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The Recent Advances of PARP Inhibitors in the Treatment of Cancer

Li Dongyue

Hong Kong Baptist University,224 Waterloo Road, Kowloon Tong, Hong Kong

101152@yzpc.edu.cn

Abstract. This article introduces the discovery and research progress of Poly-ADP-ribose polymerases (PARP) inhibitors. The catalytic sites of PARP1 and PARP2 are designed as competitive inhibitors of NAD+, so that DNA single-strand repair cannot be completed through the combination of PARP1 and NAD+.PARP is quite crucial in the process of DNA single-strand damage repair. Inhibiting PARP function will interfere with normal DNA repair and induce DNA damage accumulation into more serious double-strand breaks through replication fork folding. Homologous recombination (HR) repair is the main way of double DNA repair, which needs to be mediated by key proteins BRCA1 and BRCA2. In the same way, blocking the single chain repair and HR pathway, the synergistic lethal effect produced by combining these two nonlethal mechanisms, namely the synthetic lethality mechanism, provides a theoretical basis for PARPi. Olaparib was approved for clinical by FDA for the first time through this mechanism. The efficacy of Olaparib in the four approved indications was confirmed in clinical trials. It can benefit patients by improving the progress-free survival or objective response rate, and its safety is better than chemotherapy drugs. Even more clinically valuable combination of platinum and chemotherapy drugs has been proven to benefit significantly. At last, the paper pointed out the development emphasis and prospect of PARP inhibitors in the future.

Keywords: PARP inhibitor, Olaparib, BRCA mutation, Synthetic lethality, cancer

1. Introduction

PARPs are a series of DNA repair enzymes essential for mending single-strand DNA damage and maintaining chromosomal and genomic stability [1]. In total, there are 17 PARP family members in the species studied. PARP1 is the most abundant one, which accounts for more than 90% of PARP function and is pivotal for maintaining genome integrity [2][3]. When mending DNA single-strand breaks (SSB) and double-strand breaks (DSB), PARP-1-mediated base excision repair (BER) works as a vital mediator. PARP1 requires NAD+ to form the key component of poly ADP ribose PAR to summon DNA repair machinery for repairing the SSB of DNA.

During DNA replication, unrepaired DNA SSB can raise the DSB of DNA, while homologous recombination (HR) is the most reliable approach to repair DSB [4]. The failure of HR eventually results in cell death. The breast cancer susceptibility gene (BRCA), a typical tumor suppressor, is responsible for executing HR repair. When PARP-mediated SSB repair malfunctions, the damaged DNA becomes DSB, which relies on BRCA-mediated HR for repair.Therefore, if the loss-of-function of BRAC coincides with inhibition of PARP, DNA damage cannot be repaired, and cell apoptosis

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occurs. This kind of mechanism is known as "synthetic lethal." Therefore, inhibiting the function of the PARP enzyme becomes the key to reaching the “synthetic lethal" in BRAC mutated cancer cells. PARP-1 uses NAD+ as a substrate. Therefore, PARPi is mostly designed to mimic the structure of NAD+, competing with it, binding to the catalytic domains of PARP1/2, and restraining PARylation activity.

In the first in vitro study of PARP inhibitor, the tumor cell lines lacking BRCA1 and BRCA2 showed an over 1000 times more sensitive effect than sufficient [5]. Several in vivo studies in BRCA1 and BRCA2 deficient mice showed that, compared with either drug alone, the combination of Olaparib (PARP inhibitor) and platinum salt extended median overall survival (OS) [6]. Besides, Olaparib can be used as a treatment in carboplatin-resistant tumors and can increase median survival by 43 days. Therefore, employing the "synthetic lethal" mechanism of DNA repair gene mutation is feasible for precisely treating BRCA mutated cancer. Due to the selectivity of Olaparib in inhibiting PARP1/2, the supporting clinical evidence of PK and PD, and the convenience of the oral administration route, Olaparib became the first PARP inhibitor clinical trial with that feature [7][8]. Two clinical researches determined the maximum tolerated dose (400mg twice daily) of Olaparib and found it displayed durable objective antitumor activity for a BRCA1 or BRCA2 mutated tumor [9].

With the advances in science and technology, antitumor treatment has continuously progressed from conventional therapies to precision-targeted methods. Traditional anti-cancer therapies include surgery, radiotherapy, and chemotherapy. However, these classes of therapies have certain disadvantages, and most of them are used for early-stage tumors.

Surgical operation may produce a series of complications leading to high risk, even though some surgery can promote growth factors to regenerate blood vessels, repair tissues, and inhibit cancer growth [10][11]. Radiotherapy treats cancer and also induces cancer. Studies have confirmed that radiotherapy to the primary lesion can promote tumor cell shedding, resulting in the occurrence of lung metastasis [12]. Radiation does not have true tissue specificity and selectivity when penetrating tissues, which can lead to some toxic and side effects in the late stage of radiation, thereby severely affecting physiological function quality of life and eventually causing death (such as pulmonary fibrosis). Although the efficacy of chemotherapy is remarkable enough to cure some tumors from the blood system, its non-target characteristics bring serious adverse reactions (AEs) to healthy tissues and organs and, in some cases, even accelerate the death of patients. Besides, tumors will produce drug-fast chemotherapeutic drugs and engender recurrence [13].

New antitumor therapy brought breakthroughs in antitumor treatment, thus effectively improving patients' quality of life. As a new therapy, small molecules targeted at antitumor drugs, such as protein kinase, epigenetic regulatory protein, DNA damage repair enzyme, and proteasome, are praised for their nonspecific toxicity and less circulatory toxicity. Applying the DNA damage repair enzyme's target is precisely exploiting cancer cells' genomic instability to counteract cancer. Several antitumor drugs of this class have been approved for the market, mainly targeting PARPs for the precise treatment of cancer [14]. Several clinical trials have shown a lower value of AEs and toxicity in the patients cured with PARP suppressor compared with chemotherapy [15][16]. For instance, chemotherapy continues to be one of the most prevalent treatment options for patients with HR-negative and human epidermal growth factor receptor-2 (HER2)-negative breast cancer. Triple-negative breast cancer is the name given to this type of malignancy (TNBC). However, these patients still have a fairly poor prognosis. Due to the greater incidence of BRCA1 mutations in patients with TNBC and the high sensitivity of PARP inhibitors to BRCA mutant cells, PARP inhibitor medicines are being evaluated in preclinical and clinical research for the treatment of BRCA gene mutation solid tumors in TNBC. Pharmacodynamic studies in an important Phase I trial revealed 90% or even higher suppression of PARP in tumor tissue and peripheral blood mononuclear cells as compared with reference line values in BRCA-mutated patients, who are advised to take at least 60 mg of Olaparib twice daily [17]. Therefore, PARP inhibitors possess high therapeutic value in terms of safety for BRCA mutation patients.

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2. The efficacy of PARP inhibitors in cancers

In the following sections, we focus on the review of recent advances of the efficacy of PARPs in ovarian, breast, prostate and pancreatic cancer.

2.1. Ovarian cancer

Studies show ovarian cancer is the fifth cause of cancer deaths in developed countries and the most malignant type among female reproductive cancers [18]. Due to the undetermined early screening tool and unclear signs and symptoms, ovarian cancer is typically not diagnosed until it evolves into stage III or IV. Therefore, in the previous two decades, ovarian cancer mortality has not greatly decreased, and the survival in the 5 years is only 46.2% [19]. Hereditary factors are primary risk factors for ovarian cancer, among which BRCA1 and BRCA2 genome sudden change contributes to the 0.2% incidence of ovarian cancer [20]. Several trials in phase III have confirmed the efficacy of Olaparib as a principal therapeutic drug for BRCA-associated epithelial ovarian cancer (EOC). The primary and secondary endpoint results in the SOLO-1 trial display that the median PFS (47-50 months) in the Olaparib group marks three years higher than that with placebos [21]. In a SOLO3 trial, Olaparib presented an exceptional benefit in BRCA mutated women compared to chemotherapy (paclitaxel, topotecan, PLD, or gemcitabine). As the primary endpoint, objective response rate (ORR) shown 72% in Olaparib versus, which 21% higher than chemotherapy versus (95%CI:1.40–4.58; p=0.002). Similarly, the result of Olaparib versus are also better then chemotherapy versus in median progression-free survival (PFS) (13.4 and 9.2 months; 95% CI: 0.35–0.70; $p < 0.001$) [22][23]. In addition, Olaparib significantly affects maintaining PFS and quality of life in platinum-sensitive ovarian cancer patients with late recurrence. Impressively, the median PFS in women with BRCA changed drastically; platinum-sensitive, high-value serious, or endometrioid EOC ameliorated sufficiently from 5.5 to 19.1 months between the control and Olaparib arm [24]. Besides, the toxicity (mostly grade1or2) of the drug is controllable. Adverse events, including fatigue, nausea, diarrhea et al., could be further controlled by dose reduction or dose interruption rather than suspending treatment.

2.2. Breast cancer

Breast cancer is prevalent in females worldwide and the second reason for cancer death in women cases following lung cancer. The mortality and incidence of breast cancer in women cases are 46.3 per 100000 and 13.0 per 100000, respectively, with an increasing trend [25]. The incidence in developed countries (except Japan) is greater than 80.0 per 100000, more than twice the rate in developing countries. Familial breast cancer cases account from 15% to 20% of all cases, of which genetic factors account for 5%~10%. Pathogenic mutations of BRCA1 and BRCA2 strains account for more than 30% of breast cancer caused by genetic factors. Therefore, BRCA1 and BRCA2 mutation carriers will have an increased risk of breast cancer throughout their lifetime [26]. In an OlympiAD study, Olaparib monotherapy was compared with the common therapy (eribulin, vinorelbine, or capecitabine in 21-day cycles) for patients with metastatic breast cancer with (HER2)-negative and a BRCA mutation in the germline [27]. In the primary endpoint assessment, compared with the standard-therapy group with a median PFS of 4.2 months, the Olaparib group saw a longer median PFS . Based on this medical research, the FDA awarded Olaparib a Priority Review. Furthermore, compared with the patients who took chemotherapy, those receiving Olaparib changed positively in health-related quality of life (HRQoL), with a mean change of 3.9 and 3.6 in the Olaparib and chemotherapy group separately,with a diversity of 7.5 points on the HRQoL [28]. On the security side, the Olaparib treatment group displayed less demand in suspending treatment due to toxicity and a lower value in adverse events (grade ≥3) compared with the chemotherapy arm. Several trials of combining PARP suppressors with platinum agents are progressing to generate the suggestion of the best treatment option, treatment order, or combining other therapeutic agents at an individually personal patient angle.

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2.3. Prostate cancer

Prostate cancer is the world's second most serious cancer among males and stands at the first two leading cancer-causing deaths in American men. Age-standardized mortality values by standard world population are 29.3/100000, and Age-standardized incidence values by standard world population are 7.6/ 100000. Among the 62 countries in the world, most countries have high age-standardized 5-year net survival in the range of 70%~100% [29]. Germline gene mutation is closely related to the risk and development of prostate cancer. Moreover, 9.8% of the patients (31/316) carry pathogenic gene mutations in 18 prostate cancer-related DNA repair genes, of which BRCA2 accounts for 6.3% and BRCA1 for 0.63% [30]. According to research published by the European Society of Oncology (ESMO), PARP inhibitor contributes positively to treating metastatic castration-resistant prostate cancer (mCRPC). In a large-scale prospective, randomized, open label discovered study; male mCRPC patients were screened for mutant genes. In the cohort of patients carrying ATM and BRCA1/2 gene mutations, the median PFS of patients receiving Olaparib was 7.4 months, while the median PFS of patients receiving enzalutamide or AAP targeted therapy was 3.6 months. Besides, compared with control, objective response rate and median time to pain progression in this cohort were all superior in the Olaparib arm [31]. Several mCRPC clinical research on the association of Olaparib and other drugs are ongoing. It includes the efficacy comparison between Olaparib combined with the abiraterone group and abiraterone combined with the placebo group, safety, and tumor activity of pembrolizumab combined with Olaparib [32]. Although different PARP inhibitors are better than the control group in PFS, OS, and ORR of mCRPC, there is a lack of intuitive comparison of different clinical medications. The toxicity is acceptable and consistent with the data on Olaparib in the previous period. Among them, anemia, neutropenia, and leukopenia are the most common hematological AES, with anemia (20%) and fatigue (12%) being the most common AES in grade 3 or above.

2.4. Pancreatic cancer

The malignant degree of pancreatic cancer is extremely high, and the mortality rate is close to the incidence rate. In 2020, the new cases and deaths that occurred in Asia were 47.1% and 48.1%, respectively, followed by Europe (28.3% and 28.4%) and North America (12.6% and 11.4%). Because of unknown etiology and unclear early diagnosis, this cancer doesn't have timely treatment. It is subject to a poor prognosis, with a one-year survival of 24% and five-year survival of only 9%. Even in developed countries, such as England and Italy, the survival in the 5 years of pancreatic cancer is less than 3%. In addition, 10%–20% of pancreatic cancer is related to genetic factors. Germline mutations, such as BRCA1 and BRCA2, can be inherited, resulting in familial aggregation of pancreatic cancer [33]. In a randomized, placebo-controlled, double-blind clinical research, the placebo group was set up to collect the efficacy of Olaparib. Patients with metastatic pancreatic cancer who carried BRCA mutations and had no progress from platinum chemotherapy were enrolled and received either xx or placebo until the disease progressed or an outrageous toxic reaction occurred. The trial results revealed that the Olaparib group's median time of progression-free survival (PFS) was extremely longer than that of the placebo group (7.4 months vs. 3.8 months). To put it another way, Olapanide can be used as a maintenance therapy for germline BRCA-mutated metastatic pancreatic cancer [34]. The results from other PARP inhibitor clinical trials indicated that the most common toxic reactions of 30 patients with pancreatic cancer after weekly Gemcitabine (1000 mg/m2) radiotherapy combined with Veliparib were gastrointestinal reactions, blood toxicity, and fatigue. No grade 5 toxic reactions were found. The median PFS and median OS were, respectively, 9.8 and 14.6 months [35]. According to pre-clinical trial findings, lupaparin can inhibit the growth of tumor cells by encouraging the infiltration of CD8+ T lymphocytes when paired with an anti-PD-1 antibody. The ovarian cancer mouse model with the BRCA1 gene mutation is also adversely impacted by the combination of PARPi and anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody.

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3. Conclusion

Several suppressors, such as Veliparib, Olaparib and Niraparib have been developed to synthesize lethal antitumor suppressors in the past. With convenient oral preparations and controllable toxicity, Olaparib is regarded as the first milestone in the effective treatment of germline BRCA-mutated metastatic solid tumors. Although according to the current research and development process, the pharmacokinetic and metabolic characteristics and clinical efficacy of Olaparib have been confirmed, the objective data of comparison between several similar drugs are still lacking. Besides, it is noteworthy that several trials (NCT04734665, NCT05101551, NCT03462342) of therapeutic strategies in PARP inhibitors are also progressing to provide the best usage for different clinical environments. Then, researchers are finding more universal homologous recombination mechanisms to break through the limitations of germline BRCA1/2 mutations. Therefore, PARP inhibitors will still be the center of preclinical and clinical research and development in the next few years.

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