Ten years’ disease-free survival of advanced epithelial ovarian cancer treated by cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy

A case report and literature review

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Abstract

Rationale: One of the most distinctive features of epithelial ovarian cancer is tendency to disseminate into peritoneal cavity to form peritoneal carcinomatosis, indicating advanced disease with poor prognosis.

Patient concerns: A fifty-year-old patient had a chief complaint of an abdominal distension lasting 1 month.

Diagnoses: The patient was diagnosed with advanced epithelial ovarian cancer with peritoneal carcinomatosis by computed tomography scan, tumor markers, endoscopy examination, and pathology.

Interventions: The patient was treated with cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy followed by 8 cycles of systemic chemotherapy.

Outcomes: Till March 9, 2020, the patient has disease-free survival over 10 years.

Lessons: The application of cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy combined with systematic chemotherapy may improve survival dramatically for the patients with epithelial ovarian cancer and peritoneal carcinomatosis and should be considered as an option of a relatively new regime.

Abbreviations: AUC = area under curve, CA-125 = carbohydrate antigen-125, CA-153 = carbohydrate antigen-153, CA-199 = carbohydrate antigen-199, CC = completeness of cytoreduction, CRS = cytoreductive surgery, CT = computed tomography, DFS = disease-free survival, EOC = epithelial ovarian cancer, HIPEC = hyperthermic intraperitoneal chemotherapy, IP = intraperitoneal, OS = overall survival, PC = peritoneal carcinoma, PCI = peritoneal cancer index, PSOGI = Peritoneal Surface Oncology Group International, RCTs = randomized control trials.

Keywords: advanced ovarian cancer, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, peritoneal carcinomatosis
1. Introduction

Epithelial ovarian cancer (EOC) is one of the main causes of cancer death for women worldwide.[1] It is often diagnosed at an advanced stage and the disease remains confined to the peritoneal carcinomatosis (PC) for much of its natural history, resulting in unfavorable outcomes, with an overall 5-year survival rate <20%.[2] Since 1980s, the standard care for EOC-PC has been undertake debulking surgery followed by systemic chemotherapy with platinum and taxanes-based regimens.[3]

Over the past 30 years, cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has been developed to treat PC from various abdominal and pelvic malignancies, which combines the advantages of CRS to remove the visible tumor nodules, and HIPEC to eradicate micrometastases and free cancer cells. The success of such integrated approach has been verified in PC from colorectal cancer and pseudomyxoma peritonei from appendical original. And in recent years, researchers have also applied CRS + HIPEC to treat EOC-PC[4] with encouraging results. In particular, 3 prospective randomized controlled trials organized by the Gynecologic Oncology Group (GOG) have shown that CRS + HIPEC could improve the overall survival (OS) of patients with selected EOC-PC.[5] The sound clinical evidence prompts the National Cancer Institute (ASCO, American Society of Clinical Oncology) to recommend combined intravenous and intraperitoneal chemotherapy for stage III ovarian cancer. NCCN has recommended intraperitoneal chemotherapy as an optimal treatment option for ovarian cancer.

In China, our group has been focused on CRS + HIPEC to treat PC from gastrointestinal and gynecological cancers. And in this report, we present a successful case of EOC-PC treated by CRS +HIPEC, who has remained disease-free for over 10 years. Pertinent literatures are also reviewed.

2. Case presentation

A 50-year-old female patient was referred to our clinic on November 11, 2008, complaining about an abdominal distension that lasted one month. The patient had hypertension and nephrolith and did not have family history of cancer. Gastrointestinal endoscopy and colonoscopy identified no neoplastic lesion. Abdominopelvic doppler ultrasonography and contrast-enhanced computed tomography (CT) scan revealed solid pelvic tumors and ascites (Fig. 1A). Carbohydrate antigen (CA) 125 was 773.7 U/mL (normal range 0–35 U/mL), but the other tumor markers, such as CA-199, CA-153, alpha fetoprotein, and routine blood tests had no obvious abnormality.

2.1. The first course of operation: debulking surgery

The patient was clinically diagnosed as having ovarian cancer with ascites, and she was scheduled for surgery on November 25, 2008. Laparotomy revealed a little bloody ascites, 2 massive solid tumors on both ovaries (maximum 8 × 8 cm on the right side, maximum 10 × 8 cm on the left side). Numerous peritoneal implants scattered on the surface of uterus, cystic serosa, rectum and sigmoid colon, and the greater and lesser omentum. The peritoneal cancer index (PCI) was 19. The debulking procedure included hysterectomy, bilateral oophorectomy, and resection of implanted nodules on the peritoneum. But the residual tumor in the Cul-de-sac and in the sigmoid colon mesentery could not be completely removed, as the patient and her family refused preventive colostomy. The completeness of cytoreduction (CC) score was 3. The clinicopathology report was ovarian serous papillary adenocarcinoma (grade II–III).

2.2. Interval chemotherapy

Three cycles of adjuvant systemic chemotherapy were delivered on day 9, November 4, 2008 to February 11, 2009, after the debulking surgery, with paclitaxel liposomes at the dose of 175 mg/m², and carboplatin (area under the curve [AUC] – 5 mg). The serum CA 125 levels decreased significantly, from 90.8 to 32.9 U/mL. However, reexamination by doppler ultrasonography and CT scan revealed tumor mass at the Cul-de-sac region.

2.3. The second course of operation: CRS + HIPEC

After 3 cycles of systemic chemotherapy, the patient was reevaluated by a multidisciplinary team of surgical oncologists specialized in peritoneal carcinomatosis and gynecological oncologists. It was concluded that the patient was fit for another major surgery and there was no absolute surgical contraindication.

On February 25, 2009, the patient received a complete CRS + HIPEC. Intraoperative PCI assessment was conducted immediately after laparotomy following Sugarbaker criteria.[7] The patient had a PCI of 11, with tumor nodules on remnant greater omentum, pelvic peritoneum, and sigmoid colon. In addition, there was moderate adhesion in the lower right quadrant and the pelvic regions. Standardized CRS was performed, including greater omentectomy, complete pelvic peritonectomy with resection of rectosigmoid colon (Fig. 1B), achieving a postoperative CC score of 0. After CRS, an open-technique HIPEC was performed with mitomycin C 30 mg and cisplatin 120 mg at 43 ± 0.5°C for 90 minutes.

The pathology revealed serous papillary EOC with peritoneal metastasis and calcifications. The abdominal tumor has invaded to serosa and muscularis of the sigmoid colon (Fig. 1C).

2.4. Consolidation chemotherapy

From February 28, 2009 to August 18, 2009, the patient received 8 cycles of systemic chemotherapy for consolidation purpose. The regimen was paclitaxel liposomes at the dose of 175 mg/m², and carboplatin (AUC—5). The regimen was repeated every 3 weeks. No grade 3 or 4 adverse events occurred during the chemotherapy course. The serum CA 125 level remained low during and after chemotherapy (Fig. 1D).

2.5. Follow-up

The patient has been followed up on a regular basis. By the time of preparation of the manuscript, she remained disease-free survival (DFS) in good condition for >10 years. The treatment course of the patient was summarized in Figure 2. This case report was approved by the ethics committee of Beijing Shijitan Hospital, Capital Medical University and the informed consents were obtained from the patient.

3. Discussion

The report presents a case of EOC-PC, successfully treated by integrated multidisciplinary therapy, debulking surgery, interval chemotherapy, CRS+HIPEC, and consolidation chemotherapy. Up to the last follow-up, the patient remains disease free over 10 years.
In the background of very dismal clinical outcome for patients with advanced EOC, with 5-year survival <20%, this case deserves special attention, as it could offer useful insight into the clinical management of EOC-PC.

The key feature of this successful case is the timely application of the currently best treatment approaches. When the tumor burden was very big, debulking surgery was the only sensible option to achieve a quick tumor burden reduction. The 3 cycles of interval chemotherapy further helped reduce the tumor burden and also render the remnant tumor at very low proliferation status. After the interval chemotherapy, the standard CRS + HIPEC ensured a CC0–1 cytoreduction and total eradication of remnant tumor implants and free cancer cells in the abdomen and pelvis. Furthermore, the 8 cycles of consolidation chemotherapy post CRS + HIPEC was routinely accomplished.

Generally speaking, PC is an inevitable and incurable endpoint of EOC, but innovations in advanced EOC treatment have been going on, with major developments in intraperitoneal chemotherapy.

As early as 1993, Salle et al reported the application of peritoneal heat perfusion chemotherapy in the treatment of ovarian cancer, and showed certain efficacy and safety. Subsequently, numerous cohorts or case-control studies focused on CRS + HIPEC for primary or recurrent EOC-PC, and obtained encouraging efficacy and acceptable safety compared to traditional treatments. A literature review on these studies were detailed in Table 1. Among these studies, 2 prospective randomized control trials (RCTs) deserve special attention.

Spiliotis et al reported the first phase III RCT in 2015. This trial was conducted for 8 years in Greece. Finally, 120 patients with recurrence EOC-PC (stage IIIc and IV) were included and randomized into CRS + HIPEC group and CRS alone group. With a period of 8 years, OS was significantly longer in the CRS + HIPEC group than CRS alone group (26.7 vs 13.4 months, \( P < .05 \)). Moreover, the 3-year survival rate was 75% in CRS + HIPEC group, much better than 18% in CRS alone group (\( P < .01 \)). They also found that patients with PCI <15 and complete cytoreduction could benefit more from CRS + HIPEC.

van Driel et al reported the first large-sample-size RCT on CRS + HIPEC in primary phase III EOC in 2018. A total of 245 patients with newly diagnosed advanced EOC, fallopian tube

![Figure 1. Related results of the patient’s treatment process. (A) Before the first surgery, contrast-enhanced CT scan shows huge pelvic malignant tumors, with adhesion to the rectum and sigmoid colon. (B) After the second surgery, abdominopelvic CT scan after CRS + HIPEC shows a clean and clear pelvic floor, with circular anastomosis marker of descending colon and rectum (the red arrow). (C) Pathological analysis on the tumors. (Bi)lateral ovarian serous papillary adenocarcinoma (grade II–III). HE staining (\( \times 400 \)). (D) Serum CA125 levels during the treatment course, which remain normal range after CRS+HIPEC and consolidation chemotherapy.](image)
Figure 2. The treatment course of the patient. From the first treatment in November 2008 to the last follow-up in March 2020, the patient has been disease-free for almost 10 years.

Table 1

| Author       | Year | Country of the publication | Type of the article | Patients (no.) | Chemotherapy agents | System chemotherapy | Median OS, mo | Median DFS, mo | Median follow-up |
|--------------|------|-----------------------------|---------------------|----------------|---------------------|---------------------|--------------|---------------|------------------|
| van Driel et al[21] | 2018 | Netherland                  | Phase III trial     | 245            | DDP 100 mg/m²        | TAXOL 175 mg/m² + CBP AUC 6 | 45.7         | —             | 14.2             | 4.7 y           |
| Mercier et al[20] | 2018 | France                      | Retrospective cohort study | 210            | DDP 100 mg/m² + TAXOL 175 mg/ m² | CBP + TAXOL | —             | 69.3            | 30.3            | 43.5 mo          |
| Cesarelli et al[19] | 2018 | Italy                       | Retrospective case control | 56             | TAXOL 60 mg/m² or DDP 100 mg/m² + DOX 15 mg/m² | CBP + TAXOL | —             | *              | 57              | 14 17            |
| Manzanedo et al[18] | 2018 | Spain                       | Retrospective study  | 61             | TAXOL 75 mg/m², TAXOL or DOX or L-OHP 460 mg/m² or MMC 50 mg/m² | CBP and TAXOL or DOX liposomal and TPT | 54.2         | 5.7           | 53.8 mo          |
| Di Giorgio et al[17] | 2018 | Italy                       | Retrospective study  | 511            | DDP 75 mg/m², TAXOL or DOX or L-OHP 460 mg/m² or MMC 50 mg/m² | CBP and TAXOL or DOX liposomal and TPT | 54.2         | 5.7           | 53.8 mo          |
| Moaga et al[16] | 2017 | United State                | Retrospective study  | 93             | DDP 175 mg/m², or MMC 50 mg/m² | TAXOL 175 mg/m² + DOX 100 mg/m² or DOX 35 mg/m² | 74           | 5.7           | *              | 8.5 45.8 mo      |
| Sun et al[15] | 2016 | China                       | Retrospective study  | 245            | DDP 50 mg/m² or paclitaxel 175 mg/m² or MMC 15 mg/m² or DOX 35 mg/m² | TAXOL 175 mg/m² + CBP AUC 6 | 51           | 19            | 22 mo            |
| Kock et al[14] | 2016 | Serbia                      | Retrospective study  | 31             | DDP 50 mg/m²         | —                     | 51           | 19            | 22 mo            |
| Spiliotis et al[14] | 2015 | Greece                      | Phase III trial     | 120            | DDP 100 mg/m² + paclitaxel 175 mg/m² or MMC 15 mg/m² or DOX 35 mg/m² | TAXOL 175 mg/m² + CBP AUC 6 | 51           | 19            | 22 mo            |
| Safra et al[11] | 2014 | Israel                      | Retrospective study  | 111            | DDP 50 mg/m² + DOX 15 mg/m² or TAXOL 60 mg/m² + CBP AUC 4, or MMC 3.3 mg/L | DDP or TAXOL or DOX liposomal, TPT, GEM | —           | *             | 15              |                |
| Coccolini et al[12] | 2014 | Korea                       | Phase II study      | 54             | DDP 100 mg/m², and TAXOL 175 mg/m² | —                     | 32.9         | 12.5          | 20               |

The "∗" indicates the median survival is not reached, “—” indicates the data is not available in the article.

CBP = carboplatin, DDP = cisplatin, DFS = disease-free survival, DOX = doxorubicin, GEM = gemcitabine, LBP = lobaplatin, L-OHP = oxaliplatin, MMC = mitomycin, OC = ovarian cancer, OS = overall survival, TAXOL = paclitaxel, TPT = topotecan.
carcinoma, and primary peritoneal carcinoma were first treated by 3 cycles of paclitaxel-and-carboplatin adjuvant chemotherapy and then randomized into CRS + HIPEC group and CRS alone group. At a follow-up of 4.7 years, the median recurrence-free survival was 3.5 months longer in CRS + HIPEC group than in the CRS group (14.2 vs 10.7 month). The 3-year recurrence-free survival was 17% in the CRS + HIPEC group and 8% in the CRS only group ($P= .003$). The median OS of CRS + HIPEC group is better than CRS only group (45.7 vs 33.9 months, $P = .02$). And the adverse events of grade 3 or 4 have no difference between the 2 groups.

Based on accumulating high-level clinical evidence, the Peritoneal Surface Oncology Group International (PSOGI) has recommended CRS + HIPEC for selected patients with EOC-PC, although more international collaborations in multicenter RCTs are needed to further validate this integrated treatment package.

This work reported a case of EOC-PC successfully treated by CRS + HIPEC integrated treatment strategy. Combined with literature analysis, this case again provides evidence that complete CRS + HIPEC could be currently the most promising treatment for EOC-PC.

**Author contributions**

JZ participated in the conception of the paper and wrote the manuscript. LJM and FBW performed the experiments and analyzed the patient data. YL edited the manuscript. Raw data regarding the patient are managed strictly.

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