
From the Editor



Debu Tripathy, MD
Editor-in-Chief

In the May issue of *AJHO*, we feature an important therapeutic avenue that will likely extend to multiple types of cancer. Drs Dalton and Coleman describe the scientific background and key clinical trials that led to the approval of the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib for advanced platinum-resistant ovarian cancer. Conceptually, the development of this class of drugs is important because it reflects a strategy that will hopefully be repeated, namely, the “synthetic lethal” targeting of a key deficiency or vulnerability specific to cancer cells. In the case of PARP inhibitors, it has been shown that cells carrying a defect in one of the key pathways of DNA repair—homologous recombination—are exquisitely sensitive to the inhibition of other DNA repair pathways mediated by PARP inhibitors through complex mechanisms.

This is significant for several reasons. One is that cancers associated with BRCA deficiency—mostly breast and ovarian, but also others—all exhibit hallmarks of homologous recombination deficiency (HRD), since this is a key function of the *BRCA1* and *BRCA2* genes. Secondly, there is likely a larger group of cancer cases in addition to those with familial BRCA mutations that exhibit HRD—those with cancer-related (acquired) mutations or other alterations that involve HRD pathways. In fact, there is an assay that is just entering the clinic that measures HRD and the telltale fingerprints it leaves behind on the genome. Already, trials are in progress that are assessing the clinical benefit of PARP inhibitors in this expanded group of malignancies. Finally, and most notably, synthetic lethality of one or more drugs in the context of specific phenotypes can be rapidly screened using robotic high-throughput approaches. This can open the door to effective therapeutic strategies against a whole spectrum of cancer-driving pathways as they are identified and characterized.

PARP inhibitor therapy is therefore a trailblazer of sorts. Phase III trials of several different PARP inhibitors for advanced BRCA-related breast cancer compared with to standard chemotherapy are ongoing, as is an adjuvant trial with olaparib following standard chemotherapy in the early-stage setting. In the case of ovarian cancer, as our feature story points out, it appears that the primary benefit being seen so far is in the maintenance or refractory settings. Further trials in combination with initial chemotherapy along with assays to identify the most responsive populations are in progress, although it is clear that the different PARP inhibitors have varying biological and clinical effects as well as toxicities, particularly when combined with cytotoxic treatment. While PARP inhibitors now have a foothold in our therapeutic armamentarium, the concept of synthetic lethality will hopefully open up a new generation of cancer drugs.

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