

Mechanisms, Limitations, and Prospects of PARP Inhibitor Talazoparib and MTH1 Inhibitor Karonudib for Malignant Tumor Therapy

Ryan Rui Cheng Yang^{1, *}

¹School of Biomedical Sciences, McGill University, Montreal, Canada

*Corresponding author: ryan.r.yang@mail.mcgill.ca

Abstract

Cancer cells rely heavily on DNA damage repair mechanisms for survival, making the targeting of the DNA damage response (DDR) pathway an important direction for cancer treatment. Novel DDR inhibitors, talazoparib and karonudib, have shown potential anti-tumor effects, but drug resistance and safety issues limit their further application. This review summarizes the mechanism of synthetic lethality triggered by Talazoparib, a PARP inhibitor, in BRCA-deficient breast cancer cells and further explores how nano-talazoparib improves drug tolerability, enhances antitumor activity, and reverses efflux transporter-mediated acquired resistance. Moreover, this article elaborates on the theory of the MTH1 inhibitor karonudib killing cancer cells by inducing accumulation of oxidative DNA damage, and discusses ABCB1-driven intrinsic resistance to karonudib. In addition, this study provides theoretical and experimental support for developing advanced drug delivery systems (DDS) and combination therapy in the cancer treatment realm. Nevertheless, several challenges remain, such as Talazoparib resistance due to restoration of the homologous recombination (HR) pathway in tumor cells and karonudib side effects that have not been fully explored in early clinical studies. Future research should focus on nanoparticle drug delivery systems of Talazoparib and karonudib and their corresponding combination therapy to overcome drug resistance and further enhance their effectiveness in future cancer treatment.

Key words

DNA damage response; cancer therapy; PARP inhibitor; MTH1 inhibitor; Talazoparib; karonudib.

1. Introduction

DNA damage refers to aberrations in the original, intact double-helix structure. Both the endogenous and exogenous pathways can cause DNA damage. The Endogenous pathway is related to cellular metabolism. For instance, the byproducts of metabolism, such as reactive oxygen species (ROS), can cause oxidative DNA damage: 8-hydroxydeoxyguanosine (8-OHdG or 8-oxo-dG), further leading to single-strand breaks (SSBs) and base modifications. The Exogenous pathway is associated with physical and chemical sources. Common physical and chemical sources include ionizing radiation (IR), ultraviolet (UV) light, alkylating agents, and carcinogens, which can cause more severe DNA damage, such as double-strand breaks (DSBs), DNA adducts, and DNA-protein cross-links [1]. If DNA damage response (DDR) and other DNA repair machinery do not promptly repair DNA lesions, the accumulation of DNA damage can cause base mispairing during DNA replication, leading to permanent mutations.

DDR is a core and sophisticated cellular mechanism to detect and repair DNA damage, maintaining genomic stability. DDR sensors recognize damaged DNA and activate a cascade of signal transducers. Three major transducers in DDR are the apical kinases ATM, ATR, and DNA-PKcs, activated by DSBs, replication stress, and non-homologous end joining (NHEJ) bound ends, respectively [2]. Activated transducers will further activate mediators, which transmit signals to effector networks guarded by p53 in DDR. These effector pathways are DNA damage repair, cell cycle arrest, apoptosis, and senescence. The activation of the DNA damage repair system is the primary endpoint of the DDR. DNA damage repair has five master pathways: mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR), and NHEJ [1]. For instance, MutT homolog 1 (MTH1) is an upstream effector. It is a mammalian Nudix hydrolase that degrades 8-oxo-dG, preventing oxidative DNA damage from disrupting genome stability [3]. If DNA oxidative damage does occur, Poly (ADP-ribose) poly-

merase 1 (PARP1) in the PARP family will recognize and bind to the damaged area and SSB, further recruiting downstream DDR proteins and activating BER [2].

Nowadays, cancer therapies are developing rapidly. Conventional cytotoxic chemotherapy has become a well-established clinical application, yet it has off-target cytotoxicity, and some cancers develop drug resistance by upregulating DDR proteins. Given the limitations of conventional cytotoxic chemotherapy, DDR-targeted cancer therapy has emerged as an alternative and supportive treatment option. DDR-targeted anticancer therapy targets and inhibits key DDR proteins that cancer cells rely on, reducing off-target cytotoxicity and chemotherapy-induced drug resistance. DDR-targeted cancer therapy can effectively kill cancer cells. In addition, when DDR-targeted cancer therapy is combined with conventional chemotherapy, the effectiveness of cancer treatment will be further improved [1]. For instance, researchers combined Talazoparib, a PARP family targeted inhibitor, with two chemotherapy drugs, carboplatin and paclitaxel, to treat patients with advanced solid tumors in a clinical trial. The clinical trial results showed that the combination cancer therapy is potent in treating advanced solid tumors, particularly tumors with breast cancer-associated (BRCA) gene mutations. However, severe adverse effects, such as myelosuppression, limit the effectiveness of this combination therapy in clinical application [4].

This review will discuss the role and mechanisms of PARP1, a key member of the PARP family, and MTH1 in cancer's DDR and their corresponding inhibitors, Talazoparib and karonudib (TH1579), respectively, with related treatments. The effects of these inhibitors and treatments will be illustrated by experiments in vitro, in vivo, and clinical trials from research in the field. This review will also discuss the challenges and prospects of karonudib and Talazoparib to further validate their role and contribution in cancer treatment. This review also provides advice and guidance on the development and improvement of DDR cancer therapy and its combination therapy.

2. Talazoparib-PARP-BRCA-deficient Breast Cancer Therapy

2.1 PARP is Required for Repairing SSBs in DDR

In the sophisticated DDR network, the PARP family plays a crucial role in DNA damage and cell apoptosis. PARP1 is the most important member of the PARP family; it accounts for more than 90% of the family's functions within cells. When SSBs occur in DNA, PARP1 rapidly utilises its zinc-finger domain to bind to the damage site, where it is activated and initiates PARylation. PARylation is a process in which PARP1 uses NAD⁺ as a substrate and transfers an ADP-ribose group to target proteins, such as itself and XRCC1, a key DDR protein for BER and SSB repair (SSBR), forming PAR chains. The PARylation of XRCC1 and other proteins in the BER complex recruits them to the damage site accurately. Moreover, each PAR chain carries negative charges, while the DNA phosphate backbone also carries negative charges, resulting in repulsion. As a result, the Auto-PARylation of PARP1 will let PARP1 dissociate from DNA, allowing the BER complex to bind to the damage site [5].

2.2 BRCA Mutation and PARP Inhibition Trigger Synthetic Lethality in Cancer

Most cancers carry mutations, some of which affect key genes in DDR, such as BRCA. BRCA gene1 and gene2 (BRCA1, BRCA2) primarily mediate HR to repair DSBs, stabilizing the cell genome [6]. BRCA1 mutation is the main cause of hereditary breast cancer [7]. Women with a BRCA1 mutation have a 55–72% risk of developing breast cancer by the age of 70. In addition, 75% of these cases are triple-negative breast cancer (TNBC) [7]. TNBC is the most aggressive form of breast cancer; it has an extremely poor prognosis and is the most likely to metastasize. Mutations in either BRCA1 or BRCA2 result in the dysfunction of the HR they mediate. Therefore, cancer cells with the BRCA1/2 mutation require PARP1 and the PARP family to repair

DNA and maintain genomic stability. The interdependence between BRCA and PARP has led researchers to believe that PARP, particularly PARP1, could serve as a therapeutic target for BRCA-deficient breast cancers [6]. They developed PARP inhibitors to induce synthetic lethality in BRCA-deficient breast cancers. Synthetic lethality means that when either of two genes is silenced, cell death is not triggered; however, when both genes are silenced simultaneously, cell death is triggered. For example, when BRCA-deficient breast cancers are treated with PARP inhibitors, a large number of unrecognized and unrepaired SSBs will accumulate and convert into DSBs during DNA replication. DSBs are the most severe form of DNA damage, triggering genomic collapse and leading to cancer cell apoptosis and death due to HR dysfunction [6].

2.3 Talazoparib

Talazoparib is a novel PARP inhibitor that targets PARP1, PARP2, and PARP16 in BRCA-deficient breast cancer cells. It can competitively bind to the NAD⁺ binding pocket of PARP1, inhibiting the binding of NAD⁺ to PARP1. Thus, Talazoparib will inhibit PARylation, formation of PAR chains, and downstream BER, leading to the accumulation of SSBs and conversion to DSBs during DNA replication in BRCA-deficient cancer cells. Additionally, the inhibition of PARylation will cause PARP1 to become trapped in the DNA, forming a PARP1-DNA complex. PARP1-DNA complex will trigger replication fork stalling and eventually collapse, further producing DSBs in BRCA-deficient breast cancer cells. Consequently, Talazoparib causes BRCA-deficient breast cancer cells to generate a large number of irreparable DSBs, destabilizing their genomes and triggering synthetic lethality to kill them [6,7]. Normal cells have a functional DDR system. Therefore, Talazoparib will not trigger synthetic lethality in normal cells and kill them, demonstrating its targeted cytotoxicity.

2.4 Talazoparib and its Combination Therapy

Numerous experiments demonstrate the efficacy of Talazoparib in treating BRCA-deficient breast cancers. To compare the efficacy of Talazoparib and two other PARP inhibitors, Olaparib and Niraparib in treating the

W780 BRCA1-deficient breast cancer cell line in vitro experiments, Belz et al. performed the western blot and observed that the Talazoparib-treated W780 cell line has increasing DSBs and apoptosis compared with Olaparib- and Niraparib-treated W780 cell lines, reflected by high expression of γ -H2AX protein, cleaved PARP (c-PARP), and cleaved caspase 3 (c-caspase 3) [7]. Additionally, they found that the IC50 (half-maximal inhibitory concentration) of Talazoparib is only 2.6 nM from the dose-response curve in W780 cells, indicating that BRCA1-deficient breast cancer cells are highly sensitive to Talazoparib [7]. Furthermore, in vivo experiments compared the efficacy of Talazoparib implant treatment and Talazoparib gavage treatment in genetically engineered mice. The experiment showed that although Talazoparib gavage treatment reduced tumor growth compared with the control group, the gavage group's tumor volume remained significantly larger than that of the Talazoparib implant treatment group over the 28-day treatment period, indicating that a targeted drug delivery system (DDS) can further enhance Talazoparib's efficacy [7]. These results of in vitro and in vivo experiments prove Talazoparib's potent therapeutic efficacy in treating BRCA1-deficient breast cancer.

Based on Talazoparib's effective performance for treating BRCA1-deficient breast cancer cells in vitro and in vivo experiments, Leal et al. [4] further designed a phase I study of Talazoparib combination therapy. Eligible patients have advanced solid tumors that are sensitive to carboplatin and paclitaxel or carry somatic or germline BRCA1/2 mutations. They received carboplatin and paclitaxel at appropriate dosages, which researchers adjusted according to their condition during treatment. For Talazoparib dosage escalation, a standard 3 + 3 design was used to find its maximum tolerated dose (MTD). The results of this phase I study showed that this combination therapy of Talazoparib, carboplatin, and paclitaxel exhibits significant anti-tumour activity, especially in BRCA-deficient tumors at MTD. Nevertheless, Talazoparib combination therapy's additive toxicity would lead to more severe myelosuppression, and over half of the patients would experience grade 3 or 4 hematological toxicity. These severe side effects are primarily caused by Talazoparib's powerful ability to anchor PARP1 to DNA, causing normal hematopoietic stem and progenitor cells (HSPCs) to be unable to re-

pair DNA damage and triggering apoptosis. Moreover, the MTD for Talazoparib in the combination therapy is much lower than that of Talazoparib monotherapy. Hence, researchers delayed the dose and reduced the dose of the combination therapy to alleviate the toxicity of the combination therapy, which will limit its anti-tumor effectiveness [4].

2.5 Nano Talazoparib Therapy

Considering the severe side effects of Talazoparib combination therapy and the enhanced efficacy of Talazoparib in a targeted drug delivery system, Zhang et al. designed a bilayer nano-liposome with polyethylene glycol (PEG) to encapsulate Talazoparib [6]. This nano complex is called Nano-Talazoparib (NanoTLZ). A BRCA-deficient mouse model was used to investigate the performance of different Talazoparib administration methods in treating BRCA-deficient breast cancer. NanoTLZ treatment group demonstrated the absence of active tumor growth, significant tumor regression, and a prolonged lifespan in BRCA-deficient mice, compared with the free intravenous(i.v.) Talazoparib administration group and the free oral Talazoparib group. Moreover, free i.v. Talazoparib and oral Talazoparib treatment caused a significant reduction in body weight and alopecia, an adverse effect of Talazoparib in clinical trials, in BRCA-deficient mice, yet researchers didn't observe noticeable body weight changes and alopecia in the NanoTLZ group because the precise delivery of NanoTLZ into tumor tissue significantly reduces the amount of free Talazoparib that leads to myelosuppression. Interestingly, a decrease in Myeloid-Derived Suppressor Cells (MDSCs), which play a key role in immune suppression within the tumor microenvironment (TME), is observed in NanoTLZ-treated mice.

2.6 Nano Talazoparib Therapy and the Acquired Resistance Mediated by MRP1 and BCRP in BRCA-Deficient Cancer Cells

Meanwhile, Eskiler et al. designed and studied the performance of Talazoparib-loaded solid lipid nanoparticles (SLNs) in triple-negative breast cancer treatment [8]. They found that tumor cells upregulate MRP1 and

BCRP protein expression during free Talazoparib therapy to develop acquired resistance. MRP1 and BCRP are two key efflux transporters in cancer cells that pump out drugs and reduce their cytotoxicity. However, SLNs enter tumor cells via endocytosis and release, bypassing efflux transporters. Furthermore, SLNs will reduce MRP1 and BCRP expression in the long term. These observations prove that SLNs can overcome the specific acquired resistance of triple-negative breast cancer to Talazoparib. However, some BRCA-deficient cancer cells develop a second mutation that restores BRCA-mediated HR pathway function [9]. In this case, the efficacy of nano Talazoparib would need to be investigated further through experiments. From a mechanistic perspective, nano Talazoparib will likely be unable to overcome this resistance because synthetic lethality cannot be triggered in these BRCA-deficient cancer cells. Overall, nano Talazoparib treatment, such as NanoTLZ and SLNs, is a more effective and well-tolerated Talazoparib therapy for treating BRCA-deficient breast cancer, making it a promising direction and realm for further research [6,8].

3. Karonu- dib(TH1579)-MTH1-Cancer Therapy

3.1 RAS Oncogenes Positively Associate with ROS in Cancer

The Ras superfamily, a small GTPase superfamily, contains three human genes: HRAS, NRAS, and KRAS. They mediate cell growth signaling pathways and regulate cell proliferation and survival. In ~30% of all human cancers, mutations occur in these RAS genes, which are therefore referred to as proto-oncogenes.[10] Oncogenic KRAS is found in nearly a quarter of human cancer cases, mainly in adenocarcinomas. Oncogenic RAS mutations are positively associated with ROS production.[11] In the context of cancer, Oncogenic RAS mutations and ROS are a double-edged sword. They can help cancer to proliferate, progress, and become malignant, yet ROS and oncogenic RAS mutations will result in oxidative, metabolic, and replicative stress in cancer cells, further leading to oxidative DNA damage and

oncogene-induced senescence (OIS). Therefore, cancer cells need to minimize the adverse effects caused by ROS for their malignant proliferation.

3.2 MTH1 Prevents Oxidative DNA Damage in Cancer by Degrading Oxida- tive Nucleotides

MTH1 is a mammalian Nudix hydrolase degrading 8-oxo-dG in cancer cells. It sanitizes the genome of cancer cells, preventing the triggering of OIS and helping them to undergo malignant transformation. In a tumor with wild-type p53, MTH1 inhibition results in the accumulation of oxidative DNA damage and DNA breaks, which will be recognized by P53. P53 will activate OIS, reducing tumorigenicity. Interestingly, in a tumor with nonfunctional P53, MTH1 will engage in crosstalk with KRAS. Based on a qPCR result, low MTH1 expression will downregulate KRAS expression. Decreased KRAS expression reduces ROS production. Although the downregulation of KRAS can protect cancer DNA from oxidative damage, the low expression of MTH1 and KRAS will slow the rate of proliferation and malignant transformation.[10] These findings regarding MTH1 make it a potential target for cancer treatment.

3.3 Karonudib (TH1579): MTH1 inhibi- tor

Karonudib is a new MTH1-targeted inhibitor. It binds to the substrate pocket of MTH1 by mimicking the conformation of 8-oxo-dG, thereby inhibiting the catalytic function of MTH1 [12]. Thus, karonudib can kill cancer cells by inducing accumulation of 8-oxoG in their genome. Warpman Berglund et al. performed in vitro experiments to validate the efficacy of karonudib for cancer treatment [13]. In the cancer cells group, they found that the karonudib IC₅₀ value is 0.16μm, which means it can kill cancer cells at nanoscale concentrations. Furthermore, karonudib is less toxic to normal cells because the karonudib IC₅₀ for normal cells is 1.9μm, significantly higher than that of cancer cells. Meanwhile, the cell thermal shift assay (CETSA) showed that the cytotoxicity of karonudib and the stability of the binding between karonudib and MTH1 are positively correlated, proving its mechanism of killing

cancer.

3.4 Karonudib: Effective in Treating B-cell Lymphoma

Based on findings from in vitro experiments of karonudib, Oksvold et al. designed preclinical models to test its efficacy in treating B-cell lymphoma. B-cell lymphoma is a hematological malignancy; some subtypes, such as Burkitt lymphoma, often develop drug resistance and relapse, leading to a poor prognosis [14]. In a luminescence cell viability assay, after applying karonudib, the normal cells' viability is significantly higher than that of different types of B-cell lymphoma cells. In the Western blot results, MTH1 expression level in B-cell lymphoma cells is higher compared with normal cells, showing that B-cell lymphoma relies on high expression of MTH1 to reduce the oxidative DNA damage caused by ROS, showing that karonudib's cytotoxicity depends on the expression level of MTH1. Normal cells have wild-type RAS genes and functional DDR. Therefore, they don't require high MTH1 to prevent oxidative nucleotide accumulation, explaining karonudib's targeted cytotoxicity. Additionally, the efficacy of karonudib in vivo is validated by an immunodeficient mouse model. Immunodeficient mice are injected with BL-41, a cell line of Burkitt lymphoma. The karonudib-treated mice have a significant decrease in tumor size compared with the control group during treatment, as reflected by the luminescence results [14]. Consequently, karonudib can effectively suppress tumor growth for treating B-cell lymphoma.

3.5 High Expression of ABCB1 in Metastatic Melanoma Mediates Resistance to Karonudib in a Preclinical Model

Although karonudib has demonstrated potent efficacy in cancer treatment across many preclinical experiments, a patient-derived tumor xenograft (PDX) model of metastatic melanoma reveals that tumors with intrinsic resistance can also be resistant to karonudib [15]. In the PDX model, the RNA sequencing data show that some melanoma cells have high ABCB1 expression before karonudib is applied. ABCB1 encodes the p-glycoprotein (p-gp) pump, which transports ex-

ogenous substances, such as anti-tumor drugs, out of cells. Moreover, karonudib results in lower cytotoxicity when treating these high-ABCB1-expressing tumors. However, after applying karonudib, most tumor cells didn't significantly increase expression of ABCB1 to develop drug resistance, which is insufficient to suggest the development of acquired resistance to karonudib in melanoma. In cases of drug resistance caused by the p-gp pump, karonudib can be combined with the p-gp pump inhibitor Elacridar to successfully reverse the drug resistance and effectively kill melanoma cells, revealing and proving the therapeutic potential of the karonudib combination therapy [15].

4. Conclusion

In summary, this article systematically summarizes the research progress on PARP1-mediated DNA damage repair mechanisms and their application in the treatment of BRCA-deficient breast cancer. It focuses on the role of PARP1 in BER, the molecular basis of PARP inhibitor-induced synthetic lethality, and the antitumor effects, nanodelivery strategies, and drug resistance mechanisms of Talazoparib.

When Talazoparib is combined with conventional chemotherapy, its anti-tumor effectiveness can be further enhanced. Nevertheless, the severe adverse effects of the Talazoparib combination therapy limit its clinical application and effectiveness. Nano Talazoparib treatment, such as Nano TLZ and SLNs, can reduce the side effects of Talazoparib, enhance its efficacy, and reverse the typical acquired resistance, such as high expression of MRP1 and BCRP in tumor cells. Nevertheless, a second mutation that restores HR function in BRCA-deficient cancer cells is a crucial issue for Talazoparib and Nano Talazoparib. Based on the positive findings of nano Talazoparib therapy, this review suggests that nano Talazoparib and its combination therapy with conventional chemotherapy should be evaluated in more in vitro and in vivo experiments and clinical trials in the future, further validating its role and contribution in treating BRCA-deficient breast cancer.

RAS oncogene will lead to enhanced ROS production and levels in cancer cells. MTH1, a Nudix hydrolase, is crucial for preventing oxidative damage to the cancer genome. MTH1 will help tumor cells to grow

and become malignant, which makes MTH1 a potential target for treating tumors. Therefore, this article also summarizes the role of MTH1 in the regulation of oxidative stress and tumor survival, as well as the research progress on MTH1-targeted treatment strategies using karonudib. Karonudib exerts its anti-tumor effect by promoting the accumulation of oxidative DNA damage, but ABCB1/P-gp-mediated resistance and clinical safety issues still limit its further application. Future research should delve deeper into the resistance mechanisms and optimize treatment strategies.

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