Heated Intraperitoneal Chemotherapy in Appendiceal Cancer Treatment

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Appendiceal cancer is rare and has been treated traditionally with repeated surgical debulking; however, cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC) is becoming the preferred treatment modality because of improved survival. Nurses are responsible for knowing how to care for patients who are receiving or have received this treatment and need to be prepared to provide education on oncofertility. This case study illustrates the nursing implications of pregnancy and childbirth following CRS with HIPEC.

Cytoreductive Surgery

Staging is challenging because several histologic subtypes exist, with different survival outcomes. The subtypes and five-year disease-free survival rates are malignant carcinoid (93%), goblet cell carcinoid (81%), mucinous adenocarcinoma (58%), colonic-type adenocarcinoma (55%), and signet ring cell type (27%) (Turaga, Papas, & Gamblin, 2012). Tumors with mucinous histology are the most prevalent and are further categorized into low grade (pseudomyxoma peritonei syndrome [PMP] is the most common) and high grade. Low-grade tumors do not require systemic chemotherapy but are most often treated with CRS and HIPEC. High-grade tumors, depending on histology, often require systemic chemotherapy before and after CRS and HIPEC; in the authors' practice, that process often is described to patients as a "sandwich approach."

Appendiceal Cancer

Tumors of the appendix are relatively rare and comprise approximately 1% of all colorectal cancer cases in the United States, or about 1,500 cases per year (Sugarbaker, 2006). The majority of those tumors are discovered incidentally in appendectomy specimens, after a computed tomography (CT) scan, or during surgical exploration for another diagnosis (Benedix et al., 2010; McGory, Maggard, Kang, O'Connell, & Ko, 2005). Patients most often present with appendicitis or increased abdominal girth; however, presentation can vary by gender, with men presenting with an enlarging hernia (inguinal or umbilical) and women presenting with an ovarian mass (Sugarbaker, 2009). The clinical presentation and progression of disease depends mainly on the histology of the tumor.
Appendiceal tumors are treated with surgery and are ideally referred to a peritoneal surface malignancy program for CRS with HIPEC. The United States only has approximately 80 peritoneal surface malignancy programs to date; therefore, patients frequently self-refer to those programs after finding them through Internet searches. The spread of appendiceal tumors is influenced by three factors: the clockwise flow of peritoneal fluid, attraction of tumor cells to the omentum for nourishment, and the force of gravity that leads to tumor accumulation in the pelvis (Sugarbaker, 2009). The purpose of CRS is to surgically remove all visible evidence of the tumor throughout the peritoneum. That is achieved through varying combinations of visceral resections and peripectonectionomy procedures (Sugarbaker, 2009).

Surgery typically ranges from approximately 3–16 hours and is dependent on the location of the disease, the volume of the tumor, and the extent of resection. The Peritoneal Cancer Index (PCI) (Jacquet & Sugarbaker, 1996), which ranges from 1–39, is calculated at the time of surgery and is useful in determining prognosis. The PCI is based on the location and extent of disease in the abdomen or pelvis (13 areas are scored from 0–3) and is evaluated pre- and postresection (see Figure 2). In mucinous appendiceal neoplasms with peritoneal dissemination, the PCI score is indicative of the stage of disease (less than 6 = stage I, 6–7 = stage II, 8–10 = stage III, and 11 or higher = stage IV).

The Completeness of Cytoreduction (CC) score, which ranges from 0–3, is evaluated at the conclusion of CRS and estimates the extent of residual disease (Portilla, Sugarbaker, & Chang, 1999). A complete cytoreduction is defined by residual tumor size of 0.25 cm or smaller (CC 0 or 1); a tumor size larger than 0.25 cm indicates an incomplete cytoreduction (CC 2 or 3). Mucinous appendiceal neoplasms are believed to be well penetrated by chemotherapy, and the hard, fibrotic, nonmucinous intestinal-type cancer nodules are poorly penetrated by chemotherapy. Patients with low-grade tumors who experience a complete cytoreduction have as high as 80% survival at 20 years; that decreases to approximately 45% with high-grade tumors (Sugarbaker, 2009). All patients with an incomplete cytoreduction have died within 10 years (Sugarbaker, 2009). The tumor markers carcinoembryonic antigen, cancer antigen 125, and carbohydrate antigen 19-9 also are used to monitor the presence of disease and are drawn prior to surgery and at follow-up visits.

Heated Intraperitoneal Chemotherapy

HIPEC refers to the intraoperative delivery of heated chemotherapy into the peritoneal cavity after CRS. The purpose of this treatment is to eradicate micrometastatic disease that remains after complete cytoreduction by directly bathing the peritoneal cavity with chemotherapeutic agents. Hyperthermia by itself has antitumor effects, as the damage from heat is greater to malignant cells than to normal cells. Heat causes greater uptake and penetration of chemotherapeutic agents in malignant cells by increasing membrane permeability and improving membrane transport. Heat also can alter drug pharmacokinetics and excretion, as well as cellular metabolism, which may increase the cytotoxicity of some chemotherapeutic agents (Sticca & Dach, 2003; Sugarbaker, Mora, Carmignani, Stuart, & Yoo, 2005).

At the conclusion of CRS, two intraperitoneal catheters and two temperature probes are placed by the surgeon. A perfusion machine heats the chemotherapy to 40.5°C–42°C and continuously circulates the solution via the catheters throughout the peritoneal cavity. The average circulation time is 90–120 minutes, and then the chemotherapy agent is allowed to drain in the operating room while the patient is still under anesthesia.

After the procedure, patients are moved to intensive care overnight or are admitted directly to a surgical oncology unit, depending on the patient’s acuity and monitoring needs. In addition to maintaining safe handling of body fluids for 48 hours postprocedure, HIPEC recipients are cared for similarly to other patients who are postabdominal surgery. Patients should be carefully monitored for pain, bleeding, and infection in the postoperative period. The average length of admission at the authors’ institution is 7–12 days.

After discharge, HIPEC recipients with low-grade tumors are followed either with serial CT scans or peritoneal metastasis protocol magnetic resonance imaging (preferred because of the elimination of radiation exposure) every six months for three years, then annually for two years.
Additional years. Patients also receive a health assessment and testing of carcinoembryonic antigen, cancer antigen 125, and carbohydrate antigen 19-9 tumor markers every three months for the first three years, then annually for two additional years. If patients have no evidence of disease at five years post-treatment, they are encouraged to continue receiving annual physical examinations from their primary care physicians.

Fertility After Heated Intraperitoneal Chemotherapy

When women decide to conserve their reproductive organs during CRS and then receive HIPEC, their ovaries are bathed in chemotherapy. Although IV chemotherapy is well known for its teratogenic effects on germ cells, little is known about the risk that type of chemotherapy exposure introduces to a woman’s fertility. An international survey looking at the incidence of pregnancies after HIPEC described seven reported pregnancies worldwide (Ortega-Deballon et al., 2011). All reported pregnancies occurred in women with PMP or mesothelioma. Women ranged in age from 18–35 years at the time of their pregnancies. The interval between HIPEC and pregnancy ranged from 14–80 months. All newborns were healthy except for one with a congenital diaphragmatic hernia (Ortega-Deballon et al., 2011).

Case Study

Diagnosis and Treatment

Mrs. P, a 36-year-old woman, had been experiencing right lower quadrant pain since delivering her third child in February 2008. When she presented in September 2008 with worsening pain, a CT scan revealed the presence of a right lower quadrant tubular structure, and she underwent a laparoscopic appendectomy. Pathology indicated a low-grade appendiceal mucinous neoplasm with evidence of extravasated mucin and neoplastic epithelium involving the periappendiceal tissue with a positive margin.

Because the preoperative CT scan did not reveal peritoneal dissemination and all three tumor markers were normal, Mrs. P was given the option of watchful waiting with serial CT scans (primary recommendation) or CRS with HIPEC. Concerned about the positive margin and desiring to be more aggressive, Mrs. P chose treatment, which she received in December 2008. Ovary preservation was discussed, and Mrs. P opted to keep her ovaries for hormonal rather than fertility factors. Her PCI was 2 at the beginning and 0 at the end of the case. Her CC score was 0, indicating she had a complete cytoreduction. The duration of the surgery was approximately 3.5 hours and included exploratory laparotomy, umbilicectomy, partial parietal peritonectomy with excision of the falci-form ligament, greater omentectomy, and excision of tumor from the right paracolic gutter and cecum. At the conclusion of CRS, the surgeon placed the catheters and temperature probes (see Figure 3). Mitomycin C was heated to 42°C and was continuously perfused into her peritoneal cavity for 90 minutes. The chemotherapy was drained, the peritoneal cavity was flushed, and the catheters were removed.

Mrs. P was admitted to the intensive care unit in fair condition, extubated overnight, and transferred to the inpatient oncology unit with a fentanyl patient-controlled analgesia. Surgical pathology revealed no tumor, only a solitary, small deposit of parietal peritoneal extracellular mucin, indicating a good prognosis (see Figure 4). Mrs. P was...
discharged home on postoperative day 10. She was voiding without difficulty, ambulating, and tolerating her diet and analgesics by mouth. No additional chemotherapy was recommended.

Pregnancy and Childbirth

Mrs. P had difficulty conceiving with her earlier pregnancies because of polycystic ovaries. She received gonadotropins for her first pregnancy at age 32 and clomiphene to conceive her second child at age 35. After her diagnosis and treatment at age 36, Mrs. P did not expect to have more children. Discussions about contraception, at that time, were not a regular component of patient education.

After recovering from treatment, Mrs. P began taking hormone replacement therapy for menopausal symptoms and began having menstrual cycles. Her six-month follow-up physical, CT scan, and tumor markers were within normal limits. Shortly after her second follow-up appointment, approximately one year after treatment, she discovered she was pregnant.

Mrs. P’s pregnancy was the first time in the 10 years of the institution’s HIPEC program that a spontaneous pregnancy had occurred. A literature search at the time found only one reported case of pregnancy following HIPEC; however, that case involved a younger woman with a different diagnosis who had received cisplatin rather than mitomycin (Ortega-Deballon et al., 2011). Because of the paucity of literature, the healthcare team had limited direction to offer Mrs. P. The recommendations were to discuss the situation with her obstetrician and consult a genetics counselor. Mrs. P was followed by her obstetrician for advanced maternal age, but no other special precautions were taken. The genetics counselor admitted having never before advised a woman with this unique history. The counselor noted a lack of data regarding pregnancy following HIPEC. Mrs. P was recommended to have routine prenatal follow-up appointments to monitor fetal growth.

Mrs. P’s pregnancy was uneventful and she had a spontaneous vaginal delivery. A healthy baby boy was born at 37 weeks gestation. Five hours postbirth, the baby was moved to the neonatal intensive care unit after he became febrile because of a rare bacterial infection, *Streptococcus bovis*. *S. bovis* is uncommon in neonates, and little is known about the predisposing conditions in this young population (Gerber, Glas, Frank, & Shah, 2006). However, an association exists between *S. bovis* and colorectal tumors in adults (Abdulamir, Hafidh, & Abu Bakar, 2011; Gold, Bayar, & Salem, 2004). Mrs. P was never formally tested for *S. bovis*. The baby was treated with antibiotics and was discharged a week after his birth. The neonatologist reported having never cared for a baby post-HIPEC and that he had not seen an *S. bovis* infection in his 34 years of working in the neonatal intensive care unit.

Nursing Implications

For most patients receiving HIPEC, both ovaries are removed during CRS because of their proximity to the appendix and the high risk of seeding to that site (Evers & Verwaal, 2011; Sugarbaker, 2009). In the rare situation that a woman decides to preserve her ovaries, the healthcare team must fully educate the patient on the need to delay pregnancy post-treatment. For patients receiving IV chemotherapy, the recommendation in the authors’ practice is to delay pregnancy for at least two years. Most oncologists recommend waiting two to five years after cancer treatment before attempting to conceive, as most cancer recurrences happen during that time (Fertile Hope, 2013). The optimal length of time is unknown for HIPEC recipients, so the recommendation is two years for them as well (Ortega-Deballon et al., 2011). Oncology nurses should ensure that fertility issues are discussed on initial consultation so appropriate referrals can be made. This topic can be sensitive, with many implications; therefore, the healthcare team must be conscious of patients’ religious, cultural, and personal beliefs when having this discussion.

Conclusions

As more centers in the United States begin performing HIPEC, the number of patients receiving this treatment for appendiceal cancer and other peritoneal malignancies will continue to rise. Oncology nurses need to become familiar with the short- and long-term implications of this treatment modality so they can provide education and evidence-based care. Because appendiceal cancers are uncommon, oncology nurses also must provide patients with psychosocial support and resource information (see Figure 5). The Web site www.pmppals.org in particular is the most informative, internationally patient-driven site, developed and maintained by a patient with appendiceal cancer.

Although the case study describes an uncommon situation, the topic of oncofertility is relevant to many patients with cancer, whether or not they are expecting to have children. Oncology nurses should educate patients about fertility preservation before treatment, as well as postponing pregnancy for a specified period of time after treatment.

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References


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