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Intraperitoneal Chemotherapy for Advanced Ovarian Cancer: Questions and Answers

1. What is ovarian epithelial cancer?

Ovarian epithelial ovarian carcinoma is a disease in which malignant (cancer) cells form in the tissue covering the ovary. This cancer causes more deaths than any other cancer of the female reproductive system. The following stages are used for ovarian epithelial cancer:

- **Stage I:** Cancer is found in one or both of the ovaries and has not spread.
- **Stage II:** Cancer is found in one or both ovaries and has spread into other areas of the pelvis within the peritoneal cavity (the body cavity that contains the intestines, the stomach, and the liver).
- **Stage III:** Cancer is found in one or both ovaries and has spread to other parts of the abdomen within the peritoneal cavity.
- **Stage IV:** Cancer is found in one or both ovaries and has metastasized (spread) beyond the abdomen to other parts of the body. Cancer that is found in the tissues of the liver is also considered stage IV.

2. What are the incidence and mortality for ovarian cancer?

Ovarian cancer accounts for approximately 4 percent of all women's cancers and is the fourth leading cause of cancer-related death among women in the United States. In 2005, an estimated 22,000 women were diagnosed with ovarian cancer, and more than 16,000 women died from the disease. The incidence rate for ovarian cancer has been slowly declining since the early 1990s. Ovarian cancer has the highest mortality, or death rate, of all cancers of the female reproductive system, which reflects, in part, a lack of clearly recognizable early symptoms and proven ovarian cancer screening tests. Thus, ovarian cancer is often diagnosed at an advanced stage, after the cancer has spread beyond the ovary. White women have higher incidence and mortality rates than other racial and ethnic groups for this disease. It is estimated that approximately \$2.2 billion is spent in the United States each year on treatment of ovarian cancer.

3. What is the standard treatment for ovarian cancer?

The recommended treatment includes primary surgery for diagnosis, staging, and cytoreduction—the removal of the cancerous mass and as many “loose” cancer cells as possible -- followed by chemotherapy. That is, as much tumor as possible should be removed by a skilled surgeon so that any remaining tumor nodules are near microscopic in size (one centimeter or less). Unlike many other solid tumors, effective cytoreduction, also called debulking, has a survival benefit among women with ovarian cancer. The goal of primary surgery is to reduce the burden of ovarian cancer to little or no residual disease. The recommended initial chemotherapy following debulking is generally a platinum-and-taxane chemotherapy combination given every 3 weeks for a period of 18 weeks (6 times over the 18 week period). The platinum drug of choice is either carboplatin or cisplatin, and the taxane drug (a drug originally identified from the bark of the Pacific yew tree) is either paclitaxel or docetaxel.

4. How do taxane and platinum drugs differ in their mechanism of action?

Taxanes, which include paclitaxel (or Taxol) and docetaxel or Taxotere, are a class of drugs that were originally extracted from the bark of the Pacific yew tree, *taxus brevifolia*. These drugs prevent the growth of cancer cells by affecting cell structures called microtubules, which play an important role in cell function. Microtubules act as “highways” for the transport of materials inside the cell. Taxanes stabilize microtubules and prevent the cell from reorganizing them as needed. This blocks cancer cell growth and division. There is also evidence that taxanes can induce apoptosis, or programmed cell death.

Platinum, which include cisplatin (or Platinol) and carboplatin (or Paraplatin), have the element platinum as part of their molecular structure. These drugs form highly reactive, charged platinum complexes that can bind to DNA, resulting in cross-links between the strands of DNA. These cross-links can prevent the growth of cancer cells and cause their death.

When both taxane and platinum drugs are used in combination, they block the cancer process by different mechanisms, thereby increasing the odds of fighting the cancer.

5. What is the difference between intravenous and intraperitoneal administration of chemotherapy?

Intravenous, or IV administration, of chemotherapy drugs is done by inserting a needle into a vein in the body, usually in the arm. Intraperitoneal or IP administration of chemotherapy, usually is done through a surgically implanted catheter, which is a hollow, flexible tube that allows passage of fluids into the abdomen of a woman with ovarian cancer. The chemotherapy drugs are dissolved in saline, or salt water, warmed to body temperature, and then infused into the body via the catheter. This may be followed by an additional liter of saline to facilitate distribution of the drug within the abdominal cavity. Should the patient become uncomfortable for any reason, a second liter does not need to be entirely infused. There is no need to drain the infused fluid from the abdominal cavity. After infusion, patients are encouraged to change position at 15-minute intervals for two hours to ensure adequate drug distribution.

6. What was the design of the Gynecologic Oncology Group's study, GOG-172, which was published in the *New England Journal of Medicine*?

The trial involved 429 women with stage III ovarian cancer who were given chemotherapy following the successful surgical removal of tumors; the surgery was considered successful if a woman did not have visible disease or did not have a single tumor greater than one centimeter in size. The women were randomly assigned to treatment with intravenous paclitaxel 135 mg/m² over 24-hour followed by either intravenous cisplatin 75 mg/m² on day 2 (intravenous arm) or intraperitoneal cisplatin 100 mg/m² on day 2 and intraperitoneal paclitaxel 60 mg/m² on day 8 (intraperitoneal arm). Treatment on both arms was administered every 3 weeks for a total of six courses. Quality of life (QOL) was assessed at four time points.

7. Why was the study conducted?

Previous studies comparing IP to IV chemotherapy had not included paclitaxel. The Gynecologic Oncology Group (GOG) undertook GOG-172 to see whether the improvement in survival noted with IP treatment in other studies was still seen when paclitaxel was given with a platinum drug. GOG conducted a randomized phase III trial to compare a standard regimen of intravenous paclitaxel and cisplatin to an intensive regimen of intravenous paclitaxel and sequential intraperitoneal cisplatin and paclitaxel in previously untreated stage III ovarian cancer.

8. What were the study's main results, and what conclusions can be drawn from it?

Patients who received part of their chemotherapy via an IP route had a median survival time of 16 months longer than women who received only IV chemotherapy. The 205 women treated via the IP route fared better, even though most of them received fewer than the planned treatments. There were no significant quality-of-life differences between the arms one year after treatment. Compared with standard intravenous paclitaxel plus cisplatin, an intensive regimen of intravenous paclitaxel plus sequential intraperitoneal cisplatin and paclitaxel significantly improved progression-free and overall survival in patients with optimally debulked stage III ovarian cancer. The intraperitoneal regimen used in this study had substantial toxicity that compromised treatment delivery. Modifications to improve the tolerability of intraperitoneal treatments are needed.

9. Why do researchers think that IP administration of chemotherapy is more effective than IV?

Residual ovarian cancer after surgery and initial recurrences are primarily confined to the abdomen. IP administration of chemotherapy was first proposed several decades ago. Certain chemotherapy drugs, including cisplatin and, more recently, paclitaxel, have been found to have distinct advantages when given via an IP route. These advantages include higher drug concentrations and longer drug half-lives in the peritoneal cavity, meaning that the drugs remain active in the abdominal area for a longer period of time compared to that observed with IV administration. Administering cisplatin via the IP route increases peritoneal cavity exposure to the drug by a factor of 10- to 20-fold compared with that obtained using IV administration. In

addition, IP drug administration can result in prolonged systemic exposure to chemotherapeutic agents because the drugs slowly leave the peritoneal cavity and enter the bloodstream.

10. What evidence is there that IP administration is better than IV?

Over the past several decades, the results of seven randomized trials assessing the administration of IP chemotherapy for treatment of ovarian cancer have been published. These trials compared chemotherapy administered via the IV route (conventional therapy) to that administered via a combined IV and IP approach. In all of the trials, the chemotherapy was given after primary surgery. Some of these trials, however, had complex designs assessing multiple factors in addition to IP treatment. On average, IP therapy was associated with a 21.6 percent decrease in the risk of death. Since the expected median survival time for women with optimally debulked ovarian cancer receiving standard treatment is approximately four years, this size reduction in the overall death rate is expected to translate into about a 12-month increase in overall median survival. In GOG-172, the improvement in median overall survival was 15.9 months favoring the IP arm compared to the control arm.

11. What are the side effects and toxicities of IP treatment?

The toxicity observed during clinical trials using this procedure is associated with the presence of an IP catheter, the IP administration of chemotherapy, or the chemotherapy itself. The risk of infection and fever is higher among patients receiving IP treatment—and, thus, an IP catheter. In addition, women receiving IP therapy were more likely to have abdominal pain, nausea, and vomiting. In GOG-172, women on the IP arm of the trial experienced greater hematologic, metabolic, and neurologic toxicity than those on the IV arm. The increased toxicity observed in this study also may be due to the IP doses of paclitaxel. In general, however, the toxicity associated with IP treatment appears to be short-term and manageable. However, the administration of IP therapy may exacerbate the development of intra-abdominal adhesions, making subsequent abdominal surgery more risky. Also, delayed nausea is common with IP administration of cisplatin. Drugs used to treat nausea and vomiting, or antiemetics, often need to be maintained for 3 to 4 days after IP infusion. If a woman is not able to tolerate the infusion of the planned treatment volume of the drug(s) due to unacceptable pain or extremely slow infusion, then the IP route is abandoned, and she is treated with IV chemotherapy. Similarly, if a woman experiences severe complications related to the presence of an IP catheter, such as intra-abdominal infection, prolonged intestinal or bowel obstruction, or bowel perforation, then the complication should be managed appropriately and the route of chemotherapy switched from IP to IV. In general, a malfunctioning IP catheter should not be replaced; instead, the physician should switch to IV chemotherapy.

12. Did quality of life differ for women who received IP administration versus IV administration?

In GOG-172, patients in the IP arm reported worse health-related quality of life from the beginning of treatment through its completion; however, one year after the completion of treatment, health-related quality-of-life and pain measures were similar between the two treatment groups, except for paresthesias, or sensations when the abdomen is touched. Paresthesias were more likely to continue at moderate levels among patients on the IP/IV arm. These findings suggest that the additional toxicity, with the exception of paresthesias that may be observed with IP delivery, is generally not a long-term issue for most patients.

13. Why is IP administration not routinely used in the United States, even though it has been practiced for many decades?

IP chemotherapy has not been adopted into standard practice across the United States, despite the previous publication of results from seven studies in leading journals, a lead editorial in the *Journal of Clinical Oncology*, and numerous review articles on the topic. The best data sources suggest that less than one percent of women with ovarian cancer receive IP chemotherapy. There appear to be several potential explanations behind the failure to adopt IP chemotherapy:

- IP administration of chemotherapy is seen as an old approach, outmoded by the development of newer chemotherapy drugs.
- IP chemotherapy requires expertise in the surgical management of ovarian cancer, both to perform effective surgical debulking and to place an intraperitoneal catheter in the abdomen. In a recent the study, only 30 percent of women with ovarian cancer underwent surgery with the appropriate cancer surgeons, namely gynecologic oncologists.
- The administration of a combination of IV and IP chemotherapy is more complex and time-consuming than the administration of IV chemotherapy.
- IP/IV chemotherapy is associated with a greater risk of toxicity than IV chemotherapy. Although this toxicity is generally manageable and does not continue long term, many clinicians have chosen to avoid the increased risk of toxicity by not giving IP chemotherapy at all.

14. Why is NCI issuing this clinical announcement now?

The procedure for NCI Clinical Announcements was established some years ago. In brief, NCI and the cooperative groups responsible for a given research field select a panel-- composed of medical experts in treatment and education, as well as lay members--that is then charged to review the data, advise NCI of whether a clinical announcement should be issued, and review the contents of a proposed clinical announcement, should one be recommended. Additionally, NCI considers a clinical announcement when a clinical trial or trials have identified an intervention that substantially improves with reasonable certainty the survival outcome for a significant number of people with reasonable certainty, and when that intervention is available to the general public. Several large clinical trials over the past 10 years have shown an increased survival benefit of at least a year for most women given IP chemotherapy for ovarian cancer.

NCI issued the announcement because there has not been widespread acceptance of IP chemotherapy in the treatment community.

15. Who are the groups that are releasing the clinical announcement with NCI?

Gynecologic Cancer Foundation: <http://www.thegcf.org>
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Oncology Nursing Society: <http://www.ons.org>
Contact: Karen Hochberg, 412-859-4667

Ovarian Cancer National Alliance: <http://www.ovariancancer.org>
Contact: Sharon Flynn, (202) 331-1332

Society of Gynecologic Nurse Oncologists: www.sgno.org

Society of Gynecologic Oncologists: <http://www.sgo.org>
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16. When was the last NCI Clinical Announcement?

In 1999, NCI issued a clinical announcement that noted the improved survival with combined chemotherapy and radiation (“chemoradiation”) compared to radiation alone among women with cervical cancer.

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- Additional information regarding IP chemotherapy, including administration, clinical practice and patient education can be obtained at <http://www.gog.org>, <http://onsopcontent.ons.org/Toolkits/Chemotherapy/> and <http://www.ons.org/patientEd/Treatment/chemotherapy.shtml>
- For a digest of information on IP chemotherapy, please visit <http://www.cancer.gov/clinicaltrials/developments/IPchemo-digest>.
- For more information about ovarian cancer, please go to <http://www.cancer.gov/cancertopics/types/ovarian/>.
- For more information about clinical trials for ovarian cancer, please go to <http://www.cancer.gov/search/clinicaltrials/> and <http://www.cancer.gov/clinicaltrials/ovarian-cancer-updates>.

- For more information about cancer, please visit the NCI Web site at <http://www.cancer.gov> or call NCI's Cancer Information Service at 1-800-4 CANCER (1-800-422-6237).