PARP inhibitors and metastatic castration-resistant prostate cancer: future directions and pitfalls

A. Franz‡, M. Claps, G. Procopio

Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy

ABSTRACT
PARP inhibitors (PARPi) gained major interest among prostate cancer researchers in the last few years, thanks to the outstanding results coming from the PROfound trial and subsequent studies. Following that, PARPi gained approval also in metastatic, castration-resistant prostate cancer (mCRPC) with mutations in homologous repair (HR) – related genes. Nevertheless, some questions still remain unanswered concerning the management of drug resistance and PARPi-sensitivity in patients harboring alterations in various DNA damage response (DDR) related genes, not only BRCA1 and BRCA2.

In this perspective article we focus on the key issues concerning PARPi in mCRPC, specifically those related to drug sensitivity and resistance mechanisms, exploring the possible role of combination therapeutic approaches and trying to depict potential future addresses in translational oncology research.

Perspective Article (max: 1200 words)

The DNA damage repair (DDR) pathway gained major interest between cancer researchers since 2005, when emerging studies demonstrated that the simultaneous inhibition of both Poly(ADP-ribose) polymerase 1 (PARP1) and tumor suppressors Breast Related Cancer Antigens 1 and 2 (BRCA1 and BRCA2) generates excessive DNA instability and, ultimately, leads to cellular death. This process, called synthetic lethal theory, constituted the rationale for the development of drugs targeting PARP1 in BRCA1/2 deficient clones, the PARP inhibitors (PARPi) \([1,2]\).

In normal conditions, PARP1 plays a key role as regulator of multiple cellular processes, including DDR. When a DNA damage occurs, the activation of PARP1 results in the recruitment of several DNA repair factors, including BRCA1 and BRCA2, leading to the restoration of single-strand (SSBs) and double-strand DNA breaks (DSBs) \([1,2]\). Particularly, BRCA1 and BRCA2 act downstream the PARP1 cascade in one of the two major pathways for DSB repair, largely error free: the homologous repair (HR). Another crucial mechanism, which sees the synergic contribution of PARP1, BRCA1 and BRCA2, is the stabilization of replication fork during the S phase of the cell cycle \([2]\). As a consequence of that, heterozygous germline mutations in DDR genes, especially BRCA1 and BRCA2, dramatically increase the risk of developing multiple neoplasms (e.g. breast, ovarian, prostate and pancreatic cancers) \(^2\). In addition, somatic and germline mutations in one of these genes confer a strong sensitivity to DNA-damaging agents (e.g. platinum salts): these fundamental observations led researchers to successfully study and test pharmacological inhibition of the DDR pathway, using PARPi \([2]\).

Of note, it has been calculated that approximately 12\% of metastatic, castration-resistant prostate cancer (mCRPC) patients harbor germline DDR mutations, while 20–25\% harbor somatic DDR mutations. Overall, it is estimated that in almost 22.7\% of mCRPC patients could be identified mutations in DDR-related genes, making them a considerable number of people who could take an advantage from PARPi administration \([3]\).

In 2014, the U.S. Food and Drug Administration (FDA) granted approval to Olaparib as the first PARPi viable for women suffering from BRCA 1–2 mutated metastatic ovarian cancer both for cases previously treated with three or more lines of chemotherapy, and also as maintenance therapy following platinum-based chemotherapy \([2]\). Since that, following the consistent results described by subsequent clinical trials, Olaparib and other PARPi (e.g. Rucaparib, Niraparib) gained approval for different clinical settings in ovarian cancer and for BRCA-mutated breast, pancreatic and prostate cancer \([2]\).

In 2020, thanks to the outstanding results of the PROFound trial, the FDA approved the administration of Olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after therapy with enzalutamide or abiraterone and harboring mutations in HR-related genes \([4]\). Later the same year, the European Medicines Agency (EMA) recommended Olaparib in the same setting, with a slight but substantial difference: the main requirement was the identification of a BRCA 1 and BRCA 2 mutation (somatic or germline) in prostate cancer patients who have progressed to a prior therapy that included a new hormonal agent \([5]\).

* Corresponding author.
E-mail address: andrea.franza@istitutotumori.mi.it (A. Franz).
Similarly, Rucaparib received the FDA accelerated approval after the publication of the TRITON2 study, that showed consistent overall response rate (ORR) and Prostate Specific Antigen (PSA) response rate values in patients with BRCA1 and BRCA2 alterations [6].

Nevertheless, it is well known that DDR mechanisms, including homologous repair (HR), are characterized by the interplay of a huge number of enzymes, co-factors, and molecules, not only BRCA1 and BRCA2 [2,5]. Specifically, HR requires the intervention of co-factors as PALB2 (Partner And Localizer Of BRCA2) and RAD51 (RAD51 Recombinase) to perform an accurate repair of double strand DNA breaks. In addition, BRCA1 and BRCA2 exhibit a crucial role during the S phase of the cell cycle, as protectors of the replication fork from the degradation activity carried out by nucleases. This is why, although PARPi seem to be more effective against BRCA1 and 2 mutations, data extrapolated from clinical trials suggest a benefit also for people harboring alterations in others genes, such as PALB2, RAD51 and ATM (Ataxia-Telangectasia Mutated) [2]. The PROfound trial, considered as a milestone, enlightened this aspect and its possible implications in prostate cancer: administering Olaparib to the whole cohort of HR-deficient patients could extend the survival benefit to a significant number of people, albeit the subgroup of BRCA1 and BRCA2 mutated cohort might have generated an overestimation of this effect in that trial [7]. Further studies need to be carried out in order to perform a correct prognostic and predictive gene-signature based stratification of patients.

One of major concerns related to anti-cancer drugs, particularly targeted therapies, is drug-resistance. Even PARPi, although frequently characterized by initial good responses, ultimately loose their effectiveness, leading to disease relapse [2]. The reason is that cancerous cells learn how to escape from the pharmacological attack of PARPi via several mechanisms: upregulation of drug efflux pumps; mutations of the drug target; recovery of BRCA1 and BRCA2 function; re-establishment of replication fork stability [2,8]. The deep knowledge of these mechanisms could lead to overcome drug resistance: the most appealing hypothesis to get through this barrier appears to combine PARPi with agents affecting HR from other sides, such as Vascular Endothelial Growth Factor (VEGF) inhibitors, for which some encouraging data have been published in a cohort of ovarian cancer patients [2]. An interesting observation is also that HR deficient cancers might exhibit a high tumor mutational burden, often associated with an improved sensitivity to immunotherapy. Thus, clinical trials are now investigating the combination of PARPi and immune check-point inhibitors (ICIs) in mCRPC [9].

Furthermore, several trials are ongoing to evaluate the efficacy of the combination of PARPi and new hormone agents (i.e. Abiraterone acetate, Enzalutamide) for metastatic prostate cancer, both in the hormone-sensitive and castration-resistant phases.

Unfortunately, most of data concerning combination therapies were extrapolated from preliminary analyses of clinical trials, with many open issues still remaining. Firstly, drug safety: as previously stated in a phase I/II clinical trial, the addition of ICIs to PARPi seems to be well tolerated with no significant increase of severe adverse effects; at the same time, the administration of PARPi plus Abiraterone in mCRPC patients was investigated in a randomized, double-blind, placebo controlled phase II clinical trial, obtaining promising results in term of safety and also efficacy [2,10]. Another major concern regards the need to identify reliable biomarkers predictive of drug response, and this must be one of the addresses of future researches [1,2]. The last issue involves healthcare costs of such combinations therapies, again emphasizing the importance to perform a thorough stratification of mCRPC patients [2]. These might be some branches for future researches, to explore where and when to combine PARPi with other agents, and in which patients subgroup [1,2,9].

We have now several weapons in our hands, ready to be used, the most important represented by genomic analyses techniques [2]. In addition, following that principle of synthetic lethality, we need to hit cellular DNA repairing system from many sides, employing old and new

---

Table 1: Trials evaluating PARPi in mCRPC (adapted from: clinicaltrials.gov).

| Study ID       | Title                                                                 |
|---------------|-----------------------------------------------------------------------|
| NCT0372820    | Study on Olaparib Plus Abiraterone as First-line Therapy in Men With  |
|               | Metastatic Castration-resistant Prostate Cancer                       |
| NCT01972217   | Phase II Study to Evaluate Olaparib With Abiraterone in Treating     |
|               | Metastatic Castration-resistant Prostate Cancer.                     |
| NCT02687543   | Study of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate |
|               | in Men With Metastatic Castration-resistant Prostate Cancer (PROfound) |
| NCT03787680   | Targeting Resistant Prostate Cancer With ATR and PARP Inhibition (TRAP Trial)  |
| NCT03834519   | Study of Pembrobilizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate |
|               | or Enzalutamide in Metastatic Castration-resistant Prostate Cancer   |
| NCT03012321   | Abiraterone/Prendisone, Olaparib, or Abiraterone/Prendisone + Olaparib   |
|               | in Patients With Metastatic Castration-Resistant Prostate Cancer With DNA Repair Defects |
| NCT03434158   | Olaparib Maintenance in Patients With mCRPC After Docetaxel Treatment |
|               | Reaching Partial or Stable Response (IMANOL)                         |
| NCT03516812   | Testosterone and Olaparib in Treating Patients With Castration-Resistant Prostate Cancer |
| NCT04951492   | Olaparib for the Treatment of Castration Resistant Prostate Adenocarcinoma |
| NCT02899317   | Olaparib With or Without Cediranib in Treating Patients With Metastatic Castration-Resistant Prostate Cancer |
| NCT01682772   | Combined Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer |
| NCT05005728   | XmAb®K20,717 Alone or in Combination With Chemotherapy or Targeted Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer |
| NCT03413995   | Trial of Rucaparib in Patients With Metastatic Hormone-Sensitive Prostate Cancer Harboring Germline DNA Repair Gene Mutations |
| NCT02952534   | A Study of Rucaparib in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency (TRITON-2) |
| NCT02975934   | A Study of Rucaparib Versus Physician’s Choice of Therapy in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency (TRITON-3) |
| NCT04455750   | A Clinical Study Evaluating The Benefit of Adding Rucaparib to Enzalutamide for Men With Metastatic Prostate Cancer That Has Become Resistant To Testosterone-Derived Therapy |
| NCT03442556   | Docetaxel, Carboplatin, and Rucaparib Camosylte in Treating Patients With Metastatic Castration Resistant Prostate Cancer With Homologous Recombination DNA Repair Deficiency |
| NCT04592237   | Cabazitaxel, Carboplatin, and Cetrelimab Followed by Niraparib |

(continued on next page)
drugs. The only way to cope with this huge amount of data is to team up with different professional figures (e.g. biotechnologists, pharmacologists, biostatisticians), constructing a cooperative network system. Only by doing this we will make it up to the mountain.

Table 1 (continued)

| Study ID     | Title                                                                 | Status                  | Phase |
|--------------|----------------------------------------------------------------------|-------------------------|-------|
| NCT04821622  | Study of Talazoparib With Enzalutamide in Men With DDR Gene Mutated mCSPC | Recruiting               | 3     |
| NCT02854436  | An Efficacy and Safety Study of Niraparib in Men With Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies | Active, not recruiting   | 2     |

Table 1

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Bibliography

[1] M. Stellato, V. Guadalupi, P. Sepe, et al., The emerging role of PARP inhibitors in prostate cancer, Expert Rev. Anticancer Ther. 20 (8) (2020) 715–726, https://doi.org/10.1080/14796694.2020.1797497.
[2] M.P. Dias, S.C. Moser, S. Ganesan, J. Jonkers, Understanding and overcoming resistance to PARP inhibitors in cancer therapy, Nat. Rev. Clin. Oncol. (2021), https://doi.org/10.1038/s41571-021-00532-x. Published online July 20.
[3] D. Robinson, E.M. Van Allen, Y.-M. Wu, et al., Integrative clinical genomics of advanced prostate cancer, Cell 161 (5) (2015) 1215–1228, https://doi.org/10.1016/j.cell.2015.05.001.
[4] FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer. Accessed August 17, 2021. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.
[5] EMA: authorisation details for Lymparza (olaparib). Accessed August 17, 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/lymparza.
[6] W. Abida, A. Patnaik, D. Campbell, et al., Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration, JCO 38 (32) (2020) 3763–3772, https://doi.org/10.1200/JCO.20.01035.
[7] J. de Bono, J. Mateo, K. Fizazi, et al., Olaparib for metastatic castration-resistant prostate cancer, N Engl. J. Med. 382 (22) (2020) 2091–2102, https://doi.org/10.1056/NEJMoa2011440.
[8] S.M. Noordermeer, H van Attikum, PARP Inhibitor resistance: a tug-of-war in BRCA-mutated cells, Trends Cell Biol. 29 (10) (2019) 820–834, https://doi.org/10.1016/j.tcb.2019.07.008.
[9] C.H. Marshall, E.S. Antonarakis, Emerging treatments for metastatic castration-resistant prostate cancer: immunotherapy, PARP inhibitors, and PSMA-targeted approaches, Cancer Treat Res. Commun. 23 (2020), 100164, https://doi.org/10.1016/j.ctarc.2020.100164.
[10] N. Clarke, P. Wiechno, B. Alekseev, et al., Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial, The Lancet Oncology 19 (7) (2018) 975–986, https://doi.org/10.1016/S1470-2045(18)30865-6.