Review Article

Intraoperative adjuncts for malignant pleural mesothelioma

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Abstract: Malignant pleural mesothelioma (MPM) is a rapidly fatal disease. Multimodality surgically based therapies may extend survival in select patients, however, local relapse after resection is common. Novel intraoperative adjunctive therapies including heated intraoperative chemotherapy (HIOC), heated intraoperative povidone-iodine (PVP-I), and photodynamic therapy (PDT) target micrometastatic disease and aim to improve local control. This review details the most recent studies and trials of HIOC, heated intraoperative PVP-I, and PDT, this aims to provide an update on some of the most promising intraoperative adjuncts for patients with MPM.

Keywords: Malignant pleural mesothelioma (MPM); heated intraoperative chemotherapy (HIOC); heated intraoperative povidone-iodine (PVP-I); photodynamic therapy (PDT)

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Introduction

Malignant pleural mesothelioma (MPM) is a rare, aggressive, and rapidly fatal tumor of the pleural mesothelium commonly associated with asbestos exposure. The current standard of care, palliative chemotherapy with cisplatin and pemetrexed, typically leads to a median survival of only 12 months (1). In comparison, multimodality approaches involving surgical resection by either extrapleural pneumonectomy (EPP) or pleurectomy and decortication (PD) with chemotherapy and/or radiotherapy have been associated with longer overall survival (OS) and recurrence-free survival for selected patients. The objective of surgery in MPM is complete macroscopic resection (2). Owing to the diffusely invasive nature of this disease, R0 resection is not technically possible and local relapse will occur in the majority of cases, which has prompted investigations into intraoperative treatment adjuncts to curb micrometastatic disease and improve local control. Below we describe the most recent studies and trials of three increasingly important intraoperative modalities for MPM: heated intraoperative chemotherapy (HIOC), heated intraoperative povidone-iodine (PVP-I), and photodynamic therapy (PDT).

HIOC

Intracavitary chemotherapy (IC) offers several advantages for local control following EPP or PD, including improved drug delivery to residual tumor cells and lower toxicity as compared to systemic chemotherapy. The safety and feasibility of IC were confirmed through phase I trials of ovarian carcinoma patients in the 1980s, engendering interest in IC as a treatment adjunct for intraperitoneal malignancies (3,4). Pharmacokinetics studies of intrapleural cisplatin and mitomycin following PD in the 1990s then showed consistently similar advantages in MPM, demonstrating that IC is a safe and effective form of treatment for MPM (5,6).

Hyperthermia improves the efficacy of IC by increasing absorption into and action of chemotherapeutic agents inside tumor cells. The mechanism by which this occurs is thought to involve protein denaturation which leads to

increased membrane permeability, altered cell metabolism, and apoptosis (7). Ratto and colleagues performed one of the first studies investigating the feasibility, safety, and pharmacokinetics of hyperthermic IC using cisplatin (100 mg/m^2) (8). Comparisons of three multimodality approaches—PD with normothermic IC, PD with HIOC, and EPP with HIOC—in ten patients with epithelial or mixed, stage I or II, MPM revealed a higher local tissue/perfusate ratio of platinum concentrations after hyperthermic perfusion than in normothermic perfusion, suggesting a pharmacokinetic advantage imparted by hyperthermia. The safety and feasibility of this approach, as demonstrated through this study, established the benefits of further exploring HIOC as a therapeutic adjunct for MPM (8).

Phase I trial of EPP with HIOC and sodium thiosulfate (9)

In the phase I trial performed at Brigham and Women's Hospital, fifty patients undergoing EPP, HIOC, and intravenous sodium thiosulfate received increasing doses of intracavitary cisplatin to determine the maximum tolerated dose (MTD). This was the first dose escalation trial of hyperthermic intracavitary cisplatin performed for MPM. The MTD was determined to be 250 mg/m^2, higher than any other reported series of intrapleural cisplatin for MPM. The median length of hospital stay for this cohort was 9 days (range: 6–93 days), median age was 59 years, staging according to the Brigham staging system determined 6% of patients with stage I disease, 32% with stage II, and 62% with stage III.

Compared to a non-protocol group of 41 patients who underwent EPP without HIOC (median age 60 years, 0% stage I, 42% stage II, 56% stage III), the EPP with HIOC cohort achieved an equal mortality rate of 2%, demonstrating that mortality rate did not increase upon addition of HIOC to EPP. The HIOC patients, however, showed a statistically significant increase in deep venous thrombosis and diaphragmatic patch failure compared to those undergoing EPP alone. Measures such as hydration immediately following chemotherapy lavage, prophylactic subcutaneous heparin, and a Gore-Tex diaphragmatic patch twice as large as before were used to address these morbidities.

This study established the MTD of intracavitary cisplatin following EPP and showed that high-dose cisplatin can be delivered safely to patients with similar mortality and morbidity rates compared to patients receiving EPP alone, except for an increased incidence of deep venous thrombosis and diaphragmatic patch failure.

Phase I/II trial of P/D with HIOC (10)

This prospective study of 44 patients aimed to determine the MTD of hyperthermic intracavitary cisplatin following PD as well as to evaluate feasibility and safety of this treatment approach. Patients in the study cohort underwent PD (achieving MCR) and HIOC with cisplatin followed by intravenous sodium thiosulfate. The MTD was determined to be 225 mg/m^2, and five perioperative deaths occurred (11%), three of which were attributable to pulmonary complications leading to acute respiratory distress syndrome. Median hospital stay length was 11 days (range: 6–71 days) and median age was 71 years. The patient cohort consisted of 24 (55%) with epithelial, 17 (39%) with mixed, and 3 (7%) with sarcomatoid histology. Patients were either Brigham stage I or stage II.

The 44 patients undergoing HIOC after PD achieved a longer median survival time than the 17 patients who were deemed unable to achieve MCR and therefore did not undergo resection (13 *vs.* 9 months). Patients with epithelial histology had better survival than those with sarcomatoid/mixed histology (median survival time 19 *vs.* 8 months). Additionally, higher doses of cisplatin (175–250 mg/m^2) were associated with longer median survival compared to lower cisplatin doses (50–150 mg/m^2) (18 *vs.* 6 months). Recurrence occurred in 75% of resected patients, and the recurrence-free interval was found to be significantly related to cisplatin dose, with a longer recurrence-free interval associated with a higher dose ($P<0.0001$).

Administration of sodium thiosulfate allowed for the escalation of cisplatin dosage to twice that formerly used after resection, making it the first study to demonstrate the advantages of higher cisplatin doses in HIOC following PD. However, significant morbidity and mortality were found to be associated with this procedure, highlighting the need for better patient selection. Closer monitoring of patients and lower thresholds for anticoagulation therapy were used to address the high incidence of deep venous thrombosis, while measures such as preoperative hydration, a second infusion of sodium thiosulfate, aggressive intraoperative diuresis, and urine alkalinization aimed to decrease renal toxicity.

An interesting finding from this study included that while a nonepithelial histology was predictive of poor survival, a subset of patients with mixed histology may respond to

high dose cisplatin lavage—five patients, all treated with 225–250 mg/m^2 cisplatin, survived beyond 18 months, while almost all other mixed histology patients did not survive past 9 months. This study established the MTD, feasibility, and parameters for administration of cisplatin in HIOC following PD. It also showed that intracavitary cisplatin at or near the MTD is associated with better survival compared to lower cisplatin doses.

Phase I trial of EPP with HIOC and Amifostine (11)

While sodium thiosulfate has proven to be an excellent cytoprotective agent, past studies have shown that by directly inhibiting cisplatin, it potentially compromises the full therapeutic potential of intracavitary cisplatin (9). Therefore, the aim of this study was to determine the MTD of HIOC cisplatin after EPP with the cytoprotective agent Amifostine instead of sodium thiosulfate. Amifostine has a 100-fold preferential uptake in normal cells and thereby selectively protects normal tissue while maximizing cisplatin activity on tumor cells.

Twenty-nine patients from August 2001 to July 2002 underwent EPP, HIOC, and single dose Amifostine (910 mg/m^2) administration. The median age was 57 years and the median length of hospital stay was 15 days. Five patients presented with Brigham stage I disease, 13 with stage II, and 11 with stage III. Twenty-four patients had epithelial MPM and five patients had nonepithelial disease.

The protocol was discontinued before the MTD could be determined due to grade 3+ renal toxicity in nine patients (31%), subsequently revised doses, and no observable relationship between cisplatin dose and renal toxicity. Two postoperative deaths occurred (7%), while the most common morbidities among these patients included atrial fibrillation (66%), deep venous thrombosis (31%), pulmonary emboli (10%), and acute respiratory distress syndrome (ARDS) (10%). Patients with epithelial tumors survived longer than those with nonepithelial MPM (median survival 29 *vs.* 13 months), and higher cisplatin doses (175–200 mg/m^2) predicted longer survival than lower cisplatin doses (75–150 mg/m^2) (median survival 26 *vs.* 16 months). N2 disease was indicative of a poorer prognosis (median survival 14 *vs.* 31 months in patients without N2 disease), and stage I and II disease among epithelial subtypes predicted longer survival than did epithelial stage III (median survival 39 *vs.* 15 months). The median time to first recurrence among patients with epithelial histology was 24 months whereas that for nonepithelial histology was 5 months.

While the single dose of Amifostine at 910 mg/m^2 did not provide adequate cytoprotection for the kidneys, no adverse effect on the efficacy of HIOC cisplatin was observed and median survival time in this cohort was found to be longer than in historic controls (12). Cardiac, pulmonary, and thrombotic morbidity rates were similar to those in previously published reports, as was the mortality rate of 7%. This study encouraged further exploration into the optimal cytoprotective strategy for HIOC cisplatin, perhaps with multiple doses of Amifostine or a combination of Amifostine and sodium thiosulfate.

Phase II trial of EPP with HIOC and both Amifostine and sodium thiosulfate (13)

From January 2004 to June 2006, a phase II prospective trial was conducted in which 92 patients underwent EPP with HIOC cisplatin at the MTD of 225 mg/m^2 and intravenous sodium thiosulfate to determine feasibility, morbidity, and mortality. Twenty-seven patients also received 910 mg/m^2 Amifostine prior to hyperthermic cisplatin lavage. Median age was 60 (range: 27–78), median hospital stay length was 12 days, and MPM histological presentation was as follows: 53 epithelial (58%) and 42 sarcomatoid/mixed (42%). The majority of patients were Brigham phase III (63%) while phase I and II comprised the other 37%.

Postoperative mortality was 4.3% (4/92), and major morbidities included atrial fibrillation (24%), grade 3+ renal toxicity (10%), thrombosis (13%), and ARDS (6.5%), all at the expected rates. Renal toxicity occurred in seven of 65 patients treated with sodium thiosulfate alone and only one of the 27 patients treated with both sodium thiosulfate and Amifostine, suggesting the addition of Amifostine may have strengthened cytoprotection in the kidneys. No patients died of renal toxicity.

Median survival time of the cohort was 13.1 months, a promising finding in light of the fact that most patients were phase III (63%) and nearly half (42%) presented with nonepithelial histology. 51.1% of patients experienced recurrence of MPM, with the most common sites being the contralateral hemithorax (61.7%), abdomen (51.1%), and ipsilateral hemithorax (34.0%).

This phase II prospective trial demonstrated the safety and feasibility of using HIOC at the MTD of 225 mg/m^2 after EPP for MPM but also encouraged exploration of combination regimens of intracavitary cisplatin with other chemotherapeutic agents like pemetrexed or gemcitabine following EPP or PD. Further investigation

into cytoprotective agents to control cisplatin-induced renal toxicity was also suggested.

Phase I trial of EPP or P/D with HIOC cisplatin and gemcitabine

A phase I clinical trial investigating the MTD, toxicity, and efficacy of intrathoracic gemcitabine administered in conjunction with intraoperative heated cisplatin has recently been completed. A total of 141 patients from 2007 to 2011 (median age 68, 18% females) were enrolled, with 59 undergoing EPP (53% epithelial histology, median radiographic tumor volume 236 cc) and 41 receiving PD (71% epithelial, volume 79 cc). Gemcitabine dose escalation followed a 3+3 design from 100 mg/m^2 in 100 mg increments, while cisplatin (175–225 mg/m^2) with intravenous Amifostine and sodium thiosulfate were used.

Two peri-operative deaths (2%) occurred, and the observed morbidity rates in the EPP and PD groups were 54% and 42%, respectively. The MTD was successfully established at 175 mg/m^2 cisplatin/1,000 mg/m^2 gemcitabine with systemic cytoprotection, and median OS for epithelial patients were 26 and 59 months for the EPP and PD groups, respectively, compared to 11 and 21 months for those with nonepithelial tumors.

This latest trial demonstrated that cisplatin/gemcitabine HIOC can be safely administered following an MCR by EPP or PD, and an MTD for the combination regimen was determined. Cisplatin/gemcitabine HIOC likely extends survival for epithelial patients, with mortality and morbidity rates comparable to those reported for surgical resection without HIOC. Given these latest findings, cisplatin combined with other chemotherapeutic agents is an encouraging HIOC strategy, warranting further studies and providing potential new avenues for enhancing the efficacy of HIOC for MPM therapy.

Retrospective study of low-risk patients (14)

The purpose of this study was to more accurately evaluate the effect of HIOC on recurrence interval and OS by minimizing confounding sources of variance present in prior studies. A previously validated risk assessment algorithm was used to identify patients with a low preoperative risk of early recurrence and death and from this subset a treatment group of 72 patients who underwent MCR followed by HIOC cisplatin was compared with 31 control patients who achieved MCR but did not receive HIOC cisplatin. All variables with a potential influence on recurrence and survival, including gender, age, surgical procedure, administration of adjuvant chemotherapy or radiotherapy, pathologic subtype, lymph node status, and staging, were distributed proportionally among the two groups.

Median hospital stay length and perioperative mortality rate did not differ between the two groups suggesting the addition of HIOC cisplatin to resection does not increase time in the hospital or interfere with the risks inherent in resection. Patients in the HIOC group showed significantly better survival and recurrence time than those in the control group (median survival 35.3 *vs.* 22.8 months; median recurrence interval 27.1 *vs.* 12.8 months). The HIOC group also demonstrated significantly longer survival and recurrence time than the control group both among patients who received chemotherapy but no radiotherapy (median survival 51.1 *vs.* 20.6 months; median recurrence interval 26.3 *vs.* 10 months) and among patients with N1/N2 disease (median survival 33.1 *vs.* 17.4 months; median recurrence interval 23.5 *vs.* 11.1 months). At the same time, no significant difference in survival and time to recurrence was observed between the HIOC and control groups among patients who received both chemotherapy and radiotherapy and among those with N0 disease, suggesting that HIOC cisplatin may be particularly beneficial for patients who will not receive adjuvant radiotherapy and for those with N1/N2 disease. These findings also posit the idea that intracavitary cisplatin may have an advantage over radiotherapy in delivering high dose therapy to radiosensitive structures in the hemithorax, as is particularly warranted in patients with mediastinal or hilar lymph node involvement.

Lastly, the study showed that due to the past decade-long experience with HIOC cisplatin, currently implemented management protocols to minimize renal toxicity and morbidities like deep venous thrombosis have enabled the safe application of HIOC to cytoreductive surgeries with no observable increases in morbidity or mortality compared to surgery alone. Additionally, given the demonstrated efficacy of intracavitary cisplatin, investigations into intracavitary combination regimens with cisplatin are now recommended.

Updated patterns of failure (15)

Patterns of failure observed with multimodality therapy consisting of EPP, adjuvant chemotherapy (cyclophosphamide, doxorubicin, and cisplatin), and 2-dimensional radiotherapy were described in a 1997 study Baldini and colleagues (16). Since then, multimodality therapy has evolved to include

HIOC, pemetrexed-based chemotherapy, and more sophisticated radiotherapy. This retrospective study examined 169 patients from 2001 to 2010 undergoing this revised multimodality approach to identify changes in recurrence patterns and future directions for investigation.

A total of 132 patients in the study underwent EPP with HIOC followed by evaluation for adjuvant chemotherapy and radiotherapy. HIOC involved cisplatin (175–225 mg/m^2) with or without gemcitabine followed by sodium thiosulfate rescue with or without amifostine. Systemic chemotherapy agents included cisplatin, pemetrexed or both. Adjuvant radiotherapy included either a matched electron-photon technique (EPT) or intensity-modulated radiotherapy (IMRT).

Seventy-five percent of patients in the study developed recurrence, with the relative distribution of recurrence sites almost identical to that from the 1997 study: 72% *vs.* 67% in the ipsilateral hemithorax, 53% *vs.* 50% abdomen, 38% *vs.* 33% in the contralateral hemithorax, and 7% *vs.* 8% in distant sties (16). The ipsilateral hemithorax remained the most common site of recurrence independent of stage, likely due to regrowth of microscopic tumor from the resection site. Mediastinal, abdominal, and distant recurrence was observed more frequently with higher stage, while recurrence in the contralateral hemithorax was found to be independent of stage, indicative of the lymphatic and hematogenous spread seen in later stage disease and new primary tumor growth, respectively.

In summary, this study found that patterns of failure have not changed significantly from those observed in 1997. The finding that the major site of recurrence remains local demonstrates the continuing need to develop strategies to contain local disease. As a result, intraoperative adjuncts like HIOC, specifically in combination with other modalities, continue to hold promise for longer lasting treatment of MPM.

Heated intraoperative PVP-I

PVP-I consists of elementary iodine bound to the carrier molecule poly-(1-vinyl-2-pyrrolidone). Before its use as an adjunct for mesothelioma, PVP-I was used as an antiseptic during intra-thoracic and intra-abdominal lavage with very few side effects (17,18). *In vitro* studies of PVP-I in MPM cell lines demonstrated that PVP-I causes cell necrosis through the production of reactive oxygen intermediates, inducing an inflammatory reaction that may lead to an anti-tumor response (19). A few years later, Fiorelli and colleagues showed that a 10-minute incubation of epithelial and biphasic MPM cells with PVP-I at 0.1% concentration leads to >99% cell death, and a PVP-I concentration of 1% for 10 minutes achieves the same level of suppression in sarcomatoid MPM cells (20). PVP-I's low side-effect profile combined with its rapid inhibition of cell growth make it a promising candidate for local control of MPM (19).

The major contributions to the literature concerning the use of heated intraoperative PVP-I for MPM are provided by a single institution (21). Lang-Lazdunski and colleagues aimed to develop an alternative multimodality strategy for patients who do not qualify for EPP, including those with N2 disease or sarcomatoid histology. Subsequently, 102 patients from 2004 to 2013 underwent PD and hyperthermic pleural lavage with PVP-I followed by prophylactic radiotherapy. Hyperthermic pleural lavage with PVP-I was achieved using sterile water mixed with 10% PVP-I at 40–41 degrees Celsius for a total duration of 15 minutes, and all surgeries were performed by a single surgeon. Several analyses of this cohort are reported.

The first, occurring in 2011, consisted of 36 patients from 2004 to 2010 who completed the full treatment course of PD, heated intraoperative PVP-I, and prophylactic radiotherapy (22). Twenty-four patients presented with epithelial MPM (66.7%), 10 with biphasic (27.8%), and 2 with sarcomatoid (3.9%), and IMIG stage distribution was as follows: 5 with stage I disease (13.9%), 8 with stage II (22.2%), 18 with stage III (50%), and 5 with stage IV (13.9%). Thirty-one patients had N0 or N1 disease (86.1%) while five patients had N2 disease (13.9%). There were zero perioperative deaths, few postoperative complications, and overall median survival was 24 months, suggesting that PD with heated intraoperative PVP-I and prophylactic radiotherapy is a relatively well-tolerated multimodality therapy with low mortality and morbidity.

The next study in 2012 compared this approach with the classical multimodality regimen consisting of neoadjuvant chemotherapy, EPP, and adjuvant radiotherapy (23). Fifty-four patients from 2004 to 2011 underwent PD, heated intraoperative PVP-I, and prophylactic radiotherapy; 17 patients during the same period received neoadjuvant chemotherapy, EPP, and adjuvant radiotherapy. Patient characteristics including age, sex, histology, nodal status, and TNM stage were distributed proportionally between the two groups to allow for meaningful comparison. Patients undergoing PD followed by heated intraoperative PVP-I and prophylactic radiotherapy were found to have significantly longer survival, lower mortality, and lower

morbidity than those who received the EPP regimen (median survival time 23 *vs.* 12.8 months; mortality rate 0% *vs.* 4.5%; morbidity rate 28% *vs.* 68%), with recurrence patterns similar to those described by other studies (24,25). This report proposed that PD with heated intraoperative PVP-I and prophylactic radiotherapy is a good alternative to multimodality therapy involving EPP.

The most recent analysis of this cohort; examining 102 patients from 2004 to 2013 undergoing PD, heated intraoperative PVP-I, and prophylactic radiotherapy; showed similar findings to the earlier study, further supporting the safety and feasibility of this multimodality approach (21). Seventy-three patients had epithelial histology (71.5%), 25 had biphasic (24.5%), and 4 had sarcomatoid (3.9%). IMIG stage classifications were as follows: 7 with stage I disease (6.9%), 24 with stage II (23.5%), 58 with stage III (56.9%), and 13 with stage IV (12.7%). Seventy-six patients had N0 or N1 disease (74.5%) while 26 patients had N2 disease (25.5%). Median OS had increased to 32 months, mortality rate stayed at 0%, and morbidity remained low.

The majority of data on the use of PVP-I in MPM is derived from a single center. Given this and PVP-I's strong cytotoxic effect on MPM cells *in vitro* as demonstrated through multiple studies, further investigations into PVP-I as a treatment adjunct are needed to discover its potential impact in MPM therapy.

PDT

PDT is a light-based intraoperative adjuvant treatment in which the patient is first given a nontoxic photosensitizing agent, usually porfimer sodium Photofrin or meta-tetra hydroxyphenyl chlorin (m-THPC) Foscan, that is subsequently activated in the presence of oxygen by visible light of a specific wavelength. This reaction produces singlet oxygen, a highly reactive form of oxygen, and is thought to be the principal effector of a number of mechanisms by which PDT induces tumorigenic cell death (26). PDT kills cells through direct cytotoxic effects on cell membranes, selective destruction of neovasculature, and initiation of an antitumor immune response, and the specific mechanism by which this happens depends on several factors: the photosensitizer used, the target tissue, the route, dose, and timing of photosensitizer administration, local oxygen availability, and the amount, rate, and wavelength of light given (27,28). The ability to change any of these different elements of PDT and thereby modulate its effect makes PDT an interestingly flexible and customizable modality of treatment for MPM.

PDT is also a unique treatment modality in that it is not thought to carry a cumulative toxicity and therefore presents the option of repeat administration, unlike with radiotherapy or chemotherapy (26). Additionally, PDT is compatible with all treatment modalities as well as synergistic with certain targeted therapies, immunotherapies, and hyperthermia (29,30). The depth of penetration associated with PDT is also ideal for intraoperative procedures—PDT penetrates several millimeters below the illuminated surface, a depth that is well suited for the purposes of reaching microscopic tumor left over from cytoreductive surgery but that is also superficial enough to prevent damage to underlying lung parenchyma (31).

Over the years, proper patient education has essentially eliminated complications arising from light sensitivity before and after surgery as a result of the PDT photosensitizing agent (26). Light precautions during the surgery such as yellow filters and fluorescent lights only during incision have also contributed to a lower rate of complications from cutaneous photosensitivity (32,33). After MCR is achieved, intraoperative PDT involves first sewing isotropic light detectors into the chest cavity to monitor light dose and fluence rate, then placing a laser fiber into a modified endotracheal tube filled with light-dispersing intralipid solution, pouring dilute intralipid into the chest cavity to further disperse light, and lastly moving the light source around the chest until all light detectors register the planned light dose (26).

The first phase III trial assessing the benefit of PDT for MPM was performed by Pass and colleagues from 1993 to 1996 (34). Sixty-three patients undergoing maximum debulking surgery and postoperative cisplatin, interferon alpha-2b, and tamoxifen immunochemotherapy were randomized to receive or not receive intraoperative porfimer sodium-based PDT. Debulking to less than 5 mm was achieved in 48 patients, and both groups (25 with PDT, 23 without) had similar distributions of sex, age, tumor volume, and histology. One perioperative death occurred in the PDT group due to an inferior vena cava avulsion while two patients from each group had a bronchopleural fistula. No difference in median survival (14.4 *vs.* 14.1 months), disease free interval (8.5 *vs.* 7.7 months), or sites of first recurrence were observed. The study concluded that the addition of PDT did not prolong survival or increase local control of MPM; however, the lack of improvement may be attributed to the large number of patients with remaining

macroscopic disease, as opposed to residual microscopic disease for which PDT may be more effectively used due to its limited depth of penetration (31). A prospective phase II trial using EPP or PD followed by porfimer sodium-mediated PDT occurring from 1991 to 1996 determined that PDT dose was an independent prognostic indicator of survival for involved patients (P<0.009) (35), while a phase I/II dose escalation study of intraoperative m-THPC-PDT following EPP in 2001 determined considerable toxicity associated with PDT and local control in only 50% of studied patients (36). A 2004 study then showed the safety and feasibility of polyhematoporphyrin-mediated PDT for fourteen patients with advanced MPM under hyperbaric oxygen with an improved median survival in the PDT group (P=0.0179) (37).

Work by Friedberg and colleagues presents perhaps the most compelling evidence in support of intraoperative PDT for MPM (38). From 2005 to 2008, 38 patients with advanced MPM—37 AJCC stage III/IV (97%) and 24 N2 (63%)—underwent extended pleurectomy and decortication (EPD) and porfimer sodium-based PDT. The first 14 patients were part of a comparative study between either EPP or EPD combined with PDT that determined superior results in the EPD-PDT group and a switch to using EPD-PDT as the sole treatment strategy for subsequent studies at this institution (39). Surprisingly, MCR was achieved in 97% of patients despite the cohort comprising mostly of stage III/IV and N2 patients, demonstrating that EPD is an effective surgery-based treatment to achieve MCR. Combined with PDT, this treatment strategy led to unusually long survival: 31.7 months for all patients, 41.2 months for epithelial, 31.7 months for N2 epithelial, and 57.1 months for N0/N1 epithelial patients. Of particular interest was the almost three-fold difference between median survival and recurrence free interval for epithelial patients: 41.2 *vs.* 15.1 months, as past studies usually report only a few months between recurrence and death. This finding suggested that EPD and/or PDT, while seemingly affording poor local control, may have somehow diminished the imminence of recurrence lethality, perhaps either due to the patient being left with two lungs as a result of the lung-sparing surgery or due to PDT's immunostimulatory effects and consequent activation of an anti-tumor vaccine response (40). The study concluded that EPD-PDT can be used with low expected mortality and morbidity for advanced stage epithelial MPM patients.

Because of the poor performance of nonepithelial patients undergoing EPD-PDT, Friedberg and colleagues began limiting their study to include only those with pure epithelial histology and recently published an updated report of their findings (41). Seventy-three epithelial patients undergoing EPD-PDT from 2005 to 2013 across two prospective trials with two different photosensitizers, porfimer sodium (52 patients) and 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a (HPPH) (21 patients) were analyzed. Ninety-two percent of the patients also received chemotherapy. Intraoperative PDT was implemented as previously described and all surgeries were performed by the same person, minimizing EPD procedural variability. With 68% N2, 89% stage III/IV, and a median tumor volume of 550 mL this cohort, as before represented advanced stage patients. The nearly three-fold difference between median survival (36 months) and recurrence-free interval (14 months) was again observed, further supporting some life-prolonging role of lung-sparing surgery or PDT following disease recurrence. There was a greater impact of lymph node status observed in this study: N0 patients, 68% of whom had stage III/IV disease, had a median survival of 87 months compared to 23 months in N1/N2 patients, demonstrating that a subgroup of advanced stage epithelial patients without nodal metastases responded particularly well to this treatment approach.

As indicated through this and previous studies, the use of PDT as an intraoperative treatment adjunct for MPM therapy is promising however, the specific role of PDT as with PVP-I has not been precisely determined. An ongoing prospective randomized trial (NCT02153229) conducted by Friedberg and colleagues is currently investigating this question.

Conclusions

HIOC, heated intraoperative PVP-I, and PDT are three promising intraoperative treatment adjuncts that are currently used in multimodality therapy for MPM. Clinical trials and analyses performed by Sugarbaker showed that HIOC cisplatin given at or near the MTD following both EPP and PD can be safely and feasibly performed with no increase in morbidity or mortality compared to surgery alone. While morbidity and mortality have decreased over the years, in part due to the advancement of management protocols to combat incidences of renal toxicity and deep venous thrombosis, a more effective cytoprotective

strategy is still being sought and efforts to improve the efficacy of cisplatin-based HIOC have expanded the scope of HIOC investigations to include combination regimens with cisplatin and other chemotherapeutic agents like gemcitabine or pemetrexed. Currently, our institution is performing a phase I clinical trial (NCT02838745) of cytoreductive surgery and hyperthermic intraoperative chemotherapy with pemetrexed and cisplatin for patients with MPM.

The utility of heated intraoperative PVP-I for MPM has been reported so by Lang-Lazdunski and colleagues who have demonstrated that moderately hyperthermic PVP-I, in combination with PD and prophylactic radiotherapy, is a well-tolerated multimodal alternative to EPP with neoadjuvant chemotherapy and adjuvant radiotherapy. However, the precise effect of PVP-I could not be determined due to the use of multiple therapies in their treatment regimen. *In vitro* studies of PVP-I have shown the direct cytotoxic effect of PVP-I on MPM cell lines through necrosis, as well as its dose-dependent inhibition of tumor growth through suppression of superoxide dismutase and induction of apoptosis (19,42). These positive *in vitro* results and the scarcity of clinical information on PVP-I's effects on MPM patients warrant further examination of its use for MPM therapy.

Lastly, the technique of PDT has been refined over the years to the point that photosensitivity complications have become practically nonexistent, and morbidity and mortality rates are similar to those of patients without PDT treatment (41). Friedberg and colleagues showed that EPD with PDT leads to surprisingly long survival in advanced epithelial patients without nodal metastases, while a characteristic three-fold difference between OS and recurrence-free interval suggests a beneficial impact of lung-sparing surgery, PDT, or both, on survival following MPM recurrence. A prospective randomized trial is currently being performed to tease out the effects of PDT, if any, on MPM treatment.

Intraoperative adjuncts are a potentially useful strategy for the control of micrometastatic disease in pleural mesothelioma. Given the encouraging results of past studies, HIOC, heated intraoperative PVP-I, and PDT are increasingly used in multimodality therapy to achieve maximal disease control. The optimal combination of modalities and individual impact of these adjunctive therapies on treatment are topics of active debate and merit further investigation.

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Footnote

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