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Review

Long-term regional chemotherapy for patients with epithelial malignant peritoneal mesothelioma results in improved survival

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Abstract

Purpose: Malignant peritoneal mesothelioma (MPM) is a rare disease with about 300 new cases per year in the USA. Its natural history is described as local progression within the peritoneal space in the absence of liver metastases or systemic disease.
Methods: Cytoreductive surgery (CRS) is a series of peritonectomy procedures and visceral resections with a goal of complete removal of all visible disease from the abdomen and pelvis. Over 20 years, three protocols investigating increasing efficacy of additional chemotherapy treatments added to CRS have been initiated. Initially, hyperthermic perioperative chemotherapy (HIPEC) with doxorubicin and cisplatin was used in the operating room. Then, early postoperative intraperitoneal chemotherapy (EPIC) with paclitaxel was added for the first 5 days after CRS. The third protocol employed HIPEC, then EPIC, and then long-term intraperitoneal (IP) paclitaxel or IP pemetrexed plus intravenous (IV) cisplatin as a adjuvant normothermic intraperitoneal chemotherapy (NIPEC).
Result: The 5-year survival of 42 patients treated with CRS and HIPEC was 44%, for 58 patients treated with EPIC and HIPEC was 52% and 29 patients who received HIPEC, EPIC, and NIPEC was 75% ($p = 0.0374$). Prognostic variables of age, gender, treatment administered, peritoneal cancer index (PCI) and completeness of cytoreduction were significant by univariate analysis and treatments administered and completeness of cytoreduction significant by multivariate analysis.
Conclusions: Long-term regional chemotherapy was associated with improved survival in patients with MPM. In this rare disease, additional phase 2 investigations are suggested.

Keywords: Cytoreductive surgery; Hyperthermic perioperative chemotherapy (HIPEC); Early postoperative intraperitoneal chemotherapy (EPIC); Normothermic intraperitoneal chemotherapy (NIPEC); Cisplatin; Doxorubicin; Paclitaxel; Pemetrexed; Intraperitoneal port; Tenckhoff catheter

Introduction

Malignant peritoneal mesothelioma (MPM) is a disease that is confined to the peritoneal space throughout its natural history. On occasion, direct extension of the disease into the right hemidiaphragm and right pleural space is observed. As this characteristic clinical feature of MPM became more clearly understood, peritoneal surface oncology centers around the world recognized the possible benefits of combined surgical and regional chemotherapy treatment strategies. This was cytoreductive surgery in an attempt to remove all visible evidence of disease from the abdomen and pelvis combined with regional chemotherapy which was to maintain the surgical complete or near complete response. The early efforts of this multinational coalition to treat peritoneal mesothelioma should be recognized as the initial success of a global attack on this rare malignancy.[1–11] This literature includes a systematic review and a meta-analysis.[12,13] A multidisciplinary conference in 2006 at the National Institutes of Health sponsored by the National Organization for Rare Diseases concluded that

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CRS plus perioperative chemotherapy may be considered by the multidisciplinary team as an initial treatment plan for patients with MPM.[14] The Peritoneal Surface Oncology Group International (PSOGI) consensus conference in 2008 declared CRS and perioperative chemotherapy as the standard of care for this disease realizing that all patients are not candidates for such an aggressive treatment plan.[15] Currently, an international PSOGI registry exists to track the management of this disease around the world.[16]

Patients and methods

Clinical evaluation of patients preoperatively

All data were prospectively recorded and then retrospectively collected and statistically analyzed with the permission of MedStar Health Research Institute Office of Research Integrity. Without exception, every patient who had a diagnosis of MPM of the epithelial type was evaluated by consistent selection criteria for the 20-year study period. Patients with histologic types of cystic, papillary, biphasic, or sarcomatoid MPM were excluded. Patients with nuclear/nucleolar size of 1 (low grade disease) and 4 (poorly differentiated disease) were excluded.[17,18] Patients who had CT evidence that a complete or near complete cytoreduction would be impossible were excluded. This included patients with cancer nodules greater than 5 cm in the epigastric region or small bowel and small bowel mesentery characterized as class III changes.[19] There were no patients less than age 20 or greater than age 80. Elevated CA125 tumor marker was not an exclusion. Patient with systemic evidence of disease by preoperative CT of chest, abdomen, and pelvis were excluded. Also, patients with CT evidence of direct extension of disease through the right or left hemidiaphragm into the pleural space were excluded.

All patients in the study were assigned a prior surgical score as described by Jacquet and Sugarbaker.[20] Patients with a prior surgical score of 0 had biopsy only. Prior surgical score of 1 indicated an exploratory laparotomy of a single region. Prior surgical score of 2 indicated exploratory laparotomy with resections in 2–5 regions. Prior surgical score of 3 indicated an extensive prior cytoreduction with over 5 regions dissected.

Clinical evaluation of patients intraoperatively

The peritoneal cancer index (PCI) was determined prospectively at the time of abdominal exploration.[20] The PCI was an assessment of the distribution and extent of MPM in 13 abdominopelvic regions recorded by the surgeon at the time of abdominal exploration. Patients were grouped by PCI as less than 10, 10 through 30, or greater than 30.

A completeness of cytoreduction (CC) score was determined on all patients.[20] This score was determined by the surgeon at the completion of the cytoreductive surgical procedure. A CC score of 0 indicated no visible evidence of disease. A CC score of 1 indicated tumor nodules less than 2.5 mm in diameter without a confluence of disease at any site. A CC score of 2 indicated tumor nodules between 2.5 mm and 2.5 cm in the absence of a contiguous layer of disease at any anatomic site within the abdomen or pelvis. A CC score of 3 indicated tumor nodules greater than 2.5 cm in diameter or a confluence of disease layered out at any site within the abdomen or pelvis. Special attention to the CC score on visceral peritoneum (abdominal-pelvic regions 9–12) occurred because of the technical challenge of MPM resection on bowel mesentery.

The lymph node status was determined on all patients. At the time of cytoreductive surgery all enlarged lymph nodes and selected normal sized lymph nodes were resected and submitted for histopathologic examination. Routinely, at least 4 lymph nodes were resected and submitted for permanent histopathologic examination.[21,22]

Clinical evaluation of patients postoperatively

All patients had a standardized morbidity and mortality assessment performed postoperatively.[23] Adverse events were graded 1–5 in a standardized manner.

Strategies for surgical treatment in these groups of patients

All patients for the 20 years of this study underwent a cytoreductive surgical procedure, the goal of which was to remove all or nearly all visible disease. The overall strategy was to achieve a complete response through the use of surgery and then maintain that response through the use of regional chemotherapy. The surgery required a series of five parietal peritonectomy procedures used plus visceral resections as required to remove visible evidence of disease.[24,25] Systematic parietal peritonectomy as recommended by Baratti and colleagues was not practiced.[26] MPM layered out on the visceral peritoneal surface of small bowel, colon, or rectum usually required visceral resections.[27] A single surgeon (PHS) performed all of the cytoreductions throughout the 20 years of this clinical effort. All peritonectomy procedures and major visceral resections were prospectively recorded over the 20 years of this effort. Greater omentectomy, cholecystectomy and appendectomy were performed in all patients and were excluded from data analysis.

Perioperative chemotherapy for patients in group 1

In the first group of 42 patients, the cytoreductive surgery was followed by HIPEC. A curled peritoneal dialysis catheter (Covidien, Mansfield, MA) was used to infuse the chemotherapy solution and four outflow catheters to drain the chemotherapy solution to ensure recirculation through the heat pump. Two drugs were administered intraperitoneally in 1.5 L/m^2 of 1.5% dextrose peritoneal dialysis solution. The two drugs were doxorubicin at 15 mg/m^2 and