Intracavitary Therapeutics for Pleural Malignancies

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KEYWORDS

• Pleural malignancies • Intracavity therapeutics • Pleural space • Mesothelioma

KEY POINTS

- Intrapleural immunotherapies of pleural malignancy have shown promise in early phase clinical trials.
- Viral vector gene therapies can generate tumor-specific immune responses however translation to meaningful clinical benefit remains a challenge.
- Key advantages of local chemotherapy and immunotherapy for pleural malignancy include lower doses of administered agents and potentially lower toxicity.

INTRODUCTION

Pleural malignancies remain a serious therapeutic challenge, and are frequently refractory to standard treatment, including surgical resection, systemic chemotherapy, and immunotherapy. However, they have the advantage of occurring in an enclosed cavity readily accessible for examination, biopsy, and serial sampling. Many pleural tumors, especially malignant mesothelioma (MM), disrupt normal lung function and can lead to mortality because of local spread within the ipsilateral hemithorax. Novel therapeutics can be administered via intracavitary delivery to maximize the efficacy by targeting the site of involvement and potentially mitigating the adverse effects of systemic therapies. The easy accessibility of the pleural space lends itself well to repeated sampling and analysis to determine efficacy and toxicity of a given treatment paradigm. These factors support the rationale for delivery of novel therapeutics directly into the pleural space.

INTRAPLEURAL CHEMOTHERAPY

Intrapleural chemotherapy has been used on an experimental basis in human clinical trials to treat primary pleural malignancies and malignant pleural effusion (MPE).[1] Cisplatin is the most commonly used chemotherapeutic agent for intrapleural malignancy, most typically as an intraoperative surgical adjuvant, but several different agents and methods of administration have been evaluated.[1–3]

Intrapleural Hyperthermic Chemotherapy

Studies of intrapleural administration of hyperthermic chemotherapy for pleural malignancy have been carried out with several agents in several different primary cancers. The rationale is that intrapleural chemotherapy given in a normothermic fashion has not been proven successful in the treatment of primary or secondary pleural malignancies. The reason for this is that there are tight intracellular junctions between tumor cells in the pleural space that preclude entry of the chemotherapeutic agent deep into tumor deposits.[3] For this reason, the intracavitary chemotherapeutic is unable to induce tumor cell death beyond the superficial layer of tumor cells. Heating the chemotherapeutic liquid to a certain temperature is able to break down the intracellular junctions and allow for better penetration of chemotherapy and improved tumor cytotoxicity. This concept has been part of the standard of

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care regimen for primary peritoneal malignancies (eg, peritoneal mesothelioma) and known as heated intraperitoneal chemotherapy.[4] The incorporation of heated intraperitoneal chemotherapy into the standard treatment of peritoneal mesothelioma, primary peritoneal carcinoma, and ovarian carcinoma with peritoneal carcinomatosis lead to the exploration of similar treatment modalities in the pleural space. In addition to the use of hyperthermia to increase the local effects of chemotherapy in the pleural space, the administration of hypotonic chemotherapy solutions has also been studied, with similar goals of breaking down intracellular junctions. The safety of intrapleural administration of hyperthermic cisplatin after debulking surgery was demonstrated by Migliore and colleagues[5] in six patients with malignant pleural mesothelioma and non–small cell lung cancer (NSCLC), none of which reported treatment-related toxicity or mortality. Işık and colleagues[6] demonstrated significantly higher 1-year and overall survival in patients with MPEs who received intrapleural hyperthermic chemotherapy in comparison with two historical control groups, one receiving talc pleurodesis and the other undergoing pleurectomy/decortication using video-assisted thoracic surgery.

Ishibashi and colleagues[7] studied the safety and efficacy of pleurectomy/decortication with intraoperative perfusion of intrapleural hyperthermic cisplatin in a small case series of four patients contraindicated for extrapleural pneumonectomy. It should be noted that extrapleural pneumonectomy is not necessarily the standard of care procedure for malignant pleural mesothelioma. Extended pleurectomy/decortication, a lung-sparing procedure in which the parietal and visceral pleural are carefully and extensively dissected off the surface of the lung extending deep into the interlobar fissures and the hila of the lung, is considered an equivalent procedure for maximal cytoreduction of tumor in appropriately experienced surgical hands. Out of the four patients who underwent pleurectomy/decortication with intrapleural hyperthermic cisplatin perfusion, only one had recurrence of disease at 11 months, and the other three exhibited impressive progression free survivals of 23 to 41 months.

Yi and colleagues[8] studied the effects of intrapleural hyperthermic perfusion with cisplatin and normal saline specifically in patients with pleural dissemination of lung adenocarcinoma who had undergone curative resection. Those patients who were treated with hyperthermic chemotherapy demonstrated a significant increase in overall survival over those who had surgical intervention alone. Ba and colleagues[9] investigated whether less toxic agents could be used for intrapleural hyperthermic chemotherapy. When comparing patients with MPE who received intrapleural hyperthermic perfusion of either distilled water or physiologic saline solution, they demonstrated a nonsignificant difference in survival, and similar rates of complete and partial response between both groups.[9] Of note, the use of hypotonic solutions for intrapleural hyperthermic therapy may assist in breaking down intracellular junctions in pleural tumors improving overall efficacy.

Zhang and colleagues[10] posited that there may be a narrower cohort of patients who would most likely benefit from intrapleural hyperthermic cisplatin. Their findings showed that patients with NSCLC with mutations in the epidermal growth factor receptor (EGFR) who were treated with intrapleural hyperthermic cisplatin demonstrated significantly longer overall survival than those with wild-type (WT) EGFR undergoing the same treatment.[10] In confirmatory *in vitro* studies, they demonstrated higher cytotoxicity of hyperthermic cisplatin in EGFR mutant cell lines versus WT EGFR cell lines, and evidence of synergy of hyperthermia and cisplatin in EGFR mutant cell lines, but not in WT EGFR cell lines. In WT EGFR cell lines, no significant difference in colony formation was demonstrated between hyperthermic cisplatin and normothermic cisplatin.[10] These data suggest the possibility that the results from any evaluation of hyperthermic cisplatin may be confounded by the EGFR mutation status of the patients' tumors.

One of the largest clinical experiences with intrapleural hyperthermic chemotherapy was conducted at the Brigham and Women's Hospital by Sugarbaker's group with the implementation of heated intrapleural chemotherapy administered intraoperatively after maximal cytoreductive surgery for MM, using both intrapleural cisplatin and gemcitabine.[11] Most of these patients had extrapleural pneumonectomy for MM before hyperthermic chemotherapy. Some patients developed inflammatory and fibrotic lung injury with the use of this technique with lung-sparing procedures, such as extended pleurectomy decortication.[11]

Alternative Methods of Administering Intrapleural Cisplatin

Chao and colleagues[12] cited previous studies emphasizing the short half-life of chemotherapeutic agents in the intrapleural space to support investigation of an alternative method of administering cisplatin into the intrapleural space through drug-eluting pellets, rather than free drug. Chao and colleagues[12] demonstrated, *in vitro* and in a rabbit model, that high levels of cisplatin could be maintained for longer using drug-eluting