According to the American Cancer Society (2008), an estimated 21,650 new cases of ovarian cancer will be diagnosed in 2008 and 15,520 women will die from the disease. Because of its subtle presenting symptoms, ovarian cancer often is diagnosed at an advanced stage. Abdominal bloating or discomfort; pelvic pain; dyspepsia; nausea; changes in bowel or bladder function including constipation, diarrhea, urge, urinary incontinence, and gas; shortness of breath; abnormal vaginal bleeding; unexplained weight loss or gain; and unusual fatigue (O’Rourke & Mahon, 2003) are among the often vague symptoms that may indicate ovarian neoplasia. At diagnosis, about 68% of women have advanced stage cancer that has already metastasized (National Cancer Institute, 2004).

Ovarian cancer received little public attention until 1989 when 42-year-old actress Gilda Radner died of the disease. Her death created public awareness and, because of her family history, stirred interest in the genetic susceptibility of ovarian cancer (Gilda’s Club, 2007). A hereditary breast-ovarian cancer syndrome often caused by mutations in BRCA1 or BRCA2 genes includes a personal or family history of ovarian cancer diagnosed at any age and having two or more close relatives on the same side (maternal or paternal) with ovarian or breast cancer, particularly if they were diagnosed before age 50 (National Comprehensive Cancer Network, 2005). In families with inherited mutations, the lifetime risk of ovarian cancer can be as high as 40%–65%, whereas the lifetime risk among the general population is 1.8% (King, Marks, & Handell, 2003). Most ovarian cancers, however, are not associated with this syndrome. In about 10% of ovarian cancer cases, the woman is a carrier of genetic mutations in the BRCA1 and BRCA2 genes (Claus, Schildkraut, Thompson, & Risch, 1996).
Tomacruz, Armstrong, Trimble, & Montz, 2002). The median overall survival for optimally debulked ovarian adenocarcinoma followed by IV platinum-based and paclitaxel chemotherapy is about 50 months (Rothenberg et al., 2005).

Ovarian cancer has known chemosensitivity (Martin, 2007). The standard treatment for ovarian cancer is a combination of a platinum analog (either cisplatin or carboplatin) along with paclitaxel administered over six cycles (McGuire et al., 1996; Ozols et al., 2003). In suboptimally debulked (residual tumor > 1.0 cm) ovarian cancer, IV platinum-based and paclitaxel chemotherapy offer overall median survival of 37 months (Cannistra, 2006). Despite good response rates to IV chemotherapy, patients’ disease often relapses. Overall survival rates for patients with ovarian cancer are 75% at one year and 45% at five years. Women who are younger than 65 at diagnosis are twice as likely to survive than women who are 65 or older (American Cancer Society, 2008).

**Pattern of Ovarian Cancer Progression**

The peritoneum consists of two layers; the parietal layer covers the inner surface of the abdomen, diaphragm, and pelvic wall, and the visceral layer is wrapped around the gastrointestinal tract, liver, and spleen and forms the omentum (Fujiwara, Armstrong, Morgan, & Markman, 2007). The space between the parietal and visceral layers is the peritoneal cavity (Runyon & Such, 2002). Within that cavity, about 50 ml of sterile, peritoneal fluid allows the two layers to slide freely over each other. The pattern of peritoneal fluid distribution and circulation is a factor in promoting ovarian cancer seeding throughout the peritoneum. Peritoneal fluid circulates from the top of the to the bottom and back to the top of the abdominal cavity (Raptopoulos & Gourtsoyiannis, 2001). Intraperitoneal (IP) circulation is influenced by negative pressure under the diaphragm during exhalation, gravity, and bowel peristalsis (Raptopoulos & Gourtsoyiannis). The constant circulation and pooling of ascites in peritoneal recesses facilitate malignant seeding (Meyers, Oliphant, Berne, & Feldberg, 1987). Ovarian cancer also spreads in the lymphatic and venous systems and invades through the diaphragm (Jaaback & Johnson, 2006).

**Intraperitoneal Chemotherapy in Ovarian Cancer**

**Pharmacologic Advantages**

Higher doses of chemotherapy can be delivered directly into the peritoneum to the tumor bed than can be given safely via IV (Cannistra, 2006; Gasper, Kelsen, Alcock, & Lewis, 1983; DeGregorio, Lum, Holleran, Wilbur, & Sikic, 1986; Francis et al., 1995) (see Figure 1). IP cisplatin and carboplatin can be given at 10- to 20-fold higher concentrations than IV (Howell et al., 1982) and more than 1,000-fold for paclitaxel (Markman et al., 1992).

Because ovarian cancer metastasizes by lymphatic, venous, and direct invasion through the diaphragm, effective amounts of drug must be given systemically. Within a treatment cycle, IP chemotherapy usually is given after IV chemotherapy, but it is not given as a single treatment modality (Alberts et al., 1996; Armstrong et al., 2006; Cannistra, 2006; Jaaback & Johnson, 2006; Markman et al., 2001). Ideal chemotherapy agents for IP administration are very effective systemically against ovarian cancer, have high IP concentrations, penetrate deep into the tumor, clear slowly from the peritoneal cavity, and have rapid drug clearance from the plasma (Dedrick, Myers, Bungay, & DeVita, 1978; Fujiwara et al., 2007). Safe administration of IP chemotherapy depends on the chemotherapy being rendered into nontoxic metabolites during first pass liver metabolism and should have rapid and extensive hepatic metabolism (Almadrones, 2007; Dedrick et al.; Schneider, 1994). As a result, agents such as cyclophosphamide and irinotecan would not be used intraperitoneally because they are transformed into active metabolites after hepatic activation (Makhija, Sabbatini, & Barakat, 1999). Chemotherapy agents commonly used for IP infusion in ovarian cancer are cisplatinum and paclitaxel (Armstrong et al.); however, carboplatinum, doxorubicin, mitomycin-C, and methotrexate are among more than 10 agents that can be given for treatment of peritoneal cancers (Marin, Oleszewski, & Muehlbauer, 2007).

**Theoretical Model**

The delivery of chemotherapeutic agents directly into the peritoneum has been practiced since the 1950s when nitrogen mustard was used for malignant ascites (Weisberger, Levine, & Storaasli, 1955). Dedrick et al. (1978) are credited with using IP chemotherapy in ovarian cancer treatment. Their work involved the pharmacokinetics of drug delivery in the IP space in animal and human models. Early studies in the 1970s with IP infusions of cytotoxic agents for ovarian cancer, or “belly baths,” were conducted and demonstrated that IP drug delivery allowed for peritoneal exposure to higher cytotoxic drug concentrations than were achieved with systemic therapy (Jones et al., 1978).

In the past, cytotoxic agents were drained using mild suction or gravity after a specified dwell time, usually several hours (Sw-
In the current setting of ovarian cancer treatment, drainage is no longer part of IP administration of chemotherapy because prolonged drug contact with the tumor provides a therapeutic advantage and the fraction of drug that is absorbed systematically is believed to be of benefit (Ahayki, Hopkins, & Le, 2006; Cannistra, 2006). IP chemotherapy is diluted in two liters or more of solution to promote maximum distribution and then absorbed and excreted renally (Fleschner, 2005). IP chemotherapy gradually fell out of use in the 1980s for several reasons, including catheter complications, inadequate fluid volumes in the peritoneum, attempts to treat tumors that were too large, and clinical trials that yielded unconvincing data (Armstrong et al., 2006; Swenson & Erikson).

### Selection Criteria

Drugs given via the IP route only penetrate a few millimeters beneath the tumor surface (Los, Mutsaers, Lengley, Baldew, & McVie, 1990; Ozols et al., 1979); therefore, patients with ovarian cancer who have optimal surgical debulking or a small-volume residual tumor less than 1 cm in diameter are most likely to benefit from IP chemotherapy (Cannistra, 2006). About 20%–30% of all women with ovarian cancer are appropriate candidates for IP chemotherapy (Armstrong et al., 2006).

The presence and amount of adhesions are important in IP drug delivery. Extensive adhesions limit chemotherapy distribution and harbor cancer cells in scar tissue, preventing contact with IP drug solution (Sugarbaker, 2005). Women experiencing pain during IP infusion may be accumulating the fluid in small-volume pockets of adhesions (Markman & Walker, 2006).

### Contraindications and Considerations

For IP chemotherapy to be successful, no abdominal infection should be present because it would contraindicate abdominal port placement (see Figure 2). Preexisting conditions, including symptomatic peripheral neuropathy, malnutrition, adhesive disease in the abdomen, gastrointestinal dysfunction, hypovolemia, massive ascites, and abnormal baseline renal function, would contraindicate IP chemotherapy (Alberts et al., 2006; Marin et al., 2007). Disease outside of the peritoneal cavity and dense adhesions or fluid loculations within the peritoneal cavity also are contraindications to IP chemotherapy administration (Alberts et al., 2006). If abdominal ascites is present, it must be drained to provide optimal circulation and distribution of chemotherapy (National Cancer Institute, 2006). With the removal of ascites, fluid balance must be maintained. If the volume of ascites removed is greater than the volume of the IP chemotherapy, the deficit must be replaced parenterally over the next 24 hours. For example, if three liters of ascites are removed, followed by two liters of IP chemotherapy, then an additional liter of IV fluid would be given (National Cancer Institute, 2006).

The delivery of IP chemotherapy may be influenced by surgical considerations, including surgery involving vaginal entry and colonic resection. If initial debulking surgery involved vaginal entry, complete surgical closure and healing are necessary or chemotherapy may leak from the vagina (Markman & Walker, 2006). Women who had left colon or rectosigmoid resection at the time of initial surgery were less likely to receive an initial dose or all planned doses of IP chemotherapy (Armstrong et al., 2006; Walker et al., 2006). Further study is needed to determine whether additional time is needed for wound healing after rectosigmoid colon resection prior to starting IP chemotherapy (Walker et al.).

### Phase III Clinical Trial Results

Compelling evidence in support of combination IV and IP chemotherapy in small-volume residual, advanced epithelial ovarian cancer has been demonstrated in three multicenter, randomized phase III clinical trials (Alberts et al., 1996; Armstrong et al., 2006; Markman et al., 2001). Meta-analysis of eight relevant phase III trials involving IP chemotherapy in comparison to standard IV chemotherapy established the benefit of IP chemotherapy for increasing overall survival as well as progression-free survival (Jaaback & Johnson, 2006).

In the Gynecologic Oncology Group 172 trial (Armstrong et al., 2006), median duration of overall survival in the IV therapy group was 49.7 months versus 65.6 months for women in the IP arm, the longest survival reported to date from a randomized trial in ad-
vanced ovarian cancer (National Cancer Institute, 2006). Although optimal drug combinations and dosing schedules have not been determined, survival advantage seems to occur with IP cisplatin delivered at 100 mg/m² (National Cancer Institute, 2006). In 2006, the National Cancer Institute issued a clinical announcement recommending that IV and IP chemotherapy be used as routine treatment for advanced epithelial ovarian cancer that is optimally debulked and has small-volume residual tumor nodules (none larger than 1 cm in diameter). Prior to that announcement, the standard treatment was a platinum and taxane IV combination every three weeks for six courses (National Cancer Institute, 2006).

**Toxicities and Complications and Their Effect on Treatment**

Markman and Walker (2006) cited three reasons for discontinuing IP chemotherapy: issues with the access device, abdominal pain with infusion, and intolerance to the higher dose of cisplatin (100 mg/m²). Systemic toxicities for IP chemotherapy generally are categorized as gastrointestinal, neurologic, hematologic, and metabolic (Alhayki et al., 2006). In Armstrong et al.’s (2006) trial, all categories of systemic toxicities, including grade 3 and 4 pain and fatigue, were more common in the IP-treated group. The dose-limiting side effect of IP paclitaxel is abdominal pain (Krasner et al., 2006).

Preventive measures to reduce the risk of renal toxicity require adequate intravascular hydration before and after administration to maintain urine output at greater than 100 ml per hour (Markman & Walker, 2006). Gynecologic Oncology Group protocols required at least one liter of IV normal saline if cisplatin was administered IP (National Cancer Institute, 2006). Some protocols use IV sodium thiosulfate as a renal protectant with IP cisplatin (Howell et al., 1982; Kirmani et al., 1994).

An additional consideration of IP chemotherapy is the potential for a false elevation in CA-125 levels despite tumor regression (Schneider, 1994). Serosal irritation and chemical peritonitis caused by chemotherapy agents can cause an artificial rise in CA-125 (Schneider). Other issues associated with IP chemotherapy include depression, anxiety, and alterations in sexual functioning. Women undergoing treatment for ovarian cancer may need counseling and support for these issues particularly in light of aggressive surgery, chemotherapy regimens, and the associated toxicities (Ferrell et al., 2005; Lockwood-Rayermann, 2006).

**Complications With Intraperitoneal Catheters**

Many surgeons use the same vascular ports for IP chemotherapy as those used for IV chemotherapy (Krasner et al., 2006). Ports should be placed below the bra line to avoid irritation (Markman & Walker, 2006). When sutured to the lower rib, the port can rotate to the back of rib so the port diaphragm cannot be accessed with a Huber needle (Walker et al., 2006). IP port placement may be done laparoscopically during a second procedure to decrease the risk of infection and adhesions, particularly if initial debulking surgery involves bowel resection (Makhija et al., 2001).

Use of fenestrated catheters with multiple holes along the lumen, those with Dacron cuffs, and Tenckhoff catheters has been associated with fibrin sheaths, plugs, higher infection rates, perforations, and the formation of adhesions (Alhayki et al., 2006; Markman & Walker, 2006; Walker et al., 2006). In Armstrong et al.’s (2006) study, the primary reason for discontinuation of IP therapy was catheter-related complications, seen in 54% of patients (Walker et al.). Other complications noted were retrograde flow of fluid into the port pocket, internal kinking of the catheter and leaking fluid from port septum, port access difficulty, fluid leaking out the vagina, bowel perforation from the catheter (rectal fistula), and bowel adhesions pocketing the chemotherapy, resulting in pain and limiting the distribution of chemotherapy in abdomen (Armstrong et al.; Markman & Walker). The IP catheter should be removed as soon as treatment is completed; delayed removal can result in bowel and infection complications (Walker et al.).

**Intraperitoneal Chemotherapy Administration**

In addition to the IP port, a venous access port is implanted in the upper chest in many women for IV chemotherapy. Nurses need to emphasize that the use of the IP port is restricted only to IP chemotherapy treatment for ovarian cancer and that the catheter should not be used for IV administration of drugs or blood products. Patients should verbalize the specialized use of the abdominal port for IP chemotherapy only.

Just before the infusion begins, patients should void or an indwelling urinary catheter should be placed so that women do not need to get out of bed or use a bedpan that may dislodge the Huber point needle. Before IP cisplatin is given, IV hydration is necessary to achieve a urine output greater than 100 ml per hour for two hours (Hydzik, 2007). Ongoing nursing assessment of intake, output, laboratory values, and renal and cardiac function will signal potential fluid overload and electrolyte imbalances in magnesium, potassium, and calcium (Hydzik).

Highly emetogenic drugs given via the IP route require the same premedication as that given for highly emetogenic IV chemotherapy. Antiemetics for highly emetogenic chemotherapy should be continued for three to four days after IP infusion (National Cancer Institute, 2006). Depending on the drug(s) being given, premedication to reduce the risk of hypersensitivity reactions also must be administered. Because no current standard exists for the delivery of IP chemotherapy, patient positioning varies during the infusion; some institutions report supine positioning (Hydzik, 2007), whereas others advocate elevating the head of the bed slightly to avoid pressure on the diaphragm.

IP chemotherapy is reconstituted in two liters of normal saline, warmed to 37°C (98.6°F) by an external warming device (microwave warming is not recommended), and flows by gravity infusion as rapidly as possible; it may take 30–180 minutes to infuse. Infusion pumps are not used for IP chemotherapy because of the potential for high-volume pump pressure. The large volume of normal saline (two liters) facilitates intra-abdominal distribution (Armstrong et al., 2006).
Case Study

Amy, a 48-year-old woman, presented at a gynecologic oncology clinic with a three-week history of pelvic pain, urinary frequency, and a left adnexal mass found by a nurse practitioner at a primary care clinic. She has two healthy daughters, ages 12 and 14. Her mother had breast cancer at age 41 and is alive and well; Amy’s maternal grandmother had ovarian cancer and died at age 55. Amy currently is perimenopausal. She lost 14 lbs over the past eight weeks and noticed no change in abdominal girth but complained of intermittent constipation lasting up to three days.

The patient appeared slender and healthy and had normal vital signs. Rectovaginal examination revealed an anterior pelvic mass. Complete blood count and liver and renal functions were normal, but her CA-125 level was 1,479 u/ml (normal = 0–35). Computed tomography revealed a solid pelvic mass 10 x 8 cm in the left-central portion of the pelvis. A pelvic lymph node measured 2.7 cm in diameter.

Surgical exploration found a left adnexal lobulated mass 10 x 7.5 x 6.5 cm in the paraovarian tissue; one of five retroperitoneal lymph nodes and one of two para-aortic lymph nodes were positive for malignancy. Peritoneal washings contained malignant cells. Pathology revealed high-grade stage IIIC epithelial ovarian cancer. Small or large bowel resection was unnecessary in the debulking procedure and the residual tumor was less than 1 cm.

Adjuvant treatment was recommended, and Amy opted for a phase III trial of intraperitoneal (IP) therapy. Six weeks after the debulking surgery, she was admitted for adjuvant IP chemotherapy. Her nurse discussed the expectations of the treatment and provided written information about the side effects. The nurse also gave Amy a booklet describing the purpose of the implanted peritoneal catheter and emphasized the difference between the port implanted in her upper chest for laboratory draws and IV chemotherapy. Amy verbalized the differences between the implanted catheters and their specific uses.

On the day of her first IP treatment, Amy received IV hydration with routine premedications, including H₂, H₃, and H₄ antihistamines, dexamethasone, and 5-HT₁, and neurokinin receptor antagonist antagonetics. IP chemotherapy was diluted in two liters of normal saline, placed in an external warming device, and infused by gravity as rapidly as possible. Although the fluid was warmed, Amy’s nurse described the cool and full sensations she may experience during the rapid infusion. Amy indicated that she would report any cramping or pain. Diuretics and IV hydration were provided after the therapy was complete. Amy received a digital timer to prompt position changes every 15 minutes for two hours after the infusion. She called for pillow placement under her hips, shoulders, or extremities to help with comfort. Verbal and written information was given about signs and symptoms of catheter-related infection, reporting peripheral neuropathies, abdominal pain, nausea and vomiting, and fatigue.

An oncology social worker connected Amy with another woman who had completed IP treatment six months earlier. The women shared their experiences with the therapy and offered support to one another. Amy expressed concern for the future health of her two daughters; therefore, they were referred to genetic counseling.

Amy received four cycles of IP chemotherapy, then required a dose reduction because of grade 2 peripheral neuropathy and abdominal pain. The pain was managed with nonsteroidal anti-inflammatory drugs and resolved within 48 hours of IP completion. She reported depression, anxiety, and alterations in sexual functioning, so she was started on antidepressant therapy and received supportive counseling. Amy tolerated six cycles of IP chemotherapy and currently is being seen for surveillance by her gynecologic oncologist.

Note. Based on information from Krasner et al., 2006.

Infused fluid does not need to be drained from the abdominal cavity (Armstrong et al., 2006) because the small amount of systemic absorption is a desirable effect of therapy. The turning protocol does not begin until the infusion is complete and the Huber needle has been removed. Heparinization of the IP port after the infusion currently is not standardized and varies among institutions (Hydzik, 2007). Because the IP catheter does not yield a blood return, a 10–20 ml saline flush should be sufficient to maintain patency; however, some institutions heparinize IP ports after infusion (Hydzik). In one protocol, women turned every 15 minutes (left, right, supine, and prone) for two hours to distribute the solution (Armstrong et al.).

If an implanted port is used for IP chemotherapy, access with a 19- or 20-gauge right-angle Huber point needle 1” or 1.5” in length (Hydzik, 2007) will facilitate flow and decrease administration time. Several wound closure tapes over the Huber tubing with a stress loop and an occlusive dressing will help to avoid needle dislodgement (Marin et al., 2007). A preflush with 10 ml of normal saline will determine catheter patency. Peritoneal fluid may be aspirated from IP ports and cultured for bacteria or to assess for malignant cytology.

Nursing assessment during the infusion of IP chemotherapy is focused on the patient’s level of comfort and the location and characteristics of any abdominal pain. The infusion should be slowed or stopped based on the level of discomfort the patient is experiencing. Nurses should observe for the presence of asymmetry around the port or any leaking that would indicate possible needle dislodgement (Hydzik, 2007). An increase in respiratory rate or difficulty breathing may result from fluid pressure on the diaphragm; repositioning may be helpful. Diaphragmatic pressure must be discerned from fluid overload with the appropriate cardiorespiratory assessments and attention to changes in vital signs before and after the infusion. Discharge instructions for the patient who has completed a treatment of IP chemotherapy involve education regarding the potential for nausea and vomiting, frequent urination as the extra fluid is eliminated, constipation, diarrhea, neutropenia, thrombocytopenia, and anemia (Hydzik).

Conclusion

The reintroduction of IP chemotherapy following optimal debulking surgery for ovarian cancer when residual disease is less than 1 cm shows promising results in overall survival in women with advanced ovarian cancer. Management of the unique toxicities related to IP administration include catheter-related complications requiring diligent nursing assessment and an awareness of peritoneal drug distribution and metabolism.

Nursing care involves specific patient teaching to maintain optimal quality of life during this aggressive treatment. As research strives to decrease toxicity and provide further comparisons to standard IV therapy, this promising treatment may continue to show improved survival for women with ovarian cancer.

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