Intraoperative intracavitary hyperthermic chemotherapy for malignant pleural mesothelioma

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Abstract: Malignant pleural mesothelioma (MPM) is a dreadful disease with a poor prognosis. Multimodality therapy including surgical macroscopic complete resection is performed to treat operable MPM. Intraoperative intracavitary hyperthermic chemotherapy for MPM was reviewed. Appropriate papers published between 2006 and present were extracted by the PubMed advanced search by MPM (Title/Abstract), chemotherapy (Title/Abstract), and hyperthermia (All fields). Among the selected papers, those written in English, and treated more than ten MPM patients were reviewed. The intraoperative intracavitary hyperthermic chemotherapy has been performed following extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D) for MPM. Cisplatin was mainly used for perfusion, and the morbidity and mortality was acceptable. In conclusion, the intraoperative intracavitary hyperthermic chemotherapy following EPP or P/D for MPM might enhance local control in the chest cavity.

Keywords: Chemotherapy; hyperthermia; mesothelioma; surgery

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According to the International Mesothelioma Interest Group clinical guidelines (1), surgical macroscopic complete resection and control of micrometastatic disease play a vital role in the multimodality therapy of malignant pleural mesothelioma (MPM). Wald and Sugarbaker (2) emphasize the significance of achieving complete surgical macroscopic resection as part of a multimodality therapeutic protocol for MPM, because it remains the sole option to significantly extend the survival. The intraoperative intracavitary hyperthermic chemotherapy has been performed as one of the modalities following extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D). In this paper the intraoperative intracavitary hyperthermic chemotherapy was reviewed. Twenty-eight papers published in recent 10 years between 2006 and present were extracted by the PubMed advanced search by MPM (Title/Abstract), chemotherapy (Title/Abstract), and hyperthermia (All fields). Among the selected papers, those written in English, and treated more than ten MPM patients were mainly reviewed. Many of the appropriate papers were published from Brigham and Women's Hospital, Boston, MA, USA.

Mujoomdar and Sugarbaker (3) reviewed several phase I and II intracavitary chemotherapy studies performed in patients with MPM. A figure of the intraoperative intracavitary hyperthermic chemotherapy perfusion apparatus was shown in the paper. Intracavitary chemotherapy can deliver higher doses of drug locally with less toxicity than corresponding systemic therapy. When combined with hyperthermia, there is also an increase in local drug absorption and cytotoxic effect. To prevent the incidence of chemotherapy-induced renal toxicity, several maneuvers are performed. Patients are admitted on the night before the procedure and receive intravenous hydration overnight. Pharmacologic cytoprotection with amifostine and sodium thiosulfate is given perioperatively. Amifostine is taken up preferentially by nonmalignant cells and binds to cisplatin intracellularly. Sodium thiosulfate binds covalently to cisplatin, thereby forming an inactive complex in the plasma.

In 2006, Richards *et al*. (4) reported the feasibility of intraoperative intracavitary hyperthermic cisplatin lavage after P/D in MPM for the first time. The primary objective of this study was to prospectively determine

the maximum-tolerated dose (MTD) of intraoperative, intracavitary, hyperthermic cisplatin after P/D and to evaluate the feasibility, safety, morbidity, and mortality of this therapy. They described the procedure in detail. After tumor resection, a 1-hour intracavitary lavage using a cardiopulmonary bypass was completed with a solution of cisplatin in dialysate maintained at 42 ℃. An Omni retractor (Omni-Tract, Minneapolis, MN, USA) and plastic adhesive drape were used to create a seal around the thoracotomy incision. The inflow and outflow catheters were placed through the open thoracotomy incision in the caudal and cephalad positions. From August 1999 to April 2002, forty-four patients underwent P/D followed by a 1-hour lavage of the resection cavity (ipsilateral hemithorax) with dose-escalated cisplatin (50, 100, 150, 175, 200, 225, and 250 mg/m^2) at 42 ℃. Immediately after the lavage, intravenous sodium thiosulfate was administered for renal protection as a 4 g/m^2 bolus in 250 mL of sterile water over 10 minutes followed by 12 g/m^2 over 6 hours. Epithelioid type was in 24 patients (55%) of 44 patients. Dose-limiting renal toxicity occurred at 250 mg/m^2, establishing the MTD at 225 mg/m^2. Perioperative mortality was 11% (5 of 44 patients). The estimated median time to recurrence among all resected patients was 7.2 months. Eight (89%) of nine patients who received low-dose cisplatin lavage experienced disease recurrence compared with 25 (71%) of 35 patients who received high-dose lavage. Patients treated with high-dose cisplatin had a median recurrence-free interval of 9 months compared with 4 months for low-dose lavage. The median survival time was 13 months. Survival estimates differed significantly for resectable patients exposed to low dose (50 to 150 mg/m^2, n=9, median, 6 months) versus high doses (175 to 250 mg/m^2, n=35, median, 18 months) of hyperthermic cisplatin (P=0.0019). Results of multivariate analysis indicated that low cisplatin dose and nonepithelial histology were independently predictive of poor survival. The significant incidence of deep venous thrombosis in this study is consistent with the demonstrated influence of hyperthermia on the processes of platelet activation, fibrin formation, and fibrinolysis.

In 2009, Zellos *et al*. (5) reported a study which was undertaken to determine MTD and toxicity of intraoperative intracavitary hyperthermic cisplatin perfusion with amifostine after EPP for MPM. Between August 2001 and July 2002, 29 EPP patients underwent a 1-hour hyperthermic cisplatin perfusion (42 ℃) of ipsilateral hemithorax and abdomen with amifostine. Epithelioid type was in 24 patients (83%). Grade 3+ renal toxicity developed in 9 patients (31%). The MTD for intraoperative locoregional cisplatin in the setting of EPP, however, has not been fully explored. The mortality was 7% (2 of 29 patients). The median time to first recurrence was 16 months and the median survival was 20 months. The median survivals were 26 months for patients receiving higher cisplatin doses and 16 months for those receiving lower doses. They reported that many of the patients had extended survival relative to a historical control group.

In 2009, Tilleman *et al*. (6) published a paper describing EPP followed by intraoperative intracavitary hyperthermic cisplatin perfusion. The progression pattern of MPM is characterized by a tendency to recur locally. The local nature of disease recurrence has emphasized the need for improved locoregional control. Over a 2-year and 6-month period from January 2004 to June 2006, 92 MPM patients underwent EPP and received intraoperative intracavitary hyperthermic cisplatin perfusion, consisting of a 1-hour lavage of the chest and abdomen with cisplatin (42 ℃) at 225 mg/m^2. Pharmacologic cytoprotection consisted of intravenous sodium thiosulfate with or without amifostine. Epithelioid type was in 53 patients (58%). Forty-five of 92 patients had post-operative complications (48.9% morbidity). The most common complication was atrial arrhythmia (22 patients, 24%). Grade 3 or 4 renal toxicity occurred in 9 patients (9.8%). The use of amifostine in addition to sodium thiosulfate might reduce cisplatin-associated renal toxicity. Four of the 92 patients died within 30 days of the operation or during the postoperative hospitalization period (mortality 4.3%, POD 24, 43, 53, and 160). The most common sites of recurrence were the contralateral hemithorax (61.7% of all recurrences), abdomen (51.1% of all recurrences), and ipsilateral hemithorax (34.0% of all recurrences). With a median follow-up of 31.2 months (range, 16.7–45.8 months) median survival of the 92 patients was 13.1 months. They concluded that intraoperative intracavitary hyperthermic cisplatin perfusion following EPP could be performed with acceptable morbidity and mortality, and might enhance local control in the chest. This prospective phase II study established the safety and feasibility of administering intraoperative intracavitary hyperthermic cisplatin perfusion after EPP.

Rusch made comments in this paper that the median survivals were very similar to those observed in trials of other simpler treatment strategies, such as resection and radiation, and appeared less favorable than the median survivals in recently reported trials. And also, recurrence

in the ipsilateral thorax and peritoneum with this approach remained quite frequent.

In 2013, Sugarbaker *et al*. (7) published a paper which described the extended interval to recurrence and survival among low-risk patients with MPM who underwent cytoreductive surgery followed by intraoperative intracavitary hyperthermic cisplatin chemotherapy. The tendency for eventual relapse to occur locally in most cases has prompted them and others to investigate the use of additional modalities to improve local control. The low-risk patients had epithelial histologic findings on biopsy and were characterized as having a low risk of early recurrence and death (i.e., tumor volume ≤500 cm^3, and were either men with a hemoglobin level of ≥13 g/dL or were women. Cytoreductive surgeries (74 EPP and 29 P/D) were performed for 103 low-risk patients from 2001 to 2009. Cisplatin was the most active single agent against mesothelioma. Seventy-two patients received intraoperative intracavitary hyperthermic cisplatin 175 to 225 mg/m^2 chemotherapy for a 1-hour lavage at 42 ℃ with sodium thiosulfate rescue and/or amifostine protection, and 31 patients did not. Nephroprotection with fluid administration and the timing of amifostine and sodium thiosulfate enabled them to minimize the renal toxicity of hyperthermic intraoperative cisplatin chemotherapy. The median interval to recurrence for the low-risk cohort (103 patients) was 23.6 months after surgery, and the median overall survival was 33.1 months. The intraoperative intracavitary hyperthermic cisplatin chemotherapy group (72 patients) exhibited a significantly longer interval to recurrence (27.1 *vs*. 12.8 months) and overall survival (35.3 *vs*. 22.8 months) than the comparison group (31 patients). Among the low-risk patients, treatment with intraoperative intracavitary hyperthermic cisplatin chemotherapy appeared to be particularly beneficial for patients with stage N1-N2 nodal involvement and for those who did not undergo adjuvant therapy. They recommended incorporation of intraoperative intracavitary hyperthermic cisplatin chemotherapy into multimodality treatment strategies for patients with low-risk epithelial MPM. A phase I trial at their institution of cisplatin-gemcitabine intraoperative intracavitary hyperthermic chemotherapy after macroscopic complete resection completed accrual, and assessments of other combination regimens, including cisplatin-pemetrexed, were planned.

In 2015, Lang-Lazdunski *et al*. (8) reported P/D for MPM with hyperthermic pleural lavage with povidone-iodine. Opitz *et al*. (9) have shown that povidone-iodine has a direct cytotoxic effect on mesothelioma cells and induces necrosis of mesothelioma cells *in vitro*. One hundred and two patients with MPM had P/D between January 2004 and December 2013. Epithelioid type was 73 patients (72%). They performed a hyperthermic pleural lavage (40–41 ℃) using sterile water mixed with 10% povidone-iodine. They used a povidone-iodine concentration of 1% and an exposure time of minimum 15 minutes. Median overall survival was 32 months, and 5-year survival rate was 23.1%.

In conclusions, the intraoperative intracavitary hyperthermic chemotherapy following EPP or P/D for MPM might enhance local control in the chest cavity. Further investigations of this modality using other drugs, for example cisplatin and pemetrexed are warranted.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Rusch V, Baldini EH, Bueno R, et al. The role of surgical cytoreduction in the treatment of malignant pleural mesothelioma: meeting summary of the International Mesothelioma Interest Group Congress, September 11-14, 2012, Boston, Mass. J Thorac Cardiovasc Surg 2013;145:909-10.
2. Wald O, Sugarbaker DJ. Perspective on malignant pleural mesothelioma diagnosis and treatment. Ann Transl Med 2016;4:120.
3. Mujoomdar AA, Sugarbaker DJ. Hyperthermic chemoperfusion for the treatment of malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg 2008;20:298-304.
4. Richards WG, Zellos L, Bueno R, et al. Phase I to II study of pleurectomy/decortication and intraoperative intracavitary hyperthermic cisplatin lavage for mesothelioma. J Clin Oncol 2006;24:1561-7.
5. Zellos L, Richards WG, Capalbo L, et al. A phase I study of extrapleural pneumonectomy and intracavitary intraoperative hyperthermic cisplatin with amifostine cytoprotection for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2009;137:453-8.

6. Tilleman TR, Richards WG, Zellos L, et al. Extrapleural pneumonectomy followed by intracavitary intraoperative hyperthermic cisplatin with pharmacologic cytoprotection for treatment of malignant pleural mesothelioma: a phase II prospective study. J Thorac Cardiovasc Surg 2009;138:405-11.
7. Sugarbaker DJ, Gill RR, Yeap BY, et al. Hyperthermic intraoperative pleural cisplatin chemotherapy extends interval to recurrence and survival among low-risk patients with malignant pleural mesothelioma undergoing surgical macroscopic complete resection. J Thorac Cardiovasc Surg 2013;145:955-63.
8. Lang-Lazdunski L, Bille A, Papa S, et al. Pleurectomy/decortication, hyperthermic pleural lavage with povidone-iodine, prophylactic radiotherapy, and systemic chemotherapy in patients with malignant pleural mesothelioma: a 10-year experience. J Thorac Cardiovasc Surg 2015;149:558-65; discussion 565-6.
9. Opitz I, Sigrist B, Hillinger S, et al. Taurolidine and povidone-iodine induce different types of cell death in malignant pleural mesothelioma. Lung Cancer 2007;56:327-36.

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