Office-Based Intraperitoneal Chemotherapy for Ovarian Cancer

By William R. Robinson, MD, Cathy Coberly, Julie Beyer, RN, April Lewis, and Carrie Ballard, DO

Don and Sybil Harrington Cancer Center/Texas Tech University Health Sciences Center, Amarillo, TX

The administration of chemotherapy via the intraperitoneal (IP) route to treat ovarian cancer was first reported in 1955 by Weisberger et al.[1] In 1978, Dedrick et al[2] of the National Cancer Institute published their landmark research on the pharmacokinetics of IP chemotherapy, which prompted a near three-decade-long series of studies of the concept.

Since 1986, there have been eight clinical trials that have reported evidence in support of treatment of advanced-stage ovarian disease with IP chemotherapy. Three of these were randomized, controlled phase III trials of first-line IP chemotherapy in conjunction with surgical cytoreduction. These studies have become the basis for recommending the use of IP chemotherapy as the standard treatment for selected patients with ovarian cancer.

The first trial, by Alberts et al,[3] randomly assigned patients who had undergone optimal cytoreductive surgery to receive cisplatin at a dose of 100 mg/m^2 administered either IP or intravenously (IV), and cyclophosphamide IV at a dose of 600 mg/m^2. Overall survival (OS) was 41 months for the IV group and 49 months for the IP group, and grade 3 and 4 toxicities were lower in the IP group.

In the second trial, Markman et al[4] randomly assigned patients to receive standard IV chemotherapy with paclitaxel 135 mg/m^2 IV over 24 hours on day 1 followed by cisplatin 75 mg/m^2 IV on day 2, administered every 3 weeks for six courses. The experimental arm consisted of carboplatin (AUC = 9) IV every 4 weeks for two courses, followed by paclitaxel 135 mg/m^2 IV over 24 hours on day 1 and cisplatin 100 mg/m^2 IP on day 2 for six courses. The experimental arm showed improvement in both progression-free survival (PFS; 27.9 *v* 22.2 months) and OS (63.2 *v* 52.2 months). Grade 3 and 4 toxicities, including leukopenia and gastrointestinal disturbances, were higher in the experimental arm and were thought to be caused by the high doses of carboplatin and the increased number of total cycles.[5]

The third and most compelling trial, by Armstrong et al,[6] randomly assigned optimally cytoreduced patients to receive either IV paclitaxel 135 mg/m^2 over 24 hours plus IV cisplatin 100 mg/m^2 or IV paclitaxel 135 mg/m^2 plus IP cisplatin 100 mg/m^2 and IP paclitaxel 60 mg/m^2. The IP arm showed favorable outcomes in PFS (23.8 *v* 18.3 months) and OS (66.9 *v* 49.5 months), but the IP arm had more toxicities including leukopenia, neurotoxicity, and gastrointestinal disturbances. Only 42% of patients were able to complete the full six cycles of IP chemotherapy. A follow-up report noted that quality of life was initially worse in patients undergoing IP treatment, but had recovered to baseline after 1 year in all areas except neurotoxicity.[7]

Based on these results, the National Cancer Institute released a clinical announcement in January 2006, recommending the IP regimen described here for primary chemotherapy after optimal cytoreductive surgery.[8] It is therefore appropriate for oncologists to consider incorporating IP chemotherapy administration into the outpatient or office-based setting. However, practical concerns have limited enthusiasm for this therapeutic advance. This report analyzes the current practice of IP chemotherapy administration from the pharmacy to the infusion suite to the business office in an office-based setting.

Rationale Behind IP Chemotherapy

Ovarian cancer is generally confined to the peritoneal cavity, both at initial diagnosis and at recurrence. The ovary is a freestanding organ within the peritoneal cavity, allowing for sloughed ovarian epithelial cells to disperse widely. The ovarian epithelial cells seed the peritoneal cavity by traveling in the circulation of the peritoneal fluid. These concepts suggest that the IP administration of chemotherapy should result in a pharmacologic advantage in exposure to and penetration of tumor. The peritoneal cavity provides a potential space for chemotherapy instillation, thus allowing the drug to come into direct contact with deposits of malignant ovarian cells. This direct contact with tumor deposits, particularly those smaller than 0.5 to 1 cm in maximum diameter, has been reported to result in better penetration of individual tumors.[4] In addition, the potential for systemic toxicity may be reduced with IP chemotherapy, as high ratios of IP to serum concentrations of drug should be achievable.[9] Clearance of these drugs from the peritoneal cavity is in direct relation to molecular weight and charge. Larger and more highly charged molecules require more time for removal via circulation and lymphatics. It is therefore opportune that cisplatin and paclitaxel, the most active and best-studied agents in the treatment of ovarian cancer, have high molecular weights that result in peritoneal-to-plasma concentration ratios of 20:1 and 1,000:1, respectively.[10,11] These theoretical advantages make the use of cisplatin and paclitaxel particularly attractive for IP therapy in women with ovarian cancer.

Practical Considerations of IP Chemotherapy

In comparison to intravenous chemotherapy, IP administration requires significantly more multidisciplinary cooperation to be successful. It is typically administered on a complex, time-consuming schedule, which both patients and

oncology providers find challenging. The most important components of a successful IP team are described below.

Preoperative Clinic and Operating Room

The decision to use IP chemotherapy should be made on a patient-by-patient basis, and starts during the preoperative visit. Generally, the discussion of IP therapy begins by explaining to the patient that if optimal debulking can be achieved, the IP port can be placed at the same time as the primary surgery. Age, performance status, and previous abdominal surgery are all relative contraindications to IP therapy, and should be considered during this time as well.[12] Written informed consent for the port placement can then be obtained along with the standard consent for the procedure. In general, the optimal patients for IP therapy are those younger than 70 years, with a performance status of 0 to 1, and no history of previous abdominal (particularly intestinal) surgery. However, these criteria should only serve as guidelines and should not be considered absolutes.

In the event that optimal debulking is accomplished, the IP port is usually placed as the last part of the procedure. It is highly recommended that the same type of port be used for all patients in a facility. This allows the staff to become familiar with a single device, which increases the ease and consistency of accession. Though some investigators believe that ports designed for IV use are associated with fewer complications than those specifically designed for IP, that has not been the case at this institution. The device used at this institution in all patients for IP access is the Port-A-Cath (Pharmacia Deltic, St Paul, MN). It is also recommended that ports be placed at the same site in all patients, typically either the right or left lower chest wall. In this institution, the titanium reservoir of the port is placed on the left lower chest wall in a subcutaneous pocket created by making a 3-cm transverse incision centered on the midclavicular line below the breast. The opposite side can be used in case of anatomic abnormalities, such as previous chest wall surgery. The silicone tubing is connected to the reservoir as described in the package insert, and the reservoir is anchored to the chest wall fascia using permanent suture. The tubing is then tunneled through the subcutaneous tissue of the abdominal wall, and inserted into the peritoneal cavity at a point 2 to 5 cm lateral to the umbilicus under direct visualization. The IP portion of the tubing, including the fenestrated section, is directed into the pelvis. The Dacron polyester cuff of the tubing is sutured to the abdominal wall fascia in a purse-string fashion to minimize the possibility of leakage or migration of the device. The catheter should be checked for patency and leakage before closure of the incisions.

IP catheters can also be placed at a subsequently scheduled procedure, or by interventional radiology. It may be appropriate for catheter placement to be delayed as a result of unexpected findings at initial surgery, such as gross bacterial contamination, uncertain diagnosis, or intraoperative complications.[13] Before utilization of an IP catheter, its patency and functionality can be evaluated by injecting water-soluble contrast during a computed tomography scan. It is generally recommended to wait 3 to 4 weeks after surgery to begin treatment, to allow skin and fascial healing to proceed.

Coordination Between Infusional Suite and Pharmacy

The timing of the preparation of IP chemotherapy is critical. Both the agent and any subsequent distributional/dilutional infusion must be at body temperature before administration. When the patient is present in the infusion suite and ready for treatment, the pharmacy is notified, which can then mix and deliver all premedications, which typically include a corticosteroid, diphenhydramine, cimetidine, lorazepam, and a 5-hydroxytryptamine-3 receptor–blocking antiemetic. As these are being given, the agent and distributional/dilutional fluids are prepared and warmed. This may be performed using either a water bath or blanket warmer. The latter has proven to be less cumbersome and more reliable at this institution. The premedictions can usually be completed in the time it takes to prepare the infusions and deliver them to the suite. They can then be hung to be given sequentially with minimal time lost.

Cisplatin can be administered IP in normal saline over 30 minutes, using techniques and equipment similar to those used for IV infusions. Paclitaxel must be handled slightly differently when administered IP as compared with IV. It should be given unfiltered by gravity flow rather than via pump. Filtering will result in an unacceptably slow flow rate, and has not been used in this institution in more than 100 patients with no complications. Additionally, some IP paclitaxel protocols call for a final concentration significantly below the threshold listed in the package insert. Again, these low concentrations have been used in this institution for some time without adverse consequences.

Nurses' Role During Infusion

The infusion nurse plays a critical role in the successful completion of therapy and therefore should be certified in chemotherapy administration and experienced in IP techniques. Patients and their families are typically apprehensive when they enter the infusion suite for the first time, particularly those who are to receive IP therapy. They are frequently well aware of the difficulties associated with the treatment and are often expecting the worst. An infusion nurse who understands the IP process and calmly reassures the patient that everything she is experiencing is normal can heavily influence the patient's willingness to tolerate the treatment.

A typical plan of care therefore initially includes appropriate teaching for the patient and family regarding IP chemotherapy and ovarian cancer. Most laymen are overwhelmed by the enormous amount of information they have received by this point, and greatly benefit from hearing it again in summary form. The nurse should explain the instillation procedure itself, the adverse effects that may occur

during or immediately after the instillation of IP chemotherapy, any delayed local and systemic adverse effects, and problems specific to the port, such as infection or occlusion. Specifically, the nurse should explain that the feeling of abdominal fullness associated with IP infusions is expected, provide reassurance that it is not serious, and encourage the patient to relax so that the maximum possible amount of distributional fluid is infused.

Administration of IP Chemotherapy

IP chemotherapy requires the patient to spend relatively more time in the infusion suite, and the infusion staff will spend more time accessing the ports and monitoring the patient. The process is usually most successful when the patient can be supine, yet mobile during administration, requiring space for a bed or gurney, as well as access to bathroom facilities. Additional privacy in the form of a curtained-off area or separate room is optimal for patients receiving IP infusions, as a result of the increased exposure of the patient required to access the ports, and the possibility of acute abdominal pain during the infusion.

For accession, the patient should assume supine position in an adjustable bed or gurney. The IP reservoir should be accessed under sterile technique, generally using a right-angle, noncoring, 20 gauge, 1.25-inch gripper-type Huber needle. A longer needle may be necessary for patients with thick subcutaneous tissue on the chest wall. The port should flush easily without pain or edema at the site. Difficult or uncertain accessions can be verified by anterior-posterior and lateral radiographs. The needle can then be secured using a temporary adhesive dressing. The head of the bed should be raised no higher than 30 degrees to prevent dislodgement of the needle.

The chemotherapy drug itself should be infused first. Then, to facilitate distribution, up to 1 L of warmed normal saline is infused to patient tolerance. Some institutions prefer to mix the chemotherapeutic agent in a 1,000 mL bag, and follow that with an additional 1,000 mL of distributional fluid. The experience of this institution is that many patients will not tolerate 2 L of IP infusion, and some will not tolerate even 1 L. The infusion nurse should reposition the patient every 15 minutes during the administration, by turning her from side to side. If possible, the bed can also be alternated between the Trendelenburg and reverse Trendelenburg positions to facilitate distribution. The position of the needle in the reservoir should be carefully determined and recorded at 15-minute intervals. Ambulation is restricted as much as possible during infusion to avoid dislodgment of the needle. It is suggested that patients be encouraged to use the restroom before beginning an IP infusion.

Complications During Treatment

The infusion nurse should be aware of and check for the following complications which may arise during IP therapy: nausea, vomiting, diarrhea, gastroesophageal reflux, pain in the abdomen or port site, excess abdominal distention, tenderness, fever, chills, dyspnea, changes in mental status, tremors, and weakness. Most patients will experience some degree of abdominal bloating and discomfort during the infusion. The nurse is responsible for determining (and will learn with experience) when that discomfort is appropriate to the process and when it signifies that there may be a problem. In the former case, the nurse should be able to provide reassurance that these sensations are to be expected and will resolve on conclusion of the infusion. In the latter, the nurse should be able to quickly and easily notify the physician of the situation.

The Business Office

Many insurance carriers may not be familiar with IP therapy or the codes associated with it. It is therefore particularly important to allow sufficient time for the billing staff to accurately verify benefits, as well as review any specific coverage limitations. Precertification may be required by some plans and could result in medical review by the patient's plan before approval is issued.

The following Current Procedural Terminology (CPT) codes should be used in association with IP chemotherapy:

- 49419: "Insertion of intraperitoneal cannula or catheter, with subcutaneous reservoir, permanent (ie, totally implantable)." Usually inserted during the original surgical procedure where debulking is performed.
- 49422: "Removal of permanent intraperitoneal cannula or catheter." Again, precertification is important for insertion or removal, and it is recommended that insertion be included with the initial surgical plan.
- 96445: "Chemotherapy administration into peritoneal cavity, requiring and including peritoneocentesis." This code predated the recent recommendations for IP use. Although peritoneocentesis is rarely performed in modern regimens, Medicare has recently stated that this is the appropriate code for IP administration of chemotherapy. Revisions are possible in the future.

Also, when support medications such as dexamethasone and ondansetron are delivered by IV push, code 90775 "Each additional sequential intravenous push of a new substance/drug (List separately in addition to code for primary procedure)" should be used, with the –59 modifier appended to indicate a separate injection/site. Otherwise, code 90775 could be considered incidental to code 96445.

Late Considerations

Reasons for discontinuation of IP chemotherapy include catheter-related complications as well as toxicity from the drugs themselves. Complications may include catheter leakage, rupture or occlusion, infection, pain, bowel perforations, and access problems.[14] Intra-abdominal adhesions can form during treatment, which may cause intolerance to IP chemotherapy, typically identified by excess pain during the infusion. The pain is thought to be due to

stretching and distention of bowel-to-bowel adhesions, thus preventing thorough bathing of the entire peritoneal cavity.[11] As with most surgical procedures, the rate of catheter-related complications is likely to decline with experience and consistency in placement.

Depending on the situation, the IP catheter may be replaced or IP treatment abandoned. Patients in whom IP therapy is stopped may still receive IV chemotherapy, and most will be able to complete any remaining cycles of treatment. Once IP chemotherapy is completed and/or discontinued, it is recommended that the catheter be removed, given that complications related to unused catheters have been reported.[6]

Removal can usually be performed on an outpatient basis. Typically, the lower chest wall incision over the site of the reservoir is re-entered, and the reservoir is freed from the underlying fascia. A second incision of approximately 1 cm can then be made through the previous midline scar, at the level at which the tubing was inserted into the fascia. Again, a standard approach to placement of the catheter is recommended to facilitate removal, given that the site at which the tubing enters the peritoneal cavity may not be easily palpable through the skin, particularly in heavier patients. Sharp dissection is typically required to free the Dacron cuff from the abdominal wall fascia. When the cuff is completely free, the tubing can easily be removed intact from the peritoneal cavity.

Conclusion

The decision to use IP chemotherapy should be carefully considered. Realistically, just as not all patients are good candidates, not all office settings are able to accommodate the associated complexities. It is highly recommended that a team approach be taken to planning the initiation of an IP program.

Successful utilization is a function of volume and experience. As discussed, the study of Armstrong et al[6] reported that only 42% of patients completed six IP courses. However, this study was a combination of results from more than 20 institutions, with variable levels of IP experience and commitment. Many of those institutions were using IP chemotherapy for the first time, and only treated a relative handful of patients. In contrast, the report from Robinson et al,[12] was compiled during a 3-year period that represented the startup of a committed, coordinated IP program, using the doses and schedules suggested in the study by Armstrong et al.[6] Results from a subsequent three-year period (2004 to 2006) from the same institution during which more than 100 infusions per year were performed show significant improvement in outcome. Of 55 patients who began IP chemotherapy, 43 patients (78.1%) were able to complete six cycles of the regimen, as compared with 58% in the earlier report. Toxicities were similar but much less frequent, particularly at the grade 3 to 4 levels and there were no deaths in the later period.[15]

IP administration of chemotherapy is the most important advance in the treatment of ovarian cancer in the past decade. The survival advantage over IV therapy is undeniable. Clearly, this survival benefit comes at a cost: additional toxicity to patients, measured both in quality and quantity, and additional planning and preparation required of oncology providers. This is the likely reason that IP therapy is currently used by only a fraction of oncologists in the United States, despite the convincing evidence of survival benefit. However, timely planning and a coordinated effort among physicians, nurses, pharmacists, and business office personnel can minimize these challenges.

Corresponding author: William Robinson, MD, 1500 Wallace Blvd, Harrington Cancer Center, Amarillo, TX 79106; e-mail: wrobinson@harringtoncc.org.

DOI: 10.1200/JOP.0858503

References

1. Weisberger AS, Levine B, Storaasli JP: Use of nitrogen mustard in treatment of serous effusions of neoplastic origin. JAMA 159:1704-1707, 1955

2. Dedrick RL, Flessner MF: Pharmacokinetic problems in peritoneal drug administration: Tissue penetration and surface exposure. J Natl Cancer Inst 89:480-487, 1997

3. Alberts DS, Liu PY, Hannigan EV, et al: Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin and intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 335:1950-1955, 1996

4. Markman M: Intraperitoneal therapy of ovarian cancer. Oncologist 1:18-21, 1996

5. Markman M, Bundy BN, Alberts DS, et al: 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 III ovarian carcinoma: An Intergroup Study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 19:1001-1007, 2001

6. Armstrong DK, Bundy B, Wenzel L, et al: Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 354:34-43, 2006

7. Walker JL, Armstrong DK, Huang HQ, et al: Intraperitoneal catheter outcomes in a phase 3 trial of intravenous vs. intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: A Gynecologic Oncology Group study. Gynecol Oncol 100:27-32, 2006

8. National Cancer Institute: NCI Clinical Announcement on Intraperitoneal Therapy for Ovarian Cancer. http://www.cancer.gov/clinicaltrials/developments/IPchemo-digest

9. Dedrick RL, Myers CE, Bungay PM, et al: Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep 62:1-11, 1978

10. Howell SB, Pfeifle CL, Wung, et al: Intraperitoneal cisplatin with systemic thiosulfate protection. Ann Intern Med 97:845-851, 1982

11. Markman M, Rowinsky E, Hakes T, et al: Phase I trial of intraperitoneal Taxol: A Gynecologic Oncology Group study. J Clin Oncol 10:1485-1491, 1992

12. Robinson W, Omar H, Blades N: Toxicity of intraperitoneal chemotherapy may be related to age in women treated for optimally debulked ovarian cancer. Commun Oncol 2:271-275, 2005

13. Markman M, Walker JL: Intraperitoneal chemotherapy of ovarian cancer: A review, with a focus on practical aspects of treatment. J Clin Oncol 24:988-994, 2006

14. Runowicz CD, Dotting PB, Shafir MK, et al: Catheter complications associated with intraperitoneal chemotherapy. Gynecol Oncol 24:41-50, 1986

15. Robinson WR, Davis N, Rogers AS: Paclitaxel maintenance chemotherapy following intraperitoneal chemotherapy for ovarian cancer. Int J Gynecol Cancer 10.1111/j.1525-1438.2007.01118.x [epub ahead of print October 18, 2007]