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

Alejandro Bribriesco, MD

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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.

Malignant pleural mesothelioma (MPM) remains vexing despite decades of therapeutic refinement. Curative local control involves cytoreductive surgery (CS) by extrapleural 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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intraoperative chemotherapy (HIOC) and photodynamic therapy (PDT).[3] While newer intrapleural therapies such as cytokines and oncolytic viral constructs are being explored, we are reminded to reassess "traditional" MPM therapies.[3,4]

In this issue of *the Journal*, Hod and colleagues[5] from Brigham and Women's Hospital present a retrospective study of 501 patients with MPM who underwent CS (48% EPP), with 82% receiving cisplatin-based HIOC using a phase I/II-established protocol including renal protection.[6-8] The aim was to assess acute kidney injury (AKI) with a simple but important hypothesis: AKI is more common in patients receiving CS + HIOC. The overall incidence of AKI was 48.3% and significantly greater with HIOC (53.5% vs 24.2%). AKI was more common in EPP versus PD, and stage III AKI was associated with increased length of stay and risk of death. Notably, the observed survival benefit of CS + HIOC was limited to patients who did not develop AKI. This study was not designed to assess cancer-specific outcomes and so no data are presented on disease-free survival (DFS) or overall survival (OS). However, an impactful finding is that HIOC-associated AKI compromised the therapeutic benefit of aggressive local control.

Patient selection is critical to improving MPM outcomes. In previous work, the Brigham and Women's Hospital group created a tool based on 3 variables (epithelioid histology, anemia, tumor volume) predicting low-risk patients receiving EPP.[9] Applied ad hoc to patients with CS undergoing HIOC, 103 low-risk patients were identified with excellent median OS for the entire cohort (33.1 months).[10] With the current study, risk of AKI could be factored to create a tailored approach with PD and non-nephrotoxic intrapleural agent. This is supported by studies of lung-preserving surgery with PDT[11] and povidone–iodine,[12] which reported a median OS of 36 and 32 months, respectively.

Evidence that decreased local recurrence is not equivalent to improved survival disrupts justification of collateral damage in pursuit of local control. Friedberg and colleagues'[11] PD + PDT study showed significant discordance between DFS (median 14 months) and OS (median 36 months for cohort; 87 months for low-risk subgroup). Similarly, series of lung-sparing CS plus povidone–iodine[12] and HIOC[13] reported median OS between 22 and 32 months despite recurrence up to 90%. Recently, Batirel and colleagues[14] showed no survival advantage to macroscopic complete resection with CS in both unmatched and propensity-matched patients. In contrast, Tilleman and colleagues'[15] study of EPP + HIOC showed ipsilateral hemithorax recurrence dropped to 31.5% with DFS of 15.3 months, but median OS achieved was 13.1 months.

Local disease control has been equated to improved survival with MPM.[16] This is now being challenged, as physiologic cost associated with winning the battle for local control may not win the war for survival. Understanding the interplay of patient factors and therapeutic weapons is essential in the fight against MPM.

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Commentary: Acute kidney injury after intrapleural cisplatin: Minimizing collateral damage

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CENTRAL MESSAGE

Hyperthermic intraoperative cisplatin has significant renal toxicity and a fragile survival benefit. Its use should be avoided in patients at elevated risk of even mild acute kidney injury.

Malignant pleural mesothelioma (MPM) is perhaps one of the most vexing problems facing thoracic surgeons. Hyperthermic intraoperative cisplatin chemotherapy (HIOC) is an adjunctive option for patients undergoing cytoreductive surgery. The feasibility and safety of HIOC has been established, although a clear benefit has never been definitively proven.[1] Cisplatin administered within the pleura has significant systemic absorption, which is known to injure the renal tubules and cause direct cytotoxicity.

In this issue of the *Journal*, Hod and colleagues[2] report a retrospective observational study of their institutional prospectively maintained database for patients undergoing surgical therapy for MPM, hypothesizing that HIOC contributes to the incidence of acute kidney injury (AKI). A total of 503 patients underwent either extrapleural pneumonectomy (n = 241) or pleurectomy/decortication (n = 262) over a 9-year period. HIOC was administered to 312 patients.

Remarkably, more than 50% of the patients who received HIOC developed AKI. Ostensibly, this seems to represent an unacceptably high risk for a therapy with unproven benefit. Approximately 25% of the patients who did not receive HIOC also developed AKI.

AKI was described using the Kidney Disease Improving Global Outcomes (KDIGO) definition, composed of 3 stages. KDIGO stage I is met when serum creatinine (SCr) rises by 0.3 mg/dL (or 50%-99%) over baseline. Stage II is moderate AKI, and stage III is severe AKI and includes all patients who require renal replacement therapy. Of the patients developing AKI, 78% were classified as the seemingly benign KDIGO stage I. Risk factors for AKI included male sex, HIOC, previous cisplatin exposure, hypertension, and longer operative time.

It should be mentioned that KDIGO stage I might not even be recognized as AKI during routine postoperative care, given that the SCr level may fall within the normal laboratory reference range. Stage I is generally not alarming to surgeons or nephrologists. So why do we care? Might this study, which proclaims a surprisingly high

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