Alternative treatment of chemoresistant, recurrent or advanced ovarian cancer. Part II

Alternatywne sposoby leczenia lekoopornego, nawrotowego lub zaawansowanego raka jajnika. Część II

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Summary

Lack of satisfactory efficacy of classical chemotherapy in ovarian tumours led to attempts of treatment based on use of small molecules able to modulate or inhibit intracellular pathways engaged in cell growth, proliferation and apoptosis. The paper presents clinical trials in ovarian cancer patients using such drugs as: 1) protein kinase inhibitors, 2) molecules interfering with DNA transcription and repair, 3) inhibitors of transcription factors NF-κB and HIF-1.

Key words: ovarian cancer, PTKs, DNA, NF-κB, HIF-1.

Streszczenie

Brak satysfakcjonującej skuteczności klasycznych schematów chemioterapii w leczeniu raka jajnika spowodował podjęcie prób leczenia z użyciem cząsteczek mających zdolność modulowania i/lub hamowania szlaków komunikacji wewnątrzkomórkowej regulujących wzrost komórek, ich proliferację i apoptozę. W pracy zaprezentowano wyniki prób klinicznych, podczas których stosowano: 1) inhibitory kinaz PTK, 2) cząsteczki zaburzające transkrypcję i mechanizmy naprawy DNA guza oraz 3) inhibitory czynników transkrypcyjnych NF-κB i HIF-1.

Słowa kluczowe: rak jajnika, kinazy PTK, DNA, NF-κB, HIF-1.

Introduction

Lack of satisfactory efficacy of both classical chemotherapy and immunotherapy led to attempts of treatment based on the use of small molecules having the potential to modulate or inhibit intracellular and nuclear pathways regulating cell growth, proliferation and apoptosis. They include inhibitors of protein tyrosine kinases, nuclear transcription factor-κB (NF-κB) and hypoxia-induced factor-1 (HIF-1), as well as molecules interfering with DNA transcription and repair.

Protein tyrosine kinase inhibitors

Protein tyrosine kinases (PTKs) are key enzymes in many intracellular signal transduction pathways. They are engaged in cell proliferation, differentiation and apoptosis, thus playing a crucial role in both oncogenesis and angiogenesis of cancer tissue [1, 2]. Functional disturbances of PTKs may result in triggering the cascade of events leading to cancer development. Therefore, inhibition of PTKs could provide a new therapeutic option for recurrent or advanced ovarian cancer [3].

Almost all PTK inhibitors that have been adopted for ovarian cancer treatment target growth factor receptors, mostly vascular epithelial growth factor receptor (VEGF-R), platelet-derived growth factor receptor (PDGF-R) and epidermal growth factor receptor (EGF-R).

Sunitinib is a PTK inhibitor that targets VEGF-R1 – VEGF-R3 and PDGF-R. During a clinical trial in patients with recurrent ovarian cancer sunitinib caused a partial response in 12% and disease stabilization in 59%

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of patients [4]. There are three more phase II clinical trials ongoing to evaluate efficacy of sunitinib monotherapy: the first a German trial in platinum-resistant recurrent ovarian cancer (NCT00543049); the second in recurrent and refractory ovarian cancer (NCT00768144) performed in the USA; and the last a Canadian trial in advanced and metastatic cancer (NCT00388037) [5, 6].

Cediranib (AZD2171) inhibits PTKs for VEGF-R1 and VEGF-R2. The preliminary clinical results indicated that the overall response rate in patients with recurrent cancer was 18.5% [7], and when evaluated in the context of previous platinum therapy cediranib efficacy was 29% in platinum-resistant and 40.5% in platinum-sensitive patients [8]. The ongoing ICON6 randomized phase III trial in platinum-sensitive tumour recurrence evaluates the effects of cediranib combined with carboplatin/paclitaxel protocol [5].

Sorafenib inhibits VEGF-R and PDGF-Rβ. The GOG trial proved its moderate efficacy as monotherapy in 71 patients with recurrence of ovarian cancer 12 months after platinum therapy. The 6 months progression free time characterized 24% of patients, while 2 persons had a partial response and 20 more had stabilization of the disease [9]. In a group of patients having a history of up to three prior platinum-based regimens and tumour recurrence, sorafenib was tested in combination with gemcitabine; however, although 23.3% of patients were stabilized, only 4.7% had a partial response [10]. Moreover, a recent study of sorafenib with carboplatin/paclitaxel in neoadjuvant protocol in IIIC-IV FIGO stage failed to prove any efficacy and was stopped due to serious toxicity [11]. Sorafenib is now being tested during four phase II clinical trials in monotherapy after platinum chemotherapy (NCT00791778), together with standard carboplatin/paclitaxel treatment as a first line chemotherapy (NCT00390611) and with carboplatin/paclitaxel in recurrent cancer in both platinum-sensitive (NCT00096200) and resistant patients (NCT00526799) [5]. The combination of sorafenib with bevacizumab in recurrent ovarian tumours is subjected to study in the phase II trial NCT00436215 [6], because intermittent therapy with this drug combination has given disease stabilization for at least 4 months in 53% of patients of the Medical Ovarian Cancer Team in a phase I initial study [12].

Pazopanib belongs to the PTK inhibitor family and targets VEGF-R1 – VEGF-R3 and both PDGF-Rα and -β. The clinical effect of pazopanib in ovarian cancer was first demonstrated in patients with relapsed tumour in whom a decrease of CA-125 levels was observed in 31% of cases [13]. Based on this observation, three more trials have started and are ongoing now: a phase I trial on combined use of topotecan and pazopanib in recurrent/persistent tumours (NCT00800345), a phase II trial on pazopanib monotherapy in recurrent tumour (NCT00281632), and finally a phase III randomized trial (NCT00866697) on pazopanib maintenance therapy after first-line chemotherapy [6].

The next PTK inhibitor qualified for clinical trials was the EGF-R inhibitor erlotinib. The first clinical trials showed very moderate efficacy of this drug with only 6% regression and 44% disease stabilization rates [14]. Another phase Ib clinical trial of carboplatin/docetaxel and erlotinib as primary chemotherapy for ovarian, fallopian tube and primary peritoneal cancers showed both partial and complete responses in 52% of evaluated patients with manageable toxicity increasing along with escalation of the erlotinib dose [15]. The Chicago, PMH and California phase II trial assessed both the efficacy and tolerability of combination of bevacizumab with erlotinib in patients with recurrent ovarian, peritoneal and fallopian tube cancers; however, due to serious toxicity and gastrointestinal perforations the study was stopped. The objective response rate was observed in 2/13 patients [16]. Despite that fact, three more phase II trials on combination of bevacizumab and erlotinib either as consolidation therapy after classical chemotherapy in newly diagnosed ovarian cancer or as second-line therapy in recurrent ovarian cancer are now during continuation [6].

Molecules interfering with DNA transcription and repair

Histone deacetylase inhibitors

Histone deacetylase inhibitors (HDACI) catalyse molecular changes in histone composition that allow and facilitate the transcription of DNA, including tumour suppressor genes. This results in upregulation of pro-apoptotic proteins and simultaneous decrease of proliferation stimulators [17]. The phase II GOG trial on the use of vorinostat, a new HDACI molecule, in ovarian cancer patients with recurrent and persistent tumour showed only 7.4% rate of progression-free survival, indicating its limited efficacy in monotherapy in platinum resistant patients [18]. However, further trials are needed to exclude or confirm vorinostat usefulness in first-line therapy combined with platinum/taxane.

Poly (ADP-ribose) polymerase inhibitors

Poly (ADP-ribose) polymerases (PARP-1 and -2) are nuclear enzymes involved in the repair of DNA single-strand breaks. An alternative DNA repair pathway for DNA double-strand breaks is based on the function of both BRCA1 and BRCA2 genes. Ovarian cancer cells which have lost BRCA1 or BRCA2 are sensitive to PARP inhibition [19, 20]. Olaparib (AZD2281) is a PARP inhibitor which showed its clinical efficacy in a phase I trial on 44 patients, of whom 11 persons had BRCA muta-

tion [21]. The subsequent continuation during a phase II trial on 60 patients, of whom 19 had BRCA mutation, showed that 63% of platinum-sensitive patients indicated a clinical response or stabilization of the disease [22]. A recent phase II trial on advanced ovarian cancer with BRCA1/2 mutations showed that olaparib monotherapy was efficient in 33% of patients and the extent of response depended on dose escalation [23]. Two more randomized phase II clinical trials are ongoing now to investigate the role of olaparib in platinum-sensitive recurrent ovarian cancer and to compare its efficacy with pegylated liposomal doxorubicin in patients with BRCA mutated ovarian cancer [5].

NF-κB inhibitors

Proteasome inhibitors

Transcription factor NF-κB is a common end-target for many cellular signalling pathways including those responsible for cell proliferation, apoptosis and inflammation. NF-κB is also a target for the proteasome, which is an enzyme complex responsible for degradation of polyubiquitinated proteins [24].

Proteasome inhibitors by deactivation of proteasome components prevent NF-κB activation, thus increasing the apoptosis of tumour cells and their chemosensitivity. The best studied drug of this kind is bortezomib (Velcade®, PS-341). An *in vitro* study on ovarian cancer cells indicated that bortezomib is able to overcome platinum chemoresistance and enhance its cytotoxicity through blocking of platinum-induced copper transporter-1 (CTR1) degradation [25]. The preliminary clinical phase I studies showed lack of negative interference between bortezomib and pegylated liposomal doxorubicin [26]. A recent phase II trial on combined use of both drugs in platinum-sensitive and -resistant patients demonstrated responses only in the first group [27].

Thalidomide

Thalidomide possesses anti-angiogenic properties which were shown as a reason for teratogenic effects observed in fetuses of thalidomide users. Thalidomide exerts its effects by inducing apoptosis of the tumour cells by down-regulation of NF-κB-dependent pathways [28]. A phase I clinical study on 17 patients with recurrent ovarian cancer indicated that 18% of them experienced a partial response, and 35% disease stabilization. Typical post-thalidomide side effects (constipation, neuropathy and fatigue) were accompanied in 12% by serious complications, such as venous thrombosis [29]. A phase II clinical study of low-dose thalidomide in advanced solid tumours including ovarian cancer demonstrated that partial responses were obtained only in the group of renal cancer patients [30]. Another phase II trial which compared thalidomide + topotecan and thalidomide in 75 patients with recurrent ovarian tumours demonstrated improvement of the response rate in the group of women treated with thalidomide supplementation (47% vs. 21%) [31]. A similar randomized phase II trial on thalidomide combined with carboplatin compared to carboplatin given alone in patients with FIGO stages Ic-IV is ongoing now [32].

Non-steroid anti-inflammatory drugs

Cyclooxygenase-2 (COX-2) is up-regulated in tumours, and its product prostaglandin E_2 (PGE_2) by increasing NF-κB activity inhibits tumour cell apoptosis [33]. Some non-steroid anti-inflammatory drugs (NSAIDs) by inhibition of COX-2 have potent anti-NF-κB activity. Celecoxib belongs to this group of drugs. Preclinical studies gave encouraging effects and showed inhibition of PGE_2-dependent VEGF production; therefore, two ongoing phase II clinical trials evaluate a combination of paclitaxel and cyclophosphamide with celecoxib in advanced ovarian cancer [34, 35].

IκB kinase complex inhibitors

The proper function of NF-κB depends on the IκB kinase complex (IKK), which is responsible for degradation of IκB inhibitors, which prevent NF-κB translocation to the nucleus [36]. IKK is frequently over-expressed in ovarian cancer and connected to both poor prognosis and platinum chemoresistance [37]. Curcumin is an antioxidant isolated from the plant *Curcuma longa*. Its anti-cancer activity is based on inhibition of IκB kinase complex [38]. Preclinical *in vitro* studies showed that pre-treatment of platinum-resistant cell culture with curcumin significantly reduced the dose of both cisplatin and radiation needed for ovarian cancer growth inhibition [39]. Clinical trials are urgently needed to confirm curcumin applicability in ovarian cancer patients.

HIF-1 inhibitors

Topoisomerase inhibitors – topotecan

Hypoxia inside solid tumours initiates HIF-1 transcription factor over-expression, which positively influences tumour aggressiveness and vascularization [40]. Expression of HIF-1 was found to be increased in serous ovarian cancer compared to borderline and benign tumours, and was an adverse prognostic factor for patients' survival. Moreover, patients treated with suboptimal primary cytoreduction whose tumours stained intensively for HIF-1 had worse prognosis than patients having tumours of weak staining [41].

Type I topoisomerases enable access to the double-stranded DNA by cutting, relaxation and restoration of

the DNA strands. Topotecan, an inhibitor of topoisomerase I, was demonstrated to decrease HIF-1 concentration inside the tumour, thus leading to inhibition of VEGF-dependent angiogenesis [42]. A phase I study on etoposide and topotecan in recurrent ovarian cancer subjected to previous therapy with platinum and paclitaxel showed 28% efficacy, but treatment was accompanied with grade 4 neutropenia and thrombocytopenia after the first cycle. However, those haematological complications were transient and reversible [43]. Another phase I clinical study which evaluated an experimental drug combination (cisplatin, paclitaxel and topotecan) in previously untreated ovarian cancer women with FIGO stage III-IV gave encouraging results, despite serious neutropenia that needed extensive treatment [44]. A recent phase I study evaluates a very interesting combination of treatment with autologous haematopoietic stem cell transplantation with topotecan, cyclophosphamide and carboplatin in relapsed or persistent ovarian cancer. Median progression-free survival was 6.5 months and overall survival was 2.7 years [45].

mTOR inhibitors

An alternative way of HIF-1 regulation is based on the function of the mammalian target of rapamycin (mTOR) molecule, which promotes translation of HIF-1 mRNA into active HIF-1 protein [46]. Everolimus (RAD001) is a molecule capable of inhibiting this mTOR function. Preclinical *in vitro* and animal studies showed that clear cell ovarian cancer compared to serous cancer was characterized by especially high expression of mTOR, which markedly increased after acquisition of platinum-resistant phenotype. The efficacy of everolimus was confirmed in this resistant phenotype of ovarian cancer [47]. Safety and efficacy of everolimus combined with paclitaxel was evaluated in a phase I trial in advanced pre-treated solid tumours including ovarian cancer. Stabilization of the disease was obtained in 11/16 patients with an acceptable profile of safety [48]. The ongoing NCT00886691 phase II GOG clinical trial compares the usefulness of everolimus monotherapy with everolimus combined with bevacizumab in recurrent or persistent ovarian cancer [6].

Summary

The growing number of clinical trials evaluating the efficacy of different drugs in various combinations is in my opinion an indirect sign of our helplessness against ovarian cancer. The multidirectional approach to the problem of acquisition of chemoresistance seems to improve the results of treatment, but is frequently connected with increasing toxicity. We should have a hope that at least some of the ongoing studies will bring us closer to safe and effective models of treatment. Maybe it is time to redefine the priorities in the therapy in ovarian cancer and to concentrate more on efforts for early diagnosis and treatment.

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