Lack of Justification for Delaying Regulatory Approval of Olaparib in Ovarian Cancer

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Abstract

The PARP (polyadenosine 5'diphosphoribose polymerase) inhibitor, olaparib, has been shown in phase 1 and phase 2 trials to possess considerable biological and clinical activity against ovarian cancers in previously treated patients. In a landmark randomized placebo-controlled phase 2 study, olaparib was revealed to almost triple the median time to subsequent disease progression (11.2 months vs 4.3 months; hazard ratio, 0.18; *P* <.0001) when delivered as a single agent maintenance regimen to ovarian cancer patients who had achieved a second response to platinum-based chemotherapy. These data, plus a fundamental consideration of the rights of a cancer patient in such a clinical setting to make her or his own decision regarding the level of evidence sufficient to receive a novel antineoplastic, provide a strong rationale for approval of this agent for non-investigative use in the management of ovarian cancer.

The recent vote of the FDA Oncologic Drugs Advisory Committee against recommending the approval of olaparib as a maintenance therapy strategy following the attainment of a second response to platinum-based therapy in either known *BRCA* mutation-positive or high-grade serous ovarian cancer raises a number of serious questions worthy of both scientific and societal discussion. These include both the *level of evidence* that should be mandated prior to FDA approval of a new antineoplastic agent and the individual roles of the drug regulatory agency (and its advisory committees) versus that of the individual cancer patient (in consultation with her or his own physician and personal advisors) in the determination of when it is appropriate to consider the administration of such a drug based on the appropropriateness of the end point used and the magnitude of the benefit. The intent of this commentary is not to attempt to explain the thought processes of the committee, other than to say they apparently were not convinced that the existing data demonstrated sufficient evidence of clinical benefit.[1] Rather, what follows is a brief discussion of the data, which (in the opinion of this commentator) should unquestionably have resulted in a positive vote at the meeting and subsequent FDA approval of olaparib in this setting.

Olaparib in Ovarian Cancer

The theoretical rationale and extensive experimental data supporting the use of PARP (polyadenosine 5' diphosphosphoribose polymerase) inhibitors in *BRCA* mutation-positive or high-grade serous tumors has been reported elsewhere and will not be discussed in detail here.[2-5] In brief, tumors with homologous recombination defects (eg, *BRCA* mutations) have been shown to be effectively killed by inhibitors of PARP in preclinical studies. Similarly, PARP inhibition in the absence of such defects is inadequate to result in sufficient tumor cell kill.

Of interest, high-grade serous ovarian cancers with wild-type BRCA have been shown to possess a molecular signature that appears similar to that observed in the presence of documented *BRCA* mutations (so-called, "BRCA-ness").[3] This observation is the major justification for examining the clinical utility of PARP inhibition in patients with high-grade serous ovarian cancers in the absence of specific evidence of a *BRCA* abnormality.

Olaparib has been shown to be an active inhibitor of PARP-1, PARP-2, and PARP-3 in experimental model systems.[4] It is well absorbed when taken orally and is removed from the body in both the urine and feces.

In the initial phase 1 study of olaparib conducted among patients with several *BRCA*-mutant tumor types (ovary, breast, prostate), 9 patients achieved a partial response.[6] This study was subsequently expanded to include a total of 50 patients with a germline *BRCA* mutation, with a total objective response rate (RECIST or CA-125 response criteria) of 40%.[7] A difference in the response rate between the platinum-sensitive (69%), platinum-resistant (45%), and platinum-refractory (23%) populations was observed in this trial. These data support the hypothesis that defective homologous recombination pathways are relevant to both sensitivity of platinum agents and PARP inhibitors (such as olaparib).

Subsequent phase 2 trials further confirmed the clinical activity of olaparib in ovarian cancer. One study revealed an overall response rate of 33% when the drug was administered at a dosage of 400 mg twice daily, while a response rate of only 13% was noted when the agent was delivered at 100 mg twice daily.[8] A second study that included 65 patients revealed a 41% response

rate in the presence of a *BRCA* mutation versus 24% in the absence of such a mutation.[9] Of interest, responses in non-*BRCA* mutated cancers were limited to tumors that were platinum sensitive (50% response rate in platinum-sensitive cancers vs 4% in platinum-resistant cancers).

In a provocative randomized phase 2 trial, olaparib was directly compared to pegylated liposomal doxorubicin (PLD) as second-line therapy in patients with *BRCA*-mutated ovarian cancer.[10] A reasonable objective response rate for single-agent olaparib was observed (25% and 31% for dosages of 400 mg or 800 mg/day, respectively). However, there was no difference in progression-free survival (PFS) between the olaparib vs the PLD-treated patient population.

Individuals on the PLD control arm experienced a median PFS that was almost double that predicted (7.1 months vs 4 months) in the study design.[10] Rather than demonstrating the lack of efficacy for olaparib in this trial, these data provide strong support for the favorable utility of PLD in BRCA-mutant tumors.[11]

Finally, in an innovative randomized, double-blind, placebo-controlled phase 2 study, investigators examined single-agent olaparib when administered as a maintenance strategy in patients with ovarian cancer who had achieved a response (complete, partial, or stable disease) to a *second-line platinum* regimen.[12] It is important to acknowledge here that patients were not selected for entry into this trial based on their *BRCA* mutation status. The study revealed a highly statistically significant improvement in PFS for the olaparib regimen (median 8.4 months vs 4.8 months; hazard ratio [HR] = 0.35; P <.001).

The investigators subsequently attempted to retrospectively examine the *BRCA* mutation status (germline or somatic only) of the patients entered into the trial, ultimately obtaining these relevant molecular data on 95% of study participants.[13] When PFS was analyzed based on *BRCA* status, there was an even greater effect of treatment in the *BRCA*-mutant patient population (median 11.2 months vs 4.3 months; HR = 0.18; P <.0001). However, it is important to acknowledge that patients with wild-type BRCA also experienced a response to treatment (HR = 0.54; P = .0075).

Although there was no statistically significant improvement in overall survival associated with olaparib treatment on this trial, approximately one-quarter of patients on the study's placebo arm eventually received a PARP inhibitor in addition to other potentially clinically active antineoplastic agents that may have had a favorable impact on their ultimate survival.[14] (The issue of the appropriate clinical trial end points for regulatory approval of antineoplastic agents and the impact of subsequent treatments on an overall survival end point will be discussed by this commentator in more detail in the next issue.)

The Fundamental Role of the Patient in Deciding the Level of Evidence Required to Receive Olaparib

While it is not possible in this brief commentary to fully discuss the complex and increasingly contentious issue of the role of the FDA, or the agency's advisory committees, versus cancer patients themselves in the decision to permit an antineoplastic agent to be administered outside the confines of an investigative trial, the determination in the recent olaparib review mandates that the topic be formally acknowledged and highlighted.

In the opinion of this commentator, this debate centers on the fundamental issue of the right of a patient with a very serious medical condition (such as in the current discussion) to make her or his own decision regarding the potential benefits versus risks associated with the utilization of a particular therapeutic strategy. In this specific clinical setting, the benefits associated with a substantial delay in the essentially certain future development of symptomatic disease progression must be balanced by the potential for a variety of relatively common or rarer toxicities (eg, hematologic effects, including myelodysplastic syndrome).

Objectively, who is in the best position to make this determination, to assess the relative utility of such a postponement of the inevitable, versus the discomfort and distress of treatment-related side effects? Is it really the regulator who has studied the data, or the expert physician/researcher/biostatistician panel members who might opine on how patients they have seen in the past or how the population of study patients may theoretically respond?

Or, might it be the individual patient with ovarian cancer who has been fortunate to have achieved a second remission and who has both the personal knowledge of what symptomatic disease progression means to her and has personally experienced the toxicity of antineoplastic treatment? Surely, the answer to this question is obvious.

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REFERENCES

1. Goldberg P, Vellek T. ODAC clarifies standards for maintenance in ovarian cancer; nixes olaparib in 11-2 vote. *The Cancer Letter*. 2014;40(26):1-5.

2. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic target. *Nature*. 2005;434(7305):917-921.

3. Hennessy BT, Timms KM, Carey MS, et al. Somatic mutations in BRCA1 and BRCA2 could expand the number of patients

that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. *J Clin Oncol.* 2010;28(22):3570-3576.
4. Chen, Zhang L, Hao Q. Olaparib: a promising PARP inhibitor in ovarian cancer therapy. *Arch Gynecol Obstet*. 2013;288:367-374.
5. Ashworth A. A synthetic lethal therapeutic approach: poly (ADP ribose) polymerase inhibitors for the treatment of cancers deficient in DNA repair. *J Clin Oncol.* 2008;26(22):3785-3790.
6. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly (ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med.* 2009;361(2):123-134.
7. Fong PC, Yap TA, Boss DS, et al. Poly (ADP) ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol.* 2010;28(15):2512-2519.
8. Audeh MW, Carmichael J, Penson RT, et al. Oral poly (ADP ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*. 2010;376(9737):245-251.
9. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011;12(9):852-861.
10. Kaye SB, Lubinski J, Matulonis U, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. *J Clin Oncol*. 2012;30(4):372-379.
11. Safra T, Rogowski O, Muggia FM. The effect of germ-line BRCA mutations on response to chemotherapy and outcome of recurrent ovarian cancer. *Int J Gynecol Cancer.* 2014;24(3):488-495.
12. Lederman J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366(15):1382-1392.
13. Lederman J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol.* 2014;15(8):852-861.
14. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. *J Natl Cancer Inst.* 2009;101(23):1642-1649.