Clinical Oncology xxx (2018) 1–10

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Personalising Treatment for High-Grade Serous Ovarian Carcinoma

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Received 22 May 2018; accepted 22 May 2018

Abstract

Ovarian cancer is a heterogeneous group of cancers that differ by cell of origin and genomic features. High-grade serous ovarian cancer (HGSOC) is the commonest histiotype and is characterized by extreme genomic complexity and dysregulation of DNA damage repair pathways, particularly homologous recombination deficiency. New insights from molecular profiling into homologous recombination deficiency now offers the credible possibility of personalizing treatment choices for women with HGSOC using poly(ADP-ribose) polymerase inhibitor (PARP) therapy. Although the presence of tumour infiltrating lymphocytes (TILs) in the microenvironment is associated with improved survival in HGSOC, the role of anti-angiogenic and immune checkpoint inhibitor therapy remains unclear. PARP inhibition combined with immunotherapy is an exciting combination strategy for future therapeutic development for women with advanced HGSOC.

Keywords: Genomics; high-grade serous ovarian cancer; PARP inhibitors

Introduction

About 7400 women are diagnosed with ovarian cancer every year in the UK and 4100 die from their disease [1]. Despite incremental trials of combination chemotherapy and bevacizumab, overall survival for patients with advanced disease has not improved in the last two decades. Indeed, the mortality–incidence ratio for ovarian cancer, which is a robust measure of cancer outcomes, is only just less than that of liver, pancreas, oesophageal, brain and lung cancer. High-grade serous ovarian carcinoma (HGSOC) accounts for most of these cases and their mortality. New medicines targeting aberrant DNA repair in HGSOC now offer significant opportunities for improving outcomes. This review will focus on the major clinical challenges, including rapid identification of patients with homologous recombination deficiency and earlier use of poly (ADP-ribose) polymerase (PARP) and immune checkpoint inhibitor therapy.

Genomic Explanations for Chemosensitivity and Acquired Resistance

The defining genomic characteristic of HGSOC is profound genetic heterogeneity and very high numbers of structural changes, particularly copy number aberrations. Classical oncogenic mutations are rare and other mechanisms, including gene amplification, are thought to drive tumour biology. Most mutations cause loss of function effects, many in classical tumour suppressor genes. *TP53* mutation is a ubiquitous event in HGSOC and is diagnostically important as it excludes a diagnosis of low-grade serous carcinoma [2,3].

A significant proportion of this genetic heterogeneity may be explained by loss of DNA repair mechanisms, particularly loss of homologous recombination (HRD). Germline and somatic mutations of *BRCA1* and *BRCA2* genes are present in about 20% of ovarian cancers [4]. A further 11% of cases have methylation of *BRCA1*, which epigenetically abrogates BRCA1 protein expression. The TCGA analysis [4] suggested that up to 50% of all HGSOC cases have HRD based on additional defects in *PTEN* (6%), *RB1* (4%) and *EMSY* (6% amplification) (Figure 1). Platinum resistance was

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https://doi.org/10.1016/j.clon.2018.05.008
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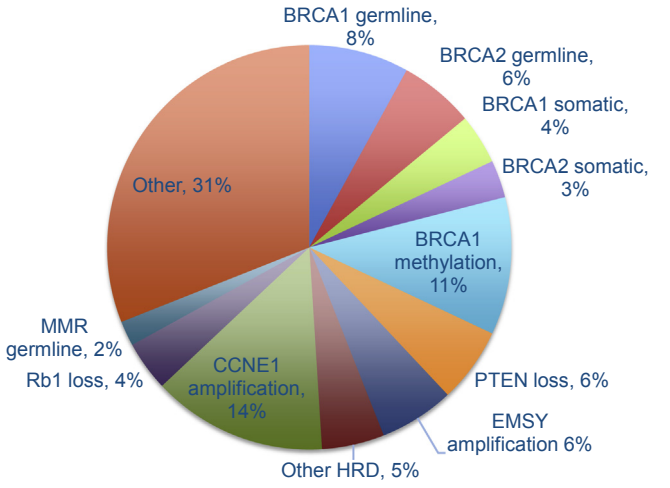

Fig 1. Frequent alterations in high-grade serous ovarian cancer, including point mutations, amplification or losses (adapted from [4]). Germline and somatic mutations of *BRCA1* and *BRCA2* are found in about 20% of ovarian cancers. Up to 50% of ovarian cancers have a deficient homologous recombination based on defects found in *PTEN*, *RB1* or *EMSY* genes.

associated with *CCNE1* amplification, which encodes an essential protein of the cyclin-dependent kinase domain, required for the normal function of the cell cycle, and was mutually exclusive with *BRCA1/2* loss.

The critical role of *BRCA1* and *BRCA2* mutation in determining platinum sensitivity is underscored by the observation that secondary or revertant mutations in *BRCA1*, *BRCA2* and other HRD genes can induce resistance to therapy [5–8]. Whole genome sequencing of post-mortem samples from germline cases who developed platinum-resistant disease showed that reversion of germline mutations of *BRCA1* and *BRCA2* genes can occur at multiple different DNA positions in different metastatic lesions within the same patient [9]. In addition, cases with methylated *BRCA1* can undergo secondary loss of methylation events to re-express BRCA1 protein.

Molecular characterisation of primary platinum-resistant cases has not been extensively carried out, although *CCNE1* amplification has been implicated as a negative predictor of response. *CCNE1* encodes the cyclin-E1 protein that is a vital component for normal functioning of the G1/S cell cycle transition. Whole genome sequencing of patients with acquired platinum resistance showed that *CCNE1* amplification was the main structural modification associated with resistance to chemotherapy [9]. Platinum resistance was also associated with a 1.6× increase in structural variants compared with primary tumours. Other potential mechanisms of resistance observed in this series included upregulation of the *ABCB1* gene, which encodes the multidrug resistant protein 1 (MDR1) and increases the cellular efflux of taxanes.

Although these recent studies provide valuable information regarding tumour heterogeneity and chemotherapy resistance, research in acquired or primary chemoresistance of HGSOC remains a priority. Although oncogenic mutations in HGSOC are much less frequent than in other malignancies, some identified mutations might be targetable (*EGFR*, *PIK3CA*, *PDGFR*, *KIT*, *HER2*) if the appropriate populations can be identified [10,11].

Increasing Dose Intensity of Chemotherapy

As the pattern of metastatic spread in HGSOC shows strong specificity for the peritoneal surfaces, various approaches have tested whether dose intensification with chemotherapy can improve outcomes. The peritoneal specificity for HGSOC metastasis may be explained by its unique biology. The secretory cell of the fallopian tube is the cell of origin for HGSOC [12,13]. Distant metastasis from the distal fallopian tube to the entire abdomen rapidly occurs as malignant cells detach early and there is no physical barrier preventing carcinoma cells shedding into the pelvis. Passive physiological movements of peritoneal fluid and migration of cells into the abdominal cavity also facilitate dispersion and implantation over the entire peritoneum.

Three randomised trials have shown that intraperitoneal chemotherapy improves outcomes after debulking surgery for advanced ovarian cancer [14–18]. In addition, a Cochrane meta-analysis showed that intraperitoneal–intravenous administration of chemotherapy is associated with a 21.6% decrease in the risk for death. However, widespread implementation of intraperitoneal therapy has not occurred owing to significant treatment toxicity and the difficulty of managing indwelling catheters. Shorter exposure to intraperitoneal chemotherapy using hyperthermic intraperitoneal chemotherapy may be a compelling alternative, as overall survival was significantly improved in a randomised trial of 245 stage III patients without increased grade 3 or 4 toxicity [17].

Feasibility of Germline Testing for *BRCA1/2*

International guidelines recommend that all patients diagnosed with an epithelial ovarian cancer, including carcinomas of the fallopian tube and peritoneum, are offered genetic *BRCA* testing regardless of age [19]. Ideally, genetic testing should be offered at diagnosis, but patients can be referred at any stage and even after the completion of treatment and during follow-up. If germline testing is negative, tumour tissue should be tested for somatic mutations, which may account for about 5% of the 20% of *BRCA1/2* mutations, thus helping to identify more patients that could benefit from PARP inhibitor therapy.

In the UK, the National Institute for Health and Care Excellence (NICE) recommends *BRCA1/2* mutation testing in all ovarian cancer patients with a risk of 10% or more [20]. A cost–benefit study showed that by testing all ovarian cancer patients in the UK for *BRCA* mutation, there would be 141 fewer new cases of ovarian cancer, 142 fewer new cases of breast cancer and 77 fewer deaths [21]. The feasibility and acceptability of offering unselected *BRCA1/2* testing to all newly diagnosed women with ovarian cancer has been formally tested in a prospective study [22,23]. Unselected

Please cite this article in press as: Cojocaru E, et al., Personalising Treatment for High-Grade Serous Ovarian Carcinoma, Clinical Oncology (2018), https://doi.org/10.1016/j.clon.2018.05.008