Treatment of Ovarian Cancer With Intraperitoneal Chemotherapy

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Ovarian cancer is the most deadly gynecologic malignancy. In the US alone, an estimated 21,500 new cases will be diagnosed in 2009, and an estimated 14,600 women will die from this disease.

ABSTRACT: In early 2006, the National Cancer Institute (NCI) issued a Clinical Announcement suggesting that intraperitoneal (IP) chemotherapy should become the standard of care for patients with newly diagnosed stage III optimally debulked epithelial ovarian cancer. IP chemotherapy, the administration of chemotherapy or biologic therapy via catheter into the peritoneal space, is new to many healthcare providers (physicians, nurses, and pharmacists). The goals of this article are to address the rationale for IP chemotherapy, present the data supporting its use, and describe the nursing management of patients undergoing this treatment. Education of patients and staff regarding IP therapy is essential for successful patient outcomes.

Ovarian cancer is the most deadly gynecologic malignancy. In the US alone, an estimated 21,500 new cases will be diagnosed in 2009, and an estimated 14,600 women will die from this disease.[1] Early-stage ovarian cancer is generally asymptomatic, so most patients with ovarian cancer present at an advanced stage of disease. The tumor stage is a significant prognostic variable, and patients with advanced disease have poorer outcomes. TABLE 1

Several large clinical trials were conducted to identify the best treatment options for women with advanced ovarian cancer. Data generated by these studies led to the 2006 National Cancer Institute (NCI) Clinical Announcement recommending that intraperitoneal (IP) chemotherapy become the standard of care for patients with newly diagnosed stage III optimally de-bulked epithelial ovarian cancer.[2] Table 1 summarizes the three main clinical trials that demonstrated a significant improvement in survival among ovarian cancer patients treated with chemotherapy via the IP route, as opposed to the intravenous (IV)-only route.[3–5] The NCI reported that clinical trials showed the IP method to be safe and effective, and this report sparked a renewed interest in IP chemotherapy.

TABLE 2

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
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<tbody>
<tr>
<td>PACLtaxel at 135 mg/m² IV over 3 hours</td>
<td>CISplatin at 75 mg/m² IP (2 L of NS)</td>
<td>CISplatin at 75 mg/m² IP (2 L of NS)</td>
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<td>Administered every 21 days x 4 cycles.</td>
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IV/IP PACLtaxel IP CISplatin Regimen Used at Memorial Sloan-Kettering Cancer Center
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In the past, healthcare providers were wary of IP chemotherapy for several reasons: IP chemotherapy required more resources and was more involved than IV chemotherapy. It required providers to master a new and complicated technique. Furthermore, there were concerns regarding IP chemotherapy study designs and outcomes. Healthcare providers needed to identify ideal candidates, that is, patients with limited, small-volume residual disease without adhesions. In addition, there were many reported toxicities with IP chemotherapy, including leukopenia and thrombocytopenia; gastrointestinal, renal, neurologic, and metabolic complications; fatigue; infection; and pain.[3–5] These toxicities may be expected with use of a higher IV cisplatin dose (100 mg/m² vs 75 mg/m²) and addition of IP paclitaxel on day eight.[6] At Memorial Sloan-Kettering Cancer Center (MSKCC), we use a lower cisplatin dose (75 mg/m²) in an attempt to reduce these toxicities (see Table 2).

The Gynecologic Oncology Group (GOG) trial 172 by Armstrong et al.[3] showed prolonged progression-free interval and time to death for the IP group, suggesting a therapeutic advantage for IP therapy. It also evaluated the effect of IP chemotherapy on patients’ Quality of Life (QOL). Patients receiving the higher dose of IP therapy experienced lower QOL initially vs those who received more conventional IV therapy. These differences disappeared over time. At 1 year, QOL and pain scores were similar between the two arms except for paresthesias, which were more likely to persist at moderate levels in patients on the IP/IV arm.[2] These findings suggest that the additional toxicity that may be seen with the IP route is transient and not a long-term issue for most patients.

The 2009 National Comprehensive Cancer Network (NCCN) Practice Guidelines for Stage II–IV ovarian cancer outline the treatment recommendations to be IP chemotherapy for patients who were optimally debulked (< 1 cm) or IV taxane/carboplatin for a total of 6–8 cycles.[7] Three years after the NCI announcement, it has been reported that IP chemotherapy has been underutilized as a treatment modality in the ovarian cancer patient, despite evidence of its benefits.[6] Several factors may account for this, including problems with study designs reported in the medical literature, toxicities, and technical complications with the procedure. Future clinical trials will study different agents and schedules to address survival outcomes and quality of life of women with ovarian cancer. A challenge is to learn how to safely administer IP chemotherapy. At some institutions, the healthcare team may only see a few cases per year, making it difficult to learn this technique and establish standards of care. One suggestion is to inform patients about IP chemotherapy as a treatment option. If patients opt for this treatment, then they should be referred to institutions that offer IP therapy as a treatment modality.[7]

Staff Education

**TABLE 3**

<table>
<thead>
<tr>
<th>Internet Resources on IP Chemotherapy</th>
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</thead>
</table>
| Gynecologic Oncology Group / International Gynecologic Cancer Society  
  - GCC/IGCS: www.gcsig.org |
| Gynecologic Oncology Group (OGO; www.gog.org)  
  - Educational materials for health professionals:  
    http://www.gog.org/ 
  - Phase II GOG clinical trial of IV vs IV chemotherapy in optimal stage II ovarian and primary peritoneal cancer (2006):  
    http://www.gog.org/2754b  
  - Clinical Oncology:  
    www.co.org  
  - Oncology Nursing Society:  
    www.cogs.org  
  - Special interest group:  
    www.sis.org  
  - Oncology Information:  
    www.oncology.com  
  - US National Institutes of Health, Clinical Trials.gov:  
    - ClinicalTrials.gov  
    - www.clinicaltrials.gov  |

Internet Resources on IP Chemotherapy
Successful implementation of IP as a treatment modality requires education and experience. Development of a procedure and standards of care is essential. At MSKCC, we found it helpful to develop an IP manual containing copies of the procedure for administration of IP chemotherapy, a skills checklist for IP chemotherapy, and pertinent literature (NCI announcements, recent studies, articles, and resources related to IP chemotherapy) so that staff members can have information and references readily available to them. (Table 3 provides selected Internet resources.)

Defining Patient Selection

The NCI recommendation for treatment of ovarian cancer includes surgery followed by chemotherapy, and IP chemotherapy is the standard of care for patients with newly diagnosed stage III optimally debulked epithelial ovarian cancer.[2] The patient's tumor size is a factor in the success of IP therapy. Because IP chemotherapy penetrates only a few millimeters into the tumor, the women most likely to respond to it are those with the smallest possible volume of residual disease. The current standard is for the woman to have optimal cytoreduction with tumor nodules no greater than 1 cm in diameter prior to IP treatment. Another consideration is the presence and amount of adhesions, as extensive intra-abdominal adhesion limits the effectiveness of IP chemotherapy.[8]

Rationale for IP Therapy

Prior to treating patients, the nurse should understand the natural history of ovarian cancer and the rationale for IP chemotherapy, and be able to identify ideal candidates. IP chemotherapy is regional administration of drug into the peritoneal cavity. There has been interest for about 30 years in use of IP therapy. It was first introduced in 1955 by Weisberger et al.,[9] who used nitrogen mustard intraperitoneally to treat malignant ascites. Dedrick et al.[10] published the landmark theoretical modeling study, which used a mathematical model that shows the pharmacokinetic rationale for IP therapy. Certain agents were shown to have a greater concentration and longer half-life in the peritoneal space vs IV administration.[10] Cisplatin has been found to have a 10–20 fold greater exposure when administered intraperitoneally vs intravenously.[11] Paclitaxel has more than 1,000-fold greater exposure when administered intraperitoneally vs intravenously.[12]

Administration and General Safety Considerations

To administer IP therapy, one must access the peritoneal cavity. This procedure is performed using sterile technique. Prior to accessing the IP port, the nurse verifies placement of the port by reviewing the postoperative notes or CT scan report. This catheter lies or floats freely in the peritoneal space. The nurse must be familiar with the regimen, specific agent(s) being administered, and clinical considerations for each agent. At MSKCC, we use a preprinted chemotherapy order set to standardize the IV/IP chemotherapy process and decrease the potential for error. MSKCC has developed administration guidelines for each agent to ensure a standard approach to preparation and administration of the agent. For example, IP cisplatin therapy requires that the patient receive 2 liters of IV hydration and premedication with antiemetics, and the patient must void at least 100 mL/hour for 2 hours prior to initiation of chemotherapy. IP chemotherapy is mixed in 2 liters of normal saline and is administered by gravity. It is recommended that the volume be greater than 1,500 mL to result in abdominal distention.

Patient assessment is needed prior to initiation of chemotherapy and the patient's medical record must be reviewed (as with any chemotherapy regimen). Some patients may have both an IV and an IP port; it is important to identify the ports correctly prior to accessing them. If an IP port is aspirated, there should be no blood return because the port sits in the peritoneal space. Prior to administering IP chemotherapy, the nurse verifies that the order is correct by identifying the “five rights”: right patient, agent, dose, route, and frequency. The nurse also ensures that the appropriate supportive medications are ordered for safe administration. The Joint Commission has issued a Sentinel Event Alert regarding tubing and catheter misconnection errors.[13] Several strategies are recommended to prevent/reduce wrong-route errors. One strategy is to educate staff about ways to reduce this risk. Next, always trace a tube/line from the patient to the point of origin before connecting the infusion. As part of the handoff process, recheck connections and trace all tubes/lines to the point of origin when caring for a new patient. Nurses need to educate patients and families about the importance of connecting the tubing to the correct site. Also, some institutions label the lines, that is, IV vs IP. At MSKCC, prior to initiating IP
chemotherapy, two nurses will trace the IP chemotherapy agent and tubing to the patient's IP port and connect the tubing in order to verify the correct route of administration. Both nurses verify the connection of the tubing to the correct site to reduce/prevent tubing misconnection errors. As with any other chemotherapy treatment modalities, staff should wear PPE (personal protective equipment) when administering chemotherapy.

**Type of IP Access**

IP therapy is administered via a Tenckhoff peritoneal dialysis catheter or an IP port. At our center, we administer IP chemotherapy via an IP port. Two different types of ports are currently used to administer IP therapy. We use an IP implantable port with a fenestrated catheter (14.3 French). Others have recommended the use of a venous implantable port connected to a single lumen venous catheter (9.6 French). See Figure 1 for pictures of both devices. **FIGURE 1**

Intraperitoneal (IP, left) and intravenous (IV, right) ports for delivery of chemotherapy.

When comparing ports, note the difference in port size and lumen size of the catheter. Also, the fenestrated end has multiple holes (openings) vs the blunt, open-ended catheter. It has been suggested that use of peritoneal catheters with fenestrations and Dacron cuffs is associated with a greater incidence of bowel adhesions and erosion into the bowel.[2] IP ports do not have Dacron cuffs at this time. To date there is no study regarding the type of implantable port to be used for IP chemotherapy.

The following three studies are based on our experience at Memorial Sloan-Kettering Cancer Center using a fenestrated IP catheter. Black et al.[14] reviewed medical records of all patients who had a fenestrated catheter placed from May 1997–May 2006 at our center.[14] They reviewed 342 patients and identified only nine (3%) who had chemotherapy discontinued because of catheter complications. Other complications included catheter-related infections (three patients), inflow obstruction (five patients), and inability to access the port (one patient). Makhija et al.[15] analyzed the charts of 301 patients and identified 30 (10%) who had catheter-related complications. A total of 19 patients (6.3%) had inflow obstruction and 11 (3.6%) experienced infection. The investigators reported that 93% of the patients completed their planned therapy. Davidson et al.[16] reviewed 227 patient charts and found that 8.8% (20 patients) had inflow obstruction, 5.3% (12 patients) had catheter-related infections, and 3.5% (eight patients) had a bowel perforation.

These studies show that catheter-related complications have decreased over time, and suggest a learning curve regarding placement technique, administration, and management of IP chemotherapy from 1991 to the present. Use of laparoscopic surgery or different chemotherapy agents to treat this disease also may be factors in the decreased incidence of complications. Further research is warranted to identify the best device with which to administer IP chemotherapy. Markman and Walker[17] stated that fenestrated catheters seem to encourage fibrous sheath formation and bowel adhesions and are difficult to remove in the ambulatory setting. In our institution's ambulatory office setting, however, we remove the IP ports without complications or difficulty.

Two controversial procedural points regarding administration of IP chemotherapy are flushing of an IP port and warming of the IP fluid. At MSKCC, the IP port is not heparinized because the catheter is not in a blood vessel. We have not experienced any problems flushing with normal saline.[14–16] Some institutions do heparinize; the heparin-flush dosing for IP ports ranges from 100–2,000 units. There are currently no evidence-based guidelines for solution temperature during IP administration. Those who support warming the solution suggest there is an added therapeutic antitumor benefit and it prevents patients from feeling cold. At MSKCC, we administer the therapy at room temperature. If patients report feeling cooler, blankets provide easy and quick relief.
Nursing Management and Patient Education

TABLE 4

Nursing Management of Patients Treated With Intraperitoneal Chemotherapy

Nurses play an essential role in caring for women with ovarian cancer who are receiving IP chemotherapy. It is important for us to understand the diagnosis, treatment plan, and potential side effects of treatment. The unique nursing management for patients receiving IP chemotherapy is outlined in Table 4.[18–23] Women receiving IV chemotherapy also have the potential to experience these problems and/or side effects (nausea, vomiting, alteration in the GI tract, myelosuppression, infection, and peripheral neuropathy), and as oncology nurses we are familiar with these potential problems.

Patients should be educated about what to expect with the IP route of chemotherapy, including possible side effects and complications. At Memorial Sloan-Kettering Cancer Center, the patient information booklet, “Your Guide to Intraperitoneal Therapy,” is the tool that we use to teach patients about this modality.[24] [Editor's note: An updated, 2009 version of this educational tool is available in the online issue of ONCOLOGY Nurse Edition, at CancerNetwork.com.] Patients should be reassured that most of the side effects they will experience subside within 48 hours after completion of chemotherapy.

Conclusions

The combination of IV/IP chemotherapy has demonstrated a significant survival benefit for women with optimally debulked epithelial ovarian cancer. Research still is needed to determine the optimal regimen and scheduling, as well as the best way to administer IP chemotherapy and manage patients receiving it. As healthcare professionals, it is essential for us to look for opportunities to improve patients' outcomes and quality of life. In the care of patients receiving IP chemotherapy for ovarian cancer, there are myriad critical points for nursing intervention that will affect the success of the procedure, the comfort of the patient, and the patient's sense of well being.

References: References
2. National Cancer Institute clinical announcement on intraperitoneal cancer for ovarian cancer.
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