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Editorial

# Ovarian cancer: a molecularly insidious disease

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**Abstract**

In this issue of the *Chinese Journal of Cancer*, European, American, and Chinese experts review the current management and future perspectives of epithelial ovarian cancer (EOC), the leading cause of gynecological cancer deaths. Although major advances have been made in understanding the cellular and molecular biology of this highly heterogeneous malignancy, the survival rate of women with EOC has changed little since the introduction of platinum-based treatment as a front-line therapy. The papers describe the progress in deciphering the molecular complexity of this disease and the newly available molecular-driven therapies, which have been applied by shifting trial designs toward restricting eligibility to specific subgroups of patients rather than testing agents in unselected populations. These new trial designs provide potential opportunities for improved efficacy in targeted populations. Given the molecular complexity of this disease, patient survival may be increased by searching for new molecular prognostic/predictive signatures as well as by translating the recent insight of microRNA involvement in EOC progression into new, targeted therapies. Particular attention has been given to the issue of fertility sparing for women affected by curable diseases.

**Key words** Ovarian cancer, standard of care, targeted therapies, miRNAs, fertility preservation

Ovarian cancer is a highly lethal disease that lacks effective screening tests for early detection. Therefore, the majority of patients are diagnosed with advanced stages of the disease and have expected 5-year survival rates below 40%[1,2]. The worldwide incidence of this cancer is 238,700 new cases per year, with a global mortality of 151,900 deaths per year[3], making ovarian cancer the leading cause of death for gynecological cancers.

Teamwork including multidisciplinary specialists is essential to face this disease. In addition to the stage at presentation, residual disease after primary surgery remains the strongest prognostic factor; therefore, surgery, which should be performed by gynecological oncology surgeons, has the purposes of removing as much cancer tissue as possible, of establishing the exact International Federation of Gynecology and Obstetrics (FIGO) stage, and of allowing for a histopathological diagnosis. Histological interpretation of resected tissues can be complex and requires specialist expertise. In particular, the histopathology of epithelial ovarian cancer (EOC) is extremely heterogeneous, and each EOC subtype harbors specific genetic alterations[4]. The change in perspective from one disease with several epithelial subtypes to several distinct diseases has also begun to affect treatment strategies[5]. Almost 10 years ago, EOCs were proposed to be classified into Type I (low-grade tumors harboring *BRAF*, *KRAS*, and *PTEN* mutations) and Type II tumors (high-grade tumors characterized by p53 gene and *BRCA1/2* mutations)[6]. Subsequent genomic studies then subdivided serious high-grade EOC into four molecular subgroups[4], but this classification has not yet been clinically applied. In this issue, Devouassoux-Shisheboran and Genestie[7] report the newly described molecular abnormalities of EOC and the 2014 World Health Organization (WHO) classification based on tumor morphology. They also discuss about the new theory of EOC pathogenesis. Traditionally, EOCs have been thought to arise from ovarian surface epithelial cells or from similar cells that line cysts immediately beneath the ovarian surface. In recent years, it has become apparent that a fraction of EOCs or primary peritoneal carcinomas can also arise from endometriosis, epithelial rests in the normal peritoneum, or the fimbriae of Fallopian tubes[8].

Despite the great heterogeneity of EOC, chemotherapeutic regimens containing platinum have been the standard of care for almost 40 years worldwide, and it has been difficult to progress beyond platinum-based therapy. The review by Della Pepa *et al*.[9] provides an overview of the available state-of-the-art alternatives to conventional treatment and the most promising new drug combinations. Although the authors recognize that a general alternative to standard treatment is not yet available, there are

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multiple strategies that can be evaluated in selected patients based not only on clinical conditions but also on tumor histology and molecular features. The awareness that ovarian cancer comprises several different subtypes with different molecular landscapes, the improved understanding of the genomics of these subtypes and the development of new active biologic agents hold the promise of improving ovarian cancer outcomes[10]. The shift in trial design toward restricting eligibility criteria rather than testing agents in unselected populations provides a potential opportunity for improved therapy in targeted populations[11], as it has been observed for poly(ADP-ribose) polymerase (PARP) inhibitors[12]. The importance of retrospective analysis on newly designed clinical trials has also been confirmed by two recent reports on the impact of patient gene expression data on the response to the anti-angiogenic agent Bevacizumab[13,14]. Knowing how molecular subgroups may respond to different targeted therapeutics may help in predicting treatment benefits. Although new drug combinations, different treatment schedules, PARP inhibitors, and anti-angiogenic agents have already entered into clinical practice[9], others targeting agents are facing phase I clinical trials. The phosphatidylinositol 3 kinase (PI3K) pathway is one of the most frequently altered signaling pathways in cancer, including EOC. However, despite a sound biological rationale and encouraging preclinical data, trials with first-generation mammalian target of rapamycin (mTOR) inhibitors in EOC have been disappointing[10]. In this issue, Cheaib *et al*.[15] discuss the relevance of the PI3K/Akt/mTOR pathway in EOC and provide an up-to-date review of the clinical trials for novel PI3K inhibitors alone or in combination with cytotoxic agents and novel therapies in EOC. Considering the inherent genomic instability of EOC, which contributes to the development of resistance to chemotherapy, targeting the tumor microenvironment provides an important adjunct to molecular therapeutics and chemotherapy that are directed toward tumor cells. In addition to the positive results obtained so far by targeting tumor vasculature with Bevacizumab[9], a new anti-neoplastic drug, trabectedin, which acts both on cancer cells and on the tumor microenvironment, is now under consideration for the treatment of platinum-sensitive patients with recurrent EOC. Indeed, trabectedin not only inhibits the growth of cancer cells but also affects the tumor microenvironment by reducing the numbers of macrophages sustaining tumor growth. This mechanism of action is extensively described in this issue by López-Guerrero *et al*.[16], who also discuss how to identify biomarkers for the selection of patients who may largely benefit from trabectedin-based therapies.

The discovery of aberrantly expressed microRNAs (miRNAs) in EOC has defined new pathways in ovarian tumorigenesis and progression. miRNA expression profiles in biological fluids can be potentially used for the detection and surveillance of EOC; however, because miRNAs may also be involved in modulating drug sensitivity, the delivery of miRNA mimetics or antago-miRNAs may affect drug responses to conventional therapies. In this issue, Sun *et al*.[17] focus their attention on miRNAs regulating the epithelial-to-mesenchymal transition, a cellular reprogramming event during which cells dedifferentiate from a relatively rigid to a more flexible cell structure/morphology, thereby increasing their motility and ability to invade. The induction of this cellular plasticity is one of the initiating events of the cancer metastatization process, which is considered a main cause for cancer mortality.

EOC is a life-threatening disease, mainly because it is often diagnosed at its advanced stage. Early-stage disease, however, although difficult to diagnose, is considered curable in the majority of cases. Nevertheless, only in rare cases can the patients' fertility be spared; this results in a consequent negative psychological impact. However, in most cases, the main cause of infertility in cancer patients is the treatment rather than the disease; therefore, consultation for fertility preservation should take place before cancer treatment. Nonetheless, a significant number of patients worldwide are not given information regarding the detrimental effects of cancer treatments on fertility or the possibilities to preserve fertility. Here, Sigismondi *et al*.[18] reports the experience of a single center regarding fertility preservation and indicates that oncofertility issues should be part of the routine evaluation of women of reproductive age who were recently diagnosed with cancer.

Given the difficulty of diagnosing and treating EOC, an effective multidisciplinary team, including specialized gynecologists, surgeons, and oncologists, should be supported by molecular pathologists and biologists, with the additional support of reproductive gynecologists, to improve patient outcomes.

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