Combination of intraperitoneal hyperthermic perfusion chemotherapy (IHPC) with intraperitoneal chemotherapy as a treatment modality for persistent ovarian cancer

D. Wydra[1], S. Sawicki[1], K. Ciach[1], A. Marciniak[2], J. Emerich[1]

[1]Department of Gynecology, [2]Department of Anesthesiology, Medical University of Gdańsk (Poland)

Summary

Persistent minimal residual disease diagnosed after the first line of chemotherapy during second-look surgery can be an indication for intraperitoneal chemotherapy. Another treatment option is intraperitoneal hyperthermic perfusion chemotherapy (IHPC) where the drug is administrated into the peritoneal cavity with the use of extracorporeal closed circuit perfusate circulation at a temperature of 41-42°C. We have started to perform, as a second-line treatment, a combination of one IHPC procedure and four cycles of standard intraperitoneal chemotherapy. In a patient who had previously undergone three different chemotherapy regimens, stabilization of the disease was achieved. In our opinion combining the IHPC procedure with intraperitoneal chemotherapy can be valuable in patients with small volume residual tumor.

Key words: Persistent ovarian cancer; Intraperitoneal hyperthermic perfusion chemotherapy; Intraperitoneal chemotherapy; Cytoreductive surgery.

Introduction

Despite significant development of chemotherapeutic modalities during the last decades, the survival rate in epithelial ovarian cancer remains unsatisfactory. In the case of peritoneal carcinomatosis or persistent minimal residual disease diagnosed after the first line of chemotherapy during second-look surgery, one of the possible therapeutic approaches is intraperitoneal chemotherapy. There are several advantages of this method. Intraperitoneal administration changes the pharmacokinetics of the cytotoxic agent. The peritoneal-plasma barrier, created by the sub-mesothelial tissue and the capillary basement membrane, decreases the reabsorption of high weight and hydrophilic drugs such as cisplatin to the systemic circulation [1]. This results in a longer presence of drugs in the peritoneal cavity, higher tumor penetration and diminished systemic toxicity compared to intravenous administration. The main factor restricting the efficacy of intraperitoneal therapy is the depth of penetration of cytotoxic agents – the best results are achieved in small residual tumor volume (up to 3 mm) [1, 2].

Another treatment option is intraperitoneal hyperthermic perfusion chemotherapy (IHPC) where the cytotoxic agent is administrated into the peritoneal cavity with the use of extracorporeal closed circuit perfusate circulation at a temperature of 41-42°C. This method was introduced in the year 1980 by Spratt in the treatment of patients with pseudomyxoma peritonei [3]. Other investigators have applied IHPC combined with mitomycin C as a treatment for peritoneal recurrence in gastrointestinal cancers [4, 5].

The main theoretical features of this method include the synergistic activity of hyperthermia and better drug distribution in the peritoneal cavity. The hyperthermic condition can result in increased drug activation, increased cell uptake, drug penetration and inhibition of the DNA repairing process [1]. El-Kareh *et al.* discussed a theoretical model for the intraperitoneal delivery of cisplatin and heat to tumor metastases in tissues adjacent to the peritoneal cavity as presented. The authors concluded that the experimental finding of elevated intracellular platinum levels up to a depth of 3 to 5 mm when the drug is delivered IP by a heated infusion solution is due to penetration of heat to this distance, causing increased cell uptake of the drug [6].

In 1976 Giovanella *et al.* evaluated the impact of hyperthermic conditions on neoplastic cells – they suggested that tumor tissue is more sensitive to heat than normal tissue due to specific thermosensivity and a lower ability of temperature normalization by vasodilatation [7].

As second-line treatment we have started to perform a combination of one IHPC procedure subsequently followed by four cycles of standard intraperitoneal chemotherapy. In our opinion such a modification can be valuable in patients with small volume residual tumor.

Material and Methods

We performed two IHPC procedures with subsequent intraperitoneal chemotherapy. The first patient (FIGO Stage IIIc) was admitted to our center with a history of two cytoreductive surgical procedures and three chemotherapy regimens. During the IHPC procedure numerous neoplasmatic tumors up to 5 mm were found. After completion of the intraperitoneal chemotherapy during surgery a significant reduction of cancer volume was achieved.

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The second patient (Stage IIIc) after cytoreductive surgery and six cycles of paclitaxel and cisplatin qualified for the IHPC procedure during a second-look laparotomy where tumors up to 1 cm were found. Intraperitoneal chemotherapy was not accomplished due to catheter obstruction.

IHPC procedure - After opening the abdomen cytoreductive surgery is performed. Two inflow drains under the diaphragm and two outflow drains into the pelvis are placed. Additionally the Tenckhoff's catheter is put in place for the subsequent chemotherapy. The temperature measurers are inserted into the drains and inside the abdominal cavity. The inflow drains pass through the extracorporeal circulation pump and then through the heat exchanger. The abdominal wall is closed tightly. The three to four liters of preheated perfusate are administrated. The maximum temperature for the IHPC procedure is 42°C.

After obtaining the proper temperature a total dose of 200 mg of cisplatin is given. Hyperthermic perfusion lasts for 90 minutes, then most of the circulating fluid is removed from the peritoneal cavity through the closed system of the drains. The velocity of the perfusion fluid counts 1200-2000 ml/min.

We did not record any complications during either of the IHPC procedures or in the postoperative period.

Subsequently after patient recovery four cycles of intraperitoneal chemotherapy were performed. The results of therapy were verified during the surgical procedure performed to remove the intraperitoneal catheter.

Discussion

At present one of the most important goals in the treatment of ovarian cancer is to establish a more effective second-line therapy for tumors that are not sensitive to platinum-based regimens. Available second-line chemotherapy permits us to achieve low response rate (22%-37%) and a short median survival (43-61 weeks) [1].

The role of intraperitoneal chemotherapy has been evaluated using large clinical trials which have confirmed its feasibility in ovarian cancer treatment as second-line therapy [2, 8, 9]. Recently, in 2006, the National Cancer Institute published a clinical announcement based on phase III clinical trials recommending that a combination of intraperitoneal and intravenous chemotherapy has a significant survival benefit over intravenous chemotherapy alone in optimally debulked patients.

The IHPC method is mainly used in cases of peritoneal carcinomatosis in the course of gastrointestinal cancer, peritoneal sarcomatosis, peritoneal mesothelioma and pseudomyxoma peritonei. During the last decade the first reports about the use of IHPC in primary or recurrent ovarian cancer were published.

Deraco et al. reported the results of a study in which 27 patients with advanced and recurrent ovarian carcinoma were treated with IHPC (cisplatin or mitomycin C) after accomplishing maximal cytoreduction [1]. Two-year overall survival was achieved in 55% and median time to progression was 21.8 months. Treatment-related morbidity, mortality and toxicity were 11%, 4% and 27%, respectively.

In the work of de Bree *et al.* IHPC with docetaxel was performed in 19 patients with early recurrent or persistent peritoneal carcinomatosis mainly of ovarian origin [10]. After a mean follow-up of 30 months, the actuarial overall one- and three-year survival rates after IHPC were 79% and 63%, respectively. Mortality rate was 10.5% - there were two deaths of elderly patients with a high tumor load. Other complications, mainly minor, were recorded after 63% of the procedures. The incidence of wound complications was relatively high and the authors suggested that the probable reason was the direct exposure of the wound to docetaxel during IHPC.

A group of 20 patients with recurrent ovarian cancer treated with a cytoreductive surgery followed by IHPC was reported by Chatzigeorgiou *et al.* [11]. The authors did not observe any complications of the therapy. There was a statistically significant difference in survival depending on the residual disease left after surgery.

In the largest trial evaluating the use of IHPC in ovarian cancer Ryu *et al.* presented very promising results [12]. Fifty-seven patients who underwent cytoreductive surgery with IHPC (carboplatin and interferon-alfa) were compared with a control group of 60 patients who underwent conventional treatment only. The overall 5-year survival rate of the IHPC group was 63.4% vs 52.8% in the control group, with significantly higher survival in the IHPC group ($p = 0.0078$). IHPC was an independent prognostic factor that was not affected by surgical staging, tumor size after a second surgery, or patient age, according to a multivariate analysis. Surprisingly high results achieved in this study need to be confirmed in larger analyses but also confirm that IHPC can be an important part of ovarian cancer treatment

Hager *et al.* presented the results of a prospective trial evaluating the feasibility of IHPC in patients with persistent ovarian cancer [13]. Thirty-six patients with documented disease progression underwent several IHPC procedures [4, 5]. Median overall survival from the diagnosis was 49 months, and 19 months from the start of intraperitoneal chemotherapy. The one-year survival rate after the first IHPC procedure was 65%. The complication rate was 1,8% - three subileus events were reported connected with the IHPC procedure.

The most complete data regarding complications of IHPC are available from studies concerning gastrointestinal cancers. There is a report of 183 patients who underwent 200 cytoreductive surgeries with IHPC. The combined rate of major morbidity was 27.0% and treatment-related mortality was 1.5% [14].

Another large group was presented by Glehen *et al.* in which 216 IHPC in patients with peritoneal carcinomatosis were prospectively studied [15]. The postoperative mortality and morbidity rates were 3.2% and 24.5%, respectively. They were mainly associated with the carcinomatosis stage and the extent of the surgical procedure. It was concluded that the IHPC procedure has an acceptable complication incidence.

All recently published reports describing the IHPC procedure in the treatment of ovarian cancer regard small groups of patients, different distribution of FIGO stages, different treatment modalities and short follow-up periods. Another factor which hinders analysis of the

IHPC effects is the lack of a uniform treatment policy – the IHPC procedure is followed by different conventional chemotherapy regimens or a no further treatment option.

In our opinion IHPC is a highly demanding method with respect to the work load, hospital staff training, higher complication rate and higher cost in comparison to other chemotherapy regimens. It is also possible that due to adhesion formation in the peritoneal cavity the effectiveness of forced perfusion which is necessary for performing the IHPC can be significantly reduced. Thus we suggest the completion of only one IHPC cycle and subsequently continuing three or four standard intraperitoneal chemotherapy cycles. The concept of connecting these two methods as the second-line treatment can result in achieving better results in cases with small volume residual disease.

We accomplished a combination of the IHPC and IPC in only one patient who had previously undergone three different chemotherapy regimens. We achieved stabilization of the disease confirmed by a decrease in the number of intraperitoneal nodules.

Conclusion

Taking into account data regarding the possibilities of the intraperitoneal hyperthermic perfusion chemotherapy procedure and well established advantages of intraperitoneal chemotherapy it would be reasonable to start a clinical trial which would provide a wider and more detailed analysis of this modality and its potential benefits to the patient in the treatment of ovarian cancer.

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Address reprint requests to:
D. WYDRA, M.D., Ph.D.
ul. Kliniczna 1 A
80-402 Gdańsk (Poland)