1</td>
<td>Twice re-operation, median chain triglycerides diet, prolonged hospital stay (77 days)</td>
</tr>
<tr>
<td>Bronchopleural fistula</td>
<td>4</td>
<td>One re-operation with pectoral muscle flap</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>1</td>
<td>Re-operation</td>
</tr>
<tr>
<td>Persistent parenchymal air leakage</td>
<td>2</td>
<td>Secondary pneumonectomy</td>
</tr>
<tr>
<td>Cellulitis wound</td>
<td>1</td>
<td>Antibiotics and hospital admission</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>2</td>
<td>Anti coagulation treatment</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>1</td>
<td>Ultrasound-guided drainage</td>
</tr>
<tr>
<td>Persistent pneumothorax</td>
<td>2</td>
<td>Prolonged thoracic tube drainage</td>
</tr>
<tr>
<td>Late hemorrhage</td>
<td>1</td>
<td>Blood transfusion (4 units packed cells)</td>
</tr>
</tbody>
</table>

dose of doxorubicin reached was 35mg/m². After that, the dosage method was changed to a dose method based on amount of liter perfusion liquid, as reported in the methods. The mean AUC perfusate/plasma ratios for cisplatin and doxorubicin were respectively 59 and 181, however these ratios may represent overestimates because no extrapolation to infinity was applied.

**Adjuvant radiotherapy**

Radiotherapy (3x8Gy) was given to 19 patients (95%). Radiotherapy has been delayed in one patient, due to impaired wound healing (Clagett procedure). In general the radiotherapy was well tolerated. A slight redness of the skin was usually seen in the radiation field.

**Survival and recurrences**

The median follow up was 14 months (range 5-29) months with a median survival of 11 months (range 3-19). The 1-year overall survival was 42% (Figure 2). The disease state at last follow-up is listed in Table 2. Fourteen patients developed recurrent disease after a median period of 8 months (range 2-14). Abdominal recurrences were found in four patients. In three of these patients the diaphragm was opened during surgery (75%).

In 10 out of 16 patients without abdominal recurrence, the diaphragm was also opened. Opening of the pericardium did not influence the localization of the recurrence.

The calculated median time to progression (mTTP) was 8 months (range 2-14). Eleven patients died of disease after a median period of 9 months (range 3-16). Three patients are alive with signs of disease after respectively 10, 18 and 19 months. One patient died without evi-
Figure 2. Kaplan-Meier overall survival curve of 20 treated patients treated with cytoreductive surgery combined with HITHOC procedure. The numbers below in the figure are patients at risk.

dence of disease four months after HITHOC procedure. This patient had a fatal hemorrhage at home, probably due to an acute bleeding from the pulmonary vessels, one month after a Clagett procedure for empyema. Five patients are alive without signs of recurrent disease after a median of 7 months (range 4-8). No difference in survival was observed between the pleurectomy/decortication group and the pleuropneumonectomy group (log-rank test; p=0.67).

Discussion

The technique of cytoreductive surgery combined with hyperthermic intra-thoracic chemotherapy for malignant pleural mesothelioma was described earlier by Ratto et al\textsuperscript{12}, Yellin et al\textsuperscript{13} and Carry et al\textsuperscript{14}. Only direct cytotoxic agents appear rational. Ratto et al\textsuperscript{12} demonstrated that hyperthermic intrathoracic perfusion with cisplatin had pharmacokinetic advantages with limited systemic toxicity. They reported on ten patients with malignant pleural mesothelioma. A pleurectomy/decortication was performed in three patients followed by normothermic perfusion. Three other patients had a pleurectomy/decortication with hyperthermic perfusion and four a pleuropneumonectomy with hyperthermic perfusion. All perfusions were performed with cisplatin alone. Systemic drug concentrations were higher after pleurectomy/decortication than after pleuropneumonectomy. The local tissue/perfusate ratio of platinum concentrations tended to be higher after hyperthermic perfusion rather than with normothermic perfusion. Major postoperative complications included one wound infection, one diaphragmatic prosthesis displacement (needing a re-operation) and 4 patients developed a transient postoperative elevation of serum creatinine. No survival data were described\textsuperscript{12}. Yellin et al\textsuperscript{13} treated 7 patients with MPM. A combination of surgery
and intra-operative hyperthermic pleural perfusion with cisplatin during 60 minutes was used. The technique was feasible, easy to perform and relatively safe. Three patients had a complication; one late empyema, one gastric herniation and one late empyema with bronchopleural fistula. A median survival of 15 months was reported. Two patients survived more than 30 months. Carry et al treated three patients with stage I MPM with pleurectomy followed by hyperthermic intrathoracic perfusion with mitomycin C. The only reported complication was pleural clotting necessitating surgery. One patient died of hepatic metastasis, four months after therapy. Another patient died after eleven months because of pleural and systemic recurrent disease. One patient is alive with disease after 22 months.

In our present study we report the results of 20 patients with stage I MPM undergoing surgery combined with intra-operative hyperthermic intrathoracic chemotherapy. Cisplatin and doxorubicin, both direct cytotoxic agents, were applied because malignant pleural mesothelioma is relatively sensitive to these agents. A favorable pharmacokinetic ratio was found for both cisplatin and doxorubicin. A pneumonectomy was only performed when the lung was too much involved or damaged, since survival after pleurectomy seems equal to survival after pleuropneumonectomy, however performing a pneumonectomy includes a higher morbidity and mortality. A pneumonectomy was deemed necessary in 40%, indicating the difficulty to
stage correctly pre-operatively. In comparison of the three above-mentioned studies we find a high complication rate of 65%. However, other large studies with multimodality treatment for malignant pleural mesothelioma also report high complication rates of around 50%. All complications in our study, except one bronchopleural fistula, could be managed with success. No chemotherapy related complications were observed. A transient slight elevation of serum creatinine was noticed only in one patient. Unfortunately, the survival figures are disappointing. So far we find a median survival of 11 months, indicating the failure of this treatment modality to significantly improve survival over the natural course of MPM. Most recurrences were in the same hemithorax despite extensive local treatment. Opening the diaphragm did not seem to influence the development of abdominal recurrence in our study. When we compare our results with the multimodality treatment of Sugarbaker et al we show worse survival. Sugarbaker et al reported a median survival of 21 months and a 2-year survival of 42% in 136 lymph node negative patients. In that study the treatment consisted of extrapleural pneumonectomy, followed by postoperative systemic chemotherapy and hemithorax radiation therapy. A study of Rusch et al with a median survival of 17 months also included hemithorax radiation. As to the reasons of failure two explanations are possible. Either mesothelioma cells are truly insensitive to doxorubicin and cisplatin, or our way of application fails to reach all tumor cells or both. A preliminary study in our center indicates a penetration depth of doxorubicin of only a few cell layers [unpublished data]. The penetration depth of cisplatin is only a few millimeters. It seems therefore likely that we just did not reach all tumor residue. Possibly further dose increases could improve results. The addition of systemic chemotherapy or hemithorax radiation can also be considered. Based on our disappointing results we conclude that even with extensive surgery, better cytotoxic agents are required to achieve long-term survival. Due to the high morbidity rate, HITHOC cannot be recommended as palliation in MPM.

References


