PROpel trial: Are PARP inhibitors ready to become the first-line treatment for mCRPC?

Abhay Singh Gaur*
Department of Urology, AIIMS, Bhubaneswar, Odisha, India
*E-mail: abhay.vibhugaur@gmail.com

SUMMARY

The knowledge of homologous recombination repair (HRR) deficiency in certain cancer cells and the advent of poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors has led to a paradigm shift in research and treatment of metastatic castrate-resistant prostatic cancer (mCRPC). The PROpel trial enrolled 796 previously untreated patients with mCRPC for a multicenter, double-blinded, randomized (1:1), phase 3 study. One group (399 patients) received abiraterone acetate (1000 mg once daily) with prednisone (5 mg twice daily) (AAP) and olaparib (300 mg twice daily), while the other group (397 patients) received AAP + placebo, irrespective of their HHR gene mutation (HRRm) status. However, HRRm testing was done in 98% of the patients at the baseline from tumor tissue and blood samples (circulating tumor cells [CTC]) by FoundationOne CDX and FoundationOne Liquid CDX tests, respectively. The samples were tested for ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, and RAD54L. HRRm were positive in 28.4%, negative in 69.3%, and unknown in 2.3% of patients. AAP + olaparib group had 27.82% (111) HRRm + and 69.9% (279) HRRm − patients. AAP + placebo group had 28.96% (115) HRRm + and 68.76% (273) HRRm − patients.

The primary endpoint, image-based progression-free survival (ibPFS), was 8.2 months more for the AAP + olaparib group compared to the AAP + placebo group (24.8 vs. 16.6 months; hazard ratio (HR) 0.66; 95% confidence interval CI 0.54–0.81; P < 0.001). The effect of the combination of AAP + olaparib was also seen among non-HRRM (HR 0.76; 95% CI 0.60–0.97). The data for the secondary endpoint, the overall survival, were not mature at the time of publication. The other secondary endpoints were time to subsequent therapy or death (TFST), time to second progression or death (PFS2), and health-related quality of life (HRQoL). TFST (HR 0.74; 95% CI, 0.6–0.90) and PFS2 (HR 0.69; 95% CI 0.51–0.94) favored AAP + olaparib group. The difference in HRQoL was not statistically significant. Objective response rate was significantly more in AAP + olaparib group (58.4% vs. 48.1%, odds ratio 1.60; 95% CI 1.02–2.53). PSA response rate was defined as the proportion of patients with a ≥ 50% decrease in PSA level from baseline to the nadir, confirmed by a consecutive PSA assessment at least 3 weeks later. The PSA response was 79.3% in the AAP + olaparib group and 69.2% in the AAP + placebo group. The median time to PSA progression was not reached in the AAP + olaparib group and was 12 months in the AAP + placebo group. Anemia, fatigue, asthenia, and nausea were among the common adverse effects of combination therapy.

The study concluded that adding olaparib to abiraterone as a first-line treatment for mCRPC irrespective of HRRm status prolongs ibPFS significantly.

COMMENTS

PARP is an important enzyme for DNA repair. It binds to single-strand breaks to recruit the repair proteins, termed PARylation. PARP inhibitors block PARylation of the defective DNA and also prevent disassociation of the PARP-DNA complexes, termed PARP trapping. The defective DNA is a signal for apoptosis. PARP-DNA complexes are more cytotoxic than defective DNA itself.

Approximately 30% of prostate cancers harbor mutations in HRR, making them eligible for PARP inhibitors. Next-generation sequencing (NGS) tests detect these mutations from either a fresh biopsy from the metastatic lesion (ideal) or archival/primary tumor biopsy or CTCs. The PARP inhibitors are most profound in BRCA1, BRCA2, and ATM mutations. The other genes include BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, and RAD54L. The list is continuously expanding.

For mCRPC, the PROfound trial showed that for those who have HRRm and have progressed on either abiraterone or enzalutamide, olaparib increased ibPFS by 2.3 months (HR, 0.49; 95% CI, 0.38–0.63; P < 0.001). The combined anti-tumor properties of AAP and PARP have been demonstrated in preclinical studies. The synergistic action
can be either because of Androgen receptor target gene suppression by PARP inhibitors or abiraterone inducing HRR deficiency and hence increasing the sensitivity to the PARP inhibitors.[1] The initial experience with adding veliparib to AAP did not show any significant difference in outcomes versus AAP alone.[4] This could be due to the lower efficiency of veliparib in PARP-trapping.

Based on PARP-trapping efficiency the PARP inhibitors are ranked from the most potent to the least (tazaloparib >> niraparib >> olaparib = rucaparib >> veliparib).[2] The PROpel (AAP + olaparib) and MAGNITUDE (AAP + Niraparib) trials have shown superior outcomes than AAP alone as first-line therapy for managing mCRPC with HRRm.[1,5]

The use of PARP inhibitors is limited by NGS tests which are neither readily available nor affordable. Interestingly in the PROpel trial, AAP + Olaparib achieved the median ibPFS of 24.8 months versus 16.6 months for AAP + placebo, irrespective of HRRm status.[1] In India, Olaparib may cost Rs. 20000–25000/day, and with the added expense of AAP, the treatment might not be within reach of everyone.

With more evidence, increased accessibility to genetic testing, and affordability of the treatment, PARP inhibitors could be added to the first line. However, till then, newer-generation anti-androgens or docetaxel remain the first-line treatment of mCRPC.

REFERENCES

1. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, Oya M, Shore N, Loredo E, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. NEJM Evid 2022;1:9. [Doi: 10.1056/EVIDoa2200043].
2. Pommier Y, O’Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med 2016;8:362ps17.
3. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382:2091–102.
4. Hussain M, Daignault-Newton S, Twardowski PW, Albany C, Stein MN, Kunju LP, et al. Targeting androgen receptor and DNA repair in metastatic castration-resistant prostate cancer: Results from NCI 9012. J Clin Oncol 2018;36:991-9.
5. Chi KN, Rathkopf DE, Smith MR, Efstathiou E, Attard G, Olmos D, et al. Phase 3 MAGNITUDE study: First results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations. J Clin Oncol 2022;40:6_suppl, 12-12