

SYSTEMIC THERAPY OF OVARIAN CANCER – THE MECHANISM OF ACTION OF ANTINEOPLASTIC DRUGS

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Summary

Ovarian cancer treatment consists of surgical options and systemic antineoplastic therapy. Systemic medicamentous therapy, involves a choice of classic chemotherapy and targeted biological treatment. Cytotoxic drugs act nonspecifically on tumor cells, damaging also certain proportion of healthy cells in human body. Such drugs act on the basis of impact on the life cycle of cells. Some work throughout the whole cell cycle, phase nonspecifically, while others work somewhat more specifically for certain phase of cell cycle. Among cell cycle nonspecific antineoplastic drugs, a platinum compounds, cisplatin and carboplatin play the main role. A cell cycle phase specific activity is seen in a few groups of antineoplastic drugs, among which a significant role in the therapy of ovarian cancer is played by taxanes paclitaxel and docetaxel, camptothecin analogue topotecan, podophyllotoxin etoposide, pyrimidine antagonist gemcitabine and anthracycline doxorubicin. In the treatment of ovarian cancer a significant place is also held by two biological medicines, the so-called “on targeted drugs”, VEGF inhibitor bevacizumab and PARP inhibitor olaparib.

KEY WORDS: *systemic antineoplastic therapy, ovarian cancer, chemotherapeutics, biological drugs, cell cycle, cisplatin, carboplatin, taxanes, paclitaxel, docetaxel, topotecan, etoposide, gemcitabine, doxorubicin, bevacizumab, olaparib.*

SUSTAVNA TERAPIJA RAKA JAJNIKA – MEHANIZAM DJELOVANJA ANTINEOPLASTIČNH LIJEKOVA

Sažetak

U terapiji raka jajnika koriste se metode operativnog liječenja i sustavna antineoplastična terapija. Sustavna, medikamentozna terapija, podrazumijeva izbor klasičnih kemoterapeutika, kao i ciljanu, biološku terapiju. Citotoksični lijekovi djeluju nespecifično na same tumorske stanice, oštećujući tako i određenu proporciju zdravih stanica u organizmu. Takvi lijekovi djeluju na temelju utjecaja na životni ciklus stanice. Neki djeluju kroz cijeli stanični ciklus, nespecifično za fazu, dok određeni broj tih lijekova djeluje usko specifično za pojedinu fazu staničnog ciklusa. Od citotoksičnih lijekova nespecifičnog djelovanja za fazu staničnog ciklusa u terapiji karcinoma jajnika temeljno mjesto zauzimaju spojevi platine, cisplatina i karboplatina. Specifično djelovanje za pojedinu fazu staničnog ciklusa ima nekoliko skupina citotoksičnih lijekova, od kojih su najistaknutiji predstavnici u terapiji raka jajnika taksani paklitaksel i docetaksel, kamptotekinski analog topotekan, podofilotoksin etopozid, pirimidinski antagonist gemcitabin te antraciklin doksorubicin. U liječenju raka jajnika značajno mjesto zauzimaju i dva biološka lijeka, tzv. ciljani lijekovi, VEGF inhibitor bevacizumab i PARP inhibitor olaparib.

KLJUČNE RIJEČI: *sustavna antineoplastična terapija, rak jajnika, kemoterapeutici, biološki lijekovi, stanični ciklus, cisplatina, karboplatina, taksani, paklitaksel, docetaksel, topotekan, etopozid, gemcitabin, doksorubicin, bevacizumab, olaparib.*

Ovarian cancer treatment consists of surgical options and systemic antineoplastic therapy.

Systemic, medicamentous therapy, involves a choice of classic chemotherapy, cytotoxic drugs with effect on cell cycle, and biological targeted treatment.

Cytotoxic drugs, cytocids and cytostatics, act nonspecifically on tumorous cells, damaging also certain proportion of healthy cells in human body. Such drugs act on the basis of impact on the life cycle of cells. Some work throughout the whole cell cycle, phase-nonspecifically, while others work somewhat more specifically for certain phase of cell cycle. Cytotoxic drugs can act as alkylating agents throughout the whole cycle, as mitotic inhibitors, as antimetabolites and as topoisomerase enzyme complex inhibitors, in the processes of DNA reparation.

These very mechanisms of their action are also the basis to group and classify these drugs (1-3).

Among cell cycle nonspecific antineoplastic drugs, in ovarian cancer therapy platinum compounds, cisplatin and carboplatin play the main role. A cell cycle phase specific activity is seen in a few groups of antineoplastic drugs, among which a significant role in the therapy of ovarian cancer is played by taxanes paclitaxel and docetaxel, camptotecin analogue topotecan, podophylotoxin etoposide, pyrimidine antagonist gemcitabine and anthracycline doxorubicin (1-6).

Platinum compounds, cisplatin and carboplatin, act as alkylating agents. Alkylating drugs are cytotoxic, mutagenic and carcinogenic. They cause alkylation by forming intermediary substances, translating alkyl group of biologically important molecules to the amino, carboxyl, sulfhydryl or phosphate group. They alkylate nucleic acids, DNA and RNA, and also proteins. Most active spots of alkylation are guanine positions N-7 and O-6. Alkylation of guanine results in abnormal nucleotide sequences, mRNA encoding errors, appearance of DNA strand crossing, with the loss of replication ability, DNA chain breaks and other errors in transcription and translation of genetic material (7-9).

The most important toxicity factor is the effect on the interlocking of DNA chains, followed by damage to the parental DNA, and interruption of chains. Less significant is the inactivation of the

enzyme participants in DNA synthesis. Alkylating drugs act nonspecifically on the cell cycle phase, although dominant activity is seen in G2 phase and at the transition from G1 to S phase of the cycle. In particular dose they destroy a specific percentage of cells. Resistance to these drugs is probably related to the ability of cells to recover damaged cellular nucleic acid, or to the inactivation by glutathione conjugation (9-11).

Cis-diaminodichloroplatinum (CDDP) or short cisplatin is a heavy metal, with an alkylating action on DNA. It binds irreversibly, covalently to the DNA, usually at the location of the N7 atom of guanine or adenine and at the N3 atom of cytosine and uracil, thus forming the interlocking of chains and intra-chain N - 7 attraction, which cause conformational changes in DNA and affect the DNA replication. It most commonly causes linking of two guanine bases in the same chain, a process extremely difficult to repair (7). Other mechanisms of cisplatin cytotoxicity include mitochondrial damage, reduced ATPase activity and revised mechanisms of cellular transport (10). Platinum transisomer anti-tumor activity is almost none. Resistance to cisplatin involves changes in the transmembrane transport of the drug, variations in the intracellular concentration of glutathione (GSH) or sulfhydryl containing proteins, and the above mentioned ability to repair DNA damage (12,13). Cisplatin is a drug that is well distributed in the body, without passing the blood-brain barrier. The half-life of the drug in the plasma is three days, and may remain in tissues for months. Up to 40% of the drug is excreted through the urinary tract in the first 24 hours, about 15% of the drug is excreted unchanged in urine, and 10% of the drug is excreted in the bile. The toxicity of the drug is dose-dependent. Cisplatin is significantly nephrotoxic, neurotoxic for peripheral sensory nervous system and ototoxic. It is highly emetic, often causes myelosuppression and electrolyte imbalance. In administering the drug it is necessary to monitor the work and excretory function of the kidneys, monitor the serum creatinine and electrolytes, ensure good hydration and diuresis for the patient, and good antiemetic prophylaxis. Caution should be exercised when using cisplatin with other nephrotoxic drugs, and dose adjustment is necessary in case of changes in renal function, while complete discontinuation of treatment is necessary in case of renal impairment. Cisplatin

interferes with renal elimination of bleomycin, etoposide and ifosfamide (7,10-12).

Carboplatin is a heavy metal with very similar action to cisplatin. It acts as alkylating agent, predominantly causing the creation of interchain DNA crossing, non-specific to cell cycle phase (8). There is a significant clinical cross-resistance between cisplatin and carboplatin. In contrast to the similarity in action, these drugs have a different profile of toxicity (9). Carboplatin contains bidentate - dicarboxylic ligand, which slows the dissolution of carboplatin in harmful products. Carboplatin has a plasma half-life 2 to 3 hours, and 70% of the drug is excreted unchanged in the urine and via the metabolites. Carboplatin toxicity is also dose-dependent. Carboplatin is 45 times less toxic than cisplatin and therefore nephrotoxicity, ototoxicity and peripheral neuropathy are less frequent. Myelosuppression, especially thrombocytopenia, is significant, especially in patients previously treated with chemotherapy, and in patients with reduced creatinine clearance. Caution should be exercised when administering carboplatin in conjunction with other nephrotoxic or myelosuppressive agents (8,9). The required dose of carboplatin is calculated by creatinine clearance and Calvert's formula, which determines the target dose by the AUC (Area under Curve) and in relation to glomerular filtration. It is important, during the joint administration of taxanes and platinum compounds, to apply the taxane chemotherapy prior to platinum.

Chemotherapeutic agents with specific action on the cell cycle include the representatives of the three standard classes of cytotoxic drugs, plant alkaloids, antimetabolites and antitumor antibiotics. The plant alkaloids include aforementioned taxanes, topotecan and etoposide.

Taxanes are drugs which affect the mitotic spindle in cell. They act as mitotic inhibitors or microtubule inhibitors, and since they "freeze" mitosis at a given time, they are also known as mitotic poisons (14). They bind actively, reversibly and tightly to microtubule proteins, specifically to the beta tubulin, leading to their polymerization and then causing resistance to depolymerization (15,16). The result of action of the taxane is creation of nonfunctional microtubule polymer, which can not be decomposed by plan, and so the planned break down of the mitotic spindle cannot occur,

nor can the planned process of mitosis proceed. Mitosis is stopped in the metaphase (17,18).

Paclitaxel is primarily isolated from the bark of Pacific yew trees. It is abundantly distributed in tissues and extensively metabolized by the microsomal cytochrome P450 system in the liver and excreted in bile and, in a large percentage, in the faeces, as hydroxylated products. Removing through the urinary tract is minimal. The concentration in plasma is biphasic, and the elimination half-life lasts between 3 and 52 hours, on average 23 hours. Depending on the dose, the toxicity of paclitaxel is achieved through myelosuppression, especially neutropenia, peripheral sensory neurotoxicity, basically reversible in character, myalgias, arthralgias and possible significant hypersensitivity reactions (19). Caution should be exercised and dosage adjustment should be done in case of positive cardiac history, hepatic dysfunction, metabolic diseases such as diabetes and in patients who have previously been treated with neurotoxic drugs (19). Paclitaxel can interact with all drugs that are metabolized by the same hepatic cytochrome system.

Docetaxel is a semisynthetic analog of 10 - DAB (deacetylbaicacine - III), an extract from European yew needles. It also acts on the basis of inhibition of microtubule depolymerization, and the binding of docetaxel to microtubules does not alter the number of protofilaments in microtubules. Docetaxel achieves high intracellular concentrations and is retained in the cells for long. Like paclitaxel, docetaxel is also extensively metabolized by cytochrome P450 system in the liver and excreted predominantly in faeces, and small part in urine. The drug is slowly eliminated from the peripheral compartment. The pharmacokinetics of the drug is not affected by the age and sex. Docetaxel is myelotoxic, can cause extreme fluid retention, almost always causes alopecia, causes a transient peripheral sensory type neuropathy, and may cause non-specific reactions, such as general body weakness and changes in laboratory parameters. The drug should not be used in case of serious liver lesions. It also interacts with all drugs that are metabolized by the same metabolic pathway, although the interactions observed were to considerably lesser extent than in paclitaxel. Given that a significant myelosuppression is often observed with docetaxel, especially neutropenia,

myelopoiesis growth factors are being applied by administering docetaxel (19,20).

Taxanes are carcinogenic, embryotoxic, fetotoxic and mutagenic. They can cause expressed hypersensitivity reactions and it is therefore necessary to apply desensitizing premedication (14).

Two other mentioned plant alkaloids, etoposide and topotecan, act by inhibiting topoisomerase enzymatic system. DNA topoisomerases are enzymes that alter DNA topology, causing disruption of chains and refilling them. They bind to DNA complex, causing cleavage of helix, allowing the unwinding of DNA in preparation for cell division. Topoisomerase I relaxes stranded DNA, creating a reversible single strand breaks in the double strand, so that the undisturbed parts of a single chain can slip past damaged parts, which will be corrected in a double superhelix. Topoisomerase II catalyzes the interruption and re-filling of double-stranded DNA and thereby enables relaxation of DNA superhelix bend, correcting nodes or improper entanglements. Topoisomerases are essential in the processes of transcription, replication, mitosis. Group I and II enzymes are possible target site of action of cytotoxic drugs. That's how the drugs interfere with transcription and replication, causing DNA damage, inhibiting the correction process and causing cell death. Topoisomerase inhibitors act phase – specific in the cell cycle, predominantly in the S phase and the late G2 phase of the cycle (21, 22).

A derivative of camptothecin, topotecan, inhibits topoisomerase I. The cytotoxic effect is achieved through blocking of DNA reparation. It stabilizes the covalent complex of enzyme and single chain DNA, which is an intermediate product of the catalytic mechanism. Consequently, a splitting of a single strand of DNA occurs. After the application, the drug is rapidly converted to the active lactone form in plasma. A minimal percentage is metabolized in the liver by microsomal cytochrome P450 system. Less than 10% of topotecan is eliminated by metabolizing. The urine, feces and plasma yield one N - desmethyl metabolite, with a similar or lower activity than the parent compound. The drug is excreted in the urine. The main mode of clearance of topotecan is by hydrolysis of the lactone ring formation and forming of the open-ring carboxylate. Topotecan is predominantly myelotoxic and usually causes myelosuppression. It can cause non-specific reactions, such

as body weakness, nausea, vomiting, digestive disturbances, arthralgia and myalgia. The drug should not be used in the damaged liver function, and in the case of low creatinine clearance it is necessary to reduce the dose (23,24).

Etoposide, epipodophyllotoxin, VP - 16, is a semisynthetic derivative of podophyllotoxin, a substance isolated from the mandrake plant. The drug acts as a nonintercalating inhibitor of the enzyme topoisomerase II, specifically in the late stages of the G2 and S phase of the cell cycle. By forming a complex of the DNA and topoisomerase II enzyme it inhibits the synthesis of the DNA. The drug is at a high rate bound to plasma proteins (mainly albumin) in the organism, and reduced levels of body protein may cause an increase in the toxicity of the drug. It is metabolized by the liver glucuronidation to less active metabolites. Forty per cent of the substance is excreted in the urine as unchanged and degraded drug, and the remaining percentage of excretion of the drug has not been fully explored. The dominant toxic effect is myelosuppression. It is emetic, can cause alopecia, hypotension during rapid administration and disturbance of liver function tests. Caution should be exercised in case of renal dysfunction, and dose reduction in the case of liver dysfunction. The toxicity of the drug is increased by calcium channel inhibitors and methotrexate (25,26).

Among the cell cycle phase specific cytotoxic drugs in the treatment of ovarian cancer there are also a pyrimidine base antagonist gemcitabine and anti-tumor antibiotic doxorubicin also belong among the cell cycle phase specific cytotoxic drugs in the treatment of ovarian cancer.

Gemcitabine is an antimetabolite, an analog of deoxycytidine. In the current form it is a pro-drug, which is phosphorylated by deoxycytidine kinase to the active form, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP) immediately after the entrance to the cell. Both active substrates then inhibit processes required for DNA synthesis. The most likely mechanism of cytotoxicity of gemcitabine is incorporation of dFdCDP and dFdCTP in DNA. After incorporation of gemcitabine nucleotides in extending DNA chain, one other deoxynucleotide is added at the end and then the polymerases can no longer continue acting in the extension of the DNA chain. This masked chain termination actu-

ally locks remedy in the chain of DNA, since the enzymes then can't remove it. Gemcitabine metabolites simultaneously act on other cell regulatory processes, all in a general manner of blocking and inhibiting cell growth. This is the so-called self-potentialization of gemcitabine, which a lot of other cytotoxic drugs do not possess. As regards the phase of the cell cycle, gemcitabine first destroys the cells in S phase, and then blocks progression through the G1 phase to the S phase. The drug is metabolized intracellularly in the liver, plasma and peripheral tissues. It is almost completely excreted in urine, as the active drug and metabolite. Toxicity depends on the applied dose of the drug. It expresses myelotoxicity, is emetic, causes indigestion, rash and hypersensitivity reactions are possible. Caution should be exercised in patients with impaired hepatic and renal function, and in patients with ongoing radiotherapy (27-29).

The antitumor antibiotic doxorubicin, or hydroxydaunorubicin, is anthracycline, which prevents DNA synthesis in S phase of the cell cycle. The substance is a secondary metabolite of aerobic bacteria of the genus *Streptomyces*. In the treatment of ovarian cancer a liposomal doxorubicin is used, where the doxorubicin is encapsulated in long-circulating liposome (microscopic vesicle with bilayer phospholipid membrane). Liposomal doxorubicin has a slower plasma clearance than the standard doxorubicin. The mechanism of drug and metabolism is unchanged compared to doxorubicin. Drug acts as intercalating inhibitor of topoisomerase II, intercalating between base pairs of DNA, but also generates free radicals, which cause damage to cell membranes, DNA and proteins, inhibits preribosomal DNA and RNA. More than two-thirds of the drug is bound to plasma proteins. It is rapidly metabolized in the liver to other compounds with cytotoxic activity. The drug is slower released, than the hepatic mechanisms can metabolize, so in this way the hepatic system is unsaturated and that causes extension of the increased levels of drug and metabolites in the plasma. Liposomal doxorubicin is hematotoxic. Beside the hematosuppression, can also cause non-specific problems in terms of fatigue, digestive disorders, emesis, infusion reactions, which disappear upon termination of the application of the drug, can cause a "recall" reactions, palmo-planter erythrodisesthesia and other allergic reactions. Dose modification is necessary in the event of an

increase in serum bilirubin, and a drug must not be used in case of congestive heart failure. Dexrazoxane inhibits the cardiotoxicity of doxorubicin, and mitomycin and trastuzumab increase it. Mercaptopurine increases the risk of doxorubicin hepatotoxicity (30-32).

In the treatment of ovarian cancer a significant place is held by two biological medicines, the so-called "on targeted drugs", bevacizumab and olaparib.

Bevacizumab is an inhibitor of vascular endothelial growth factor (VEGF). It is a recombinant humanized monoclonal antibody, produced by recombinant DNA technology from a Chinese hamster ovary cell. The drug binds selectively to VEGF (a key factor in vasculogenesis and angiogenesis of tumor) and thus prevents binding of VEGF to its receptors, VEGFR-1 and VEGFR-2, on the surface of endothelial cells. Neutralizing the biological activity of VEGF bevacizumab causes a reduction of tumor vascularization and normalization of the remaining tumor vasculature, inhibits the formation of new vasculature of tumor, thereby inhibiting growth of the tumor itself. The pharmacokinetics of the drug in doses of conventional administration is linear. The metabolism of the drug has not yet been fully established, it is similar to that of endogenous IgG molecules, first through proteolytic catabolism throughout the body, including endothelial cells, rather than elimination through the kidneys and liver (34-36). Men have a higher clearance of the drug, compared to women. The half-life is about 19 days. The rapid clearance of the drug was observed in patients with lower values of serum albumin and in the case of pronounced tumor disease burden. Bevacizumab should not be administered within 28 days of any surgery or invasive diagnostic procedure. It can cause thromboembolic incidents, gastrointestinal perforation, wound dehiscence, hypertension, bleeding, nephrotic syndrome and various complications of wound healing. As with the use of all monoclonal antibodies, the cytokine releasing syndrome associated with infusion (IR-CRS) is also possible with bevacizumab, especially during the first administration of the drug, in the form of tremors, fever, hypotension, bronchospasm and angioedema, which gradually decrease with the duration of drug administration and also the duration of treatment in general, and the symptoms can be reduced by technical measures,

changing the way and speed of administration, as well as the application of symptomatic therapy (34-36).

Olaparib is poly (ADP - ribose) polymerase (either synthase or transferase, PARP) inhibitor. PARP inhibitors are necessary in the repair of DNA single-strand breaks, when after modifications of chromatin, PARP dissociates from DNA by automodification, to allow easier access to and repair of strand by cutting bases. When olaparib binds to the location of activity of PARP in the DNA, it prevents dissociation of PARP and anchors them in the chain of DNA, thus preventing the repair process. In the dividing cell this produces a double fracture of chains, where the replication fork comes to PARP-DNA junction. In normal cells, homologous recombinative repairs, for which functional BRCA 1 and 2 genes are necessary, manage to fix these double strand breaks (36,37). In the absence of functional BRCA 1 and 2 these reparation processes are not successful. Therefore, the stronger activity of olaparib is recorded in the mutated BRCA 1 and BRCA 2 cells, compared to wild type cells, and a 1000 times higher sensitivity of mutant cells to the drug. In these cells unsuccessful repairs are being replaced by the wrong ways and attempts of reparations, resulting in a distinct genomic instability, which after a series of such processes becomes intolerable and such cells die (38). Olaparib is administered orally and achieves peak plasma concentrations in two hours after administration. The drug showed no tendency to accumulate in the organism, half-life is about 12 hours and is metabolized via CYP3A4 / 5 system in the liver. The drug is excreted in both urine and faeces, mostly as metabolites. Caution should be exercised in case of renal or hepatic dysfunction. It causes frequent side effects on the digestive system, as well as hematological toxicity. Side effects are usually mild or moderate in character, especially the side effects on the digestive system and therefore do not require discontinuation of treatment. It can interact with all drugs that induce or inhibit CYP3A4 / 5 system. The drug is genotoxic, mutagenic, embryotoxic and fetotoxic and can cause reproductive toxicity (39).

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