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PARP Inhibitors: Science and Current Clinical Development

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Abstract

Purpose of review—PARP inhibitors are a promising new area in cancer therapeutics. This review summarizes the current understanding of their mechanism of action, their state of clinical development, and possible mechanisms of resistance.

Recent Findings—PARP inhibitors were predicted to cause lethality in cells with lesions in homologous recombination, as well as to be synergistic with cytotoxic chemotherapy. Recent clinical trial results have validated both of these hypotheses. In addition, studies have begun to examine possible mechanisms of resistance.

Summary—PARP inhibitors were developed with the idea of synthetic lethality in mind, a concept from classical genetics that may be a general approach to finding new targets for cancer therapy. They show activity as monotherapy in cancers with defective homologous recombination, and they may potentiate the action of conventional cytotoxic chemotherapy.

Keywords

PARP Inhibitor; Synthetic Lethality; BRCA1; BRCA2

Introduction

PARP inhibitors are promising new area of cancer drug development. They represent the first fruits of a new concept in cancer therapy development, synthetic lethality, and in selected settings, they appear to be active both as monotherapy or together with conventional cytotoxic agents. Here we discuss the science behind their development, the current state of clinical trials assessing their activity, and potential resistance mechanisms.

The Poly ADP Ribose Polymerases

The poly ADP ribose polymerases (PARPs) are a family of enzymes capable of adding branched chains of ADP-ribose to proteins. There are 16 genes encoding structurally related proteins in this family; however, only six are likely to have polymerase activity (1, 2). These enzymes transfer NAD⁺ to glutamate and lysine residues in acceptor proteins to form branched ADP-ribose chains. PARP1 activity was shown to be activated by DNA breaks more than 30 years ago (3–5); Shall showed that this played a role in DNA repair and that inhibition of this activity could potentiate cell killing by cytotoxic agents (5). PARP1 is recruited rapidly to a variety of DNA lesions, where its catalytic activity increases greatly, resulting in the transfer of branched chain poly ADP-ribose both to itself and to neighboring

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chromatin proteins. These modifications attract a number of DNA repair activities to the site of damage, including XRCC1 (6, 7), which in turn orchestrates the completion of base excision repair, one of the fundamental DNA repair pathways. In the face of overwhelming DNA damage, poly ADP-ribose synthesis uses substantial amounts of NAD⁺, which can trigger various forms of cell death. One such condition is ischemic injury. The possible application of PARP inhibitors towards potentiation of cytotoxic agent activity and in limiting post-ischemic injury has stimulated the development of drugs in this class by the pharmaceutical industry for some time. More recently, the discovery that PARP inhibitors can selectively kill cells with defects in DNA repair by homologous recombination has intensified interest in these inhibitors as cancer therapies.

Synthetic Lethality

Targeting tumor suppressor genes and other activities with cancer-specific loss is a significant pharmacologic challenge. Leland Hartwell, Stephen Friend and colleagues pointed a way forward in a seminal 1997 article (8), suggesting that synthetic lethality offered a potential route to target identification in these situations. Synthetic lethality is a term from classical genetics that refers to a particular relationship between two genes, X and Y. Gene X and gene Y are said to have a synthetic lethal relationship if mutations in either alone in a cell results in no phenotype, but mutations in both X and Y together in the same cell lead to lethality. Applying this concept to cancer drug development, if gene X is a tumor suppressor gene, then gene Y could potentially be used as a target for pharmacological inhibition rather than mutation. The challenge has been to find genes that are synthetic lethal with a given tumor suppressor gene; this can be done through classical genetics, new high throughput methods of extinguishing gene expression (9), or by clever conjecture. In the case of PARP inhibitors, the latter method was used.

Two groups noted that in the absence of PARP activity, subnuclear foci containing Rad51 appeared in growing cells (10, 11). Since Rad51 is one of the key activities in the DNA repair pathway homologous recombination, this observation suggested that cells deprived of PARP1 activity and thus deficient in base excision repair become more dependent on homologous recombination to repair DNA damage. Base excision repair is primarily responsible for repairing hydrolyzed bases and oxidative DNA damage, which is thought to occur thousands of times per 24 hours in a given cell (12). In the absence of PARP1 activity, this damage is removed by the initial activities of base excision repair, but the resulting single-stranded breaks are not sealed; some may be converted to double-stranded breaks during replication. The accumulated damage can subsequently be repaired by homologous recombination. However, in the absence of homologous recombination, this increased load of unrepaired DNA breaks could result in cell death. Because BRCA1 and BRCA2 are essential activities in homologous recombination, these considerations led to the hypothesis that BRCA1 or BRCA2 could each individually be in a synthetic lethal relationship with PARP1; this proved to be the case.

Additional work provides strong support for this view of how PARP inhibitors cause cell death in the absence of BRCA1 or BRCA2. McCabe et al. tested a number of genes required for homologous recombination for synthetic lethality with PARP (13). These experiments demonstrated cells deficient in any of RAD51, DSS1, RPA1, or RAD54, all proteins that are integral to homologous recombination, are quite sensitive to PARP inhibitors. In addition, the signaling proteins ATM and ATR, which are known to participate in homologous recombination, also cause decreased survival when combined with PARP inhibition. Lastly, Fanconi anemia proteins, thought to contribute to homologous recombination, were also synthetic lethal with PARP inhibition. In an additional study, a high throughput RNA interference screen focused on DNA repair proteins confirmed that genes essential for

homologous recombination were synthetic lethal with PARP inhibition (14). Taken together, these results suggest that any defect inhibiting homologous recombination could cause lethality when coupled with PARP inhibition. Based on these considerations, clinical trials testing the efficacy of PARP inhibitors in any tumors with defective homologous recombination, such as BRCA1 or BRCA2 related breast and ovarian cancers, have been developed.

Clinical Development

Multiple PARP inhibitors are currently under clinical development (see Table 1).

Single-agent therapy: BRCA-mutation carriers

The initial clinical trials of PARP inhibitors as single-agent therapy have sought to exploit the observation of synthetic lethality with defects in homologous recombination in cancers arising in carriers of a BRCA1 or BRCA2 mutation. Peter Fong and his colleagues conducted a Phase 1 trial of the PARP inhibitor olaparib in a study population enriched for BRCA mutation carriers (17). Dose escalation was conducted in patients with advanced solid tumors and subsequently, an expansion cohort was opened with enrollment limited only to BRCA mutation carriers. In total, 22 of the 60 patients enrolled on this study were BRCA mutation carriers. Overall, olaparib was well-tolerated, with the predominant adverse events being nausea, fatigue, and anorexia. No responses were observed in patients who were not BRCA mutation carriers. However, in 19 patients with BRCA1 or BRCA2 ovarian, breast, or prostate cancer who had evaluable disease, 12 patients demonstrated either radiologic or tumor-marker response or radiologically stable disease. Over half of the patients on the study had received 4 lines of prior therapy, suggesting that single-agent activity could still be observed in heavily pre-treated patients in this selected population.

The results from this study have prompted further exploration of PARP inhibitors as single-agent therapy in BRCA mutation carriers. Building upon the observed activity in the Phase I study, two Phase II trials of olaparib in BRCA mutation carriers were conducted, one in breast cancer and a second in ovarian cancer, and the initial results from these studies were presented at the American Society of Clinical Oncology (ASCO) meeting in June 2009. Both of these studies had similar designs, with a single-arm sequential cohort design of two dosing cohorts (400mg twice daily and 100mg twice daily). In the breast cancer study, a total of 54 patients were enrolled (27 patients/cohort) (23). The median number of prior lines of therapy in both cohorts was 3, and 22% of the patients in the 400mg and 30% of the patients in the 100mg cohorts had received prior platinum. 10 partial responses (37%) and 1 complete response (4%) were observed in the 400mg cohort, and 6 partial responses (22%) were observed in the 100mg cohort. In the ovarian cancer study, 33 patients were enrolled to the 400mg and 24 patients to the 100mg cohort (24). All patients had received prior platinum; patients in the 400mg cohort had a median of 3 prior therapies, with 79% demonstrating platinum-resistance (defined as progressive disease less than 6 months after last receipt of platinum), while those in the 100mg cohort had a median of 4 prior lines, with 67% having platinum resistance. 11 (33%) of patients in the 400mg cohort and 3 (13%) of patients in the 100mg cohort had response by RECIST criteria. A Phase II open label study comparing the efficacy of olaparib to that of pegylated liposomal doxorubicin in recurrent advanced ovarian cancer occurring BRCA mutation carriers (ICEBERG-3) has completed enrollment, and results are pending data maturation (15).

Other PARP inhibitors are also being actively explored as single agents in BRCA mutation carriers. At the most recent ASCO meeting in June 2010, Shahneen Sandhu and colleagues presented preliminary data from a first-in-human trial of the PARP inhibitor MK-4827 in a Phase I dose escalation trial with a patient population enriched for BRCA mutation carriers

(22). Of 56 patients enrolled in the dose escalation portion of the trial, 19 ovarian cancer and 4 breast cancer patients were BRCA1 or BRCA2 mutation carriers. 6 of the ovarian cancer patients and 2 of the breast cancer patients experienced a partial response by RECIST criteria. Again, patients in this study had been heavily pre-treated, with 40 of the 56 patients having received 4 lines of prior therapy. Ongoing trials of single-agent PARP inhibitor therapy in BRCA-deficient tumors are also being conducted with ABT-888 (veliparib) and PF-01367338 (AG014699) (15). Enrollment of a single-agent trial of BSI-201 (iniparib) in BRCA-deficient ovarian cancer has been completed, but the results have not yet been reported (15).

Single-agent therapy: Sporadic cancers

The evidence of activity of PARP inhibitors as single agents in cancers occurring in BRCA mutation carriers has also prompted exploration of whether PARP inhibitors might have activity in sporadic cancers that may have deficiencies in homologous recombination. Areas of specific interest have included sporadic ovarian cancer and triple-negative breast cancer. Although only approximately 10–15% of patients diagnosed with ovarian cancer carry a germline BRCA mutation (25, 26), the significant sensitivity of ovarian cancer to platinum has led to the hypothesis that many sporadic ovarian cancers may also have defects in homologous recombination. Studies have demonstrated that a significant fraction of sporadic ovarian cancers may have disruptions in BRCA or other homologous recombination pathway members (27–29). Similarly, sporadic triple-negative breast cancers share many characteristics with breast cancers arising in BRCA1 heterozygotes (30, 31), and a proportion are cisplatin sensitive (32), giving rise to the hypothesis that some sporadic triple-negative breast cancers may also have defects in homologous recombination that might render them sensitive to PARP inhibitors.

Currently, there are several ongoing trials exploring the efficacy of single-agent PARP inhibitors in these settings. A double-blinded randomized Phase II trial investigating the efficacy of olaparib as maintenance therapy after second-line platinum-based therapy in platinum-sensitive ovarian cancer has completed accrual (15), and the dose expansion portion of the MK-4827 trial discussed above will include cohorts in sporadic platinum-resistant high-grade serous ovarian cancer and sporadic castration resistant prostate cancer (22). Additionally, Gelmon and colleagues recently presented preliminary results from a Phase II trial of olaparib in advanced serous ovarian and triple-negative breast cancers (33). In this open-label correlative study, patients were eligible if they had one of the following characteristics: 1) triple-negative advanced breast cancer; 2) known BRCA mutation positive breast cancer; 3) high-grade serous and or undifferentiated carcinoma of the ovary, fallopian tube, or peritoneum; or 4) known BRCA mutation positive ovarian, fallopian tube, or peritoneal cancer. Once patients were enrolled, all patients underwent sequencing for germline BRCA mutation. Patients had a median of 3 prior lines of therapy. In the ovarian cancer cohorts, 7 of 17 (41%) patients with germline BRCA mutation demonstrated a RECIST response to olaparib. Intriguingly, 11 of 46 (24%) ovarian cancer patients who did not have a germline BRCA mutation also demonstrated a RECIST response. While these results are potentially of great interest, a point of concern arose as no RECIST responses were observed in either the BRCA mutation (n=8) or non-mutation (n=15) breast cancer group. This result is in contrast to those presented by Tutt et al. the previous year (above) (23). It may be that there are significant differences in the baseline characteristics of the breast cancer patients enrolled in these two studies, or that the small number of breast cancer BRCA mutation carriers in the Gelmon study is not statistically robust. Of note, Gelmon et al. did observe evidence of biological activity of olaparib in BRCA-related breast cancer, although it did not meet RECIST criteria for response. Resolution of this issue awaits further clinical results.

Combination therapy

There has been significant interest in building on preclinical data that inhibitors of PARP function might potentiate the effects of chemotherapy (5). In preclinical models, PARP inhibitors appear to potentiate the activity of DNA alkylating agents such as temozolomide and topoisomerase-I inhibitors such as topotecan or irinotecan, as well as the effects of radiation therapy (34, 35). A number of studies are actively enrolling investigating the safety and efficacy of various chemotherapies in combination with PARP inhibitors, including with ABT-888, olaparib, BSI-201, PF-01367338 (AG014699), and CEP-9722 (15).

Perhaps the most significant combination PARP inhibitor study result to date was presented in preliminary form by Joyce O'Shaughnessy and colleagues at ASCO in 2009 (36). In this Phase II, multi-center, open-label study, 123 patients with metastatic triple-negative breast cancer were randomized to receive either carboplatin and gemcitabine or carboplatin and gemcitabine in combination with the PARP inhibitor BSI-201. Preliminary efficacy results demonstrated a response rate of 16% in the carboplatin/gemcitabine arm, compared to 48% in the carboplatin/gemcitabine/BSI-201 arm, with a p-value of 0.002. Additionally, there was a statistically significant progression-free survival (6.9 vs. 3.3 months, $p < 0.0001$) and overall survival (9.2 vs. 5.7 months, $p = 0.0005$) favoring the carboplatin/gemcitabine/BSI-201 arm. A Phase III study with a similar design has completed accrual, and results are expected in the near future (15). This combination regimen is also under active investigation in single-arm Phase II trials in platinum-sensitive and -resistant ovarian cancer (15). Of note, it remains unclear whether the benefit observed in the O'Shaughnessy trial was mediated by the anti-PARP activity of BSI-201 alone or whether it reflects its role as a chemopotentiator for either or both carboplatin and gemcitabine.

Resistance

The study of resistance mechanisms can provide greater insight into the details of how the therapy works and how it fails; this is particularly true with the PARP inhibitors. Jos Jonkers and his colleagues used their BRCA1 conditional p53 mouse model to study resistance to the PARP inhibitor olaparib (37). In this model, exons 5 through 13 of BRCA1 are deleted in response to the Cre recombinase driven by the keratin 14 promoter; for the purposes of studying PARP inhibitor resistance, tumors arising this model were divided and transplanted orthotopically into multiple syngeneic recipients. Initially, the tumors responded to olaparib, but eventually all developed resistance. 12 of 15 olaparib-resistant tumors showed up-regulation of the murine equivalents of the drug efflux pumps MDR1 or MDR2. Resistance was mostly avoided by adding an MDR inhibitor. Consistent with an MDR effect, tumors selected for anthracycline resistance also were resistant to olaparib. Note that in this mouse model system, the large deletion in BRCA1 prevents BRCA1 reversion mutations, a resistance mechanism discussed below.

Ashworth and his colleagues selected 12 PARP inhibitor resistant clones from the human pancreatic cell line CapaN1, which is homozygous for the BRCA2 mutation 6174delT(38). The concentration of drug required to cause a 50% reduction in growth of the resistant clones was more than 1000 fold that for similar reduction in the original sensitive cell line. These clones were also cisplatin resistant when compared with the parental cell line, but were not docetaxel resistant. Eleven of the clones had novel BRCA2 alleles containing large deletions spanning 6174delT as well as multiple exons; they all restored the reading frame and the carboxy terminus of BRCA2. The 12th resistant clone had a 458 base pair deletion encompassing 6174delT, restoring the reading frame and almost full length BRCA2. Of interest, almost all of these new deletions had short regions of sequence identity at their novel junctions, suggesting that in the absence of BRCA2, non-homologous end joining or single-strand annealing may be involved in the generation of these deletions. Most

importantly, all of these novel BRCA2 alleles in the resistance cells are competent to perform homologous recombination, and by themselves all cause olaparib resistance when moved into unmodified CapaN1 cells. The resistance of these clones to cisplatin suggests that this conventional cytotoxic drug also targets defective homologous recombination. Taniguchi took advantage of this property of cisplatin and selected cisplatin resistant clones from CapaN1 (39). They found 14 resistant clones starting with 12 million cells; seven of these clones had small deletions or insertions near 6174delT that corrected the reading frame of BRCA2. These clones were also all PARP inhibitor resistant. In a similar study of cisplatin resistance in BRCA1 and BRCA2 related ovarian cancer, 11 of 35 recurrent ovarian cancers had secondary mutations in BRCA1 or BRCA2, and all but one of these patients had disease that was clinically deemed platinum resistant (40). Most of these resistance mutations directly restored to wild type the sequence of BRCA1 or BRCA2; two were new frameshifts that restored the BRCA1 or BRCA2 reading frame and presumably restored homologous recombination function.

Clinical data also support the close relationship between platinum resistance and PARP inhibitor resistance in ovarian cancer. Fong et al. studied the relationship between platinum sensitivity or resistance at entry into a trial of monotherapy with the PARP inhibitor olaparib in 50 patients with BRCA1 or BRCA2 related ovarian cancer (41). Patients with platinum sensitive disease at the time of enrollment had the highest rate of clinical response, followed by patients with platinum resistant disease. Patients with platinum refractory disease had the lowest rates of response.

Two recent papers suggest another route of resistance to PARP inhibitors in BRCA1 related cancers (42, 43). 53BP1 is a DNA damage response protein; loss of the 53BP1 gene has been shown to rescue embryonic lethality, premature aging, and tumor susceptibility in a mouse model in which BRCA1 exon 11 has been eliminated (44). Because of these properties, the possibility that 53BP1 deletion would restore homologous recombination in a BRCA1-deficient context was investigated. This appears to be the case; 53BP1 inhibition causes PARP inhibitor resistance in BRCA1 deficient cells (43), and 53BP1 loss causes cisplatin resistance in the absence of BRCA1 but not BRCA2 (42). These observations suggest that loss of 53BP1 may be a route to PARP inhibitor resistance in BRCA1 deficient tumors, a hypothesis yet to be tested in clinical samples

Conclusion

This review has focused on the science behind the PARP inhibitors and their current state of clinical development as cancer therapeutics. The activity of these drugs in selected cancers validates the use of synthetic lethality in cancer drug development. Of note, BRCA1 or BRCA2-related breast and ovarian cancers are likely not the only tumors with defects in homologous recombination. Certainly, BRCA2-related pancreatic cancers are prime candidates in which PARP inhibitors might be tested. A reliable means of determining the homologous recombination status of a given tumor does not yet exist, but might also provide additional insight into tumors that might be candidates for PARP inhibitor therapy. Further, it is currently unclear whether tumors that respond to combinations of PARP inhibitors and conventional cytotoxic agents depend upon intrinsic DNA repair defects for response; an answer to this question will help define which cancers may benefit from this approach. These promising drugs will no doubt continue to be the subject of accelerating development in the next few years.

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Table

PARP inhibitors in clinical development

PARP inhibitor	Company	Characteristics	Route	Single-agent trials (15)	Combination trials (15)
AG014699/ PF-01367338 (16)	Pfizer	PARP1/2 inhibitor $K_i < 5\text{nM}$ $t_{1/2}$: 9.5 hrs	IV	BRCA mutation carriers	Phase 1 exploring multiple chemo regimens
Olaparib (KU-0059436; AZD2281) (17, 18)	KuDOS/ AstraZeneca	PARP1/2 inhibitor K_i (PARP1): 5nM K_i (PARP2): 1nM $t_{1/2}$ 5–7 hrs	PO	BRCA mutation carriers (Phase 2 breast and ovary) Sporadic ovarian cancer Triple-negative breast cancer Colorectal cancer	Multiple
Veliparib (ABT-888) (19, 20)	Abbott	PARP1/2 inhibitor K_i (PARP1): 5.2nM K_i (PARP2): 2.9nM $t_{1/2}$: several hrs	PO	BRCA mutation carriers	Multiple
Iniparib (BSI-201) (21)	BiPAR/ Sanofi-Aventis	$t_{1/2}$: 4 mins	IV	BRCA mutation carrier ovarian cancer	Carbo/gen/BSI-201 (Phase 3 breast) Multiple
MK-4827 (22)	Merck	PARP1/2 inhibitor K_i (PARP1): 3.8nM K_i (PARP2): 2.1nM $t_{1/2}$: 37– 42 hrs	PO	BRCA mutation carriers Sporadic ovarian cancer Castrate-resistant prostate cancer	Phase 1 planned
CEP-9722	Cephalon		PO		Phase 1 with temozolomide
INO-1001	Inotek		IV	ST-elevation myocardial infarction High-risk subjects undergoing cardiopulm bypass	Phase I with temozolomide in melanoma pts (terminated)

These PARP inhibitors vary in terms of route and schedule of delivery, as well as in how they have been developed for clinical use in ongoing trials. Two major areas of development have been under investigation: 1) single-agent therapy in selected populations, and 2) combination therapy with standard chemotherapeutic agents.