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Commentary: Cisplatin-induced nephrotoxicity following cytoreductive surgery and heated intraoperative chemotherapy for malignant pleural mesothelioma

Shawn S. Groth, MD, MS, and R. Taylor Ripley, MD

Despite improvements in survival with aggressive multimodal therapy for malignant pleural mesothelioma (MPM), approximately 35% of these patients ultimately develop recurrent disease within the ipsilateral hemithorax (67% of all recurrences), implicating a need for more efficacious methods of local tumor control.¹ A number of intraoperative adjunctive therapies have been used in an attempt to reduce recurrence rates and extend survival, including heated povidone-iodine,² photodynamic therapy,³ and heated intraoperative chemotherapy (HIOC).⁴ In one study that examined use of cisplatin HIOC in a group of patients with MPM with a favorable risk profile, HIOC led to significantly longer disease-free (27.1 vs 12.8 months) and overall survival (35.3 vs 22.8 months).⁴ The efficacy of HIOC must be balanced against its toxicities.

The major dose-limiting toxic effect of HIOC with cisplatin is nephrotoxicity. In this issue of the *Journal*, Hod and colleagues⁵ examined the incidence, predictors, and consequences of acute kidney injury (AKI) in their series of 503 patients who underwent cytoreductive surgery (with or without cisplatin-based HIOC) over a 9-year period. They found that 48.3% of patients who underwent HIOC had some degree of AKI; 3.2% required hemodialysis. Stage 3 AKI was associated with a 2.7-fold increased

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CENTRAL MESSAGE

Multimodal strategies are needed to minimize the risk and severity of acute kidney injury after cytoreductive surgery and platinum-based heated intraoperative chemotherapy for mesothelioma.

risk of death on multivariable analysis, highlighting the implications of postoperative complications on long-term survival.

Clinicians and researchers at the Brigham and Women's Hospital have a tradition of excellence in advancing the care of MPM and should be congratulated on their dedication to minimizing adverse events. The mechanism of cisplatin-induced nephrotoxicity is complex and likely involves uptake of cisplatin metabolites into renal tubular cells, which leads to activation of cell-signaling pathways that promote apoptosis and a vigorous inflammatory response. Cisplatin may also directly injure the renal vasculature, thereby promoting ischemic injury.⁶ Because of its multifactorial etiology, single-modal renal-protective strategies are ineffective; multimodal management is needed. Indeed, the group at the Brigham found that amifostine alone did not provide adequate renal protection.⁷ However, the combination of amifostine, sodium thiosulfate, and a proactive perioperative fluid-management strategy was beneficial in reducing the incidence of AKI.⁸

There are many unanswered questions regarding HIOC for MPM. The optimal duration and combination of chemotherapy agents of HIOC is unknown. Although Hod and colleagues identified risk factors for AKI, further studies are needed regarding patient selection for HIOC versus other modalities of treatment. Finally, whether the addition of other renal protective agents that have been studied in vitro and in preclinical animal models of

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cisplatin-induced nephrotoxicity (eg, antitumor necrosis factor- α , mitogen-activated protein kinase inhibitors, and cyclin-dependent kinase 2 inhibitors) to an established renal-protective strategy (eg, fluid replacement, amifostine, and sodium thiosulfate) can reduce the incidence and severity of AKI further following cisplatin-based HIOC is unknown.

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Commentary: Winning the battle for local control without losing war for survival against malignant pleural mesothelioma

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Malignant pleural mesothelioma (MPM) remains vexing despite decades of therapeutic refinement. Curative local control involves cytoreductive surgery (CS) by extrapleural

CENTRAL MESSAGE

Curative treatment of mesothelioma includes aggressive local disease control. To optimize survival, pursuit of microscopic tumor destruction must be balanced by physiologic cost to the patient.

pneumonectomy (EPP) or lung-sparing techniques like pleurectomy/decortication (PD). As part of multimodality therapy, the goal of CS is macroscopic complete resection.^{1,2} Intraoperative adjuncts to increase tumor destruction include intracavitary therapy with hyperthermic

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