Clinical experience in chemotherapy treatment for advanced-stage ovarian cancer

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Abstract

Aim: *Analyzing an alternative ovarian cancer treatment by the intraperitoneal administration of alpha-interferon plus cisplatin, as well as intravenously administering cyclophosphamide.* ***Materials and method:*** *For the study of the advanced stages of ovarian cancer (IIc-IV), that included 67 female patients, two distinct therapeutic protocols were used that followed surgery. The first protocol consists of the standard intravenous administration of cytostatic drugs (Protocol I), while the second one is primarily based on the intraperitoneal administration of cytostatics plus alpha- interferon (Protocol II).* ***Results:*** *The study shows the superiority of the intraperitoneal administration of drugs for small size residual tumors, when compared to control.* ***Conclusion:*** *Our study shows that this therapeutic protocol may be safely and effectively administered, the results obtained being promising for small size residual tumors.*

Keywords: *advanced-stage ovarian cancer, chemotherapy, intraperitoneal, interferon, cisplatin*

Introduction

Ovarian cancer represents one of the most frequent causes of death among women. The majority of the patients that present symptoms are diagnosed with advanced stage ovarian cancer due the lack of symptoms in the early stages of the disease. Ovarian cancer occupies the 7th place in frequency of cancer forms for the feminine population situated after breast cancer, cervical cancer, colon and rectum, gastric, endometrial and pulmonary cancer [(1)]. In the United States the ovarian cancer is the second most frequent genital cancer and also the most important cause of death for these patients[(2)]. The life threatening risk for women without family history is estimated to be 1.4% while for those with positive family history the risk in increases drastically[(3)].

The study published by the Gynecology Clinic of Targu Mures, Romania, from 1981 to 1985, shows an increase in the incidence of ovarian cancer in our country com pared to the other genital cancers (from 8.5% to 20.7%).

The major objectives in the treatment of ovarian cancer are the early detection of the disease and finding new drugs or therapeutic methods that would complement the standard current treatment, surgical and chemotherapeutic. Theoretically, early

diagnosis of the disease would be achievable by a bi-annual large scale screening of the feminine population with ages from 40 to 70 years old. The methods that could be used are clinical examination, trans-vaginal echography (Doppler) and determining the plasma concentration of CA-125[4,5,6]. However these initiatives are limited by the high cost of such a screening and also by the lack of equipment in the rural areas of Romania.

Therefore, finding new therapies in the treatment of ovarian cancer is a necessity, especially for the advanced stages of the disease which, like already mentioned, represent most of the patients with a clinical pathology. Among these, the intraperitoneal administration of cytostatics proved to be an innovative and efficient method of increasing the local concentration of these biologically aggressive drugs. The basic concept of this therapy was discovered approximately 30 years ago and represented the beginning of a new era in chemotherapy[7]. The popularity of this idea is primarily due to the favorable clinical response as well as to the increased sensibility of ovarian cancerous cells to high local concentration of cytostatics. Numerous studies were published that tested different drugs and combination of drugs, various concentrations of these, and many other parameters. These studies, several large-scale studies as well as small limited ones, the so-called pilot studies, ultimately helped with the optimization of the method.

In the present article, we report the results of such a pilot study that tests the efficacy of adding an immunological agent (alpha-interferon) to the intraperitoneal administration of cytostatics, as will be further mentioned.

Due to the extensive progression into the peritoneal cavity and to the presence of metastases, advanced stages ovarian cancer are treated with a combination of methods, such as surgery and chemotherapy or surgery and radiotherapy. The diagnosis of ovarian cancer is immediately followed by the assessment of the biologic status of the patient, keeping in mind that major insufficiencies of the vital organs limit the therapeutic possibilities. Furthermore, planning the therapeutic strategy requires the establishment of the clinical stage, the histological type and the grade of malignancy of the tumor.

Among the therapeutic methods used, surgery is the first employed and represents a critical step of the entire procedure. The efficacy of the supporting therapeutic methods (chemotherapy or radiotherapy) depends on the successful completion of the surgical operation; this translates as an optimal reduction in tumor size with the maximal diameter of residual tumors measuring around 1-2 cm or less ("debulking surgery").

In general, most patients require chemotherapy after the primary surgical procedure. However, the survival rates of the patients presenting an earlier stage of the ovarian neoplasm - Ia or Ib (G1 or G2) - are similar to the ones subjected only to surgery, the control lot. On the other hand, some studies demonstrated additional benefits of chemotherapy for patients having a more advanced disease - stages Ia or Ib (G3), Ic or II - when compared with the control lot.

Cytostatics are chemotherapy agents capable of inhibiting the progression through the cell cycle, for both normal and cancerous cells. The ratio between normal cells going through the cell-cycle and the total number of cells in a tissue at a specific moment represents the proliferation index; the increased index of cancerous tissue of up to 90% acts in favor of the cytostatic effect of these drugs. In time, the proliferation index of any given tumor decreases as its volume increases (>1,5 cm^3) and the progression rate of the cancerous tissue slows down; moreover, the proportion of cells going through the cell-cycle decreases and this is the cause of decreased efficacy if the cytostatic agent.

Extensive studies showed the inefficiency of mono-therapeutic continuous administration of small-dose cytostatic drugs because it kills not only the cancerous cells but also the hematopoietic cells. This could finally lead to different grades of medullar suppression manifested through anemia, leucopenia and even irreversible medullar aplasia. In addition, cellular clones that grow resistant to chemotherapy may develop. Conversely, pulse-therapy is used worldwide at the present, allowing the administration of large doses of cytostatics that destroy almost completely the cells going through the cell cycle (more than 90% of tumoral cells and only 15% of hematopoietic cells).

The ability of chemotherapy to kill a large proportion of cells increases with frequent administrations. The optimal time interval is 3 weeks during which the organism recovers from the mielo-suppresive effect of cytostatics, a side effect that represents most often the main reason of treatment failure. Increasing the interval between consequent administrations increases the risk of losing the control over tumor growth rate.

The toxic effect of the cytostatic agent increases with greater doses but the biologic tolerance of normal tissues limits the doses as well as the frequency of administrations. Ovarian cancer therapy utilize with great success poli-chemotherapy which facilitates the treatment of multiple cancerous cell lines at the same time. In this manner, the poli-chemotherapy approach inhibits a larger proportion of cancerous cells, and also prevents the appearance of resistant cell lines.

At the present moment, the standard therapy following surgery is systemic pulse poli-chemotherapy that uses variable doses dependent on the biological status of the patient. The response rate to therapy of the treated tissues is critically dependent on the residual volume of the tumor. The efficacy of chemotherapy is determined by either paraclinical investigations (CA-125 serum concentrations, echography, computer tomography, nuclear magnetic resonance, radioimmunoscintigraphy with monoclonal antibodies) or control second/third-look surgery[8,9,10]. Furthermore, monitoring the patients undergoing surgery and chemotherapy also involves monthly clinical examination and usual tests to evaluate the vital organs.

In addition to cytostatic agents, the modulating agents of the immune system are another focus point of ovarian cancer therapy. Among these, the genetically engineered alpha-interferon (alpha-IFN) proved to be an effective agent since the systemic administration of alpha-IFN showed a response rate of 18% in ovarian cancer patients[11]. Moreover, promising response rates were reported in patients subjected to a mixed therapy, cisplatin plus alpha-IFN, some of which were confirmed by histology exam.

Interferons play an important role in the defense against the cancerous proliferative characteristics, by acting directly on the target cells, as determined by increased expression of surface antigens, and also indirectly by the activation of the cytotoxic effector cells of the host. Other studies also demonstrated the increased expression of tumor suppressing genes as another effect of interferons[12].

Several studies were reported that employed the intraperitoneal administration of interferons, either mono or poli-therapy (with cytostatics or cytokines); good results were obtained with high doses of 150mU alpha-IFN in combination with 400mg/m^2 carboplatin, especially for a small residual tumor size (with the maximal diameter <2 cm).

In summary, taking into consideration both the advantages offered by the intraperitoneal administration and the anti-proliferative action of interferons, we analyzed the evolution of advanced-staged ovarian cancer following a treatment protocol in a study that lasted 3 years, as follows: alpha-IFN and cisplatin administered intraperitoneally (ip) together with systemic administration of cyclophosphamide (iv).

Materials and method

The studies done in the Obstetrics and Gynecology Clinic of The Emergency University Hospital of Bucharest in collaboration with the Chemotherapy Clinic of the Oncologic Institute of Bucharest lasted from 1995 to 1998. During this time, a total of 67 female patients diagnosed with ovarian cancer were treated in our clinic. Among these patients, 59 were diagnosed with advanced-stage ovarian cancer (IIc-IV) and thus subjected to our therapy protocols, following tumor-reduction surgery.

Protocol I - two cytostatics by iv administration:

- cisplatin 100 mg/m^2 iv, the first day
- ciclofosfamida 1600 mg/m^2 iv, the first and second day

Protocol II - cytostatics and alpha-interferon by ip administration:

- alfa-interferon 10 mU ip, the first day
- cisplatin 100 mg/m^2 ip, the first day

Protocol II also included the iv administration of:

- cyclophosphamide 1600 mg/m^2 iv, the first and the third day

The patients were included in one or the other protocol by alternation. The minimal criteria of acceptance in the therapeutic protocol were: acceptable biologic status without major insufficiencies of vital organs, leucocytes >4000/ mm^3, serum creatinine <1,5 mg/dl and the absence of any residual tumor outside the abdominal cavity.

The chemotherapy was initiated 14 days after surgery. The ip administration of cytostatics included the infusion of 2 liters of 37° warmed up physiological serum by a transitory catheter at 4-6 h intervals. Concomitant with the ip administration of the cytostatic, we also administered iv 1 liter of physiological serum, 3 g magnesium sulphate and 40 g manitol. Whenever necessary, ascites liquid was drained through a catheter before cytostatic drugs. In addition, 500mg paracetamol was administered every 6 h to prevent the pseudo-flu symptoms caused by alpha-IFN. The treatment was monitored by clinical examination, both general and local, second-look laparotomy (with the written consent of the patient), echography and computer tomography, serum levels of CA-125 and blood tests[13,14].

Results

First, the distribution by the stages of the disease in our clinical cases shows a vast majority of the ovarian cancers are advanced stages (IIc = 12 cases, III = 36 cases, IV = 11 cases), confirming the expected high percentage of advanced-stage ovarian cancer (>70%).

Within the histological types of ovarian cancers, the serous one is most frequently found (>50%), followed by the endometroid type (13%) and mucinous (7%) types. The most frequent malignancy type is G2.

The distribution of the clinical cases by age groups shows the majority (65%) of the patients belongs to the V and VI age decades, with a maximum frequency found between 55 and 64 years old (40%).

Among the patients with a small size residual tumor (<2cm), the ones subjected to Protocol I showed a favorable evolution a number of 5 out of 11 patients; on the other hand, a number of 9 patients subjected to Protocol II showed a good evolution from a total of 10 patients. We compared the two analyzed groups of patients and calculated a difference of 45 % in their clinical responses ($p = 0,031$). This analysis clearly shows the superiority in the response rates for the group of patients subjected to Protocol II.

Among the patients with a large size residual tumor (>2cm), 3 out of a total number of 20 of patients subjected to Protocol I showed a favorable progress; similarly, 2 out of 20 patients undergoing Protocol II evolved well. Our calculated difference between the two groups of patients is 5% ($p = 0.633$). This examination shows similar response rates in both groups of patients subjected to Protocol I and II.

These results show increased response rates for patients having small size residual tumor in the group undergoing Protocol II; in other terms, the data demonstrate the efficacy of ip administration of chemotherapy plus alpha-IFN in small residual tumors (<2cm), when compared with the group of patients presenting larger residual volume tumors.

The serum levels of CA-125 displayed a good correlation with the size of the residual tumor as follows: the group having small size residual volume maintained their serum levels between 65 and 1500 U/ml, with an

average value of 210 U/ml, while the large size residual volume correlated with levels of 70-6520 U/ml, averaging 500 U/ml.

The disease progression and the efficacy of chemotherapy were also monitored using results obtained by echography and computer tomography.

The hematological toxicity caused by our drugs using both administration methods, iv and ip, was analyzed and the results show higher rates of granulocitopeny (70%) and leucopeny (55%) for patients subjected to Protocol I when compared to Protocol II patients with a smaller percentage of granulocitopeny (55%) and leucopeny (40%).

In our study it was not necessary to stop the administration of cytostatics or use G-CSF because leucopeny was below 2000 leucocites/mm^3. Besides, we did not register severe infections and refractory anemia. The neutropeny fever was treated by administering paracetamol 500 mg every 6 h. Dizziness, hypoacusy, toxic neuromuscular and pulmonary effects were less frequent in the group of patients following Protocol II. However, in this group the patients complained of transient abdominal pain that was treated with oral opioids.

Second-look laparotomy was performed on patients that lacked the clinical signs of the disease after 6 series of chemotherapy to certify the absence of tumors inside the abdominal cavity. The cases that showed CA-125 levels > 35 U/ml and/or peritoneal implants or tissue metastases by echography or computer tomography were also subjected to second-look laparotomy to try a secondary reduction of the residual tumor. Some patients that evolved well clinically refused the second-look laparotomy. Moreover, this reintervention was not performed on patients having last stage ovarian cancer (IV) because of the already very poor quality of life and also because of the minimal outcome of the surgery in these patients.

Discussion

among the therapy protocols used for ovarian cancer, surgery represents an essential first step. The surgical procedures performed on patients having early stages of ovarian cancer intend to completely remove any trace of the disease, while the advanced-stages only allow a reduction in tumor size. The residual tumors are then followed by 6 cycles of poli-chemotherapy.

Data from three major clinical studies on the therapeutic strategy of advanced-stage ovarian cancer confirms our results demonstrating the superiority of the intraperitoneal administration of chemotherapy when compared to the standard systemic administration[15,16,17]. Due to the long period of time that the tumor remained stuck in the intraperitoneal cavity, the ip administration exposes the tumors and the peritoneal metastases to high local concentrations of cytostatics, in the same time decreasing the systemic toxicity of the treatment.

In our study, the ip administration of alpha-IFN plus cisplatin proved to be efficient and safe in the treatment of advanced-stage ovarian cancer. Similar results were

reported by other clinical studies as well, strengthening the conclusion of our own data[18,19].

Interferons are strong therapeutic agents that demonstrated important anti-proliferative effects by acting directly (slowing the progression of the cellular cycle, removing essential metabolites) and indirectly (modulated by the cytotoxic leucocytes of the host or by the cellular immune response).

Successful chemotherapy depends mainly on the skillful execution of the surgical procedure, its results being seen in the optimal reduction of the residual tumor. Improved results are observed in the patients that have small size residual tumors (<2 cm in the maximal diameter of the tumor). Moreover, while some toxic effects were seen in both administrations methods, systemic and intraperitoneal, the patients undergoing systemic chemotherapy presented a higher percentage of these adverse effects (Protocol I).

Our study shows that this therapeutic protocol may be safely and effectively administered intraperitoneally, the results obtained being promising for small size residual tumors. To monitor the treatment we obtained good results by using echography , computer tomography and the serum concentration of tumoral markers as CA-125. Second-look laparotomy is useful to confirm the absence of any cancerous processes by histopathological exam or to further reduce the size of residual tumors.

The optimal treatment of such a complex pathological status, the advanced-stage ovarian cancer, requires the collaboration of many highly trained medical doctors, including gynecology, oncology, chemotherapy, radiotherapy and histopathology specialists.

Conclusions

Despite the major discoveries that exist in the therapy of ovarian cancer, the advanced stages of this aggressive disease continue to be a challenge for present day medicine. Although much remains to be learned regarding the optimal drug delivery method, it is important to mention the implementation of the ip administration in present day routine oncology practice[20,21].

Medical research shows promising results in applying molecular biology methods and principles to the treatment of ovarian cancer; these positive results justify the important financial support these clinical studies receive in order to test the clinical efficacy of molecular agents, for example the vascular endothelial growth factor inhibitor or the folate-receptor inhibitor[22]. ■

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