

PARP-1 inhibitors: a novel genetically specific agents for cancer therapy

Minireview

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The nuclear poly(ADP-ribose) polymerase-1 (PARP-1) represents an important novel target in cancer therapy. The enzyme is essential for single strand DNA breaks repair via base excision repair pathway. Inhibition of PARP-1 exerts „synthetic lethality“ effect towards the tumors with defects in DNA repair by homologous recombination, specifically the tumors with mutations in the breast cancer associated *BRCA1* and *BRCA2* genes. Recent clinical data confirmed the early *in vitro* studies and suggest that PARP-1 inhibitors could be used not only as chemosensitizers but as well as single agents to selective kill tumors with defective DNA repair by homologous recombination. Such concept of „synthetic lethality“ for tumors which have lost one DNA repair pathway by targeting a second DNA repair pathway, represents groundbreaking therapeutic strategy. The review highlights our current knowledge and ongoing clinical development/trials of PARP-1 inhibitors.

Key words: PARP-1 inhibitor, BRCA1, BRCA2, DNA repair, synthetic lethality

Over recent years the investigation of DNA repair pathways is a very attractive area of research. It is well known that cells have a number of overlapping pathways to protect the genome from DNA damage. Mutations that occur within these pathways represent an increased risk of malignant transformation and chemotherapy resistance [1]. Despite much research has focused on protecting cells from DNA damage and restoring their repair function, the concept of „synthetic lethality“, that is, exploiting the vulnerability of tumor cells which have lost one DNA repair pathway by targeting a second repair pathway, is emerging and represents an interesting therapeutic approach [2].

Breast cancer is the leading cause of cancer incidence and the second leading cause of cancer mortality in women. Germline mutations of the breast tumor suppressor genes *BRCA1* and *BRCA2* have been found to contribute to the most of the familial breast cancer cases [3, 4]. Recent evidence suggests that tumor cells which have lost *BRCA1* or *BRCA2*, components essential for DNA repair by homologous recombination (HR), are particularly sensitive to inhibitors of base excision repair pathway (BER) [5]. Poly(ADP-ribose) polymerase-1 (PARP-1) is an enzyme which plays an important role in the recognition and repair of single-strand DNA breaks (SSBs) via BER [6]. Thus, targeted therapy using PARP-1 inhibitors has become an important novel strategy for treating tumor cells with deficiency in *BRCA1* or *BRCA2*.

BRCA1 and BRCA2. *BRCA1* and *BRCA2* play important roles in the repair of DNA double-strand breaks (DSBs) by HR. This error-free pathway is used to repair DSBs that occur in late S/G₂ phase of the cell cycle as well as to repair DSBs resulting from unrepaired SSBs. *BRCA1* signals the presence of DSBs, while *BRCA2* has a direct role in repair itself by driving RAD51 to the DSB site. Following recognition of DSBs, *BRCA1* is phosphorylated and leads to activation of DSB repair by HR [7–9]. In the absence of functional *BRCA1* or *BRCA2*, cells become unable to undergo DNA repair by HR and activate the non-homologous end joining and single-strand non-homologous end joining annealing pathways, which are error-prone and result in chromosomal instability or cell death (Figure 1).

Poly(ADP-ribose) polymerase-1 (PARP-1). PARP-1 is the first characterized and the best known member of the PARP family, which currently comprises 18 members [10]. PARP-1 is an abundant nuclear enzyme implicated in cellular responses to DNA injury provoked by genotoxic stress, in transcriptional regulation, and in regulation of cell survival and cell death. It binds to nicked DNA as a homodimer and mediates protection of DNA. Upon binding to DNA breaks, it cleaves NAD⁺ into nicotinamide and ADP-ribose moieties and polymerizes the latter through surface accessible glutamate residues onto nuclear acceptor proteins. When DNA is mildly dam-

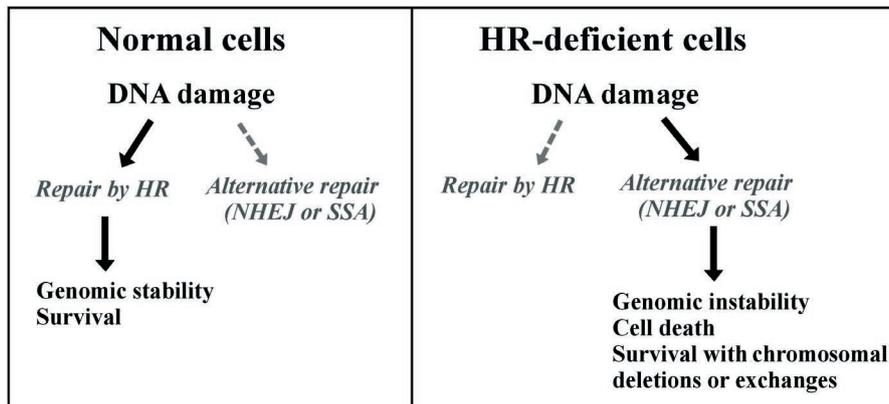


Figure 1: Loss of DNA repair by homologous recombination pathway (HR) affects the choice of DNA double-strand break (DSB) repair pathway. In normal cells DSBs are repaired predominantly by HR. In HR-deficient cells alternative pathways, such as nonhomologous end-joining (NHEJ) and single-strand annealing (SSA) repair pathways, are activated.

aged, PARP-1 is activated and participates in BER through formation of repair multiprotein complex with DNA ligase III, XRCC protein and DNA polymerase β . However, in the case of extensive DNA damage, PARP-1 is overactivated and induces a depletion of cellular NAD^+ and ATP level, leading to cell dysfunction or necrotic cell death [11–13]. Moreover, tumor cells with low cellular ATP level are highly resistant to apoptosis due to its energetic requirements and in these cells antitumor drugs could induce cell demise by necrosis only. Interestingly, cells may be protected from necrosis by inhibition or inactivation of PARP-1 in the absence of extensive cell damage [14, 15].

Due to the dual response of PARP-1 to DNA damage and its participation in cell death signaling, pharmacological modulation of PARP-1 activity constitutes a useful tool to increase the activity of DNA-binding antitumor drugs. This idea is supported by numerous studies demonstrating that PARP-1 inhibitors kill BRCA1 and BRCA2 deficient cells with extremely high efficiency while BRCA-competent cells are relatively insensitive to the treatment [16–18]. It is therefore proposed that PARP-1 inhibitors are the long-sought genetically specific drugs that are both safe and effective for treating BRCA1 and BRCA2-associated breast cancers.

PARP-1 inhibitors. The discovery of PARP-1 inhibitors was initially based on empirical, high-throughput screening, followed by optimization of chemical modifications based on structure-based design.

First generation inhibitors, nicotinamide and 3-aminobenzamide (3-AB), were identified as competitive PARP-1 inhibitors [19]. Nicotinamide is a weak PARP-1 inhibitor and at millimolar concentrations interferes with NAD^+ synthesis. 3-AB is more effective than nicotinamide, but has limited solubility in water. Furthermore, it has several drawbacks as drug candidate. It lacks the potency and specificity required to make it therapeutically useful, has limited intracellular accumulation and exerts non-specific actions, such as inhibition

of mono and poly(ADP-ribosyl)ation reactions. In addition, the doses of the compound required for reaching an effective PARP-1 inhibition *in vivo* are too high for safe human administration. Therefore, nicotinamide and 3-AB are used mainly as experimental tools to investigate the biological role of PARP-1 activation in cellular processes [20, 21].

The results of PARP-1 inhibition using first generation inhibitors and better understanding of the PARP-1 function, led to the development of second generation of potent PARP-1 inhibitors, e.g. dihydroisoquinolinones and isoquinolinones. These drugs lack some drawbacks of first generation inhibitors. Their structure is based on the structure of 3-AB with the carboxamide group attached within a ring structure. They have improved PARP-1 inhibition compared to the 3-AB and are able to reduce DNA repair and enhance cell death when combined with anticancer drugs [22, 23].

Taking into account the structural requirements for PARP-1 inhibition, the third generation inhibitors derived from benzimidazoles, e.g. benzimidazole-4-carboxamides and benzoxazole-4-carboxamides were designed and tested. Results proved that these compounds are considerably more active than 3-AB [24–26]. Additionally, the structurally modified derivative of these drugs, 2-(4-hydroxyphenyl)-1H-benzimidazole-4-carboxamide (NU1085), potentiates by about 3-fold the cytotoxicity of the monofunctional alkylating agent temozolomide and of the topoisomerase I inhibitor topotecan. Because of the potency, easy synthesis and good solubility in water, this drug has been adopted as a standard PARP-1 inhibitor [27]. Another group of third generation inhibitors is represented by derivatives of phthalazin-1(2H)-one, particularly its methyl, ethyl or benzyl substituents. Biological evaluation of these compounds revealed that they are potent PARP-1 inhibitors with nanomolar inhibitory activity and good metabolic stability [28, 29]. Structurally related quinazolinones were derived from these phthalazinones through the union of the second ring nitrogen. Quinazolin-4-ones and quinazolin-2,4-dione

show PARP-1 inhibition, with IC_{50} values of about 10 μ M [30]. Most potent derivative 8-hydroxy-2-methylquinazolin-4(3H)-one (NU1025) is about 10-fold more effective than 3-AB, and enhances the action of alkylating agents (with IC_{50} value of 0.4 μ M) [31]. So far, phenanthridinones are reported as the most potent PARP-1 inhibitors [32]. For example *N*-(6-oxo-5,6-dihydrophenanthridin-2-yl)-2-(*N,N*-dimethylamino) acetamide (PJ 34) showed PARP-1 inhibition, with IC_{50} values from 0.3 μ M to 1 μ M. Furthermore, this drug protects neuron against oxygen and glucose deprivation, and is also useful against various diseases including inflammatory processes and allergic encephalomyelitis [33].

PARP-1 inhibitors as chemosensitizers. It has been shown that increased PARP-1 activity is one of the mechanisms by which tumor cells avoid apoptosis caused by DNA-damaging agents. As PARP-1 is essential for the repair of SSBs through the BER pathway, its inhibition sensitizes tumor cells to cytotoxic therapy (e.g. temozolomide, cisplatin, topoisomerase I inhibitors, or irradiation), which induce DNA damage that would normally be repaired through the BER pathway. A significant window seems to exist between the ability of PARP-1 inhibitors to potentiate therapeutic benefit versus potentiation of undesirable side effects. Interestingly, PARP-1 inhibitors have not potentiated agents that do not damage DNA. Moreover, there did not seem to be a correlation between the antitumor activity and the toxicity of the PARP-1 inhibitor-DNA damaging agent combinations. Instead, it looks like the toxicity and chemosensitization are driven by different mechanisms.

PARP inhibitors in the treatment of DNA repair deficiency-related cancers. Despite PARP-1 inhibitors are promising chemosensitizers in combination with antitumor drugs, they appear to be particularly potent as well as single agents in patients who have defects in DNA repair. Usually, in normal cells, PARP-1 inhibition leads to failure of SSB repair, resulting

in the formation of DSBs in the DNA when a replication fork encounters the SSBs [34]. Generated DSBs can be repaired by HR and the fidelity of the genome is maintained. However, if cells carry defects in BRCA1 or BRCA2, DSB repair by HR is defective, resulting in an attempted repair of the DSBs by the more error prone pathways. As a result, the cells acquire lethal levels of DNA damage and cellular viability is lost. The effect of this “synthetic lethality” represents a powerful tool to treat the tumor cells with defective of one DNA repair mechanism (e.g. HR) by ceasing the functionality of a second repair pathway (e.g. BER) [2]. As most BRCA1 and BRCA2 carriers have one normal allele, the inhibition of BER through the inhibition of PARP-1 should be preferentially selective for tumor cells. This idea was confirmed by studies using different chemical classes of PARP-1 inhibitors [5, 16]. Results clearly demonstrated that both BRCA1 and BRCA2 deficient tumor cells are sensitive to inhibition of PARP-1, and that BRCA2 deficient cells are more than 1000 times more sensitive to nanomolar concentrations of PARP-1 inhibitors [17]. These studies confirmed that tumor cells with deficiency in BRCA1 and BRCA2 are sensitive to the mechanism of PARP-1 inhibition due to defective repair of DSBs by HR, whereas the rest of the patient’s cells are insensitive. Additionally, recent study showed that cells deficient in phosphatase and tensin homolog (PTEN), tumor suppressor gene function in HR, are hypersensitive to PARP-1 inhibitors as well [35]. This suggests that assessment of PARP-1 inhibitors might be extended beyond BRCA-deficient cells to a larger group of patients that are defective in DNA repair by HR.

PARP-1 inhibitors in clinical trials. The profound sensitivity of BRCA1 and BRCA2 mutant cells to PARP-1 inhibition has led to the development of a number of clinical trials to test the efficiency of this approach. Currently, several PARP-1 inhibitors have entered the clinical trials [36]. Their current status is summarized in Table 1.

Table 1: PARP-1 inhibitors in clinical trials (according to <http://clinicaltrials.gov/>)

Agent	Combination with	Disease	Clinical status
BSI-201	Irinotecan, topotecan, temozolomide, gemcitabine, carboplatin/paclitaxel	Advanced solid tumors, malignant glioma, uterine carcinosarcoma	Phase I - II
	Gemcitabine, carboplatin	Triple negative metastatic breast cancer	Phase II - III
AG-014699	Single agent	Locally advanced or metastatic breast cancer	Phase II
	Carboplatin, paclitaxel, cisplatin Pemetrexed	Advanced solid tumors	Phase I
INO-1001	Temozolomide	Melanoma	Phase I
MK-4827	Single agent	Advanced solid tumors	Phase I
KU-0059436	Carboplatin, paclitaxel, cisplatin	Triple negative metastatic	Phase I - II
			Phase I
CEP-9722	Single agent	Advanced solid tumors	Phase I
ABT-888	Temozolomide	Metastatic breast cancer	Phase II
	Carboplatin, topotecan	Leukemia, myelodysplastic syndromes	Phase I - II
	cyclophosphamide, doxorubicin		
	Mitomycin C	Metastatic solid tumors	Phase I
	Temozolomide	Melanoma, breast cancer	Phase II
	Topotecan, carboplatin, paclitaxel	Ovarian cancer	Phase I - II

The ongoing clinical trials focus on the treatment of *BRCA* mutation carriers, particularly those with breast, ovarian, or prostate cancer, with PARP-1 inhibitors as single-agents or in combination with several DNA damaging agents. From the current data, it is becoming clear that PARP-1 inhibitors are useful chemosensitizers not only in patients whose tumors exhibit *BRCA* deficiency, but they are effective as well for those tumors exhibiting the HR defects in general, including triple-negative (estrogen-, progesterone-, HER2-receptor negative) breast cancer, known as an aggressive subtype of breast cancer.

Resistance to PARP-1 inhibitors. Despite of the potency of PARP-1 inhibitors, the cancer cells could develop the resistance to these agents. Recent studies suggest that resistance of highly sensitive *BRCA2* deficient cells to PARP-1 inhibitors is caused by genetic reversion that leads to restoration of open reading frame of *BRCA2*. Such cells become HR competent [37]. The identical mechanism of resistance was observed as well for carboplatin resistant tumors [38]. It is likely that a similar mechanism may cause resistance to PARP-1 inhibitors in *BRCA1* mutation carriers. So far it is not yet clear whether a wide range of *BRCA* mutations can also be reverted in a similar fashion. Additionally, mutation reversion seems to be not the only route leading to PARP-1 inhibitors resistance. Recent study showed that in addition to genes known to be involved in HR, some kinases such as MAPK12, STK36, STK22c and CDK5, also modify sensitivity of tumor cells to PARP-1 inhibitors [39]. That suggests, that other genes except of genes involved in HR might be used as well to sensitize the tumor cells to chemotherapy. Inhibition of these genes could increase the efficacy of PARP-1 inhibitors helping to prevent or even overcome PARP-1 resistance.

In conclusion, PARP-1 inhibitors provide a major advance in the treatment of *BRCA1* and *BRCA2* associated breast cancers. Due to „synthetic lethality“ effect against tumor cells with deficiency in HR, they are the long-sought genetically specific drugs that are both safe and effective. Further advancement in understanding of the molecular mechanism of HR deficiency in cells with no *BRCA1* and *BRCA2* mutations but with sensitivity to PARP-1 inhibitors, will be very useful for revealing full therapeutic potential of these inhibitors. Additionally, the ongoing preclinical research will undoubtedly help in discovery and development of new and more potent PARP-1 inhibitors with potential to further improve response rates while causing fewer treatment-related toxicities.

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