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

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

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Summary

Despite improved surgical treatment and modern chemotherapy the prognosis in advanced ovarian cancer is poor, mainly due to observed tumour chemoresistance against protocols based on cisplatin and taxanes. The paper describes different forms of immunopotentiation of the anti-cancer host response based on immunotherapy with the use of monoclonal antibodies, cytokines, dendritic cell vaccines or activated T cells. Immunotherapy used separately or in combination with chemotherapy could, at least to some extent, enhance the efficacy of ovarian cancer treatment.

Key words: ovarian cancer, monoclonal antibodies, cytokines, dendritic cells, T lymphocytes.

Streszczenie

Pomimo postępów w leczeniu operacyjnym i we współczesnej chemioterapii rokowanie w zaawansowanym raku jajnika jest wciąż niekorzystne, zwłaszcza ze względu na fakt obserwowanej chemiooporności na leczenie preparatami platyny i taksanami. W pracy opisano różnorakie sposoby wzmagania odpowiedzi immunologicznej gospodarza przeciw guzowi nowotworowemu, oparte na immunoterapii przy użyciu: przeciwciał monoklonalnych, cytokin, szczepionek z komórek dendrytycznych i aktywowanych limfocytów T. Immunoterapia stosowana osobno lub w połączeniu z chemioterapią może, co najmniej w pewnym stopniu, wzmocnić skuteczność leczenia w raku jajnika.

Słowa kluczowe: rak jajnika, przeciwciała monoklonalne, cytokiny, komórki dendrytyczne, limfocyty T.

Background

Ovarian cancer is one of the most fatal gynaecological malignancies, being responsible for at least 5% of female deaths caused by malignant tumours [1]. Due to scarce symptomatology during early development and aggressive growth of the tumour, most women worldwide are diagnosed in advanced clinical FIGO stage III/IV. Despite improved surgical treatment and modern chemotherapy the prognosis in advanced ovarian cancer is poor, and the overall survival rate is still unsatisfactory. Moreover, observed tumour chemoresistance against protocols based on cisplatin and taxanes necessitates the investigation of the possible benefits of alternative management which could augment or replace the classical chemotherapy. There are many forms of alternative therapies, including immunotherapy and therapy with inhibitors/modifiers of intracellular signalling pathways.

Immunotherapy

Monoclonal antibodies

Monoclonal antibodies (mAb) are directed against different molecules produced by the tumour, which are involved in its growth and spread. The most intensively studied candidates for mAb targets are: mucin (cancer

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antigen-CA-125, MUC16), vascular-endothelial growth factor (VEGF), epidermal growth factor receptor-2 (HER-2), epidermal growth factor receptor-1 (EGFR-1), insulin-like growth factor-I (IGF-I) and folate receptor [2-4].

Oregovomab

Mucins function as lubricants of the epithelial surface and regulators of adhesion and signalling between epithelium and other cells. A mucin classically associated with serous ovarian cancer and used commonly for treatment monitoring is CA-125, which was shown to inhibit the host (natural killer) NK cell cytotoxic activity against the tumour [5, 6]. Murine mAb oregovomab (B43.13, OvaRex™) forms strong complexes with CA-125, and being foreign for the host provokes effector cells to attack ovarian tumour [7]. Patients treated with oregovomab who showed proliferation and activation of T cells and occurrence of anti-CA-125 antibodies were characterized by significantly longer survival [7, 8]. Management was found to be safe, and side effects were usually mild and transient [8]. However, prospective phase II trial indicated that despite effector response observed in 58% of patients with recurrent ovarian cancer, in only 23% was it accompanied by stabilization of the disease [9]. To overcome that problem, oregovomab was combined with carboplatin-paclitaxel chemotherapy in a phase II randomized trial in advanced ovarian cancer, showing moderate clinical improvement [10]. An alternative form of treatment tested in a phase II clinical trial was combination of ^{131}I(iodine)-labelled OC125 mAb for intraperitoneal treatment of disseminated recurrent ovarian cancer [11]. During therapy with anti-CA-125 mAb the serum levels of that mucin are not representative for the real tumour spread; thus anti-CA-125 mAb hampers monitoring of the disease progression/regression [12]. The murine mAb HMFG1 (human milk fat globule 1) against another mucin antigen CA-15.3 produced by mucinous ovarian tumours was tested in a phase I clinical trial, but despite an immunological response seen in a minority of treated patients (38%), it did not show satisfactory clinical efficacy [13].

Bevacizumab

Vascular-endothelial growth factor (VEGF) is engaged in tumour neo-vascularisation and interactions with tumour-associated macrophages (TAMs) and dendritic cells (DCs). Therefore, anti-VEGF mAb is suspected to prevent these mechanisms [14]. Bevacizumab (Avastin®) is a murine-human chimeric IgG_1 mAb directed exclusively against VEGF-A [15]. Although preclinical studies on mice inoculated with human ovarian cancer showed regression of the tumour [16, 17] randomized controlled trials with bevacizumab monotherapy were not able to show significant improvement of survival in ovarian cancer patients [18]. Treatment improved the clinical status and decreased ascites in only 20% of patients [19]. Moreover, in patients subjected previously to chemotherapy treatment with bevacizumab was associated with serious toxicity including intestine perforation (11%) [20]. Phase II randomized trials [21] of combined anti-VEGF/chemotherapy protocols showed a low response rate of 16-24% of patients with advanced cancer [22, 23]. However, when given as a first line treatment, they showed a response rate of up to 80% of patients [24]. Several trials (about 25) are underway in order to evaluate the role of bevacizumab in both mono- and combined therapy for ovarian cancer [reviewed in 4, 25]. Bevacizumab monotherapy in cancer recurrence after previous therapy and as a maintenance therapy is assessed in the NCT00866723 phase II trial. One of the most important trials assesses combined therapy with chemotherapeutics. The ICON7 phase III trial compares carboplatin/paclitaxel therapy with or without addition of bevacizumab followed by 12 cycles of bevacizumab monotherapy in newly diagnosed patients. The GOG 218 phase III trial in previously untreated FIGO III/IV patients compares three arms: carboplatin/paclitaxel versus carboplatin/paclitaxel + bevacizumab versus carboplatin/paclitaxel + bevacizumab + maintenance bevacizumab monotherapy. The GOG 213 phase III trial investigates patients with platinum-sensitive recurrence treated with carboplatin/paclitaxel versus carboplatin/paclitaxel + bevacizumab prior to secondary debulking surgery. The similar OCEANS phase III trial is devoted to study of carboplatin/gemcitabine versus carboplatin/gemcitabine + bevacizumab in patients with platinum-sensitive recurrence. The TEACO phase II trial on newly diagnosed FIGO IB-IV patients assesses the protocol of oxaliplatin/docetaxel + bevacizumab. The interesting NCT00491855 phase I trial in advanced peritoneal carcinomatosis studies the effects of intraperitoneal oxaliplatin/paclitaxel with intravenous paclitaxel/bevacizumab [25].

Another anti-VEGF agent is aflibercept (VEGF Trap), which consists of VEGF receptor binding regions combined with human IgG_1. Preliminary results of a randomized phase II trial in patients with platinum-resistant ovarian cancer indicated a 11% partial response rate [26].

Trastuzumab and pertuzumab

Human epidermal growth factor receptor-2 (HER-2) controls expression of pro-angiogenic factors, including VEGF, and is present in up to 16% of epithelial ovarian cancers [27, 28]. Trastuzumab (Herceptin®) is a chimeric murine-human IgG_1 mAb that binds to an extracellular domain of HER-2 and increases tumour apoptosis [29, 30]. Similarly as in the case of bevacizumab, preclinical studies on murine models showed reduction of growth of HER-2-positive ovarian tumours [30, 31], but when implemented in humans during phase II clinical trials they failed to show satisfactory results (overall respon-

se rate 7%) [32]. Low efficacy is connected with resistance to trastuzumab, which depends on some molecules overexpressed on the tumour surface, such as MUC4, CD44 or insulin-like growth factor-I receptor (IGF-I R) [33]. Pertuzumab (Omnitarg™) is another anti-HER-2 mAb, having a different binding site than trastuzumab, but exerting similar effects. The clinical efficacy of pertuzumab therapy was evaluated in a phase II clinical study performed on patients with advanced ovarian cancer refractory to chemotherapy. Both the response rate and stabilization of disease were low and reached about 5%, while patients reported some serious side effects [8]. Another phase II randomized study evaluated the use of gemcitabine with or without pertuzumab in a group of platinum-refractory patients. The results suggested a moderate advantage of the combined protocol over gemcitabine monotherapy [34]. In contrast to trastuzumab, pertuzumab does not require HER-2 overexpression to exert cytotoxic effects and has limited efficacy in cases of trastuzumab resistance [35, 36].

Cetuximab

Epidermal growth factor receptor-1 (EGFR-1) belongs to HER-2-related receptors activating cellular proliferation and angiogenesis [37]. Its presence in up to 70% of epithelial ovarian tumours was confirmed [38-41]. Cetuximab (Erbitux™) is a murine-human chimeric mAb that binds to the EGFR extracellular domain [42]. Although preclinical *in vitro* studies confirmed cetuximab efficacy, especially in combination with docetaxel and pertuzumab [43], clinical studies in humans on use of platinum and cetuximab in platinum-sensitive patients showed unsatisfactory efficacy with a relatively high rate of toxicity [41].

Anti-IGF-I-R therapy

Insulin-like growth factor-I (IGF-I) is involved not only in regulation of metabolism by insulin hormone, but also in induction of cell invasion and proliferation. It indirectly regulates angiogenesis by stimulating cyclooxygenase-2 (COX-2) and VEGF, and positively influences migration of tumour cells [44, 45]. Therefore, immunotherapy using different mechanisms of IGF-I neutralization was introduced to management of ovarian cancer. One of them was the use of a soluble form of IGF-I receptor (IGF-I-R) designated 486/STOP. Its efficacy was demonstrated in preclinical *in vitro* and animal studies [46], similarly to another drug composed of mAb against IGF-I-R called EM164 [47]. Both immunotherapeutics reduced ovarian tumour proliferation and survival. There are two clinical trials ongoing to estimate efficacy of anti-IGF-I-R mAb AMG-479: as an additional drug to classical carboplatin/paclitaxel chemotherapy in optimally debulked FIGO grade III/IV ovarian cancer patients, and as therapy for platinum-sensitive patients with recurrent cancer [48, 49].

Farletuzumab

Alpha-folate receptor (α-FR) is a tumour-associated antigen that induces immune responses in about 70% of breast and ovarian cancer patients [50]. Farletuzumab (MORAb-003) is an example of mAb against α-FR that increases both cell-mediated and complement-dependent anti-tumour cytotoxicity [51]. A phase II clinical trial on combined treatment in platinum-sensitive patients with ovarian cancer recurrence showed significant prolongation of remission time compared to patients treated with chemotherapy only [52]. Ongoing clinical trials include: a phase II trial on efficacy of farletuzumab combined with carboplatin/taxane therapy in platinum-resistant primary and recurrent tumours, and a phase III trial on safety of the same combined therapy in platinum-sensitive relapsed tumours [4].

Cytokines

Interferons indicate *in vitro* cytotoxic activity against ovarian cancer cells [53-55]. Although phase I clinical trials in patients with persistent ovarian cancer revealed that intraperitoneal administration of interferon-α (IFN-α) after platinum-based chemotherapy resulted in a 36-53% response rate [56, 57], a phase II multicentre study indicated that intraperitoneal IFN-α had no better effectiveness than platinum given alone as second-line chemotherapy [58, 59]. Synergistic effects of intraperitoneal IFN-α combined with platinum failed to show any advantage over monotherapy [60, 61]. Phase III studies of IFNα2a given subcutaneously after completion of first-line chemotherapy or intraperitoneally together with platinum also failed to show satisfactory results [62, 63]. With a high rate of side effects, IFN-α seems to be a doubtful solution for ovarian cancer patients. Subcutaneous IFN-γ was initially found to be effective in a combined regimen with cisplatin and cyclophosphamide for less advanced ovarian cancer (Ic-IIIc FIGO), as well as for advanced (III/IV FIGO) ovarian cancer in first-line combined therapy with paclitaxel and carboplatin [64, 65]. However, recent randomized trials either in optimally/sub-optimally debulked patients, or in patients qualified for neoadjuvant therapy were unable to confirm previous results [66].

Because administration of higher doses of IL-2 was connected with serious toxicity, only low doses of IL-2 were found useful for clinical testing [67]. A pilot study on low-dose recombinant IL-2 (rIL-2) given intraperitoneally together with tumour-infiltrating lymphocytes expanded *in vitro* in rIL-2-enriched medium gave unsatisfactory results [68]. Another phase II study of intraperitoneal administration of rIL-2 in taxane/platinum refractory ovarian cancer showed complete/partial response or disease stabilization in about 40% of patients [69]. Due to the scarcity of studies on this form of immunotherapy in ovarian cancer, a definite conclusion regarding its efficacy cannot be drawn [70].

Immunological cells

Recognition of cancer cells by host effector lymphocytes depends on the proper function of antigen-presenting dendritic cells (DCs). The main goal of DC-based immunotherapy is to deliver previously extracted and prepared host own DCs back to the patient in order to restore anti-tumour cytotoxic activity (so-called DC vaccines) [71]. The preparation of DCs means that they are pulsed *in vitro* with tumour-derived antigen(s) or whole cancer cell lysate in order to potentiate and direct their antigen-presenting capacity [72]. An alternative source of functional DCs could be tumour-associated macrophages (TAMs) isolated either from ascites or from the tumour itself [73]. Although the effectiveness of DC vaccines for induction of tumour-specific CD8+ cytotoxic Th1-biased T lymphocytes was proved in *in vitro* studies [74, 75], clinical trials performed on patients with advanced ovarian cancer, using HER-2/MUC-1 pulsed DCs, induced immunological responses but no satisfactory clinical response [76-78]. The exception was the study on a vaccination regimen created with autologous dendritic cells engineered with mRNA-encoded α-FR [79], which indicated 50% regression of para-aortic lymph node metastases and decrease of CA-125 serum levels 16 months after DC vaccination. However, the study was based on a single case.

Besides DCs, also T lymphocytes were tested for their usefulness in adoptive immunotherapy of ovarian cancer. Autologous T cells subjected to *in vitro* sensitization against cancer folate receptor were tested in a phase I trial, which however did not show reduction in tumour size [80]. In most studies an increased number of CD4+CD25+Foxp3+ T regulatory cells (Tregs) in peripheral blood, lymph nodes and ascites was noted, correlating with worse prognosis for patient survival [81-83]. Elimination of tumour-tolerogenic Tregs function could be based on use of anti-CTLA-4 mAbs, which block CTLA-4-dependent Tregs suppressive properties. Clinical trials performed on ovarian cancer patients showed that anti-CTLA-4 mAb was able to reduce CA-125 levels and produce tumour necrosis, but with no satisfactory tumour regression [84, 85]. Moreover, effective anti-tumour responses obtained by Tregs manipulation were accompanied by serious side effects, such as uveitis, hepatitis, nephritis and colitis [86]. What is even more important, too strong Tregs "switch off" could adversely interfere with anti-tumour defence [87].

Other forms of immunotherapy

The possible future techniques that may be considered for immunotherapy of ovarian cancer include: targeting human leukocyte antigen-G (HLA-G) [88], indoleamine 2,3-dioxygenase (IDO) [89], or CD200 molecule on cancer cells [90]; adoptive immunotherapy using $\gamma\delta$T cells [91] or natural killer T (NKT) cells [92]; or modulation of TAMs [93]. As some tumour-associated antigens are over-expressed on both the placenta and tumour surface, there is a possibility of immunoplacental therapy that could enhance host defence against multiple tumour targets [94, 95].

Summary

Immunotherapy of ovarian cancer has not demonstrated satisfactory efficacy in most studied cases, despite promising results of preliminary preclinical studies. Also disappointing is the fact that the immunological response in the host induced by immunotherapy is not equivalent to a clinical response and prolonged survival. The plethora of mechanisms employed by the tumour to avoid host immunosurveillance necessitates the use of combined protocols based on immunotherapy with classical chemotherapy. However, this increases treatment toxicity. And last, but not least, immunotherapy was assessed mostly in advanced cancer, when reversal of unwanted immunological events is very difficult, if possible at all. Moreover, not every type of ovarian cancer is a good candidate for every form of immunological treatment, as only some of the tumours are characterized by expression of sufficient amounts of a particular antigen. All these problems await a solution, and further clinical trials are needed to draw nearer to victory over ovarian cancer.

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