PROFOUND trial—a new era in targeted therapeutics for prostate carcinoma

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SUMMARY

The PROfound study, a prospective, randomized, open-label, phase 3 trial was carried out at 206 sites in 20 countries[1] and evaluated the safety and efficacy of olaparib (poly ADP-ribose polymerase [PARP] inhibitor) in men with metastatic castrate-resistant prostate cancer (mCRPC) who progressed while receiving a new hormonal agent (enzalutamide or abiraterone). Patients older than 18 years of age, with confirmed castration-resistant prostate cancer were screened \( (n = 4425) \) and 387 eligible patients were enrolled in the study. Eligible patients were divided into two groups; cohort A had at least one alteration in BRCA1, BRCA2, or ATM, and cohort B had at least one alteration in BRIP1, BASRD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54 L. Patients were randomly assigned in a 2:1 ratio to receive either Olaparib (300 mg twice daily, \( n = 245 \)) or the physician’s choice of enzalutamide (160 mg once daily) or abiraterone (1000 mg once daily) plus prednisone 5 mg twice daily (control group, \( n = 142 \)).

The primary end-point was radiological progression-free survival (PFS) which was defined as the time from randomization to soft-tissue progression (RECIST 1.1), bony lesion progression (PCWG-3), or death. The study reported a significantly longer median imaging-based PFS in the olaparib arm, 7.4 months versus 3.6 months (olaparib vs. control) and the hazard ratio (HR) for progression or death was 0.34 with a 95% confidence interval (CI) (0.25–0.47; \( P < 0.001 \)).

In the secondary end-points, the confirmed objective response rate was 33% versus 2%, a 50% reduction in PSA was seen in 43% versus 8%, the clearance of circulating tumor cells was 30% versus 11%, and the median overall survival was 18.5 versus 15.1 months (olaparib vs. control group). The median time to pain progression was also longer in the olaparib group than that in the control group (HR, 0.44: 95% CI, 0.22–0.91: \( P = 0.02 \)).

The common adverse events of any grade in the olaparib group were anemia (46% vs. 15%) followed by nausea and fatigue, whereas in the control group, it was fatigue or asthenia (42% vs. 41%). The overall incidence of Grade 3 or more adverse events was higher in the olaparib group (51% vs. 38%).

COMMENTARY

The evolution of new therapies, in the form of androgen signaling inhibitors (abiraterone and enzalutamide) and taxanes, has given a new dimension to the management of mCRPC. Current NCCN prostate cancer guidelines recommend germ line testing for all patients with metastatic, regional, very high-risk disease, or high-risk disease regardless of the family history and in all the patients with a family history of high-risk germ line mutations (BRCA1/2, Lynch mutation).[2]

This landmark trial provides level 1 evidence supporting olaparib for the treatment of mCRPC that has progressed despite enzalutamide or abiraterone in patients, with homologous recombinational repair (HRR) mutations. Although, the radiographic PFS improved, the trial did not report overall survival as a primary endpoint. Further, nearly 50% of the patients in the treatment arm reported anemia, and 4% of the patients developed pulmonary embolism, which is of concern and needs further evaluation. The study also had a few limitations; abiraterone and enzalutamide (control arm) have a significant cross-resistance, thus sequencing them one after the other, as in the trial, is considered suboptimal. The use of this sequencing/crossover as the control arm can be considered inappropriate as the intent of this trial was to establish the efficacy of a novel drug, olaparib. Besides, the low detection rate (22%) of HRR mutation in patients with mCRPC, the relative unavailability of genetic testing, and the high cost of the treatment are also a hurdle.

Olaparib is an oral agent, first approved by the FDA in the year 2014 for the treatment of advanced ovarian cancer. It is an inhibitor of PARP enzymes, including PARP1, PARP2, and PARP3 and is available both in tablet and capsule formulations, and the oral formulation is absorbed rapidly (median peak plasma concentrations typically achieved 1.5 h after dosing).[3]
In the TOPARP-A study, the antitumor activity of olaparib 400 mg twice a day, showed a 100% response in the patients with the BRCA2 mutation. The median PFS and the median overall survival, in the patients with genomic aberrations, were 9.8 and 13.8 months, respectively.[4]

TOPARP-B study randomized patients into two groups to either 300 mg or 400 mg of olaparib. The overall response rate (combined primary end-point) was 54% in the 400 mg cohort and 37% in the 300 mg cohort. The overall median PFS was 5.4 months. Patients with BRCA1/2 mutations showed the best response to PARP inhibitor olaparib.[5]

At present, multiple clinical trials [Table 1] are underway to evaluate the potential role of PARP inhibitors in metastatic prostate cancer, which has opened the door for targeted therapeutics. There has been a significant advancement in the field of therapeutic biomarkers, and soon PARP inhibitors may be one of the frontline drugs for the treatment of mCRPC. Olaparib (Lynparza®) is imported in India at an approximate cost of Rs. 40,000 (8 tablet - 150 mg). In India, genetic testing for prostate cancer is still in the introductory stage and is available at a few selected centers, at a price varying approximately from Rs. 20,000–30,000. However, the availability and affordability of genetic testing and the treatment will remain a concern for the developing countries.

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