

Case Report

CRS and HIPEC in a patient with recurrent ovarian cancer after PDS and adjuvant chemotherapy, a case report and MDT discussion

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Abstract

Background: Ovarian cancer is the most lethal gynecologic malignancy worldwide and is plagued by a high recurrence rate. Cytoreductive surgery and adjuvant chemotherapy are considered the gold standard treatment for advanced ovarian cancer patients. Hyperthermic intraperitoneal chemotherapy (HIPEC) is a relatively new option, especially for patients with peritoneal and recurrent disease. **Case:** We intend to present a case of a patient with recurrent ovarian cancer managed initially with primary debulking surgery plus adjuvant chemotherapy and afterward with secondary cytoreduction and HIPEC. **Conclusion:** Complete cytoreduction remains the ultimate goal in the surgical treatment of patients with advanced stage ovarian cancer. Moreover, patients would benefit from the use of HIPEC after the optimal cytoreduction, especially in those with peritoneal metastases. Several studies have shown the utility of HIPEC regarding disease-free and overall survival after extended debulking surgery.

Keywords: Cytoreductive surgery; HIPEC; Recurrent ovarian cancer

1. Introduction

In 2020, newly diagnosed ovarian cancer cases were estimated to be almost 22,000 with 14,000 deaths to be occurred by this malignancy in the US [1]. Worldwide in 2018, 295,000 women were diagnosed with ovarian cancer and approximately 185,000 patients died from this lethal malignancy. These numbers rated ovarian cancer as the most lethal gynecological malignancy. More specifically, in the US ovarian cancer accounts for more deaths than all the other gynecological malignancies combined in 2018 [2].

Due to its indolent clinical course, approximately only 25% of the patients will diagnose in early stage (stage I), while two thirds of the newly diagnosed patients will have advanced disease with spread outside of the pelvis. Regarding the patterns of the spread, ovarian metastases can occur through direct extension to regional tissues (bladder, rectum for example), through exfoliation of tumor cells to ascites and into the peritoneal cavity, through lymphatic drainage, or through hematogenous dissemination. These routes explain all the possible sites of metastases of this malignancy.

Treatment of ovarian cancer patients depends on their stage and histologic type of lesion and can include primary or interval debulking surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC), neoadjuvant or adjuvant systematic chemotherapy. The gold standard regarding the treatment of these patients remains the complete cytoreduction without any residual macroscopic lesion whenever the cytoreductive surgery is done [3]. There is some evidence that neoadjuvant chemotherapy may decrease tumor size and consequently, improve surgical outcomes of the interval debulking surgery. Over-expression of homol-

ogous recombination DNA repair pathways, and breast cancer gene *BRCA*, are associated with improved outcomes of this therapeutic strategy. It seems that these genomic factors ameliorate the management of patients with high-grade serous ovarian cancer offering higher overall survival rates [4]. In 2018, van Driel *et al.* [5] reported the results of a multi-center, open-label, phase III randomized trial about the utility of HIPEC in ovarian cancer patients who underwent neoadjuvant chemotherapy and interval debulking surgery. They concluded that patients who received HIPEC had longer median overall survival compared to those who were treated with surgery alone (45.7 vs 33.9 months, respectively), without any difference in adverse effects. After that several studies have demonstrated the utility of HIPEC in the management of ovarian cancer patients [6], with optimal timing of HIPEC use to be debated [7]. However, HIPEC use in ovarian cancer patients remains debatable and many published articles by distinguished scientists question its safety and utility [8–10]. Furthermore, serous primary peritoneal carcinoma is almost indistinguishable from primary ovarian tumors as they share similar clinical presentation, histological features, and pattern of spread. Whether HIPEC is of benefit for the management of the serous primary peritoneal carcinoma has not yet been clarified and should be addressed in specifically designed trials [11]. Moreover, after the publication of van Driel's trial several comments criticize its methods and results [10].

In this article, we present a case of a patient with ovarian cancer who treated primary with an extended debulking surgery followed by systematic adjuvant chemotherapy, had a recurrence, and were treated with a second cytore-



duction plus HIPEC. We aim to discuss the possible role of HIPEC in these patients and to highlight the role of a Multi-Disciplinary Team (MDT) in the management of this malignancy.

2. Case presentation

A 49 years old woman, para 0, was referred to our Department of Gynecologic Oncology due to an ovarian mass found on annually preventive medical examination with transvaginal ultrasound. Mass from ultrasound was referred to as solid, with abnormal vascularization. Moreover, the ultrasound revealed free intraperitoneal liquid, probably ascites. From her family history, it was known that her mother died of ovarian cancer at the age of 57. Her medical history included an invasive ductal breast cancer grade 3 stage IA, *BRCA* negative, treated 6 years before with partial mastectomy, axillary lymph node dissection, chemotherapy, radiotherapy, and hormonal manipulation with tamoxifen until one year before.

On physical examination, no palpable mass can be detected from the ovaries. However, it was obvious that the abdominal cavity was full of ascites. Magnetic Resonance Imaging (MRI) of the lower abdomen revealed a mixed nature mass arising from the right ovary measuring $5 \times 4 \times 5$ cm, an adequate amount of ascites and multiple peritoneal metastases, and possible involvement of the right colon. Upper abdominal CT revealed multiple peritoneal metastases, right diaphragmatic peritoneal lesions, disease on the liver surface, lesion in the parenchyma of the spleen. Surprisingly, no lymph node involvement (lymph node larger than 1 cm) has been detected and chest CT was without any suspicious lesion. Serum levels of CA-125 were found to be extremely high (CA-125: 2257.6 U/mL), while HE-4 was calculated to be 877.4 pmol/L. The patient underwent a colonoscopy to clarify the possible involvement of the right colon. Examination revealed pressure outside of the intestinal lumen without infiltration of the epithelium.

After MDT discussion about all the possibilities regarding the patient's treatment, the patient underwent primary cytoreductive surgery. An extended surgery was performed. The patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, pelvic peritonectomy, diaphragmatic peritonectomy, resection of liver surface lesions, resection of the round ligament of the liver, splenectomy, distal pancreatectomy, extended right colectomy, and pelvic and para-aortic lymph node dissection. Optimal cytoreduction was achieved (CC = 0). Her final ascites volume was calculated at approximately 2.5 L. Patient was admitted to the Intensive Care Unit (ICU) postoperative for 2 days and then was hospitalized for 7 days in our Department with no major adverse effects to be noticed. During her surgery and her postoperative care, the patient was transfused with 3 Packed Red Blood cells (PRBCs), 2 intraoperatively and 1 postoperatively.

Cytology examination of ascites was taken as a standard protocol of our department and was positive for glandular type malignancy. Histological examination revealed a serous type ovarian carcinoma of both ovaries, appendix, on the specimen of right colectomy, on liver lesions, on the spleen, and multiple sites of peritonectomy specimen. Peritoneal cancer index (PCI) was 19. Therefore, the patient was diagnosed with serous ovarian cancer stage IVB, due to spleen parenchymal lesion.

She underwent adjuvant chemotherapy with 6 cycles of carboplatin, paclitaxel, and bevacizumab. The first administration was 34 days post cytoreductive surgery due to post-operative wound infection.

1 year after the initial surgery, with a Platinum free Interval (PFI) of 6 months, PET/CT scan revealed recurrent disease on liver surface of segment II and segment IV, positive celiac trunk lymph nodes, and limited peritoneal metastases mostly on the pelvis. The MDT decided on a secondary cytoreduction in combination with HIPEC. Partial peritonectomies, wedge resection for the removal of surface liver lesions and removal of the bulky lymph nodes on celiac trunk were performed. No residual macroscopic disease was recognized after the secondary cytoreduction and HIPEC administration was performed without any adverse effects. The closed abdomen technique was used with a dose of 100 mg/m² cisplatin and 175 mg/m² paclitaxel in the abdominal cavity for 90 mins. These regimens were selected by MDT based on our experience and previously published literature [7,12]. Adjuvant systematic chemotherapy with carboplatin, paclitaxel, and bevacizumab was administrated afterward.

Approximately 1.5 years after the secondary cytoreduction plus HIPEC patient is alive without any recurrence.

3. Discussion

Ovarian cancer, despite all the progress in its treatment, remains the most lethal gynecologic cancer worldwide. Since Vergote and his colleagues reported that patients who suffered from ovarian cancer stage IIIC or more and were treated with neoadjuvant chemotherapy followed by interval debulking surgery had the same oncologic result with less surgical effort, most of these patients in our Gynecologic Oncology Department are managed by this way. Nevertheless, the ultimate goal independently of the use or not of neoadjuvant chemotherapy, remains the complete cytoreduction [13].

Intraperitoneal chemotherapy was used several years before. Interestingly, in 2006 a Gynecologic Oncology Group (GOG) trial (GOG-172) reported the utility of intraperitoneal injection of cisplatin plus paclitaxel in ovarian cancer patients with some really promising results [14]. This intraperitoneal concept led several scientists throughout the world to use HIPEC in cases of ovarian cancer patients [15]. Hotouras *et al.* [16] in a systematic review of the literature included 16 studies and overall 1168 patients and

concluded that cytoreductive surgery plus HIPEC is associated with some promising results regarding the survival of patients with recurrence of the disease. From these included studies, one was conducted in our hospital. It was the first prospective randomized phase III trial regarding the use of HIPEC in recurrent ovarian cancer. Survival of patients ($n = 60$) that were treated with Cytoreduction surgery (CRS) plus HIPEC plus adjuvant chemotherapy was almost double compared to this of patients treated with CRS plus adjuvant chemotherapy alone (26.7 vs 13.4 months, respectively) [12]. Regarding the reported in these studies treatment-related side effects, those were mainly related to myelosuppression and nephrotoxicity. However, differentiation between surgical complications and HIPEC remains challenging. The Overall survival (OS) and Progression free survival (PFS) rates are overall compatible with those reported in the OCEANS, DESKTOP, and CALYPSO trials; nevertheless, due to the separate designs of these trials, direct head to head comparison is not feasible [17].

Moreover, as we mentioned before, van Driel's *et al.* [5] article was a breakthrough regarding the treatment of ovarian cancer patients. After that, HIPEC is an option in patients with ovarian cancer. This article changed the opinion about HIPEC throughout the scientific community [18]. This change was mentioned in a survey conducted through email sent to Oncologists before Peritoneal Surface Oncology Group International (PSOGI) International Symposium on Advanced ovarian cancer in 2019. Regarding the utility of HIPEC, half of the participants answered that there is a role of HIPEC in ovarian cancer patients undergoing interval debulking surgery and, while almost 70% answered positively about the utility of HIPEC in the recurrence of the disease [6].

Despite that aforementioned trend, several distinguished scientists controvert the utility of HIPEC in the treatment of ovarian cancer patients. Indicatively, Zhang *et al.* [19] in a review reported that in recurrent ovarian cancer HIPEC was associated with improved OS (HR = 0.45, 95% CI: 0.24 to 0.83), but for the PFS no correlation was observed between HIPEC group and the non-HIPEC group (HR = 0.55, 95% CI: 0.27 to 1.11). Moreover, Vergote *et al.* [8] in a review article question the outcome of OVHIPEC trial. More specifically, the authors mentioned the contradictory results between OVHIPEC trial and a randomized trial from Lim *et al.* [20] from Korea. Lim *et al.* [20] declared that there was no statistically significant difference for ovarian cancer patients who were treated with primary debulking surgery between HIPEC and no HIPEC group regarding PFS and OS. Furthermore, patients treated with HIPEC had elevated creatinine levels compared to non-HIPEC group (15.2% vs. 4.3%, $p = 0.026$). However, they mentioned that there was a favor for the HIPEC group in PFS and OS regarding patients who were treated with Neoadjuvant chemotherapy (NACT) and afterward debulking surgery. Additionally, Vergote *et al.* [8] criticize

the methods of OVHIPEC trial regarding the number of included studies, the randomization procedure, the heterogeneity of the results from different recruited centers, and finally the complete report of adverse effects.

It is obvious though, that further studies should be conducted to enlighten the possible utility and the optimal timing of HIPEC in ovarian cancer patients' treatment. Moreover, HIPEC should be offered by highly experienced teams in appropriately selected patients.

Author contributions

AF, VP and AP collected the data. AF and VP wrote the manuscript. CI conceptualized the project and reviewed the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The patient gave her informed consent for inclusion. The ethics approval is not applicable.

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Conflict of interest

The authors declare no conflict of interest. AF, VP, AP and CI are the Guest Editors of this journal, given their roles as Guest Editors, had no involvement in the peer-review of this article and had no access to information regarding its peer-review. CI is serving as one of the Editorial Board members of this journal. We declare that CI had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Enrique Hernandez.

References

- [1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA: A Cancer Journal for Clinicians*. 2020; 70: 7–30.
- [2] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics. 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2018; 68: 394–424.
- [3] Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, *et al.* Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *New England Journal of Medicine*. 2010; 363: 943–953.
- [4] Tsonis O, Gkrozou F, Vlachos K, Paschopoulos M, Mitsis MC, Zakynthinakis-Kyriakou N, *et al.* Upfront debulking surgery for high-grade serous ovarian carcinoma: current evidence. *Annals of Translational Medicine*. 2020; 8: 1707.
- [5] van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH,

- Schreuder HWR, Hermans RHM, *et al.* Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *New England Journal of Medicine*. 2018; 378: 230–240.
- [6] Iavazzo C, Fotiou A, Tsiatas M, Christopoulou A, Spiliotis J, Sugarbaker P. Survey on the current gynaecological approach of ovarian cancer patients: the utility of HIPEC. *Pleura and Peritoneum*. 2020; 5: 20190029.
- [7] Spiliotis J, Iavazzo C, Fotiou A, Kopanakis N, Terra A, Efstathiou E, *et al.* Upfront or intermediate treatment of advanced ovarian cancer patients with cytoreduction plus HIPEC: results of a retrospective study. *Journal of Surgical Oncology*. 2021; 123: 630–637.
- [8] Vergote I, Harter P, Chiva L. Hyperthermic intraperitoneal chemotherapy does not improve survival in advanced ovarian cancer. *Cancer*. 2019; 125: 4594–4597.
- [9] Harter P, du Bois A, Sehouli J, Mahner S, Vergote I, Chiva L, *et al.* Is there a role for HIPEC in ovarian cancer? *Archives of Gynecology and Obstetrics*. 2018; 298: 859–860.
- [10] Vergote I, Chiva L, du Bois A. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *New England Journal of Medicine*. 2018; 378: 1362–1363.
- [11] Rassy E, Assi T, Boussios S, Kattan J, Smith-Gagen J, Pavlidis N. Narrative review on serous primary peritoneal carcinoma of unknown primary site: four questions to be answered. *Annals of Translational Medicine*. 2020; 8: 1709.
- [12] Spiliotis J, Halkia E, Lianos E, Kalantzi N, Grivas A, Efstathiou E, *et al.* Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. *Annals of Surgical Oncology*. 2015; 22: 1570–1575.
- [13] Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, *et al.* Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: society of gynecologic oncology and American society of clinical oncology clinical practice guideline. *Journal of Clinical Oncology*. 2016; 34: 3460–3473.
- [14] Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, *et al.* Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *New England Journal of Medicine*. 2006; 354: 34–43.
- [15] Iavazzo CR, Kopanakis ND, Spiliotis JD. Hyperthermic intraperitoneal chemotherapy for ovarian cancer: peritoneal surface disease severity score-preliminary results. *Journal of Surgical Oncology*. 2018; 118: 591–592.
- [16] Hotouras A, Desai D, Bhan C, Murphy J, Lampe B, Sugarbaker PH. Heated IntraPERitoneal Chemotherapy (HIPEC) for patients with recurrent ovarian cancer: a systematic literature review. *International Journal of Gynecological Cancer*. 2016; 26: 661–670.
- [17] Boussios S, Sadauskaite A, Kanellos F S, *et al.* Neoadjuvant, HIPEC and maintenance treatment in ovarian and peritoneal serous cancer: current status. *Gynecology and Pelvic Medicine*. 2020; 3: 19.
- [18] Spiliotis J, Iavazzo C, Sugarbaker P. Management of patients with advanced ovarian cancer—role of complete cytoreduction and HIPEC: attitudes of gynaecologist oncologists in two different continents. *Australian and New Zealand Journal of Obstetrics and Gynaecology*. 2021; 61: E1–E2.
- [19] Zhang G, Zhu Y, Liu C, Chao G, Cui R, Zhang Z. The prognosis impact of hyperthermic intraperitoneal chemotherapy (HIPEC) plus cytoreductive surgery (CRS) in advanced ovarian cancer: the meta-analysis. *Journal of Ovarian Research*. 2019; 12: 33.
- [20] Lim MC, Chang S, Yoo HJ, Nam B, Bristow R, Park S. Randomized trial of hyperthermic intraperitoneal chemotherapy (HIPEC) in women with primary advanced peritoneal, ovarian, and tubal cancer. *Journal of Clinical Oncology*. 2017; 35: 5520.