Intraperitoneal Chemotherapy for Ovarian Cancer

Paula Anastasia, RN, MN, AOCN®

Ovarian cancer remains an uncommon cancer compared to other female malignancies, such as breast, lung, and colon cancer. However, ovarian cancer is the leading cause of death among all gynecologic malignancies and the second most prevalent of the reproductive cancers (Siegel, Naishadham, & Jemal, 2012). According to the National Comprehensive Cancer Network ([NCCN], 2012b), the standard of care for advanced epithelial ovarian cancer (EOC) consists of an IV platinum and taxane-based chemotherapy for 6–8 cycles, or combination IV and intraperitoneal (IP) chemotherapy for patients with stage II or III cancer who have had optimally debulked (less than 1 cm residual) surgery (see Figure 1).

The Gynecologic Oncology Group (GOG) conducted a randomized, phase III trial, GOG 172 (Armstrong et al., 2006), that compared IP chemotherapy to IV chemotherapy and reported a median overall survival of 65.6 months in the IP group compared to 49.7 months for women receiving IV chemotherapy. As a result, the National Cancer Institute ([NCI], 2006) issued a clinical bulletin suggesting that all women with stage III EOC who have undergone optimal cytoreductive surgery should be considered for IP chemotherapy because of statistically significant improvement in overall survival.

Case Study

L.T., a 50-year-old, single, nulligravida, Caucasian woman, was diagnosed with stage IIIC, grade 3, papillary serous adenocarcinoma of the ovary. She underwent optimal cytoreductive surgery and presented for a second opinion six weeks after surgery for continuation of care. After review of pathology and medical records, it was recommended that L.T. immediately begin adjuvant chemotherapy with two cycles of IV carboplatin and paclitaxel every three weeks followed by IP port placement and completion of chemotherapy with an additional four cycles of combination IV and IP chemotherapy. The placement of the IP port would be performed as a laparoscopic outpatient procedure three weeks after completing L.T.'s second chemotherapy cycle. That surgery would also allow her gynecologic oncologic surgeon, who did not perform her original surgery, to assess for any residual disease.

The rationale for the IP chemotherapy for L.T. is based on research showing improved survival outcomes and her young age, excellent performance status, and previous optimal cytoreductive surgery. Three phase III trials have produced results that support using IP therapy in this patient population (Alberts et al., 1996; Armstrong et al., 2006; Markman et al., 2001). Alberts et al. (1996) and Markham et al. (2001) reported an eight- and nine-month overall survival, respectively, in the IP group compared to the IV group. Armstrong et al. (2006) showed a progression-free survival of 18.3 months in the IV arm and 23.8 months in the IP arm. The results were impressive because only 42% of patients in the IP arm completed all six cycles of planned treatment (Armstrong et al., 2006). Because L.T. did not have an IP port placed at the time of her surgery, she was started with traditional IV chemotherapy to prevent additional treatment delay. L.T. was counseled that she would potentially benefit from four cycles of IP therapy. The study by Armstrong et al. (2006) reported the average number of IP cycles was three, and those patients also demonstrated improved overall survival.

Intraperitoneal Therapy

Not all patients are candidates for IP therapy. Excluded are patients with bulky or residual disease greater than 1 cm. In addition, several conditions may prevent continuation of IP chemotherapy, such as catheter complications (e.g., improper placement, leakage, inability to infuse), comorbid diseases, and intolerable side effects including severe nausea, vomiting, electrolyte imbalance, or persistent abdominal pain (Markman & Walker, 2006). Patients receiving IP therapy require more frequent nursing assessment because of the potential for these challenging side effects (Potter & Held-Warmkessel, 2008). In addition, physician offices and infusion centers inexperienced with IP administration may shy away from recommending this route of therapy.

In the GOG 172 protocol, the IP regimen demonstrated a distinctly different side effect profile from IV chemotherapy. More grade 3 and 4 events took place in the IP regimen, specifically leukopenia (76% versus 64%), gastrointestinal (46% versus 24%), metabolic (27% versus 7%), neuropathy (19% versus 9%), and fatigue (18% versus 4%) (Armstrong et al., 2006). In addition, quality of life was evaluated using the Functional Assessment of Cancer–Ovarian questionnaire; those who received the IP regimen reported a worse quality of life. However, at one-year follow-up, the quality-of-life results for both groups remained similar (Armstrong et al., 2006; Wenzel, Huang, Armstrong, Walker, & Cella, 2007).

Nursing Management of Intraperitoneal Chemotherapy

Paclitaxel is administered before cisplatin because of a potential allergic reaction from paclitaxel and a potential decreased renal clearance from platinum-based therapy (Almadrones, 2007; Eisenhauer et al., 1994). In the author's practice, paclitaxel may be infused over the course of three hours instead of 24 hours as described in the published protocol. Otherwise, the patient would

Regimen 1
Patients should be treated with IV paclitaxel 135 mg/m^2 via continuous infusion for 24 hours on day 1, intraperitoneal (IP) cisplatin 75 mg/m^2–100 mg/m^2 on day 2, and IP paclitaxel 60 mg/m^2 on day 8. The regimen should be repeated every three weeks for six cycles.

Patients with stage II or III disease should have optimally debulked (less than 1 cm) disease.

↓

Regimen 2
Treatment should consist of IV paclitaxel 175 mg/m^2 over three hours, followed by IV carboplatin at an AUC of 5–7.5 over one hour on day 1. Repeat this regimen every three weeks for six cycles.

↓

Regimen 3
Patients should receive IV docetaxel 60–75 mg/m^2 over one hour, followed by IV carboplatin at an AUC of 5–6 over one hour on day 1. This should be repeated every three weeks for six cycles.

↓

Regimen 4
Dose-dense IV paclitaxel 80 mg/m^2 should be administered over one hour on days 1, 8, and 15, followed by IV carboplatin at an AUC of 6 over one hour on day 1. Repeat every three weeks for six cycles.

AUC—area under the curve

Figure 1. Primary Chemotherapy for Stage II, III, and IV Ovarian Cancer

Note. Based on information from National Comprehensive Cancer Network, 2012b.

require an inpatient hospitalization for a two-day infusion protocol. Initially approved as a 24-hour infusion, paclitaxel infused in three hours has proven to be the most common, convenient, and cost-effective infusion method (Eisenhauer et al., 1994). However, infusion durations affect the toxicity profile. The paclitaxel 24-hour infusion has less neurotoxicity but more neutropenia (Eisenhauer et al., 1994). Neurotoxicity is more frequent and myelosuppression is less frequent with a three-hour infusion, but the combination of paclitaxel and cisplatin increases the risk for both events.

Nursing competencies must include identification of risk and management for infection, peripheral neuropathy, nausea, vomiting, and fatigue. Standard premedication for paclitaxel includes dexamethasone, an H_1 blocker such as diphenhydramine, and an H_2 blocker such as ranitidine (Hydzik, 2007). Cisplatin is highly emetogenic in both the acute and delayed setting (NCCN, 2012a). To protect against acute and delayed chemotherapy-induced nausea and vomiting (CINV), prior to paclitaxel, administration of antiemetics such as palonestron, a long-acting serotonin receptor antagonist, and fosaprepitant, a neurokinin-1 receptor antagonist, is recommended (NCCN, 2012a).

Patients receiving IP chemotherapy should have IP hydration before and after administration of the chemotherapy. IP hydration serves as a distillate, allowing exposure of tissues to the chemotherapy, and provides a source of travel into the peritoneal cavity (Almadrones, 2007). In the clinical trials that have demonstrated improved responses (Alberts et al., 1996; Armstrong et al., 2006; Markman et al., 2001), two liters of normal saline (NS) were infused into the peritoneal cavity—this included the total dose of cisplatin. A peripheral or central IV line should be used for premedication and hydration and the IP port restricted to IP chemotherapy (Potter & Held-Warmkessel, 2008). Two different infusions will be occurring simultaneously, so labeling and identifying the IV tubing will be essential. The peripheral or central IV line should be used for premedication and IV cisplatin hydration, whereas the IP port is for the additional dilution hydration and IP chemotherapy (Potter & Held-Warmkessel, 2008). A warmed 500 cc bag of NS is infused via gravity into the peritoneal port, followed by a separate 500 cc bag of cisplatin to ensure the patient has received the total chemotherapy drug. The remaining liter of NS is infused via IP independently. That fluid is not removed and will be absorbed by the body in several days.

Although patients are encouraged to tolerate the full liter of NS, many patients ask to stop the IP hydration after 500 cc because of abdominal discomfort and bloating. Therefore, the cisplatin and NS are not to be infused in one large IV bag. It should be noted that, in the clinical trials that showed improved responses with the IP therapy compared to the IV therapy, a volume of two liters of NS was used (Almadrones, 2007).

Nurses need to assess the IP port prior to, during, and following infusion for any signs of erythema, fluid leakage, or malfunction. Following infusion of IP chemotherapy and hydration, the Huber needle is removed and the patient is instructed to turn side to side every 15 minutes for drug distribution throughout the peritoneal cavity (Potter & Held-Warmkessel, 2008). The bed is also placed in the Trendelenburg position for the final 15-minute segment. Ideally, 15-minute position changes should occur for two hours, but no less than one hour (Hydzik, 2007). The use of heparin to flush the IP port is not advisable because it is not in a vein. However, that policy may vary among institutions (Armstrong et al., 2006; Hydzik, 2007).

The IP regimen is much less tolerated than the IV regimen, and many patients may need or request to convert to IV-only therapy. Neutropenia, abdominal pain, ototoxicity, and neuromuscular toxicity were found to be higher in the IP arm than the IV arm (Anderson & Hacker, 2008; Armstrong et al., 2006). Knowledge of the expected side effects and preventive intervention, such as adequate hydration and antiemetic therapy (e.g., using combinations of 5-hydroxytryptamine-3 receptor antagonists and substance P/neurokinin-1 antagonists), may improve the patient's physical and emotional status in addition to maintaining treatment adherence. Because of the myriad of symptoms (e.g., abdominal discomfort, gastrointestinal distress, fatigue), other syndromes can often be overlooked, including depression and anxiety (Anderson & Hacker, 2008). Oncology nurses are in a prime position to obtain the necessary referrals for psychosocial support.

Management of Side Effects

L.T. experienced abdominal discomfort during IP hydration and cisplatin infusion. The head of the bed was elevated to semi-fowlers position and the rate of infusion via gravity was made slower. For future treatments, L.T. was encouraged to empty her bladder immediately prior to treatment and advised to wear loose-fitting clothes because the abdomen expands temporarily with the addition of fluid. Three days after IV paclitaxel and IP cisplatin, L.T. complained of fatigue, nausea, queasiness, and the inability to

adequately eat because of early satiety. She was brought into the infusion center for four hours of hydration and administered IV dexamethasone and metaclopramide. For improved management in the future, she was instructed to use an oral dexamethasone taper for three days following chemotherapy and oral metaclopramide 10 mg every six hours as needed for persistent CINV (NCCN, 2012a). In addition, daily IV hydration was scheduled for three days following IP chemotherapy in the event L.T. was unable to adequately self-hydrate. A neurologic assessment focusing on sensory and motor skills was conducted monthly because of the potential effects from combination paclitaxel and cisplatin (Kiser, Greer, Wilmoth, Dmochowski, & Naumann, 2010).

L.T. returned on day 8 for IP paclitaxel, but was apprehensive about nausea and bloating because she was just beginning to return to her normal routine and activities. However, except for the abdominal bloating from the IP fluid, L.T. experienced fewer side effects because the visit was during her week without cisplatin. The social worker met with L.T. to address emotional issues surrounding her illness and to assist her in identifying support systems. In addition, the interdisciplinary team identified another woman who had successfully completed IP therapy. That woman volunteered to be a buddy for L.T., providing additional support and friendship.

Conclusion

The administration of IP chemotherapy requires advanced knowledge of the regimen and the management of more challenging side effects than with an IV route. Supportive care includes hydration, antiemetic therapy, and infusion management in addition to psychosocial care to maintain optimal quality of life (Potter & Held-Warmkessel, 2008). Oncology nurses are vital interdisciplinary team members that can make a difference in the patient's cancer experience. Reassuring patients and helping them to identify early side effects can help oncology nurses manage symptoms more efficiently and increase the comfort level of the patient. Nursing research should continue to focus on nursing assessment, patient teaching, and symptom management to ensure the best patient outcomes for IP chemotherapy.

Paula Anastasia, RN, MN, AOCN®, is a gynecology-oncology clinical nurse specialist at Cedars-Sinai Medical Center in Los Angeles, CA. No financial relationships to disclose. Anastasia can be reached at anastasiap@cshs.org, with copy to editor at ONFEditor@ons.org.

Digital Object Identifier: 10.1188/12.ONF.346-349

References

Alberts, D.S., Liu, P.Y., Hannigan, E.T., O'Toole, R., Williams, S., Young, J.A., . . . DuBeshler, B. (1996). Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *New England Journal of Medicine, 335,* 1950–1955. doi:10.1056/NEJM199612263352603

Almadrones, L. (2007). Evidence-based research for intraperitoneal chemotherapy in epithelial ovarian cancer. *Clinical Journal of Oncology Nursing, 11,* 211–216. doi:10.1188/07.CJON.211-216

Anderson, N., & Hacker, E.D. (2008). Fatigue in women receiving intraperitoneal chemotherapy for ovarian cancer: A review of contributing factors. *Clinical Journal of Oncology Nursing, 12,* 445–454. doi:10.1188/08.CJON.445-454

Armstrong, D.K., Bundy, B., Wenzel, L., Huang, H.Q., Baergan, R., Lele, S., & Burger, R.A. (2006). Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *New England Journal of Medicine, 354,* 34–43.

Eisenhauer, E.A., ten Bokkel Huinink, W.W., Swenerton, K.D., Gianni, L., Myles, J., van der Burg, M.D., . . . Columbo, N. (1994). European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: High-dose versus low-dose and long-versus-short infusion. *Journal of Clinical Oncology, 12,* 2654–2666.

Hydzik, C. (2007). Implementation of intraperitoneal chemotherapy for the treatment of ovarian cancer. *Clinical Journal of Oncology Nursing, 11,* 221–225. doi:10.1188/07.CJON.221-225

Kiser, D., Greer, T.B., Wilmoth, M.C., Dmochowski, J., & Naumann, R.W. (2010). Peripheral neuropathy in patients with gynecologic cancer receiving chemotherapy: Patient reports and provider assessments. *Oncology Nursing Forum, 37,* 758–764. doi:10.1188/10.ONF.758-764

Markman, M., Bundy, B.N., Alberts, D.S., Fowler, J.M., Clark-Pearson, D.L., Carson, L.F., . . . Sickel, J. (2001). Phase III trial of standard dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small volume stage II ovarian carcinoma: An intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *Journal of Clinical Oncology, 19,* 1001–1007.

Markman, M., & Walker, J.L. (2006). Intraperitoneal chemotherapy of ovarian cancer: A review, with a focus on practical aspects of treatment. *Journal of Clinical Oncology, 24,* 988–994.

National Cancer Institute. (2006). Abdominal chemotherapy for ovarian cancer improves survival. *NCI Cancer Bulletin, 3*(2), 1.

National Comprehensive Cancer Network. (2012a). *NCCN Clinical Practice Guidelines in Oncology: Antiemesis* [v.1.2012]. Retrieved from http://www.nccn.org/professionals/physician_gls/PDF/antiemetics.pdf

National Comprehensive Cancer Network. (2012b). *NCCN Clinical Practice Guidelines in Oncology: Ovarian cancer* [v.1.2012]. Retrieved from http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf

Potter, K., & Held-Warmkessel, J. (2008). Intraperitoneal chemotherapy in women with ovarian cancer: Nursing care and considerations. *Clinical Journal of Oncology Nursing, 12,* 265–271. doi:10.1188/08.CJON.265-271

Siegel, R., Naishadham, D., & Jemal, A. (2012). Cancer statistics, 2012. *CA: A Cancer Journal for Clinicians, 62,* 10–29. doi:10.3322/caac.20138/08

Wenzel, L.B., Huang, H.Q., Armstrong, D.K., Walker, J.L., & Cella, D. (2007). Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: A Gynecologic Oncology Group study. *Journal of Clinical Oncology, 25,* 437–443.

Do You Have an Interesting Clinical Experience to Share?

Clinical Challenges provides readers with a forum to discuss creative clinical solutions to challenging patient care issues. Case studies or descriptions may be submitted with or without discussion or solutions. Materials or inquiries should be directed to *Oncology Nursing Forum* Associate Editors Anne Marie Flaherty, MSN, RN, AOCNS®, at aflaherty@humed.com, or Karen K. Swenson, RN, PhD, AOCN®, at karen.swenson@parknicollet.com.

Clinical Highlights: Intraperitoneal Chemotherapy for Ovarian Cancer

Definition

Intraperitoneal (IP) chemotherapy is medication administered through a surgically implanted catheter into the peritoneal cavity of a women with ovarian, fallopian tube, or primary peritoneal cancer. The chemotherapy is mixed with saline and infused into the body via the IP catheter, followed by additional fluid to facilitate distribution of a drug within the abdominal cavity (Armstrong et al., 2006; National Cancer Institute, 2012).

Rationale

Three phase III trials (Alberts et al., 1996; Armstrong et al., 2006; Markman et al., 2001) have authenticated using IP chemotherapy in women with optimally debulked stage III ovarian cancer. These trials resulted in longer overall survival compared to IV chemotherapy.

Side-Effect Profile

The IP regimen contributes to a distinctly different side effect profile from IV therapy. Neutropenia, abdominal pain, ototoxicity, and neuromuscular toxicity were higher in the IP arm than the IV arm in Armstrong et al. (2006). More grade 3 and 4 events were noted in the IP regimen compared to the IV route. Several conditions may prevent continuation of IP chemotherapy: catheter complications (e.g., improper placement, leakage, inability to infuse), comorbid diseases, and intolerable side effects such as nausea and vomiting, electrolyte imbalance, or persistent abdominal pain (Anderson & Hacker, 2008; Armstrong et al., 2006). The patient receiving IP therapy also requires more frequent nursing assessment because of the potential for abdominal discomfort from abdominal distention (Potter & Held-Warmkessel, 2008).

Interventions

IV paclitaxel is administered before IP cisplatin because of a potential allergic reaction from paclitaxel and a potential decreased renal clearance from platinum-based therapy (Almadrones, 2007; Eisenhauer et al., 1994). Nursing assessment includes identifying the risk of infection, peripheral neuropathy, nausea and vomiting, fatigue, and abdominal pain. Cisplatin is well known to be highly emetogenic in the acute and delayed setting; therefore, a long-acting serotonin receptor antagonist and a neurokinin-1 receptor antagonist to protect against acute and delayed chemotherapy-induced nausea and vomiting may be indicated (National Comprehensive Cancer Network, 2012).

Patients receiving IP chemotherapy need to have IP hydration before and after administration of the chemotherapy. That serves as a distillate, allowing exposure of the chemotherapy and providing a source of travel into the peritoneal cavity (Almadrones, 2007). Monthly neurologic assessments focusing on sensory and motor skills should be conducted to evaluate for potential neurotoxic effects from combination paclitaxel and cisplatin (Almadrones, 2007).

Nursing Implications

The administration of IP chemotherapy requires knowledge and understanding of the regimen and entails the management of more significant symptoms than with the IV route of chemotherapy. Supportive care has improved with the development and approval of growth factors, antiemetics such as 5-hydroxytryptamine-3 receptor antagonists, and substance P/neurokinin-1 antagonists. Oncology nurses caring for patients receiving IP chemotherapy can make the difference in their cancer experience and quality of life by providing symptom management, education, and reassurance. Knowledge of the expected side effects and preventive intervention can improve how the patient feels and help to maintain treatment adherence. Finally, identifying interdisciplinary team members and necessary referrals for the patient and family will help to support them in planning and organizing their care during this challenging treatment.

References

Alberts, D.S., Liu, P.Y., Hannigan, E.T., O'Toole, R., Williams, S., Young, J.A., . . . DuBeshler, B. (1996). Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *New England Journal of Medicine, 335,* 1950–1955. doi:10.1056/NEJM199612263352603

Almadrones, L. (2007). Evidence-based research for intraperitoneal chemotherapy in epithelial ovarian cancer. *Clinical Journal of Oncology Nursing, 11,* 211–216. doi:10.1188/07.CJON.211-216

Anderson, N., & Hacker, E.D. (2008). Fatigue in women receiving intraperitoneal chemotherapy for ovarian cancer: A review of contributing factors. *Clinical Journal of Oncology Nursing, 12,* 445–454. doi:10.1188/08.CJON.445-454

Armstrong, D.K., Bundy, B., Wenzel, L., Huang, H.Q., Baergan, R., Lele, S., & Burger, R.A. (2006). Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *New England Journal of Medicine, 354,* 34–43. doi:10.1056/NEJMoa052985

Eisenhauer, E.A., ten Bokkel Huinink, W.W., Swenerton, K.D., Gianni, L., Myles, J., van der Burg, M.D., . . . Columbo, N. (1994). European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: High-dose versus low-dose and long versus short infusion. *Journal of Clinical Oncology, 12,* 2654–2666.

Markman, M., Bundy, B.N., Alberts, D.S., Fowler, J.M., Clark-Pearson, D.L., Carson, L.F., . . . Sickel, J. (2001). Phase III trial of standard dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small volume stage II ovarian carcinoma: An intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *Journal of Clinical Oncology, 19,* 1001–1007.

National Cancer Institute. (2012). Epithelial ovarian cancer: Epithelial cancer. Retrieved from www.cancer.gov/cancertopics/pdq/treatment/ovarianepithelial/HealthProfessional/page5#Section_484

National Comprehensive Cancer Network. (2012). *NCCN Clinical Practice Guidelines in Oncology: Ovarian cancer*. Retrieved from http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf

Potter, K., & Held-Warmkessel, J. (2008). Intraperitoneal chemotherapy in women with ovarian cancer: Nursing care and considerations. *Clinical Journal of Oncology Nursing, 12,* 265–271. doi:10.1188/08.CJON.265-271