Factors affecting response of chemotherapy in women with ovarian cancer

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Summary

Chemotherapy plays an important role in the treatment of ovarian cancer. Patients' response to chemotherapy is determined by a variety of acknowledged factors, but one might expect that many of them are yet to be described. The aim of this paper was to present the most essential yet still to be generally assessed in clinical practice, factors, which include: E-cadhedrin, hypoxia inducible factor α, survivin, COX-2, clusterin, BRCA1 protein, TP53 protein, YY1 protein, multidrug resistance protein, and interleukin-8.

Key words: Ovarian cancer; Chemotherapy; Factors affecting chemotherapy.

Introduction

The aim of chemotherapy is to exert a lethal effect on cancer cells via damage to structures (mainly DNA) crucial for their growth and division. Efficacy of this therapeutic method depends on many factors, including molecular – held responsible for the malignant phenotype associated with, among others, resistance to cytostatics. Advances in molecular biology present clinical implications for the introduction of targeted therapy, which causes damage to the cancer cell and eventually its death with little or no side-effects to healthy tissues and organs of the patient treated.

Selected factors, mainly genes and proteins, are presented below that comprise prognostic factors related to the response chemotherapy.

E-cadhedrin (Endothelial cadhedrin)

E-cadhedrin belongs to the type I cadhedrins – adhesion molecules responsible for Ca+ - dependent cell-cell adhesion in epithelial tissue. Cadhedrins, transmembrane proteins are linked to the actin cytoskeleton of a neighboring cell via catenins (another type of adhesion molecules), thus forming a tightly adherent complex.

Cell adhesion plays a key role in the regulation of cell growth, migration, and apoptosis – processes essential for cancer development [1]. Decreased expression of adhesion molecules is related to cell motility, which, in the case of cancer, leads to dissemination and metastasis. Sawada *et al*. [2] revealed that E-cadhedrin is also active in combination with other adhesion molecules; inhibition of E-cadhedrin function induces α_5-integrin, which via the MAPK pathway mediates cancer progression. Ho *et al*. [3] in the study of 61 ovarian clear cell adenocarcinoma patients at Stages IIC to IV after cytoreductive surgery discovered that E-cadhedrin expression in more than 75% of patients. Patients receiving paclitaxel-based chemotherapy (paclitaxel/paclitaxel-cisplatin) with positive E-cadhedrin expression demonstrated a significantly better five-year overall survival than those receiving cisplatin. Positive E-cadhedrin expression and paclitaxel-based chemotherapy are a positive prognostic factor in ovarian clear cell carcinoma.

Hypoxia inducible factor α (HIF-1α)

HIF-1 is a protein which, under normoxic conditions (oxygen concentration in cells about 7%), undergoes rapid proteasomal degradation after binding to ubiquitin molecules. Under hypoxic conditions however, it pairs with the HIF-1β subunit to form a heterodimer, which activates expression of various hypoxia-responsive elements (HRE_S), e.g. *VEGF*, *EPO*, *LEP*, *NOS*, *GLUT1 and CXCR4*, which then release a range of substances that stimulate new vessels to form within the tumor, as well as cell migration to new sites – causing cancer dissemination [4, 5]. Abnormal cancer vessels restrain blood supply (as well as penetration of cytostatics) to the tumor, a malignant phenotype of neoplasm develops, followed by chemo- and radioresistant metastases. HIF-1α overexpression correlates with P-gp (P-glycoprotein) overexpression, which is a product of the *MDR1* gene (multidrug resistant gene) and with the cell cycle arrest at G0/G1 phase. This leads to reduced intracellular drug accumulation and presence of large quantities of cells phase-insensitive to cytostatics, which explains the paclitaxel-resistance mechanism [6, 7]. Follow-up of patients after adjuvant therapy in 66 ovarian cancer patients revealed that HIF-1α overexpression, as well as FIGO stage, were independent negative prognostic factors of overall survival [8].

Survivin (IAP-4, inhibitor of apoptosis protein)

Survivin is one of the eight proteins that regulates the cell cycle and via the BIR (baculovirus IAP repeat) domain, which enables binding with caspases (blockade

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of caspase-7 and activation of procaspase-9) inhibits apoptosis [9, 10].

Survivin is not present in normal tissues of adult organisms; it is expressed in small amounts only in proliferating tissues (e.g. endometrial). However it is virtually ubiquitous in all types of cancer tissue (with different variants in cytoplasm and nucleus).

The review by Urbaniak [11] analyzed survivin expression in many types of neoplasms and weighed opinion as to survivin's utility as a diagnostic/prognostic marker and its possible therapeutic use.

Recently, research results have been presented on survivin and TP53 expression in 453 ovarian cancer patients treated with PC (platinum and cyclophosphamide) and TP (taxol and platinum) therapy. Nuclear survivin expression was found in 92% of cancer tissue and cytoplasmic in 74%. High expression of nuclear survivin in patients treated with TP regimen yielded a significantly lower risk of disease recurrence and death with an accompanying increase in platinum sensitivity, however only in TP53 positive patients – which identifies survivin as one of the prognostic factors in ovarian cancer [12].

COX-2 (Cyclooxygenase-2)

COX-2 is an enzyme, one of the two products of the cyclooxygenase gene *(COX),* that catalyzes the conversion of cell membrane phospholipids to prostanoids (prostaglandin, thromboxane, prostacyclin), and is activated mainly in inflammatory processes and immunological response. Under physiological conditions, it is present in the brain, ovaries, and testicles; however its expression changes with cancer conditions – it participates in angiogenesis and cell migration, which contributes to cancer growth and metastases [13]. Some studies revealed its tight correlation with VEGF and p53 expression, clinicopathologic factors, and non-mucinous histologic subtype of ovarian cancer [14, 15].

In the analysis of women with cancer, COX-2 expression was found to be of prognostic value in ovarian cancer. However in one study (160 female patients) positive expression correlated with longer survival, whereas in the other (183 female patients), positive COX-2 expression was associated with shorter survival [16, 17].

Ferrandina *et al*. [18] investigated clinical outcomes of 87 patients with ovarian cancer and indicated that positive COX-2 expression correlates with shorter time to recurrence and shorter overall survival due to resistance to platinum derivatives. According to the authors, ovarian cancer patients with COX-2 overexpression should be considered candidates for individualized treatment.

Clusterin (Apoliprotein J)

Clusterin is a glycoprotein expressed in many human tissues, contained in body fluids, and involved in processes relevant to physiology, as well as cancer development, such as cell growth and apoptosis, cell cycle regulation, adhesion, and DNA repair [19].

Clusterin overexpression was confirmed in over 40% of ovarian cancer patients and correlated with FIGO stage and histological type. Clusterin overexpression also conferred shorter survival [20].

Wei *et al*. [21] in their analysis of ovarian cancer cell lines revealed that clusterin location (cytoplasmic or nuclear), as well as its different isoforms, mediate different biological effects, e.g. cisplatin resistance. Retrospective immunohistochemical study of clusterin expression in 62 patients with grade III serous ovarian cancer revealed that its overexpression correlates with increase in paclitaxel resistance due to interaction between clusterin and paclitaxel [22, 23].

BRCA1

BRCA1 is a suppressor gene localized on the 17q21 chromosome, and its product, BRCA1 protein, is involved in the repair of damaged DNA strand preventing by the same loss of control over the cell. It is also associated with transcription regulation and cell division [24].

The present state of knowledge allows to confirm that firstly, the evaluation of expression levels and secondly, the evaluation of BRCA1 gene mutation may serve as predictive factors for ovarian cancer patients: an altered response to the chemotherapy applied, especially in treatment with taxanes and platinum derivatives, renders this statement true [25, 26]. The relationship was demonstrated between BRCA1 mRNA expression and survival after chemotherapy treatment: patients with lower expression levels had a better response to platinum-based therapy, whereas patients with higher expression responded better to taxanes and the overall survival rates for patients with higher mRNA *BRCA1* expression increased in the group chemotherapeutically treated with taxanes. *BRCA1* induces over 1,000-fold sensitivity to chemical factors that cause damage to the mitotic spindle.

In light of recent findings, it is implicated that treatment with platinum and new drugs, namely poly ADP-ribose polymerase (PARP) inhibitors, which are presently under clinical trials, may be in the nearest future the recommended therapy for patients with diagnosed mutation in the *BRCA1* gene [27].

TP53

Mutations in the suppressor gene p53 resulting in the formation of an abnormal protein TP53 are present in a significant percentage of ovarian cancer patients and are associated with worse prognosis; they also contribute to increase in cell sensitivity to taxanes [28, 29]. A meta-analysis of 62 published studies was released in 2009 compiling data from 9,948 ovarian cancer patients concerned with the correlation between the p53 status and patient survival, as well as clinicopathologic factors and response to the treatment [30]. Despite large heterogeneity of the trials, a statistically worse prognosis was reported for patients with abnormal p53 gene. Some of the studies implied correlations between the p53 status and

response to platinum-based treatment, while treatment with taxanes showed great disparity. In the meta-analysis under discussion, the biochemical marker that is the mutated p53 gene, was not considered a useful prognostic factor in the clinical practice.

YY1

The YY1 protein was discovered in 1991 by Shi *et al*. in adenovirus cells [31]. It is present in both normal and cancer cells.

Matsumara's analysis [32] provided evidence of strong positive correlation between YY1 expression, the YY1 encoding gene, and the E2F transcription factor in serous ovarian cancer cells. High YY1/E2F activity correlates with survival in patients receiving paclitaxel treatment. Increased sensitivity to taxane therapy, not observed in treatment with platinum derivatives, was characteristic for NCI60 cell line, on which the study was performed. Reduction of YY1 expression resulted in decreased cell growth and proliferation, but also in increased taxane-resistance along with lack of cisplatin resistance.

MDR - multidrug resistance proteins

Resistance to chemotherapy in ovarian cancer patients is associated with multi-drug resistance proteins, which comprise: MRP1 protein – product of the ABCC2 gene, M10 protein (also called lung resistance related protein, LRP), BCRP protein (breast cancer related protein) – product of the ABCG2 gene and P-glycoprotein (P-gp) - product of the MDR1 gene, also known as ABCB1 [33-36]. All mentioned substances are transport proteins, including P-gp, a transmembrane transporter, and are present in both normal and cancer cells. MRP1 expression in ovarian cancer cells is associated with resistance to anthracycline, *vinca* alkaloids, and etoposide [34, 37-40]. Detection of M10 in cancer cells correlates with resistance to doxorubicin, *vinca* alkaloids, and platinum derivatives (cisplatin and carboplatin) [41], whereas presence of BCRP – to anthracyclin, mitoxantrone, and topotecan [42, 43]. P-gp expression was found to be associated with resistance to anthracyclin, *vinca* alkaloids, actinomycin, taxol, etoposide, cisplatin, mitomycin-C, topotecan, and colchicines [44].

It seems valid to state that the resistance to ovarian cancer treatment is acquired via activation of the MDR1 gene, which is linked to a higher P-gp expression in cancer cells in patients with neoplastic recurrence in comparison to expression in primary tumor cells, as it was made evident in the work of Van der Zee *et al*. [45], where the P-gp presence was noted in 15% of cancer cells obtained from primary tumor and in 47% of cells from patients with neoplastic recurrence. A possibly efficient and safe gene therapy with the use of adenoviruses may be applied in the future for ovarian cancer patients with a diagnosed MDR1-mediated resistance to chemotherapy [46].

Interleukin 8

Interleukin-8 (IL-8) is a cytokine produced by monocytes, neutrophils, fibroblasts, epithelial, endothelial, and mesothelial cells as a response to inflammation as well as to tumor cells [47]. It plays an important function in inflammatory processes, and its role in the promotion of cancer cell growth, pro-angiogenic activity in many neoplasms, and involvement in metastasis is currently under analysis [47, 48]. High protein expression is associated with more advanced stages of cancer and higher differentiation of ovarian cancer cells which portends worse survival for patients, as reported in the research by Merritt *et al*. [49]. The analysis of 102 patients demonstrated high levels of IL-8 in a group of 43 subjects, and from this group 42 were in Stages III or IV of advanced cancer; all of the 43 patients still showed low cancer cell differentiation *(grade 3)*, contrary to the patients with low IL-8 expression. Comparison of median survival in both groups is 1.62 and 3.79 years, respectively. Both endogenous as well as exogenous IL-8 was reported to induce cisplatin and paclitaxel resistance in non-IL8-expressing A2870 cell line cells, whereas deletion of the endogenous IL-8 in IL-8-overexpressing SKOV-3 cell lines resulted in sensitivity to antineoplastic drugs [50]. For this reason, modulation of IL-8 expression or IL-8 signaling pathway may be a promising method of sensitizing cells to chemotherapy in drug-resistant ovarian cancer.

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