PARP Inhibitors: the Story is Still Unfolding

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The opening chapters in the investigation of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors as cancer therapeutics have been interpreted by some as a quantum leap forward in targeted and personalized medicine and by others as another example of disappointment following a flurry of promising preclinical and early clinical trials based on elegant biology.

Against this backdrop, where have the clinical trials led us? At the outset, one has to recognize important biological details, which the authors mention. First, PARP1 is a multifunctional enzyme that is involved not only in base excision repair but also in chromatin state and gene transcription, leading to growth and remodeling effects in diverse tissues; in addition, in its activated state, it consumes nicotinamide adenine dinucleotide (NAD) to produce ADP-ribose, with eventual energy depletion and the induction of apoptosis.[4-13] Second, there are other mechanisms for single-base excision repair—specifically, nucleotide excision and mismatch repair—that are mediated by other networks [reviewed in 14]. Third, the mutation rate and underlying genetic diversity and intratumoral heterogeneity are likely to be very different in human disease than in preclinical models, resulting in clinical intrinsic or acquired resistance through a variety of bypass pathways. Thus, it is likely that all PARP inhibitors are different—in fact, since the time iniparib was initially developed for clinical trials, it has been discovered that this particular PARP inhibitor is a weak PARP1 inhibitor and that it probably exerts its activity through an as yet uncharacterized mechanism of action. Therefore, it will be important to assess each agent separately, both in terms of the clinical endpoints as well as with regard to any information that can be gleaned from the small number of tumor tissue and germline correlative studies.

Olaparib was one of the first agents to enter clinical trials after very promising preclinical activity was seen with olaparib analogs in BRCA1- and BRCA2-deficient cell-line models.[2] Clinical results using olaparib as a single agent suggested that activity was primarily confined to cancers associated with known BRCA1 or BRCA2 mutations, as well as serous ovarian cancer without mutations.[15-17] However, one pilot trial did not yield tumor responses in breast cancers regardless of BRCA status,[17] and unfortunately, this drug is not currently being developed for breast cancer. The trials assessing PARP inhibitors AGO14699 and MK4827 as single agents also showed activity in BRCA1- or BRCA2-related tumors, but in addition, activity was seen with MK4827 in sporadic cancers.[18,19] The authors point out that PARP inhibitors are more likely to be active when combined with chemotherapy agents—theoretically, more so with those that are DNA-damaging—although formal proof from ongoing randomized phase II trials is awaited.

On the other hand, iniparib, which as mentioned earlier is now known not to be a strong inhibitor of PARP1, generated significant enthusiasm when a randomized phase II trial showed a dramatic survival advantage.[20] However, the follow-up phase III trial did not meet its stated objectives. In part this was because aggressive endpoints were sought, with statistical power divided over the co-primary endpoints of progression-free survival and overall survival.[21] But, as Rios and Puhalla discuss, there may also have been other reasons for the discrepancy between the phase II and phase III trial results, including the facts that more patients crossed over in the phase III trial and that there were some imbalances in factors known to affect outcome, such that multivariate adjustments did
reveal a significant difference in progression-free survival with the addition of iniparib. In addition, the larger effect seen in the subgroup receiving second-/third-line therapy, compared with the group receiving first-line therapy, could reflect biological differences between these groups: there may have been some selection for patients with more chemo-responsive tumors to receive second- or third-line therapy, since such patients would be viewed as better candidates for later lines of therapy—and this may have enriched for enhanced iniparib responsiveness. BRCA status was not assessed prospectively in either the phase II or phase III study, but gene profiling of tumor and germline analyses are being done in a subset of subjects from the phase III trial, with the tumor studies preliminarily showing a mixture of intrinsic subtypes, and interestingly, with a minority of cases being classified as the “basal” subtype.[21]

Despite the amount of attention being paid PARP inhibitors, many of the early trials are still in progress and may not be large enough to answer pressing questions, the most important of which are nicely reviewed by the authors. First, what is the phenotype that optimally predicts response—is it a known BRCA1 or BRCA2 mutation, might it be defined by a broader assay for “BRCaness”, or is it perhaps a measure of deficient homologous recombination that accounts for genetic and epigenetic alterations in a host of genes? Second, what will be the most appropriate chemotherapy partner? There have been hints that platinum agents might be selectively more toxic in BRCA1-deficient cells,[22,23] and one randomized phase II trial comparing veliparib with and without carboplatin in breast cancer with known BRCA1/2 mutations is in progress.[24] A study combining temozolomide (Temodar), which methylates the O6-guanine position in DNA, with veliparib is showing early activity, with responses confined to BRCA-associated breast cancer cases.[25] So far, however, all the studies are too small to permit any meaningful conclusions regarding optimal chemotherapy partners. The design and future of the next generation of larger PARP inhibitor trials in breast cancer are still in flux, but it will be critical to design rigorous correlative studies to define the optimal regimens and candidate populations.

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References:

REFERENCES


