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Commentary

Olaparib for BRCA Mutant Pancreas Cancer: Should the POLO Trial Change Clinical Practice?

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Over the last decade, there have been a number of advances in the treatment of metastatic and unresectable pancreatic cancer, including the frontline use of folinic acid, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX), nab-paclitaxel, and gemcitabine as well as the approval of liposomal irinotecan in the second-line setting. However, despite these new therapies, metastatic pancreatic cancer remains incurable, and median survival is usually limited to a matter of months. In this context, the disease constitutes an unmet medical need for drug developers.[1] On December 27, 2019, the US Food and Drug Administration (FDA) granted accelerated approval of olaparib, an inhibitor of poly(adenosine diphosphate ribose) polymerase, for patients with germline BRCA mutations whose disease has not progressed on at least 16 weeks of platinum therapy. The FDA decision was based on evidence from Pancreas Cancer Olaparib Ongoing (POLO), a phase 3 randomized controlled trial. In this commentary, we review this pivotal randomized controlled trial and raise questions about whether olaparib should be considered standard of care in this patient population.

The POLO trial evaluated the efficacy of olaparib as maintenance therapy for metastatic pancreatic cancer.[2] The trial randomized patients completing at least 4 months of FOLFIRINOX therapy with a germline BRCA mutation to olaparib or a placebo. POLO met its primary endpoint and found an improvement in progression-free survival (PFS; 7.4 vs 3.8 months; hazard ratio for disease progression or death, 0.53; confidence interval, 0.35-0.82; $P = .004$). Overall survival (OS) was unchanged (median, 18.9 vs 18.1 months; $P = .68$), although final analyses have not yet been reported. Twenty percent of patients responded to olaparib, whereas 9.7% responded among those on the placebo. We have 3 fundamental concerns with POLO: 1) the primary endpoint, 2) the choice of the control arm, and 3) the extent to which olaparib offers high-value care to our patients.

The primary endpoint of POLO was PFS. PFS is used for several reasons, including the concern that OS events may take years to occur; thus, using PFS may shorten the length of the study and expedite getting new treatments approved and available to patients.[3] Yet, in this case, the median OS was reached in both arms. This is not surprising because of the high fatality rate of metastatic pancreatic cancer; this is a very different context than metastatic breast cancer. In clinical trials involving advanced pancreatic cancer chemotherapy, there have been reports that PFS can serve as a surrogate for OS.[4,5] However, in the POLO trial, although the olaparib arm showed significantly longer PFS than the placebo arm, there was no difference in OS between the 2 groups, and this challenges the validity of the use of PFS in the maintenance setting.

Our second concern is related to POLO's suboptimal control arm. Patients entering the POLO study had to have received 16 weeks of platinum-based therapy and were randomized to olaparib or a placebo. This is different than clinical practice in 2 ways. First, if a patient is responding to and tolerating chemotherapy, it is standard practice to administer therapy for 20 weeks or potentially longer. Yet, only 33% of the patients in the olaparib arm and 34% in the placebo arm received 20 or more weeks of first-line chemotherapy, whereas the rest received less than 20 weeks or data were missing. Second, many providers would continue 5-flurouracil (5-FU), a component of FOLFIRINOX therapy, even after this time period. Thus, the control arm for POLO should have permitted continued chemotherapy or a switch to 5-FU monotherapy.

Because the patients enrolled in the trial did not progress while on they were first-line chemotherapy, halting chemotherapy would be impractical, and it is likely that patients would have gained more benefit from completing a full 6 months of treatment. As for the design of the control arm, the absence of maintenance chemotherapy in the placebo arm of the POLO trial indicates that those patients received suboptimal standard of care. The results from the phase 2

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PRODIGE 35-PANOPTIMOX trial show that a combined regimen of folinic acid and fluorouracil (LV5FU2) as maintenance therapy is beneficial (NCT02352337), and suboptimal standards of care appear in 17% of randomized trials used for FDA approval.[6]

As evidence that continued therapy would have improved outcomes for patients assigned to the control arm, in the POLO trial, approximately 10% of the placebo group responded to an inert pill. This response rate to the placebo seems unexpectedly high in comparison with the overall placebo response rate of ~3% in all placebo-only arms of randomized cancer trials.[7] The most likely explanation for this finding is that the control arm in the POLO trial showed continued chemotherapy effects after its discontinuation. Yet, what if the POLO trial required 20 weeks of first-line chemotherapy to maximize its effects and then used 5-FU maintenance therapy in the control arm? Likely responses would have deepened, and the response rate would have risen. We think that it is possible that the PFS in the control arm would have been similar or better than the PFS in the olaparib arm. The lack of a head-to-head comparison between olaparib and maintenance chemotherapy should make clinicians uncomfortable about stopping cytotoxic treatment (with ongoing disease stability/response) to switch to an expensive medicine with no proven OS benefit.

Finally, we cannot ignore the fact that olaparib involves a costly process even before the drug is used. To evaluate candidacy for olaparib, germline BRCA testing is required. Although the rate of BRCA mutation was ~8% among the patients in the POLO trial, the actual rate in unselected cases of pancreatic adenocarcinoma is estimated to be only 2% or less.[8] The additional drug cost of olaparib (currently priced at more than $12,000/mo) together with the need for widespread germline BRCA testing will further strain health care budgets.[9] It becomes even more difficult to justify this cost when one considers the lack of benefit for OS and the fundamental design flaws of the POLO trial.

In summary, on the basis of the lack of a survival benefit, the suboptimal control arm design, and the overall health care costs, we do not believe that olaparib represents a major advance for our patients with pancreatic cancer. Despite the hype surrounding this study, it will not change our own clinical practice, in which we will advocate to continue platinum-based chemotherapy (with or without maintenance 5-FU) among patients with stable/regressing disease. The POLO trial illustrates that as a community, even in settings where there is a huge need, we must be rigorous in our methodology and mindful that we not lower the bar for new therapies. Our patients expect us to offer treatments that provide robust, meaningful improvements in their quantity and quality of life.

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