A phase I study of extrapleural pneumonectomy and intracavitary intraoperative hyperthermic cisplatin with amifostine cytoprotection for malignant pleural mesothelioma

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Objective: This study was undertaken to determine maximum tolerated dose and toxicity of intraoperative intracavitary hyperthermic cisplatin perfusion with amifostine after extrapleural pneumonectomy for malignant pleural mesothelioma.

Methods: Patients with mesothelioma were prospectively enrolled. Those with resectable disease received amifostine and 1-hour hyperthermic cisplatin perfusion of ipsilateral hemithorax and abdomen. Morbidity, recurrence, and survival were recorded.

Results: Forty-two patients were enrolled; 29 underwent resection (operative mortality 7%, 2/29). Median age was 57 years. Eighteen were in pathologic stage I or II; 11 were in stage III. Median hospitalization was 15 days. Common complications were atrial fibrillation (66%, 19 patients), deep venous thrombosis (31%, 9 patients), and grade 3+renal toxicity (31%, 9 patients). Feasibility was determined. Renal toxicity was unrelated to cisplatin dose, with no maximum tolerated dose determined. Overall median survival was 17 months (resected 20 months, unresected 10 months). Median survivals were 26 months for patients receiving higher cisplatin doses and 16 months for those receiving lower doses ($P = .35$). Survival was significantly longer with negative extrapleural nodes (31 vs 14 months, $P = .0115$) and early stage (all resected 35 months for stage I–II vs 14 months for stage III, $P = .0022$, epithelial 39 months for stage I–II vs 15 months for stage III, $P = .0072$).

Conclusion: Early stage and negative extrapleural lymph nodes were associated with prolonged survival. Single-dose amifostine did not protect adequately against cisplatin-induced renal toxicity. Additional cytoprotective strategies are needed to allow determination of cisplatin maximum tolerated dose.

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Despite aggressive surgery plus chemotherapy and chest radiation, malignant pleural mesothelioma (MPM) remains a disease characterized by relentless local progression and locoregional recurrence in most patients undergoing surgical resection.[1-5] Extrapleural pneumonectomy (EPP) represents the most extensive form of cytoreductive surgery possible, but other techniques, such as locoregional chemotherapy in conjunction with surgery either intraoperatively or postoperatively, have been attempted for various malignancies, including MPM, with manageable toxicity and improved local control and survival.[6-11]

Cisplatin has been used extensively for locoregional perfusion in thoracic malignancies. We have recently published a phase I and II study of intraoperative locoregional cisplatin perfusion after pleurectomy for MPM that determined 225 mg/m^2 to be the maximum tolerated dose (MTD), with a suggested survival advantage for patients who received higher doses of cisplatin within the limitations of a nonrandomized trial.[6] The MTD for intraoperative locoregional cisplatin in the setting of EPP, however, has not been fully explored. The goal of achieving enhanced local drug delivery at the site of resection in the thorax by using higher doses of cisplatin has been limited by renal toxicity resulting from systemic absorption of the cisplatin. The relative effectiveness of pharmacologic renal cytoprotective strategies will likely impact the cisplatin MTD achieved in phase I studies. The use of an effective cytoprotective agent to preserve the kidney is appealing, particularly in the setting of EPP, in which traditional use of postoperative hydration to limit renal toxicity may be limited to avoid excessive contralateral lung fluid retention and resulting hypoxia in the postoperative period.

Our previous studies with intraoperative hyperthermic cisplatin (IOHC) have used sodium thiosulfate as a protective agent. Although sodium thiosulfate provides excellent renal protection, its mechanism of action involves inactivation of cisplatin and therefore may compromise cisplatin's potential therapeutic effect. For this reason, it is of interest to explore alternative strategies for renal protection in the setting of IOHC.

Amifostine (Ethyol, ALZA Corporation, Mountain View, Calif) has been added in various systemic chemotherapeutic

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Abbreviations and Acronyms
EPP = extrapleural pneumonectomy
IOHC = intraoperative hyperthermic cisplatin
MPM = malignant pleural mesothelioma
MTD = maximum tolerated dose

protocols as a cytoprotective agent in regimens involving alkylating and platinum-related agents for head and neck, thoracic, and gynecologic malignancies, as well as melanoma.[12-16] The preferential 100-fold uptake of amifostine by normal cells results in selective protection of normal tissues by intracellular radical salvage and binding of chemotherapeutic agents, with preservation of tumoricidal properties of cisplatin in the malignant cells. Single-dose amifostine has been used in cisplatin-based protocols and in this study was dosed according to the American Society of Clinical Oncology Clinical Practice Guidelines.[16]

We conducted this phase I study to determine the feasibility, toxicity, and MTD of cisplatin in patients undergoing intraoperative intrathoracic and intraperitoneal hyperthermic perfusion of cisplatin after EPP and after intravenous administration of amifostine.

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MATERIALS AND METHODS

Eligible Patients

Patients who came to Brigham and Women's Hospital with a confirmed diagnosis of MPM and who were candidates for EPP were considered for enrollment in the institutional review board– and scientific review committee–approved protocol after appropriate consent was obtained. Appropriate patients for enrollment were men or nonpregnant women (older than 16 years) who were good operative candidates with good functional status and had no significant comorbidities or cancer other than MPM, which was confined to the ipsilateral hemithorax as determined by computed tomographic scan and magnetic resonance imaging.[1] Postoperative predicted forced expiratory value in 1 second greater than 0.8 L, preoperative creatinine less than 2.0 mg/dL, and availability for follow-up were required. Patients who had received neoadjuvant chemotherapy or radiation were excluded. Appropriate candidates were registered with the Quality Assurance for Clinical Trials office during the preoperative visit. Three patients were scheduled at each dose level, followed by escalation of the dose for the next 3 patients provided there were no dose-limiting toxicities, addition of 3 patients at the same dose in case of 1 dose-limiting toxicity, and de-escalation of the dose if 2 or more dose-limiting toxicities were observed among 6 patients. Dose-limiting toxicities were defined as any grade 3 or higher complication not definitively caused by surgery according to the National Cancer Institute common toxicity criteria version 2.0.

Surgical Technique and IOHC

Those patients who had less than 1 cm^3 residual tumor, as evaluated with visual inspection by the operating surgeon, after the tumor was resected and before the diaphragmatic and pericardial reconstructions were performed, received the IOHC cisplatin perfusion for 1 hour in the chest and abdomen at 42°C. To reduce the renal toxicity of cisplatin and allow maximal dose escalation of cisplatin, intravenous amifostine was administered before the initiation of the intraoperative chemotherapy at a dose of 910 mg/m^2 according to the American Society of Clinical Oncology Clinical Practice Guidelines.[16] Intravenous fluids, dopamine, mannitol, and furosemide were used to maintain perfusion pressure and urinary output (at 100 mL/h) during the intrapleural cisplatin treatment and for 1 hour thereafter. At the conclusion of the IOHC perfusion, all the chemotherapy perfusate was evacuated, and the reconstructions were performed. Details of the technique have been described elsewhere.[6,17]

Follow-up

Patients were followed up after entry into the trial, and postoperative morbidity and mortality were recorded. Laboratory tests were done daily in the immediate postoperative period and at 2 weeks and 1 month postoperatively. Lower extremity venous ultrasonography was performed on postoperative day 7 or before discharge, according to the institutional review board–approved protocol, to evaluate for deep venous thrombosis. Echocardiograms were obtained at 1, 3, and 6 postoperative months to assess heart function, and computed tomography of the chest and abdomen was performed at least every 6 months, or sooner if symptoms arose, to monitor for recurrence of MPM. The recurrence-free interval after surgery and survival were recorded. Although no adjuvant therapy was included in the protocol, some patients received additional treatment off protocol at the discretion of their local physicians according to their clinical presentations and courses.

Statistical Analysis

The sample size of 19 to 53 patients was calculated by the institutional statistician and approved by the scientific review committee and institutional review board. The time to disease recurrence was defined as the interval between the date of surgery and the date of the first radiographically confirmed clinical recurrence. Survival was defined as the interval between the date of surgery and date of last follow-up or date of death. Kaplan–Meier curves of survival and time to recurrence were constructed 48 months after the last patient was registered. The log-rank statistic was used for univariate analysis of prognostic factors.

RESULTS

Between August 2001 and July 2002, a total of 42 patients were enrolled in the protocol. Thirteen patients were found at thoracotomy to have unresectable disease (9 with chest wall invasion, 3 with chest wall and mediastinal invasion, and 1 with cardiac invasion). Twenty-nine patients had their MPM resected to smaller than 1 cm^3 (Table 1). There were 22 male and 7 female patients, with a median age of 57 years. The stage distribution was as follows: 5 patients with stage I disease, 13 with stage II, and 11 with stage III. Twenty-four patients had epithelial disease, and 5 patients had nonepithelial tumors. All the patients who underwent resection received amifostine and successfully underwent hyperthermic cisplatin lavage as previously described elsewhere.[6]

Morbidity

There were 2 postoperative deaths among the 29 patients who underwent resection (7%). One patient died of a pulmonary embolus on postoperative day 11; the other died of a bronchopleural fistula on postoperative day 57. Median hospitalization for patients who underwent resection was 15 days (Table 2).

TABLE 1. Stage of disease, type of mesothelioma, margins and other characteristics by side of resection (n = 29)

	Right side		Left side	
	No.	%	No.	%
	16	55%	13	45%
Male	13	81%	9	69%
Epithelial type	12	75%	12	92%
Brigham and Women's Hospital stage				
1	2	13%	3	23%
2	6	38%	7	54%
3	8	50%	3	23%
N stage				
0	8	50%	5	38%
1	1	6%	6	46%
Extrapleural nodes	7	44%	2	15%
Margins				
Positive	12	80%	7	54%
Unable to be assessed	1	6%	0	

The most common morbidity was atrial fibrillation, with 19 patients (66%) having atrial fibrillation develop during hospitalization. Deep venous thrombosis was seen in 9 patients (31%). Three patients had pulmonary emboli. Reoperations for infections, bleeding, or diaphragmatic patch complications occurred in 6 of 29 patients (21%). Four patients (14%) had adult respiratory distress syndrome, and 2 required tracheostomy and feeding tubes. Three patients (10%) had empyema develop; 1 required a Clagett window, and the other two were treated with video-assisted thoracoscopy and irrigation.

Maximum Tolerated Dose

The dose escalation, de-escalation, and revision of the protocol after consultation with the institutional review board in response to grade 3+ renal toxicity are shown in Table 3. Overall, grade 3+ renal toxicity developed in 9 patients (31%), with 2 requiring temporary renal dialysis and 1 with permanent renal failure (Table 2). The median time to peak creatinine was 5 days, and the median time to recovery to baseline creatinine level was 16.5 days. This renal toxicity was unrelated to cisplatin dose and occurred at low and high cisplatin dose levels, resulting in premature closure of the protocol to accrual without determination of MTD.

Overall Survival

The patients were entered into the study from August 2001 to July 2002. At the time of this analysis, 6 patients remained alive and 36 had died. All patients with unresectable disease have died. The overall median survival for the 42 patients enrolled in the protocol, both those with resectable disease and those with unresectable disease, was 17 months (range 11 days–61 months). The median survival for the 13 patients with unresected disease was 10 months, whereas that for the 29 patients who underwent resection was 20 months ($P = .0052$, Figure 1). The 24 patients who underwent resection of epithelial subtype tumors survived significantly longer than did the 5 patients with nonepithelial disease (median survival 29 months vs 13 months, $P = .006$; Figure 2). The 15 patients who received higher cisplatin doses (175–200 mg/m^2) had a survival of 26 months, and the 14 patients who received lower doses

TABLE 2. Morbidity and mortality among patients undergoing resection (n = 29)

	Common toxicity criteria grade					
	1	2	3	4	5	Total
Mortality						2 (7%)
Morbidities						
Atrial fibrillation	0	0	18	1	0	19 (66%)
Non–Q wave myocardial infarction	0	0	0	1	0	1 (3%)
Pericarditis	0	8	0	0	0	8 (28%)
Respiratory failure	0	0	0	4	1	5 (17%)
Adult respiratory distress syndrome	0	0	0	3	1	4 (14%)
Tracheostomy/feeding tube	NA	NA	NA	NA	NA	2 (7%)
Vocal cord injury	0	3	0	0	0	3 (10%)
Pneumonia	0	1	0	2	0	3 (10%)
Aspiration	0	0	0	1	0	1 (3%)
DVT and PE	0	0	8 DVT	1 PE, 1 DVT+PE	1 PE (fatal)	11 (31%)
Creatinine elevation	3	10	5	4	0	22 (76%)
Renal failure requiring dialysis	0	0	2	1	0	3 (10%)
Neuropathy (motor)	0	0	0	1	0	1 (3%)
Empyema	0	0	0	2	1	3 (10%)
Bronchopleural fistula	0	0	0	1	1	2 (7%)
Reoperations for bleeding, patch failure, infections	NA	NA	NA	NA	NA	6 (21%)

Data are expressed as numbers of patients. *NA,* Not applicable; *DVT,* deep venous thrombosis; *PE,* pulmonary embolism.

TABLE 3. Renal toxicity at each dose level

Dose level	Cisplatin (mg/m^2)	N	Renal toxicity grade 1	2	3	4
1	175	3	1	1	—	—
2	200	3	—	1	1	1
3	175	9	1	4	1	2
4	150	2	—	1	1	—
5*	75	3	—	1	—	—
6*	100	3	—	1	—	—
7*	125	5	1	1	2	—
8*	100	1	—	—	—	1
Total		29	3	10	5	4

Data are expressed as numbers of patients. *Protocol revision.

(75–150 mg/m^2) had a median survival of 16 months (P = .36). The 10 patients without positive surgical margins had 30-month median survival, whereas the 19 patients with positive margins had a 17-month median survival (P = .410). Patients with negative extrapleural lymph nodes survived significantly longer as a subset. The 20 patients without N2 disease had a median survival of 31 months, whereas the 9 patients with N2 disease had a 14-month median survival (P = .0115; Figure 3). The 18 patients with Brigham and Women's Hospital–Dana-Farber Cancer Institute stage 1 to 2 disease[1] had a median survival of 35 months, whereas the 11 patients with stage 3 disease had a 14-month median survival (P = .0022; Figure 4, *A*). Among the subset of patients with resected disease of epithelial type, the 16 patients with Brigham and Women's Hospital–Dana-Farber Cancer Institute stage 1 to 2 disease had a 39-month median survival, versus 15 months for the 8 patients with stage 3 disease (P = .0072; Figure 4, *B*).

Patterns of Recurrence

Radiographic or pathologically confirmed recurrence of MPM was observed in 23 patients with resected disease (79%), 3 of whom at the time of this analysis remained alive at 52, 57, and 61 months. Three patients (10%) died without radiographic or pathologic evidence of recurrence. Three patients (10%) were alive at the time of this analysis without evidence of recurrence at 48, 50, and 51 months.

The median time to first recurrence among patients with resected disease was 16 months. Patients with epithelial histologic type had a 24-month median time to first recurrence, whereas patients with nonepithelial histologic type had a median time to first recurrence of 5 months (P = .0008). Patients with N2 nodes uninvolved with MPM had a 23-month median time to first recurrence where as patients with N2 nodes involved with MPM had a median time to recurrence of 9 months.

Initial recurrences involved the ipsilateral hemithorax alone in 5 patients (17%), the abdomen alone in 7 patients (24%), and the contralateral hemithorax in 3 patients (10%). Several patients had recurrence simultaneously at multiple sites. One patient (3%) had initial recurrence in both the ipsilateral hemithorax and the abdomen, 4 patients (14%) had initial recurrence in both the abdomen and the

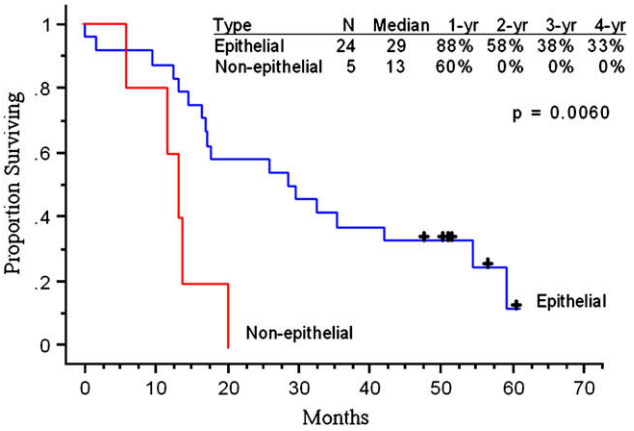

FIGURE 2. All patients with resected disease, survival by cell type. *Blue line* represents epithelial cell type; *red line* represents other types.

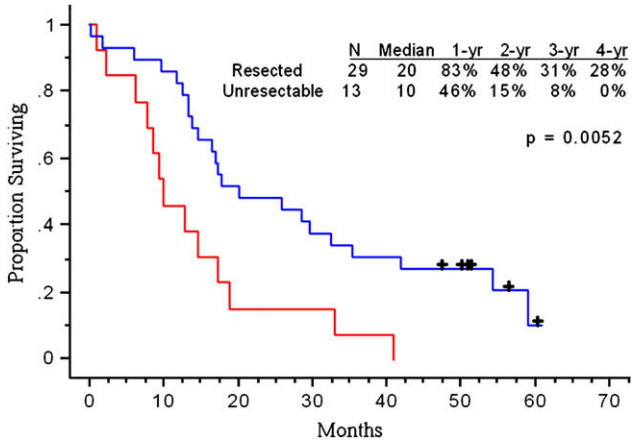

FIGURE 1. All patients enrolled, survival by resection. *Blue line* represents resection; *red line* represents no resection.

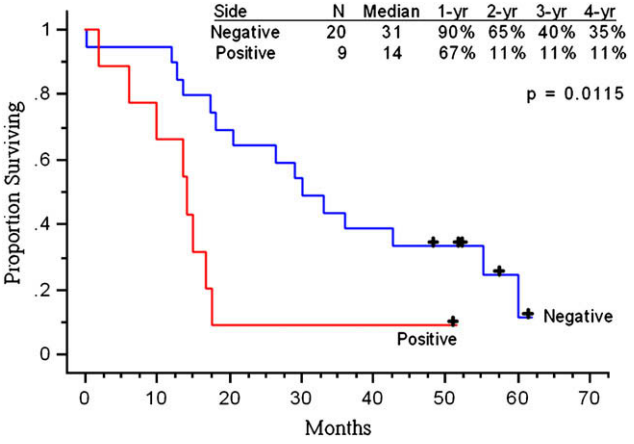

FIGURE 3. All patients with resected disease, survival by N2 status. *Blue line* represents negative status; *red line* represents positive status.

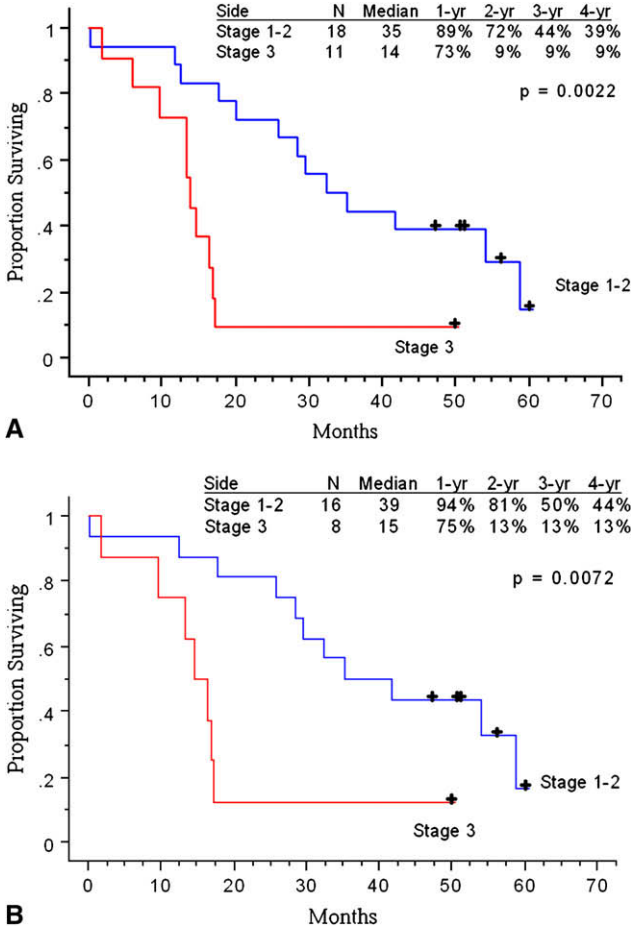

FIGURE 4. A, Patients with resected disease, survival by Brigham and Women's Hospital stage. *Blue line* represents stages 1 and 2; *red line* represents stage 3. B, Patients with resected epithelial disease, survival by Brigham and Women's Hospital stage. *Blue line* represents stages 1 and 2; *red line* represents stage 3.

contralateral hemithorax, and 3 patients (10%) had simultaneous recurrence in all three cavities. Total recurrence in the ipsilateral hemithorax was 31% (9 patients), total recurrence in the abdomen was 52% (15 patients), and total recurrence in the contralateral hemithorax was 32% (10 patients).

DISCUSSION

Renal toxicity is a major factor preventing escalation of dose during IOHC when single-dose amifostine is used for cytoprotection. Nine patients had grade 3 or greater creatinine elevation. Among these, 8 had reversible grade-3 or grade-4 toxicity, and 1 patient had irreversible renal failure and is alive on dialysis 4 years after the procedure with no evidence of disease. Because the renal toxicity was not consistently related to the cisplatin dose, we discontinued the study and concluded that the cytoprotection regimen of single-dose amifostine at 910 mg/m^2 provided inadequate protection in the context of intracavitary cisplatin.

Although amifostine alone was an ineffective cytoprotective agent, it had no obvious adverse effect on the efficacy of IOHC with cisplatin. The 100-fold preferential uptake of amifostine by normal cells relative to tumor cells, as opposed to the direct covalent binding of sodium thiosulfate to cisplatin in the circulating blood volume, provides more selective cytoprotection, with preservation of the cisplatin's therapeutic benefit. This is consistent with other studies that have used amifostine cytoprotection against platinum toxicity.[12-15,18] For example, Betticher and associates[14] reported that in a randomized phase II trial, addition of amifostine to carboplatin therapy reduced thrombocytopenia duration and hospitalization stay with no evidence of tumor protection by amifostine. Similarly, Schiller and colleagues[12] used amifostine for cisplatin and vinblastine therapy for metastatic non–small cell lung cancer, with an excellent response rate and 17-month median survival. Addition of amifostine for renal protection resulted in a 12% rate of reversible grade 3 renal toxicity. In contrast, sodium thiosulfate binds covalently to inactivate cisplatin, providing excellent cytoprotection, but probably at the expense of some potential therapeutic benefit.

Cardiac and pulmonary complications constituted the primary nonrenal morbidities, similar to our previous published experience with EPP.[1,17] The thrombotic morbidity has been noted in the context of hyperthermia[19-21] and is equivalent to that in our previous IOHC studies.[6,17] The mortality of 7% is comparable to those in published reports of EPP without IOHC.[5]

Although this study did not identify a dose at which amifostine protected the kidney, many of the patients have had extended survival relative to a historical control group. We have previously reported our experience with trimodality therapy involving EPP for MPM in a 183-patient cohort. In that study, positive margins, positive extrapleural lymph nodes, advanced stage of disease, and nonepithelial histologic type were found to adversely affect survival in this cohort of patients. Patients with stage I and II disease reported on here had a median survival of 32 months. This compares favorably with our previous experience with patients not receiving IOHC.[1]

Additional studies will be required to determine the optimal cytoprotective strategy for IOHC in this clinical setting. Although agents such as sodium thiosulfate are highly effective, our experience has consistently shown a negative impact of sodium thiosulfate on the therapeutic effect of cisplatin. For example, one study of EPP conducted by our group that used IOHC cisplatin with simultaneous infusion of sodium thiosulfate did not show a dose effect on survival.[17] In contrast, the pleurectomy study with IOHC cisplatin followed by sodium thiosulfate infused after the IOHC perfusion[6] did show a dose effect on survival, suggesting that concurrent sodium thiosulfate administration may have attenuated the cisplatin therapeutic effect in the

EPP trial.[17] One reasonable strategy for future trials would be to delay administration of sodium thiosulfate by a few hours, instead of administering it immediately at the conclusion of the chemotherapy perfusion, to determine whether a further increase in therapeutic effect could be achieved without increased renal toxicity.

The timing of amifostine administration is also critical to effective cytoprotection. Amifostine infusion needs to be initiated long enough before chemotherapy administration to allow intracellular distribution.[16] Clearly, a single 910-mg/m^2 amifostine dose was not sufficient to protect from cisplatin renal toxicity, and we no longer use this strategy alone for cytoprotection during IOHC. Further exploration of cytoprotective strategies is needed, and multiple doses of amifostine or a combination of amifostine and sodium thiosulfate may provide improved cytoprotection with greater therapeutic benefit.[22-24]

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