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OVARIAN CANCER – SYSTEMIC THERAPY AND THE ROLE OF BIOMARKERS

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Summary

Ovarian cancer is typically a disease susceptible to systemic antineoplastic treatment. Systemic antineoplastic therapy is indicated in almost all FIGO stages of ovarian cancer. In very early stage, well differentiated disease, benefit gained with chemotherapy (CT) is no bigger than the 5-year survival rate per se, 90-98%, therefore CT is not indicated in these stages. In all other stages, the systemic antineoplastic therapy is aplicable and desirable. It is based on platinum compounds, cisplatin and carboplatin, with addition of paclitaxel. For years, there was no advance in systemic chemotherapy treatment in ovarian cancer. The disease is treated as early, advanced and recurrent, and recurrent as platinum sensitive and platinum resistant disease, and this is how the drugs are being applied. Platinum basis, along with taxane partner is the basis and standard protocol, precisely carboplatinum – paclitaxel. There are also some other active agents, such as pegylated liposomal doxorubicin, topotecan etc. Beside the chemotherapy, a biological therapy holds an important spot in treating (epithelial) ovarian cancer. Bevacizumab showed efficiency and benefit in platinum resistant and platinum sensitive recurrent disease, as well as in advanced, nonmetastatic and nonrecurrent disease. PARP inhibitor olaparib gained accelerated approval on the basis of significantly improved fast overall response rate and duration of response. It is yet to be shown, whether all the benefits of neoadjuvant approach, dose dense regimen, metronomic chemotherapy and intraperitoneal way of application of CT in treating ovarian cancer are being explored.

KEY WORDS: *epithelial ovarian cancer, systemic treatment, carboplatinum, paclitaxel, bevacizumab, olaparib, FIGO stages, platinum - sensitive disease, platinum - resistant disease*

RAK JAJNIKA – SUSTAVNA TERAPIJA I ULOGA BIOMARKERA

Sažetak

Rak jajnika u načelu je bolest osjetljiva na sustavnu antineoplastičnu terapiju. Sustavno antineoplastično liječenje indicirano je u gotovo svim FIGO stadijima bolesti. U vrlo ranom, dobro diferenciranom raku jajnika, benefit postignut kemoterapijom ne razlikuje se od 5 –godišnje stope preživljenja same po sebi, stoga kemoterapija u ovim stadijima nije indicirana. U svim drugim stadijima, sustavna antineoplastična terapija primjenjiva je i poželjna. Temeljena je na derivatima platine, cisplatini i karboplatini, uz dodatak paklitaksela. Godinama u sustavnoj terapiji raka jajnika nije bilo napretka. Bolest se liječi kao rani, uznapredovali te rekurentni rak jajnika, a rekurentna bolest kao platina - rezistentna i platina – osjetljiva bolest i na taj način se primjenjuju i lijekovi. Platinska baza uz taksanski partner, točnije karboplatina – paklitaksel temelj su i standardni protokol liječenja. Također su aktivni i neki drugi agensi, poput pagiliranog liposomalnog doksorubicina, topotekana i sl. Osim kemoterapije, važnu ulogu ima i biološka terapija. Bevacizumab se pokazao učinkovitim i donio benefit u liječenju rekurentnog paltina – rezistentnog, paltina – osjetljivog , kao i u liječenju uznapredovalog, nemetastatskog nerekurentnog raka jajnika. PARP inhibitor olaparib dobio je odobrenje ubrzanim postupkom na temelju značajno poboljšane brze sveukupne stope odgovora te trajanja odgovora. Ostaje za vidjeti jesu li i koliko iskorištene prepoznate prednosti neoadjuvantnog pristupa, dose dense režima primjene, metronomičke terapije te intraperitonealnog načina apliciranja terapije.

KLJUČNE RIJEČI: *epitelni karcinom jajnika, sustavno liječenje, karboplatina, paklitaksel, bevacizumab, olaparib, FIGO stadiji, platina – osjetljiva bolest, platina – rezistentna bolest*

ARTICLE

Ovarian cancer is the fifth most common malignancy and the fourth most common cause of death from malignancy in women. Most often suffer older, postmenopausal women, with the tip of the incidence of the disease in the eighth decade of life. A clear cause of the disease is not known, but there are indisputable risk factors that contribute to increased risk of disease, such as reproductive history (earlier menarche, late menopause, fewer pregnancies, a total of longer reproductive age and the number of ovulations over a lifetime), obesity, family history and ethnicity, as well as some of the mutations of somatic and germ cells, such as the BRCA genes (1).

The ovarian cancer is mostly epithelial origin and according to World Health Organization it is divided into several subtypes. These are serous, endometrioid, clear-cell, mucinous, Brenner transitionary, mixed epitheloid and undifferentiated and unclassified epitheloid ovarian cancer. Non-epithelial ovarian neoplasms are germ cell and stromal tumors, or tumors of sexual trace. Subtypes of ovarian cancer showed prognostic significance (2). A degree of differentiation, and tumor grade are also significant prognostic factors. There are several systems of graduation, none is universal and adjustment to the subtype of tumor is necessary. The most common among listed epitheliоid subtypes of ovarian cancer is serous subtype and in over 80% of cases of detected advanced ovarian cancer it is about invasive serous carcinoma. The disease is heterogeneous and there is a general classification by the dual model, into type 1 and type 2 tumors (3). To the subtypes of a higher degree of malignancy, so-called ovarian neoplasms type 2, belong extremely aggressive tumors of high grade and degree of aggressiveness. Type 1 tumors are indolent neoplasms, with low-grade and less aggressive nature. Ovarian cancer is graded according to FIGO (International Federation of Gynecology and Obstetrics) classification.

Access to the treatment of ovarian cancer begins by choosing adequate surgical methods of treatment. In the early, localized ovarian cancer, surgery is undertaken within the meaning and purpose of tumor resection and adequate staging of the disease. In advanced ovarian cancer surgical treatment aims at maximum cytoreduction, or removal of all visible signs of the disease, as far as possible. This proved important in prolonging the survival without relapse (PFS), and in prolongation of overall survival (OS) (4). Surgical treatment in recurrent ovarian cancer makes sense, and is associated with prolongation of survival, only if complete resection of the tumor is possible (5).

Ovarian cancer is typically a disease susceptible to systemic antineoplastic treatment. Systemic antineoplastic therapy is indicated in almost all FIGO stages of ovarian cancer. The stages IA and IB of well differentiated ovarian cancer have high five-year survival rate, 90 to 98 %, which does not change with the application of adjuvant chemotherapy (CT), therefore it is not indicated in these stages (6). In stage IA and IB grade 2 observation is indicated, or three to six cycles of intravenous CT. High risk patients, such as those with stage IB and IC disease and grade 2/3, those with any stage of disease and grade 3, stage II, as well as the patients with clear-cell ovarian cancer, recorded a clear benefit from the administration of adjuvant chemotherapy in comparison to the observation only, the absolute benefit in the survival rate of 8 %, compared to those patients treated with CT after relapse (74 % vs. 82 %) (7, 8).

The boom of a systemic treatment of ovarian cancer began with the appearance of cisplatin (C) followed by carboplatin (K). All the entry studies except one of French authors, showed equal efficiacy of C and K, along with a better toxicity profile of K (9-11). The conclusion of this first-generation platinum derivative studies, submitted in AOCTG metaanalysis, was inconclusive, but suggested benefit in survival compared with nonplatinum protocols, the benefit of the combination compared to monotherapy with platinum derivatives, and equivalent efficacy of C and K, along with a much better tolerability and toxicity profile of K (9).

The next generation of studies gave rise to the monochemotherapy with K as the gold standard for adjuvant systemic therapy of ovarian cancer. Thus, compared to the CAP protocol (cyclophosphamide, doxorubicin, cisplatin) monotherapy with K was equally effective in prolonging the OS (both treatments achieved median survival of 33 months, with a two - year OS 60% in both groups), yet less toxic (12, 13). After the discovery of paclitaxel (P), in the 1980 – ies, and after its activity was proven in recurrent ovarian cancer, research of its application in the adjuvant che-

motherapy of ovarian cancer was conducted. Thus, the combination of cisplatin and paclitaxel (CP) in the treatment of advanced ovarian cancer was shown to be superior, compared to combination of cyclophosphamide and cisplatin, with the greater objective response rate (oRR, 59% vs. 45%), clinical complete response (CCR, 41% vs. 27%), less minimal residual disease (MRD), longer PFS (median 15.5 vs. 11.5 months) and OS (median 35.6 vs. 25.8 months), which has become the standard choice for the treatment (14,15). The combination of paclitaxel with carboplatin (PK) was equally effective, as compared to the combination of the CP, in oRR, CCR, PFS and OS, with a simplier administration and a better toxicity profile of PK combination. Therefore, this combination becomes the new standard in the treatment of advanced ovarian carcinoma (16, 17). In a study comparing a standard CT doublet PK with triplet CAP, standard protocol proved equally effective and, again, less toxic as compared to the triplet, and once more the possibility of choosing K monotherapy, due to its low toxicity, was proven (13). Application of adjuvant CT with PK combination, in the optimally operated patients with stage III ovarian cancer, showed prolongation of PFS for seven months (21 vs. 28 months), and median OS for five months (52 vs. 57 months), in comparison to former standard protocols, which did not contain P (cisplatin, cyclophosphamide) (14). If surgical treatment is not optimally carried out, the results are worse.

Neoadjuvant systemic antineoplastic therapy for now in the treatment of ovarian cancer is not a standard approach and is used mainly in the case of weaker performance status of the patient, when it is impossible to immediately access the surgical treatment. Instead, on average, three cycles of standard intravenous CT (PK protocol) is administered preoperatively, followed by surgery (18). So, the surgical approach is through interval cytoreduction, inbetween the applied chemotherapy. Compared to standard adjuvant therapy, it showed no advantage in PFS nor OS (19). Ongoing studies will eventually undoubtedly position the possibilities of neoadjuvant treatment in ovarian cancer (CHORUS, Kumar, JCOG0602) (20).

In stage II and III disease, other than intravenous CT, the intraperitoneal chemotherapy (IPK) takes into account. This is, in the case of optimal debulking, when the tumor mass is less than 1 cm, and in the absence of residual disease after surgical treatment. In these patients, IPK showed benefit in OS of nearly 66 compared to 49 months, with standard intravenous CT (21). IPK comprises of applying part of CT, commonly a platinum agent, directly into the peritoneal cavity through the catheter. Since it is more demanding and more toxic, it did not become part of standard clinical practice. Nevertheless, IPK in the optimally operated patients with stage III disease proved to be arguably the most effective and in these cases is still recommended.

In order to achieve maximum efficiency in the application of P a dose - dense regimen of therapy is also in use. With this approach, there was a clear benefit in PFS and OS after three years of follow-up (extension of the OS for 38 months, 100 vs. 62), and longer follow-up confirmed the undoubted benefit in patients with residual disease greater than 2 cm (22). P means application on a weekly basis at a dose of 80 mg / m2, with the use of K in the standard way, every three weeks. This regimen expressed myelotoxicity, even up to 92% of patients (23). In case of prophylactic use of G-CSF, grade 3 or 4 neutropenia appears in only 35% of patients (24). For now, said treatment regimen is considered optional, but not standard clinical practice.

Despite optimal treatment of surgical techniques and adjuvant systemic therapy, 70% of patients with ovarian cancer will experience a recurrence within three years. In order to prevent recurrence, a consolidation therapy and maintenance therapy were investigated. Consolidation therapy was a short-term application of high doses of CT, immediately after completion of primary treatment, while maintenance therapy accounted for extended administration of monotherapy (25). None of these CT approaches has shown benefit in OS. Maintenance therapy by prolonged administration of P showed a benefit in PFS (26), but the final results and the possible impact on the OS are still pending (27).

Prognosis and effectiveness of second-line therapy, or likely response to the second and each subsequent line of therapy, mostly depends on the period between the last application of CT and reported disease progression. According to the latest consensus, the disease can be divided into platinum - refractory ovarian cancer, when the progression is recorded during treatment or with-

in four weeks after the last administration of platinum-based therapy; platinum - resistant disease, when the disease progression established within six months of the last cycle of the platinum therapy; partially platinum - sensitive disease, when the progression appears between six and 12 months from the last cycle of platinum therapy and platinum - sensitive ovarian cancer, when the disease progresses after more than 12 months since the last cycle of therapy based on platinum (28). This division is conditional, based on observational studies and likelihood of assumed answer is not always the same. Platinum - resistant and refractory disease have a poor prognosis, with expected overall survival of less than 12 months. In these patients, treatment is aimed at improving the quality of life and relieving symptoms. Possible therapeutic option in these situations are weekly or three - weekly P, docetaxel, topotecan, pegylated liposomal doxorubicin (PLD), gemcitabine, vinorelbine, oral etoposide, and the response rate to these drugs in the study was about 15%, with a median PFS of approximately three to four months. Topotecan showed activity similar to that of P, when administered to patients with relapse after platinum therapy (29), and no difference was seen in the comparison with pegylated liposomal doxorubicin in this indication (30). Also, even in platinum - drug resistant disease, sometimes platinum therapy can still be applied, for example, dose dense regimen. Among the mentioned therapeutic choice, no drug has proved superior to the others and the selection of the drug in these situations is based on the assessment of toxicity, the clinical condition of the patient and the possibility, or convenience of administration. Combination therapy showed no advantage over monotherapy, and toxicity is higher. Therefore, it is recommended to use sequential monotherapy.

In patients with relapsed disease, established after more than six months after the last application of platinum therapy, especially after more than 12 months, carboplatin doublet PK is the treatment of choice, which is the only one that showed benefit in OS in studies (31). In the platinum-sensitive disease, a number of different therapeutic combinations can be considered, usually containing platinum.

In order to avoid toxic side effects, and with the effect on the tumor growth continuous administration of low doses of cytotoxic drugs, so called metronomic therapy is tested. In the platinum - resistant ovarian cancer low doses of cyclophosphamide administered continuously per os demonstrated benefit in PFS, without the side effects (32). Since this actually blocks tumor angiogenesis, the benefit was observed with cyclophosphamide metronomic therapy in combination with anti-VEGF therapy (bevacizumab) in time to progression, PFS and OS (33).

Although a clearly higher toxicity of standard CT protocols was recorded in elderly patients (> 65 y), in studies involving older patients it was shown that a significant portion of them can withstand the default of the standard CT and has significant benefit of it (31, 34, 35) . With individual access, there can clearly be distinguished a proportion of older patients who will undoubtedly benefit from the standard applied CT doublets (36).

Apart from the above mentioned standard CT regimens, systemic therapy of ovarian cancer involves a choice of endocrine therapy (ET). It is rarely used in epithelial ovarian cancer, and is quite common in use in stromal tumors. In premenopausal patients LHRH agonists goserelin and leuprolide are in use, and in postmenopausal women lowering of estrogen levels is achieved with the use of aromatase inhibitors. Tamoxifen is in use in advanced epithelial cancer. In patients who have previously received cytotoxic treatment, tamoxifen does not induce an objective answer, but high percentage of these women experience at least short-term objective stabilization of disease (37). In the platinum - resistant recurrent epithelial ovarian cancer tamoxifen showed the median of survival 15 months, median PFS 4 months, and oRR as the only element of significant predictive value for PFS (38). Effect in the treatment of advanced ovarian cancer resistant to first or second line CT is seen also with medroxyprogesterone acetate (39).

The systemic treatment of ovarian cancer also involves biological therapy. Since angiogenesis is an important element of the growth of ovarian cancer, VEGF inhibitor bevacizumab was shown to be effective in addition to CT. Bevacizumab is approved by the European Medicines Agency, in first line treatment, at a dose of 15mg / kg, with PK through six three – week cycles, and then to a maximum of 15 months of application, or observed disease progression. Precisely, the bevacizumab maintenance therapy during one year, af-

ter six cycles of three – week CT, significantly reduces the risk of progression or death, with good tolerability and almost same side effects as the control group (GOG 218 trial) (40). Nevertheless, bevacizumab is not used consistently, and in the United States is not even approved in this indication. Greater benefit in survival is observed in high-risk patients with stage III – IV disease and residual disease > 1 cm, but the drug showed effect also in high-risk patients in the early stages of the disease (40, 41). Addition of bevacizumab to CT containing K and P is most strongly recommended in patients with advanced disease, poor prognostic factors such as stage IV disease or suboptimal debulking achieved previously (41). Bevacizumab has also been approved in the treatment of disease relapse. In the platinum - sensitive ovarian cancer, administered with gemcitabine and carboplatin CT, it showed significantly better PFS (median 12.4 vs. 8.4 months), improvement in the overall oRR (78.5 % vs. 57.4 %), and improvement in OS, containing a higher number of discontinuation in treatment and hypertension, as compared to the control group (34). Bevacizumab has proven effective in prolonging PFS and raising the response rate (RR) also in patients with platinum - resistant relapsed disease, when applied with some of the available CT agents in case of resistance to platinum compounds and then as maintenance therapy until progression. Thus, with topotecan, PLD and weekly P it showed significant improvement in PFS, oRR, OS and safety profile (42).

Pan TK inhibitor and the inhibitor of angiogenesis pazopanib showed significant prolongation of PFS compared to placebo, without the median OS reached, in the maintenance therapy, in patients that have not progressed to first-line therapy of advanced ovarian cancer, and with a relatively well tolerability (43). Also, in platinum – resistant disease, administered with paclitaxel, pazopanib prolonged PFS significantly, but with high incidence and severity of side effects, therefore it is not indicated (44).

Important role in treatment is also played by PARP (poly - ADP ribose polymerase) inhibitors, new drugs that work in a way to prevent tumor DNA repair, once it is damaged by other chemotherapeutics. PARP inhibitors have shown the greatest efficiency in BRCA mutant patients with recurrent disease (45). The most famous in use is the olaparib, which has proven successful in the treatment of recurrent platinum - sensitive disease in patients with BRCA mutations, as well as in patients with serous ovarian cancer and high-grade, without the mutations, in addition to CT and then as maintenance therapy (46). The drug has extended PFS but not OS, and was approved by accelerated procedure on the basis of significantly improved oRR (34%) and duration of response (median DOR 7,9 months) (47). It is necessary to further study the effectiveness of the drug in platinum - drug resistant disease.

In the screening, diagnosis and follow-up, during and after completion of primary treatment of patients with ovarian cancer, it is helpful to measure levels of tumor marker CA125. Reliability increases linearly with the degree of severity of the disease. It is elevated in only 50% of patients with early-stage ovarian cancer, and increases up to 85% in the advanced stage of the disease (48). The absolute value of CA125 measured before applying the therapy showed prognostic value (49), and serum CA125 halflife during initial treatment is an independent prognostic factor for survival, rate of progression and likelihood of achieving complete remission (50). In cases where it is unclear whether the tumor is of gastrointestinal origin, or primary ovarian mucinous tumor, levels of CEA and CA19-9 are also being measured. During treatment, levels of CA125 should be measured during each cycle of therapy. The important role of CA125 is in evaluating recurrence. Serial measuring the level of CA125 can detect recurrence even three to five months before clinical signs of the disease (51). According to GCIG criteria, it is necessary to measure the serial values of marker, as well as at least two measured and confirmed elevated CA125 values, with at least one week interval between measurements (52). Initiation of treatment of disease specified by the return value of CA125 increase did not show benefits in OS, compared to a method of waiting until the appearance of clinical symptoms, and quality of life of patients in this group were lower, clearly, because of earlier and greater total exposure to a chemotherapeutic treatment (53).

Ovarian cancer remains an incurable disease for many patients. The most controversial area remains the treatment of recurrent disease. After many years without news in the systematic treatment with chemotherapy, the last few years follows the blossoming of biological therapy. The

success of biological agents, such as inhibitors of angiogenesis was observed in the treatment of other solid tumors, and, given the molecular mechanisms and signaling pathways underlying ovarian cancer, there was an attempt to achieve the same in the ovarian cancer. At this point, a sure place in systemic therapy of ovarian cancer is posessed by bevacizumab and PARP inhibitors, and on the horizon are other biologic agents, likewise or modified in activity, and phase III trials, which will bring out the necessary evidence for a definite introduction of the same in everyday clinical practice. Also, it is yet to exhaust the possibilities of various modes of systematic chemotherapy treatment, such as neoadjuvant treatment, metronomic therapy, dose - dense regimen of administration and intraperitoneal chemotherapy, in which the benefits were undoubtedly recognized.

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