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Commentary

Combining PARP and CDK4/6 inhibitors in MYC driven ovarian cancer

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The potential of PARP inhibitors in the management of ovarian cancer is mitigated by the fact that ovarian cancers with intrinsic homologous recombination (HR) proficiency do not respond as well as HR-deficient cancers. Additionally, responses to PARP inhibitors are all too frequently transient. A predominant mechanism of acquired PARP inhibitor resistance in HR-deficient cancers is the acquisition of HR proficiency as a consequence of secondary genetic or epigenetic events such as secondary mutations in BRCA1 or BRCA2, or reversal of BRCA1 promoter methylation that restore HR and lead to PARP inhibitor resistance.

Combinations of PARP inhibitors with drugs that inhibit HR might represent an effective strategy to sensitize epithelial ovarian cancers with primary or secondary HR proficiency to PARP inhibitors and potentially expand the use of these drugs beyond HR-deficient ovarian cancers. In this issue, Yi and colleagues demonstrate therapeutic synergy for combined PARP and CDK4/6 inhibition and identify MYC status as a determinant of sensitivity to combined PARP and CDK4/6 inhibition in ovarian cancer cells [1]. Treatment with the CDK4/6 inhibitor palbociclib led to downregulation of MYC-regulated HR repair pathway genes as well as reduced RAD51 nuclear foci (a marker for the competency of homologous recombination repair) but increased γH2AX nuclear foci formation (a surrogate marker for DNA double strand breaks) in those ovarian cancer cell lines that demonstrated synergistic interactions to combined treatment with the PARP inhibitor olaparib and the CDK4/6 inhibitor palbociclib. Yi and colleagues also sought to investigate the molecular mechanism underlying the differential treatment responses to combined PARP and CDK4/6 inhibition. Combination treatment-responsive cell lines had significantly higher MYC protein levels than nonresponsive cell lines. Furthermore, MYC knockdown abrogated the synergistic growth inhibitory effect. Conversely, enforced expression of MYC sensitized otherwise nonresponsive cells to combined PARP and CDK4/6 inhibition.

The ability to identify tumors with activated MYC signaling may open up the opportunity for targeted treatment using a combination approach with PARP and CDK4/6 inhibitors. MYC amplification is present in up to 30% of epithelial ovarian cancers but has not uniformly shown adverse prognostic relevance [2]. In contrast, gene expression signatures that reflects the level of MYC transcriptional activity have been shown to be highly predictive of poor prognosis and suggest their potential clinical application in the identification of MYC driven tumors that might respond to MYC-targeted therapies [3].

To date a number of other drugs have been studied in combination with PARP inhibitors in an attempt to induce HR deficiency in tumors with intact HR to cause PARP sensitivity or to increase the efficacy of PARP inhibition. These include inhibitors of signaling through the phosphatidylinositol 3-kinase (PI3K) pathway, vascular endothelial growth factor receptor (VEGFR), and cell cycle checkpoints including WEE1 [4–6]. Moreover, synergistic activity was also seen for PARP and MEK inhibitor combinations in RAS mutant tumors [7]. A drug synergy screen that combined olaparib with 20 well-characterized epigenetic drugs identified bromodomain and extra-terminal domain inhibitors as drugs that acted synergistically with olaparib in HR-proficient cancer cells [8]. Likewise heat shock protein 90 inhibitors may suppress HR and thus revert HR-proficient to HR-deficient tumors [9].

Currently, however, it is unclear whether the promising results of these preclinical drug interaction studies will translate into improved clinical activity. For example, results of a phase 1b study for patients with ovarian cancer were recently published that evaluated the α-specific PI3K inhibitor alpelisib (BYL719) in combination with olaparib [10]. Although responses were seen in 10/28 (36%) study patients, the observed activity may not be strong clinical evidence for the synergy that has been seen at a preclinical level. The observed clinical activity was not substantially higher than an overall response expected from olaparib as a single agent in a cohort where 17 of 28 (61%) patients had mutations in BRCA or other HR genes [10]. Clearly, combinations of PARP inhibitors with drugs that inhibit HR might represent an effective strategy to sensitize ovarian cancers with de novo or acquired HR proficiency to PARP inhibitors, however, larger studies with appropriate control arms and better patient selection will be needed for successful clinical translation of novel preclinical PARP combination rationales and potentially expand the use of PARP inhibitors beyond HR deficient tumors.

Conflict of interest

GK has received personal fees from AstraZeneca, Clovis and Tesaro, and research funding paid to the University of California outside the scope of this work from Pfizer, Merck and Lilly.

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