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Olaparib: Transcending mutational barriers

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SUMMARY

Poly-ADP-ribose polymerase (PARP) inhibitors have recently attracted the interest of researchers across the globe in treating metastatic castrate-resistant prostate cancer (mCRPC). PARPs are enzymes that repair single-strand DNA breaks utilizing the base excision repair pathways and their inhibition, in turn, leads to an accumulation of DNA single-strand breaks culminating in cell death. DNA double-strand breaks are further repaired by the error-prone nonhomologous end-joining or by homologous recombination repair (HRR) which is assisted by genes such as BRCA1/2 and ATM. A cell with intact HRR mechanism can survive despite PARP inhibition. On the other hand, cells with mutations in HRR genes such as BRCA1/2 and ATM have an impaired HRR pathway, leading to accumulation of double-strand DNA breaks and eventual cell death. This genetic instability of tumor cells with HRR mutations makes them vulnerable to cell death via PARP inhibitors.[1] Olaparib, a PARP inhibitor, received the United States Food and Drug Administration breakthrough therapy designation in January 2016[1] on the basis of the novel TOPARP-A trial,[2] for mCRPC patients with ATM or BRCA1/2 gene mutations who have received prior taxane-based chemotherapy or enzalutamide/abiraterone. Based on the preclinical studies suggesting synergistic activity[3] with androgen deprivation, a randomized, double-blinded, placebo-controlled Phase II trial comparing combination of olaparib with abiraterone in mCRPC irrespective of HRR gene mutations was recently published in the *Lancet Oncology* on June 4, 2018.[4] The study was funded by AstraZeneca Pharmaceuticals.

The study enrolled 142 mCRPC patients (who had received docetaxel previously irrespective of response) from November 2014 to July 2015 across 41 centers in North America and Europe. The results were analyzed on September 22, 2017. The patients were randomized into two arms: olaparib (300 mg BD) + abiraterone (1000 mg OD with 5 mg prednisolone BD) (n = 71) and placebo + abiraterone (n = 71). The primary end point of the study was radiographic progression-free survival (rPFS). A variety of secondary end points were also analyzed though the study was not powered to analyze them, namely overall survival (OS), proportion of patients achieving an objective response, health-related quality of life (HRQOL) as well as change in circulating tumor cells (CTCs). The patient's serum, whole blood samples, and tumor samples (when available; n = 68) were analyzed for HRR mutations encompassing 15-h genes.

A significant difference in terms of rPFS was observed between the two arms, median rPFS being 13.8 months in the olaparib group versus 8.2 months in the placebo group (hazard ratio: 0.65, 95% confidence interval: 0.44–0.97, P = 0.034). When stratified on the basis of HRR mutations, the patients in the olaparib arm demonstrated a significantly longer rPFS, irrespective of the mutation status. The median duration of response albeit longer in the olaparib arm (17.8 months vs. 12.1 months) did not reach statistical significance. The patients in the two arms showed no significant difference in terms of OS, PSA response, and change in CTCs. Despite a longer PFS, Grade 3 or worse adverse events were noted more frequently in the olaparib including myocardial infarction (4 vs. none), pneumonia (4 vs. 3), and anemia (15 vs. none). Cardiovascular events were especially higher in the olaparib arm, comprising myocardial infarction in four patients, fatal cardiac failure in one, and fatal ischemic stroke in another patient. Only one patient suffered from a thrombotic stroke in the placebo arm. These adverse events attributed to four deaths in the olaparib arm with one death each due to pneumonitis, ischemic stroke, cardiac failure, and mediastinitis. Although a higher proportion of patients suffered adverse events, the deterioration in HRQOL in both the arms was similar. This was attributed to the increased burden of disease in the placebo arm owing to natural history of the disease. Twenty (28%) patients in the olaparib arm and 29 (41%) in the placebo arm received subsequent anticancer therapy; time to first subsequent therapy being longer in the olaparib arm.

COMMENTARY

A multitude of agents are available for treating mCRPC patients, but unfortunately, the response is often

short-lived. The TOPARP-A trial[2] was a landmark study which inducted olaparib into the armamentarium of urologists and oncologists for treating mCRPC with HRR mutations who had progressed despite receiving docetaxel and enzalutamide or abiraterone. Although an important breakthrough, its applicability is limited only to patients with BRCA1/2 or ATM gene mutations.[1] Asim *et al.*[3] in a genetic study demonstrated the concept of "synthetic lethality," whereby androgen receptor inhibition leads to an increase in PARP activity, as occurs in cells with HRR mutations. Their study suggested the synergy between PARP inhibitors and drugs inhibiting androgen synthesis, forming the background for this study. The present study highlights the improvement in rPFS noted in patients receiving combination therapy regardless of the HRR mutation status. Hence, it suggests the applicability of combination therapy to a broader population, with a potential to provide additional and practice-changing therapeutic options to patients with mCRPC.

The patients in the olaparib arm suffered serious adverse events, especially myocardial infarction and anemia. The cardiovascular events lead to mortality in three patients. This shall be a serious deterrent to the widespread use of this drug, and caution must be advised to all patients before prescribing combination therapy. No OS benefit was seen between the two arms; larger studies adequately powered to study OS shall answer this question. A Phase III randomized control trial[5] (NCT02987543; PROfound study) evaluating olaparib as monotherapy in mCRPC patients with an HRR mutation and previous antihormonal therapy is underway. With limited options for mCRPC, the present study lays the foundation for expanding the benefits of combination therapy with olaparib and abiraterone to a broader subset of mCRPC patients. However, the results should be taken with a pinch of salt as the gain in rPFS comes at the cost of increased adverse events.

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