Review

Current Development of Clinical Inhibitors of Poly(ADP-Ribose) Polymerase in Oncology

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Abstract   Poly(ADP-ribose) polymerase (PARP) is a nuclear enzyme that signals the presence of DNA damage by catalyzing the addition of ADP-ribose units to DNA, histones, and various DNA repair enzymes and by facilitating DNA repair. PARP has been gaining increasing interest as a therapeutic target for many diseases and especially for cancer. Inhibition of PARP potentiates the activity of DNA-damaging agents, such as alkylators, platinums, topoisomerase inhibitors, and radiation in *in vitro* and *in vivo* models. In addition, tumors with DNA repair defects, such as those arising from patients with BRCA mutations, may be more sensitive to PARP inhibition. At least five different companies have now initiated oncology clinical trials with PARP inhibitors, ranging in stage from phase 0 to phase 2. This review summarizes the preclinical and clinical data currently available for these agents and some of the challenges facing the clinical development of these agents.

Background

Discovery and roles in cellular injury. Poly(ADP-ribose) polymerase (PARP) is a DNA nick-sensor that signals the presence of DNA damage and facilitates DNA repair (as shown in Fig. 1). The polymerase catalyzes the addition of ADP-ribose units to DNA, histones, and various DNA repair enzymes, which affects cellular processes as diverse as replication, transcription, differentiation, gene regulation, protein degradation, and spindle maintenance. The first PARP enzyme was described over 40 years ago (1), and is the prototype for a superfamily of 17 members (2). PARP-1 is a nuclear protein whose zinc-finger DNA binding domain localizes PARP-1 to the site of DNA damage. In knockout mouse models, deletion of PARP-1 impairs DNA repair but is not embryonically lethal (3–5). The residual PARP activity (~10%) is due to PARP-2. Double knockout PARP-1 and PARP-2 mice die during early embryogenesis, suggesting the critical role that PARP-2 plays in the absence of PARP-1 (6) and that only PARP-1 and PARP-2 need to be inhibited to stall DNA repair (6–8).

The zinc-finger domain of PARP binds to ssDNA breaks (SSB; refs. 7–9), cleaves NAD^+, and attaches multiple ADP-ribose units to the target protein. This results in a highly negatively charged target, which in turn leads to the unwinding and repair of the damaged DNA through the base excision repair pathway. Overactivation of PARP results in depletion of NAD^+ and energy stores, leading to cellular demise by necrosis. An alternate mechanism has been identified where PARP overactivation can induce cell death through apoptosis by releasing the apoptosis-inducing factor from mitochondria (10). PARP-1 activity seems to be down-regulated by the activation of the sirtuin SIRT1, a NAD^+-dependent deacetylase (11), leading to a marked increase in poly(ADP-ribose) synthesis in *sirt1*-null cells. The lack of regulation of PARP-1 in the absence of SIRT1 results in apoptosis-inducing factor–mediated cell death. Consequently, multiple mechanisms exist to prevent overactivation of PARP. Auto-poly(ADP-ribosyl)ation negatively regulates PARP activity (12). In addition, the cleavage of PARP by caspases yields a peptide fragment that acts as a transdominant negative inhibitor for uncleaved PARP. Poly(ADP-ribosyl)ation of proteins is a dynamic process with a short half-life of <1 min. Degradation of these polymers is catalyzed by poly(ADP-ribose) glycohydrolase (13), which cleaves ribose-ribose bonds, and ADP-ribosyl protein lyase (14), which removes the protein proximal to the ADP-ribose monomer. Once the polymer is cleaved, PARP is released and inactivated, allowing it to bind another site of DNA damage.

PARP-1 is also known to bind dsDNA breaks (DSB). The enzyme activates several proteins involved in the homologous recombination repair and the nonhomologous end-joining pathways (15–20). It is believed that PARP-1 is an antirecombinogenic factor that prevents accidental recombination of homologous DNA. PARP-1 has also been implicated in BRCA1- and BRCA2-dependent homologous recombination repair (21–23). When PARP-1 is inhibited, SSBs persist and result in stalled replication forks and DSBs. In BRCA1- and BRCA2-deficient cells, these lesions are not repaired through homologous recombination repair, leading to cell cycle arrest and apoptosis. There is also evidence to suggest that there is an alternate pathway to nonhomologous end joining for DSB repair. This pathway is directly dependent on PARP-1 and involves XRCC1 and DNA ligase III, proteins that play roles in SSB repair through the base excision repair pathway (24). Comparatively, less is known about the contribution of PARP-2 to DNA repair, although it seems that PARP-1 and PARP-2 both participate in overlapping DNA damage signaling processes and may partially compensate for one another (25).

Role in DNA repair in tumor cells. Enhanced PARP-1 expression and/or activity has been shown in several tumor cell lines, including malignant lymphomas, hepatocellular carcinoma, cervical carcinoma, colorectal carcinoma, non-Hodgkin's lymphoma, leukemic lymphocytes, and colon adenomatous polyps (26–32). This may allow tumor cells to withstand genotoxic stress and increase their resistance to DNA-damaging agents. Aberrations in PARP activity in conjunction with transcription factor CAAT/enhancer binding protein α as well as the DNA repair proteins Ku70 and Ku80 have been seen
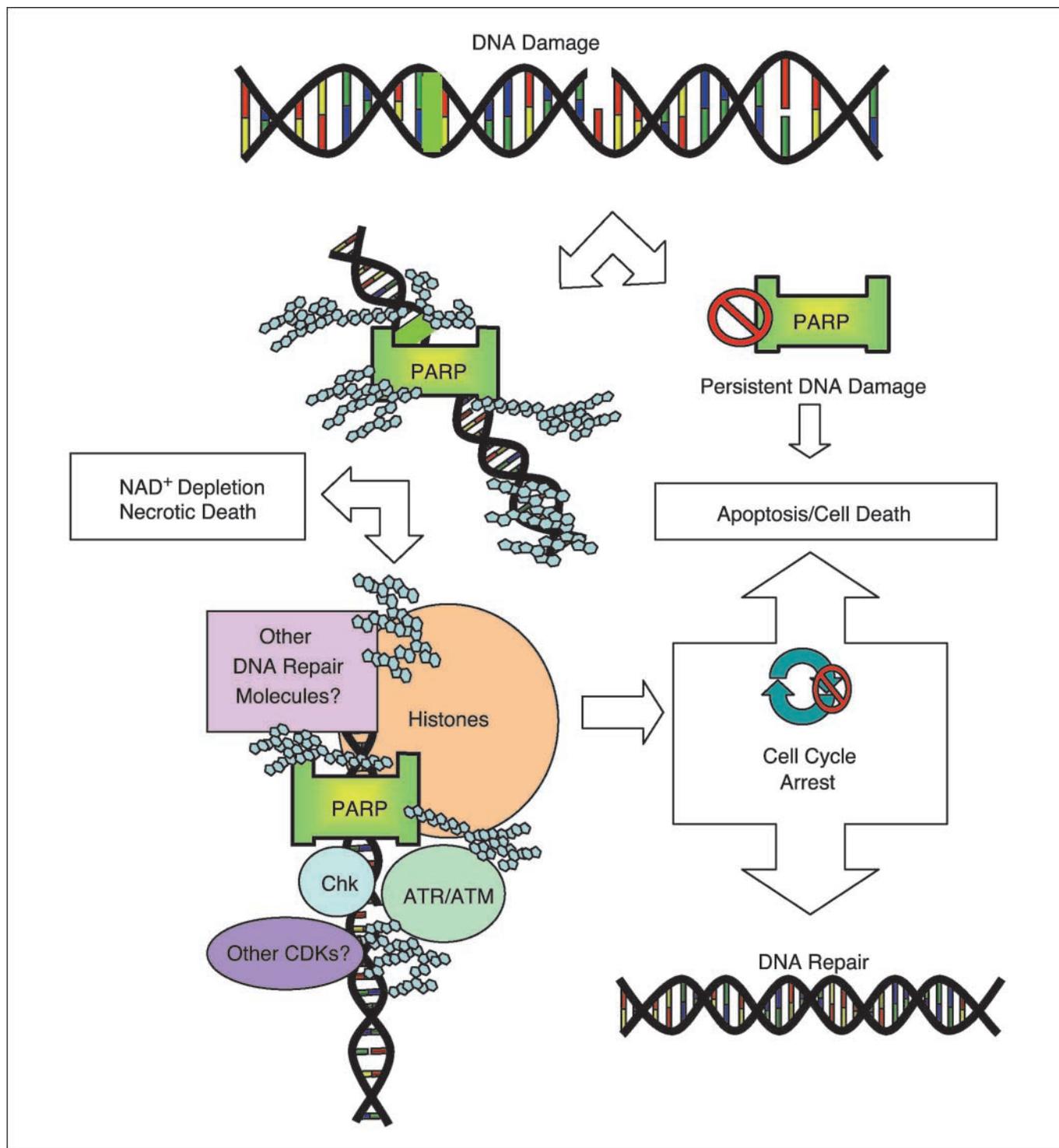

Fig. 1. Mechanism of PARP action. DNA-damaging agents, such as chemotherapeutics, radiation, or replication errors, activate PARP, resulting in poly (ADP-ribose) – branched chains attached to DNA, recruiting associated repair proteins and cell cycle checkpoint mediators. This cascade may lead to cell cycle arrest while the cell commits to either DNA repair or apoptosis. Overactivation of PARP will lead to NAD^+ depletion and necrotic cell death. PARP inhibition is thought to impair DNA repair function, leading to cellular dysfunction and death, and may also affect other PARP mediated DNA modulating effects.

Table 1. PARP inhibitors in cancer therapy

Agent	Company	Single/ Combination therapy	Route of administration	Disease	Clinical status
AG014699	Pfizer (New York, NY)	Combination with temozolomide	I.v.	Solid tumors, metastatic malignant melanoma	Phase 1 in solid tumors complete, phase 2 in melanoma complete
KU59436	AstraZeneca/KuDOS (London, United Kingdom)	Single	Oral	Advanced solid tumors	Phase 1 ongoing
ABT-888	Abbott Laboratories (North Chicago, IL)	Single	Oral	Refractory solid tumors and lymphoid malignancies	Phase 0 ongoing
BSI-201	BiPar (Brisbane, CA)	Single	I.v.	Advanced solid tumors	Phase 1 ongoing
INO-1001	Inotek/Genentech (Beverly, MA)	Combination with temozolomide, single	I.v.	Melanoma, glioblastoma multiforme	Phase 1 ongoing
GPI 21016	MGI Pharma (Bloomington, MN)	Combination with temozolomide	Oral	Solid tumors	Phase 1 planned

in prostate cancer cell lines (33). The interaction between PARP-1 and Ku80 has also been implicated in hepatocellular cancer (19). Cells, in which these associations were observed, had increased sensitivity to radiation and impaired nonhomologous end-joining and homologous recombination repair pathways.

Role in angiogenesis. PARP-1 has also been implicated in angiogenesis. cDNA microarray analysis during skin carcinogenesis showed that PARP-1 modulates expression of genes involved in angiogenesis, such as *Hif-1α*, *Pecam-1*, and *OPN* (34). In particular, inhibition of PARP-1 seems to result in decreased accumulation of the transcription factor hypoxia-inducible factor-1α. Hypoxia-inducible factor-1α is thought to regulate tumor cell adaptation to hypoxia by inducing several proteins required for this process, including vascular endothelial growth factor (35, 36). Decreased hypoxia-inducible factor-1 function in tumors may contribute to tumor cell death.

PARP Inhibition

Early and new generation PARP inhibitors. Early studies on PARP inhibition used nicotinamide and 3-aminobenzamide and other substituted benzamides, which had specificity for PARP in the low micromolar range (37, 38). PARP inhibitors examined to date are competitive inhibitors of NAD^+. The relatively low potency of these agents has led to development of more potent and specific proprietary PARP inhibitors. The optimization of PARP inhibitor structures to increase potency and specificity, such as benzimidazoles and dihydroisoquinolinones (39), pyrrolocarbazoles (40), and phthalazinones (41, 42), have been published by some of the leading industry groups. An excellent review of different chemical classes of PARP inhibitors has been written by Southan and Szabo (43).

Potentiation of DNA-damaging chemotherapeutics. Increased PARP activity is one of the mechanisms by which tumor cells avoid apoptosis caused by DNA-damaging agents. PARP is essential for the repair of SSBs through the base excision repair

pathways (8, 44). Inhibition of PARP sensitizes tumor cells to cytotoxic therapy (e.g., temozolomide, platinums, topoisomerase I inhibitors, and radiation; refs. 45–48), which induce DNA damage that would normally be repaired through the base excision repair system. A significant window seems to exist between the ability of a PARP inhibitor to potentiate therapeutic benefit versus potentiation of undesirable side effects (39, 49). PARP inhibitors have not potentiated agents that do not damage DNA (50).

Potentiation of radiation. Tumor cells have shown increased sensitivity to γ- and X-radiation in the presence of PARP inhibitors (49, 51–55). Radiosensitization by PARP inhibition seems to have greater effect on cells in the S and G_2 phases of the cell cycle, and noncycling cells exhibit minimal sensitivity (51, 52). Although radiosensitization is partly due to the inhibition of SSB repair, it is likely that DSB repair, which may be more cytotoxic, is also affected. Although PARP activity seems important for repair of both SSBs and DSBs caused by ionizing radiation, one study has found that a PARP-1 knockout cell line is immune to the radiosensitization effects of PARP-1 inhibitors at low doses of radiation (51). It is thought that, in this instance, PARP-2 compensates for the lack of PARP-1, whereas at high doses of radiation, and consequently greater DNA damage, PARP-2 is unable to do so.

Studies have also shown that the combination of DNA-dependent protein kinase inhibitors and PARP inhibitors have an additive effect on radiation-induced DNA damage (55, 56). Both the enzymes are involved in the binding and repair of DSBs. The combination seems to prevent 90% of DSB repair.

Therapeutic role as single agent in DNA repair-deficient tumors. Germ-line mutations in *BRCA1* and *BRCA2* indicate high risk for breast, ovarian, and other malignancies. BRCA1 and BRCA2 are thought to be involved in homologous recombination repair and cells deficient in these proteins seem to be highly sensitive to PARP inhibition compared with wild-type cells (21, 22). In these cells, PARP inhibition results in cell cycle arrest and apoptosis. This suggests a role for PARP inhibitors as single agents in cancers exhibiting *BRCA1* and

BRCA2 mutations. Interestingly, these findings were questioned when a study using the CAPAN-1 pancreatic cancer cell line carrying a loss-of-function BRCA-2 mutation did not seem to be sensitive to the older generation PARP inhibitors, 3-aminobenzamide and NU1025 (57). However, McCabe et al. (58), after evaluating CAPAN-1 with the more potent inhibitor KU0058948, suggested that the sensitivity of BRCA1- and BRCA2-deficient cells to PARP inhibition seems to be dependent on the potency and/or specificity of the PARP inhibitor.

These results suggest that the concept of synthetic lethality, in which two pathway defects that alone are innocuous, but combined become lethal, may be a relevant approach to inhibiting DNA repair in tumors. PARP inhibitors may be more effective in patients with tumors with specific DNA repair defects, such as BRCA mutations, or with other therapeutics that inhibit other DNA repair pathways. Possible strategies for targeting other DSB repair pathways are discussed in a succinct review by Lord et al. (59).

Current Clinical Development of PARP Inhibitors

Five PARP inhibitors are currently known to be in clinical oncology trials and one more is expected to enter clinical trials shortly, and their current status is summarized in Table 1. Below is a summary of what has been published or presented about each of these agents.

Pfizer: AG014699. AG-014699 was the first PARP inhibitor to be evaluated in humans for cancer therapy (60). Preclinical data derived with this agent indicated that the combination of AG-014699 with irinotecan and with irradiation delayed xenograft tumor growth and caused xenograft tumor regression with temozolomide (49). The phase 1 study combined i.v. AG014699 with temozolomide in solid tumors, initially evaluating PARP activity in peripheral blood lymphocytes with reduced doses of temozolomide until PARP inhibition was observed and then escalating temozolomide to standard doses (200 mg/m^2 daily for 5 days every 4 weeks) at a fixed AG-014699 dose (60). No dose-limiting toxicities were observed. The terminal half-life ranged from 7.4 to 11.7 h and clearance was 25 L/h. Area under the curve and maximum plasma concentration were linearly proportional with dose. Population pharmacokinetics of AG-014447 (the parent compound of AG-014699) was described by a three-compartment model, with saturable and nonsaturable distribution to peripheral compartments (61). The recommended dose for the phase 2 trial was 12 mg/m^2 AG-014699 with 200 mg/m^2 temozolomide. In the phase 2 trial, 40 patients with metastatic malignant melanoma were evaluable, with seven (18%) partial responses seen (62). There was enhancement of temozolomide-related myelosuppression and one toxic death occurred. The dose was reduced to 150 mg/m^2 in 12 patients.

AstraZeneca: KuDOS KU-0059436. KU-0059436 is currently being evaluated in a phase 1 trial in patients with advanced tumors in the United Kingdom and the Netherlands (63). This study initially began with daily and twice a day dosing of the oral inhibitor 14 days of a 21-day cycle and is now evaluating continuous twice a day dosing (64). Minimal toxicity has been reported. Pharmacokinetic data showed dose proportionality with mean elimination half-life being 6.91 h and V_d of 39.8 L. Pharmacodynamic studies showed dose-dependent inhibition of PARP activity in peripheral blood mononuclear cells. A

patient with ovarian cancer and a family medical history suggestive of BRCA mutation had a partial response on this trial, whereas a patient with metastatic soft tissue sarcoma experienced stable disease for 24 weeks.

Abbott: ABT-888. ABT-888 is an oral PARP inhibitor that is the first oncology agent to be studied in a phase 0 clinical trial by the National Cancer Institute under an exploratory Investigational New Drug application (65). In the phase 0 study, participants with biopsiable tumor are given a single dose of ABT-888 to determine the dose range at which PARP is effectively inhibited in peripheral blood mononuclear cells and tumor cells. The study also aims to assess the pharmacokinetic characteristics of the agent and the time course of PARP inhibition. Phase 1 combination studies with temozolomide, irinotecan, cyclophosphamide, and carboplatin will be initiated by Abbott and the National Cancer Institute in 2007.

BiPAR: BSI-201. BiPAR Sciences announced in a press release (March 7, 2006) that its lead compound, BSI-201, entered clinical trials in March of 2006, and combination studies will begin at the end of 2006. BSI-201 is being tested as i.v. monotherapy in solid tumors with the objective to determine a maximum tolerated dose and a pharmacokinetic profile (identifier NCT00298675).[3] BiPAR also indicates that at least one other PARP inhibitor, BSI-401, will enter oncology clinical trials in 2007.

Inotek: INO-1001. INO-1001, an indenoisoquinolinone-based PARP inhibitor, has been evaluated in phase 1 trials as an agent for acute cardiovascular diseases. It has been granted orphan drug status by the Food and Drug Administration for prevention of postoperative aortic aneurysm repair complications and is currently in phase 2 trials for cardiovascular indications. It is also being studied in combination therapy in metastatic melanoma and glioma and as a single agent in cancer for BRCA1- and BRCA2-deficient tumors. A preliminary analysis of a phase 1 trial, which evaluated INO-1001 in combination with temozolomide in unresectable stage III/IV melanoma, reported one patient with objective tumor regression (66). The investigators found that nonhematologic toxicities were mild and mostly related to temozolomide. Genentech (South San Francisco, CA) and Inotek announced (press release, July 25, 2006) that they had entered into an alliance to develop and commercialize PARP inhibitors.

MGI Pharma: GPI-21016. MGI Pharma is developing GPI-21016, an orally available inhibitor of PARP-1 with a K_i of 50 nmol/L (67). In preclinical models, the related MGI PARP inhibitor GPI 15427 potentiated temozolomide in an intracranial melanoma model, indicating adequate brain penetration of this agent (68). Interestingly, GP-21016 ameliorated cisplatin-induced neuropathy at the same time that antitumor efficacy was enhanced, suggesting a role for PARP inhibitors to improve the therapeutic margin of some chemotherapeutics (67). A phase 1 study is being planned for 2007.

Issues with PARP Inhibitor Development

PARP inhibitors are an interesting new class of agents with the potential to improve the therapeutic efficacy of several commonly used chemotherapeutics in oncology. From preclinical and toxicology studies and initial clinical reports, it seems

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[3] http://www.clinicaltrials.gov/

that these agents have relatively little single agent toxicity and may be quite tolerable in combination with other agents. The possibility that some toxicities may even be reduced, such as cisplatin nephrotoxicity (69) or doxorubicin cardiotoxicity (70), provides further incentive to evaluate these agents.

Issues in development of PARP inhibitors as therapeutic sensitizers. Although there has been much interest in the possibility of using a PARP inhibitor as a single agent in certain selected settings, it is more likely that the role of PARP inhibitors will be as therapeutic sensitizers. Thus, clinical trial designs must accommodate selecting the most appropriate dose and schedule of both the PARP inhibitor and the other therapeutic agent and be able to identify which combinations are most suitable for advancement into efficacy trials.

Because most agents that would be combined with a PARP inhibitor are already administered at or near a maximum tolerated dose and the toxicities of those agents are related to the mechanism of action, the addition of another potentiating agent is as likely to increase toxicity as efficacy. Although preclinical models using PARP inhibitors have suggested that the PARP inhibitor may ameliorate toxicity while improving efficacy (67–70), the single reported human experience combining a PARP inhibitor with temozolomide reported probable exacerbation of temozolomide-induced hematologic toxicity (62). In addition to toxicity issues in normal tissues, PARP inhibition may also have the potential to disrupt normal DNA repair processes in normal tissues (such as from sun exposure or other environmental processes), although normal tissue may be less reliant on a single pathway for DNA repair compared with susceptible tumors. Strategies to evaluate phase 1 combination clinical trials with toxic agents are likely to require a starting dose of the therapeutic agent below the dose customarily given before escalation to the usual dosing, with cautious escalation of the PARP inhibitor once the therapeutic is being administered at a usual dose.

Determining the optimal schedule for the PARP inhibitor will be more challenging as surrogate end points for improved efficacy are not available in the early development setting. Although it seems obvious that PARP should be inhibited before administration of the DNA-damaging agent, it remains unclear what the optimal amount and duration of PARP inhibition should be after the therapeutic is given. Practical constraints on duration of therapy may limit dosing for i.v. formulations and gastrointestinal toxicities, if any, for oral formulations. Biomarker studies may also provide insight into optimizing dosing schedules.

Pharmacodynamic markers of target effect. Because of the number of cellular processes affected by PARPs, several possible biomarkers can be identified that may correlate with PARP activity. Screening assays used to determine the potency of PARP inhibitors in *in vitro* models, such as evaluating NAD^+ turnover, are difficult to practically apply in a clinical setting.

Plummer et al. (71) have described a method of determining PARP activity in peripheral blood mononuclear cells and tumor tissue that was used on samples from patients undergoing treatment with temozolomide. Kinders et al. (72) have developed an immunoassay to quantitate poly(ADP-ribose) in peripheral blood mononuclear cells and tumor tissue. Neither of these reports describes the results of these assays in patients treated with PARP inhibitors, although both indicate their intention to be used as pharmacodynamic assays in clinical trials. In addition, KuDOS has reported preliminary data from its single-agent phase 1 clinical trial of KU-0059436 in patient samples (>50% PARP inhibition at 40 mg/d), but the method they used for determining inhibition was not described (63). Data generated from using these assays in clinical studies will be helpful to determine biologically effective doses, but additional clinical data will be required to correlate these results with clinical outcomes.

Conclusions

PARP inhibition as a therapeutic strategy in oncology is generating increasing enthusiasm from researchers in academia and in the pharmaceutical industry because of its potential to widen the therapeutic index of chemotherapy and radiotherapy, its low side effect profile, and the possibility that target populations with higher sensitivity can be identified. At least half a dozen different agents are anticipated to be in oncology clinical trials by the end of 2007. As with all new therapeutic areas, the usefulness of this target is unproven, but the potential effect of this class of agents is large. Shrewd early clinical trial designs and continuing biomarker development will be essential to the efficient development of these agents.

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