Clinical Determinants of Treatment Failures After Cytoreductive Surgery and Intraperitoneal Chemotherapy in Patients with Pseudomyxoma peritonei

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Summary: Background: Pseudomyxoma peritonei (PMP) is a disease that shows low biological aggressiveness but disseminates widely throughout the abdomen-pelvic cavity prior to diagnosis. Complete control of the disease process on peritoneal surfaces should translate into long term disease free survival in a majority of patients.

Methods: In a series of 120 patients with PMP, 46 were defined as treatment failures after cytoreductive surgery and regional chemotherapy, and these patients were evaluated.

Results: Clinical features that correlated significantly with treatment failure were tumor site (colon vs. appendix), histopathology grade (grade II vs. grade I), preoperative cancer volume, and completeness of cancer removal by cytoreductive surgery. For grade I histopathology, treatment failure was 10 times more common after incomplete vs. complete cytoreduction. For grade II histopathology treatment failure was 3 times more common with incomplete cytoreduction. Death from other causes was more common over the age of 65 and stroke was the most common diagnosis. The major causes of morbidity and mortality were related to progressive disease in the abdomen causing intestinal obstruction, and biliary obstruction.

Conclusions: When treatment failures were categorized as surgical (failure to cytoreduce) vs. medical (failure of chemotherapy to sustain a response) there were 27 surgical and 10 medical treatment failures. Improvements in the cytoreductive approach await the development of surgical technologies to increase the total clearing of cancer from the abdominal cavity, and chemotherapeutic treatments that will more adequately sustain control of small volume residual disease on peritoneal surfaces.

Klinische Determinanten bei Behandlungsversagen nach chirurgischer Tumorreduktion und intraperitonealer Chemotherapie in Patienten mit Pseudomyxoma peritonei


Introduction

Pseudomyxoma peritonei (PMP) is a low grade locally persistent cancer that arises from a mucinous epithelial tumor of the gastrointestinal tract or ovary. The clinical syndrome is characterized by a mucus producing primary tumor of low malignant potential that causes an extensive spread of mucinous tumor deposits throughout the abdomen and pelvis. It has a characteristic clinical syndrome and histopathology that has recently been described by Sugarbaker et al. (1) and by Zahn et al. (2).

Clinically, this disease is characterized by a "redistribution phenomenon" in that mucinous tumor deposits are present in large volume on the greater omentum, undersurface of right and left hemidiaphragm, abdominal gutters and pelvis, but are relatively absent from the peritoneal surfaces of the gastrointestinal tract. The primary tumor constitutes only a minute part of the mass of abdomino-pelvic cancer (3, 4). The hallmark of this disease is the "omential cake" (5).

Clinically, these patients may show long term survival independent of treatment (6, 7). This long term survival is related to the slowly progressive nature of the malignant process; also this malignancy rarely metastasizes to liver or to lymph nodes (1).

Despite the low-grade tumor biology and the absence of a metastatic process, this is a locally expansive disease process that has always caused death by a mass effect within the abdominal and pelvic cavity. Bowel function is lost because of extensive tumor accumulation within the pelvis, surrounding the antrum of the stomach, and compressing the ileocecal valve region. Intestinal obstruction eventually occurs. As the free passage of intestinal contents is lost, obstruction occurs and fistulas become increasingly common. These fistulas may occur spontaneously involving the gut or the bladder or may occur following attempts at surgical removal of tumor.
Recently, we have attempted to improve the results of treatment in this disease using a locally aggressive treatment strategy that involves multiple peritoneectomy procedures combined with intraperitoneal chemotherapy (8, 9). Compared to historical controls, this "cytoreductive approach" may result in improved long term survival (1, 10). However, even extensive abdominal and pelvic surgery plus aggressive regional chemotherapy is not universally successful in providing control. In order to critically evaluate the results of treatment with PMP of colorectal, appendi-

cal and ovarian origin, we reviewed our results of treatment in a group of 120 consecutive patients. Locally persistent tumor continued to be the major problem in all patients who recurred resulting in inoperable disease and eventually in death. Our conclusion was that resistance to mitomycin C and 5-FU chemotherapy (medical treatment failures), an inability to surgically clear the abdomen of tumor (surgical treatment failures) and overly aggressive treatment of aged patients were the 3 major factors that lead to undesirable treatment results. Improved results of the cytoreductive approach may occur if this disease is definitively treated early, at the time of initial diagnosis, is treated by more effective intraperitoneal chemotherapy, and is more adequately resected by further development of surgical procedures that would clear the abdomen of cancer.

Subjects and methods

This is an epidemiological (retrospective) review of 120 consecutive patients who underwent treatment for PMP. The purpose of the study was to assess the associations of prognostic factors such as pathologic grade, preoperative tumor volume, completeness of resection, site of disease, age, and sex in terms of treatment failure. All patients in this series had the primary tumor within the appendix (108), within the colon or rectum (8), or ovary (2). 2 patients could not have the primary site for their mucinous tumor determined. However, in this clinical situation a small primary appendiceal tumor obscured by a large volume of abdomino-pelvic tumor is thought to be the most likely origin of the disease process. Histologically, all of these patients had colloid material occupying more than 90% of the histologic field of view. The cytological grade of the tumor was used to categorize these patients into Grades I and II. Grade I PMP showed a single layer of cytologically bland cells with nuclear polarity preserved. These cells were dispersed within or were surrounded by the mucus accumulations with little or no fibrous stroma beneath the epithelium. The grade II PMP showed multiple layers of cells around the mucus deposits. The cells showed some atypia and loss of nuclear polarity. There was a more abundant fibrous stroma. Patients with mucinous adenocarcinoma or colonic adenocarcinoma whose cancer had disseminated to lymph nodes or to liver were not included in this study (1). This manuscript was limited to the patients with the most全面推进 and extensively described elsewhere (12).

After a thorough review of the charts of all PMP patients 46 patients with persistent or recurrent cancer not responsive to further therapy within the abdomen and pelvis were selected for analysis. Also all deaths from other causes within the follow-up period were collected. The sites of regrowth of disease, the mechanisms of disease recurrence and the causes of death of these patients are the subject of this study.

Preoperatively the volume of abdomino-pelvic malignancy was classified using a uniform scale. Patients were categorized by preoperative tumor as volume 1 (V1), volume 2 (V2), or volume 3 (V3). V1 patients had no disease or very small disease in the abdomen. All nodules were < 0.5 cm in diameter. V2 was char-

terized by an absence of disease conflunce at any site in the abdomen. Tumor nodules were from 0.5 to 5 cm in diameter. In V3 the intraperitoneal tumor showed either a conflunce of disease that matted bowel loops and peritoneal surfaces together or tumor nodules > 5 cm in diameter (13).

The adequacy of the cytoreductive surgery was measured in a standardized fashion. Patients were assessed as having residual disease R1, R2 or R3. In the R1 category tumor nodules < 0.25 cm in diameter remained at the completion of the cytoreductive surgery. In R2, tumor nodules between 0.25 and 2.5 cm remained behind. In neither R1 or R2 was there a conflunce of disease. In R3 the tumor nodules were 2.5 cm or greater in diameter and/or disease persisted as a conflunce on parietal or visceral peritoneal surfaces (1).

Patients were categorized after all data had been assimilated as surgical treatment failures, medical (chemotherapy) treatment failures, or surgical morbidity and mortality treatment failures. In this study, surgical treatment failure was defined as the inability to remove tumor at the time of cytoreductive surgery so that moderate or gross disease remained behind in the abdominal cavity. Patients with surgical treatment failure were recorded as having an R2 or R3 cytoreductive surgery. Those patients categorized as medical treatment failures had a cytoreduction that was thought to be adequate (R1) but who developed cancer recurrence. In other words, medical treatment failures included patients with recurrent PMP who had an R1 cytoreduction but chemotherapy failed to maintain a remission. Many of the patients with treatment failures have gone on to die of malignancy while others have slowly progressive cancer. Morbidity and mortality treatment failures included postoperative deaths and deaths from other causes within the period of follow-up after the cytoreductive treatment.

Statistical analyses

Chi square test was applied to evaluate the association of all study variables with end points (failure). Fisher exact test was also performed due to the limitation of sample size for certain variables (14). Mantel-Haenszel test was applied to adjust for variables confounding effect as each of them relates to study end point in a 3-way classification (15). Also, the results of the logistic analyses allowed an assessment of the relative risk for each variable as well as combination of variables (16). All test were declared significant at alpha = 0.05.

Results

This clinical study comprises 120 patients with a mean age of 50 years (range 27 to 76 years). There were 80 males and 40 females. All of these patients were taken to surgery for cytoreduction. In all patients there was an attempt to deliver intraperitoneal chemotherapy. 46 of these 120 patients fulfill the definition of treatment failure. In these 46 patients, 35 have died and 11 remain alive with progressive disease and no further treatment options. This is a treatment failure rate of 38% overall. However, mortality amongst the patients who have treatment failure is extremely high (35/46, 76%) and is expected to eventually reach 100%. The mean follow-up for the series was 24 months (range 1 to 112 months).

Clinical features of 46 treatment failures in 120 PMP patients

The clinical features that may impact on treatment failure in these 120 patients with PMP are shown in Table 1. Clinical features analyzed were tumor site, preoperative cancer volume, histopathology grade, completeness of cytoreduction, sex, and age. A proper examination of the association of prognostic variables with different study outcomes requires an examination for association among the variables themselves in order to eliminate any confounding effect. Grade was found to be significantly associated with the completeness of cytoreduction (p = 0.03) for the chi-square test association. The Fishers exact test confirmed a significant association between grade and the completeness of cytoreduction (p = 0.010).