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.

References

1. Baldini EH, Recht A, Strauss GM, DeCamp MM Jr, Swanson SJ, Liptay MJ, et al. Patterns of failure after trimodality therapy for malignant pleural mesothelioma. *Ann Thorac Surg*. 1997;63:334-8.
2. Lang-Lazdunski L, Bille A, Papa S, Marshall S, Lal R, Galeone C, 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.
3. Friedberg JS, Culligan MJ, Mick R, Stevenson J, Hahn SM, Sterman D, et al. Radical pleurectomy and intraoperative photodynamic therapy for malignant pleural mesothelioma. *Ann Thorac Surg*. 2012;93:1658-65; discussion 1665-7.
4. Sugarbaker DJ, Gill RR, Yeap BY, Wolf AS, DaSilva MC, Baldini EH, 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.
5. Hod T, Freedberg K, Motwani SS, Chen M, Frendl G, Leaf DE, et al. Acute kidney injury after cytoreductive surgery and hyperthermic intraoperative cisplatin chemotherapy for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg*. 2021;161:1510-8.
6. Pabla N, Dong Z. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. *Kidney Int*. 2008;73:994-1007.
7. Zellos L, Richards WG, Capalbo L, Jaklitsch MT, Chirieac LR, Johnson BE, 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.
8. Tillemann TR, Richards WG, Zellos L, Johnson BE, Jaklitsch MT, Mueller J, 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.

See Article page 1510.

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

Alejandro Bribriesco, MD

Alejandro Bribriesco, MD

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

From the Section of Thoracic Surgery, Department of Thoracic and Cardiovascular Surgery, Heart Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio. Disclosures: The author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication June 29, 2020; revisions received June 29, 2020; accepted for publication June 29, 2020; available ahead of print July 10, 2020.

Address for reprints: Alejandro Bribriesco, MD, Section of Thoracic Surgery, Department of Thoracic and Cardiovascular Surgery, Heart, Vascular and Thoracic Institute, Cleveland Clinic, 9500 Euclid Ave/Mailstop J4-1, Cleveland, OH 44195 (E-mail: bribria@ccf.org).

J Thorac Cardiovasc Surg 2021;161:1520-2

0022-5223/\$36.00

Copyright © 2020 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2020.06.092>

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 colleagues⁵ 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 PDT¹¹ 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–iodine¹² and HIOC¹³ reported median OS between 22 and 32 months despite recurrence up to 90%. Recently, Batirel and colleagues¹⁴ showed no survival advantage to macroscopic complete resection with CS in both unmatched and propensity-matched patients. In contrast, Tillemann 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.

References

1. Sugarbaker DJ. Macroscopic complete resection: the goal of primary surgery in multimodality therapy for pleural mesothelioma. *J Thorac Oncol*. 2006;1:175–6.
2. Rusch V, Baldini EH, Bueno R, De Perrot M, Flores R, Hasegawa S, 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.
3. Bertoglio P, Aprile V, Ambrogio MC, Mussi A, Lucchi M. The role of intracavitary therapies in the treatment of malignant pleural mesothelioma. *J Thorac Dis*. 2018;10:S293–7.
4. Pease DF, Kratzke RA. Oncolytic viral therapy for mesothelioma. *Front Oncol*. 2017;7:179.
5. Hod T, Freedberg K, Motwani SS, Chen M, Frendl G, Leaf DE, et al. Acute kidney injury after cytoreductive surgery and hyperthermic intraoperative cisplatin chemotherapy for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg*. 2021;161:1510–8.
6. Zellos L, Richards WG, Capalbo L, Jaklitsch MR, Chirieac LR, Johnson BE, 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.
7. Richards WG, Zellos L, Bueno R, Jaklitsch MT, Jänne PA, Chirieac LR, 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.
8. Burt BM, Richards WG, Lee HS, Bartel S, Dasilva MC, Gill RR, et al. A phase I trial of surgical resection and intraoperative hyperthermic cisplatin and gemcitabine for pleural mesothelioma. *J Thorac Oncol*. 2018;13:1400–9.
9. Gill RR, Richards WG, Yeap BY, Matsuoka S, Wolf AS, Gerbaudo VH, et al. Epithelial malignant pleural mesothelioma after extrapleural pneumonectomy: stratification of survival with CT-derived tumor volume. *AJR Am J Roentgenol*. 2012;198:359–63.
10. Sugarbaker DJ, Gill RR, Yeap BY, Wolf AS, DaSilva MC, Baldini EH, 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.
11. Friedberg JS, Simone CB II, Culligan MJ, Barsky AR, Doucette A, McNulty S, et al. Extended pleurectomy-decortication-based treatment for advanced stage epithelial mesothelioma yielding a median survival of nearly three years. *Ann Thorac Surg*. 2017;103:912–9.
12. Lang-Lazdunski L, Bille A, Papa S, Marshall S, Lal R, Galeone C, 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.
13. Ambrogio MC, Bertoglio P, Aprile V, Chella A, Korasidis S, Fontanini G, et al. Diaphragm and lung-preserving surgery with hyperthermic chemotherapy for malignant pleural mesothelioma: a 10-year experience. *J Thorac Cardiovasc Surg*. 2018;155:1857–66.e1852.
14. Batirel HF, Metintas M, Caglar HB, Ak G, Yumuk PF, Ahiskali R, et al. Macroscopic complete resection is not associated with improved survival in patients with malignant pleural mesothelioma. *J Thorac Cardiovasc Surg*. 2018;155:2724–33.

15. Tillemann TR, Richards WG, Zellos L, Johnson BE, Jaklitsch MT, Mueller J, 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.
16. Sugarbaker DJ, Flores RM, Jaklitsch MT, Richards WG, Strauss GM, Corson JM, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. *J Thorac Cardiovasc Surg.* 1999;117:54-63; discussion 63-5.

See Article page 1510.

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

Michael I. Ebricht, MD

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 colleagues² 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

Michael I. Ebricht, MD

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.

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

From the Section of Thoracic Surgery, Columbia University Medical Center, New York, NY.

Disclosures: The author reports no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication June 23, 2020; revisions received June 23, 2020; accepted for publication June 24, 2020; available ahead of print July 12, 2020.

Address for reprints: Michael I. Ebricht, MD, Section of Thoracic Surgery, Columbia University Medical Center, 161 Fort Washington Ave, 3rd Floor, New York, NY 10032 (E-mail: mie2110@cumc.columbia.edu).

J Thorac Cardiovasc Surg 2021;161:1522-3

0022-5223/\$36.00

Copyright © 2020 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2020.06.095>