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Emerging treatment strategies in recurrent platinum-sensitive ovarian cancer: Focus on trabectedin ☆

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ABSTRACT

Ovarian cancer (OC) is the leading cause of death from gynecological malignancies. In spite of high response rates to the standard front-line treatment for advanced disease with cytoreductive surgical debulking, followed by platinum/taxane-based chemotherapy, most patients eventually relapse developing drug-resistant disease. Owing to the molecular heterogeneity, genetic instability and mutagenicity of OC, increases in survival might be achieved by translating recent insights at the morpho-molecular levels to individual therapeutic strategies. Several emerging treatments have been shown to be active in platinum-sensitive (PS) recurrent OC (ROC), but an optimal strategy still has not been established. Based on the recent results, it is likely that the introduction of novel non-platinum based chemotherapies and molecular targeted therapies will have a major impact on the management of ROC. Some current strategies are focused on the extension of platinum-free interval (PFI) in patients with PS, particularly in those with partially PS disease. Apparently, the PFI extension by an effective non-platinum intervention, such as trabectedin plus pegylated liposomal doxorubicin (PLD), may reduce cumulative platinum-induced toxicities leading to longer survival after the reintroduction of subsequent platinum. The introduction of novel therapies, such as the antiangiogenic monoclonal antibody bevacizumab, opens a new field of targeted therapies in this indication. In this review, we aim to outline the therapeutic potential of new emerging approaches, particularly the role of non-platinum therapy with trabectedin in combination with PLD in patients with PS ROC.

Introduction

Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies, with 50% of all cases occurring in women over 65 years of age, and the fifth most frequent cause of death by cancer in women with approximately 125,000 deaths annually worldwide [1]. Approximately 75% of women with ovarian cancer (OC) present advanced stage of disease associated with poor outcome. Over the past two decades the standard first-line treatment paradigm for advanced epithelial OC has been maximal cyto-reductive surgical debulking followed by platinum-based chemotherapy with the prognosis of therapy closely related to the disease stage at diagnosis and the extent residual disease following surgery [2]. Yet, while the median survival has been extended to more than 4 years, overall survival (OS) has not changed over the last 30 years.

In spite of high response rates to primary therapy (70–80%) [2–5] only approximately 15% of women achieve cure [5]. The remaining patients have drug-resistant disease or ultimately develop incurable recurrent disease with an overall 5-year survival rate lower than 50% [5,6]. Therefore, identification of new drugs and emerging treatment strategies for recurrent OC (ROC) represents a clinical challenge.

Treatment of recurrent platinum-sensitive ovarian cancer

ROC is not a curable disease; thus, the principal objective of salvage treatments is to prolong survival in patients with platinum-

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sensitive (PS) disease, improve quality of life (QoL), particularly in patients with platinum-resistant (PR) disease, and alleviate cancer-related symptoms. Re-treatment with platinum-based chemotherapy is common practice in recurrent disease after relapse; however, its effectiveness is highly correlated with platinum-free interval (PFI) [7]. In 2010, the 4th Ovarian Cancer Consensus Conference of the Gynecological Cancer InterGroup meeting held in Vancouver established the definition of PFI as the interval from the last date of platinum dose until documented progressive disease [8]. The initial bipolar empiric categorization of patients with ROC on PR and PS patients, with a PFI of <6 months and ⩾6 months, respectively, did not sufficiently reflect the disease prognosis since PFI is a continuous variable rather than one dichotomized at 6 months [9–11]. Therefore, it was agreed that the PFI should be used to subcategorize patients into the following subgroups: platinum-refractory patients, with disease progression while receiving last line of platinum-based therapy or within four weeks of last platinum dose, PR (PFI <6 months), partially PS (PFI of 6–12 months) and fully PS (PFI >12 months) [8,12]. In addition to PFI, duration of response to previous therapy, disease stage at time of diagnosis, as well as patient's tolerability, performance status and preference of a particular treatment are the main criteria for selecting therapies for ROC and also the most important prognostic factors.

Patients with a fully PS relapse typically receive a salvage second-line therapy based on rechallenge with platinum-containing regimens with response rate ranging from 30% to 75% [13]. These patients generally undergo a series of salvage treatments, with each subsequent treatment associated with progressively shorter PFI during disease remission. Markman et al. have reported that the length of a prior response to platinum-based therapy seems to be highly predictive of the upper limit of the response duration of a subsequent platinum treatment, assuming the same or similar drug/s are used for subsequent treatment [14]. Nevertheless, patients treated with a regimen consisting of platinum plus an agent not administered during their prior treatment may have secondary responses of longer duration than the previous one [14].

Among PS patients, those patients with partially PS (PPS) disease after primary platinum-based therapy, obtain substantially lower response rate to platinum re-challenge (27–33%) [15]. Women with PPS disease represent ~20–40% [16–20] of all patients, for whom controversies and uncertainties still exist regarding the best post-progression treatment. It has been proposed that PFI extension through intercalation of a non-platinum therapy prior to subsequent platinum rechallenge may increase the likelihood of response of a later platinum re-treatment [21–27].

The treatment of ROC continues to evolve as new drugs with diverse mechanisms of action are introduced into the oncologist's armamentarium. The aim of this review is to identify the position of emerging treatment strategies in the treatment algorithm for ROC that fits with the potential of those drugs. Moreover, since there are women with ROC who could benefit from a delay in platinum re-treatment, who are not good candidates for platinum-based therapy or this agent is not the best treatment option for them, the selection of suitable patients who may largely benefit from non-platinum based therapy was also reviewed.

Genomic heterogeneity of ovarian cancer: toward patient-tailored therapy

OC is a broad term for different heterogeneous cancers that are derived from different, often non-ovarian tissues, resulting in the different OC histotypes (i.e., mucinous, endometrioid, clear cell and serous, high grade and low grade serous). Therefore, OC is a misleading term for a series of genomically and etiologically heterogenic diseases that often do not arise from ovarian tissue and simply share an anatomical location [6,28]. Given the complexity of OC, the current single approach to treatment of OC as a single disease has to move toward patient-tailored therapy based on molecular and histotype-driven treatments. Recently, the Cancer Genome Atlas Research Network (TCGA) has described the genomic and epigenomic abnormalities of 489 patients with advanced-stage, high-grade serous OC, with the aim to identify molecular abnormalities that influence pathophysiology, outcomes, and constitute therapeutic targets [29]. The integrated analysis performed by TCGA has definitely demonstrated the low mutation rate of high grade OC except for TP53 and BRCA1/2 genes which were affected in 96% and 22% of OC, respectively, but without a clear correlation between the expression and methylation patterns of those genes and clinical outcomes. In contrast, extensive focal and broad DNA losses and gains were seen through the genome of OC with DNA deletions and amplification in many genes. Yet again, the patterns of methylation and gene expression across the samples did not strongly correlate with clinical outcomes. Therefore, it has been proposed that serous OC might not be targeted with drugs, challenging if our understandings of the plethora of genomic data will translate into clinically useful approaches (Birrer MJ, Genomic Analysis. Keynote Lecture, 9th Advanced Ovarian Cancer Symposium, Valencia, Spain. March 2013; unpublished results). Regarding the association of BRCA1/2 mutation with survival and sensitivity to platinum-based chemotherapy, this and other genomic analyses of OC have confirmed improved OS and overall response rate (ORR) in patients with germline BRCA mutations as compared non-carriers [29–32]. Indeed, deficiencies of the homologous recombination pathway in DNA repair can impair DNA cross-links repair introduced by platinum-based chemotherapy and result in higher survival rates due to an improved response in BRCA-deficient patients. Furthermore, these homologous recombination defects sensitize tumors for targeted therapies such as poly (ADP-ribose) polymerase (PARP) inhibitors [33]. Therefore, in a variety of malignancies including OC, enhanced expression of the DNA repair proteins, such as BRCA1/2 and excision repair cross complementation group 1 (ERCC1), have correlated with resistance to both platinum and PARP inhibitors [31,34–38]. Additionally, preclinical models and *ex-vivo* results also demonstrated that the tumor microenvironment has become an important focus of attention as an adjunct to molecular therapeutics and chemotherapy in ovarian cancer. Therefore, drugs ability to modulate the tumor microenvironment might be largely responsible for the antitumor effects by decreasing the factors potentially relevant for tumor growth, progression, and metastatic spread [39].

Treatment endpoints in recurrent ovarian cancer

The optimal treatment for women with epithelial ROC is rapidly evolving in parallel with our understanding of the pathways and networks controlling cell signaling, proliferation, and cell death. However, decision-making strategies for optimal treatment of ROC are complex as many active cytotoxic drugs and an increasing number of biological agents are becoming available [40]. This represents challenges in defining the endpoints, optimal timing and sequencing of most drugs or treatment regimen, such as monotherapy or in combination, particularly in the development of new clinical trials. The most controversial issue of the ROC treatment surrounds the lack of an OS advantage observed with the number of investigational regimens and compounds, often being associated with increased toxicity and no improvements in patients QoL [17,18,20,41,42]. Therefore, the selection of clinically-meaningful scientific objectives and standardized study endpoints is critical [7]. In contrast with first-line therapy, where an excellent correlation has been observed between progression-free

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