MINI REVIEW

Stumbling Blocks on the Path to Personalized Medicine in Breast Cancer: The Case of PARP Inhibitors for BRCA1/2-Associated Cancers

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The popular vision for the future of oncology includes the rational design of therapies inhibiting specific targets, for which development would be less expensive and the chance of success greater because the agent, the target, and a population predicted to benefit maximally would be known from the outset. In the breast cancer arena, successful targeted therapies have entered clinical practice. Recently, patients with BRCA-associated cancers have been identified as eligible for novel investigational therapies targeting their genetic deficiency. Preclinical data, phase I results, and 2 phase II proof-of-concept studies support the continued development of PARP inhibitors, either as single agents or in combination with specific cytotoxic drugs in this setting. In this article, we provide a brief review of current developments concerning PARP inhibitors in BRCA-associated cancers and express concerns about challenges to further development.

Summary: PARP inhibitors may represent a new and promising targeted therapy for patients with BRCA1/2-associated cancer. In this review we summarize the main challenges in the clinical development of these agents.

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INTRODUCTION

Breast cancer has been the beneficiary of targeted therapies since before this phrase became popular. Hormonal agents to treat receptor-positive tumors have been FDA approved for nearly 35 years; 5 agents are approved for treatment in the United States and Europe. Agents targeting HER2 have transformed the outcomes for patients whose tumors overexpress the HER2 kinase. Other breast cancers (so-called triple-negative tumors) do not express estrogen receptor, progesterone receptor, or HER2; these tumors are often sensitive to cytotoxic chemotherapies, but identification of important molecular targets for therapeutic exploitation is still to come. The recent development of PARP [poly(ADP-ribose) polymerase] inhibitors for treatment of breast cancer based on the concept of synthetic lethal strategies in tumors with deficient BRCA1- or BRCA2-associated DNA repair has led to new opportunities for targeted therapies for more women with this disease.

Meanwhile, targeted therapies for rare tumors and subsets of more common cancers have been successfully developed (Table 1). Imatinib, a small-molecule inhibitor of KIT, has been approved by the FDA and European Medicines Agency (EMA) for treatment of chronic myelogenous leukemia (4,500 cases/year in the United States), gastrointestinal stromal tumors (GIST) with mutations in cKIT (3,500 cases/year in the United States; ref. 1), and dermatofibrosarcoma protubers in adults (1,000 cases/year in the United States). This targeted therapy was granted orphan designation for treatment of these rare tumors with unmet medical need. More recently, identification of specific genomic defects has made it possible to develop other targeted therapies with potential impact on subsets of common diseases. For the 3% of lung cancer patients with ALK-EML rearrangements, the oral ALK kinase inhibitor crizotinib shows a 60% response rate (2). In other exciting data, use of the RAF inhibitor PLX4032 resulted in an 81% response rate in the nearly 40% of melanomas with BRAF V600E mutations (3). A DNA-based companion diagnostic test to enable selection of patients is being codeveloped by the same pharmaceutical company that is developing the drug. Although neither PLX4032 nor crizotinib has been approved by the FDA at this time, both drugs are on the FDA’s “fast track.” A small phase III trial of crizotinib versus conventional chemotherapy is currently under way; positive results from this study could lead to its approval. These 2 compounds exemplify the popular vision.

ABSTRACT

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for the future of clinical oncology: rational design of therapies inhibiting specific targets, for which development would be less expensive and the chance of success greater because the agent, the target, and a population predicted to benefit maximally would be known from the outset.

Traditional phase II clinical trials have been designed to identify tumors in which activity of a new agent can be shown. Subsequent evaluation of specific subsets of potential responders is often empirical, requiring relatively large numbers of patients and retrospective efforts to distinguish those patients who derive the most benefit. This strategy typically requires large and expensive trials that show little benefit in the broad group, as well as unplanned and underpowered subset analyses, which often do not reach conclusions sufficiently robust to assist on a path to registration. Clinical trials for novel agents targeting molecular subsets of even the more common cancers face different obstacles, such as the smaller number of patients who will ultimately receive the treatment and the need for an accurate diagnostic test to define the group.

The development of anti-Her2 treatment in cancer is a classic story in the targeted therapy arena; strong preclinical data were subsequently confirmed in studies of advanced and early breast cancer and was finally extrapolated to other HER2-positive solid tumors. Amplification and overexpression of HER2 occur in approximately 20% to 25% of patients with breast cancer and is associated with aggressive disease and decreased survival. In the early 1990s, preclinical evidence that HER2 caused malignant transformation stimulated interest in HER2 as a therapeutic target in breast cancer. Trastuzumab, a recombinant DNA-derived humanized monoclonal antibody that binds with high affinity to the extracellular domain of the HER2 protein, was developed and shown to be active as a single agent or in combination with chemotherapy (4). The series of positive clinical trials with trastuzumab in the setting of advanced disease led to its approval as monotherapy in patients who have received one or more chemotherapy regimens for metastatic disease and for use in combination with taxanes as a first-line therapy. After an impressive 50% reduction in the risk of breast cancer recurrence and a 33% reduction in the risk of death in the adjuvant setting, trastuzumab was granted a new clinical indication at diagnosis. Quite recently, the clinical benefit of adjuvant trastuzumab in a 4-year follow-up analysis has confirmed its great therapeutic impact (5). Anti-HER2 therapy continues to evolve, increasing strategies for synergism with other therapies as resistance mechanisms are identified.

Clinical trials designed for an upfront biomarker-driven selection of patients require the approval of an appropriate diagnostic test by regulatory agencies. Currently, the FDA has encouraged randomized trials that include both biomarker-positive and biomarker-negative study populations before the agent can be approved. This traditional approach will almost certainly need to change if new targeted therapies based on strong biomarkers are identified and translated with successful results. The ideal scenario for development of targeted therapies would not include the enrollment of patients who are less likely to benefit a priori.

Within this context, PARP inhibitors are being developed in BRCA1 and BRCA2 mutation–associated breast and ovarian cancer, representing a significant step toward truly personalized medicine. Development of the agents is based on a strong hypothesis, robust preclinical data, exciting phase I results, and a promising efficacy and safety profile in proof-of-concept phase II trials. However, a final step is required to move into the registration phase, which would represent a new milestone in cancer drug development because sensitivity to the drug is not based on a specific tumor type, but rather on the germline mutation of a homologous recombination (HR) repair gene and subsequent loss of the wild-type allele, which underlies the development of primary cancer in a range of organs, dominated by the breast and ovary. This model may provide the true silver lining for individuals who have had to bear the burden of extraordinary cancer risk: an effective targeted therapy for young patients with tumors whose development could not be avoided. Targeting the molecularly deregulated pathway could also make it possible to broaden the agent’s clinical application to patients with sporadic tumors that share similar molecular defects, following an initial registration that reveals the strongest proof of concept in the population with the predicted maximum benefit.

### DEVELOPMENT OF PARP INHIBITORS FOR BRCA-DEFICIENT CANCERS

#### Rationale and Preclinical Data

Cancer cells frequently harbor defects in specific DNA repair pathways; this characteristic leads to chromosomal instability and genetic abnormalities that can foster...
tumorigenesis, as has been observed in tumors that lack BRCA1 or BRCA2 proteins. Heterozygous germline mutations in BRCA1 or BRCA2 genes have been shown to confer a 50% to 85% lifetime risk of breast cancer and a 15% to 40% lifetime risk of ovarian cancer, as well as significantly increased risks of pancreatic, prostate, and male breast cancers (6). These genes are classified as “genome caretaker” tumor suppressor genes because they maintain genomic stability by promoting error-free DNA repair through the HR pathway. Carriers of a germline mutation are at increased risk of developing cancer when the wild-type allele is inactivated, whether by somatic loss, a second mutation, or an epigenetic event. Cells deficient in BRCA1 or BRCA2 function show a high degree of chromosomal instability, and although aberrations accumulate spontaneously, they can also be enhanced by DNA-damaging agents, such as ionizing radiation, interstrand crosslink–inducing agents, topoisomerase inhibitors, and others. Both BRCA1 and BRCA2 interact with the RAD51 protein and promote genetic stability through their roles in the error-free repair of double-strand breaks by HR. When this DNA-repair pathway is altered, foci of RAD51 protein do not form in the nucleus after DNA double-strand breaks. Therefore, the absence of RAD51 foci may serve as a biomarker of a defective HR repair pathway and, consequently, a BRCA-defective tumor.

PARPs constitute a family of enzymes involved in base-excision repair, a key pathway in the repair of DNA single-strand breaks. Loss of PARP1 function can induce the formation of nuclear RAD51 foci as a result of the increased formation of DNA lesions that need to be repaired by the HR pathway. Because BRCA1 and BRCA2 are key effectors of the HR pathway, it was hypothesized that inhibition of PARP1 in BRCA-deficient cells would cause an accumulation of DNA lesions that would not be adequately repaired, leading to apoptosis (Fig. 1).

In 2005, preclinical work performed independently by Farmer and colleagues (7) and by Bryant and colleagues (8) provided in vitro evidence for a 1,000-fold differential sensitivity of BRCA2<sup>−/−</sup> cells to PARP inhibition by several PARP inhibitors (AG14361, NU1025, and Ku0058948) when compared with isogenic BRCA2<sup>+/−</sup> and BRCA2<sup>+/+</sup> cells. Similar were shown in BRCA1<sup>−/−</sup> (deficient) cells (7). The results presented by these 2 research groups suggested a new mechanism-based approach to the treatment of patients with BRCA1- and BRCA2-associated cancers, provided robust hypotheses, and indicated a wide therapeutic window requiring testing in clinical trials (Fig. 2). If successful, this approach would turn a genetic susceptibility to cancer into a potential therapeutic opportunity for those who developed cancer. In addition, the approach provides an example of, and a potential clinical application for, the long-described scientific concept of synthetic lethality (when a mutation in either of 2 genes individually has no effect but mutations in both genes lead to cell death), in this case using a PARP inhibitor to interfere with the base-excision repair pathway in a cell that was already genetically defective in another DNA-repair pathway (HR by BRCA deficiency). This observation and emerging preclinical data stimulated initiation of a phase I trial using a PARP inhibitor as single-agent therapy in patients with advanced solid malignancies.

Phase I Results

In June 2005, investigators at London’s Institute of Cancer Research and Royal Marsden Hospital, along with pharmaceutical partner Kudos, began a first-in-humans phase I trial with olaparib, an oral PARP inhibitor. The trial had a planned expansion cohort of BRCA1 and BRCA2 mutation carriers and enrolled 60 patients, of whom 22 were carriers

![Figure 1. Mechanism of action of PARP inhibitors and tumor-selective synthetic lethality. Image courtesy of A. Tutt and A. Ashworth (Breakthrough Breast Cancer Research Center, London, UK).](image1)

![Figure 2. Tumor-specific synthetic lethality and therapeutic window of PARP inhibitors in BRCA-deficient tumor cells. Image courtesy of A. Tutt and A. Ashworth (Breakthrough Breast Cancer Research Center, London, UK).](image2)
of a BRCA1 or BRCA2 mutation. An additional patient had a strong family history suggestive of a BRCA mutation but declined genetic testing. Many important lessons were learned from this trial, reported in 2009 (9). The study showed that the drug was well tolerated, overall, at the maximum tolerated dose, with only minor side effects and no differences in toxicity observed between BRCA mutation carriers and noncarriers. In addition, an initial signal of durable antitumor activity was seen in most patients with a BRCA1 or BRCA2 mutation, regardless of their tumor site of origin. Pharmacodynamic analysis showed inhibition of PARP in circulating mononuclear cells. Downstream pharmacodynamic analysis of the effect on the DNA damage response showed formation of γH2AX foci (a marker of DNA double-strand breaks) after treatment with olaparib in surrogate tissues. These results provided the first clinical signal that a defect in HR was a predictive marker of response to a targeted therapy and justified formal prospectively designed proof-of-concept studies in BRCA1- and BRCA2-associated breast and ovarian cancer. These findings also suggested a possible expansion of the clinical application of this agent to other tumor types associated with an HR defect.

Phase II Results

Two proof-of-concept trials with single-agent treatment using olaparib in patients with germline BRCA1 or BRCA2 mutations and either advanced breast or advanced ovarian cancer were designed during the phase I study and conducted as soon as the maximum tolerated dose and an initial efficacy signal were noted. The results of these studies were reported in 2010 (ref. 10, 11; Fig. 3). As enthusiasm began to grow, both trials accrued patients quickly at sites in several countries. These trials further corroborated the data from the preclinical and phase I trial, with 40% response rates in both groups. Olaparib was shown to be an effective antitumor agent with a notable clinical benefit rate even in a heavily pretreated population and, as predicted by basic and preclinical data, was associated with a favorable toxicity profile.

Overall, the rapid success of these early studies suggested that development of some types of anticancer agents might be accelerated. The basic and preclinical work had identified the right target population. The test for the biomarker (BRCA1/2 germline mutation) had been clinically available internationally for years, although it has not obtained regulatory approval. A phase I trial had provided the maximum tolerated dose, a signal of clinical activity in the target population, and evidence of the predicted mechanism of action. Results had been corroborated in 2 formal proof-of-concept phase II trials in the predicted specific target populations. It seemed that a better scenario for drug approval could not exist.

OTHER PARP INHIBITORS CURRENTLY IN DEVELOPMENT IN BRCA-ASSOCIATED AND SPORADIC TRIPLE-NEGATIVE BREAST CANCER

Additional PARP inhibitors have begun to appear in the past few years. AGO14699 is an intravenous PARP inhibitor that has shown in vitro and in vivo efficacy in human cancer cell lines with mutated or methylated BRCA1 or BRCA2 (12). This agent is being clinically tested in a phase I/II trial in patients carrying a BRCA1/2 germline mutation with advanced breast or ovarian cancers (ClinicalTrials.gov identifier: NCT00664781). In a randomized phase II trial, AGO14699 is being evaluated in combination with cisplatin, compared with cisplatin alone, in patients with stage I to III triple-negative breast cancer and germline BRCA1/2 mutations who showed residual disease in the breast after completion of neoadjuvant chemotherapy and surgery (ClinicalTrials.gov identifier: NCT01074970). Veliparib, an oral PARP inhibitor, has been tested clinically in combination with the alkylating agent temozolomide in a phase II trial in patients with advanced breast cancer, and a 37% response rate (3 of 8 patients) was reported in the subgroup with a BRCA1 or BRCA2 mutation (13). These results may prompt a phase III trial program. A phase I trial with another oral PARP inhibitor, MK-4827, has also shown encouraging results, with demonstrated PARP inhibition,
a good safety profile, and clinical efficacy in both BRCA-associated and sporadic advanced solid tumors (14).

Simultaneously, iniparib (BSI-201), a small molecule with PARP-inhibitory capacity, has gone through rapid development from a phase I to a phase III trial in combination with chemotherapy. In its randomized phase II trial, iniparib in combination with carboplatin and gemcitabine showed a clear improvement in overall survival and overall response rate. The investigators observed no increase in treatment-related toxicity, compared with chemotherapy alone, in patients with advanced triple-negative breast cancer (15). A phase III trial was promptly launched to obtain regulatory approval in this still heterogeneous subgroup of patients. Unfortunately, in a recent news release, the pharmaceutical company reported that the phase III trial had not achieved the prespecified level of significance required for the dual primary end points of progression-free survival (PFS) and overall survival. In light of these results, the expanded access program to this compound with gemcitabine and carboplatin as a first-line therapy for patients with metastatic disease has been canceled. The data will be presented in upcoming clinical meetings and will become available for widespread review at that time. This unexpected result has raised questions about the specific mechanism of activity of the agent (i.e., whether it is truly a PARP inhibitor) and the optimal strategy for developing the drug, going forward. The early enthusiasm for iniparib may turn out to be justified in light of its promising overall profile with regard to antitumor effect and toxicity, but a new strategy will be needed to bring it into the breast cancer therapeutic arsenal. At this time, we cannot assume that data from trials in patients with unselected triple-negative breast cancer will provide information on BRCA1 and BRCA2 mutation carriers.

OLAPARIB DEVELOPMENT IN GERMLINE BRCA OVARIAN CANCER

The small phase II trial of sequential doses of olaparib (100 mg or 400 mg twice daily) for advanced ovarian cancer with BRCA1 or BRCA2 germline mutations provided an almost 40% overall response rate and a PFS duration of 6 months (11). A randomized phase II trial in patients with platinum-resistant tumors and BRCA mutation compared pegylated liposomal doxorubicin with olaparib, 400 mg twice daily, and olaparib, 200 mg twice daily. Although PFS curves were similar among the 3 arms of the study, response rates were 39%, 59%, and 38%, respectively (16). In the population with sporadic ovarian cancer, 2 trials have completed accrual and results are pending. One of these studies is a randomized trial of placebo versus olaparib maintenance in platinum-sensitive serous cancer (ClinicalTrials.gov identifier: NCT00753545); the other is investigating the use of olaparib in combination with conventional chemotherapy versus chemotherapy alone (ClinicalTrials.gov identifier: NCT01081951). If we consider the significant rate of sporadic high-grade serous ovarian cancer with a “BRCA-ness” phenotype (e.g., somatic BRCA1 mutation, promoter hypermethylation, or low expression), the logical next step is to target a wider population than carriers of germline BRCA mutations; however, this broadening of population may risk possible dilution of effect for a core first indication in BRCA carriers.

CURRENT CHALLENGES TO THE REGISTRATION PATHWAY FOR PARP INHIBITORS IN BRCA1 AND BRCA2 CARRIERS

BRCA-associated tumors occur as subsets of more common classical epithelial cancers and may benefit from standard therapies that are traditionally given for these histologic types (i.e., anthracycline- or platinum-based agents). As such, they are not sufficiently rare to qualify for orphan drug designation and registration on the basis of results from phase II trials. Therefore, single-arm phase II trials in BRCA1/2 mutation carriers, with response rate as the primary end point, are unlikely to satisfy regulatory agencies because the patient population may benefit from other standard treatments. Consequently, a randomized phase III trial of PARP inhibitors, in comparison with conventional treatment, appears to be necessary. However, such a trial creates several challenges. First, timely accrual of an adequately powered study cohort will require multinational collaboration and the acceptance of multiple sites in multiple countries, each recruiting modest numbers of patients despite competing generic breast and ovarian cancer trials. Second is the challenge of identifying an appropriate control arm: Should it be an “investigator’s best choice” from the small range of regulatory agency–approved options of similar efficacy in the sporadic cancer setting? Concerns have been expressed that one specific regimen could limit accrual. Also problematic is the use of an unapproved chemotherapy regimen, such as those containing platinum salts, which have gained some use in BRCA carriers on the basis of little level 1 evidence from clinical trials. Third, what is the optimal primary end point of such a study—overall survival or PFS? Is it possible to allow crossover for those patients who experience a progression in the control arm and have no other access to these agents? Fourth, the diagnostic genetic test for identification of BRCA1/2 mutation carriers is not formally FDA-approved. In the international context required for a phase III randomized trial, determination of BRCA mutation status will involve multiple genetic testing clinics, laboratories, and validated methodologies. Solutions for these novel problems must be incorporated into the design of a registration trial of this nature. Finally, the desire to expand the concept to sporadic cancers that share histopathologic features or a molecular phenotype, although a rational as well as clinically and commercially important issue, may risk dilution of therapeutic effect and further complicate study design. Nonetheless, such challenges must be addressed in the development of these and future targeted agents.

CONCLUSIONS

PARP inhibitors have emerged as a promising new class of antineoplastic agents (Box 1). These agents have already begun to show potential as single therapies for tumors with known defects in HR repair in women with germline BRCA1 or BRCA2 mutations. As knowledge of tumor biology increases, it is possible that PARP inhibitors, used correctly, will figure into the treatment of sporadic cancers with specific
DNA-repair deficiencies or as partners with certain chemotherapeutic agents that induce specific defects in DNA repair or radiation. In consideration of the strong preclinical data and encouraging initial clinical results, PARP inhibitors have the potential to become the next targeted therapy in breast cancer. It is therefore disappointing that unanticipated stumbling blocks have delayed the development of these agents, particularly for the subgroup of patients with BRCA1/2 mutations, whose positive outcomes have added a great deal to the proof of concept for these agents.

Disclosure of Potential Conflicts of Interest

J. Balmaña reports no conflicts of interest; S.M. Domcheck reports consulting and participation in an advisory board of Abbott; A. Tutt reports a commercial research grant from Sanofi-Aventis, a payment from the Institute of Cancer Research “Rewards to Inventors programme” for work on the use of PARP inhibitors to target BRCA1 and BRCA2-associated cancers, and participation in advisory boards of Eisai, Sanofi Aventis, and Pfizer; J.E. Garber reports research support to Dana-Farber Cancer Institute from AstraZeneca and Abbott Laboratories and consulting for Generation Health, Inc. Laboratories and consulting for Generation Health, Inc.

References

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