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Mechanisms and Clinical Practice of PARP1 Inhibitors for Synergistic Sensitization Therapy of Glioblastoma

Jingyi Feng

Qingdao No.9 High School, Qingdao, China
elyfeng532@outlook.com

Abstract. This review discusses the potential of poly (ADP-ribose) polymerase-1 (PARP1) inhibition for enhancing temozolomide (TMZ) efficacy against glioblastoma multiforme (GBM) cells. Through the analysis of PARP1 repair in multiple DNA damage-response processes, including single-strand break repair (SSBR), replication stress, and mismatch repair (MMR), as well as the repair of TMZ-mediated damage, it can be concluded that PARP1 inhibition has a biological rationale for enhancing the effect of TMZ on GBM cells. Preclinical studies of the PARP1 inhibitors olaparib and talazoparib have shown that a PARP1 inhibitor plus TMZ combination can enhance TMZ-induced cytotoxicity and inhibit the survival of GBM cells. However, the clinical application of this strategy remains limited by insufficient clinical evidence and pharmacological barriers, such as hematological toxicity and restricted penetration of some PARP inhibitors across the blood-brain barrier (BBB). Therefore, future research directions should focus on improving sustained central nervous system exposure, optimizing combination regimens, and selecting sufficient samples. In these ways, the effectiveness of TMZ in treating GBM cells may be enhanced in clinical settings.

Keywords: PARP1 repair, TMZ-mediated damage, PARP1 inhibition

1. Introduction

Glioblastoma multiforme (GBM) is the most aggressive diffuse glioma of astrocytic lineage and corresponds to grade 4 based on the World Health Organization (WHO) classification. It is one of the most common brain tumors in adults, with a median diagnosis age of around 64, and is more prevalent in males. Because of its rapid growth rate, high molecular heterogeneity, and invasiveness, GBM has a median survival time of only 3 to 4 months despite standard treatments. Conventional methods for overcoming temozolomide (TMZ) resistance in GBM treatment rely solely on increasing the dose of TMZ, removing the tumor, or combining TMZ with other chemotherapies, approaches that may increase toxicity and disrupt nearby brain tissue. For example, tumor resection can reduce tumor burden but rarely eliminates all tumor cells because GBM cells can invade the surrounding tissues and acquire their nutrients and resources for their own proliferation. Similarly, intensified radiotherapy can damage nearby non-target brain tissue, so the efficacy of radiotherapy is limited by the tolerance of the surrounding brain tissue, resulting in a median survival time of 12.1 months with radiotherapy alone. Although combining TMZ with radiotherapy can increase the

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median survival time to 14.6 months [1], effective tumor suppression should focus on the tumor's specific DNA proliferation mechanism [2].

O^6-methylguanine-DNA methyltransferase (MGMT) expression is silenced by promoter methylation in approximately half of GBM tumors, and clinical studies have shown that elevated MGMT protein levels or the absence of MGMT promoter methylation is associated with TMZ resistance [2]. Specifically, MGMT directly removes the TMZ-induced O^6-methylguanine damage, an action that reduces DNA damage induced by TMZ and contributes to resistance [2].

Although conventional approaches can only partially inhibit DNA repair, poly (ADP-ribose) polymerase-1 (PARP1) inhibition, a recent strategy, has shown a high potential to disrupt DNA repair and enhance TMZ efficacy. PARP1 is a member of the PARP family that regulates cell division, acts as a sensor for DNA damage, and is activated upon detection of DNA breaks. In the context of TMZ treatment, however, PARP1 may repair TMZ-induced DNA lesions, which reduces the effectiveness of TMZ. Therefore, inhibiting PARP1 in tumor cells may improve TMZ efficacy by impairing the repair of these DNA lesions. Talazoparib is another representative PARP1 inhibitor that acts as a "PARP trap" by inhibiting the catalytic function of PARP and promoting the accumulation of PARP1 at DNA damage sites [2].

Based on the above experimental evidence, this review will examine the feasibility and clinical utility of different PARP1 inhibitors in enhancing the effectiveness of TMZ in GBM.

2. Repair mechanisms of PARP1

In 1963, DNA-dependent synthesis of a polyadenylic acid-like compound was first observed. Later studies identified this compound as poly(ADP-ribose) (PAR) and linked PARP1 to the enzyme that produces PAR. Poly(ADP-ribose) polymerase-1 (PARP1) is an enzyme in cells that regulates DNA damage signaling. When DNA damage occurs, PARP1 binds to DNA breaks through its DNA-binding domains and becomes activated. Activated PARP1 catalyzes the synthesis of PAR chains using nicotinamide adenine dinucleotide (NAD+) as a substrate [3]. In one of the DNA repair processes, PARP1 binds to single-strand breaks (SSBs) and then recruits proteins that promote single-strand break repair (SSBR). The breaks can be directly caused by damage to the sugar-phosphate backbone or can occur indirectly as a result of DNA repair processes [3].

X-ray repair cross-complementing protein 1 (XRCC1) is a scaffold that recruits and organizes several proteins in SSBR. Recruitment of XRCC1 to DNA damage sites requires the PAR chains generated by PARP1. When the BRCA1 C-terminal (BRCT) domains of XRCC1 recognize the PAR produced by PARP1 and PARP2, XRCC1 is first recruited to the DNA damage site and then retained there during DNA repair [3]. Once recruited, XRCC1 begins to organize and coordinate downstream repair proteins, such as DNA polymerase β, DNA ligase III, and other components of SSBR [3, 4]. PARP1-dependent repair mechanisms are required for the repair of damage caused by temozolomide (TMZ) because the efficacy of TMZ depends on how multiple DNA alkylation lesions are processed through DNA excision repair pathways. TMZ alkylation causes damage to tumor DNA, and then PARP1 is activated to recruit DNA repair factors to repair those damaged sites. Thus, the effect of TMZ is greatly reduced [3, 4]. In addition, PARP1 activity is not restricted to the repair of DNA damage such as SSBs and double-strand breaks (DSBs). In the normal S phase, PARP is bound to unligated Okazaki fragments that form abnormal DNA structures, and these structures can thus activate PARP1 activity. Accumulation of unligated Okazaki fragments may result in replication-associated stress and cause damage to the genome. Based on the above results, PARP1 is required for the maintenance of genomic integrity during normal DNA replication [4-6].

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PARP1 recruits repair factors such as XRCC1 through PAR synthesis, which participates in single-strand break repair and base excision repair. The phenomenon identifies PARP1 as a key mechanistic node which restricts the therapeutic effect of TMZ.

3. Sensitizing effect of PARP inhibitors on temozolomide-sensitive cells

3.1. MGMT-mediated repair and its role in TMZ resistance

MGMT-mediated repair plays an important role in TMZ resistance. MGMT (O^6-methylguanine-DNA methyltransferase) is a protein that can repair TMZ-induced O^6-methylguanine (O^6-MetG) DNA lesions by transferring O^6-MetG from DNA to its own active site [5, 6].

In GBM tumors with an unmethylated MGMT promoter, which occur in approximately 60 percent of patients, MGMT rapidly removes TMZ-induced O^6-MetG adducts, and the tumors thus develop resistance to TMZ. However, methylation of normally unmethylated sites in the cytosine-phosphate-guanine (CpG) islands in the DNA-repair gene region leads to a loss of expression of such genes in cancer cell lines and primary tumors. When demethylating drugs were used in an in vitro experiment, expression of MGMT was restored, a result that indicated that methylating drugs inhibit MGMT expression [5, 6].

In a clinical study that used carmustine as standard treatment, 12 of the 19 patients with methylated tumors (63 percent) had a partial or complete response to carmustine, whereas such a response was observed in only 1 of the 28 patients with unmethylated tumors (4 percent, $P<0.001$). As carmustine and TMZ are both alkylating agents, MGMT promoter methylation may in turn enhance the efficacy of TMZ in DNA alkylation, a finding that demonstrates the therapeutic potential of MGMT inhibition in TMZ treatment [5, 6].

Moreover, MGMT-mediated repair is not the only canonical mechanism for repairing DNA lesions induced by alkylating agents. PARP1, through PARylation, can directly interact with MGMT in a non-catalytic manner. That is, MGMT is modified by PARP1-mediated PARylation after DNA damage, and O^6-methylguanine repair is enhanced upon MGMT PARylation. Specifically, PARylation enhances the ability of MGMT to recruit new DNA repair proteins and activates MGMT function, which increases the efficiency of MGMT in DNA lesion repair [7].

Furthermore, long-term TMZ exposure during clinical treatment induces PARylation of MGMT and increases the binding of PARP1 and MGMT to chromatin in cells, which in turn undermines the efficacy of TMZ in glioma treatment [7].

3.2. PARP1-mediated replication fork protection

PARP1-mediated replication fork protection is another mechanism relevant to TMZ resistance. In GBM cells, PARP1 has been shown to protect and restart stalled replication forks under replication stress, a finding that suggests PARP1-mediated replication-fork protection may contribute to the ability of tumor cells to tolerate replication-associated DNA damage [4, 8].

As mentioned above, when an SSB occurs in DNA, the DNA-binding domain of PARP1 binds to the damaged DNA, and this binding activates PARP1, which then produces PAR using NAD^+ as a substrate and recruits DNA repair proteins [5-7].

In the context of TMZ treatment, when SSBs and other DNA discontinuities arise during DNA replication, their repair becomes more closely linked to replication-associated processes. That is, DNA repair focuses not only on repairing DNA lesions but also on maintaining normal replication fork progression. Replication stress describes the impaired progression of a normal replication fork

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that occurs when replication machinery detects DNA damage and DNA abnormalities. Replication stress can be alleviated through multiple pathways, including direct DNA repair, lesion bypass, repriming, and fork remodeling. In direct DNA repair, PARP1-mediated DNA damage signaling is particularly important for maintaining genome stability when DNA discontinuities arise during replication. PARP1 serves not only as a sensor of SSBs but also as an "employer" that recruits new repair genes and proteins as its "new employees" to repair the DNA lesion. Besides direct DNA repair, other pathways include translesion synthesis (TLS), DNA polymerase theta-primase (PRIMPOL)-mediated repriming, and replication fork reversal. Specifically, TLS bypasses the DNA lesion to continue DNA replication, and PRIMPOL-mediated repriming restarts DNA replication after the DNA lesion. In addition, fork reversal temporarily remodels the stalled fork to provide opportunities to repair DNA lesions in the future [4, 8].

The role of the PARP1 pathway in replication stress is also strongly associated with Okazaki fragments. Okazaki fragments are DNA fragments in the lagging strand of DNA replication. If multiple Okazaki fragments are not correctly positioned or properly removed, DNA gaps and nicks may result. Such gaps and nicks damage DNA during replication and, in some cases, worsen the situation under replication stress. The abnormal DNA structure can activate PARP1 and trigger DNA repair signaling, so PARP1 is employed to help cells address replication-associated DNA damage via the SSBR pathway [4, 8].

The recruited XRCC1 in this repair mechanism can help coordinate repair factors such as PARP1, DNA polymerase β, and DNA ligase III at the damaged site, thereby accelerating the completion of base excision repair (BER) and SSBR. Under the influence of TMZ, the BER pathway is engaged to repair the N3-methyladenine (N3-meA) and N7-methylguanine (N7-meG) damage it causes, and this repair process extends the life of cancer cells. Therefore, XRCC1 repair may reduce TMZ-induced cytotoxicity and thus inhibit the effectiveness of TMZ [4, 8].

Other repair factors also respond to replication-associated gaps. For example, apurinic/apyrimidinic endonuclease 2 (APEX2) participates in BER and contains a proliferating cell nuclear antigen (PCNA)-interacting motif. Together with other repair factors such as flap endonuclease 1 (FEN1), APEX2 may contribute to the processing of replication-associated DNA gaps, which demonstrates the cooperation between different DNA repair pathways. Once the DNA gaps are successfully repaired, however, repair factors will turn to repairing the TMZ-induced lesion. As a result, the participation of other repair factors in replication gap repair may indirectly and potentially lead to a reduction in TMZ cytotoxicity [4, 8].

PARP1 participation in DNA repair in GBM cells is not limited to the direct repair of single-strand breaks. Instead, PARP1 can respond to replication-associated DNA discontinuities and contribute to the direct repair or restart of stalled replication forks under replication stress. With the help of XRCC1 and other repair factors, DNA damage could be rapidly repaired. However, these repair mechanisms may help to repair the DNA damage caused by TMZ and thus enable GBM cells to continue proliferating in the presence of toxicity. Consequently, PARP1-mediated replication stress responses may promote TMZ resistance, and PARP1 inhibition can enhance the effect of TMZ by increasing TMZ-induced DNA damage [4, 8].

3.3. DNA repair of PARP1 in MMR

When TMZ disrupts DNA by forming O6-methylguanine, this O^6-methylguanine (O6meG):T mismatch will recruit the mismatch repair (MMR) pathway into action. The MMR pathway involves two main heterodimers, MutSα and MutLα [9]. The MutSα heterodimer, which comprises proteins MutS homolog 2 (MSH2) and MutS homolog 6 (MSH6), helps to recognize the O6meG:T mispair.

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The MutLα heterodimer, which comprises proteins MutL homolog 1 (MLH1) and postmeiotic segregation increased 2 (PMS2), acts as an endonuclease to nick the DNA once the mispair is recognized. The MutLα heterodimer likely recruits exonuclease I (EXO1) to remove the thymine lesion and to create space for a new nucleotide to be inserted. However, DNA polymerase will likely fill the nicked space with thymine before MutLα acts because the polymerase may mistakenly regard the missing thymine as an essential part of DNA [9, 10].

As a result, after the MMR machinery repeatedly removes the newly incorporated thymine, DNA polymerase is unable to add thymine continuously, which leads to a futile cycle of mismatch recognition and thymine removal [11]. Therefore, this futile cycle will not repair the lesion and is expected to increase the cytotoxicity of TMZ in cells lacking effective MGMT-mediated repair [10]. Liu et al. observed that the mismatch-dependent repair of 5'-directed excision was strongly promoted by PARP1 and thus inferred that PARP1 helps MMR target mismatch DNA for excision more efficiently and specifically [10]. Analysis of protein-protein interactions has identified other proteins that are in close association with PARP1 such as MutSα, EXO1 and replication protein A (RPA). Together, these data show that PARP1 is required for nicking mismatch DNA in MMR and may be involved in repairing the futile cycle of MMR induced by TMZ [11]. Although studies on how PARP1 undermines TMZ efficacy in MMR are scarce, further insights into the functional relationship between PARP1 and MMR come from a study of 5-fluorouracil (5-FU) treatment in colorectal cancer stem cells. In 5-FU treatment, PARylated PARP1 interacts with MSH6 and promotes MMR activity. In contrast, treatment with ABT-888, which inhibits PARP1, disrupted the interaction between PARP1 and MSH6 and thereby prevented PARylation and suppressed MMR activity. These effects in turn led to DNA mismatch and to cell death. Although these findings were obtained in 5-FU-treated colorectal cancer stem cells rather than in TMZ-treated glioblastoma, they provide additional evidence that PARP1 can regulate MMR through interactions with MMR proteins such as MSH6 in another type of cancer [11].

Even though PARP1 may promote mismatch repair through PARylation and interactions with MMR-related proteins to repair the damaged sites, the repeated excision and resynthesis are still blocked by the misrecognition caused by O6-meG thymine, which results in a futile repair cycle and persistent DNA damage. Studies of 5-FU provide supporting evidence for the role of PARP1 in regulating MMR, but the specific function of PARP1 in GBM and TMZ treatment still needs further evidence. Therefore, PARP1-mediated regulation of MMR may represent an important mechanism limiting the efficacy of TMZ and provide theoretical evidence for combining PARP1 inhibitors with TMZ to enhance tumor sensitivity [9-11].

4. Clinical evidence of PARP1 inhibition

Previous studies analyzing the mechanism of PARP1 suggest that PARP1 inhibition may enhance the efficacy of TMZ against GBM cells by suppressing DNA damage repair. However, whether this strategy can be directly applied in the clinic depends on several factors, namely whether the drug can achieve effective exposure within tumor tissue and whether the combination regimen is tolerable. Patient selection is another important factor. Clinical studies have begun to evaluate the dosage safety, tolerability, and preliminary efficacy of combining PARP inhibitors with TMZ, but this strategy is not yet widely used. This final chapter will focus on relevant clinical studies and will discuss the potential for clinical application of this therapeutic approach as well as its current limitations.

A study in 2022 based on the OPARATIC trial investigated the three factors mentioned above regarding olaparib combined with low-dose TMZ in patients with recurrent glioblastoma. Using a

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phase 3+3 dose-escalation design followed by a dose-expansion cohort, the study evaluated different olaparib dosing schedules and directly measured olaparib concentrations in tumor tissue obtained during neurosurgical resection. The results showed the median concentrations of 496 nM in tumor cores and 512.3 nM at tumor margins, which confirmed that olaparib can penetrate the brain tumor. Furthermore, since the results showed that the combination of Olaparib and TMZ could cause excessive harm to the blood, intermittent dosing had to be used to prevent the treatment from poisoning patients. Therefore, in the second phase, the recommended dose was olaparib 150 mg three days per week combined with TMZ 75 mg/m² daily for 42 days. Out of 39 evaluable patients, 14 patients (36%) were progression-free at 6 months. Overall, the OPARATIC trial showed that olaparib can reach recurrent glioblastoma at a suitable concentration when given intermittently with TMZ, but the issue of blood disorders still needs to be addressed [12].

Talazoparib (TAL) was also used as a PARP1 inhibitor in a TMZ treatment study. The results of the study showed that a combination of TMZ and TAL could significantly induce double-strand breaks in vitro in glioma cells with either high or low MGMT. Likewise, in a mouse study, the median survival of mice that received TAL with TMZ was extended from 50 days to 76 days, indicating that PARP1 inhibition is a promising target in TMZ treatment against glioma [13].

However, the effect of TAL in GBM is limited by its poor penetration of the blood-brain barrier (BBB). Kizilbash et al. found that the brain-to-plasma ratio of TAL was only 0.02 after administration [13]. Knockout of multidrug resistance protein 1 (MDR1) increased this ratio approximately tenfold to 0.23, suggesting that efflux mediated by MDR1 is a major barrier to TAL accumulation in the brain. Therefore, although PARP1 inhibition shows good preclinical efficacy, limited BBB penetration may hinder the transport of TAL to GBM cells [13].

In 2026, a study on the safety of PARP1 inhibitors included a total of 12 trials and 795 patients. The pooled disease control rate (DCR) of all the included studies was 27%. However, the twelve studies had different factors and norms, different groups of people in them, and they were very diverse with a large prediction interval (0.4-97.1%). Therefore, this pooled estimate should be taken with caution and is not a reliable indicator of the clinical benefit in all patients. The pooled rate of grade 3 or higher adverse events was 13%, and this rate was relatively low. However, the wide prediction interval (2.2-51.2%) and significant heterogeneity show that this estimate is quite uncertain. Survival results of the various subgroups were also shown. Although factors such as isocitrate dehydrogenase (IDH) status, MGMT promoter methylation, disease setting, and concomitant therapy may influence treatment outcomes, these findings still need further exploration (Table 1). The reasons include the limited number of studies, differences in clinical settings, and substantial between-study heterogeneity [14].

Overall, available evidence suggests that PARP inhibitors have investigational activity and an overall acceptable safety profile in selected glioma populations, yet the variation across different studies should also be considered. These analyses should be regarded as theoretical rather than definitive clinical evidence. In conclusion, Rashidi et al. suggest that larger randomized, biomarker-stratified trials with harmonized outcome definitions are required before PARP inhibitors can be assigned a clear therapeutic role in high-grade glioma (HGG) [14].

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Table 1. Comparison of PARP1 inhibitors

PARP1 inhibitors	Brain tissue / plasma issue ratio	BBB penetration	Clinical Evidence	Key limitation
Olaparib	<0.1	reported in GBM	OPARATIC study	hematologic toxicity
Talazoparib	0.1-0.2	Limited by efflux	In vivo study, frank study of mice	Poor central nervous system (CNS) exposure
Veliparib	0.47	Relatively favorable	Clinical trials	Limited clinical efficacy

5. Conclusion

Glioblastoma is highly invasive and heterogeneous. Traditional surgery, increasing the dose of temozolomide, or combined chemotherapy are difficult to achieve a radical cure and may easily exacerbate toxicity. This paper focuses on the DNA damage repair mediated by PARP1, revealing that it repairs the damage caused by temozolomide through pathways such as single-strand break repair, replication stress response, and mismatch repair. It also interacts with MGMT to enhance the repair ability and protect replication forks, thereby weakening the efficacy. Based on this, the biological rationality of inhibiting PARP1 to sensitize temozolomide is demonstrated.

Pre-clinical studies have shown that inhibitors such as olaparib and talazoparib can enhance the cytotoxicity of temozolomide. Clinical studies have confirmed that olaparib can penetrate tumor tissues but is limited by hematological toxicity. Talazoparib is restricted by the blood-brain barrier and MDR1 efflux. Existing evidence suggests that they have research activity and acceptable safety, but the high heterogeneity is insufficient to establish a clear therapeutic position.

Looking forward, this field will evolve towards enhancing central nervous system exposure, optimizing combination regimens, and precise stratification. In drug design, efforts will be made to develop more brain-penetrating PARP1-selective inhibitors or trappers. Delivery efficiency will be improved by using nanocarriers, receptor-mediated transport, and temporarily opening the blood-brain barrier. Meanwhile, drug-resistance mechanisms such as MDR1 efflux will be intervened. In terms of treatment strategies, intermittent administration, dose optimization, and combination with radiotherapy, immunotherapy, and DNA repair inhibitors will be the focus, aiming to improve efficacy while controlling bone marrow suppression and long-term toxicity. In patient selection, stratification will be based on MGMT methylation, IDH status, mismatch repair function, and replication stress markers. Survival benefits will be verified with unified endpoints and randomized controlled trials, promoting the shift of PARP1 inhibition from broad-spectrum sensitization to individualized combination therapy.

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