Editorial

Some like it hot: the potential role of hyperthermic intrathoracic chemotherapy in the multimodality treatment of pleural mesothelioma

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Comment on: Klotz LV, Hoffmann H, Shah R, *et al*. Multimodal therapy of epithelioid pleural mesothelioma: improved survival by changing the surgical treatment approach. Transl Lung Cancer Res 2022;11:2230-42.

Keywords: Pleural mesothelioma; intrathoracic chemotherapy; malignant pleural mesothelioma (MPM); diffuse pleural mesothelioma (DPM)

Submitted Jan 16, 2023. Accepted for publication Feb 01, 2023. Published online Feb 09, 2023.
doi: 10.21037/tlcr-23-46
View this article at: https://dx.doi.org/10.21037/tlcr-23-46

Diffuse pleural mesothelioma (DPM) is an aggressive cancer, typically occupying the entire hemithoracic cavity. Due to its long latency period, patients often present with unresectable disease at the time of diagnosis. Combination chemotherapy, using cisplatin/pemetrexed, and combination checkpoint inhibitor therapy, with ipilimumab/nivolumab, are the standard front-line regimens for patients with unresectable disease (1). For resectable disease, the trimodal therapy regimen of cytoreduction, chemotherapy, and radiation therapy has demonstrated improved outcomes compared to chemotherapy alone (2). While recent advancements, such as immunotherapy and novel agents, have improved outcomes for some patients, the overall prognosis for patients with DPM remains poor with median survival under two years (1). Other approaches, such as hyperthermic intrathoracic chemotherapy (HITOC) treatment, have previously been investigated, but the feasibility and overall benefit remains controversial due to the lack of an established standardized protocol and studies limited by their observational, retrospective, or phase I/II designs (3).

In their article, Klotz *et al.* presented a retrospective study of patients with epithelioid DPM treated at a single center (4). From 2001 to 2018, the outcomes of 189 patients were reviewed following either chemotherapy, trimodal extrapleural pneumonectomy (EPP), or extended pleurectomy/decortication combined with HITOC and adjuvant chemotherapy (EPD/HITOC).

Patients in the EPD/HITOC cohort had a median overall survival of 38.1 months, significantly longer than the EPP and chemotherapy cohorts (24.0 and 15.5 months, respectively). In addition, patients undergoing EPD/HITOC had decreased perioperative morbidity when compared to patients undergoing EPP (36.2% *vs.* 18.0%). Although this study has limitations, it highlights the substantial increase in median overall survival for patients with DPM who receive treatment with EPD/HITOC relative to chemotherapy or EPP.

The benefits of performing lung-sparing techniques [pleurectomy/decortication (P/D) and extended P/D (EPD)] are well established and P/D has become the more commonly used procedure (5-7). In a study of 1,307 patients, Verma *et al.* found the incidences of patients undergoing surgery for newly diagnosed DPM were 79% and 21% for P/D and EPP, respectively (8). In addition, in a study of 4,852 patients, Magouliotis *et al.* showed P/D to have fewer complications and improved 30-day mortality and median overall survival when compared to EPP (9).

Klotz *et al.* reported 30-day mortalities for the EPD/HITOC and EPP cohorts of 0% and 2.9%, respectively. While the lower mortality of lung-sparing surgery is concordant with other studies, the morbidity and mortality rates for both surgical cohorts remain significantly lower than what is reported in existing literature (10). Furthermore, it is important to note that only the EPD/HITOC cohort was found to be significantly associated with improved overall survival relative to chemotherapy after multivariate analysis.

The results reported by Klotz *et al.* with adjuvant HITOC are promising, however, the overall benefit and safety of this therapy remains to be proven. The reported adverse effects from HITOC treatment varies greatly across studies, with the incidence of acute renal injury as high as 48% from cisplatin-based HITOC treatment alone (11). In addition, many studies have investigated the benefits of trimodal EPP and reported that many patients are unable to tolerate chemotherapy and/or radiation following surgery. Successful completion of trimodal EPP is generally achieved by only 45–50% of patients (12). Therefore, it is unexpected that 83% of the patients in the trimodal EPP cohort were able to complete both neoadjuvant chemotherapy and adjuvant radiation. This may reflect the use of stringent selection criteria for patients in this cohort, which would increase the proportion of patients who were able to tolerate this difficult regimen. Unfortunately, the criteria used to determine whether patients underwent trimodal EPP versus EPD/HITOC was not described and remains unclear, and the reported outcomes may be affected by potential selection bias. In addition, the total number of patients with DPM treated at this high-volume center during this 20-year period is unknown. This information would provide useful context to the number of patients who were selected for inclusion in each cohort. Ultimately, we are unable to discern the true benefit of HITOC in this study due to the absence of a control group and the significant differences in performance status and tumor stages between the patient populations.

Although interesting and important, the study by Klotz *et al.* did not provide the evidence necessary to change our current practices. Perhaps the most important lesson learned from this study is that it continues to highlight the increasing need for a multi-center, randomized controlled trial to determine the benefits of HITOC. Only then, through the combined efforts of our community, will we be able to make substantial progress in advancing the adjuvant therapy guidelines for treatment of DPM.

Acknowledgments

Funding: This work was partially supported by a National Cancer Institute Cancer Center Support Grant to Memorial Sloan Kettering Cancer Center (No. P30 CA008748).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-46/coif). In the last 3 years, MGZ has received consulting fees from Curis, Ikena, Takeda, GlaxoSmithKline, Aldeyra Therapeutics, and Novocure and honoraria from PER, Medscape, Research to Practice, Medical Learning Institute and OncLive. Memorial Sloan Kettering receives research funding from the Department of Defense, the National Institutes of Health, Precog, GlaxoSmithKline, Epizyme, Polaris, Sellas Life Sciences, Bristol Myers Squibb, Millenium/Takeda, Curis, and Atara for research conducted by MGZ. MGZ serves as Chair of the Board of Directors of the Mesothelioma Applied Research Foundation, uncompensated. PSA declares research funding from ATARA Biotherapeutics; Scientific Advisory Board Member and Consultant for ATARA Biotherapeutics, Bayer, Carisma Therapeutics, Imugene, ImmPactBio, Johnson & Johnson, Orion Pharma, Outpace Bio; Patents, royalties, and intellectual property on mesothelin-targeted CAR and other T-cell therapies, which have been licensed to ATARA Biotherapeutics, issued patent method for detection of cancer cells using virus, and pending patent applications on PD-1 dominant negative receptor, on a wireless pulse-oximetry device, and on an *ex vivo* malignant pleural effusion culture system. Memorial Sloan Kettering Cancer Center has licensed intellectual property related to mesothelin-targeted CARs and T-cell therapies to ATARA Biotherapeutics and has associated financial interests. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Branch K, Adusumilli PS, Zauderer MG. Some like it hot: the potential role of hyperthermic intrathoracic chemotherapy in the multimodality treatment of pleural mesothelioma. Transl Lung Cancer Res 2023;12(2):187-189. doi: 10.21037/tlcr-23-46