Asian Journal of Andrology (2016) 18, 592–593

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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

The promising role of poly(ADP-ribose) polymerase inhibitors in prostate cancer

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Asian Journal of Andrology (2016) **18**, 592–593; doi: 10.4103/1008-682X.172821; published online: 19 February 2016

The TOPARP study showed the beneficial utility of olaparib in a heavily pretreated population of metastatic castration-resistant prostate cancer who were biomarker-positive for aberrations in DNA repair gene. A higher response rate to olaparib of 88% (14 out of 16 patients), time to radiographic progression as well as overall survival, was seen in patients who were biomarker-positive compared to those who were not. This study showed a promising way of targeting prostate cancer with an enriched population of patients who harbor these deleterious genes. This paves the way for offering new therapeutic opportunities for men who have otherwise few remaining options.

Prostate cancer that has progressed to metastatic castration-resistant disease poses a challenging treatment dilemma given lack of response or durable response in patients with refractory disease even to conventional treatments such as chemotherapy or novel androgen-targeted signaling agents. It is now widely recognized that metastatic castration-resistant prostate cancer (mCRPC) does possess genomic alterations that hinder mechanisms of DNA repair. Olaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor that blocks enzymes involved in repairing damaged DNA. The use of PARP inhibitors is now considered standard in patients with advanced ovarian cancers that have failed prior therapies with associated BRCA 1 and 2 gene mutations as evidenced by a companion diagnostic by Myriad Genetic Laboratories.[1]

TOPARP (A Trial of PARP Inhibition in Prostate Cancer), led by Dr. Johann de Bono,[2] reported in the New England Journal of Medicine, was a targeted, biomarker, open-label, single-group, multi-site phase II trial design mostly in the United Kingdom, looking at the utility of olaparib in those who harbor deleterious germline BRCA2 mutations.

The TOPARP trial enrolled a cohort of 45 mCRPC patients in this two-stage design (30 patients in the first cohort and 15 patients in the second). They had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2 and no prior exposure to any platinum, cyclosphosphamide, or PARP inhibitors. The primary endpoint of the study was response rate based on RECIST criteria version 1.1, calculated using two-sided exact binomial 95% confidence interval, PSA reduction of 50% or more, or circulating tumor cell (CTC) conversion 5 or more per 7.5 ml of blood at baseline to <5 per 7.5 ml during treatment that was confirmed after 4 weeks. The secondary endpoints included radiologic progression-free survival and overall survival, calculated according to Kaplan–Meier methods, as well as time to PSA progression, proportion of patients with conversion, as well as safety and adverse events. The biomarkers planned were all prospectively obtained pre- and during-treatment with fresh biopsy samples from tumors (28 from bone marrow source and 22 from nodal or visceral metastases), and whole-exome sequencing and transcriptome studies were performed as well as PTEN and ERG testing by immunohistochemistry. Germline whole-exome sequencing was obtained from salivary DNA, next generation sequencing, and copy number data validation using Bio-Rad, and the CTC platform used CellSearch by Veridex. For purposes of the trial, patients who harbor a homozygous deletion or deleterious mutation to DNA repair genes or PARP inhibition sensitivity were considered biomarker-positive.

All patients enrolled were heavily pretreated and had received prior docetaxel (100%). The majority of the patients had also received prior abiraterone (98%) while Cabazitaxel had been used in 58% of the patients and only a quarter (28%) received enzalutamide and only 1 patient had prior radium. Results showed that of the 49 patients enrolled in the study, 33% (16 of them) had a response to olaparib with a median time of 40 weeks, using the composite definition defined above. Some of these responses were durable with 12 patients maintained on olaparib for more than 6 months while four patients for over a year. For the biomarker evaluations, of the 49 patients who could be evaluated for a response, 43 had fresh tumor samples while the rest had archival tissue for analysis. Of these, 16 patients were found to have DNA repair gene abnormalities. BRCA2 was the most commonly detected gene aberration which occurred in seven patients, of whom two had homozygous deletions, two with combined somatic and LOH (loss of heterozygosity), while 3 of the 7 had germline mutation with loss of the 2nd allele. ATM mutations were the 2nd most common aberrations with three of them having germline mutations with truncated ATM protein and 2 of the 3 with aberrant alleles in somatic DNA. Still, three others had FANCA (Fanconi's anemia) deletion in three patients.

Objective responses in patients who were biomarker-positive were higher, with 14 of 16 patients having an 88% response with only two of the biomarker-negative having any response (6%). Similarly, radiographic responses were also more durable in the biomarker-positive patients, with a median of 9.8 months versus only 2.7 months in the

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biomarker-negative. There was a doubling of the overall survival to 13.8 months in the biomarker-positive group versus 7.5 months in the biomarker-negative group, all statistically significant.

Overall, olaparib was well-tolerated in most patients although 6% had to discontinue because of adverse events. The majority of grades 3 or 4 adverse events were hematologic, with 20% experiencing anemia, 12% having fatigue, 6% having leukopenia, and 4% with thrombocytopenia and neutropenia. While the anemia was felt to be drug-related, most of these patients also had extensive bone disease which could have partly explained the adverse events.

The results of the TOPARP trial marks one of the new waves of clinical trials that look at molecular subset and targeting of prostate cancer in a biomarker-driven fashion. Studies that looked at the splice variant of AR-V7 that predicted for enzalutamide or abiraterone failure,[3] also heralds the beginning of this biomarker approach. To this end, some trials have started advocating for such approach to enrich the population of patients who may benefit from certain drug therapies (such as Tokai's galeterone in AR-V7 splice variant patients, clinicaltrials.gov NCT02438007).[4]

However, much work needs to be done to fully harness the utility of molecular profiling and adopting a truly "personalized medicine" approach for such patients. It is conceivable to think that since about one-third of the patients are destined to not respond robustly or to have early progression on novel androgen-targeted signaling agents, targeting aberrant DNA repair enzyme would be an alternative or subsequent mechanism of pathway inhibition to explore. Platinum agents have been used in prostate cancer and, in a subset few patients, may have responses. It is interesting to note that there was a subgroup of patients who responded to satraplatin in the phase III SPARC trial[5] despite insufficient overall responses to meet the primary endpoint in the registration trial. Nonetheless, having a response that was seen in olaparib in this heavily pretreated patient population is encouraging and should pave the way forward for future studies exploring PARP-inhibitors in prostate cancer.

COMPETING INTERESTS

The author declared no competing interests.

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