Pathol. Oncol. Res. (2010) 16:469–478
DOI 10.1007/s12253-010-9266-6

PARP and PARG Inhibitors—New Therapeutic Targets in Cancer Treatment

Nilufer Jasmine Selimah Fauzee · Juan Pan · Ya-lan Wang

Received: 23 December 2009 / Accepted: 29 March 2010 / Published online: 12 April 2010
© Arányi Lajos Foundation 2010

Abstract Today, the number of cancer patients throughout the world is increasing alarmingly and as per the World Health Organisation (WHO) data and statistics the prediction for the year 2020 will be 15 million new cases as compared to only 10 million cases in year 2000 leaving us dumbfounded. A lot of effort has been put in by researchers and scientists over decades to find drugs helpful in the treatment of cancers for the benefit of patients—The latest being the Poly ADP-ribose polymerase (PARP) and the Poly ADP-ribose glycohydrolase (PARG) inhibitors. This review highlights their mechanism of action under the rationale of their use and current development in the field of cancer.

Keywords PARP · PARG · PARP inhibitors · PARG inhibitors

Abbreviations
PARP Poly ADP ribose polymerase
PARG Poly ADP-ribose glycohydrolase

Introduction

Poly ADP-ribose polymerase (PARP) is an enzyme important for genomic stability in our body; usually in a normal cell it arrests cell death. In brief, it is a nick-sensor that signals the presence of DNA damage and facilitates DNA repair. The first PARP enzyme was discovered more than 40 years ago by Chambon et al. [1] and it is the prototype for a superfamily of 18 members [2] whereby only PARP-1 and PARP-2 are known to act in DNA damage [3]. It also catalyses long branched homopolymers of ADP ribose e.g PAR (poly ADP–ribose) from molecules of NAD+. The above cellular suicidal mechanism has been reported in the pathomechanism of stroke, shock, myocardial ischemia, arthritis, colitis, traumatic central nervous system injuries, allergic encephalomyelitis, diabetes and diabetes associated with cardiovascular dysfunctions as well as other inflammatory processes. Another interesting feature is its involvement in the regulation of several transcription factors like Nuclear Factor Kappa-B in the expression of chemokines, adhesion molecules, inflammatory cytokines and mediators [4].

PARG (Poly ADP-ribose glycohydrolase) is the main enzyme in catabolising PAR to ADP-ribose. To date, only one single PARG gene has been detected in mammals [5] encoding for 3 cDNAs which generates 3 isoforms namely 110 kDa, 102 kDa and 99 kDa [6], amongst which its major form is 110 kDa. The latter has been localized to the nucleus, the cytoplasm [7]; co-localised with cytochrome C [8] and during mitosis has been identified in the spindle body and centrosomes too [9]. However, human PARG known as full length 111 kDa is confined to the nucleus due to a NLS (nuclear localization signal) encoded by exon1 [10]. It has been found that PARG is not only expressed in different subcellular compartments of the neuronal tissues but also heart, testis and kidneys; mainly in their mitochondrial/cytosolic fraction [8]. Since, the poly ADP-ribosylation of nuclear proteins is an ongoing process; so, nuclear-cytosolic shuttling of PARG is constant and at the same time, the endo-glycosylase activity of PARG which is physiologically important continuously generates protein free ADPr polymers that can interact with histones and

N. J. S. Fauzee · J. Pan · Y.-l. Wang (✉)
Department of Pathology, Molecular Medicine and Cancer Research Center, Chongqing Medical University, Chongqing 400016, China
e-mail: wangyalan074@126.com

other nuclear proteins useful in intracellular pathways [1]. PARG has proved itself in various post-traumatic inflammatory reactions, in mediation of oxidative and excitotoxic neuronal death, intestinal injuries, stress challenges like streptozotocin induced hyperglycemia and endotoxin induced septic shock [5]. However, here we will mostly discuss about PARP and PARG inhibitors in relation to cancer.

Mechanism of Action of PARP and PARG in the Body

PARP Catabolism

Poly ADP-ribosylation is a dynamic process where poly (ADP-ribose) polymer- PAR is rapidly degraded by PARG and ADP ribosyl protein lyase [4]. The half-life of ADP-ribose polymers estimated to be less than 1 min is due to PARG that cleaves the ribose-ribose bonds [11, 12] of both linear and branched portions of the polymer, specifically the glycosidic and glycosidic linkages of pADPR [13] and on the other hand, it is the ADP-ribosyl protein lyase which removes the protein proximal to the ADP-ribose monomer [11]. After the polymer is split and inactivated, there is the release of PARP so that it can now bind to a new site of DNA damage and the whole process starts over again.

In DNA Repair PARP and PARG go Hand in Hand

PARP has multiple intra-cellular functions such as: synchronising repair enzymes, operating as a modulator of BER capacity, recruiting repair enzymes at damaged sites, signaling DNA damage, recognizing and binding to DNA strand break generated by genotoxic agents (monofunctional alkylating agents, oxygen radicals, and ionizing radiation) [14]. Activation of PARP is one of the earliest DNA damage responses amongst other DNA sensing molecules such as DNA-PK, ATM and p53 which is a tumor suppression protein activated after DNA damage; closely related to PARP-1[15]. In the sense that, an absence of PARP-1 leads to an accumulation of P53 which activates specific DNA binding and favors transcriptional activity for DNA damage.

DNA base excision repair (BER) constitutes a major mechanism for genomic stability. It is well established that BER is facilitated by poly ADP-ribosylation whereby, in the ligation step PAR serves as a source of ATP. Recombinant BER proteins including Polβ, XXRC1, Lig III, FEN1 and APE-1 show that both PAR and DNA synthesis are enhanced due to lack of energy i.e ATP; hence showing their importance in some pathological states [16]. On the other hand, it has been shown that deficiency of several proteins (ATR, ATM, NBS1, CHK1 and CHK2) in the Homologous Recombination (HR) system useful in DNA damage signaling, tend to increase cellular sensitivity to PARP inhibitors therefore, demonstrating their respective importance in the combat against cancer [17].

Moreover, PARG also plays an important and effective role in DNA repair. It has been found to be re-localised at sites of DNA breaks induced by UV-A laser micro-irradiation in HeLa cells [9] and its interaction with XRCC1, a DNA repair factor that is recruited during DNA damage activates PARP-1.

Evidence shows that together, through a series of steps both PARP and PARG repair DNA [1]. When PARP binds to DNA strand breaks, it activates an enzyme causing shuttling of PARP and subsequently, opening of the chromatin. PARG enters nucleus, moves to the PARP substrate and DNA strand breaks are repaired. Due to excessive PARG, PAR decreases and thus, chromatin adopts back its original structure.

Role of PARP and PARG in Cellular Death

Two main pathways of cell death related to PARP-1 are apoptosis and necrosis. Apoptosis is an active process requiring energy while necrosis is a passive process. DNA damage causes an over activation of PARP which depletes intracellular ATP irreversibly leading to necrotic cell death rather than an apoptotic one. Therefore, PARP activation seems to control the mode of cell death by influencing ATP levels [18] but, several lines of study and research have concluded that PARP-1 is dispensable for apoptosis [4]. During apoptosis, it is noted that both PARP and P53 are released [19] along with the activation of a cascade of cystein proteases called caspase. So, PARG and PARP cleaved by caspase-3 during apoptosis suggest a primordial function of PAR metabolism during cell death [20] unlike in many neurodegenerative conditions [21] where there is the release of apoptosis inducing factor (AIF) [11]. Poly ADP-ribosylation has an important role in modulating cellular responses in both mild and moderate stress conditions but, in severe stress following acute injury or ischemia, there is over activation of PARP-1 resulting in abnormal PAR synthesis and subsequently widespread cell death. Thus, PAR signaling regulated by either PARP-1 or PARG is a mediator of cell death. Furthermore, it has been noted that in glioma cells there are both pathways of cell death as well as an indication for the existence of intermediate forms of cell death [22]. A new function of PARP-1 brought to light in cell death mediation is the promotion of autophagy in oxidatively stressed cells [23].

PARP inhibitors are known to block necrotic cell death but not apoptosis; like in Burkitt's lymphoma [24], endothelial cells [25] and LLC-PK1 renal epithelial cells [26]. However, in ischemic-reperfusion models, PARP

inhibitors have shown to preserve NAD+ and ATP through activation of P13/Akt pathways leading to cytoprotective effects in heart [27] by minimizing size of infarcts; in the brain [28] during stroke by restoring mitochondrial respiration; in vascular diseases by improving endothelial cell functioning [29]; in hemorrhagic shock ameliorating liver microcirculation [30], having neuroprotective effects on NMDA induced retinal injury [31] and furthermore, prevention of Type 1 diabetes in mice models has been underlined [32]. PARP inhibitors reversing the mode of cell death from necrosis to apoptosis have also been reported [33] and hence, PARP inhibitors might be of therapeutic use in the future in cases of inflammatory conditions, stroke, cardiovascular insufficiency and other major diseases.

While, PARG though having a low cellular abundance, has a high sensitivity as its deficiency enhances cellular death after genotoxic stress. Hydrolysis of PAR by PARG has a protective role; as the accumulation of PAR leads to apoptotic cell death [21]. Disruption of PARG leading to peri-implantation lethality appears to be mostly apoptotic in PARG null TS (embryonic trophoblastic stem cell) cells but however, non-apoptotic mechanisms cannot be ruled out [6]; in *D. Melanogaster* inactivation of PARG resulted in severe PAR accumulation in neuronal cells and consequently apoptotic lethality at the larval stage [34] while in XRCC1 deficient cells, the combined activities of PARP-1 and PARG led to non-apoptotic cell death [35]. PARG down regulation does not somehow interfere with the cascade of events leading to apoptotic cell death but instead, it increases the threshold activation of programmed cell death [10].

Action of PARP and PARG in Cell Proliferation and Differentiation

Normal cells undergo a series of proliferative steps so that they can acquire multiple functions and in the long run are differentiated into specialized cells but, some cells like lymphocytes, fibroblasts, and hepatocytes conserve their ability to proliferate [4]. However, combined co-expression of PARP-1, PARP-2 and PARG is known to favour normal cell growth; like PARP-1 along with ATM has been shown to be essential in early embryonic development [36].

The inactivation of PARP by chemicals or genetic mutations slows down cell replication, proliferation, differentiation; increases sister chromatid exchange (SCE); micronuclei formation; chromosome instability and shortens telomeres [1, 37]. Chromosome associated proteins [38], centromere proteins [39] and replication factors such as DNA polymerase alpha, topoisomerase I, II and proliferating nuclear antigen [4] implicated in cellular differentiation in tumor genesis are usually poly ADP-ribosylated [38]; hence, over expression of PAR promotes cell cycle arrest in NB4 acute pro-myelocytic leukemia cells [40], in acute myeloid leukemias [41] and down modulation of PARP in human TUR leukemia cells [42], trophoblastic cell differentiation [43] and mouse embryonal stem cell differentiation in teratocarcinomas [44] also halts cellular proliferation.

PARG has also been found to be necessary in cell proliferation and differentiation. An arrest of the embryological development phase in PARG-/- embryos was due to an increase in PAR which prevented cellular replication characterized by unhatched blastocysts [6] and in C6 glioma tumor dividing cells there was a high PARG activity therefore, lack of PARG could anticipate cell growth arrest [45], showing that PARG protein deficiency may have a crucial role in tumor treatment.

Regulation of Gene Expression

PARP transcriptional history began at the time when Roeder and his collaborators [1] identified a factor TFIIC which increased specificity of RNA polymerase II transcription initiation and was later identified as PARP, which has 2 main roles in transcriptional regulation; namely the modification of histones and as a component enhancer in regulatory complex mechanisms, both needed for gene regulation in vivo [46]. PARP in reconstituted systems eliminates any non- specific transcription resulting from the presence of SSBs (Single Stranded Break) in the transcription template without alteration of the specific promoter driven transcription at least in vitro; hence, not requiring enzymatic activation, as observed by Slattery et al. [1]. PARP may play additional roles such as transcriptional co-activator and enhancer when interacting with transcription factors like activator protein-2 (AP-2) [1], retinoic acid receptor (RAR) for Rarβ gene [47], β-catenin/ TCF4 complex dependent transcription [48] and in EWS (Ewing's Sarcoma cells) transfected with ETS 1 antisense cDNA [49]. PARP-1 is known to maintain basal expression levels and transcriptional regulation of a wide variety of genes on a wide scale genome like in ES (embryonic stem) cells, in livers of mice [50], in myeloid differentiation [41] and human dendritic cell function [51]. Nevertheless, with transcriptional activator Sp1, PARP-1 has had a dual regulatory function in gene expression [52] whereas, PARP-1 together with P53 is known to maintain genomic stability whereby mutation or inactivation of p53 gene has lead to soft tissue tumors (liposarcomas), lymphomas, leukemias [53] and medulloblastomas in mice [54]. Compiled evidence showed that PARP regulated gene expression of several transcriptional factors such as YY1 [55], Oct-1 [56], NF-κB [57], E47 [58] and TEF-1 [59]. Besides, it appears possible that poly ADP-

ribosylation can even regulate transcription during DNA damage [60].

PARG being the main enzyme in PAR metabolism is essential in gene expression. Whereby, poly ADP-ribosylation is involved in chromosomal separation [9], DNA processing, cellular defense mechanisms via transcriptional regulation and PARG isoforms produced at transcriptional level are either by alternative splicing or promoter selection [61]. Lack of PARG activity led to transcriptional dysregulation altering circadian periodic length in Arabidopsis [6] and use of a PARG inhibitor (gallotannin-GT) in A549 cells suppressed expressions of cytokines and chemokines blocking the activation of transcription factors NF_KB and activator protein-1 (AP-1) showing that GT has an impressive suppressive action in inflammatory gene expression [62].

PARP-1 and PARG, even with opposing enzymatic activities, can localize to target promoter sequences and act in a similar way to regulate gene expression [63], concluding that coordinated action of PARP and PARG is required for proper cellular response and maintenance of genomic stability [13, 64]. So, both selective inhibitors may ultimately be used to improve cancer regression.

PARP and PARG in the Angiogenesis of Tumor Growth and Metastasis

Tumor angiogenesis is the proliferation of new blood vessels within the cancerous tissues, providing oxygen and nutrients to the latter and this process is achieved upon the signaling of certain genes in the host thus, making proteins encourage new growth. It is an important point of control in cancer progression and its inhibition is of valuable approach in cancer therapy.

Among the main activators of angiogenesis are VEGF (vascular endothelial growth factor) and bFGF (basic fibroblast growth factor) released from tumor cells which on encountering endothelial cells bind to their receptors, activating a cascade and promoting new endothelial cell growth. Usually, for tumors to increase in size and have some metastatic potential there should be over-expression of pro-angiogenic factors (i.e VEGF) allowing the angiogenic switch; nevertheless, its inhibition leads to suppression of angiogenesis [65]. Thus, hampering of growth factors VEGF and placental growth factor by PARP inhibitor did have an anti-angiogenic effect in knockout mice [66]. PARP inhibitor abolished VEGF-triggered phosphorylation of ERK1/2 (Extracellular Signal Regulated Kinase), p38, Akt, providing a molecular basis of its anti-angiogenic effects [67]. Reduction of VEGF actions also inhibited proliferation of human umbilical vein endothelial cells (HUVEC) in vitro [68] and sprouting of aortic rings [69] when, usually PARP is known to promote capillary morphogenesis in vitro and neovascularisation in vivo. cDNA microarray analysis during skin carcinogenesis showed that PARP-1 modulates expression of several genes such as HIF-alpha, Pecam-1 and OPN important in angiogenesis [11] and that inhibiting PARP-1 activity can also attenuate certain pathologies associated with hepatocellular carcinoma, cervical cancer, non-Hodgkin's lymphoma, CLL (chronic lymphocytic leukemia), adenomatous polyps and colorectal carcinoma [70–74]. Recently, Gallotannin used as PARG inhibitor in colorectal carcinoma proved that PARP and PARG expressions associated with VEGF and bFGF were lower in treated cells, so probably preventing growth and metastasis [75].

PARP and PARG Inhibition

PARP inhibition is an important approach in sensitizing cancer cells to both monotherapy or along with chemotherapy and radiotherapy [14]. PARP inhibitors are lethal in BRCA deficient cells due to persistence of DNA lesions that would normally be repaired by BRCA mediated HR pathways or in a BRCA dependent fashion [76]. Not only BRCA1 or BRCA2 cells showed extreme sensitivity to PARP inhibitors but also any disruption in the components of the HR system (ATM, ATR, PTEN, Rad51 and others) conferred selective PARP inhibitor sensitivity. This phenomenon of synthetic lethality is the key to ongoing clinical trials and it is supported by recent publications of Ashworths Laboratory on a siRNA screen which identified genes for DNA repair and kinases extending the list of enzymes showing synthetic lethality when applied with PARP-1 inhibitors [77–79]. A highly specific clinical treatment for the BRCA deficient tumor cells could be delineated on PARP-1 pathway becoming essential in HR deficient cells [80] or in pathways lacking HR proteins [17] and so further studies are to be encouraged in this line. Carriers of heterozygous mutations in BRCA1 or BRCA2 [11] are strongly predisposed to both breast and ovarian cancers [81]; observations suggest that PARP inhibitors might be an effective monotherapy in these cancers. In non-neoplastic BRCA2 deficient cells in heterozygous females and in post operative patients in whom BRCA2 deficiency has led to the spread of the tumor, PARP inhibitors could be considered to be a potent prophylactic treatment. As clinically speaking, it is not the potency of a drug that is most important but its efficacy [82]. Some studies have indicated that mouse BRCA1−/−mammary cancer cells showed only mild specificity while, on the other hand, PARP inhibitors seem to uniformly inhibit the growth of human breast cell lines regardless of the BRCA1 genotype [82]. Since BRCA associated tumor genesis constitute of a stage of sensitivity to PARP inhibition followed by a stage

of insensitivity, strategic therapies for hereditary breast cancer with mutant cells relies strongly on their susceptibility to the PARP inhibitors [83].

Now, concerning the role of PARP inhibition involved in the potentiation of radiation (e.g ionizing radiation) and cytotoxic chemotherapeutic agents such as DNA alkylating agents (temezolomide and cyclophosphamide); platinium analogues (cisplatin, carboplatin and oxaliplatin); and topoisomerase I poisons (irinotecan and 9-topotecan) [2, 84]. The main difference is that cells that are exposed to ionizing radiation lead to a hydroxyl radical-mediated DNA injury whereas alkylating agents directly damage DNA [4]. In radiosensitisation of PARP inhibitors only certain cell cycles for example S and G2 phase are affected [11, 85]. Inhibition of SSBs (Single Strand Break) repair resulted in radiosensitization of cells and an accumulation of SSBs led to conversion of DSB (Double Strand Break) during the S phase hence, increasing levels of DSBs correlating to higher levels of cytotoxicity [85]. The following is supported by cells with dysfunctional BRCA2 that are characterized by an increased sensitivity to γ-irradiation or DNA damaging agents because of the absence of error free DSB repair mechanisms [76]. PARP importance in cytotoxic response to alkylating agents [15] has been highlighted by PARP-1 deficient cells which led to an increase accumulation and activation of P53 known to down regulate both spontaneous and DSB induced HR for suppression of tumor genesis [86]. In brief, studies have proved that PARP inhibition potentiates the cytotoxicity of anti-cancer drugs and ionising radiation.

PARG inhibition could also be one of the pathways selected for cancer management due to its increase sensitivity to both radio and chemotherapy. Deficiency of full length isoform PARG enhanced cytotoxic sensitivity induced by MNNG, Menadione in PARG-/- cells [6], MMS and γ-irradiation in PARG-/- ES cells and augmented sensitivity of mice to DNA damaging agents [7]. PARG inhibition also led to a down-regulation of cellular adhesion molecules (CAM) expressions, such as ICAM-1, P-selectin, VCAM-1 which play a role in inflammatory processes [87] and knockout PARG led to neuronal death in Drosophilia M [34]. PARG inhibition was found to suppress the expressions of both PARG and PARP [13].

PARP and PARG Inhibitors- The Saga

First generation of PARP inhibitors were identified 30 years ago, these included nicotinamide, benzamide, and 3-aminobenzamide (3-AB) [87], 5-Aminoisoquinolinone (5-AIQ) were shown to be competitive inhibitors of PARP. Initially they lacked both specificity and potency but, a second generation was developed in the 1990s, producing 170 specific inhibitors. All were classified as analogues of benzamide and acted in the reaction between PARP and NAD+ [88]. A third generation of inhibitors; benzamidazoles, were discovered later which resolved many mysteries around the inhibition of PARP and its activity. Among them was AG014699, an important inhibitor currently being used in clinical trials [14]. Nowadays, various pharmaceutical laboratories have put some forward, including libraries of benzimidazoles (Abbott), pthalazinones (Kudos), ideno[1, 2-c]isoquinolinones (Inotek), and tricyclic indoles (Pfizer).

PARG inhibitors have not been so well developed as compared to PARP inhibitors. Amongst which we have Nobotanin-B [6], adenosine diphosphate hydroxymethyl pyrrolidinediol (ADP-HPD) as well as its permeable derivative known as 8-octylamino ADP-HPD. GPI 18214, a PARG inhibitor was used in septic shock treatment in mice [89], Gallotannin a complex mixture of hydrolysable tannins from oak gall was used as PARG inhibitor, Pargamicin was also studied [90] and others include Mono- galloyl glucose derivatives were found to be potent inhibitors [91]. All PARP and PARG inhibitors have different chemical structures, bioavailabilities and tend to have a short half-life; so, frequent doses are required to achieve their targets in the human body.

PARP and PARG Inhibitors in Experimental Trials

Many studies and researches have been carried out using various cell lines in order to support the fact that PARP and PARG inhibitors do play an important and fundamental role in the inhibition and treatment of cancers. The generation and characterization of PARP and PARG deficient mouse models have been instrumental in defining the biological role of the molecules and their involvement in the pathogenesis of various diseases. Experimental trials show a much better understanding and their applications in clinical settings are carved out for the future.

Breast cancer—being amongst the most common cancers in females can either be hereditary or sporadic [92] with high levels of metastasis. Mutations in breast cancer susceptibility genes BRCA1 and BRCA2 are responsible for the majority of hereditary breast cancers; however associated mutations with BRCA1 have been identified as 50% being familial breast cancer and 90% are familial breast and ovarian cancers. Trials on human mammary tumor cells (4 cell lines were used) using 3 PARP inhibitiors- NU1025, AG14361, and 3 AB showed that they inhibit growth of cells irrespective of their BRCA1 genotypes and have important clinical significance in treatment [93]. A more potent PARP inhibitor used in the investigation cell line of p53-deficient breast cancer cells

was ANI (4-amino-1, 8-naphthalimide) whereby, usually these cells showed resistance to chemotherapeutic agent doxorubicin (antitumor anthracycline antibiotic) drug but together with ANI, they potentiated drug induced cell death in tumor cells categorizing it as a chemo and radio potentiator [94]. It is considered to be a great step in the field of breast cancer treatment as it involves both chemotherapy and radiotherapy. Further, promising studies showed that BRCA associated breast and ovarian cancers as well as triple negative breast cancers (accounting for 15% of breast cancers) showed sensitivity to PARP inhibitor-AZD2281 alone as well as its association with platinium drugs [95]. On the other hand, BRCA2 deficient mammary tumor cell lines were also strongly inhibited to growth with AZD2281 or in synergistic action with Cisplatin, showing an ideal way for treatment of cancer in the form of monotherapy and combined therapy.

Lung Cancer—is the leading cause of cancer deaths in the world [96]. ABT-888 is a PARP inhibitor which has been widely used in studies concerning lung cancers, skin cancers and brain tumors. H460 lung cancerous cells showed a radiosensitizing effect with ABT-888 which caused tumor growth delay and increased apoptosis. Hence, ABT-888 and radiotherapy proved to be an important line of treatment in non-small cell lung cancer [97].

Colon Carcinoma—Human Colo 829 cell lines showed decrease PAR levels with a single dose of ABT-888, impressively relating the significance of monotherapy [98]. ABT-888 also potentiated radiation in HCT-116 colon carcinoma model [99] while, potent non- toxic PARP inhibitors used in LoVo human colon carcinoma cells showed excellent chemopotentiation for relevant anti tumor therapies [100]. Another PARP inhibitor, 5-Aminoisoquinolinone (5-AIQ) was found to prevent adhesion of HT-29 colonic cells to HUVEC [101] and in CT26 mouse adenocarcinoma cells it inhibited proliferation, migration of tumor cells, down-regulated NF-$_K$B as well as its expression genes in metastasis such as integrinβ1, MMP-2 and MMP-9 thus, putting forward its use in clinical trials [102]. Gallotannin (PARG inhibitor) used in CT26 colon carcinoma cell lines was found to suppress tumor growth factors [75].

Melanoma—is a common cancer affecting a great number of people with a high incidence of distant metastasis. The potentiation of TMZ (a methylating agent) by ABT-888 [85] and melanoma cell lines susceptible to TMZ by PARP inhibitor 3AB had a better antitumor activity against metastatic melanoma and other incurable forms of cancer. This combination is really effective as it is neither sensitive to differences in the tumor repair capacities nor to tumor growth rates [103]. Even monotherapy with ABT-888 was appreciated in human melanoma cell lines A375 [98]. GP15427 a novel PARP-1 inhibitor which has the ability to cross blood brain barrier (BBB) was used in malignant melanoma which has serious brain involvement. It has been shown that the combination of the inhibitor and TMZ decreased tumor growth; minimised melanoma cells infiltration in the brain tissues and lowered incidence of pulmonary metastasis as compared to TMZ used alone and survival rate was prolonged in lymphoma cases [104]. However, only few PARG inhibitors have been put to experimental trials amongst them is (a PARG inhibitor N-bis-(3-phenyl-propyl) 9-oxo-fluorene-2, 7-diamide also called GPI 16552) used in relation to malignant melanoma. Its combination with TMZ in B16 melanoma cell line showed that there was a reduction in tumor growth, poor extracellular matrix infiltration, minimal lung metastasis and mice which had intracranial lesions had a longer life span; so improving morbidity and mortality rates. Here, PARG inhibition has proved itself in the domain of local infiltration and metastasis of tumor in an experimental model [105].

Glioblastoma Multiforme (GBM)—is the commonest primary brain tumor difficult to achieve a certain treatment. TMZ and ABT-888 combination crossed BBB thus, causing shrinkage of the tumor up to 67% and hence, has a favorable outcome for treatment of intracranial tumors [85]. TMZ and GP15427 in GBM was noticed to have only relative tumor infiltration in the ventricles as compared to single used models, showing that combination therapy is far more relevant [104]. Hsp90-Heat Shock Protein (17-AAG) enhanced radio-sensitisation of AZD2281 in HR deficient cells showed importance of combination therapy in management of GBM [106].

Others—NU1025 enhanced cytotoxicity of DNA methylating agents and ionizing radiation by inhibiting DNA repair and further showed that PARP inhibitors may be potentially useful in combination with topoisomerase I inhibitor in anticancer chemotherapy [84]. AG14361 another small molecule of PARP inhibitor also showed promises in preclinical models [97]. Somehow, more study trials are to be forecasted for PARG inhibitors. Many experimental models have shown that both PARP and PARG inhibitors do have reliable pharmacological targets for effective therapy in patients.

PARP Inhibitors in Clinical Oncology Trials

In 2009, the American Society of Clinical Oncology (ASCO) meeting held in Orlando presented two surprise compounds namely PARP inhibitors Olaparib (AstraZeneca) and BSI-201(BiPar/Sanofi Aventis). Other PARP inhibitors involved in clinical trials for breast cancer (including triple negative breast cancer), ovarian cancer, prostate cancer, lung cancer, melanomas, gliomas and pancreatic tumor are currently on the run.

Several trials which have already been done include:

The first PARP inhibitor used in human trial was AG-014699 (Pfizer). A Phase 1 study of the PARP inhibitor AG-014699, in combination with TMZ in patients with advanced solid tumors was carried out. Part 1 was opened to patients of all tumor types. Clinical benefit was observed in both parts 1 and 2. There was one complete and one partial response in patients with metastatic melanoma, another partial response in patient with desmoid tumor and prolonged disease stabilization for ≥ 6 months was observed in 7 more patients. A first and final report of a phase II study of the PARP inhibitor; AG14699, in combination with TMZ in patients with metastatic malignant melanoma showed that 17% of patients had partial progression and 17% more had disease stabilization for ≥ 6 months [14].

The inhibition of PARP in tumors in BRCA mutant carriers was a phase 1 trial, whereby there was the use of AZD2281 (Olaparib) as monotherapy, evaluated in United Kingdom and the Netherlands. 23 patients who had BRCA mutation were treated and clinical benefit was achieved in 63% of patients [107]. In phase II clinical trial in BRCA deficient advanced ovarian cancer it appeared that there was a higher response rate in platinium resistant patients as compared to phase I trials which were beneficial for BRCA patients with EOC (Epithelial Ovarian Cancers) [108].

The first ABT-888 (Abbott) human study was in advanced malignancies or hematological cancers; the first phase 0 within 5 months rapidly lead to a phase 1 trial where there was the combination of ABT-888 along with DNA damaging agents. A phase I trial with TMZ in non-hematological malignancies and metastatic melanomas has been completed.

INO-1001 (from Inotek) along with TMZ in unresectable stage 3 / 4 melanoma reported one patient to have tumor regression. Tolerated or no side effects have been reported in both experimental and clinical studies [11]. Phase II clinical trial including either monotherapy or combination therapy is being carried out in patients with metastatic melanoma.

BSI-201 in Phase I study; out of 24 patients, 6 had disease stabilisation for ≥2 months and 1 patient had for ≥ 9 months. Currently, a phase II monotherapy trial in triple negative metastatic breast cancer, BRCA deficiency in advanced ovarian, fallopian tube and peritoneal cancers as well as a phase II trial with Gemcitabine and Carboplatin on metastatic breast cancer is being carried out.

Phase I studies of MK4827 (From Merck) and CEP-9722 (From Cephalon) as monotherapy in advanced solid tumors are currently recruiting participants

Some further studies recruiting participants for study trials are:- (i) The study of BSI-201 in patients with newly diagnosed malignant glioma phase I/phase II, (ii) Phase III trials in untreated squamous cell lung cancer patients with or without BSI-201, (iii) a phase II study with BSI-201 in ovarian tumors previously treated with chemotherapy and in platinium resistant recurrent ovarian cancers and a phase II trial combination of BSI-201 with standard chemotherapy in triple negative breast cancers, (iv) phase 1 study with AZD2281 and Carboplatin in hereditary breast cancers, metastatic breast cancers and ovarian tumors, (v) treatment of triple negative metastatic breast cancer and advanced ovarian cancer AZD2281 together with Carboplatin and Paclitaxel is on the run as phase 1 trial, (vi) a phase II trial Olaparib with Paclitaxel in recurrent and metastatic gastric carcinomas and in previously treated stage 4 colorectal carcinomas with Opalarib (vii) phase II study comparing combination of Olaparib with Paclitaxel and Carboplatin and Paclitaxel with Carboplatin alone in advanced ovarian cancer, (viii) Olaparib in confirmed hereditary breast cancer phase II trial, (ix) a phase I study ABT-888 with Carboplatin in advanced solid tumors and ABT-888 with TMZ in colorectal carcinoma, (x) ABT-888 with Topotecan in refractory solid tumors and lymphomas in phase I and phase II in patients with ovarian cancer and primary peritoneal cancers, (xi) a phase II trial using AG014699 in treating patients with locally advanced or metastatic breast cancer or advanced ovarian cancer, (xii) phase I study of PARP inhibitor (PF-01367338) with several chemotherapeutic regimens in advanced solid tumors. (www.clinicaltrials.gov)

Yet, no such concrete use of PARG inhibitors have been put to clinical oncology trials; but, encouragement is there to bring them forward in clinical studies. Besides, some tests and biomarkers have already been developed to study the activity for therapeutic applications of these inhibitors molecules. Hopefully, we expect the trials to go on and bring more fruitful outcomes.

Conclusion

Researchers and pharmaceutical companies are eager to continue both experimental and clinical trials since both PARP and PARG inhibitors sensitivity and specificity have been delineated as well as their radio and chemotherapeutic potentiating effects or use along with the combination of other drugs. Their introduction in clinical trials is new hope for cancer patients. Further encouragement is there in for the study of these inhibitory molecules so as to achieve our targets in the treatment of cancers.

Grants support This work was supported by the National Nature Science Foundation of China (NSFC: 30870946)

References

1. D'amours D, Desnoyers S, D'silva I, Poirier GG (1999) Poly (ADP-ribosyl)ation reactions in the regulation of nuclear functions. J Biochem 342:249–268
2. Parise RA, Shawaqfeh M, Egorin MJ, Beumer JH (2008) Liquid chromatography-mass spactometric assay for quantitation in human plasma of ABT-888, an orally available, small molecule inhibitor of poly (ADP-ribose) polymerase. J Chromatogr B Analyt Technol Biomed Life Sci 872(1–2):141–147
3. Hochegger H, Dejsuphong D, Fukushima T, Morrison C et al (2006) Parp-1 protects homologous recombination from interferenve by Ku and Ligase IV in vertebrate cells. EMBO J 25:1305–1314
4. Virag L, Szabo C (2002) The therapeutic potential of poly (ADP-ribose) polymerase inhibitors. Pharmacol Rev 54:375–429
5. Meyer RG, Meyer-Ficca ML, Jacobson EL, Jacobson MK (2003) Human poly (ADP-ribose) glycohydrolase (PARG) gene and the common promoter sequence it shares with inner mitochondrial membrane translocase 23 (TIM23). Gene 314:181–190
6. Koh DW, Lawler AM, Poitras MF et al (2004) Failure to degrade poly (ADP-ribose) increased sensitivity to cytotoxicity and early embryonic lethality. PNAS 101(51):17699–17704
7. Cortes U, Tong WM, Coyle DL et al (2004) Depletion of the 110-Kilodalton isoform of poly (ADP-ribose) glycohydrolase increases sensitivity to genotoxic and endotoxic stress in mice. MCB 24(16):7163–7178
8. Poitras MF, Koh DW, Yu SW et al (2007) Spatial and functional relationship between poly (ADP-ribose) polymerase-1 and Poly (ADP-ribose) glycohydrolase in the brain. Neuroscience 148 (1):198–211
9. Miwa M, Matsutani (2007) PolyADP-ribosylation and cancer. Cancer Sci 98(10):1528–1535
10. Blenn C, Althaus FR, Manlanga M (2006) Poly (ADP-ribose) glycohydrolase silencing protects against H2O2-induced cell death. J Biochem 396:419–429
11. Ratnam K, Low JA (2007) Current development of clinical poly (ADP-ribose) inhibitor in oncology. Clin Cancer Res 13 (5):1383–1388
12. Decker P, Miranda EA, De Murcia G, Muller S (1999) An improved nonisotopic test to screen a large series of new inhibitor molecules of poly (ADP-ribose) polymerase activity for therapeutic applications. Clin Cancer Res 5:1169–1172
13. Cuzzocrea S, Paola RD, Mazzon E et al (2005) PARG activity mediates intestinal injury induced by splanchnic artery occlusion and reperfusion. FASEB J 19:558–566
14. Plummer R, Jones C, Middleton M et al (2008) Phase I study of the poly (ADP-ribose) polymerase inhibitor, AG014699, in combination with temozolomide in patients with advanced Solid Tumors. Clin Cancer Res 14(23):7917–7923
15. Valenzuela MT, Guerrerro R, Nunez MI et al (2002) PARP-1 modifies the effectiveness of P53 mediated DNA damage response. Oncogene 21(7):1108–1116
16. Oei SL, Ziegler M (2000) ATP for the DNA ligation step in base excision repair is generated from poly (ADP-ribose). J Biol Chem 275:23234–23239
17. McCabe N, Turner NC, Lord CJ et al (2006) Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly (ADP-ribose) polymerase inhibition. Cancer Res 66(16):8109–8115
18. Eguchi Y, Shimizu S, Tsujimoto Y (1997) Intracellular ATP levels determine cell death fate by apoptosis or necrosis. Cancer Res 57:1835–1840
19. Kumari SR, Mendoza-Alvarez H, Alvarez-Gonzalez R (1998) Functional interactions of p53 with poly(ADP-ribose) polymerase (PARP) during apoptosis following DNA damage: covalent poly(ADP-ribosyl)ation of p53by exogenous PARP and non-covalent binding of p53 to the Mr 85,000 proteolytic fragment1. Cancer Res 58:5075–5078
20. Affar EB, Germain M, Winstall E et al (2001) Caspase-3-mediated processing of poly (ADP-ribose) glycohydrolase during apoptosis. JBC 276(4):2935–2942
21. Koh DW, Dawson TM, Dawson VL (2005) Mediation of cell death by Poly (ADP-ribose)-1. Pharmacol Res 52(1):5–14
22. Bhaskara, et al (2009) Differrential PARP cleavage: an indication for existence of multiple forms of cell death in human gilomas. Neurology India 57(3)
23. Hung Q, Wu YT, Tan HL, Ong CN, Shen HM (2009) A novel function of PARP-1 in modulation of autophagy and necrosis under oxidative stress. Cell Death Diff 16:264–277
24. Lee Y, Shacter E (1999) Oxidative stress inhibits apoptosis in human lymphoma cells. J Bio Chem 274:19792–19798
25. Walisser JA, Thies RC (1999) Poly (ADP-ribose) polymerase inhibition in oxidant stressed endothelial cells prevents oncosis and permits caspase activation and apoptosis. Exp Cell Res 251 (12):401–413
26. Mathews MT, Berk BC (2008) PARP-1 inhibition prevents oxidative and nitrosative stress–induced endothelial cell death via transactivation of the VEGF receptor 2. Arterioscler Thromb Vasc Biol 28:711–717
27. Kovacs K, Toth A, Deres P et al (2006) Critical role of PI3-kinase/Akt activation in the PARP inhibitor induced heart function recovery during ischemia–reperfusion. Biochem Pharmacol 71(4):441–452
28. Klaidman L, Morales M, Kem S et al (2003) Nicotinamide offers multiple protective mechanisms in stroke as a precursor for NAD^+, as a PARP inhibitor and by partial restoration of mitochondrial function. Pharmacology 69(3):150–157
29. Filipovic DM, Meng X, Reeves WB (1999) Inhibition of PARP prevents oxidant-induced necrosis but not apoptosis in LLC-PK1 cells. Am J Physiol Renal Physiol 277:428–436
30. Roesner JP, Vagts DA, Iber T et al (2006) Protective effects of PARP inhibition on liver microcirculation and function after haemorrhagic shock and resuscitation in male rats. Intensive Care Med 32(10):1649–1657
31. Oku H, Goto W, Tsujimoto M et al (2003) Effects of Poly(ADP-ribose) polymerase (PARP) Inhibitor on NMDA-induced retinal injury. Invest Ophthalmol Vis Sci 44: E-Abstract 27
32. Charron MJ, Bonner-Weir S (1999) Implicating PARP and NAD^+ depletion in type I diabetes. Nat Med 5:269–270
33. Ha HC, Snyder SH (1999) Poly (ADP-ribose) polymerase is a mediator of necrotic cell death by ATP depletion. PNAS 96:13978–13982
34. Hanai S, Kanai M, Ohashi S et al (2004) Loss of poly (ADP-ribose) glycohydrolase causes progressive neurodegeneration in Drosophila melanogaster. PNAS 101(1):82–86
35. Keil C, Gröbe T, Oei SL (2006) MNNG-induced cell death is controlled by interactions between PARP-1, Poly (ADP-ribose) glycohydrolase, and XRCC1. J Biochem 281:34394–34405
36. Ménissier-de Murcia J, Mark M, Wendling O, Wynshaw-Boris A, de Murcia G (2001) Early embryonic lethality in *PARP-1* Atm double-mutant mice suggests a functional synergy in cell proliferation during development. MCB 21(5):1828–1832
37. Yang YG, Cortes U, Patnaik S, Jasin M, Wang Z (2004) Ablation of PARP-1 does not interfere with the repair of DNA double-strand breaks, but compromises the reactivation of stalled replication forks. Oncogene 23:3872–3882 [abstract]
38. Nozaki T, Masutani M, Watanabe M et al (1999) Syncytiotrophoblastic giant cells in Teratocarcinoma like tumors derived

from Parp-disrupted mouse embryonic stem cells. PNAS 96 (23):13345–13350
39. Saxena A, Saffery R, Wong LH et al (2002) Centromere proteins Cenpa, Cenpb, and Bub3 interact with poly (ADP-ribose) polymerase-1 protein and are poly (ADP-ribosyl) ated. J Biol Chem 277:26921–26926
40. Bhatia M, Kirkland JB, Meckling-Gill KA (1996) Overexpression of poly (ADP-ribose) polymerase promotes cell cycle arrest and inhibits neutrophilic differentiation of NB4 acute promyelocytic leukemia cells. Cell Growth Differ 7(1):91–100
41. Bhatia M, Kirkland JB, Meckling-Gill KA (1995) Modulation of poly (ADP-ribose) polymerase during neutrophilic and monocytic differentiation of promyelocytic (NB4) and myelocytic (HL-60) leukaemia cells. J Biochem 308:131–137
42. Harnacke K, Kruhoffer M, Orntoft TF, Hass R (2005) Down-modulation of poly(ADP-ribose) polymerase-1 (PARP-1) in human TUR leukemia cells restores transcriptional responsiveness for differentiation and cell cycle arrest. Eur J Cell Biol 84 (11):885–896 [abstract]
43. Masutani M, Nozaki T, Watanabe M et al (2001) Involvement of poly(ADP-ribose) polymerase in trophoblastic cell differentiation during tumorigenesis. Mutant Res 477:111–117
44. Shiokawa M, Masutani M, Fujihara H et al (2005) Genetic alteration of poly(ADP-ribose) polymerase-1 in human germ cell tumors. Jpn J Clin Oncol 35(2):97–102
45. Sevigny MB, Silva JM, Lan WC, Alano CC, Swanson RA (2003) Expression and activity of poly(ADP-ribose) glycohydrolase in cultured astrocytes, neurons, and C6 glioma cells. Mol Brain Res 117(2):213–220 [abstract]
46. Kraus W, Lis J (2003) PARP goes transcription. Cell 113 (6):677–683
47. Pavri R, Lewis B, Kim TK et al (2005) PARP-1 determines specificity in a retinoid signaling pathway via direct modulation of mediator. Moll Cell 18(1):83–96 [abstract]
48. Idogawa M, Yamada T, Honda K et al (2005) Poly(ADP-ribose) polymerase-1 is a component of the oncogenic T-cell factor-4/beta-catenin complex. Gastroenterology 128(7):1919–1936 [abstract]
49. Soldatenkov VA, Albor A, Patel BKR et al (1999) Regulation of the human poly(ADP-ribose) polymerase promoter by ETS transcription factor. Oncogene 18(27):3954–3962
50. Ogino H, Nozaki T, Gunji A et al (2007) Loss of Parp-1 affects gene expression profile in a genome-wide manner in ES cells and liver cells. BMC Genomics 8:227. doi:10.1186/1471-2164-8-227
51. Aldinussi A, Gerlini G, Fossati S et al (2007) A key role for poly (ADP-ribose)-1 during human dendritic cell maturation. J Immuno 179:305–312
52. Zaniolo K, Desnoyers S, Leclerc S, Guérin S (2007) Regulation of poly(ADP-ribose) polymerase-1 (PARP-1) gene expression through the post-translational modification of Sp1: a nuclear target protein of PARP-1. BMC Genomics 8:96. doi:10.1186/1471-2199-8-96
53. Tong WM, Hande MP, Lansdorp PM, Wang ZQ (2001) DNA strand break-sensing molecule poly(ADP-Ribose) polymerase cooperates with p53 in telomere function, chromosome stability, and tumor suppression. Mol Cell Biol 21(12):4046–4054
54. Eberhart CG (2003) Medulloblastoma in mice lacking p53 and PARP. Am J Pathol 162(1):7–10
55. Oei SL, Griesenbeck J, Schweiger M, Ziegler M (1998) Regulation of RNA polymerase II-dependent transcription by poly(ADP-ribosyl)ation of transcription factors. JBC 273:31644–31647
56. Hassa PO, Buerki C, Lombardi C, Imhof R, Hottiger MO (2003) Transcriptional coactivation of nuclear factor Kappa B-dependent gene expression by p300 is regulated by poly (ADP)-ribose polymerase-1. JBC 278(46):45145–45153
57. Nie J, Sakamoto S, Song D, Qu Z, Ota K, Taniguchi T (1998) Interaction of Oct-1 and automodification domain of poly (ADP-ribose) synthetase. FEBS Lett 424(1–2):27–32
58. Dear TN, Hainzl T, Follo M (1997) Identification of interaction partners for the basic-helix-loop-helix protein E47. Oncogene 14:891–898
59. Butler AJ, Ordhal CP (1999) Poly (ADP-Ribose) polymerase binds with transcription enhancer factor 1 to MCAT1 elements to regulate muscle-specific transcription. Mol Cell Boil 19(1):296–306
60. Taniguchi T, Agemori M, Kameshita I, Nishikimi M, Shizuta Y (1982) Participation of poly(ADP-ribosyl)ation in the depression of RNA synthesis caused by treatment of mouse lymphoma cells with methylnitrosourea. J BC 257:4027–4030
61. Shimokawa T, Masutani M, Nagasawa S et al (1999) Isolation and cloning of rat poly (ADP-ribose) glycohydrolase: presence of a potential nuclear export signal conserved in mammalian orthologs. J Biochem 126:748–755
62. Erdelyi K, Kiss A, Bankondi E et al (2005) Gallotannin inhibits the expression of chemokines and inflammatory cytokines in A549 cells. Mol Pharmacol 68:895–904
63. Frizzell KM, Gamble MJ, Berrocal JG (2009) Global analysis of transcriptional regulation by poly(ADP-ribose) polymerase-1 and poly(ADP-ribose) glycohydrolase in MCF-7 human breast cancer cells. J Biol Chem 284(49):33926–33938 [abstract]
64. Wang ZQ, Stingl L, Morrison C et al (1997) PARP is important for genomic stability but dispensable in? Apoptosis. Genes Dev 11:2347–2358
65. Folkman J (2002) Role of angiogenesis in tumor growth and metastasis. Semin Oncol 29:15–18
66. Tentori L, Lacal PM, Muzi A et al (2007) Poly(ADP-ribose) polymerase (PARP) inhibition or PARP-1 gene deletion reduces angiogenesis. Eur J Cancer 43(14):2124–2133
67. Pyriochou A, Olah G, Deitch EA, Szabo C, Papapetropoulos A (2008) Inhibition of angiogenesis by the poly (ADP-ribose) polymerase inhibitor PJ-34. IJMM 22:113–118
68. Rajesh M, Mukhopadhyay P, Bátkai S et al (2006) Pharmacological inhibition of poly (ADP-ribose) polymerase inhibits angiogenesis. BBRC 350(2):352–357
69. Rajesh M, Mukhopadhyay P, Godlewski G (2006) Poly (ADP-ribose) polymerase inhibition decreases angiogenesis. BBRC 350(4):1056–1062
70. Berger NA, Adams JW, Sikorski GW et al (1978) Synthesis of DNA and poly (Adenosine Diphosphate Ribose) in normal and chronic lymphocytic leukemia lymphocytes. J Clin Inves 62:111–118
71. Wielckens K, Garbrecht M, Kittler M, Hilz H (1980) ADP-ribosylation of nuclear proteins in normal lymphocytes and in low- grade malignant non-Hodgkin lymphoma cells. Eur J Biochem 104:279–287
72. Hirai K, Ueda K, Hayaishi O (1983) Abberation of poly (adenosine diphosphate ribose) in human colon adenomatous polyps and cancers. Cancer Res 43:3441–3446
73. Fukushima M, Kuzuya OK, Ikai K (1981) Poly (ADP-ribose) synthesis in human cervical cancer cell diagnostic cytological usefulness. Cancer Lett 14:227–236
74. Shiobara M, Miyazaki M, Ito H et al (2001) Enhanced polyadenosine diphosphate ribosylation in cirrhotic liver and carcinoma tissues in patients with hepatocellular carcinoma. J Gastroenterol Hepatol 16:338–344
75. Lin L, Li J, Wang YL et al (2009) Relationship of PARG with colorectal carcinoma PARP, VEGF and b-FGF in colorectal carcinoma. Chin J Cancer Res 21(2):135–141
76. Leal AP et al (2009) PARP inhibitors: New partners in the therapy of cancer and inflammatory diseases. Free Radic Biol Med (in press). Doi:10.1016

77. Lord CJ, McDonald S, Swift S et al (2008) A high-throughput RNA interference screen for DNA repair determinants of PARP inhibitor sensitivity. DNA Repair (Amst) 7:2010–2019
78. Turner NC, Lord CJ, Iorns E et al (2008) A synthetic lethal siRNA screen identifying genes mediating sensitivity to a PARP inhibitor. EMBO J 27(9):1368–1377
79. Ashworth A (2008) A synthetic lethal therapeutic approach: poly (ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. J Clin Oncol 26 (22):3785–3790
80. Bryant HE, Schultz N, Thomas HD et al (2005) Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 434:913–917 [abstract]
81. Turner N, Tutt A, Ashworth A (2005) Targeting the DNA repair defect of BRCA tumours. Curr Opin Pharmacol 5 (4):388–393
82. De Soto JA, Wang X, Tominaga Y et al (2006) The inhibition and treatment of breast cancer with poly (ADP-ribose) polymerase (PARP-1) inhibitors. Int J Biol Sci 2(4):179–185
83. De Soto JA, Deng CX (2006) PARP-1 inhibitors: are they the long-sought genetically specific drugs for BRCA1/2-associated breast cancers? Int J Med Sci 3(4):117–123
84. Curtin NJ (2005) PARP inhibitors for cancer therapy. Expert Rev Mol Med 7(4):1–20 [abstract]
85. Liu X, Shi Y, Guan R et al (2008) Potentiation of temozolomide cytotoxicity by poly(ADP)ribose polymerase inhibitor ABT-888 requires a conversion of single stranded DNA damages to double-stranded DNA breaks. Mol Cancer Res 6(10):1621–1629
86. Suesse S, Scholz CJ, Buerkle A, Iler LW (2004) Poly (ADP-ribose) polymerase (PARP-1) and P53 independently function in regulating double strand break repair in primate cells. Nucleic Acids Res 32:2669–2680
87. Purnell MR, Whish WJD (1980) Novel inhibitors of poly (ADP-ribose) synthetase. J Biochem 185:775–777
88. Banasik M, Komura H, Shimoyama M, Ueda K (1992) Specific inhibitors of poly (ADP-ribose) synthetase and mono(ADP-ribosyl) transferase. J Biol Chem 267:1569–1575
89. Genovese T, Di Paola R, Catalano P et al (2004) Treatment with a novel poly(ADP-ribose) glycohydrolase inhibitor reduces development of septic shock-like syndrome induced by zymosan in mice. Crit Care Med 32(6):1365–1374
90. Masutani M, Shimokawa T, Igarashi M et al (2002)Inhibition of poly(ADP-ribose) glycohydrolase activity by cyclic peptide antibiotics containing piperazic acid residues. Proceedings of the Japanese academy; Ser B, physical and biological sciences 78 (1):15–17
91. Formentini L, Arapistas P, Pitelli M et al (2008) Mono-galloyl glucose derivatives are potent poly(ADP-ribose) glycohydrolase (PARG) inhibitors and partially reduced PARP-1 dependent cell death. BJP 155:1235–1249
92. Yang X, Lippman ME (1999) BRCA1 and BRCA2 in breast cancer. Breast Cancer Res Treat 54(1):1–10
93. De Soto JA, Wang X, Tominaga Y et al (2006) The inhibition and treatment of breast cancer with poly (ADP-ribose) polymerase (PARP-1) inhibitors. Int J Biol Sci 2(4):179–185
94. Munozo-Gamez JA, Martin-Olivia D, Aguilar-Quesada R (2005) PARP inhibition sensitizes p53-deficient breast cancer cells to doxorubicin-induced apoptosis. Biochem J 386:119–125
95. Rottenberg S, Jaspers JE, Kersbergen A et al (2008) High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. PNAS 105(44):17079–17084
96. Gopall R, Hong C & Yi S (2009) Gefitinib as monotherapy in the first-line setting in non-small cell lung Cancer. http://www.ispub.com/journal/the_internet_journal_of_pulmonary_medicine/volume_11_number_2_5/article/gefitinib-as-monotherapy-in-the-first-line-setting-in-non-small-cell-lung-cancer.html
97. Albert JM, Cao C, Kim KW et al (2007) Inhibition of poly(ADP-ribose) polymerase enhances cell death and improves tumor growth delay in irradiated lung cancer models. Clin Cancer Res 13(10):3033–3042
98. Kinders RJ, Hollingshead M, Khin S et al (2008) Preclinical modeling of a phase 0 clinical trial: qualification of a pharmacodynamic assay of poly (ADP-ribose) polymerase in tumor biopsies of mouse xenografts. Clin Cancer Res 14(21):6877–6885
99. Donawho CK, Luo Y, Penning TD et al (2007) ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. Clin Cancer Res 13(9):2728–2737
100. Calabrese CR, Batey MA, Thomas HD (2003) Identification of potent nontoxic poly (ADP-ribose) polymerase-1 inhibitors: chemopotentiation and pharmacological studies. Clin Cancer Res 9:2711–2718
101. Hao LX, Wang YL, Cai L, YY LI (2007) Inhibitory effect of 5-Aminoisoquinolinone on Parp activity in colon carcinoma cell line HT-29. Chin J Cancer 26(6):566–571
102. Li M, Threadgill MD, Wang YL, Cai L, Lin X (2009) A poly (ADP-ribose) polymerase inhibition down-regulates expression of metastasis-related genes in CT26 colon carcinoma cells. Pathobiology 76:108–116
103. Tentori L, Portarena I, Barbarino M et al (2003) Inhibition of telomerase increases resistance of melanoma cells to temozolomide, but not to temozolomide combined with poly (ADP-ribose) polymerase inhibitor. Mol Pharmacol 63:192–202
104. Tentori L, Leonetti C, Scarsella M et al (2003) Systemic administration of GPI 15427, a novel poly(ADP-ribose) polymerase-1 inhibitor, increases the antitumor activity of temozolomide against intracranial melanoma, glioma, lymphoma. Clin Cancer Res 9:5370–5379
105. Tentori L, Leonetti C, Scarsella M et al (2005) Poly(ADP-ribose) glycohydrolase inhibitor as chemosensitiser of malignant melanoma for temozolomide. Eur J Cancer 41(18):2948–2957
106. Dungey FA, Caldecott KW, Chalmers AJ (2009) Enhanced radiosensitisation of human glioma cells by combining inhibition of PARP with inhibition of Hsp90. Mol Cancer Ther 8(8):2243–2254
107. Fong PC, Boss DS, Yap TA et al (2009) Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 361:123–134
108. Gien LT, Mackay HJ (2010) The emerging role of PARP inhibitors in the treatment of epithelial ovarian cancer. J Oncol. doi:10.1155/2010/151750