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Ovarian cancer: Novel molecular aspects for clinical assessment

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ABSTRACT

Ovarian cancer is a very heterogeneous tumor which has been traditionally characterized according to the different histological subtypes and differentiation degree. In recent years, innovative molecular screening biotechnologies have allowed to identify further subtypes of this cancer based on gene expression profiles, mutational features, and epigenetic factors. These novel classification systems emphasizing the molecular signatures within the broad spectrum of ovarian cancer have not only allowed a more precise prognostic prediction, but also proper therapeutic strategies for specific subgroups of patients. The bulk of available scientific data and the high refinement of molecular classifications of ovarian cancers can today address the research towards innovative drugs with the adoption of targeted therapies tailored for

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single molecular profiles leading to a better prediction of therapeutic response. Here, we summarize the current state of knowledge on the molecular bases of ovarian cancer, from the description of its molecular subtypes derived from wide high-throughput analyses to the latest discoveries of the ovarian cancer stem cells. The latest personalized treatment options are also presented with recent advances in using PARP inhibitors, anti-angiogenic, anti-folate receptor and anti-cancer stem cells treatment approaches.

1. Introduction

Ovarian cancer (OC) is a common gynaecologic malignancy at high incidence in Europe and North America (Siegel et al., 2015) which primarily occurs in post-menopausal age (Ledermann et al., 2013) and is often diagnosed as advanced disease (Jemal et al., 2009).

Major studies of the past few years proved that OCs prevalently include epithelial tumors at high heterogeneity with different histological subtypes as well as genetic and biological features leading to peculiar clinical evolution (Jonsson et al., 2014). Therefore, in relation to histotype, pathogenesis, tumor growth, prognosis and response to therapy, OCs have been grouped in type I (low-grade) and type II (high-grade) with specific peculiarities. Type I, are low-grade (LG) tumors that represent 25% of OCs and include serous (SC), endometrioid (EC), clear cell (CCC), and mucinous (MC) carcinomas that derive from pre-neoplastic lesions like dysplastic conditions or endometriosis and usually show slow growth with a variable resistance to conventional chemotherapy. By contrast, type II high-grade (HG) SCs arise *de novo* from the walls of ovarian cysts, the ovarian surface, or fallopian tube and represent more than 70% of all OCs. These latter tumors show a peculiarly aggressive behavior since are diagnosed in advanced stage and are characterized by high sensitivity to chemotherapy. To this regard, besides the anti-angiogenic treatments that have definitely improved the progression-free survival in patients with stage III–IV OCs, HGSCs are initially sensitive to platinum-based chemotherapy, but tend to relapse shortly after an initial response, in approximately 70–80% of cases, while the surgical cytoreduction is considered the primary treatment.

Novel insights in understanding the pathogenesis of OCs have recently been provided by several studies defining their molecular characterization. In 90% of patients, OCs originate as sporadic tumors and in absence of a family history of the disease, often associated with spontaneous somatic mutations of *TP53* (Cancer Genome Atlas Research, 2011; Hollis and Gourley, 2016) while a particular importance has been ascribed to both germline and somatic mutations of *BRCA1* and *BRCA2*. In carriers of germline *BRCA1/2* mutations, *TP53* is somatically mutated during the malignant transformation and the wild-type *BRCA* allele is lost resulting in survival during telomere crisis, genetic instability, and homozygous deficiency in homologous DNA repair (Christie and Oehler, 2006; Daly et al., 2014). These evidence provided useful suggestions to introduce novel drugs as PARP inhibitors in the treatment of OCs with inherited or somatic mutations of *BRCA* genes, in addition to the anti-angiogenic treatment primarily devoted to counteract the high vasculogenic behavior of these tumors in their progression.

However, other intracellular molecular pathways are critically involved in OC pathogenesis and extensive analysis derived from TCGA studies showed that their derangements may classify at least four distinct genomic profiles of HGSC, namely *mesenchymal, immunoreactive*, *proliferative*, and *differentiated.* This novel molecular characterization of OCs may be useful for clinical purpose for proper adoption of current treatments of these tumors and here we review the recent knowledge on their molecular typing to provide a tool for clinicians for the modern interpretation of OCs.

This review revisits and correlates the common histologic patterns of OC with recently assessed molecular profiles to cluster the phenotype occurrence of ovarian cancers. It also includes a potential assessment of their genomic profiles as derived from the extensive literature, with respect to the therapeutic responses to anti-angiogenetic drugs, in order to potentially translate the use of genomic analysis to clinical management for predicting the response to treatment. The latest personalized treatment options are also presented with recent advances in PARP inhibitors, anti-angiogenic, anti-epigenetic factors, anti-folate receptor and anti-cancer stem cells approaches.

2. Major clinical aspects of OC

In agreement with the pathogenic hypothesis supporting a relationship between repeated injuries within the ovarian epithelium and OC occurrence (Fathalla, 1971), the reproductive history significantly correlates with the OC risk in women and early menarche, late menopause and nulliparity as well as obesity are usually considered risk factors for this cancer. A major risk factor, however, is provided by the family history of OC in a first degree relative although most ovarian malignancies are not associated with germline mutations and cannot be considered as hereditary (Ledermann et al., 2013). On the contrary, the short reproductive life span and utilization of oral contraceptives are apparently protective factors against OC.

Major challenges for both Oncologists and Gynecologists include the lack of an effective screening for OC prevention. At stage I as earliest disease, this cancer may develop in one or both ovaries and the patients are often symptomless or complain vague illness. However, once cancer cells spread to other organs in the pelvis, namely at stage II or III when diffused into the abdominal cavity, clinical signs are usually represented by abdominal pain and distension as well as early satiety and constipation. Several patients may also present uro-gynecological symptoms as vaginal bleeding and urinary frequency. This is why a majority of patients (about 60%) are frequently diagnosed with stage III OC, whereas in stage IV as advanced disease the OC is characterized by cancer cell proliferation inside abdominal organs as liver and spleen (Fig. 1), and spread to extra-abdominal sites as lungs, bone, and brain. Once the cancer spreads across the diaphragm and causes pleural effusion, dyspnea and other respiratory symptoms are frequent. Timely diagnosis is correlated to a better outcome with 10-year survival rate dropping from 55% to 15% in case of advanced-stage disease (Narod, 2016).

The two main steps for the early OC treatment include both debulking surgery and platinum-based intravenous chemotherapy, especially in women at high risk of recurrence. The American National Comprehensive Cancer Network (NCCN) recommends the neo-adjuvant chemotherapy in selected patients with high-volume disease and comorbidity, although the tumor shrinkage is variable and chemoresistant cells are usually incompletely removed by surgery (Morgan et al., 2013). Another therapeutic option is represented by intraperitoneal chemotherapy for women with small size tumor, namely less than 1 cm, or no residual disease, after surgery. Despite the promising results described by Tewari et al. (Tewari