

Editorial

Hyperthermia: Has Its Time Come?

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In the March issue of the *Annals of Surgical Oncology* there were two articles that deal with the use of hyperthermia combined with chemotherapy in the management of difficult oncologic problems, malignant pleural mesothelioma, and peritoneal carcinomatosis.^{1,2} These articles raise several issues, some of which are unique to the diseases treated.

The article by van Ruth et al. describes the use of immediate adjuvant hyperthermic chemotherapy for treatment of malignant pleural mesothelioma.¹ Twenty patients were treated in this nonrandomized surgical series with either extrapleural pneumonectomy (EPP) (n = 8) or pleurectomy and decortication (P/D) (n = 12) followed by heated (40–41°C.) doxorubicin and cisplatin. Adjuvant radiotherapy was administered to the thoracotomy incision and tube thoracostomy scars (19 of 20 patients). Although no perioperative mortality was noted, a significant morbidity rate of 65% was seen with this approach, including 4 bronchopleural fistulae (20% of all patients treated) and 2 cases of diaphragmatic rupture. The median survival was only 11 months, and 14 of 20 patients developed recurrent disease after a median period of 8 months.

The use of intrapleural chemotherapy for treatment of mesothelioma seems almost intuitive. The tumor is often limited by the parietal pleura, and it would seem that instillation of a chemotherapeutic agent would be a perfect idea in limited disease or in an adjuvant fashion immediately following tumor resection to enhance local control. When patterns of failure are analyzed more than 67% of recurrences were in the ipsilateral hemithorax,³ indicating some type of adjuvant treatment is needed.

Unfortunately, the relatively disappointing experience reported here is not unique. Intrapleural chemotherapy has been shown to be feasible and favorable from a pharmacokinetic standpoint (high levels of pleural chemotherapy with tolerable systemic absorption).⁴ These authors reported 28 patients who were treated with intrapleural cisplatin and mitomycin following P/D. Although the overall survival in this series of primarily early-stage patients was 17 months, there were serious toxicities, and 16 of 20 patients experienced a locoregional relapse.⁵

The addition of hyperthermia to chemotherapy in the treatment of pleural mesothelioma is a logical extension of intrapleural adjuvant chemotherapy, especially in light of the disappointing results of chemotherapy alone. Hyperthermia has theoretical advantages for improving the efficacy of chemotherapy with its salutary effects on drug absorption and drug action by a number of mechanisms, including effects on DNA synthesis, alteration of cell membrane permeability, effects on cytoskeletal function, enhancement of apoptosis, and other reported effects.⁶ Carry et al. pioneered this approach in the treatment of pleural-based malignancy and reported a series of five patients (three with mesothelioma) treated with heated mitomycin-C or cisplatin following pleurectomy in (4 of 5). Two of the three mesothelioma patients were dead at 4 and 11 months, and both of those resected developed early ipsilateral pleural recurrence.⁷

The results of adjuvant intrapleural chemotherapy for mesothelioma with or without hyperthermia have been less than hoped for. What could explain the relatively poor clinical outcomes noted? The lack of significant benefit from both hyperthermic as well as normothermic treatments argues against “thermo-resistance”. One reason may be the choice of operative procedure performed in the majority of these studies, with most studies examining the use of adjuvant intrapleural chemotherapy after P/D rather than EPP. Although EPP is a more involved operative procedure, the complete removal of the ipsilateral diaphragm, pericardium, and lung lessen the

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chance that gross residual disease will be present and may allow for better local control with adjuvant local therapies. Another important consideration may be the underestimation of the complexity of the topography of the pleural space. The interfaces between the mediastinal organs and the spine and hilum, as well as the esophagus and hilar structures are areas where tumor often resides and may not be adequately exposed to the instilled chemotherapy or agent. Adjuvant radiotherapy may well be more effective as an adjuvant local control modality, as these areas can be "overlapped" by radiation fields. The application of complex conventional schemes for administration of adjuvant irradiation, as well as the use of newer modalities such as intensity-modulated radiotherapy, especially following EPP, may well be more efficacious.⁸

Another consideration could be a similar approach, but with the use of newer molecular or biologic agents in the pleural space instead of conventional chemotherapy. Gamma-interferon among other agents have been tried and have been found to be well tolerated, but the oncologic results have not been impressive.⁹ One theoretically promising approach is to use intrapleural agents that sensitize mesothelioma cells to subsequent radiation or chemotherapy. We have been working with alteration of expression of bcl-2 family proteins to achieve these goals and have noted that the expression of all pro-apoptotic proteins such as BAX and BAK are intact in mesothelioma cells, but that only one anti-apoptotic protein is expressed at high levels, BCL-XL. By using various means to down-regulate this protein in mesothelioma cells, we have been able to both induce apoptosis and to prime cells for subsequent conventional treatments such as chemotherapy.^{10,11}

It is likely that a combination of treatments, including effective systemic treatment, will be necessary to make a real impact on this disease. Certainly, local control is the first goal, and this goal has not been completely realized. However, we are beginning to see a change in the natural history of the disease in that with more effective local therapies more patients are dying from distant metastatic disease.¹² More effective systemic therapies are desperately needed such as the multitargeted folate inhibitor premetrexed, which has demonstrated high response rates in mesothelioma patients, along with aggressive local control measures, which will have an impact on what continues to be a clinically frustrating and deadly disease.¹³

Unlike mesothelioma, not all of the reports on the use of intraperitoneal hyperthermic chemotherapy (IPHC) for carcinomatosis have been quite so bleak. Although in general the survival of patients with carcinomatosis from

gastrointestinal malignancies is grim, there are reports of long-term survival after IPHC. The article by McQuellon et al. examines long-term survival and quality of life (QOL) after IPHC for peritoneal carcinomatosis.² These authors have previously reported on the perioperative QOL after IPHC in 64 patients, finding that while the operation resulted in significant decreases in several QOL subscales, a return to baseline was usually seen by 3 months after surgery.¹⁴ In this report, the authors studied and interviewed 17 (15.6%) of an initial cohort of 109 patients who underwent IPHC during the study period. These 17 patients were among the 29 patients (26.6%) who were believed to have survived at least 3 years. The tumor types of these patients were appendiceal, 10, colon, 5, and 1 each for ovary and primary peritoneal carcinomatosis. Six different instruments were used to assess QOL including the Functional Assessment of Cancer Therapy-Colon scale, the SF-36 tool, Center for Epidemiologic Studies Depression scale, Eastern Cooperative Oncology Group performance status rating scale, Life appreciation scale, and the Stem Cell Concerns Questionnaire. By all measures the vast majority of patients reported a very high QOL and none of the patients reported regretting having undergone the procedure. Approximately two thirds of the patients who were not retired had returned to work.

This article has three major considerations. The first is that despite an aggressive approach, most patients who survived had a very high QOL. Second, however, relatively few patients were available to be evaluated. The third and most important point is that there were, in fact, five patients with carcinomatosis from a colon primary who were alive (and functional) more than 3 years out from diagnosis. Unfortunately, from this report we do not know what the denominator was from which these five patients were derived. Nevertheless, when this information is combined with the recent report at the American Society of Clinical Oncology by Zoetmulder et al. of a randomized trial of IPHC, it could cause one to reassess the management of carcinomatosis.¹⁵ In this study 94 patients were randomized (of 104 patients entered) to palliative surgery, plus systemic chemotherapy or maximal tumor debulking, plus peritoneal perfusion, followed by systemic chemotherapy. Those in the treatment arm had a mean survival of 21 months compared with 10 months for those who did not; the 2-year survival rates were 43% and 16%, respectively ($P = .0145$). Only 15 of the patients in this study had an appendiceal primary. The most significant concern with this study, however, is that more than one variable was present (cytoreductive surgery vs. palliative surgery and perfusion vs. no perfusion). There are currently several centers

across the United States where the procedure of IPHC is currently used routinely for appendiceal tumors. Given the paucity of long-term survivors among patients with carcinomatosis from colon cancer, these data would suggest that we should consider conducting an appropriately designed and powered, multi-institutional randomized trial of this approach. Such a study could be conducted under the auspices of the American College of Surgeons Oncology Group or other appropriate cooperative group. The costs and short-term morbidity (and occasional mortality) of this procedure are not insignificant and must be weighed against any benefit and can only be done adequately in a randomized trial. Given the tens of thousands of patients each year who will develop carcinomatosis from colon cancer, there is a large enough patient population to conduct an appropriate trial and to come to a definitive answer regarding this therapeutic approach.

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