On the Road to PARPi-Platin

Michael A. Bookman

Correspondence to: Michael A. Bookman, MD, University of Arizona Cancer Center, 1515 N Campbell Ave, Rm 1903, Tucson, AZ 85724-5024 (e-mail: mbookman@email.arizona.edu).

Perhaps the most urgent clinical priority for patients with high-grade ovarian cancer is defining the optimal integration of inhibitors of poly-ADP ribose polymerase (PARP) with conventional care, including platinum-based chemotherapy. In this issue of the Journal, Lee et al. report preliminary clinical and biomarker data from a cohort of patients with either breast or ovarian cancer associated with BRCA1/2 mutations and treated with a combination of carboplatin and PARPi (1).

Based on synthetic lethality, single-agent PARPi has a dramatic impact in a proportion of patients with germ-line or tumor-based (somatic) mutations in BRCA1 or BRCA2. Favorable response data have also been observed in a subset of patients without evidence of BRCA1/2 mutations, and there is emerging consensus that other molecular alterations in DNA repair pathways, including homologous recombination deficiency (HRD), can increase the likelihood of response to PARPi as a single agent.

There is also evidence that patients with BRCA1/2 mutations or HRD are also more likely to respond to repeated courses of conventional therapy with platinum compounds and other agents associated with DNA damage, such as polyethylene-glycosylated liposomal doxorubicin (2). This can substantially complicate the nonrandomized clinical assessment of combinations that include chemotherapy and PARPi because the baseline response to both agents will be independently enhanced.

It has been hypothesized that concurrent administration of PARPi with platinum agents would interfere with DNA repair, resulting in increased tumor toxicity, even in the setting of normal BRCA1/2 function and in the absence of HRD. This is important because it potentially opens the door for evaluation of PARPi with chemotherapy in all patients with ovarian cancer, regardless of genomic background.

Emergence of platinum resistance remains a hallmark of high-grade ovarian cancer, reflecting increased damage tolerance, accelerated drug detoxification, and impaired detection of DNA damage with failure to trigger apoptosis. Over the last 30 years, multiple agents have been evaluated with the goal of overcoming platinum resistance, based on focused preclinical models using established cell lines. However, none of these agents has achieved meaningful benefit when evaluated in randomized clinical trials, and some interventions have been complicated by increased host toxicity, with inferior clinical outcomes (3).

Preclinical and early clinical studies with PARPi and carboplatin have documented at least additive antitumor effects at the expense of increased bone marrow suppression, particularly in patients with multiple prior treatment regimens. Pharmaceutical sponsors and investigators are weighing various scenarios for PARPi development and regulatory approval, including monotherapy maintenance (after chemotherapy) and/or concurrent therapy with carboplatin, either as a component of primary treatment or in the setting of recurrent disease. Clinical trial enrollment could be restricted to patients with confirmed BRCA1/2 mutations, extended to patients with tumors that have molecular evidence of HRD, or opened to all patients with analysis of biomarkers and outcomes, with associated regulatory implications.

At this point, it seems critical to apply innovative solutions to obtain as much predictive data as possible, with the goal of maximizing potential benefits for the largest group of patients. Lee et al. report exploratory proteomic data with pS209-ELF4E and FOXO3a, demonstrating correlation with response duration, but randomized studies will be necessary to determine whether these novel markers are predictive of outcomes and could facilitate patient selection. Efficient randomized trials are needed to help guide the selection of regimens for larger definitive studies. Ideally, enrollment should be open to all patients with high-grade ovarian cancer, with biospecimen collection to validate biomarkers. Enrichment of key populations (such as patients with BRCA1/2 mutations) could be incorporated on the basis of an interim analysis.

As noted, the potential interactions of PARPi with chemotherapy are complex, especially in populations with HRD. The report by Lee et al. defines a tolerable regimen using intermittent PARPi dosing to minimize the risk of serious hematologic toxicity. The response data are encouraging but difficult to interpret because of the increased likelihood of response to chemotherapy and PARPi among cancer patients with BRCA1/2 mutations.

Their approach toward mitigation of toxicity was limited to conventional dose reduction and/or exposure truncation, as used in other studies with PARPi combinations. Drug sequencing has perhaps been overlooked as an alternative strategy, and there are examples with platinum-based therapy to suggest that hematologic toxicity can be substantially reduced with schedule-reversal of conventional agents, such as topotecan (4). Of relevance to drug sequencing, solid tumors tend to have capillary leak and poor lymphatic drainage, contributing to high interstitial pressures that can delay drug uptake and subsequent drug clearance, compared with normal compartments such as the bone marrow. In theory, it would be possible to administer several doses of PARPi before chemotherapy, allow 12 hours for bone marrow washout, and then administer full-dose carboplatin. After 72 hours, PARPi could probably be resumed, without expectation of increased marrow toxicity (Figure 1). Using this example, treatment of a small cohort...
of patients should be sufficient to validate safety, followed by a randomized phase II trial to define clinical outcomes.

Although the historical experience with agents intended to overcome platinum resistance has been disappointing, innovative combinations with PARPi and carboplatin should merit our attention, with the goal of improving clinical outcomes for all patients with high-grade ovarian cancer.

References

Note
M. A. Bookman has participated in ad-hoc advisory boards for AstraZeneca, Clovis Oncology, and AbbVie Pharmaceuticals related to the development of PARP inhibitors and has received reimbursement for travel and advisory board participation.

Affiliation of author: University of Arizona Cancer Center, Tucson, AZ.