Fatal Neutropenic Candidemia After Intraperitoneal Chemotherapy with Carboplatin in an ESRD Patient

AUTHORS:
Ozment ZM[a]; Sur MD[b,c], Labow DM[b,d]

CORRESPONDENCE AUTHOR:
Malini D. Sur, MD, FACS
980 Johnson Ferry Road, Suite 980
Atlanta, GA 30342
Phone: (404) 300-2140
E-mail: malini.sur@northside.com

AUTHOR AFFILIATIONS:
[a]Department of Surgery, Icahn School of Medicine at Mount Sinai, 5 East 98th Street, 14th Floor, New York, NY 10029
[b]Division of Surgical Oncology, Department of Surgery, Icahn School of Medicine at Mount Sinai, 19 E. 98th Street, 7th Floor, New York, NY 11102
[c]Department of Surgery, Mount Sinai Queens, 25-20 30th Ave, Rm A5-306, Long Island City, NY 11102
[c]Department of Surgery, Mount Sinai St Lukes and Mount Sinai West, 425 W 59th St, 7th Floor, New York, NY 10019

Background	Applications of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal surface malignancies have grown over the last three decades. Severe complications typically relate to infectious sequelae of extensive debulking and perioperative cardiopulmonary events. Although cytopenias represent a known complication of HIPEC, they are usually self-limiting and rarely fatal. The authors present the case of a patient with isolated peritoneal mesothelioma and end-stage renal disease (ESRD) with excellent performance status who developed fatal neutropenic candidemia following HIPEC.
Summary	A 57-year-old male with hypertension, coronary artery disease, and ESRD presented with isolated peritoneal mesothelioma. He underwent laparoscopic omentectomy and HIPEC with carboplatin. He initially did well but was readmitted with neutropenia that failed to respond to filgrastim. He developed neutropenic enterocolitis with candidemia and expired from fulminant sepsis.
Conclusion	There is a paucity of data regarding renal dosing of IP chemotherapy. Despite low systemic absorption of chemotherapeutic agents with HIPEC, this case suggests that toxicity may be magnified in ESRD patients. Avoidance of platinum-based agents, dose reduction, and increased dialysis should be considered in this population.
Keywords	HIPEC; ESRD; mesothelioma; neutropenia; candidemia; carboplatin

DISCLOSURE STATEMENT:
The authors have no conflicts of interest to disclose.

To Cite: Ozment ZM, Sur MD, Labow DM. Fatal Neutropenic Candidemia After Intraperitoneal Chemotherapy with Carboplatin in an ESRD Patient. *ACS Case Reviews in Surgery*. 2020;3(1):28–31.

Case Description

Neutropenia is a known complication of HIPEC; it is typically self-limited and not associated with increased mortality.[2] The authors report a case of fulminant neutropenic candidemia in patient with ERSD who underwent HIPEC for peritoneal mesothelioma.

A 57-year-old active male with coronary artery disease and hypertension presented with vague abdominal pain and distension. He was diagnosed with new-onset ESRD and began hemodialysis. Computed tomography revealed an isolated 7.6 cm omental mass, which was percutaneously biopsied and showed malignant peritoneal mesothelioma (MPM). Positron emission tomography confirmed localized disease. Of note, he had no prior verified asbestos exposure.

Diagnostic laparoscopy was performed to confirm resectability. The primary lesion was resected due to stigmata of biopsy-related hemorrhage. No other lesions were found on the peritoneal, diaphragmatic, mesenteric, and serosal surfaces. Final pathology confirmed epithelioid type MPM with negative peritoneal washings. His peritoneal cancer index (PCI) was 3, confirming stage 1 disease.

Following multidisciplinary review including cardiology and nephrology consultation, CRS-HIPEC was recommended given its well-established role as the treatment of choice for early stage MPM and the poor prognosis of untreated MPM. Dose reduction was considered unnecessary given the low systemic absorption of intraperitoneally-administered chemotherapy. The patient then underwent an uncomplicated laparoscopic completion omentectomy and HIPEC with carboplatin dosed at 1000 mg/m^2 for 90 minutes. Estimated blood loss was 25 cc. He was discharged home in stable condition on postoperative day two; at this time, he had a white blood cell (WBC) count of 7.4 x 103/uL and platelets of 117 x 103/uL.

On postoperative day seven, the patient was readmitted with progressive diarrhea, abdominal pain, and hematuria. Labs showed a WBC count of 0.94 x 103/uL and platelets of 83 x 103/uL. CT revealed nonspecific wall-thickening of the bladder and colon suggestive of cystitis and colitis. Clostridium difficile assay was negative. High dose filgrastim and empiric antibiotics were initiated, but the bone marrow failed to respond with a WBC count remaining in the range of 0.17-0.44 x 103/uL. Progressive thrombocytopenia and coagulopathy required transfusion support. On postoperative day 14, he developed sepsis and abdominal distension without peritonitis. Interval CT showed diffuse nonspecific enteritis and ileus. Antifungal coverage was added and he was transferred to the intensive care unit. He developed atrial fibrillation and cardiac arrest unresponsive to resuscitative efforts, and he expired on postoperative day 16. Final blood cultures revealed *Candida tropicalis*.

Discussion

MPM is a rare surface malignancy first described in 1908.[1] Incidence in the US is 1.94 and 0.41 per 100,000 for men and women, respectively.[4] Asbestos is a widely recognized risk factor, but only 33–50 percent of patients report prior exposure.[2] Clinical presentation is nonspecific, but common symptoms are abdominal pain, increased abdominal girth, anorexia, weight loss, and ascites.[3] Axial imaging may reveal a solid, heterogeneous, enhancing peritoneal mass with irregular margins.[5] The differential diagnosis includes carcinomatosis of gastrointestinal or gynecologic origin. The markers CEA-125 and serum mesothelin-related protein (SRMP) are not diagnostic but may be useful for monitoring tumor progression.[2] Pathologic diagnosis is made via percutaneous or laparoscopic biopsy.

Staging is based on disease burden (T), nodal involvement (N), and extraabdominal metastasis (M).[7] The T stage is determined by the PCI score, with scores of 1–10, 11–20, 21–30, and 31–39 corresponding to T stages of I, II, III, and IV, respectively. Stage I (T1N0M0), stage II (T2–3N0M0), and stage III (T4 or N1 or M1) disease correspond to five-year survival rates of 87 percent, 53 percent, and 29 percent, respectively.[7]

Although treatment strategies for MPM have not been evaluated by randomized trials, CRS-HIPEC emerged as a first-line therapy after a retrospective study of 18 patients showed a median survival (MS) of 22 months in those who responded to treatment compared to five months in non-responders.[8] A review of 401 MPM patients undergoing complete or near-complete cytoreduction had a three- and five-year survival of 60 percent and 47 percent, respectively.[14] Similarly, a meta-analysis of 1,047 MPM patients treated with CRS-HIPEC found three- and five-year survival rates of 59 percent and 42 percent, respectively.[14] Systemic chemotherapy is not supported.[10]

CRS-HIPEC is associated with low mortality (<5 percent) but significant morbidity (22–35 percent), including sepsis (2–15 percent) and neutropenia.[11,13] Although older studies reported up to 40 percent rate of neutropenia,[15,16] a more recent study of 81 patients had no reported neutropenia.[17] From a prospectively collected database, our institution has had no other occurrence of fatal neutropenia after cytoreductive surgery and HIPEC in over 417 cases in 361 patients, of whom 86 developed neutropenia.

There are no data specifically evaluating outcomes of IP chemotherapy in ESRD patients. For MPM, described IP regimens include combinations of pemetrexed, cisplatin, and gemcitabine with carboplatin proposed as an alternative to cisplatin due to improved tolerance.[2] Platinum-based agents are primarily eliminated through the kidney (90 to 95 percent), and dose reduction is recommended for when administered intravenously.[18] However, the depth of tissue penetration of IP chemotherapy is limited, averaging less than 1 mm. Thus, the rationale for dose reduction during IP administration is unclear. Nonetheless, this patient's outcome suggests that standard IP dosing of platinum-based agents may contribute to increased toxicity in ESRD patients.

Lessons Learned

Patients with ESRD may have an increased risk of mortality following HIPEC. Consideration should be given to avoidance of platinum agents, dose reduction, and increased dialysis postoperatively.

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