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Review Article

PARP inhibitors: Clinical utility and possibilities of overcoming resistance

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HIGHLIGHTS

- Indications and toxicities of clinically applicable PARP inhibitors
- Novel biomarkers to predict PARP inhibitor response
- Molecular mechanisms of PARP inhibitor resistance
- Managing PARP inhibitor resistant ovarian cancer

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ABSTRACT

PARP inhibitors represent a major breakthrough in ovarian cancer care. Almost half of all ovarian cancers have deficiencies in the homologous recombination (HR) DNA repair pathway, namely BRCA1/2 mutations. Given the limited therapeutic options for recurrent ovarian cancer patients there has been a significant effort to develop novel therapies to exploit DNA repair deficiencies. In 2005 and 2006, inhibiting PARP enzymes was first observed to be highly effective against cancers with HR deficiencies. PARP inhibitors are being utilized in the clinic to manage recurrent ovarian cancers that display defects in the HR repair pathway. However, PARP inhibitors also show significant clinical benefit in patients without HR deficiencies. There are currently three FDA-approved PARP inhibitors for recurrent ovarian cancer and an additional two PARP inhibitors being evaluated in late stage clinical trials. Given the expanding clinical use of PARP inhibitors and the high likelihood of acquired resistance, there is a significant need for clinical strategies to manage PARP inhibitor resistant disease. This review will examine PARP inhibitors in the context of: indications and toxicities, novel biomarkers to predict response, targeted-therapy resistance, and potential approaches to manage resistant disease.

Contents

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1. Introduction

The development of Poly(ADP-ribose) polymerase inhibitors (PARPi) for therapy is a successful application of bench-to-bedside medicine and nowhere is the impact more appreciated than in the treatment of advanced and recurrent ovarian cancer. Between December 2014 and July 2017, three PARPi (olaparib, rucaparib and niraparib) were approved for the treatment of recurrent ovarian cancer and approvals for additional disease indications are anticipated. In the coming years the focus will be to: define the clinical use of PARPi, examine the possibility of retreatment, and confront the inevitable challenge of PARPi resistance. This review will familiarize the reader with the science underlying PARP inhibition in ovarian cancer, the current approved indications for PARPi, the difference between available therapeutics, and finally introduce the concept of PARPi resistance and potential management strategies.

1.2. Ovarian cancer and homologous recombination repair

Homologous recombination (HR) DNA repair is involved in repairing DNA double strand breaks and functions to limit genetic instability, a hallmark of cancer. Notably, up to 50% of all high grade serous ovarian cancers (HGSOC) have detectable germline and somatic mutations or epigenetic silencing via DNA methylation of genes (e.g. *BRCA1/2*) involved in HR DNA repair [1]. *BRCA1/2* mutation and silencing occurs in approximately 30% of HGSOC and frequently results in diminished HR activity. HR DNA repair is critical in the accurate repair of DNA following double strand breaks (DSB). HR repair is cell cycle dependent and is most active in the S to M transition [2] [Reviewed in [3,4]]. Briefly, DNA DSBs promote the recruitment of nuclease complexes, such as Mre11/Rad50/Nbs1 (MRN) and Retinoblastoma-Binding Protein 8 (CtIP), to the sites of damage, which leads to Ataxia telangiectasia mutated (ATM) and ATM- and RAD3-related (ATR) mediated phosphorylation of histone 2Ax (γH2Ax). A BRCA1/2/PALB2-containing complex is then recruited to sites of DSBs, which facilitates the loading of a recombinase, RAD51, onto the MRN/CtIP processed DNA strands. RAD51 then plays a critical role in forming Holliday junctions (HJ) with homologous regions on the sister chromatid. HJs are then resolved through a combination of DNA helicases, nucleases, and topoisomerases, resulting in the DNA being unwound and repaired in a highly accurate fashion.

In 2005 and 2006 publications in *Nature*, *Cancer Research* and *Cancer Biology and Therapy* described inhibition of alternate DNA repair pathways, including base excision repair (BER) and single-strand break repair (SSBR), via PARP selectively promoted lethality in HR deficient (BRCA1/2-mutated) cancers [5–7]. There are 17 distinct PARP enzymes, however only PARP1-3 play a role in BER. PARPs function by binding to single strand DNA breaks and undergoing auto-modification (auto-PARylation) via polymerizing branched negatively charged poly(ADP-ribose) polymers. The PARP mediated increase of a localized negative electrostatic charge is hypothesized to recruit DNA repair enzymes [Reviewed in [8]]. In the context of PARP inhibition, the lack of a functional HR repair pathway leads to irreparable single-strand breaks, replication fork stalling, accumulation of DNA DSBs, and catastrophic mitotic failure [5]. Independent of BRCA1/2, mutations in other HR repair molecules, such as *PALB2*, *ATM*, *BRIP1*, *CHEK2*, and *RAD51*, are now appreciated to convey increased PARPi sensitivity [9–12]. However, one of the approved PARPi, niraparib, was observed to have a significant clinical benefit in patients without detectable mutations in HR components, which indicates that in addition to HR genes there are other potential predicative biomarkers and mechanisms that contribute to PARPi sensitivity. The next section will examine the status of current PARPi, including both Food and Drug Administration (FDA)-approved therapeutics and those in clinical development (Fig. 1).

2. PARP inhibitors

2.1. FDA-approved

FDA approval of olaparib (AstraZeneca) was announced on December 2014 for monotherapy of germline *BRCA* (g*BRCA*) mutated ovarian cancer after third line therapy based on a nonrandomized study of olaparib monotherapy in g*BRCA* mutated cancers [13,14]. A subgroup of patients in this study was extracted for FDA submission and included 137 recurrent ovarian cancer patients with measurable disease after three or more lines of chemotherapy. Patients received 400 mg (8 capsules) olaparib twice daily until progression or intolerable toxicity. Retrospective *BRCA1/2* mutation analysis of 61 treated patient samples demonstrated high concordance with initial testing 96.7% (59/61; 95% CI, 88.7–99.6) [14]. RECIST 1.1 objective response rate was 34% (range 26%–42%) with a median duration response of 7.9 months (5.6–9.6 months) in this heavily pretreated group. Toxicities were similar in the entire group and in ovarian cancer patients specifically and included nausea and fatigue in over 60% of patients. Most toxicities were managed by dose interruption and dose reduction. More recently, olaparib maintenance therapy of recurrent platinum sensitive g*BRCA* mutated ovarian cancer in the Phase III SOLO2/ENGOT-Ov21 trial showed a dramatic improvement in progression-free survival (PFS) of 19.1 months versus 5.5 months (hazard ratio [HR] = 0.3, 95% confidence interval [CI]: 0.22–0.41) in treated patients using a 300 mg (two tablets) twice daily formulation [15]. Overall survival has been not yet been calculated in SOLO2 study. The SOLO2 findings confirmed Study 19, which had demonstrated a PFS benefit and a non-significant survival benefit and led to European and not United States FDA approval for maintenance olaparib. The US FDA had at that time declined approval based on lack of survival benefit [16,17]. Nausea, fatigue, vomiting and anemia were all more common with olaparib than placebo but the majority of adverse events were grades 1 and 2. A clinical trial to evaluate maintenance olaparib following first line platinum-based chemotherapy (SOLO1, NCT01844986) is on-going.

FDA approval of rucaparib (Clovis Oncology) was announced on December 19, 2016 based on the results of two multicenter randomized open label trials, Study 10 and ARIEL, parts 1 and 2 [18,19]. The two phase (I/II) Study 10, reported in early 2017, enrolled 56 patients with

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