Review Article

Efficacy of PARP Inhibitors, Bevacizumab and Platinum Based Chemotherapy in Treatment Regimen of Patients with BRCA1/2-mutated Ovarian Cancer

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Ovarian cancer is a frequent gynaecological malignancy that can affect a wide variety of tissue types. 90% of them are epithelial cell types while the remaining ovarian tumours are non- epithelial. Rare pathological forms including carcinosarcoma and small cell cancer also exist. The molecular alterations, clinical manifestations, and therapeutic outcomes of ovarian cancer vary depending on the tissue type. However, the prognosis for ovarian cancer in various tissues is generally poor, and the rare carcinosarcoma, which contains both sarcomatous and epithelial components, also has a very bad prognosis. [1] Six to sixteen percent of patients have BRCA1/2 germline mutations, which are the greatest known genetic risk factors for epithelial ovarian cancer.[2,3] Among cervical, uterine, and other gynaecological cancers, ovarian cancer has the highest mortality rate in developed countries. [4] The prognosis for primary peritoneal, fallopian tube, and ovarian malignancies is poor, and over 80% of cases recur. [5] Serous, endometrioid, clear cell, and mucinous histologies are among the various histologies that reflect epithelial ovarian cancer (EOC), and each has unique genetic and clinical traits. [6]

Patients with these tumors have historically received multidisciplinary treatment that includes prolonged surgery, cytotoxic anticancer drugs, and anti-VEGF antibodies. [7-9] The majority of patients are diagnosed with advanced disease, which is linked to a low overall survival rate and a high likelihood of recurrence.[10]

Seventy percent of patients are diagnosed at an advanced stage, seventy percent relapse within two to three years, and only thirty to forty percent survive for five years. The majority of patients have an insidious onset. In the context of comprehensive management, initial treatment is especially important for patients with recently diagnosed advanced ovarian cancer. An important part of the overall treatment of ovarian cancer is maintenance therapy. When bevacizumab, an antiangiogenic agent, is added to first-line platinum-based chemotherapy and then bevacizumab maintenance therapy, patients with stage III or IV ovarian cancer who have had primary debulking surgery have a better progression-free survival (PFS) than those who receive chemotherapy alone. [7] PFS has been demonstrated to be improved in patients

with ovarian cancer receiving maintenance treatment with poly(ADP-ribose) polymerase (PARP) inhibitors in addition to bevacizumab, both in first-line and recurrent situations. [5,11-13]

With its developing clinical evidence, poly ADP ribose polymerase inhibitors (PARPi) have often amazed the globe. [14] By trapping PARP on the DNA strand and causing replication stress, which stops the replication fork, PARP-is accelerate the buildup of DNA damage. Therefore, especially in cells with homologous recombination (HR) impairment, imprisoned PARP can result in replication fork collapse and ultimately cell death [15]. The US Food and Drug Administration (FDA) has approved three PARPis—olaparib, niraparib, and rucaparib—for use as maintenance therapy in patients with OC. [16] For platinum-sensitive, relapsed, BRCA1/2-mutated ovarian cancer that has responded completely or partially (CR/PR) to platinum-based chemotherapy, olaparib, niraparib, and rucaparib have been licensed in Europe for maintenance and third-line treatment, respectively. Platinum-based drug sensitivity is thought to be an important clinical biomarker for predicting the response to PARP-is in malignancies, even though a response to platinum-based agents does not guarantee a response to PARP-is [17] Unfortunately, during maintenance therapy with PARP-is, a significant number of patients experience disease progression. The most well-known and prevalent mechanism is the restoration of HR pathway function, which leads to an acquired resistance to PARP-is and platinum-based drugs.[16,18]

Within two years of starting treatment, over 75% of patients relapse [19] , and patients who have platinum-sensitive relapse are advised to receive platinum-based chemotherapy again until platinum resistance. However, if platinum resistance develops, the prognosis is quite bad, with a median overall survival of about 12 months, and the response rate to successive therapy is only roughly 10–25%. [20] Treatment with poly (ADP-ribose) polymerase inhibitors (PARPi) produced a notable response based on "synergistic lethal effects." [21] There are currently a number of PARP inhibitors available for the clinical treatment of ovarian cancer patients. [22] Furthermore, some research has contrasted the distinctions between platinum-based chemotherapy and PARPi monotherapy. The ongoing OPAL-C trial is investigating the superiority of PARPi monotherapy over Platinum-Taxane in neoadjuvant chemotherapy for patients with homologous recombination deficiency (HRD)-positive tumors.[23] The NGR-GY004 study, for instance, found that the median PFS of PARPi monotherapy was superior to platinum-based chemotherapy for platinum-sensitive recurrent ovarian cancer patients with BRCA1/2 mutations. [24] Nevertheless, the overall survival results have not yet been published. Due to a higher risk of death in patients receiving more than three lines of chemotherapy, the FDA has revoked many indications for PARPi monotherapy. [25]

Hence it is concluded that PARPi monotherapy has more efficacy than other treatment regimens although further information is required to determine whether PARPi monotherapy might improve survival for individuals who have already received two lines of chemotherapy in the past.

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