Chemotherapy of patients with malignant tumors of the ovary

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Summary: Reviewed information about treatment of malignant ovarian tumors is summarized. First and second-lines chemotherapy as well as intra-abdominal and targeted therapy of ovarian cancer are discussed.

Key words: ovarian cancer, chemotherapy.

According to the International Agency for Research on Cancer (IARC), ovarian cancer (OC) take seventh place in the structure of total cancer incidence and the fifth leading cause of cancer-related death among women. Worldwide, there are about 165,000 new cases are diagnosed annually and more than 100,000 women die of this disease. Only around 30% of women are diagnosed at the earliest I-II stages while advanced stages account for 70% of cases.

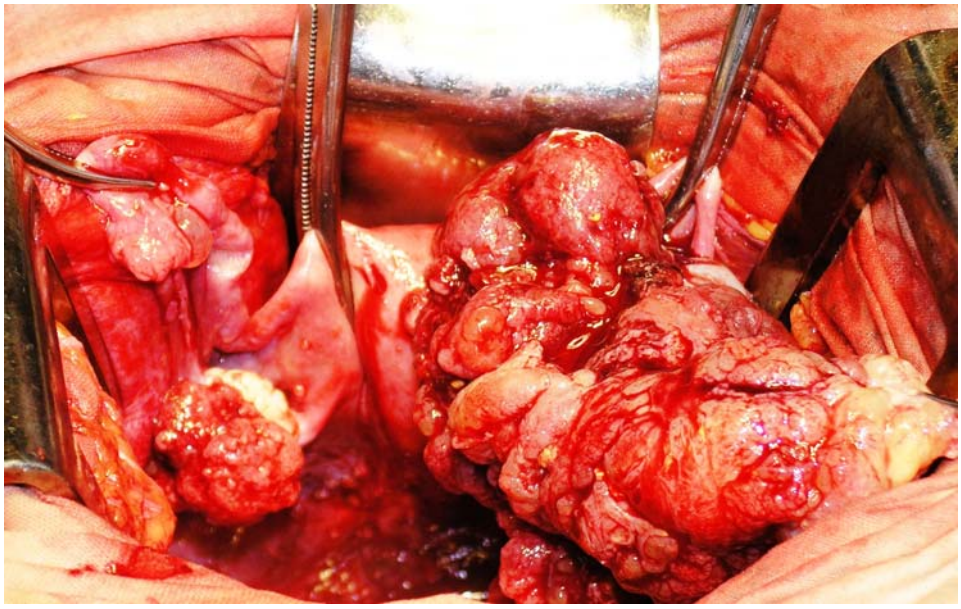

Figure. Advanced ovarian cancer (view during cytoreductive surgery)

OC is a disease of postmenopausal women, with only 10% to 15% discovered in premenopausal patients. The mortality rate for patients with OC in

the first year after diagnosis is 35%. According to the population-based cancer registries in Europe, 1-year relative survival of patients with OC is 65%, 3-year - 41%, 5-year - 35%.

According to the Ukrainian National cancer registry, OC incidence take seventh place among all malignancies (5%) and the third place among gynecological tumors, after uterine and cervical cancer. More than 4,000 new cases are diagnosed each year (15,8 on 1000,000) and almost 2,000 young women die. Despite the development of more effective chemotherapy with complex compounds of platinum and taxanes 5-year survival rate has not been improved significantly and doesn't exceed 25-30%.

Compulsory component of I-line chemotherapy for treatment of OC patients is platinum derivatives, which is confirmed by the results of a meta-analysis of individual data of nearly 10,000 patients from 45 randomized trials. These studies showed advances in survival rate of OC patients if chemotherapy started with platinum derivatives or with combination of platinum derivatives compared to chemotherapy without platinum derivatives or platinum monotherapy. In combination with cisplatin, cyclophosphan (regimen CP) or cyclophosphan and doxorubicin (regimen CAP) can be given. Meta-analysis showed that CAP yielded a higher rate of tumor response and longer 2-year and 5-year survival than CP. Further development of chemotherapy was associated with the study and clinical utility of taxanes. The challenge now facing investigators is to develop strategies to maximize therapeutic benefits with the taxanes in treatment of OC [20-25]. The result of randomized studies was the recognition of combination of paclitaxel + carboplatin AUC 5 as the I-line chemotherapy. In randomized comparative study (SCOTROC) of carboplatin AUC 5 with docetaxel or paclitaxel combination, docetaxel demonstrated good response rates and an acceptable toxicity profile and is decent replacement of paclitaxel, and can be used to develop approaches to individualization of treatment [1-4]. However, this study contradicted results of ICON3 and GOG 132 studies, according to which carboplatin or cysplatin is the preferred in the I-line chemotherapy.The combination of platinum derivatives with

paclitaxel does not lead to the significant improvement of short and long-term outcomes compared with platinum monotherapy **[5-7].**

Active search for effective combinations of I-line chemotherapy drugs continues in different directions: study of triplet combinations, new regimens and modifications of regimens based on existing standards, methods of drug administration, intra-abdominal chemotherapy, and study of new targeted cytotoxic drugs.

The use of triplet regimen (paclitaxel + carboplatin + hemzar) allowed achieving complete remission in 53% of patients with advanced epithelial OC [M. Hesley, 2005]. The use of other triplet regimen (keliks + paclitaxel + carboplatin) achieved the overall effect in 81.3% of patients [J. Arranz, 2005]. The same effect was achieved as well in patients with advanced OC after use of other triplet regimens ([P. Escobar, 2005]) [8-13].

The most significant results were obtained in the clinical trial GOG182 in 4312 patients with epithelial OC stage III-IV after cytoreductive surgery. In the I-line chemotherapy, the third cytotoxic agent (gemcitabine or liposomal doxorubicin) was inluded in combination to carboplatin + paclitaxel or alternation of cytotoxic drugs with different mechanisms of action [14]. Analysis of the treatment results showed that the inclusion of the third cytotoxic agent or alternation of different cytotoxic drugs does not improve patients' outcome, but significantly enhances the hematology toxicity.

Thus, the present standard of I-line chemotherapy is a combination of two drugs - carboplatin and paclitaxel. The same conclusion has been obtained in studies conducted by Italian and Greek investigators – triplet combination of cytotoxic drugs with inclusion of other cytotoxic drugs (hemzara, topotecan, kampto, liposomal doxorubicin) didn't significantly improve the results of chemotherapy of patients with OC compared to standard chemotherapy [15-16].

It seems that with these cytotoxic drugs (carboplatin, paclitaxel and others) the limit of current capabilities of chemotherapy in the treatment of patients with OC has been reached.

Therefore, new drugs with pharmaceutical targeted action on tumor cells or other methods of cytotoxyc drugs administration for patients with OC are needed. From this perspective, attention is drawn to the scale randomized trial GOG (about 800 patients), which conducted a comparative study of two regimens (carboplatin AUC + paclitaxel and cisplatin + paclitaxel) in OC patients with stage III after optimal cytoreductive surgery. According to the study, the effectiveness of treatment was similar, but more often signs of toxicity were observed. The results demonstrate the need to develop new approaches to improve the treatment of locally spread forms of OC, namely effective methods of consolidating and maintenance therapies to improve the survival of patients with OC.

Currently some experience in consolidating and maintenance chemotherapy conducted after achieving complete clinical remission has been obtained. Consolidating therapy is relatively short cycle of treatment, which may include high-dose chemotherapy, radiation therapy and administration of radioactive phosphorus, imunoradiation therapy. None of the consolidating therapies didn't affect the overall survival of patients. Maintenance therapy is chemotherapy carried out after achieving long clinical complete remission. Maintenance treatment may include monochemotherapy, increasing the total number of cycles of induction chemotherapy, intra-abdominal chemotherapy, immunotherapy.

Increasing the number of cycles of induction chemotherapy from 5-6 to 8-12 as well as the additional four cycles of topotecan or epirubicin chemotherapy does not increase the time to tumor progression and survival of patients.

For the maintenance therapy, paclitaxel, which refers to taxanes, is used. It is known that taxanes in addition to cytotoxic action have anti-angiogenic action and especially effective for tumors with *TP53* mutations.

Approximately, in 16-18 months after induction chemotherapy in OC patients, progression of tumor process is observed. Is it possible to prevent such situation by maintenance therapy? The answer to this question the researchers tried to obtain in a study, in which patients, who achieved complete tumor regression after 6 cycles of platinum and paclitaxel derivatives chemotherapy,

additionally received 3-12 courses of paclitaxel maintenance chemotherapy, but this treatment did not significantly affect the survival of OC patients.

A number of studies pay attention to the relationship between concentration of CA-125 in blood serum and the efficiency of the I-line chemotherapy. When the concentration of CA-125 less than 10 U / ml, 12 courses of maintenance therapy significantly increased survival of patients. Maintenance therapy didn't have any effect when concentration of CA-125 was more than 10 U / ml. In other words, the additional therapy during 12 months may be effective in patients with high sensitivity of tumors to chemotherapy, because the concentration of CA 125 is less than 10 U / ml is indirect evidence of the high sensitivity of tumors to cytotoxic drugs. Obviously, the concentration of CA-125 after induction chemotherapy can be considered as important prognostic factor.

In a II-line chemotherapy, most experts observed the following algorithm. When the "light" period (interval between the last chemotherapy and disease relapse) is over then 6 months, platinum derivatives combination and other drug is most effective. When the interval is less than 6 months - monotherapy with other cytotoxic agents is recommended. In a study conducted in Denmark, OC patients with tumor relapse after I-line chemotherapy (taxanes and platinum derivatives) received combination of drugs - liposomal doxorubicin + gemcitabine every 3 weeks. In terms of patients' survival (median time to recurrence - 212 days, the median of survival - 234 days), this combination of drugs recommended as the II-line chemotherapy in patients with short "light" gap [17].

Thus, at present there is no same regimen of polychemotherapy of I- and II-lines, the use of which would be most effective. This is due to the fact that the effectiveness of chemotherapy depends on many factors, including the type of cytoreductive surgery, tumor stage, tumor aggressiveness, resistance to cytotoxic drugs and many other factors.

The development of new group of targeted agents has opened new opportunities for the treatment of malignancies, including OC. Thus, for ovarian tumors with overexpression of epidermal growth factor up to 35-70% there is a

need to use its inhibitors. This mechanism has a number of chemotherapeutic agents including Glivec - specific competitive inhibitor of c-kit receptor-tyrosine kinase, Herceptin - an inhibitor of HER-2/neu, celecoxib - cyclooxygenase 2 inhibitor, lapatinib - an inhibitor of HER-2 and HER-1 and hefitinib (iressa), erlotinib (tarseva), cetuximab (Erbitux) [A. Garcia, 2005, R. Burger, 2005].

Angiogenesis inhibitors blocking vascular endothelial growth factor (VEGF) are also studied. Drug with angiogenesis inhibiting action is bevacizumab (avastin) [33]. The results of the study of regimens with bevacizumab + II-III lines of chemotherapy with cyclophosphamide in OC patients have showed partial remission in 21%, stabilization of tumor process - in 59%, tumor progression - in 21% of patients, the median of patients' survival to OC relapse was 5,8 months. (A. Garcia, 2005, R. Burger, 2005). At the same time, targeted drugs like cytotoxical drugs have a high toxicity. Iressa in the II-III lines of chemotherapy caused neutropenia of the IV grade in 16%, toxic manifestations on the skin - in 46%, diarrhea - in 76% of patients [R. Schilder, 2005]. Toxic manifestations on the skin occurred also under combination of paclitaxel + carboplatin I AUC6 + tarseva in I-line chemotherapy in OC patients [V. Blank, 2005]. Febrile neutropenia in 12%, diarrhea in 6%, acne-like rash in 88% of patients after the use of paclitaxel + carboplatin I AUC6 + cetuximab in I-line chemotherapy have been described [3. Aghajanian, 2005].

Thus, these data suggest many unresolved issues associated with chemotherapy of OC patients and effectiveness of chemotherapy depends on many factors, including the regimen of treatment, the mechanism of action of cytotoxic drugs, their toxicity and resistance of tumor cells to anticancer drugs.

Analysis of the mechanisms of resistance to cytotoxic drugs showed its dependence on various features of the complex regulatory processes in the cell including tissue specificity, genetic alteratios that occur in the cell during malignant transformation and tumor progression.

The development of intra-abdominal chemotherapy refers to 1978 and is connected with the name of R.L. Dedrick, who theoretically motivated the

feasibility and perspective of intra-abdominal (i /a) administration of chemotherapy drugs in OC patients. In fact, i/a chemotherapy can be seen as an attempt to intensify chemotherapy by increasing the concentration of drugs in the abdomen. However, the effect of i/a chemotherapy is realized only in the surface layer of the tumor, because the local penetration of cytostatic drug in tumor is limited to 2.3 mm (experimental data). From this perspective, patients with small, often microscopic residual tumor are an ideal cohort for i/a chemotherapy, while large tumor masses limit the use of this regimen. There are many results of randomized trials of i/a polychemotherapy. In clinical trial SW OG8501/GOG104 two groups of patients were studied. I group of patients received cisplatin i/a 100 mg/m^2+ cyclophosphamide 600 mg/m^2 intravenously. II group patients received cisplatin+ cyclophosphamid intravenously in the same doses. I/a chemotherapy yielded 8-months increase of disease-free survival.

In another study GOG 114/SWOG9227 outcomes of two groups of OC patients with different treatment regimens and different way of chemotherapy also have been studied. Patients with OC stage II-IV who received i/a cisplatin chemotherapy had a slight advantage in disease-free and overall survival, but the toxicity and quality of life was higher than in control group.

Study GOG 172: I group of patients - paclitaxel intravenously in 1st day, cisplatin i/a in the 2nd day and paclitaxel i/a in the 3rd day. II group of patients - paclitaxel intravenously+cisplatin intravenously. It has been revealed the reduction risk of OC relapse by 28%, increase in median survival under i/a chemotherapy - 66.9 months versus 49.5 months under intravenously chemotherapy (2006). It is well known that the i/a chemotherapy has rational components: the possibility of direct penetration of cytotoxic drugs directly into the tumor, especially in case of a large area of peritoneal tumor dissemination; the possibility to increase doses of drugs with minimal side effects. Clinical studies also have shown the advantage of i/a chemotherapy for prolonged disease-free survival.

There are comparative studies on the effectiveness of intravenous and i/a ways of paclitaxel and carboplatin administration in the I-line chemotherapy. One

study clearly demonstrated significant increase the time to tumor relapse in patients with advanced OC as well as overall survival under i/a paclitaxel chemotherapy (intravenous in the 1st day), cisplatin chemotherapy (i/a in the 2nd day) and paclitaxel at a reduced dose (i/a on the 8th day of treatment). It should be noted that i/a chemotherapy had more toxicity - leukopenia in 76%, thrombocytopenia grade III in 12% of patients compared with intravenous administration of cytotoxic drugs – 64% and 4% of patients, respectively.

At the same time disadvantages of i/a chemotherapy have also been described, namely weak cytostatic effect under retroperitoneal spread of tumors with metastases in the liver, pleura, lymph nodes that occur in 60% of OC patients. Under i/a administration of chemotherapy drugs, pain, infection, disturbed bowel function may occur that can not only lead to reduced quality of life of the patient, but also to the development of intestinal obstruction or perforation of hollow organs. According to some researchers, further surgery in patients after i/a chemotherapy is practically impossible [18]. According to the protocol GOG172, i/a chemotherapy has the advantage in disease-free and overall survival of patients with OC without residual tumor or with minimal residual tumor after surgery. However, considering the toxicity profile of this administration, careful selection of patients is needed for the i/a chemotherapy with excluding patients after extensive operations with the presence of microtraumas or resection of the bowel, as well as with marked adhesive process and the symptoms of irritable bowel.

New promising directions of i/a chemotherapy in patients with OC are consolidating therapy, i /a therapy with positive findings during surgery, i/a chemotherapy with hyperthermia, i/a immunotherapy and radiation immunotherapy with monoclonal antibodies. For i/a therapy, new drugs (interleukin 6, interleukin 12, Advexin, FLT3-ligand, Ontak, tgDDC-E1, EDGEN 001) are used, effectiveness if which continue to be studied [19].

Study of the metronomic chemotherapy - the use of low-dose chemotherapy at short intervals has recently begun.

In general, it should be noted, that in any kind of OC relapse, the II-line

chemotherapy significantly increases the survival and quality of life. Recently, the spectrum of anticancer drugs that are active in the II-line chemotherapy has greatly been expanded, allowing a further improvement in its effectiveness.

Thus, by increasing radicalism of surgery and improving chemotherapy, the use of new drugs, including targeted, perspective in effective treatment of OC has been emerged. New drug development gives a hope that in the near future we will be able to cure the majority of patients with disseminated tumor processes or achieve prolonged survival.

REFERENCES

1. Andreopoulou. E. et al. Phase I/ pharmacology study of intraperitoneal (IP) 3-5 day topotecan alone and with cisplatin on day 1. ASCO 2005, abst.5045.
2. Chinet-Cnorrot P et al. Association of pegylated liposomal doxorubicin and Ifosfamide in early recurrent ovarian cancer patients. ASCO 2005. abst.2005.
3. Deborah K., Amstrong M.D. et al. Intraperitoneal Cisplatin and Paclitaxel in ovarian cancer. N Engl J Med 2006.
4. Garcia A.A. et al. Interim report of a phase 2 clinical trial of bevacizumab and low dose metronomic oral cyclophosphamide in recurrent ovarian carcinoma. ASCO 2005 abst.5000.
5. Gordon M.S. et al. Clinical activity of Pertuzumab in advanced, refractory or recurrent ovarian cancer. ASCO 2005. abst 5051.
6. Herzog T. et al. Phase study of Paclitaxel/ Carboplatin for 1st line induction and maintenanca therapy of stage III/IV ovarian carcinoma. ASCO 2005. abst 5012.
7. Kaye B.S. et al. What are the clinical trial priorities of the future? Eur J Cancer 2003; 1 (6): 147-54.
8. Ledermann J.A. Randomised trial of Paclitaxel in combination with platinum chemotherapy v.s platinum-based chemother apy in the treatment of relapsed ovarian cancer(ICON 4/OVAR2.2) On behalf of ICON and AGO Collaborators, 2003.
9. mcMeekin D.S. et al. Final results of a phase II study of weekly trabectidin in second/ third line ovarian cancer. ASCO 2005, abst.5011.
10. Pfisterer B. et al., Hensley M. et al., Arranz J. et al. ASCO 2005 Abstract book . abst. 5007, 5016, 5139.
11. Salzberg M., Thurlimann B. Current Concepts of Treatment strategies in Advanced or Recurrent Ovarian Cancer. Oncology 2005: 68: 293-8.
12. Schilder R.J. Novel Therapies: Update on Biologic Targeted Strategies for

Ovarian Cancer. ASCO 2005.
13. Stanley B., Koye H.D. Chemoterapy for Ovarian Cancer Futur Potential for new and Existing Drugs. ASCO 2005, 411-5.
14. Thigpen J.T. Current Controversies in ovarian cancer: Maintenance Chemotherapy as standard care. Oncology 2005: 68:293-8.
15. Tremllay A. et al. Canada Efficacy of third-Line chemotherapy for recurrent ovarian carcinoma ASCO 2005, abst. 5136.
16. Vergote I. Controversies in surgery in ovarian cancer - what is its real role? European Journal of Cancer 2003;1(6):115-25.
17. Vergote I.B. Neoadjuvant chemotherapy in Advanced Ovarian cancer. AS CO. Education book 2004, 285-29
18. Vermorken J.B. Intraperitoneal Chemotherapy in Advanced Ovarian cancer: At last recognition. Educational lectures 17th ICACT 2006.
19. Viens P., Petit T. et al. A phase II study of Paclitaxel and Oxaliplatin combination in platinum-sensitive recurrent advanced ovarian cancer patients. Ann Oncol 2006, 17(3) 429-36. .
20. Блюменберг А.Г. Диссеминированные формы рака яичников (лечение и факторы прогноза): Дис. ...д-ра мед. наук.– М., 2002.
21. Бохман Я.В. Руководство по онкогинекологии.- СПб.: Фолиант, 2002.- 540 с.
22. Гарин А.М., Горбунова В.А., Бычков М.И. и др. Под ред. НИ Переводчиковой. Химиотерапия опухолевых заболеваний. 2000 г.
23. Жордания К.И. Совр. онкол. 2000; 2 (2): 51–52.
24. Новикова Е.Г., Корнеева И.А Неоадъювантная химиотерапия в лечении распространенного рака яичников //Материалы VII Российской онкологической конференции М., 27 ноября 2003 г С
25. Урманчеева А.Ф. Современная химиотерапия рака яичников. Практич онкол 2002;3(4).