Control of malignant ascites using HIPEC in 2 patients with ovarian cancer: A case-report

Vladislav Nikulin (✉ vlislavn@gmail.com)

Pervyj Moskovskij gosudarstvennyj medicinskij universitet imeni I M Secenova <https://orcid.org/0000-0002-8958-9805>

Amir Abdullaev

Pervyj Moskovskij gosudarstvennyj medicinskij universitet imeni I M Secenova

Mikhail Davydov

Pervyj Moskovskij gosudarstvennyj medicinskij universitet imeni I M Secenova

Alexey Rumyantsev

Pervyj Moskovskij gosudarstvennyj medicinskij universitet imeni I M Secenova

Vladislav Kirsanov

Pervyj Moskovskij gosudarstvennyj medicinskij universitet imeni I M Secenova

Elena Bogush

Pervyj Moskovskij gosudarstvennyj medicinskij universitet imeni I M Secenova

Sergei Tjulandin

Pervyj Moskovskij gosudarstvennyj medicinskij universitet imeni I M Secenova

Alexandra Tyulyandina

Pervyj Moskovskij gosudarstvennyj medicinskij universitet imeni I M Secenova

Case report

Keywords: malignant ascites, ovarian cancer, recurrence, platinum-refractory, HIPEC, heated chemotherapy.

Posted Date: August 1st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-43656/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Objective: to demonstrate an efficacy of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in management of malignant ascites (MA) in patients with platinum-refractory ovarian cancer (OC).

Background: MA in OC patients can dramatically affect quality of life. HIPEC is an investigational treatment modality that can be effective in MA setting but evidence-based data supporting this method are lacking.

Cases presentation: 2 women 50-year-old, FIGO stage IV and 60-year-old, FIGO stage IIIC presented at our center, both had recurrent MA. Patients were treated with HIPEC after platinum-refractory recurrence. The first one had total control of MA with no evidence of disease at the time of last follow-up examination. The 2nd had 9 months of disease control – a relatively long time considering her MA recurrence rate.

Conclusions: HIPEC can be successfully used for MA management in selected patients with epithelial OC refractory to standard chemotherapy, however more data are needed from randomized clinical trials.

Background

Ovarian cancer (OC) is the seventh leading cause of death among women with gynecological malignancies.(1) Incidence rate is 295000 new cases with 184000 of death yearly, which means more than half of patients will succumb to the disease. Commonly patients are presented at advanced stages of the disease because of tumor biology.(2) Surgery plays a key role in OC treatment and is one of the most important outcome predictors. Patients with no residual disease (R0 resection) have significantly longer survival time in comparing to patients with residual disease.(3)

Despite the previous treatment, vast majority of patients will have the relapse.(4) The main goal of further treatment is to achieve as long disease-free survival as possible and to maintain acceptable quality of life (QoL). Therapy modalities may include either chemotherapy or secondary cytoreductive surgery followed by systemic therapy. Malignant growth in the abdominal cavity can result in enhanced revascularization and lymphatic drainage obturation, disrupting both production and absorption of peritoneal fluid leading to fluid retention and malignant ascites (MA).(5) Usually, almost two-thirds of the abdominal fluid is reabsorbed by the lymph channels, which are mainly distributed under the diaphragm.(6) MA can dramatically affect QoL causing dyspnea, extreme fatigue, protein and electrolyte disturbances.

Invasive procedures such as laparocentesis provide only temporary benefit especially in case of chemotherapy-refractory disease.(7) Heated cytotoxic drugs' solutions given intraperitoneally after debulking surgery with diaphragmatic peritonectomy can be an appropriate treatment. Hyperthermia facilitate drug penetration and absorption from abdominal cavity enhancing drug delivery to the deeper layers of tumor cells.(8) Also temperature contributes to DNA-adducts formation, leading to malignant cell apoptosis.(9) Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is an investigational treatment modality that can be effective in MA treatment. Nevertheless, evidence-based data supporting intraperitoneal drug infusion under hyperthermic conditions for patients with chemotherapy-refractory OC are lacking. Here we report two cases of advanced refractory OC patients who were treated with HIPEC.

Patients And Methods

The following methodology was adopted for patients' treatment:

Removal of the peritoneum of the domes of the diaphragm and lateral canals. Firstly, cytoreductive surgery was performed with mandatory removal of the diaphragmatic and parietocolic gutter's peritonectomy. After completion of surgical phase of treatment four drain tubes were placed in the abdominal cavity: 2 for the inflow and 2 for outflow of fluid. Outflow drainages were set behind the right lobe of the liver and under the left side of diaphragmatic cupula. Inflow drainages were placed in mesogaster and in small pelvis. In order to increase contact area of abdominal cavity with cytostatic drug usually the Thompson retractors or analogues were used (Fig. 1).

Hyperthermic Intraperitoneal Chemotherapy was initiated upon drainage placement. In both cases open-technique with pumps had been used (Fig. 2). Cisplatin was chosen as chemotherapeutic agent. Dose of 100 mg/m² was continuously perfused for 90 minutes at 43.5 C. Time of perfusion was based on T $\frac{1}{2}$ of cisplatin in peritoneal cavity.(10)

Case Presentation

1st case

50-year-old Caucasian women presented at our clinic with complaints to abdomen enlargement and pain and progressive shortness of breath. On examination we revealed extensive peritoneal carcinomatosis, bilateral pleural effusion and large ovarian masses. Her pretreatment CA-125 level was 905.8 U/L, HE4–849 picmole/L with corresponding ROMA index 98.8%. On 27th of February 2018 the patient underwent upfront complete debulking surgery with peritoneal port implantation for intraperitoneal (IP) delivery of anticancer agents. The pathologist classified the disease as high-grade endometrioid ovarian carcinoma with FIGO disease stage IV. Mutations in *BRCA1/2* genes were not found via Next Generation Sequencing (NGS). Afterwards from 19th of April 2018 the patient received 1st line of chemotherapy with IP drug delivery: paclitaxel 135 mg/m² intravenously (IV) on day 1, cisplatin 75 mg/m² IP on day 2, paclitaxel 60 mg/m² IP on day 8–6 cycles of chemotherapy with partial biological response (posttreatment CA-125 level was 106 U/L). Treatment tolerability was satisfactory except for abdominal pain and grade 3 anemia before cycle 5 which required transfusion of 3 blood units. 6 cycles of 1st line chemotherapy had been finished by 18th of July 2018.

In the beginning of September 2018, 3 months after initial treatment completion the patient returned to our clinic with abdomen enlargement, shortness of breath and ECOG performance status 2. Laparocentesis was performed at our department and up to six liters of ascitic liquid were extracted. Cytological examination revealed the presence of malignant cells. The CT scan revealed new tumor lesions in hepatic zone, carcinomatosis of pelvis and mesenterial lymph nodes enlargement. Since October 2018 *2nd line chemotherapy* with topotecan 1 mg/m² on day 1–5 IV and bevacizumab 7.5 mg/kg on day 1 with granulocyte colony stimulating factor (G-CSF) prophylaxis were performed – totally 5 cycles of therapy. Despite of stable measurable disease there was need in laparocentesis of 5-9L of ascites sequentially after each cycle of chemotherapy through intraperitoneal chemo-port. Platelet concentrate transfusions due to grade 4 thrombocytopenia with hemorrhagic syndrome were carried out.

Given to the disease resistance to standard cytotoxic chemotherapy it was decided to perform secondary debulking surgery with HIPEC. Patient's pre-HIPEC CA-125 level was 116 U/L. The procedure was performed on 26th of January 2019 with optimal debulking (residual disease < 1 cm). Timing of surgery was four and a half hours. The patient was discharged 10 days after surgery, no significant complications was detected except for grade 2 lower extremity deep vein thrombosis of the legs. One month after surgery follow-up visit didn't reveal any evidence of residual disease via ultrasound (US), CA-125 = 30 U/l. At last follow-up examination in December 2019 there were no evidence of disease and ascites; patient had ECOG 0, CA-125 = 8.96 U/l. Her progression-free survival after HIPEC equals to 11 months.

2nd case

55-year-old Caucasian woman presented at our center with abdomen enlargement and pain. On examination bilateral adnexal mass and ascites were revealed. Pretreatment CA-125 level was 60 U/l, HE4 with corresponding ROMA index were not estimated. Upfront complete debulking surgery with omentectomy and bilateral adnexectomy was performed. Pathology revealed serous low-grade adenocarcinoma T3cNxM0 with FIGO stage IIIC; BRCA mutation were not found by NGS testing. Afterwards the patient received multiple lines of chemotherapy (Table 1): from September 2013 to October 2018 totally 8 lines of chemotherapy were performed after 7 sequential relapses. Every relapse was accompanied by verified symptomatic MA and led to sequential laparocentesis. IP drug infusions were performed after laparocentesis with insignificant clinical improvement.

Table 1. Summary of 2nd patient's treatment.

Line	Treatment	Dates	Off-treatment interval	Best Effect
1 st	Paclitaxel 175 mg/m ² + carboplatin AUC 6 Q3W 6 cycles	September - December 2013	25 months	Stable disease
	Maintenance with Letrozole 2.5 mg PO daily	January 2014 - January 2015		
2 nd	Gemcitabine 1000 mg/m ² on day 1, 8 + oxaliplatin 130 mg/m ² Q3W for 6 cycles, followed by cisplatin 1 mg/kg IP	January 2015 - May 2015	10 months	Progressive disease
3 rd	Carboplatin AUC 5 + Doxorubicin 50 mg/m ² Q3W for 5 cycles	March 2016 - July 2016	NA	Progressive disease
4 th	Topotecan 1.2 mg/m ² on days 1-5, bevacizumab 7.5 mg/m ² day 1 Q3W for 6 cycles, followed by bevacizumab maintenance	July 2016 - January 2017	3 months	Stable disease
	Paclitaxel 60 mg/m ² IP	24 th of January 2017		
	Carboplatin AUC 5 IP	21 st of March 2017		
5 th	Oral Etoposide days 1-10 Q3W for 4 cycles	April 2017 - June 2017	NA	Progressive disease
6 th	Cisplatin 60 mg/m ² on day 1 + paclitaxel 60 mg/m ² on days 1, 8, 15 Q3W for 4 cycles	June 2017 - September 2017	NA	Progressive disease
7 th	methotrexate 2.5 mg BID PO, on days 1-2 Q1W + cyclophosphamide 50 mg daily PO	September 2017 - October 2017	NA	Progressive disease
	Incomplete debulking surgery (partial peritonectomy, residual masses > 1 cm) with HIPEC	18 th of December 2017	7 months	Stable disease
	Maintenance with Tamoxifen 10 mg PO daily	January 2018 - July 2018		
8 th	Vinorelbine 20 mg/m ² on days 1, 8 + cisplatin 60 mg/m ² on day 1 IV Q3W for 6 cycles	July 2018 - October 2018	4 months	Stable disease

NA – not applicable. IV – intravenously. PO – per os. BID – twice a day. Q3W – every 3 weeks. IP – intraperitoneally.

From 2nd line chemotherapy till 7th the patient was administered with systemic treatment continuously because of symptomatic ascites form of disease progression. Therefore, incomplete debulking surgery (partial peritonectomy, residual masses > 1 cm) with HIPEC was done as attempt to stop ascites accumulation. Maintenance treatment with tamoxifen was done after surgery. The patient was living without any symptoms of disease for 6 months in a good quality of life. The next progression was without ascites.

Progressive disease was revealed on the proximal follow-up appointment in February 2019, ascites was confirmed via US examination. 9th line of chemotherapy with ixabepilone and bevacizumab was prescribed, but patient died because of disease progression in April 2019. Totally 8 lines of palliative chemotherapy were conducted. Rate of ascites accumulation was slowed since debulking surgery with HIPEC had been performed. In 4 years totally 9 paracentesis procedures were done from diagnosis to HIPEC following secondary debulking surgery. In 2 years after investigational treatment option only 1 paracentesis was performed.

Discussion

MA is an adverse prognostic factor for survival rate, that accompanies OC and impair QoL of patients. An ascites volume also has a negative impact on patients' survival rate. According to retrospective and cohort studies, 50–76% of patients are presented with MA at initial diagnosis.(11, 12, 13). Approximately 10% of patients have recurrence of disease with ascites contributing to even more unfavorable prognosis.(14)

Laparocentesis remains the front-line symptomatic therapy of MA. Nevertheless due to multiple recurrences followed by adhesions formation, the method cannot be 100% effective, especially after several procedures.(7) Our 2nd case was a good example because of last paracentesis in July 2018: only 0.5 L of ascitic fluid was evacuated due to entrapment of liquid, which was probably caused by iterative damaging of abdominal cavity. Diuretics are appropriate agents for ascites treatment, but both paracentesis and diuretic drugs give only symptomatic relief, that doesn't last long.(15) The use of chemotherapy if an ascites is a part of relapse is mandatory. According to the subgroup analysis of phase III AURELIA study, ascites control after use of chemotherapy alone was achieved in 83% of patients, in 98% patients receiving chemotherapy with bevacizumab, all patients had platinum-resistant recurrence.(16) Intraperitoneal infusion of cisplatin with or without bevacizumab was also shown as an acceptable treatment modality in phase III trials(17)(18). In 2018 Van Driel et al. showed in phase III study the superiority of cytoreductive surgery with HIPEC in patients with incomplete cytoreduction. In the study 76 patients (62%) in the surgery group and 61 patients (50%) in the surgery-plus-HIPEC group had died (hazard ratio, 0.67; 95% P = 0.02), resulting in death risk reduction by 44%. Unfortunately, data about ascites control was not presented there.(19) After this trial an interest in HIPEC was reawaken, however the 1st line of therapy was investigated in the study.

The peritoneum affected by the tumor produces a greater volume of ascites fluid while its absorption is limited. We suggested that palliative diaphragmatic peritonectomy can restore drainage function of abdominal cavity. The ability of high temperature to facilitate DNA-adducts formation can synergistically enhance cisplatin's direct mechanism of action. Hyperthermia itself can have a cytotoxic effect on tumor cells, also providing increased penetration of chemotherapeutic drugs into tumor and peritoneal tissue up to 3 mm.(8) The safety profile of

HIPEC is superior to conventional intraperitoneal and intravenous chemotherapy due to schedule of administration: heated cytotoxic drugs' infusion is performed once by the side of regular administration in 2 other schedules.(10) According to retrospective study, rate of MA resolution was dependent from extent of CRS: MA was failed to resolve in 86% of patients with R2 cytoreduction, that can be demonstrated in our second case (relatively low effectiveness in comparing to the first case).(20)

Conclusions

Aggressive surgery to remove all metastatic lesions in combination with HIPEC can be successfully used for MA management in women with epithelial OC refractory to standard chemotherapy, both of our case-reports support data from retrospective and prospective studies. Routine use of HIPEC is uncommon in treatment of relapsed ovarian cancer, nevertheless this investigational method can be performed by experienced team in referral cancer centers for management of ascites course of the disease. However, we need more data from prospective randomized trials of HIPEC in patients with relapsed OC with ascites.

Abbreviations

OC: ovarian cancer;

Declarations

Ethics approval and consent to participate. Not applicable

Consent for publication. Consent for publication was obtained from participants.

Availability of data and materials. Not applicable.

Competing interests. The authors declare that they have no competing interests.

Funding. No sources of funding for the research reported are declared.

Authors' contributions. V. Nikulin wrote the manuscript. A. Abdullaev and M. Davydov performed HIPEC procedure. V. Kirsanov, E. Bogush, prepared patient's data for analysis. A. Rumyantsev, A. Tyulyandina, S. Tjulandin reviewed the manuscript. All authors approved the final manuscript.

Acknowledgements. Not applicable.

References

1. USCS Data Visualizations - CDC [Internet]. [cited 2019 Dec 19]. Available from: <https://gis.cdc.gov/Cancer/USCS/DataViz.html>
2. Bagnato A, Rosanò L. Epithelial-mesenchymal transition in ovarian cancer progression: A crucial role for the endothelin axis. In: Cells Tissues Organs. 2007. p. 85–94.
3. Winter WE, Maxwell GL, Tian C, Carlson JW, Ozols RF, Rose PG, et al. Prognostic factors for stage III epithelial ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol. 2007 Aug 20;25(24):3621–7.

4. Capriglione S, Luvero D, Plotti F, Terranova C, Montera R, Scaletta G, et al. Ovarian cancer recurrence and early detection: may HE4 play a key role in this open challenge? A systematic review of literature. *Med Oncol*. 2017;34(9).
5. Kipps E, Tan DSP, Kaye SB. Meeting the challenge of ascites in ovarian cancer: New avenues for therapy and research. *Nat Rev Cancer* [Internet]. 2013;13(4):273–82. Available from: <http://dx.doi.org/10.1038/nrc3432>
6. Cavazzoni E, Bugiantella W, Graziosi L, Franceschini MS, Donini A. Malignant ascites: Pathophysiology and treatment. *Int J Clin Oncol*. 2013;18(1):1–9.
7. Becker G, Galandi D, Blum HE. Malignant ascites: Systematic review and guideline for treatment. *Eur J Cancer*. 2006;42(5):589–97.
8. El-Kareh AW, Secomb TW. A Theoretical Model for Intraperitoneal Delivery of Cisplatin and the Effect of Hyperthermia on Drug Penetration Distance. *Neoplasia* [Internet]. 2004;6(2):117–27. Available from: <http://dx.doi.org/10.1593/neo.03205>
9. Van De Vaart PJM, Van Der Vange N, Zoetmulder FAN, Van Goethem AR, Van Tellingen O, Ten Bokkel Huinink WW, et al. Intraperitoneal cisplatin with regional hyperthermia in advanced ovarian cancer: Pharmacokinetics and cisplatin-DNA adduct formation in patients and ovarian cancer cell lines. *Eur J Cancer*. 1998 Jan;34(1):148–54.
10. Sugarbaker PH, Van der Speeten K. Surgical technology and pharmacology of hyperthermic perioperative chemotherapy. *J Gastrointest Oncol*. 2016;7(1):29–44.
11. Szender JB, Emmons T, Belliotti S, Dickson D, Khan A, Morrell K, et al. Impact of ascites volume on clinical outcomes in ovarian cancer: A cohort study. *Gynecol Oncol*. 2017 Sep 1;146(3):491–7.
12. HUANG H, LI YJ, LAN CY, HUANG QD, FENG YL, HUANG YW, et al. Clinical significance of ascites in epithelial ovarian cancer. *Neoplasia* [Internet]. 2013 [cited 2020 Jan 19];60(05):546–52. Available from: http://www.elis.sk/index.php?page=shop.product_details&flypage=flypage.tpl&product_id=3473&category_id=102&option=com_virtuemart
13. Parsons SL, Lang MW, Steele RJC. Malignant ascites: A 2-year review from a teaching hospital. *Eur J Surg Oncol*. 1996;22(3):237–9.
14. Eskander RN, Tewari KS. Emerging treatment options for management of malignant ascites in patients with ovarian cancer. *Int J Womens Health*. 2012;4(1):395–404.
15. Husain A, Bezjak A, Easson A. Malignant ascites symptom cluster in patients referred for paracentesis. *Ann Surg Oncol*. 2010;17(2):461–9.
16. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32(13):1302–8.
17. Zhao H, Li X, Chen D, Cai J, Fu Y, Kang H, et al. Intraperitoneal administration of cisplatin plus bevacizumab for the management of malignant ascites in ovarian epithelial cancer: results of a phase III clinical trial. *Med Oncol*. 2015;32(2):1–7.
18. Alberts DS, Liu PY, Hannigan E V., O'Toole R, Williams SD, Young JA, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med*. 1996;335(26):1950–5.

19. Van Driel WJ, Koole SN, Sikorska K, SchagenvanLeeuwen JH, Schreuder HWR, Hermans RHM, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med*. 2018;378(3):230–40.
20. Randle RW, Swett KR, Swords DS, Shen P, Stewart JH, Levine EA, et al. Efficacy of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in the management of malignant ascites. *Ann Surg Oncol*. 2014;21(5):1474–9.

Figures

Figure 1

Thompson retractors in use during chemotherapeutic drug infusion.

Figure 2

Open-technique Hyperthermic Intraperitoneal Chemotherapy infusion with pumps.