Clin Transl Oncol (2017) 19:273–278
DOI 10.1007/s12094-016-1547-4

REVIEW ARTICLE

Combining PARP inhibitors with radiation therapy for the treatment of glioblastoma: Is PTEN predictive of response?

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Received: 18 July 2016 / Accepted: 1 September 2016 / Published online: 21 September 2016

Abstract Glioblastoma (GBM) is fatal. The standard radiotherapy and chemotherapy (temozolomide) followed by an adjuvant phase of temozolomide provide patients with, on average, a 2.5 months benefit. New treatments that can improve sensitivity to the standard treatment are urgently needed. Herein, we review the mechanisms and utility of poly (ADP-ribose) polymerase inhibitors in combination with radiation therapy as a treatment option for GBM patients and the role of phosphatase and tensin homologue mutations as a biomarker of response.

Keywords PARP inhibitor · Glioblastoma · Biomarkers · PTEN

Glioblastoma

Glioblastoma (GBM) is a uniformly lethal disease that has had few therapeutic advances over the past century. The standard treatment for GBM consists of radiotherapy (RT) combined with temozolomide (TMZ) chemotherapy followed by at least six cycles of TMZ. The median survival is less than 15 months. Survival is significantly worse for patients whose tumor is unmethylated at the O^6-*methylguanine-DNA methyltransferase* (*MGMT*) promoter, because they do not respond to the TMZ component of the therapy. Approximately, 50–60 % of GBMs are *MGMT* unmethylated, and while it is generally accepted that these patients do not respond to the standard treatment, alternative therapies for this group of patients are lacking, creating a critical unmet need.

A number of studies have investigated the use of poly (ADP-ribose) polymerase (PARP) inhibitors to inhibit the DNA repair process. PARP inhibitors include veliparib (ABT-888; Abbvie), olaparib (AstraZeneca), talazoparib (Biomarin), and niraparib (Tesaro). Veliparib and olaparib are currently being investigated in GBM patients. The Alliance study in the US randomises GBM patients with methylated *MGMT* promotor to the standard RT and TMZ followed by TMZ or RT and TMZ followed by TMZ and veliparib. The VERTU study in Australia is currently recruiting primary GBM patients whose tumor is unmethylated at the *MGMT* promoter. Patients receive veliparib in combination with radiotherapy followed by an adjuvant course of veliparib and TMZ. In the United Kingdom, the Oparatic trial is treating recurrent GBM patients with a combination of olaparib and TMZ. This review outlines the use of PARP inhibitors and irradiation in GBM and the limited and conflicting evidences, regarding the impact of mutations in the phosphatase and tensin homologue (*PTEN)* gene upon this treatment.

Role of PARP in DNA repair

Poly (ADP-ribose) polymerase family member 1 (PARP1) is a nuclear enzyme involved in the recruitment of repair proteins required for base excision repair (BER) and single-strand break repair (SSBR). PARP1 binds to single-strand breaks (SSB) or SSB intermediates generated during BER [1]. Upon binding, PARP1 catalyses the formation of poly ADP-ribose (pADPr) chains onto itself and other

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proteins, including the DNA damage scaffold protein X-ray repair cross-complementing protein 1 (XRCC1). These pADPr chains signal and attract repair proteins [2].

There is conflicting evidence regarding whether PARP1 is required for BER/SSBR [3], merely speeds it up [4], or is not essential. Following siRNA knock down of PARP1, Godon et al. [5] found SSBR continued, whilst Strom et al. [6] found that there was no accumulation of SSB intermediates. Strom et al. [6] propose that PARP1 only binds to SSB intermediates which become uncoupled during BER.

Recent studies suggest that PARP1 also binds to double-strand breaks (DSB) and may play a role in restart of collapsed DNA replication forks and in an alternative non-homologous end-joining (NHEJ) pathway [7]. PARP1 is responsible for 85–95 % of pADPr production in humans [8]. Less is known about the role of poly (ADP-ribose) polymerase family member 2 (PARP2); however, it is suggested that PARP2 acts at later stages of BER/SSBR [1].

Use of PARP inhibitors in cancer treatment

There are a number of PARP inhibiting drugs currently being tested. Most PARP inhibitors (PARPi) are competitive inhibitors, which compete with NAD^+ to bind to PARP's active site [9]. Whilst it is generally thought that PARPi act to prevent or delay SSBR, there are conflicting views regarding the mechanism(s) by which this occurs. It has been proposed that the binding of PARPi to PARP1's active site prevents the formation of pADPr chains required to recruit repair proteins, thus delaying BER/SSBR and leading to the accumulation of SSB [10]. Alternatively, it is suggested that PARPi prevent the release of PARP1 from SSB/SSB intermediates, thereby preventing their repair [5, 9]. The latter view is consistent with findings that to dissociate from DNA; PARP1 must attach a pADPr chain to itself [11]. It also provides an explanation for findings that PARPi result in greater radiosensitivity and delays in SSBR than PARP depletion [5].

However, as noted by Lupo and Trusolino [12], these mechanisms are not mutually exclusive. Both will result in unrepaired DNA damage, which in replicating cells will lead to further damage requiring homologous recombination (HR) for repair. This could be due to persisting SSB causing collapse of replication forks and the generation of DSB during DNA replication [13, 14]. Alternatively, further damage could be due to trapped PARP-DNA complexes preventing DNA replication and requiring HR for repair [9]. Figure 1 illustrates the role of PARP1 in SSB DNA repair and the mechanisms by which PARPi are thought to generate further damage. The investigations of PARPi in cancer

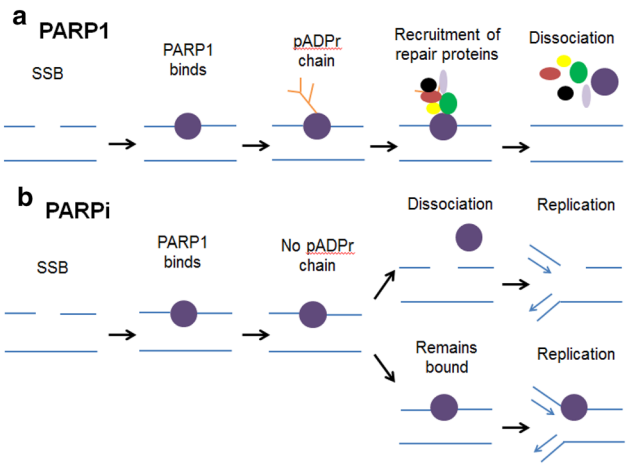

Fig. 1 Poly (ADP-ribose) polymerase family member 1 (PARP1) and PARP inhibitors (PARPi) in single-strand break DNA repair. **a** Simplified diagram showing the function of PARP1 in single-strand break DNA repair. PARP1 binds to single-strand breaks (SSB)/SSB intermediates and catalyses poly ADP-ribose (pADPr) chains to recruit repair proteins, before dissociating from repaired DNA. **b** Illustrates the effect of PARPi on PARP1. After binding to SSB/SSB intermediates, PARP1 is unable to catalyse a pADPr chain to recruit repair proteins. It has been suggested in the absence of repair proteins, PARP will dissociate from the DNA, leaving an unrepaired single-strand break which will cause collapse of the replication fork during DNA replication, generating a double-strand break that requires homologous recombination (HR) for repair. Alternatively, it is proposed that PARP1's inability to catalyse a pADPr chain will result in PARP1 remaining bound to the single-strand break, hindering DNA replication, and requiring HR for repair

treatment have focused upon their use to potentiate the effects of chemotherapy and/or radiotherapy and their use as a single agent in tumors with defects in HR [15].

Use of PARPi to potentiate irradiation

The primary mechanism by which ionising radiation causes damage is through the generation of free radicals that interact with DNA [16]. Whilst these interactions can damage nucleotides and lead to SSB and DSB, SSB are the most prevalent [15]. Damage to nucleotides and SSB is primarily repaired by BER/SSBR, whilst DSB are repaired primarily by NHEJ [13]. However, DSB which occur during DNA replication are repaired by HR [17].

The use of PARPi, to inhibit or delay the BER/SSBR process, in combination with irradiation can, therefore, assist in converting radiation-induced nucleotide damage and SSB into more toxic DSB [15]. However, as demonstrated by Noel et al. [18], this will only occur in replicating cells.

Whilst cells proficient in double-strand break repair (DSBR) can fix this damage, given the amount of damage irradiation can induce in a short period, it is possible that

these repair mechanisms may become overwhelmed [19]. Based upon studies implicating PARP1 in the recruitment of proteins involved in replication fork restart, it is possible that PARPi may directly effect this HR-mediated process [7]. PARPi and irradiation could also take advantage of defects in DSBR pathways [20], such as reduced expression of HR proteins which has been found in hypoxic cells [21]. In the absence of repair, DSB can result in cell-cycle arrest, apoptosis, or senescence [17].

The use of PARPi in combination with irradiation has been shown to increase the radiosensitivity of commercial GBM cell lines [13, 14, 22], primary GBM initiating cells [23], and in in vivo studies [14]. However, the findings of Venere et al. [23] suggest that the radiosensitising effects may be primarily due to their impact upon GBM initiating cells (GIC), with decreased viability only seen in one of the three non-GIC specimens. There is, however, criticism of the marker used by Venere et al. [23] to identify GIC's, with studies showing that $CD133^{+}$ cells are not the only cells with initiating properties [24]. Furthermore, as the cell lines used in the other studies would also have contained GIC's, these results are not necessarily contradictory.

In contrast to these studies, Clarke et al. [25] found veliparib and irradiation resulted in no additional survival benefit compared with irradiation alone, using the primary GBM orthotopic models. Surprisingly, they also found veliparib and TMZ had a greater effect than combined veliparib, TMZ, and irradiation in the GBM12 cell line, whilst the results in the GBM22 cell line were not significant. However, as acknowledged by the authors, these results are based upon very limited data. Majuelos-Melguizo et al. [26] reported no additional benefit from the use of veliparib and irradiation compared with veliparib alone in commercial GBM cell lines. However, they do not include any data to support these findings and unlike the other in vitro studies, appear to rely upon an MTT assay to measure cell viability, rather than clonogenic survival assays. Given the limitations of these studies, the weight of evidence tends to suggest that PARPi radiosensitise GBM.

PARPi and synthetic lethality

The use of PARPi alone in breast cancer 1 and/or breast cancer 2 (together BRCA) deficient cells has been shown to result in increased sensitivity. The BRCA proteins play an essential role in HR and it is believed that PARPi-induced effects upon SSBR, in cells deficient in HR, result in synthetic lethality [27]. As GBM's do not commonly have defects in genes coding for proteins directly involved in HR [16], it is not known what factors may mediate sensitivity to PARPi in these tumors.

PTEN

PTEN is located on the long arm of chromosome 10 and codes for a lipid and protein phosphatase. PTEN contains a phosphatase domain in its N terminal region and a C terminal region believed to play a role in the nucleus [28]. Loss of one allele of the long arm of chromosome 10 is found in 70 % of GBM patients, with somatic mutations occurring in 25–40 % of cases [29].

PTEN's role in the PI3 K/Akt pathway

In the cytoplasm, PTEN negatively regulates the phosphoinositide 3-kinase (PI3 K)/Akt pathway, through its dephosphorylation of phosphatidylinositol 3,4,5-trisphosphate (PIP3). The pathway is activated by the binding of growth factors to tyrosine kinase receptors, which, in turn, activate PI3 K, which phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to generate PIP3 [29]. In the absence of PTEN, PIP3 phosphorylates Akt, which, in turn, phosphorylates other molecules involved in cell-cycle progression, growth, angiogenesis, and the inhibition of apoptosis [30].

The loss of PTEN has been linked to radioresistance, as a result of unchecked activation of Akt and Akt's negative effect upon levels of checkpoint kinase 1 (Chk1). Chk1 plays a critical role in suppressing DNA replication and activating G2/M cell-cycle arrest to allow time for DNA repair [31].

Studies have shown *PTEN* mutations confer radioresistance in GBM. Wick et al. [32] and Kao et al. [33] demonstrated the introduction of the *PTEN* gene to *PTEN* mutant ($PTEN_{mt}$) GBM cell lines sensitised the cells to irradiation. The former study demonstrated that the phosphatase domain of PTEN was required for this effect. Kao et al. [33] also showed the introduction of *PTEN* decreased levels of phosphorylated Akt and led to the persistence of γ-H2AX, a marker for unrepaired DSB. McEllin et al. [34] reported that GBM cell lines deficient in PTEN were more radioresistant and found that the deletion of PTEN in murine astrocytes resulted in radioresistance. The addition of PTEN has also been shown to lead to radiosensitivity and impaired DSBR in $PTEN_{mt}$ lung and prostate cancer cells [35, 36]. However, Fraser et al. [37] found that the depletion of PTEN in primary prostate cancer cells led to radiosensitivity, leading the authors to suggest cells which develop in the absence of *PTEN* which may function differently to those, in which PTEN is experimentally removed.

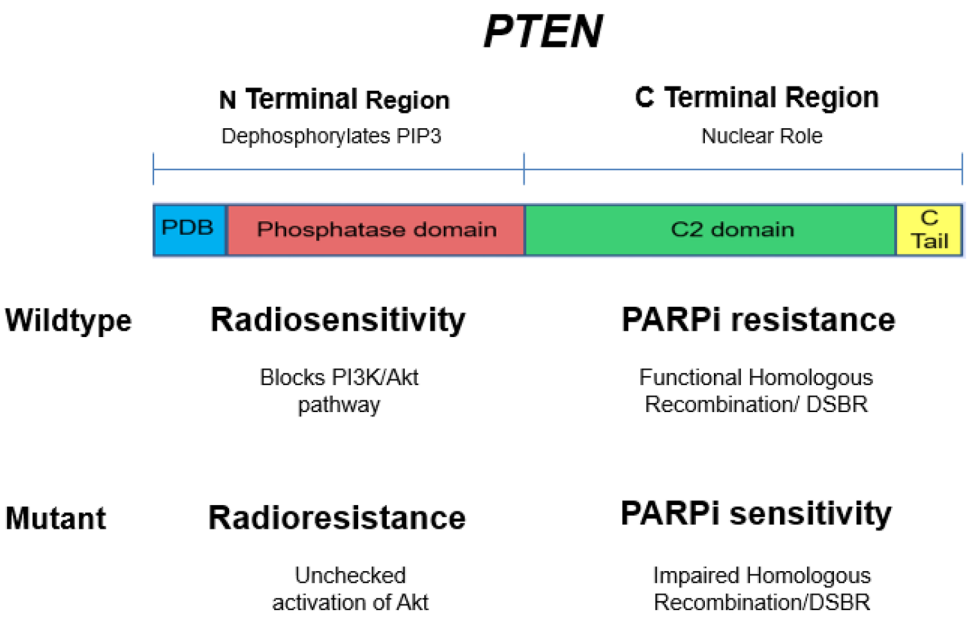

Fig. 2 Location of the PTEN mutation may determine the response to PARP inhibitors (PARPi) and irradiation. Summary of the proposed effects of irradiation and PARPi upon the N and C terminal regions of PTEN, the impact of mutations in each region, and the mechanisms by which these effects are thought to occur. The status of the phosphatase domain in the N terminal region of PTEN has an impact upon the cells response to irradiation. Cells with functional N terminal regions are radiosensitive, whilst those with mutations in this region are more radioresistant. Mutations in the C terminal region may impact upon the cells response to PARPi. Cells with mutations in the C terminal region of PTEN have been shown to be sensitive to PARPi, whilst those with functional C terminal regions have been shown to be resistant to PARPi. *PBD* PIP2-binding domain, *DSBR* double-strand break repair

PTEN's role in the nucleus

Significantly less is known about PTEN's role in the nucleus. In addition to contributing to chromosomal integrity, it has been suggested that PTEN regulates *RAD51* [38]. RAD51 is recruited to the site of collapsed replication forks and plays an essential role in HR [13]. Although subsequent studies have moved away from the notion that PTEN directly regulates *RAD51*, many studies suggest *PTEN* mutations affect DSBR. There is, however, a little consensus regarding the mechanism(s) by which this occurs. Mendes-Pereira et al. [39] reported a reduction in RAD51 foci following DNA damage, whilst McEllin et al. [34] found a decrease in RAD51 paralogs, believed to assist RAD51, in $PTEN_{mt}$ astrocytes. Using embryonic kidney cells, Mukherjee and Karmakar [40] found reduced RAD51 foci and loss of the G2/M checkpoint in $PTEN_{mt}$ cells. Minami et al. [41] reported reduced RAD51 foci and levels of MRE11, which is also involved in HR, in $PTEN_{mt}$ lung cancer cells. More recently, He et al. [42] (2015) found RAD51 dissociated from replication forks in $PTEN_{null}$ HeLa cells, suggesting that PTEN may play a role in recruiting RAD51 to collapsed replication forks.

However, there are also studies suggesting that *PTEN* mutations may have no effect upon HR. Using the same cell lines as Shen et al. [38], Gupta et al. [43] found no reduction in RAD51, nor increased residual DNA damage in $PTEN_{mt}$ cells. Differences in the findings have been attributed to different methods used [44], with the findings of Shen et al. [38] based on spontaneously arising DSB, whilst Gupta et al. [43] used irradiation prior to measuring DSB. The studies also used different antibodies to detect RAD51, which Gupta et al. [38] found led to markedly different results. Fraser et al. [37] also reported finding no association between *PTEN* status, RAD51, and HR in primary prostate cancer cells. Despite this, they found the use of siRNA to knock down PTEN in H1299 lung cancer cells resulted in increased sensitisation to PARPi. In light of their conflicting findings, they suggest that there may be a difference in the phenotype of cells that develop without *PTEN* and those in which PTEN is knocked down using siRNA. However, this does not explain contrary findings in cell lines, where the PTEN expression was not experimentally reduced [39, 41]. Fraser et al. [37] also propose that the interaction between PTEN and DSBR pathways may be cell/tissue specific. The findings of Miyasaka et al. [45] suggest that this could be the case, with $PTEN_{mt}$ cells in endometrial cancer cell lines showing both the greatest and least levels of resistance to PARPi.

The potential interaction between PTEN and RAD51 has led to studies investigating the use of PARPi in $PTEN_{mt}$ cells. Mendes-Pereira et al. [39] used PARPi in a range of commercial tumor cell lines, including GBM, finding a

significant reduction in HR in $PTEN_{mt}$ cells. However, only cells with mutations in the C terminal of PTEN ($PTEN^{C-}$) displayed increased sensitivity to PARPi, whilst those with mutations limited to the N terminal ($PTEN^{N-}$) were resistant. Consistent with these findings, Gong et al. [46] found that $PTEN_{wt}$ cells were less sensitive to PARPi, whilst $PTEN^{C-}$ cells showed similar sensitivity to $PTEN_{null}$ cells. Sun et al. [47] reported increased DSB in $PTEN_{null}$ and $PTEN^{C-}$ cells. These findings suggest that it is the loss of the PTEN C terminal that confers sensitivity to PARPi and may provide an explanation for the different findings regarding PARPi and PTEN status. The broadly agreed the role of the two regions of PTEN and the potential effect of mutations in these regions is summarised in Fig. 2.

Use of PARPi and irradiation in $PTEN_{mt}$ GBM

Examination of earlier studies that included GBM cell lines with known *PTEN* mutations provides conflicting evidence. Dungey et al. [13] found that the use of PARPi did not increase radiosensitivity or reduce cell survival in U87MG $PTEN_{mt}$ GBM cells, whilst Barazzuol et al. [22] found a modest radiosensitising effect in this cell line. Conversely, U251MG $PTEN_{mt}$ GBM cells were highly sensitised to PARPi and irradiation [13, 14, 22]. Whether these differences are potentially attributable to the $TP53_{mt}$ present in U251MG cells [48], the location of the *PTEN* mutation is the evidence that different cells may respond differently to PARPi is unknown.

Summary

Approximately 70 % of GBM patients harbor mutations in the *PTEN* gene. It is, therefore, imperative that we gain a better understanding of the role of PTEN in mediating the response to treatment with PARPi and irradiation. However, evidence in the literature regarding the role of PTEN and the response to PARPi in GBM is limited and conflicting. It is estimated that >50 genes, many mutated in cancer, can confer sensitivity to PARPi. It is, therefore, important that we test all patient tumors that are enrolled in PARPi clinical trials for biomarkers of clinical response.

Compliance with ethical standards

Conflict of interest None.

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