PARP Inhibitor-Induced Synthetic Lethality

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Contributor: Bac Viet Le , Paulina Podszywałow-Bartnicka , Katarzyna Piwocka , Tomasz Skorski

The advanced development of synthetic lethality has opened the doors for specific anti-cancer medications of personalized medicine and efficient therapies against cancers. One of the most popular approaches being investigated is targeting DNA repair pathways as the implementation of the poly-ADP ribose polymerase 1 (PARP) inhibitor (PARPi) into individual or combinational therapeutic schemes. Such treatment has been effectively employed against homologous recombination-defective solid tumors as well as hematopoietic malignancies. In the most common aspect of precision medicine, PARPi triggers synthetic lethality in cancer cells harboring *BRCA1/2* mutations/deficiencies.

bone marrow microenvironment | DNA repair | PARP inhibitors | PARPi resistance | leukemia cells | synthetic lethality

1. Introduction

Synthetic lethality is a biological process inducing cell death, which is based on the simultaneous inhibition of two pathways that act parallelly in a process required for cell survival. Meanwhile, the inhibition of only one pathway results in cell survival. The synthetic lethality strategy has been widely implemented in anti-cancer therapies. As one pathway may be inactivated in cancer cells due to transformation-related changes, targeting the other pathway triggers cell death while sparing healthy cells [1].

One of the critical features of cancer cells is genomic instability generated by the accumulation of DNA damage, including DNA double-strand breaks (DSBs), which are one of the most lethal DNA lesions in cells [2][3]. However, cancer cells are able to survive and proliferate by modulating their DNA repair pathways, which may differ from those in normal cells [4].

DSBs can be repaired by two major mechanisms: BRCA1/2-mediated homologous recombination (HR) and canonical DNA-PKcs-mediated non-homologous end joining (c-NHEJ) [5]. HR is the major DSB repair mechanism in the S cell cycle phase, whereas c-NHEJ repairs DSBs throughout the cell cycle [6][7]. When HR is inactivated due to deficiencies in BRCA1/2, the prevention and repair of DSBs highly depend on poly-ADP ribose polymerase 1 (PARP1)-mediated base excision repair (BER) and alternative-non-homologous end-joining (a-NHEJ) [8][9]. a-NHEJ is also called microhomology-mediated end-joining (MMEJ) [10], and a-NHEJ/MMEJ involving DNA polymerase theta (Polθ) is called Polθ-mediated end-joining (TMEJ) [11]. Therefore, the inhibition of PARP1 can lead to the induction of the synthetic lethality in proliferating cells harboring HR deficiency (HRD) due to mutations in *BRCA1*

and *BRCA2*—for example, [12][13][14][15][16]. Those studies led to the development and implementation of the synthetic lethality triggered by the PARP inhibitor (PARPi), which is currently one of the most effective agents against HR-deficient malignancies [17]. Concomitant c-NHEJ deficiencies enhance PARPi-mediated synthetic lethality in HR-deficient cells [18].

FDA-approved PARPi has been administered to patients with *BRCA1/2*-mutated cancers such as breast and ovarian carcinomas [19][20][21][22]. Although leukemia has not been recognized as a typical *BRCA1/2*-mutated cancer, researchers' group and others have recently reported that certain types of leukemias and other hematopoietic malignancies display HR with/without concomitant c-NHEJ functional deficiency caused by leukemia-inducing mutations [18][23][24][25][26]. In addition, HR and/or c-NHEJ deficiency could be induced by the treatment of leukemia/solid tumors with the tyrosine kinase inhibitors (TKi) against the cancer-driven oncogenic tyrosine kinases (e.g., FLT3(ITD), JAK2(V617F), c-KIT(N822K), IGF-1R, EGFR). Therefore, oncogenic tyrosine kinase (OTK)-driven malignancies can effectively respond to PARPi after the inhibition of OTK [27][28][29][30][31].

2. PARPi-Induced Synthetic Lethality in *BRCA1/2*-Mutated Cancers

The usage of PARPi, which predominantly blocks the activity of PARP1, PARP2 and PARP3, is a well-established example of synthetic lethality-based therapy in *BRCA1/2*-mutated cancers with a limited toxicity towards normal cells and tissues [12][13][14][15]. In fact, the effectiveness of PARPi in the *BRCA1/2*-mutated breast/ovarian tumors has initiated an era of personalized medicine with the utilization of PARPi [32][33][34]. Mechanistically, mutations in *BRCA1/2* inactivate the HR pathway, and in order to survive, *BRCA1/2*-mutated cancer cells require the activity of PARP1 in BER and/or a-NHEJ, to prevent the formation of DSBs from unrepaired DNA single-strand breaks (SSBs) during DNA replication. Therefore, the inhibition of PARP1 by PARPi results in stalled replication forks and the accumulation of lethal DSBs, leading to cell death.

Recently, another mechanism has been proposed to regulate PARPi-triggered synthetic lethality in *BRCA1/2*-mutated cells: the single-strand DNA replication gaps [35][36]. Enhanced replication gaps in BRCA1/2-deficient cells were coupled with PARPi sensitivity. Besides working effectively in *BRCA1/2*-mutated cancers, PARPi-mediated synthetic lethality is capable of sensitizing c-NHEJ-deficient cancer cells. For example, the downregulation of LIG4 (involved in the c-NHEJ pathway to perform DNA ligation) induced the sensitivity of melanoma cells to PARPi (olaparib), without a cytotoxic effect on normal melanocytes [37].

Initially, the major mechanism of the efficiency of PARPi has been associated with the interference of the accessibility of NAD^+ to the PARP1 catalytic domain, leading to the inactivation of the PARylation process and the inhibition of BER and/or a-NHEJ [38]. However, recent studies have shown that the inhibition of the catalytic activity of PARPs is not the only mechanism triggering synthetic lethality [39]. Additionally, PARPi can cause the trapping of PARP1 (and probably also PARP2), resulting in DNA replication, transcriptional arrest and the accumulation of DSBs. The magnitude of synthetic lethality triggered by PARPi corresponds to their capability of PARP1 entrapment [40]. PARPi talazoparib (also known as BMN673) has been reported to be approximately 20–200 times

more efficient than previous versions of PARPi, such as olaparib [41]. The elevated efficacy of talazoparib results from its enhanced PARP1-trapping capacity, thus making talazoparib one of the best PARP-trapping agents among currently available PARPi [42].

3. PARPi in Clinical Trials of *BRCA1/2*-Mutated Cancers

Olaparib (commercial name—Lynparza®) is the first pharmacological PARPi that has been administered in clinical trials. Until now, olaparib is the most common PARPi used in BRCA1/2-deficient cancers. Historically, olaparib became the first PARPi approved by the FDA in December 2014, based on its significant efficacy in the treatment of relapsed ovarian cancer individuals with *BRCA1/2* mutations [43]. In August 2017, olaparib obtained the second approval from the FDA as an extensive therapy for patients with recurrent fallopian tube, peritoneal or epithelial ovarian cancer who have achieved partial or complete remission after the systematic standard chemotherapy [44] [45]. Additionally, the potential of olaparib in the anticancer therapy has been extended in January 2018, when the FDA licensed the PARPi as a therapeutic strategy for germline *BRCA1/2*-mutated metastatic breast cancer patients who previously received chemotherapy [46]. This marked olaparib as the first FDA-approved compound working effectively in individuals with hereditary breast cancer. Besides the trials in *BRCA1/2*-mutated breast and ovarian cancer, olaparib was also granted approval by the FDA in different solid tumors. This includes *BRCA1/2*-mutated metastatic pancreatic cancer in 2019 [47], fallopian and primary peritoneal carcinoma in a combinational intervention with bevacizumab [48] and HR-deficient metastatic castration-resistant prostate cancer in 2020 [49].

In addition, two other PARP inhibitors, rucaparib and niraparib, which also target polymerase enzymatic activity, have obtained approval for clinical trials. In detail, the FDA accepted the clinical trials of rucaparib for *BRCA1/2*-mutated advanced ovarian carcinomas undergoing multiple chemotherapy treatments in 2016 [50], reoccurring ovarian, fallopian and primary peritoneal carcinoma without *BRCA1/2* mutational status in 2018 [51] and *BRCA1/2*-mutated metastatic castration-resistant prostate cancer in 2020 [52]. Meanwhile, niraparib achieved the approval of the FDA for reoccurring ovarian, fallopian and primary peritoneal carcinoma with complete or partial chemotherapeutic response in 2017 [53], HR-deficient reoccurring ovarian, fallopian and primary peritoneal carcinoma without chemotherapeutic response in 2019 [54] and advanced ovarian carcinomas with complete or partial chemotherapeutic response in 2020 [55].

On the other hand, based on the significant PARP1 trapping capacity, talazoparib has been clinically employed in breast cancer patients with germline mutations of *BRCA1/2* and other types of cancer that contain impaired DNA damage responses [22][56]. For example, phase III clinical trials of talazoparib demonstrated the increased overall survival rate of metastatic breast cancer patients [57], and it has been approved by the FDA since 2018 [58]. Besides talazoparib, another orally available PARPi (veliparib) is currently undergoing clinical trials [59]. It shows the best selectivity against PARP1/2/3 catalysis, though this PARPi exhibits a limited efficacy of PARP1 trapping [60]. This demonstrated that PARPi, which exerts a more potent and selective inhibitory effect on the PARylation process, is also capable of entering clinical trials.

4. Therapeutic Potential of PARPi in Hematopoietic Malignancies

Many recent studies, including ours, have shown that even if *BRCA1/2* mutations are rarely detected in leukemias, PARPi-induced synthetic lethality can be effectively exploited in BRCA1/2-deficient hematopoietic malignant cells. Using a comprehensive Gene Expression and Mutation Analysis strategy, researchers were able to identify acute myeloid leukemias/acute lymphoblastic leukemias (AMLs/ALLs) that displayed HR and/or c-NHEJ deficiency and were also sensitive to PARPi [18]. These DSB repair defects were detected by direct measurements of the expression of HR and c-NHEJ genes by mRNA microarrays, real-time PCR and/or flow cytometry. In addition, genetic alterations inducing hematopoietic malignancies, such as oncogenes driving myeloid and lymphoid malignancies, including *AML1-ETO* (also known as *RUNX1-RUNX1T1*), *BCR-ABL1*, *PML-RARα*, *TCF3-HLF*, *IDH1/2*^{mut} and *IGH-MYC*, and loss-of-function mutations in tumor suppressor genes (e.g., *TET2, WT1*), can lead to the deregulation of HR and/or c-NHEJ activity, thus rendering cells susceptible to a synthetically lethal effect triggered by PARPi [23][24][25][61][62][63][64][65][66][67][68][69][70][71][72][73] (**Figure 1**A and **Table 1**). In addition, mutations in the core cohesion complex gene *STAG2* (Stromal Antigen 2) induce DNA damage, stalled replication forks and a high genetic dependency on PARP1 in AML/myelodysplastic syndrome (MDS) cells. Therefore, those cells are sensitive to PARPi talazoparib both in vitro and in vivo; however, the mechanism remains unexplored [74].

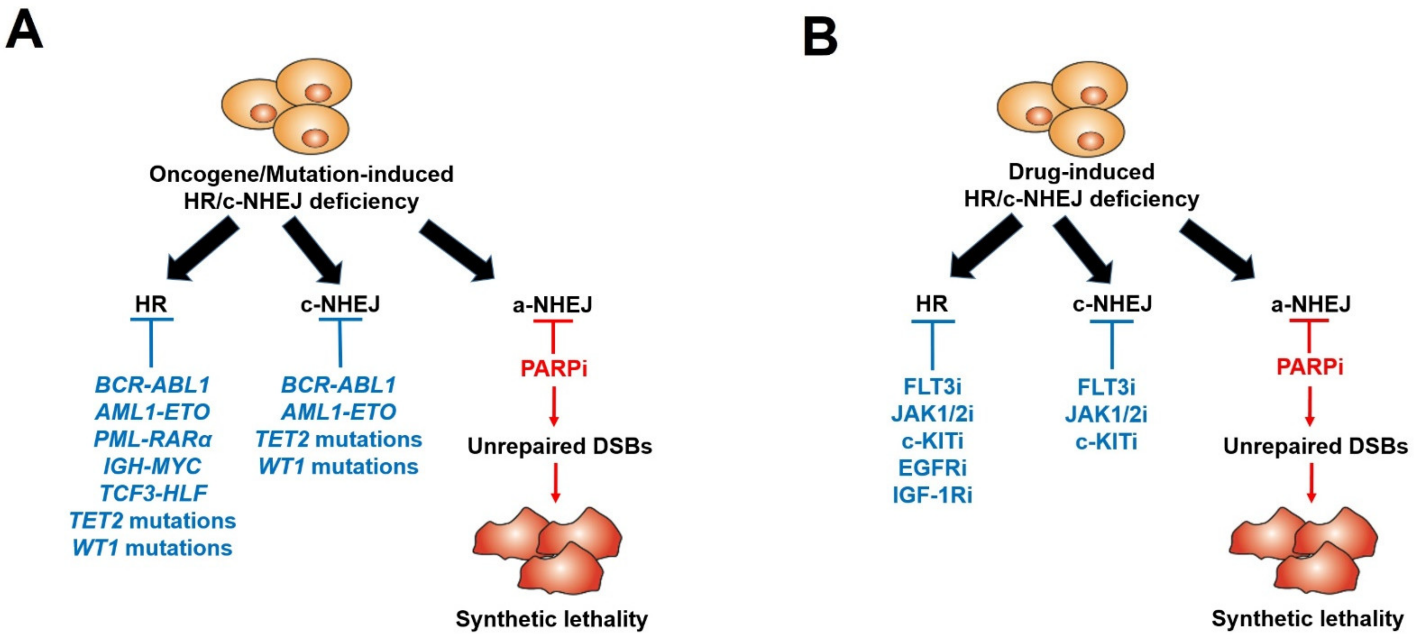

Figure 1. Scheme of PARP inhibitors administered in hematopoietic malignancies and other tumors displaying HR/c-NHEJ deficiency induced by oncogenes/mutations (**A**) and tyrosine kinase inhibitors (**B**).

Table 1. Oncogenes/Mutations inducing HR/c-NHEJ deficiency.

Disease	Oncogene/Mutation-Induced HR/c-NHEJ Deficiency	Deregulated Protein	References
CML	*BCR-ABL1*	BRCA1, DNA-PKcs	[18][23][64][68][73]
AML	*AML1-ETO*	BRCA1, BRCA2, Ku70	[25]
AML	*PML-RARα*	BRCA2, RAD51C	[25][69]
Burkitt lymphoma	*IGH-MYC*	BRCA2	[24]
AML	*IDH1/IDH2* mutants	ATM	[66][70][71]
AML/ALL	*TCF3-HLF*	BRCA1, BRCA2	[62]
AML	*FLT3*^{ITD}*+TET2* mutant	BRCA1, LIG4	[67]
AML	*FLT3*^{ITD}*+WT1* mutant	BRCA1, LIG4	[67]
AML/MDS	*TET2* mutant	BRCA1	[72]

oncogenic levels of oxidative DNA damage and DSBs due to the increase in ROS production [75][76][77]. However, OTK-positive cells were capable of escaping from the cytotoxic effect of DSBs due to enhanced/modulated DSB repair. Remarkably, the inhibition of these OTKs by FDA-approved specific tyrosine kinase inhibitors (TKi) (JAK1/2 inhibitor ruxolitinib, FLT3 inhibitor quizartinib, ABL1 inhibitor imatinib) resulted in acute HR/c-NHEJ deficiency (due to the downregulation of BRCA1, BRCA2, RAD51 and/or LIG4) and the sensitivity to PARPi (**Figure 1**B) (**Table 2**). Therefore, the combination of TKi and PARPi was capable of eradicating both proliferating and quiescent malignant hematopoietic stem and progenitor cells [18][27][28][29][61]. All these promising results have made up a rationale for clinical trials with PARPi in patients with leukemias and other related hematopoietic malignancies [26].

Table 2. Therapeutic drugs inducing HR/c-NHEJ deficiency.

Disease	Drug-Induced HR/c-NHEJ Deficiency	Deregulated Protein	References
Myeloproliferative neoplams [JAK2(V617F)]	JAK1/2 kinase inhibitor (Ruxolitinib)	BRCA1, RAD51C, LIG4	[27]
AML [FLT3(ITD)]	FLT3 kinase inhibitor (Quizartinib)	BRCA1, BRCA2, PALB2, RAD51, LIG4	[28]
AML [c-KIT(N822K)]	c-KIT kinase inhibitor (Avapritinib)	BRCA1, BRCA2, DNA-PKcs	[29]
Breast cancer	EGFR kinase inhibitor (Lapatinib)	BRCA1	[30]
Breast and ovarian	IGF-1R kinase inhibitor	RAD51	[31]

Disease	Drug-Induced HR/c-NHEJ Deficiency	Deregulated Protein	References
cancers			[78]

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combinational therapy of veliparib + temozolomide in 48 patients with relapsed/refractory AML (NCT01139970) [79], veliparib combination with topotecan and carboplatin in a clinical study of 99 patients with relapsed/refractory AML, chronic myelomonocytic leukemia or aggressive myeloproliferative neoplasms (NCT00588991) [80], and olaparib in 15 patients with relapsed CLL, T-prolymphocytic leukemia or mantle cell lymphoma [81]. In 2021, the results of a clinical trial (NCT04326023) examining the efficiency of PARP inhibitors, including olaparib, rucaparib, niraparib, talazoparib and veliparib, in 178 patients with MDS and AML were reported [82]. Although 104 in 178 MDS/AML participants were recorded with positive outcomes, PARPi increased the risk of MDS/AML in adults over 18 [82]. Additionally, a phase I clinical trial of the DNA methyltransferase inhibitor decitabine and talazoparib has been demonstrated in 25 patients with relapsed/refractory AML [83].

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