Review Article

Management of recurrent epithelial ovarian cancer

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Abstract: Epithelial ovarian cancer is the fifth most common cancer in women. It is usually diagnosed at an advanced stage and is the leading cause of death from gynecologic cancers in women. The overall survival rate at five years is 50% and its treatment is still poor. We need new treatments for patients with recurrent ovarian cancer who are incurable with current management. We review the effectiveness of new biological agents and morbidity and mortality of cytoreductive surgery. Since the hyperthermic increases the effectiveness of chemotherapy and the chance of survival, hyperthermic intraperitoneal chemotherapy has been proven to be a promising option, however it still requires further study to be the standard treatment.

Keywords: Epithelial ovarian cancer; hyperthermic intraperitoneal chemotherapy; cytoreductive surgery; morbidity and mortality; biological agents

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Introduction

Epithelial ovarian cancer affects more than 200,000 women, with 125,000 deaths annually worldwide (1). In U.S. 2012, 22,280 women were diagnosed with ovarian cancer and 15,500 died from this disease, making the ovarian cancer, usually diagnosed at an advanced stage, the fifth leading cause of cancer death (2,3) and the leading cause of death in women with gynecological cancers. Cytoreductive surgery and first-line chemotherapy with platinum and taxanes have increased the disease-free and overall survival, but recurrence of the disease is common in these patients. The overall 5-year survival is 50%, requiring better treatments for patients with recurrent ovarian cancer (platinum-sensitive or resistant) that are incurable with current management, where life expectancy is 12 to 18 months (3,4).

After recurrence, response rates to second-line chemotherapy for platinum-sensitive patients are 30% or higher; however, patients with platinum-resistant disease have significantly lower response rates of 10-25% to chemotherapeutic agents, such as liposomal doxorubicin, taxanes, etoposide, topotecan and gemcitabine. Given the poor response of recurrent disease to traditional cytotoxic agents, approaches with biologic agents that target the mechanisms of tumor growth and spread have been pursued. One of these agents is bevacizumab, a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF).The increased expression of VEGF is associated with a poor prognosis and a decreased disease-free interval disease. The use of bevacizumab for recurrent ovarian cancer has been reported response rates of 16-21% with an additional 39-55% of patients exhibiting stable disease (5).

The combination of bevacizumab and cyclophosphamide should be considered for use in patients with recurrent ovarian cancer due to its impressive response rate, favorable side-effect profile, and tolerability (5).

Hyperthermic intraperitoneal chemotherapy also provides a promising option (4); because there are laboratory data demonstrating the ability of hyperthermia to enhance the efficacy of chemotherapy (4-7).

After diagnosis and surgical stratification, primary optimal cytoreduction (surgical efforts aimed at the total elimination of the gross tumor) is one of the important prognostic factors for survival of women with epithelial ovarian cancer, although optimal debulking surgery is controversial even with most implants defined as residual tumor <1 cm in maximum diameter. Although the size of

residual tumor masses after surgery has been shown to be an important prognostic factor for advanced ovarian cancer, it is unclear whether surgery is directly responsible for the outcomes that are associated with the lowest residual disease (6-8). The standard treatment for ovarian cancer is the optimal primary debulking surgery followed by platinum-based chemotherapy. Among women receiving clinical remission after completion of initial combination therapy, although most (60%) with advanced epithelial ovarian cancer ultimately develop recurrence and its treatment is not defined, surgery in recurrent ovarian cancer is associated with increased overall survival (3,7).

Hyperthermic intraperitoneal chemotherapy studies in epithelial ovarian cancer

The most important feature of epithelial ovarian cancer is intraperitoneal dissemination at the time of presentation. Intraperitoneal chemotherapy management is reasonable. The tumor tissue directly exposed to high concentrations of chemotherapy into the peritoneal cavity, which has been shown to improve survival overall and disease-free (4) considering intraperitoneal chemotherapy with cisplatin for patients with advanced ovarian cancer, optimal cytoreduction or with residual disease <1 cm, with toxicity, catheter-related problems, such as infection or occlusion (8,9). Failing to complete chemotherapy cycles, only 42% finished the six cycles. Although 19% did not complete the treatment, not the standard management, overall survival improved compared to those on chemotherapy intravenously (10-17). Reports of intraperitoneal cisplatin administration at the time of primary surgery followed by chemotherapy intravenously are of acceptable toxicity with the benefit of no need to repeatedly place the catheter intraperitoneal chemotherapy. Even using intraperitoneal chemotherapy at the time of surgery and/or in the immediate postoperative period facilitates the administration of chemotherapy and avoids prolonged peritoneal access complications. It is unknown how many minimum of intraperitoneal chemotherapy cycles are needed to improve survival for the moment, which provide the same cycles used in intravenous chemotherapy (18).

Another study in patients with epithelial ovarian cancer who have a pathologic complete response, the 8-year progression-free survival rates were 63.16% in hyperthermic intraperitoneal chemotherapy with paclitaxel group and 29.17% in the control group (P=0.027); and the 8-year overall survival rates were 84.21% in the hyperthermic intraperitoneal chemotherapy with paclitaxel group and 25.00% in the control group (P=0.0004). Therefore the hyperthermic intraperitoneal chemotherapy with paclitaxel should be considered as a consolidation treatment option (4,19).

The main drawback is that intraperitoneal chemotherapy using cisplatin is more toxic and difficult to handle compared to carboplatin, which is the current standard intravenous chemotherapy agent (19). Carboplatin has replaced cisplatin as the standard chemotherapy, which has led to calls for IP therapy to prove its worth once again (12). Carboplatin administering IP in the cavity is absorbed from the surface within 24 hours peritoneal similar to intravenous administration, although intraperitoneal platinum is 17 times greater than when carboplatin was given to intraperitoneally (12,19), demonstrating that there is possible residual of intraperitoneal carboplatin in handling cases with suboptimal debulking (13); 70 mg/m^2 cisplatin in 1 L of normal saline was administered intraperitoneally 24 hours after surgery and then adjuvant chemotherapy was started 2-4 weeks postoperatively (11).

Intraoperative administration with cisplatin 75 mg/m^2 to 41.5 ℃ for 90 minutes was given to patients with residual tumor <1 cm after cytoreductive surgery. When all patients receiving adjuvant chemotherapy with platinum and taxane combination, adverse events and response to primary treatment were evaluated: there were no deaths or morbidity; the most common adverse events affected the hematologic system, followed by the gastrointestinal system. Most adverse events were anemias requiring transfusion and nausea/vomiting requiring medication, the 93% experienced complete remission, and 7% had progressive disease (14).

A recently study had been evaluating the intravenous administration of paclitaxel at 135 mg/m^2 on day 1 followed by intraperitoneal cisplatin 75 mg/m^2 on day 2 and then intraperitoneal paclitaxel on day 8, which also includes the combination and bevacizumab maintenance in another, all stage III patients receiving neoadjuvant chemotherapy, patients who respond will accept interval cytoreductive surgery. If there is residual disease after this optimum is <1 cm, they will be randomly assigned to one of three arms control with the combination intravenous paclitaxel in 135 mg/m^2 followed by carboplatin on day 1. Intravenous intravenous paclitaxel to 60 mg/m^2 on day 8 is the second arm as the control, but the carboplatin was given intraperitoneally. The third arm is given bevacizumab, awaiting results, recommending doctors who participate in these studies to assess whether intraperitoneal chemotherapy is important (15,20,21).

To determine the first-cycle maximum tolerated dose of intraperitoneal carboplatin in combination with intravenous paclitaxel and then evaluate the feasibility of this dose over multiple cycles, start dose intraperitoneal carboplatin or intravenous paclitaxel of 175 mg/m^2; toxicity due to neutropenia is a common dose-limiting. The addition of hematopoietic growth factors may allow increased rate of termination and continuation of this dose (22-24).

Discussion

Although the standard treatment for advanced epithelial ovarian cancer is optimal debulking and adjuvant chemotherapy with intravenous platinum and taxane (3,18,25), the response rates are high. Many patients turn to and die of peritoneal carcinomatosis. The addition of hyperthermic intraperitoneal chemotherapy to standard management is feasible and can improve morbidity and mortality (26,27).

Intestinal obstruction is a common feature of advanced ovarian cancer or recurrent. Patients with bowel obstruction are generally in poor physical condition, with a limited life expectancy. Therefore, maintaining patients' quality of life with effective control of symptoms is the primary goal of management of intestinal obstruction and prolonged survival surgery. During primary surgery for advanced epithelial ovarian cancer, doctors should make every effort to achieve complete cytoreduction (8). When this is not possible, the surgical goal must be the optimal residual disease (<1 cm). Evidence suggests that optimal cytoreductive surgery or ultra-radical leads to improved survival (3,8). It was unclear whether there were any differences in progression-free survival, quality of life and morbidity. There is also evidence of survival benefit by adding hyperthermic chemotherapy, a secondary debulking surgery for ovarian cancer stage III and salvage cytoreduction for recurrent ovarian cancer (28).

The optimal cytoreduction improves survival in selected patients. Studies with additional monitoring are needed to determine the effects of hyperthermic intraperitoneal chemotherapy on survival (21).

There is less evidence of benefit with intraperitoneal hyperthermic chemotherapy for early stage (I-II). Postoperative mortality is not higher after cytoreductive surgery and Hyperthermic intraperitoneal chemotherapy (0.7%) than after cytoreductive surgery (1.4%). Hyperthermic intraperitoneal chemotherapy debulking palliative without disabling ascites in patients with recurrent ovarian cancer has been used hyperthermic intraperitoneal chemotherapy after cytoreduction in patients with gastric cancer with ovarian metastasis, with few complications. To improve disease-free period, however, it is recommended only for ovarian metastases (4,6).

Hyperthermic intraperitoneal chemotherapy has recently been recommended as the standard management in patients with advanced ovarian cancer for the treatment of residual disease. It is reported that a laparoscopic cytoreductive surgery and hyperthermic intraperitoneal chemotherapy have been recently recommended as the 'new standard of care' in the treatment of patients with stage IV ovarian cancer of no evidence of extra-abdominal metastases who received intraperitoneal hyperthermic chemotherapy for laparoscopic (29). The overall response rate after intraperitoneal hyperthermic chemotherapy for laparoscopic (neoadjuvant and/or adjuvant) was 100%, with decreasing size of neoplastic deposits. The laparoscopic intraperitoneal hyperthermic chemotherapy before optimal debulking is associated with improved overall survival and disease-free. Diagnostic laparoscopy was valuable in preoperative evaluation of the extent of peritoneal carcinomatosis, and improved patient selection for cytoreductive surgery and Hyperthermic intraperitoneal chemotherapy (30). The optimal cytoreduction and hyperthermic intraperitoneal chemotherapy show promising results, but require further study to justify its effectiveness.

Conclusions

In the management of ovarian cancer, the amount of residual disease at the end of debulking surgery is an important prognostic factor in the initial response to platinum-based chemotherapy treatment and prognosis defined at the time of recurrence. First-line chemotherapy should include the combination of platinum and taxane, which is also promising with the addition of bevacizumab, and the role of hyperthermic intraperitoneal chemotherapy in the current standard treatment; theoretical sense given the high rates of recurrence after standard treatment and research protocols must be made to justify its effectiveness.

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