

REVIEW

Poly(ADP-ribose) polymerase inhibition: a new direction for *BRCA* and triple-negative breast cancer?

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Abstract

Inhibitors of poly(ADP-ribose) polymerase (PARP)-mediated DNA repair have shown promise in early clinical studies in the treatment of specific subgroups of breast cancer. Notably, phase II trials indicate that olaparib, an oral PARP inhibitor, has activity as a single agent in *BRCA*-related tumours, and that a combination of iniparib, an intravenous PARP inhibitor, and chemotherapy offers a survival advantage, compared with chemotherapy alone, in triple-negative breast cancer. Phase III data on the latter indication are expected in 2011. Intriguingly, iniparib does not increase toxicity when used as a chemo-potentiating agent, suggesting that it differs in its mechanism of action from other agents in this class. Overall, PARP inhibitors represent a potentially important new class of anti-cancer agents with two potential modes of action, as single agents causing synthetic lethality and as chemo-potentiating agents.

Introduction

Breast cancer is the most commonly diagnosed cancer in the UK, with more than 45,000 new cases per year, and a lifetime risk of 1 in 9 [1]. Incidence rates have risen over the past 20 years in industrialised countries, but the same period has seen the development of many new treatments, and eight out of ten women diagnosed with breast cancer are now expected to survive 5 years or more [1,2]. The improvements in treatment include novel cytotoxic drugs and many targeted agents, such as trastuzumab, lapatinib and the aromatase inhibitors.

Within the past 5 years, it has become apparent that another powerful class of agents - the poly(ADP-ribose)

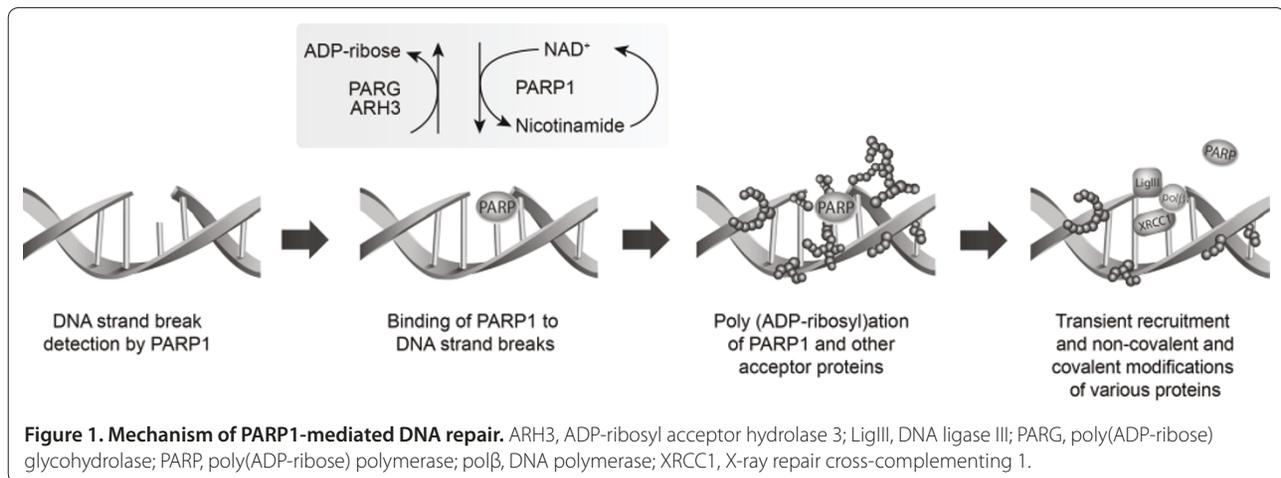
polymerase (PARP) inhibitors - has activity in defined groups of patients with breast cancer [3-11]. These agents target a DNA repair pathway via a novel mechanism of action that can be exploited to the benefit of patients with breast cancer. This review will briefly discuss the development of PARP inhibitors, and the data supporting their potential clinical use in breast cancer, as single agents and in combination with chemotherapy.

PARP activity and inhibition

The PARP family of enzymes was first described over 40 years ago [12]. PARP1 and PARP2 occur in the cell nucleus, and are activated by DNA damage [13]. PARP1, the most abundant form of the enzyme [14], acts as a 'molecular nick sensor' to signal DNA single-strand breaks (SSBs) and assist in their repair [15]. It is inactive until bound to a DNA strand break via its zinc finger DNA-binding domain. After binding, PARP1 uses NAD⁺ to form long, branched polymers of poly(ADP-ribose) on acceptor proteins, including PARP itself. This auto-poly(ADP-ribosyl)ation creates a negatively charged target at the SSB, which recruits the enzymes required to form the base excision repair multi-protein complex [16,17]. Following ADP-ribosylation, PARP1 has reduced affinity for DNA; it is released, opening up the chromatin and allowing access to the damaged site for the other repair complex proteins. Subsequently, the enzyme poly(ADP-ribose) glycohydrolase (PARG) removes the poly(ADP-ribose) polymer from PARP, allowing the enzyme to be recycled and reactivated at other areas of DNA damage (Figure 1).

Most of the PARP inhibitors currently undergoing clinical investigation have been designed to compete with NAD⁺ for its substrate binding site [18]. It is likely that these drugs inhibit both PARP1 and PARP2 [18]. Inhibition of PARP1 compromises a cell's ability to overcome damage to the genome by repairing DNA SSBs. Many commonly used anticancer treatments, such as radiotherapy, alkylating agents and camptothecins, damage DNA by causing SSBs, and prevention of SSB repair has been shown in preclinical studies to improve

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cell kill [19]. For this reason, PARP inhibitors were first developed as radio- or chemo-potentiating agents [20,21], the aim being to overcome cancer cell resistance to a DNA-damaging agent by preventing repair of the potentially lethal damage to the cancer cell caused by the treatment.

Potent PARP inhibitors first entered early clinical trials in 2003 [22], and there has been rapid expansion of the field in the past 5 years. Several PARP inhibitors are being investigated for a range of indications [23,24], mainly cancers (Table 1). Early clinical studies suggest that PARP inhibitors will have a role in the treatment of breast cancer, with promising data emerging from trials in two specific areas: hereditary *BRCA*-deficient breast cancer (single-agent PARP inhibition) and triple-negative breast cancer (TNBC; PARP inhibition in combination with chemotherapy) [3-6,7-11]. However, with improved understanding of the mechanisms of PARP1 inhibition in these two clinical scenarios, it is likely that a wider group of patients with breast cancer may also benefit from this approach to treatment.

Single-agent PARP inhibitors in hereditary *BRCA*-deficient cancer

The publication in 2005 of paired pre-clinical papers in *Nature*, demonstrating hypersensitivity of *BRCA*-deficient cancer cells to single-agent PARP inhibitors, opened the door to clinical research into these agents as monotherapy [25,26], and provided the clearest demonstration to date of a class effect. Before this ground-breaking research was published, it had been argued that PARP inhibitors would have no activity when used alone, and drug developers were chasing the elusive goal of chemopotentiation in tumours without an increase in toxicity in normal tissue.

Initial preclinical experiments in cell lines and xenografts demonstrated that cells with loss of the

homologous recombination repair pathway for DNA double-strand breaks (DSBs) are hypersensitive to blockade of SSB repair with a PARP inhibitor. The key to this mechanism of action is the role that *BRCA1* and *BRCA2* play in signalling DSBs (*BRCA1*) and the repair of such breaks via the homologous recombination pathway (*BRCA2*) [27].

The proposed mechanism for the cytotoxicity of PARP inhibition is that blockade of SSB repair leads to the formation of unrepaired DSBs at the replication fork. In normal or *BRCA*-heterozygous cells, the lesion can be repaired by DSB mechanisms, and DNA replication and cell division continue. However, in cells that lack functional DSB repair, such as those with a homozygous mutation in *BRCA1* or *BRCA2*, loss of two DNA repair pathways causes synthetic lethality and cell death [25,26].

This proposition was first tested clinically in a phase I study of AZD2281 (olaparib), looking at its potential activity as a single agent [28]. This study used an oral formulation of olaparib, and assessed the pharmacokinetics and pharmacodynamics of doses ranging from 10 mg daily for 2 out of 3 weeks to 600 mg twice daily on a continuous schedule. Nine of the 19 patients with confirmed *BRCA* mutations had a partial response to olaparib, representing a 47% response rate in this population. No responses were seen in 37 patients who did not have a *BRCA* mutation. The dose-limiting toxicities were myelosuppression and central nervous system side effects. Toxicities to normal tissue were similar in the *BRCA*-deficient and normal populations. An increase in γ H2AX foci was found in plucked eyebrow hair follicles 6 hours after olaparib treatment, compared with baseline. These foci indicate accumulation of DNA DSBs, so the finding demonstrated a proof of mechanism of the process of synthetic lethality, whereby preservation of SSBs by PARP inhibition leads to the formation of DNA DSBs in the absence of an external DNA-damaging agent.

Table 1. PARP inhibitors under clinical investigation in malignant disease

Agent (year entered clinical research)	Manufacturer	Single/combination therapy	Oral/intravenous	Clinical indication(s)	Status
AG014699, PF0367338 (2003)	Pfizer (New York, NY, USA)	Single agent; multiple combinations	Intravenous and oral	Solid tumours; melanoma; <i>BRCA</i> germline	Phase I and II melanoma studies complete. Phase II <i>BRCA</i> studies open
KU59436, AZD2281, olaparib (2005)	AstraZeneca/KuDOS (London, UK)	Single agent; multiple combinations	Oral	Various, including <i>BRCA</i> germline	Phase I complete. Numerous phase II studies ongoing
ABT-888, veliparib (2006)	Abbott Laboratories (North Chicago, IL, USA)	Multiple combinations	Oral	Solid tumours; melanoma; lymphoid malignancies	Phase 0/I completed in some indications. Numerous phase II studies ongoing
BSI-201, SAR 240550, iniparib (2006)	BiPar (South San Francisco, CA, USA; Sanofi Aventis)	Combination with gemcitabine and carboplatin; temozolomide	Intravenous	TNBC; lung cancer; glioma	Phase II studies completed. Phase III study in TNBC recruiting. Phase II study in lung near completion
INO-1001 (2005/2006)	Inotek/Genentech (Lexington, MA, USA)	Single agent; combination with temozolomide	Intravenous	Melanoma; malignant glioma	Phase Ib in melanoma completed
MK4827 (2008)	Merck Sharp Dohme (Hoddesdon, UK)	Single agent; combination with chemotherapy	Oral	Solid tumours; <i>BRCA</i> -related ovarian cancer	Phase I ongoing
CEP-9722 (2009)	Cephalon (Frazer, PA, USA)	Single agent; combination with temozolomide	Oral	Solid tumours	Phase I ongoing
GPI 21016 (2010)	MGI Pharma (Bloomington, MN, USA)	Combination with temozolomide	Oral	Solid tumours	Phase I ongoing
E7016 (2010)	MGI Pharma (Bloomington, MN, USA), Eisai (Baltimore, MD, USA)	Combination with temozolomide	Oral	Solid tumours	Phase I ongoing
LT673 (2011)	Lead Therapeutics/Biomarin (Novato, CA, USA)	Single agent and combination planned	Oral	Solid tumours	Phase I planned

PARP, poly(ADP-ribose) polymerase; TNBC, triple-negative breast cancer.

It must be noted, however, that the mechanistic proof was demonstrated in normal tissue, not in the tumour. It is not clear from the publication whether this pharmacodynamic effect was seen in *BRCA* carriers with a heterozygote defect in all cells, or in all patient groups. These data, which suggest a risk of accumulation of DNA damage within normal tissue, raise concern over the potential dangers of prolonged, continuous dosing. In theory, there could also be an accumulation of tumorigenic mutations and second malignancies, so caution in the use of these agents in the adjuvant setting over prolonged periods may be advisable.

The phase I findings have been confirmed by two phase II studies of olaparib in *BRCA1* or *BRCA2* mutation carriers in patients with breast [3,4] or ovarian [5,6] cancer previously treated with a median of three chemotherapy regimens. Both studies assessed response and toxicity in sequential cohorts of patients treated with 400 mg twice daily or 100 mg twice daily. The activity of olaparib as a single agent was confirmed in the 400 mg cohorts, but there was less activity at the lower dose, suggesting that the extent of PARP inhibition is important for response. In the breast cancer study, 27 patients with metastatic disease were treated at each dose, and the confirmed response rate was 41% in those

receiving the 400 mg schedule and 22% in the 100 mg cohort [3,4]. Toxicity was reduced with the lower dose, compared with the higher dose, but mild overall. Fatigue, nausea and vomiting were the commonest adverse events with this well tolerated agent.

A similar dose response was found in the phase II study of ovarian cancer, in which 33 patients were treated with olaparib 400 mg twice daily and 24 with 100 mg twice daily. There was a 33% confirmed partial response rate at the higher dose and 13% at the lower dose [5,6]. Responses were seen in carriers of *BRCA1* or *BRCA2* mutations, and in patients with either platinum-sensitive or platinum-resistant disease. However, these results are not consistent with findings from previous studies that acquired resistance to platinum-based treatment in ovarian cancer is associated with regain of *BRCA* function [29,30].

The findings of these small, non-randomised phase I and phase II studies require confirmation at phase III. Meanwhile, they do provide the exciting suggestion that single-agent therapy with PARP inhibitors will be of benefit in *BRCA*-positive patients, and offer low toxicity. Phase II studies in this indication are ongoing with the PARP inhibitors PF01367338 (AG014699) and ABT-888 (veliparib). A phase I single-agent study with the novel

PARP inhibitor MK-4827 has also confirmed the potential for activity with low toxicity in this group of patients [31].

PARP inhibitors as chemo-potentiating agents

As discussed above, PARP inhibitors were initially envisaged as chemo-potentiating agents. In previous studies, using inhibitors of methyl guanine methyl transferase to prevent DNA repair during cytotoxic therapy, the dose of chemotherapy needed to be reduced because of enhanced toxicity with the treatment combination [32-34]. Similarly, in some of the first studies of PARP inhibitors in combination with chemotherapy, a higher level of myelosuppression was observed than would have been expected with the chemotherapeutic agent alone [7,22,35-37]. Two further studies required protocol amendments in light of dose-limiting toxicities associated with olaparib in combination with chemotherapy - in particular, myelosuppression [8,38]. These findings present two challenges to physicians and scientists designing trials with combinations of chemotherapy with PARP inhibitors. First, should clinical studies be designed with the maximum dose of chemotherapy possible, or a maximal dose of PARP inhibitor accepting a chemotherapy dose reduction? The answer to this will lie in the clinical outcome data and also how the PARP inhibitor is being used - for its single agent activity or as a true chemo-potentiating agent. Second, there is a need to investigate the mechanism by which PARP inhibitors enhance damage to normal tissue when used with some of the agents reported (platinums, bifunctional alkylating agents such as cyclophosphamide or the antimetabolite, gemcitabine), where repair of cytotoxic damage is not thought to be achieved via a PARP-dependent mechanism. There is one molecule in the class - BSI-201 (SAR 240550, iniparib) - for which normal tissue toxicity appears to be less of an issue, and so far this is the PARP inhibitor that has progressed furthest in the clinic.

PARP inhibitors in triple-negative breast cancer

Following encouraging results with iniparib in combination with chemotherapy with various solid tumours [39], clinical investigators have gone on to study this agent with chemotherapy in TNBC, a disease with a biological phenotype similar to *BRCA1*-defective cancers [40]. It must be borne in mind that iniparib may act via a different mechanism to the PARP inhibitors discussed above, and does not appear to have the limitation of enhanced toxicity in normal tissue [39,41,42].

Evidence of an improvement in anti-tumour activity has been reported in patients previously treated with two or more cytotoxic regimens who received iniparib in combination with carboplatin and gemcitabine, compared with those who received the chemotherapy

regimen alone [9]. In this phase II study, 123 patients with TNBC were randomised to receive carboplatin (AUC2) and gemcitabine (1,000 mg/m²) on days 1 and 8 of a 21-day cycle, with or without iniparib 5.6 mg/kg on days 1, 4, 8 and 11. The objective response rate was 52% in the iniparib group, compared with 32% in those who received chemotherapy alone ($P = 0.02$), median progression-free survival was 5.9 versus 3.6 months, respectively ($P = 0.01$), and overall survival was 12.3 versus 7.7 months, respectively ($P = 0.01$) [9,10]. No difference was observed in the rate of adverse events between the two treatment groups. A phase III study of iniparib in combination with carboplatin and gemcitabine for the same indication was initiated in 2009, and rapidly completed recruitment. It is hoped that preliminary results will be reported at the American Society of Clinical Oncology (ASCO) 2011 meeting. However, initial indications from the manufacturer, Sanofi-Aventis, are that the phase III trial did not meet the primary endpoints of overall and progression-free survival [43].

It is possible that the intermittent dosing regimen used in the studies cited above helps to protect against enhanced myelosuppression and hence toxicity. However, if iniparib is acting as a PARP inhibitor, it is intriguing that this intermittent schedule also provides an increase in overall treatment efficacy, compared with chemotherapy alone. It is possible that iniparib is acting as a single agent on the *BRCA*-like phenotype of TNBC, or that it is somehow able to prevent repair to treatment-induced DNA damage within the tumour without increased damage to normal tissue. If they confirm the phase II data, the results of the phase III study of iniparib and chemotherapy in TNBC may lead to an advance in the treatment of patients, but they will also present an intriguing puzzle to scientists working with PARP inhibitors.

It is also interesting to note that single-agent olaparib was described as having activity in TNBC at the ASCO 2010 meeting [11]. This was the first trial to evaluate the efficacy of a PARP inhibitor as a single agent for the treatment of sporadic TNBC, and responses were seen only in tumours that occurred on a background of *BRCA1* germline mutation [11].

Conclusion

Research into PARP inhibition is beginning to show the potential of targeting DNA repair as a strategy in the development of new anti-cancer agents. This is a class of drugs with activity as monotherapy and in combination with treatments that cause DNA damage [4,8,38]. It is very unusual in cancer therapy for a new drug to be used solely as monotherapy, and research to date suggests that PARP inhibitors are likely to be used also as components of combination regimens. Indeed, the single-agent and

DNA-damaging-potentiating facets of PARP inhibition present an interesting challenge to drug developers as we try to improve treatments for our patients. If we wish to exploit the single-agent activity of a PARP inhibitor as part of a combination regimen, we may need to consider scheduling PARP-based treatment separately to any DNA-damaging component of the combination. However, when using a PARP inhibitor as a chemopotentiation, concomitant treatment would be appropriate.

The phase III trial of iniparib in TNBC is nearing completion. If the data confirm the earlier findings, it will provide a promising new treatment for this patient group. However, there remain many scientific questions about the underlying mechanism of action of iniparib in this setting, and the differences between the individual agents in the PARP inhibitor class.

Whatever the explanation, PARP inhibition may eventually offer an effective treatment approach for patients with *BRCA*-related breast cancer and TNBC, and the array of compounds in development will allow clinical investigators to exploit the differences to extend our scientific knowledge and thus benefit a wider range of patients.

Abbreviations

ASCO, American Society of Clinical Oncology; DSB, double-strand break; PARP, poly(ADP-ribose) polymerase; SSB, single-strand break; TNBC, triple-negative breast cancer.

Competing interests

The author is an inventor on a patent of use of the PARP inhibitor PF0367338 and has received research funding from Pfizer GRD for the development of this agent. Additionally, she has received funding to cover the costs of clinical trials activity relating to AZD2281, ABT888 and BSI-201 (iniparib) and laboratory research funding for pharmacodynamic research with BSI-201.

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