review

memo (2019) 12:144–148
https://doi.org/10.1007/s12254-019-0478-5

memo
magazine of european medical oncology

Resistance to chemotherapy and anti-angiogenic therapy in ovarian cancer

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Received: 22 October 2018 / Accepted: 6 February 2019 / Published online: 21 February 2019

Summary Ovarian cancer (OC) is the foremost lethal gynaecologic malignancy and among the top five deadliest cancers in women. Current treatment comprises a combination therapy of surgery, platinum-based chemotherapy and anti-vascular endothelial growth factor (VEGF) antibodies. However, patients typically experience a disease relapse within two years. Recurrent OC is incurable and resistance to platins and anti-VEGF treatment is a major determinant of prognosis. Understanding the molecular mechanisms that contribute to tumour metastasis and chemoresistance are essential to improve patient outcome and especially survival. In a current OC model, tumour metastasis and chemoresistance critically depend on the biology of cancer stem cells (CSCs). Recent studies also suggest that intratumour heterogeneity is the main cause of treatment failure due to chemoresistance. Furthermore, the proinflammatory tumour microenvironment seems to contribute to metastasis and chemoresistance. Despite an improved understanding of the complex interplay between classical mechanisms of drug inactivation or efflux, clonal selection and the tumour microenvironment, mechanisms of resistance in human OC are poorly understood. This review summarises current concepts in the treatment of OC, mechanisms of resistance to chemotherapy and angiogenic inhibitors and approaches to overcome drug resistance.

Keywords Ovarian cancer · Chemoresistance · Platinum resistance · Angiogenic inhibitors · VEGF

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Introduction

The frontline therapy of ovarian cancer (OC) consists of surgery and platinum-based chemotherapy (usually carboplatin area under the curve [AUC] 5–6 and paclitaxel 175 mg/m^2 every 3 weeks for six cycles as demonstrated in the GOG-158 study) [1]. Patients with advanced disease (i.e. FIGO IIIb and higher) additionally receive anti-angiogenic therapy during chemotherapy (GOG-218: bevacizumab 15 mg/kg from second cycle carboplatin/paclitaxel; hazard ratio (HR) for progression or death 0.908 [95% confidence interval (CI), 0.795 to 1.040; $P=0.16$]) and for maintenance (16 cycles after chemotherapy; HR 0.717 [95% CI, 0.625 to 0.824; $P<0.001$]) [2]. Although response rates and complete responses after first-line treatment of advanced disease are >80% and 40–60%, respectively, most patients will relapse with a median progression-free survival (PFS) of 18 months [3]. In general, patients who respond to primary treatment and relapse within 6 months are considered "platinum-resistant", and patients who relapse more than 6 months after completion of initial therapy are characterized as "platinum-sensitive" [4]. Interestingly, most of "platinum-sensitive" patients will respond to further platinum-based chemotherapy with response rates ranging from 30 to 90% [5]. In contrast, "platinum-resistant" patients typically have low response rates (15%) to subsequent chemotherapy and the outcome of these patients is poor with a median survival not exceeding 12 months [5]. Primary "platinum-refractory" OC patients (those that progress during treatment) are quite uncommon and usually seen with non-serous ovarian cancers such as clear cell or mucinous cancers rather than the more common high grade serous ovarian cancer (HGSOC). "Platinum-refractory" patients also exhibit a poor clinical outcome with comparable low median survival.

Tumour angiogenesis is an essential process of cancer growth and metastasis and influences the progression of ovarian cancer [6]. Vascular endothelial growth factor (VEGF) is an important promoter of the formation of new blood vessels that contribute to "feeding cancer" [6]. The expression of VEGF and its receptors in ovarian tumours directly correlate with poor prognosis, suggesting that angiogenesis, possibly mediated at least in part by VEGF, influences disease progression [7, 8]. To date, anti-angiogenic therapy has been identified as one of the most promising targeted therapies in OC. Bevacizumab, a recombinant, humanized, monoclonal VEGF antibody, has been implemented in the first-line treatment with a platinum-based chemotherapy but also in platinum-sensitive (OCEANS trial) and resistant (AURELIA trial) recurrent OC [2, 9, 10]. More specifically, in platinum-sensitive recurrent OC gemcitabine and carboplatin plus bevacizumab followed by bevacizumab until progression resulted in a better PFS compared with chemotherapy plus placebo (HR 0.484; 95% CI, 0.388 to 0.605; $P<0.0001$) [9]. Combining bevacizumab with chemotherapy in platinum-resistant OC also improved PFS (HR 0.48; 95% CI, 0.38 to 0.60; $P<0.001$) [10].

Influences on platinum sensitivity and mechanisms of platinum resistance

Different tumour-specific factors such as histological subtype, clonal selection, tumour mutations and microenvironment but also pharmacokinetic factors influence response and resistance to chemotherapy and anti-angiogenesis [11]. Platinum sensitivity and resistance is well known in patients with HGSOC. Endometrioid, clear cell, mucinous and low-grade serous OC are less common histotypes and differ from HGSOC in clinical course, tumour mutations, molecular aberrations and in response to chemotherapy. Mucinous, clear cell and low-grade serous cancers tend to be resistant to standard-of-care [12]. However, patients are still treated with platinum-based chemotherapy first-line due to the lack of proven alternatives. Since mucinous OC shares several common pathological and molecular features with gastrointestinal tumours, it has long been hypothesized that standard gastrointestinal treatments could be more effective for this histotype than the current standard-of-care. In all the phase I/II cohorts of platinum-refractory OC patients treated with some of these approaches (e.g., capecitabine, oxaliplatin, FOLFOX, gemcitabine + oxaliplatin), only a very small number of mucinous OC patients were included, meaning it was difficult to draw clear conclusions [13].

Germ-line mutations in *BRCA1* and *BRCA2* are well-known risk factors for developing HGSOC [14]. OC patients with germline (BReast CAncer) *BRCA* mutations exhibit a favourable outcome and higher responsiveness to platinum-based therapies [15–17]. However, many sporadic HGSOCs exhibit phenotypic characteristics of germline *BRCA* mutated tumours. This so-called BRCAness can be defined as a defect in homologous recombination repair and can be, for example, caused by somatic mutation of *BRCA1/2*, epigenetic hypermethylation of the *BRCA1* promoter, amplification of EMSY (also known as *C11orf30*) resulting in *BRCA2* silencing, and loss of function mutations of the Fanconi anaemia complementation group family of genes [18]. Importantly, a BRCAness gene expression profile was shown to predict platinum responsiveness [19].

The cytotoxic effect of platins relies on single or double strand DNA breaks and may also cause mitochondrial damage and in turn cell death [19]. Platinum resistance may stem from reduced platinum uptake into the cell or increased efflux evoked by alterations of transport proteins. An increase in DNA repair by alterations of repair proteins such as nucleotide excision repair, mismatch repair, homologous recombination or base excision repair is also classically associated with platinum resistance. These various mechanisms may already exist at diagnosis or are acquired over time [12].

OC stem cells (OCSC) seem to play a potential role in OC recurrence following chemotherapy. Cancer stem cells typically exhibit a slow cycling rate which makes them inherently resistant to standard chemotherapy which, by definition, targets actively proliferating cells [20]. However, the underlying mechanisms that regulate the chemoresistance of OCSCs remain unclear [21]. Kryczek et al. and Silva et al. defined OSCSs via the presence of aldehyde dehydrogenase (ALDH) and CD133 [22, 23]. Furthermore, the presence of ALDH and CD133 positive cells in debulked primary tumour specimen correlated with reduced PFS and overall survival (OS) in ovarian cancer patients [23]. This may be because of the association of high ALDH1A1 expression/activity with platinum-resistant cells in vitro. In an in vivo orthotopic mouse model of ovarian cancer, ALDH1A1 silencing sensitized both taxane- and platinum-resistant tumours to chemotherapy [24]. Reimer et al. demonstrated that truncated isoform Vav3.1 is highly expressed in OCSCs and clinically relevant in predicting prognosis and platinum-response as Vav3.1 may be decisively involved in mechanisms causing genuine multidrug resistance [25]. In contrast, in the environment-mediated drug resistance (EMDR) model, cancer cells interact with their surrounding microenvironment and enter a quiescent state due to the complex interplay between tumour and its microenvironment. These surviving populations, which may or may not be OCSCs, can contribute to cancer relapse [26].

Patients who have an initial response to platinum-based chemotherapy are believed to have tumours with intratumour heterogeneity of both in-

trinsically platinum-resistant cells and also sensitive cells. The sensitive cells undergo apoptosis following chemotherapy (tumour response) but the resistant subpopulation of cells persist and expand, leading to early recurrence in "platinum-resistant" disease. "Platinum-sensitive" patients may respond to platinum, due to the regrowth of the sensitive population. Ultimately however, the "sensitive" cells may alter or mutate, rendering them resistant, or the resistant cell population will outgrow the sensitive population [5].

Mechanisms of anti-VEGF resistance

Evidence suggests that mechanisms of resistance to anti-VEGF therapy might be mediated by tumour cells and by members of the tumour microenvironment [11, 27, 28]. Tumour hypoxia is a major molecular controller of an "angiogenic switch" that determines a time-restricted event during tumour progression in which the balance between pro- and anti-angiogenic factors tilts towards a pro-angiogenic outcome [27, 29, 30]. Blocking the VEGF pathway inhibits vessel formation but also promotes recruitment of vascular progenitors and vascular modulators such as tumour-associated macrophages (TAMs), immature monocytes and hemangiocytes. Growing evidence indicates that inflammation controls angiogenesis as infiltrating tumour-associated macrophages have been linked to the escape from anti-angiogenic therapy [29]. Further, M2 polarized TAMs promote tumour vascularization by producing proangiogenic factors and growth factors, including transforming growth factor (TGF-β) and VEGF, and attracting leukocytes to further enhance angiogenesis [31].

Recent genomic interrogation of large numbers of HGSOC samples indicated high complexity in terms of genetic aberrations, intra- and intertumor heterogeneity and underscored their lack of targetable oncogenic mutations [32–34]. Subclassifications of HGSOC based on expression profiles, termed "differentiated", "immunoreactive", "mesenchymal" and "proliferative", were shown to have prognostic value. Proliferative and mesenchymal subtypes exhibit poorest survival but derive a comparably greater benefit from treatment with bevacizumab [35].

Concepts to overcome drug resistance

The response to cytotoxic chemotherapy remains the essential determinant of OC prognosis [36]. The lack of a detailed understanding of the mechanisms that underlie clinical drug resistance has not deterred investigators from initiating a range of clinical trials that aim to tackle the problem. Novel approaches include disruption of homologous recombination (HR) (i.e. poly-ADP-ribose-polymerase [PARP] inhibitors), reversing inflammation or tumour immune escape and simultaneous targeting of multiple angiogenic pathways using anti-angiogenics. Due to its inherent genomic heterogeneity, molecularly defined subgroups of HGSOC ("differentiated", "immunoreactive", "mesenchymal" and "proliferative") may require different approaches.

BRCA1/2 mutated OCs and OCs with a BRCAness phenotype have demonstrated sensitivity to PARP inhibitors due to underlying deficiencies in DNA homologous recombination; however, clinical responses are often partial and highly dependent on platinum sensitivity. PARP inhibitors such as olaparib, niraparib and rucaparib are already approved for treatment of recurrent EOC and their indications are partially overlapping: niraparib [37] and olaparib [38] have been approved for maintenance therapy after partial or complete remission in recurrent ovarian cancer. Further, olaparib [39] and rucaparib [40] have been approved as monotherapy for advanced recurrent OC. More recently, olaparib has demonstrated impressive activity in *BRCA*-mutated OC as maintenance following first-line chemotherapy (SOLO-1 trial; HR for disease progression or death, 0.30; 95% CI, 0.23 to 0.41; $P<0.001$). Today, probably another promising therapeutic approach in this context is the blockade of immune checkpoints, such as programmed cell death 1 (PD-1), its ligand PD-L1 or cytotoxic T-lymphocyte associated protein 4 (CTLA4), which demonstrated impressive response rates in malignant melanoma and non-small-cell lung carcinoma (NSCLC). Considering this and a positive expression of check point molecules in OC which is associated with clinical outcome [41] many clinical studies investigate check point inhibitors in OC, especially platinum-resistant or recurrent OC [42]. Various simultaneous anti-angiogenics may improve the therapeutic benefit and counteract compensatory escape mechanisms [43]. Additional studies are necessary to determine optimal combinations that could be either vertical (e.g., bevacizumab with other angiogenesis inhibitors like sorafenib, vandetanib, sunitinib), horizontal (e.g., inhibitors of phosphatidylinositol-4,5-bisphosphate 3-kinase [PI3K] pathway, MAP kinase-ERK kinase [MEK], angiopoietin), or direct (e.g., bevacizumab with thrombospondin-1 or vascular disrupting agents such as combretastatin A1 phosphate [OXi4503]) [11].

Collectively, resistance to chemotherapy and anti-angiogenic approaches depends on multiple factors that are challenging to control in a clinical setting until today. Insights into tumour biology and the tumour microenvironment may help to overcome mechanisms of resistance to tackle OC progression. Increasing availability of novel (mechanistically distinct) treatment approaches in OC and the selection of patients that benefit from particular treatment modalities may improve OC survival. Addressing these issues will require further clinical investigations and identification of predictive biomarkers.

Funding Open access funding provided by University of Innsbruck and Medical University of Innsbruck.

Conflict of interest V. Wieser and C. Marth declare that they have no competing interests.

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