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Case Report

Hyperthermic Intra-Thoracic Chemotherapy (HITeC) for the management of recurrent ovarian cancer involving the pleural cavity

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Introduction

Approximately 22,000 new cases of ovarian cancer will be diagnosed in the United States in 2013 (American Cancer Society, 2013). Cytoreductive surgery with adjuvant taxane and platinum based chemotherapy has been established as the gold-standard treatment (Bristow et al., 2002). 70–80% of women will present with advanced disease at the time of diagnosis. Surgical debulking and adjuvant chemotherapy can result in a complete clinical remission in 50% of these patients. However, more than 70% of patients who respond to initial therapy will recur (Leitao and Chi, 2009).

Incorporation of intraperitoneal (IP) delivery to intravenous (IV) delivery of chemotherapy for the treatment of optimally debulked ovarian cancer has been well studied. IP plus IV chemotherapy has been shown to improve overall survival in multiple large randomized clinical trials when compared to systemic chemotherapy alone (Armstrong et al., 2006; Alberts et al., 1996; Markman et al., 2001). Hyperthermic intraperitoneal chemotherapy (HIPEC) adds the beneficial effects of hyperthermia by increasing drug permeability and metabolism of malignant cells. HIPEC has been described for treatment of recurrent ovarian cancer, however there is no general consensus regarding its efficacy (Chua et al., 2009; Fagotti et al., 2012).

Maximal cytoreductive effort has been expanded to include Video-Assisted Thoracic Surgery (VATS) for the evaluation of disease spread. VATS has been demonstrated to provide improved accuracy of surgical staging without increasing significant morbidity (Klar et al., 2012). Administering chemotherapy directly into the chest cavity in patients with pleural involvement of ovarian cancer has not, to our knowledge, been previously investigated. Hyperthermic Intra-Thoracic Chemotherapy (HITeC) after VATS debulking of disease is a novel technique that exploits the established advantages of cytoreduction, intracavitary chemotherapy, and hyperthermia. We present our experience with HITeC in pre-treated patients with recurrent disease in the pleural cavity. The primary objectives of this study were to assess the feasibility of and morbidity associated with HITeC. The secondary objectives were to evaluate the local control and disease recurrence.

Methods

We reviewed the patients with recurrent ovarian cancer involving the pleura treated with VATS and HITeC between July 2011 and June 2012. Each procedure was a joint effort between gynecologic oncologists and thoracic surgeons. HITeC was administered after all pleural disease was resected to less than 5 mm. The regimens included: Paclitaxel (135 mg/m^2) + Cisplatin (80 mg/m^2), Adriamycin (15 mg/m^2) + Cisplatin (80 mg/m^2), or Paclitaxel (175 mg/m^2) alone. Each agent was prepared in 3 l of saline. The choice of chemotherapy was dictated by the previous treatment response. VATS and tumor resection were performed by the thoracic surgeon. After the disease was resected, right angle chest tubes were inserted through the inferior VATS port sites. These chest tubes were then connected to the hyperthermia pump, and chemotherapy was perfused at an effluent temperature of 42 °C for 45 min (Fig. 1). When 2 agents were used, each drug was perfused sequentially, with 1 l of saline flushed in between. After the completion of the heated chemotherapy infusion, the pleural cavity was irrigated with 1–2 l of normal saline. The 2 right angle chest tubes were then removed. A straight chest tube was then placed through one of the incisions and left in place for post-operative management. Chest tubes were removed prior to discharge from the hospital. Post-operative management and discharge home were at the discretion of the treating physicians.

This retrospective case series was approved by the Institutional Review Board of University Hospitals Case Medical Center. Data for each patient was abstracted from inpatient and outpatient medical records. Intra-operative and post-operative variables, 30-day morbidity, local control, and disease recurrence were reported. The data was analyzed primarily with descriptive statistics. The results are reported as

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Table 1
Patient demographics and treatment history.

Patient	Age at time of HITeC (years)	Original FIGO stage	Tumor histology	# Prior chemotherapy regimens	# Prior chemotherapy cycles
1	44	IV	Undifferentiated with transitional cell, papillary serous, and clear cell components	1	6
2	61	IIIB	High grade papillary serous	3	18
3	67	IIIC	High grade papillary serous	1	8
4	67	IV	High grade papillary serous	7	30

medians with ranges since the distribution of the data was considered non-normal.

Results

Four patients with recurrent papillary serous ovarian cancer involving the pleura underwent VATS and HITeC. Two patients had one thoracic cavity treated and two had bilateral sequential procedures, with the second hemithorax treated 4 weeks after the first. A total of 6 thoracic cavities were thus treated.

Demographic and history details are listed in Table 1. Median age was 64 years (44–67). All patients had a GOG performance status of 0–1. They had a median of 2 (1–7) prior chemotherapy regimens and of 13 (6–30) prior chemotherapy cycles. All patients had recurrent disease in the pelvis, abdomen, and chest, and were being treated with systemic chemotherapy prior to VATS/HITeC. This was the first recurrence for two of the patients. One patient had completed the initial treatment with optimal surgical debulking followed by 6 cycles of IV/IP cisplatin and taxol. She was diagnosed with recurrence more than 1 year after completion of this initial therapy. The other patient being treated for the first recurrence presented initially with metastatic disease in the spine. She completed systemic chemotherapy and spine radiation 4 months prior to her recurrence. The other two patients had received more than one prior chemotherapy regimen.

Table 2 lists intra-operative details. No intra-operative complications were noted. Median length of hospital stay was 2 days (2–6). One patient required admission to the Surgical Intensive Care Unit post-operatively for acidosis, which resolved with supportive care. No other peri-operative complications were identified, and there were no re-admissions within the 30-day post-operative period. All the patients received systemic chemotherapy within 6 weeks of VATS/HITeC.

The mean pre-operative and post-operative CA-125 levels were 42.8 (19.3–71.5) and 15.5 (6.9–29.6). Long-term local control, as measured by imaging and CA-125, was observed in all patients. Disease free interval in the treated thoracic cavities ranged from 6 to 12 months. Two patients developed chest wall recurrences at VATS port sites – one patient 12 months after and the other patient 17 months after VATS/HITeC. Both were successfully surgically excised. Median followup at the time of this manuscript preparation was 13.5 months (range 9–18). 3 of the 4 patients received additional systemic chemotherapy after HITEC.

At the time of this writing, all patients who underwent VATS/HITeC are alive. Since VATS/HITeC, subjects have received a median of 3 (1–4) different systemic chemotherapy regimens with a median of 12 (8–20) cycles. Three patients are being treated for extra-thoracic recurrence with stable chest disease. The 4th patient progressed in her chest following 18 months of stable thoracic disease.

Discussion

The majority of women with advanced epithelial ovarian cancer will develop recurrent disease, and survival for 2 or more years following initial relapse is not uncommon. Secondary surgical cytoreduction can be considered for patients with recurrent ovarian carcinoma (Chi et al., 2006). Typically, this is limited to disease in the abdomen or pelvis, although some patients are candidates for resection of pleural disease. The concept of directly instilling chemotherapy into the chest cavity takes advantage of the established benefits of intraperitoneal chemotherapy in optimally debulked patients.

The treatment of recurrent ovarian cancer often includes a multimodality approach and a combination of chemotherapy, surgery, and radiation. Options can quickly become limited, especially in patients with platinum resistant disease or in those with multiple prior therapies. In this series of patients with recurrent ovarian cancer involving the pleural cavity, we demonstrate that the technique of VATS/HITeC is technically feasible and is well-tolerated without significant morbidity. Despite being heavily pre-treated, patients who underwent HITeC appeared to have excellent local control. One limitation of our study is the variety of chemotherapeutic regimens that were employed. A single regimen has not been identified as optimal, and choice of agent should be patient specific. Patients with platinum sensitive disease are candidates for the administration of platinum containing regimens directly into the thoracic cavity. Those that are platinum resistant may benefit from alternative agents. Future studies with larger numbers of patients divided into subgroups based on platinum response will be necessary. Other limitations include the small number of included patients and the retrospective nature of the analysis. HITeC is a promising new technique for the management of recurrent ovarian cancer and warrants further study.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.gynor.2014.05.001.

Conflict of interest statement

The authors report no conflicts of interest.

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