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MODERN APPROACHES TO THE SYSTEMIC TREATMENT OF RECURRENT OVARIAN CANCER

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INTRODUCTION:

Introduction: *Recurrent ovarian cancer is one of the most challenging issues in medical oncology. Being the fifth in the cancer mortality list among women, ovarian cancer is the reason of more deaths than any other cancer of the female reproductive system. A meta-analysis was conducted to investigate the optimal treatment options for recurrent platinum-sensitive and platinum-resistant ovarian cancer.*

Methods: *Data for writing this article was collected from the publications in English, Russian and Italian from 2002 to 2023. PubMed and Web of Science were searched for the relevant articles. Survival rates, particularly overall survival (OS), progression-free survival (PFS), and adverse events (AEs) of the chemotherapy regimens were discussed. We analyzed the literature data comparing the effectiveness and safety of chemotherapy, antiangiogenic therapy, the use of poly-ADP ribose polymerase (PARP) inhibitors, and checkpoint inhibitors in the treatment of recurrent ovarian cancer.*

Results: *An overview of the literature devoted to modern approaches to the systemic treatment of recurrent ovarian cancer is given in the article. General principles of classification and treatment of recurrent ovarian cancer are analyzed. The existing regimens of chemotherapy in combination with targeted therapy are given separately for various types of ovarian cancer relapses. Chemotherapy with doublet platinum compounds (carboplatin or cisplatin) continues to be the standard of care in platinum-sensitive relapsed ovarian cancer with or without targeted therapy. Treatment with poly-ADP ribose polymerase inhibitors, vascular endothelial growth factor inhibitors, immunotherapy with checkpoint inhibitors, and antibody-drug conjugate for patients with folate receptor alpha-positive, can be considered in platinum-resistant epithelial ovarian cancer.*

Conclusion: *In summary, we can conclude that despite the success of the primary treatment of ovarian cancer, the majority of patients with a widespread tumor process develop a relapse of the disease over the next two years, which is the cause of death of these patients. The development of effective treatment regimens for recurrent ovarian/fallopian tube/primary peritoneal cancer remains particularly acute and important in gynecological oncology and requires further study*

KEYWORDS: *platinum-sensitive, platinum-resistant, platinum-refractory relapsed ovarian cancer, chemotherapy, targeted therapy, immunotherapy.*

INTRODUCTION

Ovarian cancer is one of the leading causes of death in gynecological oncology and accounts for about 4% of all new cancer cases in women. Most ovarian cancer cases are seen in postmenopausal patients and only 15% of the women with this malignant disease are premenopausal [*Shen F et al., 2017*].

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According to the study conducted by Razi et al. (2016), in Asia, five countries that had the highest standardized incidence of ovarian cancer, were: Singapore at 9.9 per 100,000, Kazakhstan at 7.9 per 100,000, Beruni at 8.8 per 100,000, Armenia at 5.8 per 100,000, and Japan with 4.8 per 100,000, respectively.

Being the fifth in cancer deaths among women, ovarian cancer is the reason of more deaths than any other cancer of the female reproductive system. Women have about 1 in 78 risk of getting ovarian cancer during their lifetime and 1 in 108 chance of dying from ovarian cancer [*Torre L.A. et al.,2018*]. The main reason for mortality is the high rate of relapse that happens after 1st line treatment [*Ushijima K, 2014*]. It is accepted to classify the relapse of ovarian cancer based on the time of the recurrence after the latest platinum cycle. Based on this factor 3 types of recurrent disease are described: platinum-sensitive relapsed ovarian cancer, platinum-resistant relapsed ovarian cancer, and platinum-refractory relapsed ovarian cancer [*Caeiro C et al., 2022*].

An overview of the literature devoted to modern approaches to the systemic treatment of recurrent ovarian cancer is given in the article. General principles of classification and treatment of recurrent ovarian cancer are analyzed. The existing regimens of chemotherapy in combination with targeted therapy are given separately for various types of ovarian cancer relapses.

In the treatment of platinum-sensitive relapses of ovarian cancer, combined platinum-containing chemotherapy is recommended [*Gadducci A et al., 2021*]. The combination of platinum derivative (cisplatin or carboplatin) together with another antitumor drug, not previously used for the treatment of this patient, is indicated [*Zhang C et al., 2022*]. When the platinum-free interval lasts more than 12 months, it is possible to re-prescribe a combination of a platinum derivative and taxanes for the treatment of relapse in case of absence of high-grade neuropathy after first-line treatment with paclitaxel [*Rezaee R et al., 2019*]. If the duration of the platinum-free interval is 6 to 12 months, mono chemotherapy with a non-platinum or the combination of two non-platinum agents to increase the platinum-free interval by more than 12 months is possible or whenever it is not possible to prescribe a platinum agent because of toxicity profile, thereby gaining time and prescribing a combination with a platinum derivative in case of the second relapse [*Tyulyandin S et al., 2015; Dockery L et al., 2019*]. Other options are liposomal doxorubicin + carboplatin or carboplatin + gemcitabine (preferable in patients with residual neurotoxicity after the first line of chemotherapy) [*Wagner U et al., 2012*]. Doublet therapy based on carboplatin is more effective than mono chemotherapy with carboplatin, although it may be more toxic. Based on the results of ICoN4 and GCIG Phase II clinical studies combinations of oxaliplatin with paclitaxel and pegylated liposomal doxorubicin (PLD) with carboplatin demonstrated approximately the same response rate, but at the same time, each combination had a certain toxicity profile [*Parmar M et al., 2003*]. Clear-cell ovarian cancer is considered to be one of the most aggressive types of ovarian cancer, which tends to have more relapses. According to the results of Sugiyama T et al. (2016), no significant survival benefit was found when comparing Irinotecan + Cisplatin with Paclitaxel + Carboplatin. Both regimens were well tolerated, but the toxicity profiles differed significantly. Treatment with existing anticancer agents has limitations in improving the prognosis of clear-cell ovarian cancer. Both regimens were well tolerated, but the toxicity profiles differed significantly [*Sugiyama T et al., 2016*]. Treatment with existing anticancer agents has limitations in improving the prognosis of clear cell ovarian cancer. When combining pegylated liposomal doxorubicin with carboplatin, alopecia and neurotoxicity were less common, but more often neutropenia, mucositis, and palmar-plantar syndrome were observed. Neurotoxicity and neutropenia are the frequent complications of the combination of oxaliplatin and paclitaxel [*Viens P et al., 2004; Ferrero J et al., 2007*].

It is possible to add bevacizumab (in a dose of 7.5 or 15 *mg/kg* IV once every 3 weeks until progression) to chemotherapy for all patients with recurrent ovarian cancer [*Oza A et al., 2015*]. Bevacizumab should be continued until disease progression or unacceptable toxicity [*Li J et al., 2015*].

In platinum-sensitive relapses, bevacizumab was studied in combination with gemcitabine and carboplatin (OCEANS study), in a platinum-resistant relapse in combination with weekly paclitaxel,

pegylated liposomal doxorubicin and topotecan (AURELIA study) [*Tyulyandin S et al., 2015, Coleman R et al., 2017*].

According to the recommendations of the Association of Oncologists of Russia, the Russian Society of Clinical Oncology, "Ovarian Cancer/ Fallopian Tube Cancer/Primary Peritoneal Cancer, 2020" at the recurrence of the disease with the duration of the platinum-free interval from 6 months to 24 months, it is recommended to treat with the platinum derivative (cisplatin or carboplatin) in combination with another antitumor medication, not previously used for the treatment of this patient [*Bolotina L et al., 2020*]. Acceptable regimens of chemotherapy of the second and subsequent lines (the average duration of chemotherapy of the second line is 4-6 cycles) include:

Combined chemotherapy, including cisplatin 75 *mg/m²* 2 *hours* or carboplatin AUC 5-6 1 *hour* on day 1 of the 21-day cycle in combination with one of the following agents: - doxorubicin 30-40 *m/mg²* 5-30 *minutes* on day 1 of the 21-day cycle; - carboplatin AUC 5 + pegylated liposomal doxorubicin 30 *mg/m²* 1 *hour* on day 1 of the 28-day cycle; - carboplatin AUC 5 + paclitaxel *175mg/m²* 3 *hours* on day 1 of a 21-day cycle (or 60-80 *mg/m²* IV 1 *hour* on days 1, 8 and 15 of a 21-day cycle); – docetaxel 75 *mg/m²* 1 *hour* on the day 1 of the 21-day cycle; and other regimens.

Single-agent chemotherapy and metronomic chemotherapy with etoposide 100 *mg* orally on days 1-10 of a 21-day cycle; Doxorubicin 50-60 *mg/m²* 30 *minutes* on day 1 of the 21-day cycle; vinorelbine 25 *mg/m²* 6-10 *min* on days 1, 8 of the 21-day cycle; topotecan 1.25 *mg/m²* 1-5 days of a 21-day cycle or 4 *mg/m²* 30 *min* 1, 8, 15 days of a 21-day cycle; pegylated liposomal doxorubicin 40-50 *mg/m²* 1 *hour* on day 1 of the 28-day cycle; gemcitabine 1000 *mg/m²* 30 *min* on the days 1, 8 and 15 of the 28-day cycle; paclitaxel 80 *mg/m²* 1 *hour* weekly; docetaxel 75 *mg/m²* 1 *hour* on the day 1 of the 21-day cycle; pemetrexed 500 *mg/m²* 10 *min* on day 1 of the 21-day cycle.

Endocrine therapy with letrozole 2.5 *mg* per day orally daily; Anastrozole 1 *mg* orally daily; tamoxifen 20-40 *mg* orally daily; megestrol 160 *mg* per day orally daily.

For the patients with platinum-sensitive relapse of high-grade ovarian cancer who responded (full or partial response) to platinum-containing chemotherapy, maintenance monotherapy with olaparib is recommended until disease progression at a dosage olaparib tablets (150 *mg* 2 tablets twice daily) or olaparib in capsules (200 *mg* 2 capsules twice daily) [*Bolotina L et al., 2020*].

The authors of the practical recommendations developed the level of persuasiveness of the recommendations on the scale "A, B, C". The presented recommendations were evaluated by the authors on this scale.

"A" – strong recommendation (all efficiency criteria (outcomes) are considered important, all studies have high or satisfactory methodological quality, and their conclusions are consistent with the outcomes of interest);

"B" – conditional recommendation (not all efficiency criteria (outcomes) are considered important, not all studies have a high or satisfactory methodological quality, and/or their conclusions on the outcomes of interest are not agreed upon);

"C" – weak recommendation (lack of evidence of proper quality (all efficiency criteria (outcomes) are considered unimportant, all studies have low methodological quality and their conclusions on the outcomes of interest are not agreed upon). Unfortunately, a number of recommendations were evaluated according to the "B" criterion, and most of the recommendations - according to the "C" criterion.

Thus, in the main part of the recommendations, at least, not all efficiency criteria were important, not all studies had high or satisfactory methodological quality.

According to the latest NCCN recommendations of [*Abu-Rustum et al., N 2023*] for patients with platinum-sensitive recurrent ovarian cancer preferred chemotherapy regimens are: carboplatin\ gemcitabine +/- bevacizumab; carboplatin\ liposomal doxorubicin +/- bevacizumab; carboplatin\paclitaxel +/- bevacizumab; cisplatin\gemcitabine. In these recommendations, a large spectrum of targeted therapy agents is offered - bevacizumab, niraparib, olaparib, and rucaparib.

NORA trial with PARP. Niraparib showed a potentially favorable overall survival trend irrespective of gBRCA status with niraparib maintenance treatment for patients with platinum-sensitive relapsed ovarian cancer. Niraparib maintenance ther-

apy using an individualized starting dose demonstrated a favorable overall survival trend compared with placebo in the intention-to-treat population in both patients with germline BRCA-mutated and non-germline BRCA-mutated, platinum-sensitive, relapsed ovarian cancer [*Wu X et al., 2021*].

Among other regimens, Pazopanib is offered as a targeted therapy [*Kim J, et al., 2018*]. The limitation of this study is that it was performed in the East Asian population and we don't know the efficacy of this regimen in other ethnic groups.

Clinical recommendations also offer a number of hormonal agents for the treatment of recurrent ovarian cancer – letrozole, megestrol, leuprolide, tamoxifen, and a new medication for ovarian cancer – fulvestrant. Ovarian cancer arises from surface epithelium which expresses ERα receptors. The observation that more than 60% of primary ovarian and breast tumors express epithelial ERα suggests there should be parallels between estrogen action mechanisms in ovarian and breast cancer cells [*Lindgren P et al., 2004*]. Recurrent mucinous ovarian cancer has been shown to be less responsive to platinum-based chemotherapy compared to other subtypes. Several investigators have confirmed this disease to be platinum-resistant [*Babaier A, Ghatage P, 2020*]. Response rates are between 12% and 35% in mucinous carcinoma compared to 70% in high-grade serous carcinomas. The use of 5-fluorouracil\leucovorin\ +/- bevacizumab or capecitabine\oxaliplatin \+/- bevacizumab regimens is proposed for this histological subtype, and - carboplatin\paclitaxel in patients over 70 years old.

For clear cell carcinomas, it is recommended to use the irinotecan\paclitaxel. Entrectinib or larotrectinib for neurotrophic tyrosine receptor kinase gene fusion-positive tumors, dabrafenib/trametinib for BRAF V600E -positive tumors, and selpercatinib for RET gene fusion-positive tumors are also offered as target therapy.

Immunotherapy is a rapidly developing sphere in oncology that was first implemented in melanoma with the invention of checkpoint inhibitors. Nowadays many cancer types are being treated with these groups of drugs, like CTLA 4, PD1, and PDL1 inhibitors. However, despite promising results of small pilot studies, clinical use of immunotherapy in ovarian cancer has still not been implemented, mostly due to insufficient experimental evidence of their effectiveness Unlike cervical and endometrial cancer where immunotherapy is already a standard of care at advanced stages and there many ongoing studies in neoadjuvant as well as adjuvant settings, ovarian cancer is relatively sensitive to chemotherapy and resists to immune checkpoint inhibitor treatment. The role of immunotherapy in metastatic ovarian cancer still needs to be determined. [*Siminiak N., et al., 2022; Ma W et al., 2023*].

The main immune checkpoint inhibitors used in ovarian cancer are pembrolizumab and dostarlimab-gxly for MSI-high/dMMR or patients with TMB-H tumors [*Abu-Rustum et al., N 2023*].

The cases with platinum-resistant relapses are much more difficult since it is clear that the platinum derivatives in this situation are useless and treatment should be carried out with the use of other cytostatic agents [*Parmar M et al., 2003*]. In fact, in case of these relapses, patients are classified as those who are eligible for new platinum-based therapy or those for whom platinum is not suitable. For patients with early relapse after or progression during previous platinum-based chemotherapy and patients with platinum intolerance, a non-platinum regimen should be prescribed [*Pignata S et al., 2017*].

For this category of patients, possible treatment options are the use of cytostatic therapy; participation in clinical trials; and hormonal therapy (such as tamoxifen and others). In some patients, a decision may be made to stop the treatment: 1) - in case of progression of the disease during the treatment; 2) - stable disease; 3) - relapse less than 6 months after the end of treatment [*Urmancheeva A, 2010*].

A number of non-platinum agents offered for the treatment of platinum-resistant patients have comparable activity, but different toxic profiles. Among the large number of drugs used in clinical practice as second-line therapy for resistant ovarian cancer are pegylated liposomal doxorubicin, oral etoposide, cyclophosphamide, vinorelbine, gemcitabine, docetaxel, topotecan, including a large range of target therapy agents [*Malvezzi M et al., 2016*]. Patients who did not receive bevacizumab in the first line can get it during the relapse treatment together with chemotherapy [*Pignata S et al., 2017; Pignata S et al., 2019*].

According to the NCCN Guidelines (2023), the following medications are offered for patients with platinum-resistant and platinum-refractory ovarian cancer recurrences. cyclophosphamide\ bevacizumab, docetaxel, etoposide, gemcitabine, liposomal doxorubicin\bevacizumab, paclitaxel, paclitaxel\bevacizumab, topotecan, topotecan\ bevacizumab. It is also suggested to use bevacizumab, niraparib, olaparib, rucabarib and as target therapy Endocrine therapy includes letrozole, megestrol, leuprolide, tamoxifen, fulvestrant, and immunotherapy with pembrolizumab is recommended [*Abu-Rustum et al., N 2023*]. Another monoclonal antibody, Mirvetuximab soravtansine-gynx is already approved for recurrent platinum-resistant ovarian cancer only for folate receptor alpha expressing tumors) [*Gonzalez-Ochoa E et al., 2023*]. The limitation of the use of this regimen is its specificity and availability to prescribe only to patients with folate receptor alpha.

In recent years, the arsenal of drugs has expanded with the addition of targeted drugs, in particular bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), and oral poly (ADP-ribose) polymerase (PARP) inhibitors. The introduction of targeted drugs has greatly expanded treatment options and facilitated the development of individual strategies for the treatment of ovarian cancer. Knowledge of BRCA mutation analysis or homologous recombination deficiency has become essential for the selection of therapeutic options [*Khokhlova S, 2019; O'Malley D et al., 2023*].

For the treatment of platinum-resistant relapses after no more than two previous anti-angiogenic chemotherapy regimens, bevacizumab is approved in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin. The efficacy and safety of bevacizumab in combination with chemotherapy in ovarian cancer was evaluated in the treatment of relapse in patients, sensitive to platinum drugs (OCEANS study) [*Aghajanian C et al., 2012; Aghajanian C et al., 2015*], as well as in platinum-resistant relapses (AURELIA study). In general, the addition of bevacizumab to chemotherapy has been shown to increase progression-free survival. At the same time, the tolerability profile is acceptable, and the quality of life is preserved [*Pujade-Lauraine E et al., 2002; Pujade-Lauraine E et al., 2014*].

An estimated 25% of newly diagnosed ovarian cancers harbor BRCA 1/2 mutations, Currently, a number of antitumor agents demonstrate high efficacy in the treatment of patients with mutations in the BRCA1 and BRCA2 genes. Genetic mutations beyond BRCA mutations may lead to homologous recombination deficiency. In this regard, PARP inhibitors have already been recognized as a very promising group, in particular, olaparib, niraparib and rucaparib that registered in Europe and the USA. In Russia olaparib was registered in 2016. Olaparib is one of the promising targeted agents already included in recommendations [*Ledermann J et al., 2016*]. This medication is most effective in patients with hereditary mutations in the BRCA1/2 genes. According to phase III SOLO2/ENGOT-Ov21 studies, maintenance therapy with olaparib significantly (more than 3 times) increased progression-free survival [*Pujade-Lauraine E et al., 2017*]. It is important to note the convenience of using this agent: the oral form and outpatient use allow the patient to live a normal life without the restrictions imposed by regular hospitalizations [*Moore K et al., 2018*]. The most common adverse events are anemia, asthenia or fatigue, grade 3 and grade 4 neutropenia. Intestinal obstruction was registered in *2%* of patients [*Artamonova E et al., 2008*].

There are now ongoing clinical trials with triplet therapy checking the combined effectiveness of PARP inhibitors, VEGF inhibitors, and immune checkpoint inhibitors. One of these trials is an OPAL study for platinum-resistant ovarian cancer examining the triplet of dostarlimab, niraparib, and bevacizumab. The objective response rate was 17.9 with 7 partial responses and zero complete responses, 23 patients had stable disease as their best response and the overall disease control rate was 76.9% [*Joyce Liu et al., 2021*].

An analysis of the literature shows that there is no convincing data that would allow to determine the optimal regimens and sequence of using therapeutic agents since the efficacy ranges from *20-30%,* and direct comparative studies in recurrent ovarian cancer are few. In the available literature, there are also very few works on the evaluation of various chemotherapy regimens depending on the

tumor histological subtypes [*Tyulyandin S et al., 2015; Coleman R et al., 2017*].

Conclusion

It should be noted that despite the success of the primary treatment of ovarian cancer, the majority of patients with a widespread tumor process develop a relapse of the disease over the next two years, which is the cause of death of these patients.

Targeted therapy is considered promising in the strategy of treating ovarian cancer, mainly not as a single agent treatment, but as a combination with optimal chemotherapy. The introduction of targeted drugs, in particular bevacizumab and the PARP inhibitors, has significantly expanded treatment options and facilitated the development of individual treatment strategies. At the same time, the success associated with the use of targeted drugs is limited by the lack of an increase in the overall life expectancy of patients, the frequency and severity of side effects. Recommendations for the treatment of recurrent ovarian cancer are limited to listing the drugs used and their combinations without specifying the criteria for their use.

One of the major limitations of the study is the lack of updated information regarding relapsed ovarian cancer in the elderly population, as well as age-specific survival. Also, there are very few studies that reflect the treatment efficacy in different ethnic groups.

Summing up, we can conclude that there is an urgent need to development of effective treatment regimens for recurrent ovarian cancer which remains particularly acute and relevant in gynecological oncology and requires further study.

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