

PARP inhibitors in various cancers

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Abstract: Poly (ADP-ribose) polymerase which is component of DNA repair processes, especially base excision repair (BER). SSBs in DNA are repaired by BER. SSBs aggregate and create double strand breaks when BER is suppressed, which inhibits PARP. Alternative repair processes, including as nonhomologous end joining and homologous recombination (HR), become more important as the frequency of DSBs increases. Patients with a faulty HR, such as BRCA deficient cell lines, are highly sensitive to BER pathway disruption. PARP inhibitors destroy cancer cells in BRCA mutant cancer cell lines more effectively than normal cancer cell lines. PARPi also enhance cytotoxicity by limiting repair in the context of SSB-generating chemotherapies. In a clinical environment, these two ideas were put to the test. Because of its shown efficacy as a single agent in BRCA1 or BRCA2 related ovarian or breast malignancies, as well as in conjugation with chemotherapy in triple negative breast cancer, interest in this class of drugs has risen in recent years. This article addresses the mechanism of PARPi and their involvement in different Cancers.

Keywords: PARP, BER, SSB, DSB, BRCA, Cytotoxicity, chemotherapy, Homologous recombination.

Introduction:

PARP is part of the base excision repair pathway, which is responsible for repairing SSD breaks [1]. PARP accelerate transference Adenosine diphosphate-ribose units to nuclear acceptor protein from intracellular nicotinamide adenine dinucleotide (NAD⁺) resulting in ADP-ribose polymers. The recovery of chemotherapy, radiation, and other treatments is dependent on this PARP-mediated process [2]. PARP proteins consist of two ribose moieties per unit of polymer and two phosphates. PARP1 and PARP2 are enzymes in the BER DNA repair pathway. The most famous PARP is PARP1 [3]. Three methods may control the activity of PARP-1: (1) competitive NAD binding (2) disruption of PARP-1's interactions with histones and (3) blockage of DNA binding PARP-1 [4]. This enzyme was discovered for the first time in 1963 [5]. Every PARP inhibitor currently under research is believed to inhibit both PARP1 and PARP2 activity. Despite the fact that nicotinamide's ability to inhibit PARP was originally discovered in 1971, the investigation of this type of agent has only lately become more comprehensive [6][7][8]. Nicotinamide analogues were among the first group of inhibitors to be developed. The antioxidant 3-aminobenzamide was discovered to inhibit PARP in the 1980s, but it was not deemed a selective agent since it was not as strong as newer inhibitors at the time [9][10]. 3-Aminobenzamide is a more powerful compound than the second generation. Under addition, third generation PARP inhibitors, which are currently in development, have higher PARP potency and selectivity as compared to inhibitors of previous generations [11].

Mechanism:

Individual PARPi:

PARP inhibitors were used to kill BRCA2-deficient cells in xenograft models and in vitro at concentrations that were safe for healthy cells [12][13]. When compare to wild-type cell, BRCA2- inadequate cells were 90 times more susceptible for the PARP inhibition [14]. In BRCA-deficient cells, PARP inhibition was shown to be three times more powerful than cisplatin cytotoxicity. Tumor development of mice treated with BRCA2-deficient cells was decreased with the PARP inhibitor Ku0058684, but not in healthy cells. [13].

PARP inhibitors with cytotoxic treatment:

In preclinical studies, PARP inhibitors have been shown to increase the effects of a variety of chemotherapy treatments. DNA methylating agents produce SSB, which necessitated the usage of BER. It was discovered that PARP1 conferred resistance to the effects of methylating chemicals, which was countered by the inclusion of a PARP inhibitor in the experiment [15]. The development of DSBs from the accumulation of SSBs may lead to overstimulation of the HR pathway and cell death. Deficient cells in mismatch repair (MMR) do not react well to the DNA methylating drug temozolomide, which is used to treat cancer (TMZ). MMR either corrects replication errors in wild-type cells or causes replication arrest or cell death when it is present [16]. AG14361, a PARP inhibitor and a sister drug to AG 14699, increased the impact of TMZ in mismatch repair inadequate cells more than it did in MMR-competent cells, indicating that AG14361 is more effective in MMR-deficient cells [17]. It was shown that using Veliparib and TMZ together, rather than TMZ alone, substantially reduced tumour growth in an orthotopic rat glioma model [18]. It was shown that when AG14361 was combined with topoisomerase inhibitors, the lethal concentration (LC50) was substantially reduced, and resistance to topoisomerase inhibition in BER capable cells was overcome [19]. XRCC1, a protein involved in the repair of DNA SSBs caused by exposure to ionising radiation and alkylating chemicals, may be overexpressed in the body, which can result in the development of resistance to camptothecins in certain cases. Paracetamol inhibits PARP, which interferes with XRCC1 recruitment to the DNA break site, thus overcoming this resistance mechanism. In a mouse xenograft, veliparib increased the interaction of carboplatin and cisplatin in a BRCA-mutated breast cell line, which was subsequently evaluated in a laboratory

environment [18]. Nicotinamide in conjunction with cisplatin improved the lifespan of an ovarian cancer xenograft mouse that had become resistant to cisplatin [20].

PARP inhibitors with ionising radiation:

PARP inhibitors increase radiation efficiency by suppressing BER. Following radiation exposure, DSBs increase in cells with weak PARP function. Radiation-resistant cells treated with radiotherapy (XRT) showed a 73% increase in tumour growth inhibition after exposure to AG14361 when compared to XRT alone [21]. Additionally, PARP inhibitors may improve XRT by impairing NF-B activity [22][23]. It was shown that adding veliparib to radiation treatment may increase survival time from 23 to 36 days in mice with colon cancer xenografts; more importantly, one of the mice in this research had a complete response (CR) [18].

PARPi in Cancers:

Ovarian Cancer:

By exploiting synthetic lethality that results in cell illness or death, PARPi exploit deficiencies in DNA repair. When PARPi is given to patients whose tumours have lost the ability to repair DS DNA disruptions through a homologous recombination process, synthetic lethality, the principle that two deficiencies of cellular mechanisms can lead to apoptosis but not to cell death individually, is demonstrated [24]. Intense investigations have revealed that miRNAs are key drug resistance regulator in cancer cells. MiR-506-3p improves PARPi response and chemotherapy for serious OC by targeting EZH2/ β -catenin directly [25]. PARP inhibition produces an build of DNA-SSB, which leads to the development of DNA-DSB at replication forks [26]. DNA repair mechanism like homologous recombination (HR) in normal cells are capable of efficiently repairing double-strand breaks [27]. Alternative DNA repair processes, like nonhomologous end joining (NHEJ), are utilised when there is no active BRCA1 or BRCA2 proteins, leading into apoptosis and chromosomal instability [28]. Consequently, women who have inherited BRCA1 or BRCA2 mutations are significantly more likely to develop OC, with lifetime chances of OC for BRCA1 mutant carriers being 54 percent and 23 percent, respectively for BRCA1 and BRCA2 mutation carriers [29]. BRCA mutation carriers who are treated with PARP inhibitors take advantage of the notion of synthetic lethality, which involves coupling BER suppression with a faulty HR DNA repair mechanism [30]. PARP inhibitors have been shown to be effective as a single treatment in clinical studies for recurrent ovarian cancer, which is encouraging. When examined in individuals with BRCA mutations, olaparib was found to be well tolerated, with very minor side effects of nausea, vomiting, and tiredness. Clinical trials with doses of 100 mg daily and higher revealed substantial PARP1 inhibition in malignant cells following drug exposure [31][32][33]. There have already been reports of three randomised Phase II trials employing olaparib monotherapy, which is an encouraging development. The first study randomised women with recurrent, BRCA- inadequate epithelial OC to olaparib 200 mg twice daily, olaparib 400 mg twice daily, and pegylated liposomal doxorubicin. In the second study, women with recurrent, BRCA- inadequate epithelial OC were randomly assigned to one of three treatment regimens: Pegylated liposomal doxorubicin (PLD), olaparib 400 mg twice daily, olaparib 200 mg twice daily [33][34][35]. The first study randomised BRCA women with recurrent epithelial OC to PLD, 400 mg olaparib twice daily, 200 mg olaparib twice daily [36]. Initial finding show that the median PFS is 7.1, 8.8 and 6.5 months, respectively. Greatest response rate to olaparib was 31% in the high-dose group. Olaparib was compared with placebo as a maintenance drug after complete platinum therapy in patients with recurrent OC twice a day in a second phase II trial. [35]. The research showed that olaparib maintenance treatment PFS was substantially longer than placebo in patients with BRCA-mutated OC, with PFS of 11.2 and 4.3 months, respectively. Minor side effects including vomiting, nausea and anaemia were the most common in these trials. 80% Response rate and an 18-month PFS revealed in a recent study of the combination of olaparib and cediranib in recurrent OC related to a BRCA gene mutation [37]. In contrast, the RR for olaparib-only patients was 48 percent with PFS 9 months. Significantly, while negative impact for women receiving combination medication were more frequent, they were manageable when treatment doses were decreased. Several Phase II and III studies in combination with chemotherapy are currently studying olaparib [38][35][39]. Inhibition of PARP in conjugation with DNA-damaging drug may increase chemotherapeutic effects and possibly retard tolerance to treatment [40]. A recent Phase II study employing paclitaxel and carboplatin in combination showed substantially better PFS than carboplatin and paclitaxel alone, afterwards maintenance treatment [41]. Sporadic ovarian cancer with HR deficiencies caused by the loss of activity of DNA repair proteins such as ATR, ATM, and RAD51 may also benefit from the use of PARP inhibitors [42]. These spontaneous seem to resemble BRCA1 or BRCA2 deficient tumours, but they lack the 'BRCAness' gene defects [43].

Lung cancer:

Small cell lung cancer (SCLC) is, accounting for 13–15 percent of all lung cases and sixth largest cause of cancer-related death [9][44]. SCLC is regarded to be an aggressive and deadly, pathologically, molecularly and physiologically substantially distinct neuroendocrine malignancy than other types of pulmonary cancer. Almost all SCLC patients include RB1 homozygote loss, which codes the G1-S cell cycle control point primary regulator, and TP53, which is a gene important for different DNA (DDR) pathways [45][46][47][48][49][50]. In 2012, Byers et al. carried out a major research identifying possible goals uniquely SCLC for the reverse-phase proteins (RPPA) of 74 non-SCLC(NSCLC) and 34 SCLC. The study demonstrated, SCLC cell lines expressed higher PARP1 protein than NSCLC cell lines. Additionally, SCLC patient tumours show greater PARP1 protein expression as compared to other NSCLC and neuroendocrine malignancies. In vitro line drug response tests with rucaparib and olaparib showed that, unlike NSCLC cell lines, the majority of SCLC lines examined are very responsive to PARPi therapy [51]. SLFN11, a member of the Schlafen family, has recently been discovered as a potential predictive biomarker for SCLC PARPi sensitivity. Many independent investigations showed a relationship between high levels of SLFN11 gene or protein expression and enhanced susceptibility to PARPi therapy [52][53][54][55][56]. Polley et al examined 63 SCLC cell lines in reaction to treatment with various cancer medicines (AZD-2461, rucaparib, niraparib, olaparib and talazoparib) and 423 FDA-approved experimental substances. Increasing SLFN11 gene expression was linked with decreased IC₅₀ (inhibitory concentration) values for all test PARPi values. It should be

emphasized that neither PARP1 nor PARP2 expression levels were found to be prognostic [52]. In a research by Murai et al., a strong connection was also found between expression levels of SLFN11 and responsiveness to talazoparib. Significantly, the connection between PARPi sensitivity and SLFN11 expression has been established as causal, with CRISPR- induced genetic knockout of SLFN11 resulting in resistance to both olaparib and talazoparib in four high SLFN11 cell lines (leukaemia, prostate DU145, CCRF-CEM, Ewing sarcoma EW8 and MOLT4) compared to their parents. Further confirmation was obtained in the case of leukaemia K562 cells (with low endogenous SLFN11 transcript) generated by exogenous SLFN11 expression, resulting in both olaparib and talazoparib. Murai et al. found that SLFN11 is a major factor in PARPi susceptibility in these tumour cells [53]. Lok et al. discovered protein expression concentrations and SLFN11 gene linked to PARPi response in SCLC cell lines and patient-derived xenograft (PDX) mice model [47]. Research found that greater SLFN11 expression has been linked to higher sensitivity to different PARPi in cell line data sets (i.e., talasoparib, veliparib, rucaparib and olaparib) (i.e., talasoparib, veliparib, rucaparib and olaparib). PARPi resistance was developed in SCLC cell lines by functional SLFN11 genetic knockdown and knockout. These results were corroborated by immunohistochemistry (IHC) SLFN11 staining in several talazoparib-treated PDX models [54]. Stewart et al. identified two possible biomarkers (ATM and SLFN11) with predicted PARPi response capacity in SCLC. In this research, 170 RPPA quantified proteins were examined as possible predictive biomarkers in response to talazoparib single-agent therapy. Outcomes have suggested that low ATM and high expression of SLFN11 protein are significantly related with SCLC PDX treatment response models. High levels of IRS1, IGF1R and CHK1 beta related to resistance. The results were confirmed at the level of mRNA which illustrates the strongest relationship between high SLFN11 and talazoparib, low CHEK1 and low ATM expression in SCLC PDX models [55]. Mu et al. found that SLFN11 interacts with replication protein A (RPA), resulting in HR suppression. SLFN11 destabilized RPA1-ssDNA complexes, enabling HR downstream to repair DNA efficiently [57]. Murai et al. found that SLFN11 is attracted to areas of DNA damage, where it binds to RPA and subsequently to an MCM DNA helicase, which is required for DNA replication. However SLFN11 does not engage in the early phases of replication, the unwinding heterochromatin SLFN11 delayed and eventually inhibited replication fork formation [58]. Li et al. discovered that SLFN11 suppressed ATR protein and ATM synthesis indirectly. Due to the absence of these DNA repair proteins, DNA-damaging agents were more sensitive [59].

Renal Cell Cancer:

The commonest RCC subtype is the clear-cell type. The papillary RCC (PRCC) and the chromophobic RCC are two other less often established kinds of RCCs. Papillary carcinomas are malignant tumours that have a bad result. PRCCs are classified into 2 morphological types: type 1, with tiny, low-powered cells organized in a single layer on fragile papilla nodes, and type 2 with big eosinophilic cytoplasm, higher nuclear grades and large-papilla pseudostratified nuclei [60][61]. A novel histopathological variation has recently been discovered of PRCC called oncocytic PRCC (OPRCC). Although such tumours include overlapping Type 1 and Type 2 PRCC, these tumours were considered by Lefevre et al to be a distinct PRCC subtype [61]. The variability of PRCC and the discovery of new kinds of cancer has strengthened the quest for more targeted and efficient treatments. Because certain anomalies are rare, big experiments frequently are not possible. One of these genetic characteristics is the Ataxia Telangiectasia Mutated (ATM) tumour suppressors gene and DNA damage response factor. ATM is a PI3K family member that encodes a serine/threonine protein kinase that is required for increased radiosensitivity, cell loss, and malfunction [62][63]. After double-strand breaks (DSB), ATM kinase phosphorylates hundreds of substrates to stimulate the activation and repair of cell cycle control points by non-homologous end or homologous recombinants. 3 percent (20 out of 688) of RCCs analysed in the Catalog of Somatic Mutations in Cancer have revealed ATM mutations (COSMIC) [64]. In the Kidney Renal Clear Cell Carcinoma TCGA (The Cancer Genome Atlas) datasets, ATM mutations were identified in 2.9 percent (12 of 417) and 1.8 percent (2 of 112) of sequenced tumours, respectively [65][66]. Despite recent progress in renal cell therapy, most patients are resistant to conventional medicines and need new therapeutic targets. ANDP-ribose polymerase (PARP)-inhibitor therapy of ATM-deficient tumours causing synthetic mortality leads to their particular death and may be a new therapeutic strategy to PRCC or OPRCC resistant. A new research demonstrates that the PARP inhibitor decreases tumour development and prolongs the lifespan of mice carrying Mantle Cell Lymphoma Xenograft with ATM deficiency [67].

Colorectal cancer:

The third largest cause of cancer-related mortality in the Western world is colorectal cancer (CRC). While 5-year survival rates for individuals with localised CRC are 85%–90%, they are drastically reduced to approximately 12% for those with metastatic CRC (mCRC) [68][69]. CRC carcinogenesis is caused by a complicated and well-defined series of molecular processes. Among them, mismatch repair (MMR) changes are the carcinogenic event responsible for 5%–15% of all CRC cases [70][71]. The status of MMR means that CRC may be categorised in two main subtypes: instable microsatellite (MSI) or stable microsatellite (MSS). MSS and MSI CRCs are regarded as separate and etiologically different illnesses and treatment options [72]. Genomic changes in the DNA (DDR) pathway emerge as new objectives in therapy of many kinds of cancer. The two major types of medicines presently active against cancer cells with DDR changes first identified in breast and ovarian malignancies, and which are being expanded to prostate and pancreas cancer, are platinum compounds and polymerase (PARPI) polymerase inhibitors [73][74][43]. The function of DDR changes in CRC is still largely understood and only limited and fragmented evidence on their clinical effect can be found [75][76]. As the risk factor for CRC, germline pathogenic mutations of BRCA1 are increasing, because BRCA1/2 changes have been linked to early-onset CRC [77][78]. Recent findings indicate the characteristics of a subset of CRCs in DDR genes include germline and/or somatic genetic abnormalities [79][80][81][82]. There have been reports of somatic DDR faults in the CRC ranging from 10 to 30 percent [76][81][83][84].

Conclusion:

PARP drugs have changed the therapeutic landscape for BRCA-mutated ovarian and breast malignancies, as well as when homologous DNA repair is absent. Because all studies to far show that tumours caused through these mutations have excellent response rates, the use of a PARP inhibitor for patients with homologous recombination repair mutations (e.g. BRCA) is anticipated to become a regular choice. This emphasizes the need of accurate molecular analysis to determine these likely responders. Up to 26% of BRCA mutations are found in ovarian cancer, suggesting that this is a substantial and clinically relevant category. In BRCA-mutated cancers, PARP medicines have changed the landscape of expectations. More patients, even those without a homologous recombination defect, will be able to take advantage from these revolutionary medicines as more acceptable combinations emerge.

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