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REVIEW

Management of pseudomyxoma peritonei

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Abstract

Pseudomyxoma peritonei (PMP) is a rare disease. It refers to a progressive disease process within the peritoneum which originates from the appendix or ovaries and is characterised by the production of copious amounts of mucinous fluid resulting in a "jelly belly". If untreated the condition is fatal. The traditional approach to PMP is based on repeated surgical debulking procedures, often associated with intraperitoneal or systemic chemotherapy. The natural history of this disease has been drastically modified since the introduction of a new surgical approach defined as a peritonectomy procedure. This paper is to review the literature on this treatment strategy.

Key words: Pseudomyxoma peritonei; Peritonectomy; Hyperthermic intraperitoneal chemotherapy; Sugarbaker procedures

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INTRODUCTION

Pseudomyxoma peritonei (PMP) is a rare disease[1]. It refers to a progressive disease process within the peritoneum which originates from the appendix or ovaries and is characterised by the production of copious amounts of mucinous fluid resulting in a "jelly belly". If untreated the condition is fatal. With the progress of immunohistochemistry, PMP should be considered as a border line malignant disease because of its inevitable persistence and progression. PMP is an indolent disease, which is most prevalent in women aged between 50 and 70 years. The cases of ovarian origin outnumber those of appendiceal origin. A large proportion of ovarian tumours are secondary to appendiceal tumours. More women appear to suffer from this condition then men. However, the appendix is the primary source of most PMPs, which may then spread to other sites like the ovaries[2]. Clinically, although painless, deterioration of general health begins long before diagnosis. Acute presentation during advanced stage of the disease is common. The main complaints are abdominal pain and distension besides a host of non-specific symptoms. Inflammatory changes associated with peritoneal tumour implants can lead to fistula formation and adhesions, which in turn can cause intermittent or chronic partial bowel obstruction. Localized masses are frequently present in PMP of appendiceal origin. Surprisingly, signs and symptoms of cancer such as cachexia are rare. The characteristic PMP dissemination within the peritoneal cavity is defined by Sugarbaker[3] as a complete redistribution phenomenon, indicating a complete and sequential invasion of the peritoneal cavity with large tumor volume localization at predetermined anatomical sites and minimal invasion at other sites. The modalities of dissemination are strongly influenced by the histopathology of the primary tumor[4,5]. The traditional approach to PMP is based on repeated surgical debulking procedures, often associated with intraperitoneal or systemic chemotherapy. The natural history of this disease has been drastically modified since the introduction of a new surgical approach, proposed by Sugarbaker[3] who defines it as a peritonectomy procedure consisting of the complete removal of the tumor. Surgery is followed by local drug administration aimed at eliminating microscopic and/or minimal residual disease left in the abdominal cavity following surgical manipulations[6]. The additional effects of hyperthermia, through the use of a special pump, increase local tissue drug concentration and consequently antiblastic drug activity[7]. This technique has been defined as hyperthermic intraperitoneal chemotherapy (HIPEC). These methods can achieve satisfactory results in patients with PMP [8-12]. We here review the application of peritonectomy and hyperthermic intraperitoneal chemotherapy in the treatment of PMP.

PERITONECTOMY PROCEDURE

This fundamental technique requires the removal and stripping of all tumour tissues involving the parietal and visceral peritoneum. Small cancer deposits on the visceral peritoneum, especially on the surface of tubular structures, are individually electroevaporated. Large tumour nodules

in the small bowel must be resected and all visible tumors must be removed to maximize the benefits of peri-operative intraperitoneal chemotherapy. The surgical technique has been described in detail previously and is based on the Sugarbaker principles of peritonectomy[13,14] with a few modifications. In brief, peritonectomy procedures are performed on the basis of disease extension by the following steps: (1) greater omentectomy and right parietal peritonectomy with or without right colon resection, (2) pelvic peritonectomy with or without sigmoid colon resection as well as hysterectomy and bilateral salpingo-oophorectomy, (3) lesser omentectomy and dissection of the duodenal-hepatic ligament with or without antrectomy and cholecystectomy, (4) right upper quadrant peritonectomy and glissonian capsule resection, (5) left upper quadrant peritonectomy and left parietal peritonectomy with or without splenectomy, and (6) other intestinal resection and/or abdominal mass resection.

HIPEC

Intraperitoneal chemotherapy is only required to eradicate microscopic residual disease for its complete success. The pharmacokinetic advantage of the intraperitoneal route of drug administration is not compromised when used as a planned part of a surgical procedure. The high molecular weight of chemotherapy agents and their water solubility (hydrophilic) cause a prolonged retention in the peritoneal space. Also, use of selected drugs under hyperthermic conditions can increase cytotoxicity on the peritoneal surface but not systemic (bone marrow) toxicity. Hyperthermia can improve drug penetration into tumor tissue and optimize the dose intensity of chemotherapy on the abdominal and pelvic surfaces. The combined use of hyperthermia and intraperitoneal chemotherapy enhances the cytotoxicity of chemotherapeutic agents and increases tissue penetration by chemotherapy in cancerous tissue as compared to normal tissue. HIPEC is performed after completion of the anastomosis. The closed-abdomen technique is used for all patients. Two inflow catheters are inserted, one in the right subphrenic space, the other deep in the pelvic cavity. Two outflow catheters are inserted, one in the left subphrenic space, the other more superficially in the pelvic cavity. Six thermocouples are used to continuously monitor the inflow, outflow, and intraperitoneal cavity temperatures. Temporary abdominal skin closure is carried out following a tight continuous nylon stitch. The catheters are then connected to an extracorporeal perfusion circuit. The intraperitoneal temperature is maintained at 42.5℃ during the perfusion. Different chemotherapeutic agents are used depending on the tumor histological characteristics. Intraperitoneal chemotherapy regimens are as follows: (1) cisplatin (CDDP; 25 mg/m^2 per liter) and mitomycin C (MMC; 3.3 mg/m^2 per liter)[15] for pseudomyxoma peritonei and colorectal and gastric carcinomatosis, (2) CDDP (43 mg/L of perfusate) and doxorubicin (15.25 mg/L of perfusate)[16,17] for mesothelioma, ovarian carcinomatosis, and sarcomatosis. The perfusate is then instilled into the peritoneal cavity at a mean flow rate of 600 mL/min.

CURRENT STRATEGY FOR COMBINED TREATMENT

Peritonectomy in combination with hyperthermic intraperitoneal chemotherapy is devided into four major steps: electrosugery for tumour resection and peritonectomy, hyperthermic intraperitoneal chemotherapy, reconstruction, and early post-operative intraperitoneal chemotherapy. Dedicated instruments and specific surgical techniques are essential to achieve optimum results[18-22].

Intra-abdominal dissection is facilitated by electroevaporative surgery using a 0.3 cm ball-tipped diathermy. The electrosurgical generator is set at a very high voltage between 200 MW and 250 MW. A maximal pure cut that evaporates the tissues on contact is used for dissection, which minimizes blood loss from small vessels up to 1.5 mm in diameter. Larger vessels are electrocoagulated or ligated in continuity and divided. Heat damage can be reduced by a frequent intermittent saline irrigation at the site of dissection. Heat necrosis at the tumour's margin of resection could reduce the likelihood of cancer dissemination and local recurrence.

The selection of agents for peri-operative intraperitoneal chemotherapy is based on the drug's ability to produce a cytotoxic effect over a short time period and to show heat synergy. Mitomycin C, doxorubicin and cisplatin have a slow clearance from the peritoneal cavity. The effects of these agents are potentiated by hyperthermia to achieve a maximum cancer cell kill. Intraoperative intraperitoneal chemotherapy can absorb 75%-90% of mitomycin C and cisplatin within the first hour. Despite the greatly enhanced drug cytotoxicity because of high concentrations and heat synergy, the technique is effective only in treating small volume peritoneal disease. The use of early post-operative intraperitoneal chemotherapy may be restricted due to the co-morbidity state of patients.

EFFECTIVENESS OF PERITONECTOMY AND HIPEC

Several prospective studies have shown promising results when peritonectomy and HIPEC were used to treat peritoneal carcinomatosis[23-26]. Verwaal *et al*[27] demonstrated that this new treatment strategy can prolong the survival time of patients with carcinomatosis of colorectal origin. The institution that has a program to treat peritoneal carcinomatosis requires not only highly specialized human resources, but also complex technological facilities to perform the peritonectomy plus HIPEC[28], which minimizes treatment-related morbidity and mortality and maximizes results in terms of survival and quality of life. In this context, identification of risk factors for postoperative complications is of major concern. Small-bowel perforations and anastomotic leaks are the most common complications associated with a surgical procedure unusually involving a long operative time, numerous and complex resections, peritoneal stripping, and a heated intraperitoneal chemotherapy component. Bryant *et al*[29] showed that patients with PMP may benefit

from the Sugarbaker procedure and have an estimated 5-year and 10-year survival of approximately 50% and 18%, respectively. In contrast, the 2-year, 3-year and 10-year survival rates of patients after HIPEC are 90%, 60%-90%, and 60%-68%, respectively. The percentage of patients with no evidence of disease at the end of follow-up after the Sugarbaker procedure ranges from 41% to 82%. Similarly, the percentage of patients alive with disease at the end of follow-up after HIPEC ranges from 9% to 35%. Mortality of the disease ranges from 2% to 31% after the Sugarbaker procedure.

DISCUSSION

Pseudomyxoma peritonei is a rare disease which is characterized by a large amount of mucinous ascites with peritoneal and omental implants. A clear understanding of its natural history has been hampered by the fact that tumors of various sites under the heading of PMP have significantly different biologic behaviours leading to dilemma in diagnosis and management. PMP is referred to an extensive mucinous accumulation within the peritoneal cavity associated with a malignant cystic neoplasm arising commonly from the appendix or ovary. Other sites include pancreas, bile duct, colon, gall bladder and urachus. No controlled clinical studies have been conducted on PMP because of its rarity (1 case/million per year), and up until now, treatment has been directed at palliation and delaying the lethal outcome that seems inevitable for these patients. Peritonectomy and hyperthermic intraperitoneal chemotherapy can prolong the survival of these patients. Peritonectomy is a complex approach and leads to postoperative complications. This technique is also employed in the treatment of other malignancies, such as gastric, ovarian, and colon cancer and peritoneal mesothelioma, in which peritoneal dissemination remains an important cause of surgical treatment failure[30-31]. Understanding the treatment and mastery of surgical skills to manage the peritoneal surface spread of cancer can prolong the survival of selected patients. Combination of this treatment strategy with proper patient selection has reduced the mortality and morbidity. The success of peritonectomy and hyperthermic intraperitoneal chemotherapy depends on a long-term dedication to achieve the full potential of a curative outcome.

In conclusion, peritonectomy in combination with hyperthermic intraperitoneal chemotherapy is a feasable treatment for pseudomyxoma peritonei.

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