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Intraperitoneal Chemotherapy in Ovarian Cancer

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Abstract

Epithelial ovarian cancer (EOC) is the fifth leading cause of cancer death in women. Primary surgery, followed by adjuvant chemotherapy is the basis of treatment for this disease. A standard treatment includes primary surgery and if possible optimal debulking surgery (tumor residue of < 1 cm), followed by a chemotherapy; paclitaxel-carboplatin is the standard regimen in ovarian cancer. Given that the main method of spreading this disease is in the peritoneal cavity, the systemic chemotherapy brings about numerous complications; moreover, as the method of prescribing a drug inside the peritoneum causes a high drug concentration in the peritoneal cavity, conducting an intraperitoneal chemotherapy has been examined clinically. In cases of ovarian cancer recurrence, performing a secondary cytoreductive surgery, in addition to hyperthermic intraperitoneal chemotherapy (HIPEC), has led to a good survival among patients. Currently, studies are ongoing to better explain the effects of this treatment method compared to previous methods.

Keywords: Epithelial Ovarian Cancer, Intraperitoneal Chemotherapy, HIPEC

1. Introduction

Epithelial ovarian cancer is one of the most prevalent gynecologic tumors and is known as the fifth leading cause of death caused by cancer among women (1).

Primary surgery and doing comprehensive staging should be performed as much as possible by a gynecologist oncologist. In cases where the surgical procedures are done by a gynecologist oncologist, their outcomes are better than those performed by other surgeons (2).

A surgical cytoreduction leads to an increase in the survival duration. The residual volume of the disease after performing a cytoreductive surgery has an adverse effect on the survival duration of a patient (3).

Currently, surgery followed by a systemic chemotherapy with a paclitaxel-carboplatin regimen is a standard patient management method in advanced stages of epithelial ovarian cancer. Even if this method of treatment has a good response rate, recurrence of the disease occurs in about 70% of cases in stage III. In this case, if the metastatic disease is outside of the peritoneal cavity, a definitive cure does not occur and the contraindication of performing a cytoreductive surgery is along with HIPEC. The survival duration depends on the time interval from the primary treatment to recurrence, and long-term survival duration has only been reported to be 20% to 30% (4-8). However, in most cases, the most prevalent method of spreading the disease is in the peritoneal cavity and the basic principle of prescribing chemotherapeutic agents inside the peritoneal cavity was confirmed by applying available pharmacokinetics, pharmacodynamics, and preclinical information. In comparison with the intravenous method, prescribing a drug inside the peritoneum causes a multiplier increase in the concentration of the drug in the peritoneal cavity. Moreover, clinical trials have shown that the intraperitoneal treatment, as a primary treatment for ovarian cancer, has many benefits survival rate. In most patients, epithelial ovarian cancer, which also includes fallopian tube and peritoneal carcinoma, is limited to the peritoneal cavity at the time of diagnosis, and the disease is limited to the peritoneal cavity in most recurrences. This is why ovarian cancer is an ideal condition for the intraperitoneal treatment. Pharmacokinetic studies have indicated that prescription of the intraperitoneal chemotherapy results in a high ratio of the intraperitoneal drug to the plasma level of the drug; the peak concentration of chemotherapy drugs occurs for cisplatin, paclitaxel, carboplatin, and docetaxel (9, 10). Figure 1 depicts how the drug is disseminated.

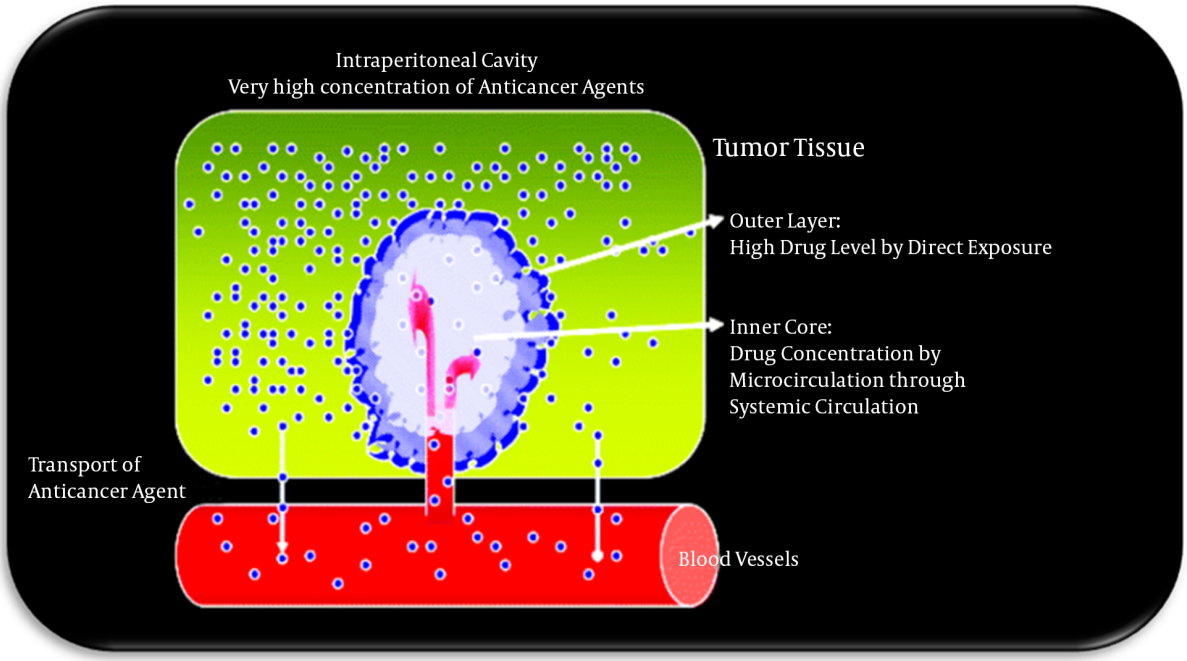

Figure 1. This Schematically Shows the Pharmacokinetic Intraperitoneal Chemotherapy and How the Drug Is Disseminated in the Peritoneal Cavity

2. Patient Selection

2.1. Intraperitoneal Chemotherapy

According to the available clinical data, the intraperitoneal chemotherapy may be the most effective method of adjuvant therapy in patients who underwent a cytoreductive surgery due to stage III of epithelial ovarian cancer and reached the optimal debulking of < 1 cm. Those patients whose disease remains without having a gross and underwent the cytoreductive surgery gain benefit the most from the intraperitoneal chemotherapy and have better survival duration.

In addition, some of these methods are used for women with epithelial ovarian cancer who underwent neoadjuvant chemotherapy and had reached an optimal cytoreduction during the surgery (11).

On the other hand, it is assumed that avascular tumoral (without vessels) cells are exposed to a higher concentration of the drug in the course of the intraperitoneal chemotherapy compared to the intravenous chemotherapy. Furthermore, the systemic complications of the drug also reduce (12, 13).

Moreover, there is a consensus that the intraperitoneal chemotherapy should not be used for stage IV of the disease or in cases where the tumor residue is more than 1 cm and the optimal debulking is not performed. Meanwhile, a phase II study conducted on 26 patients demonstrated the effectiveness of the intraperitoneal chemotherapy in women with residual tumor of more than 2cm (14).

Additionally, there are reports of the intraperitoneal chemotherapy during pregnancy. In a case report conducted by Smith et al., a 36-year-old primigravida was diagnosed with grade III serous adenocarcinoma and stage IIB in her 12 weeks of pregnancy. After having a full consultation, she accepted having the intraperitoneal chemotherapy. The patient underwent 4 courses of chemotherapy during her pregnancy; the treatment was complicated due to thrombocytopenia and preeclampsia. The patient underwent a cesarean section at 37 weeks of pregnancy, (15).

2.2. Basic Principles of the Intraperitoneal Chemotherapy

It seems that catheter and port insertion can be best done during a surgical staging and cytoreduction; however, it can be postponed and done after the surgery as a separate action. In this case, it is performed by applying a laparoscopy and a mini-laparotomy or an interventional radiology and is usually performed a few weeks after the primary debulking (16, 17).

The intraperitoneal chemotherapy is prescribed 24 hours after the surgery or in the operating room. However, in cases where it is performed earlier, the renal toxicity should be considered. Some physicians wait as long

as the patient returns to the normal bowel movement and the ileus is resolved after the surgery to ensure that there are no preoperative complications (18).

In those patients whose IP port is inserted in a second surgical procedure, the treatment may begin 2 hours after the catheter insertion.

The necessary measures that should be taken into consideration include routine premedication, which usually contains an administration of antihistamines and dexamethasone. The temperature at which the drug is dissolved should be 37°C. During conducting the procedure (infusion of the drug), the patient should be in supine, semi-Fowler's condition, and the head should not be more than 30 degrees above the bed. After infusion of the drug, the patient should be displaced from side to side every 15 minutes for 1 hour to ensure that the drug has spread throughout the abdomen. After the administration of the chemotherapy drug, the port and catheter are washed with at least 10 mL of heparin 100 units/mL (19).

After the completion of chemotherapy, the catheter should be removed as soon as possible.

IP contraindications are as follow:

- Intolerance of a cytoreductive surgery
- Active peritonitis or sepsis
- Severe intra-abdominal adhesions that prevent an appropriate release and dissemination of chemotherapy agents in the peritoneal cavity
- Extensive peritoneal contamination
- Inappropriate renal function for clearance of cisplatin
- Failure to perform the intraperitoneal chemotherapy schedule (17)

2.3. Ovarian Cancer Recurrence and HIPEC

In cases of ovarian cancer recurrence, the secondary cytoreductive surgery, in addition to hyperthermic intraperitoneal chemotherapy (HIPEC), is an option that leads to a relatively good survival and can be performed when no gross residue are seen after the surgery (20).

Currently, despite the fact that the cytoreductive surgery accompanied with HIPEC has not been agreed upon in cases of ovarian cancer recurrence due to a lack of a randomized trial, there are several reports indicating that the median overall survival was 19 to 57 months and the progression-free survival (PFS) was 10 to 31 months (21).

2.4. Complications and Disadvantages of the Intraperitoneal Chemotherapy

Despite the improvement of the survival duration, using intraperitoneal chemotherapy is not widely accepted. This can be due to a number of reasons including high cost, inappropriate administration, high toxicity, and consequently, discontinuation of the treatment by patients or by their physicians (22). Complications associated with catheter include obstruction, leakage, malposition, infection, or metastasis, which should be considered since these complications are responsible for several cases of discontinuation of the treatment (23). Like all new therapeutic patterns, the benefits of HIPEC in treating patients with ovarian cancer should be examined along with its complications. Nevertheless, 35% toxicity and 5% mortality rate were reported (24). Studies conducted to investigate the quality of life have shown that mental and psychological health and quick return to the preoperation condition following HIPEC can be reached (25).

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