PARP inhibitors and more

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Abstract

Polyadenosine diphosphate (ADP) ribose polymerase (PARP) lends a panoramic view to the inner mystery of protection of integrity of deoxyribonucleic acid (DNA) in a cell genome. They are a balancing part of an even more dynamic equilibrium of normalcy against daily assaults. PARP finds its companion candidates in other tumor suppressors, with the most prominent and glaring one being breast cancer (BRCA) 1 and 2. The strength of both is split by PARP inhibitors, inculcating the synthetic lethality of tumor cell, which is now in the market for ovarian cancer treatment. There are many reasons for the resistance of such inhibitors, which are now becoming clinically important. These are seen along with other damage repair approaches. (J Turk Ger Gynecol Assoc 2015; 16: 107-10)

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Introduction

The history of polyadenosine diphosphate (ADP) ribose polymerase (PARP) invention is fascinating. Japanese did equally well when a French group (1) discovered in an experiment of kidney cortical nuclei that more phosphate is absorbed from nicotine adenine dinucleotide (NAD). This gives rise to branched poly’s of ADP ribose, which not only could anchor on the single stand defects of DNA but could also bring the other players of single strand repair to the field, X-ray repair cross-complementing protein 1 (XRCC1) and other proteins are such players. The initiation of repair is a little confusing activity of the protein enzyme PARPs, which has its 17 types working mainly through types 1 and 2. Inflammation, chemical, and radiation injury are the least known about that activity. They have the onus to manage about ten thousand single strand breaks (SSB’s) of a mixed etiology per day. In the presence of inhibitors, PARP cannot prevent stand breaks, instead SSB’s pile up at fork to cause double strand breaks (DSB). This DSB is historically managed by breast cancer (BRCA) 1 in female breasts and in male breasts, particularly with tumor suppressor twin BRCA 2. They repair DSB, but being mutated congregates huge load of unrepaired DSB causing “synthetic lethality” of cancer cell. (2-4). These inhibitors will even be tried now in related tumors with BRCAAness (5). BRCAAness is a behavior of certain tumors, such as some non BRCA ovarian cancer and triple negative breast cancer. “BRCAAness” traits in some sporadic cancers are similar to either BRCA1- or BRCA2-mutation carriers. They have 396 well appearances reciprocating those of BRCA negatives.

In the pharmaceutical industry, the invention of PARP inhibitor (PARPi) and eventual availability in the market of first molecule of its kind, such as olaparib, becomes possible only after very stringent clinical trial. Then, there will be a question of resistance, which could be as high as more than seventy percent in refractory group (6). We will take a look at the progress of the subject in following few paragraphs.

Olaparib

A new era begun in targeted therapy horizon when on 19th December last year, a first-in-class PARP inhibitor drug olaparib was approved in the United States for the treatment of advanced ovarian cancer patients with BRCA mutations who have had three or more lines of chemotherapy. It may be noted that in the early part of 2014, Oncologic Drugs Advisory Committee (ODAC) of the US Food and Drug Administration (FDA) voted against the approval of olaparib. This is not very surprising because the trial that the company placed before the committee was a placebo-controlled trial in 136 patients with platinum-sensitive ovarian cancer (7). Olaparib as a maintenance therapy in relapsed ovarian cancer did not fare well. Clinical Trials.gov, number NCT00753545. Hence, the committee defeated the proposal by an 11 to 2 vote.

On the basis of data from the same placebo-controlled trial in 136 patients with platinum-sensitive ovarian cancer, a second interim analysis (8) of overall survival and a retrospective, preplanned analysis of data by BRCA mutation status company found support of the hypothesis that patients with platinum-sensitive recurrent serous ovarian cancer with a BRCA mutation have the greatest likelihood of benefiting.
from olaparib treatment (8). It is rather astonishing that FDA gave this compound an accelerated approval in December 19th, 2014 after an expedited review process over the same trial on the basis of second interim analysis. On the other hand, a diagnostic company announced approval from the U.S. FDA on the same day for their BRACAnalysis CDx diagnostic kit to be used as the only companion diagnostic in conjunction with olaparib. BRACAnalysis CDx is this company’s first FDA-approved companion diagnostic for use with a novel PARP inhibitor. It is a highly accurate molecular companion diagnostic test that identifies deleterious or suspected deleterious mutations in BRCA1 and BRCA2 genes using DNA obtained from a blood sample. Olaparib was approved for a similar indication in the European Union just only a day earlier than done by USFDA after a recommendation for approval obtained in October from the European Medicines Agency. Breast cancer, which is associated with lesser percentage of such mutation (10% against 15%), is reasonably in the pipeline as a trial of this cancer is in phase III and is under way (NCT00516724, NCT01445418).

Nicotinamide, iniparib, and other PARPi
However, if we see nicotinamide as a primary inhibitor, different basic small molecules and molecules with appropriate scaffold (Figure 1) have come up as inhibitors of this PARP. Phthalazinone scaffolding has given rise to olaparib. With others in phase II, small molecule iniparib’s tragic attempt and failure as PARPi teaches us a good lesson worthy of describing. It has since become a poster child in how not to develop a drug and also shows how a review article may play a crucial role in development of a drug. The preclinical experiments are still very challenging and it is proved by the fact that this small molecule, which is an 3 iodo 4 nitro derivative of benzamide, is a nicotinamide derivative. Although it had other mechanism for being apoptotic to cancer cells, it has no particular PARP inhibitory property. Fojo et al. (9) the National Cancer Institute suggested in a commentary that the clinical trial design, which allowed the placebo arm to cross over and receive iniparib after their disease had progressed, may have biased the overall survival data in favor of iniparib. The drug’s failure would not have been so dramatic had it not also slowed the pace of research. It led whole PARPi chapter to disrepute so that people would give up doing PARP as a whole. This subject’s uniqueness of targeting a weakness rather than strength had been the center of controversy and confusion. Thus, further development up to olaparib is believed to be a paradigm shift to a later easy phase of rapid development. We may delve now to a chartable clinical picture in the context this article aims for.

Resistance
They already tested no less than 89 patients in a retrospective review of patients with BRCA1/2 mutation carrier ovarian cancer (PBMCOC) who received chemotherapy following disease progression on olaparib, administered at 200 mg twice daily for 1 month or more (10). An increased platinum-to-platinum interval was associated with an increased OS and likelihood of response following post-olaparib platinum. Heavily pretreated PBMCOC that are PARPi resistant retain the potential to respond to subsequent chemotherapy, including platinum-based agents. There are currently no other preclinical or clinical data to support this hypothesis; further work is certainly warranted in this regard. Therefore, what it leads to is a thorough search for inhibitor resistance pathways. They are described below following an order where postulates with more proofs needed are placed in last.

Decreasing intracellular availability of PARPi
Established molecule, P-glycoprotein 1 (P-gp), has a great importance in this subject. This acts by decreasing the intracellular availability of PARPi. The P-gp belongs to the ABC transporter family, which is inhibited by ADP ribose, a product of catalytic activity of PARP-1 (11). While Rottenberg et al. (12) elucidated its poly ADP dependence, P-gp inhibitors prevent the decrease of PARPi in human colorectal carcinoma cell line (HCT116) (13). This is made even robust with an available bio-
marker. The monitoring of poly ADP ribosylation and radiation sensitive gene (Rad51) foci formation as surrogate markers for PARP activity and homologous recombination (HR), respectively, supported their candidacy for biomarkers of PARP-1i responses. The multidrug efflux transporters, ATP-binding cassette sub-family G member 2 (ABCG2) (human breast cancer resistance protein (BCRP)) and ATP-binding cassette sub-family G member 1 ABCB1 (P-gp, multi drug resistance 1 (MDR1)), affected the oral availability and brain penetration of PARPi. Transport could be inhibited by the small-molecule ABCB1 and ABCG2 inhibitors zosuquidar and indole-3-propanoic acid 1.1-dimethylethyl ester (Ko143) (14).

**Increased homologous recombination (HR) capacity pathways**

53BP1 (also called TP53BP1) is a chromatin-associated factor that promotes immunoglobulin class switching and DNA DSB repair by non-homologous end joining. Assessment of 53BP1 is among candidate predictive biomarkers inducing Ataxia telangiectasia mutated (ATM)-mediated HR. Loss of 53BP1 allowed a partial ATM-dependent HR repair making these cells resistant to PARPi (15). Here, secondary mutations in BRCA2 is associated with clinical resistance to a PARPi (16).

Other postulated pathways among increased HR capacity are overexpression of BRCA via downregulation of a microRNA (miR-182) or PARP-1, increased activity of RAD51, and altered non-homologous end joining (NHEJ) capacity with a decrease in NHEJ capacity could increase their resistance to PARPi, as shown in BRCA 2-deficient cells by inhibition or downregulation of Ku80, a protein encoded by the XRCC5 gene, Artemis, or DNA-dependent protein kinase (DNA-PK) (17).

**Reverse mutation of BRCA**

Except above two, there is a third prominent and more “counting” routes for such possible inhibitions. It is a reverse mutation of BRCA prompting power for repair once again. For BRCA2, reverse mutation was in part due to the intragenic deletion of the c.6174delT mutation and restoration of the open reading frame (18-20) and for BRCA1, it is hypomorphistic mutation (21).

**Decreased levels or activity of PARP-1**

Decreased levels or activity of PARP-1 is another one at hand though it is difficult at this moment to rationalize the link between cytoplasmic PARP-1 and resistance to PARPi.

**Manipulation of other damage repair pathways**

Whereas breakthrough researches in sub-pathway battery of PARP inhibitor resistance may prove to be lucrative addendum to this PARP theory, even more basic should be other damage repair pathways manipulation, which may give rise to elementary vis-à-vis synergistic sister pathways predicted to be acting with many chemotherapeutic cocktail. We may like to summarize those effectively. A few established links, which have roots in alternate damage saving power are:

- **Tumor suppressor gene phosphatase and tensin homolog (PTEN)** has links with many cancers, including 25%–40% of glioblastomas sensitive to PARP inhibitors with implication in prostate, colorectal, and endometrials cancers, which also have this dysfunction in DNA repair pathways (18). Locating DNA mismatch repair gene MSH mutation in tumors like hereditary non-polyposis colon cancer could be a key predictor of methotrexate sensitivity of the tumor. O’-methylguanine–DNA methyltransferase (MGMT) repairs chemical DNA its mutation in acute myeloid leukemia makes the cancer responsive to temozolomide.

**Conclusion**

Clinical research is basically uncertain. Theory and practice may not coincide. Specificity is not always elicited in preclinical studies. Use of defects specific to cancer cell is not always harmless as it does not become apparent until trials have begun. Testing drug cocktails is a tough task, particularly with DNA damage repair inhibited synthetic lethality. While this is only a beginning of a whole new era of targeting weakness, there will be long perilous path for traversing till one may expect for some panacea.

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