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Review

PARP inhibitor combinations in prostate cancer

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***Abstract*:** Polyadenosine-diphosphate-ribose polymerase (PARP) inhibitors cause deoxyribonucleic acid (DNA) damage that can be lethal to cells with deficient repair mechanisms. A number of PARP inhibitors are being tested as treatments for men with prostate cancer, both as monotherapies and in combinations that are based on purported synergies in treatment effect. While the initial single-agent development focused on men with identified deficiencies in DNA-repair pathways, broader patient populations are being considered for combination approaches. This review summarizes the current clinical development of PARP inhibitors and explores the rationale for novel combination strategies.

Keywords: DNA-damage repair, PARP combinations, PARP inhibitor, prostate cancer, synthetic lethality

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Introduction

Treatment options for men with advanced prostate cancer have largely focused on the pillars of hormonal blockade, chemotherapies and bone-targeting agents. Attempts to develop novel combination strategies have been frustrated by the unique androgen-dominated biology of this common cancer. The recent discovery that a significant minority of men with advanced prostate cancer carry or develop alterations in deoxyribonucleic acid (DNA)-damage repair (DDR) proteins has uncovered a new potential therapeutic area. Moreover, polyadenosine-diphosphate-ribose polymerase (PARP) inhibitors are being explored in a number of combination treatments, aiming to harness the potential synergies seen in preclinical models.

Rationale for targeting DNA repair

Daily exposure to external toxicants and intrinsic pressures causes damage to DNA. In order to survive, cells require the ability to repair DNA damage. There are over 150 human genes identified having a role in DNA repair.[1] When the damage is confined to a single strand of DNA, the repair often involves a scaffolded base excision repair, utilizing the complex of PARP genes. In the more high-risk scenario when the break involves both strands of DNA, the preferred repair mechanism is homologous recombination (HR), using BRCA (originally named as breast cancer susceptibility genes), RAD51, PALB2 (the 'partner and localizer of BRCA2') and ataxia–telangiectasia-mutated (ATM) serine/threonine kinase. If HR repair is not possible, more error-prone alternative mechanisms are used, such as nonhomologous-end joining (NHEJ), which restores DNA integrity but often results in faults. If a cell is relying on NHEJ, the accumulation of errors in key cellular pathways can result in critical failures and cell death.

The value of understanding DDR pathways is in the ability to exploit it as a novel target in the treatment of cancer. When there is a deficiency in the proteins required for HR, cells are particularly vulnerable to therapies that cause double-strand DNA breaks. Vulnerable cells may be missing HR proteins due to a hereditary deficiency in all cells, sporadic mutations within cancer cells or environmental suppression of heterozygous function within the tumour microenvironment. Identifying HR deficiency has provided an explanation for the sensitivity to DNA damage from platinum chemotherapies in a number of cancers

including urothelial cancer[2] and is also the suggested mechanism for exceptional responses reported following radionuclide treatment for prostate cancer in men with germline deficiencies.[3,4]

PARP inhibitors are another strategy to force cells into developing double-strand DNA breaks. PARP inhibitors are generally thought to act by trapping the repair complex at the site of a single-strand break, stalling replication and causing further damage, although additional mechanisms including direct toxicity have also been proposed.[5] In the absence of intact DDR pathways, the use of these agents can cause cell death, so called 'synthetic lethality'.[6] The inhibitors currently in clinical development differ in the potency with which they trap PARP on the DNA complex[7] and in their ability to inhibit PARP3,[8] but these variations do not appear to impact the degree of tumour inhibition in xenograft models.[9]

DDR alterations in prostate cancer

Hereditary BRCA defects were initially recognized in people with breast cancer, which for many years was the focus of familial clustering studies and germline testing. The development of PARP inhibitors was initially developed for use in people with ovarian and breast cancers. More recently, the prevalence of DDR germline alterations in men with prostate cancer has been highlighted. Robinson and colleagues sequenced 150 men with castration-resistant prostate cancer (CRPC) and found that 32 (21.3%) had alterations in key DDR pathways, many of which were biallelic.[10] A larger cohort tested for germline defects revealed DDR alterations in 82 of 692 men with metastatic prostate cancer (11.8%), with approximately half of these (37 = 5.4%) involving BRCA.[11] Importantly, the presence of germline DDR alteration was not adequately predicted by family history or age at diagnosis. A similar prevalence of germline alterations has been reported in cohorts of men with high-risk 'nonindolent' but nonmetastatic prostate cancer (47 of 477 men = 9.9%),[12] with suggestions that the histological variant of ductal or intraductal cancer may associate with germline pathogenic DDR alterations.[13] Low-risk prostate cancer samples appear to have a markedly lower prevalence of DDR alterations (ATM/BRCA1/2 in 7 of 486 men = 1.4%),[14] consistent with the belief that they associate with more aggressive disease and worse prognosis.

Progress with single-agent PARP inhibitors in prostate cancer

An early phase I study of olaparib (Lynparza, AstraZeneca and MSD) focused on people with germline BRCA defects, including men with advanced prostate cancer,[15] with observations of clear biochemical and radiographic benefit. Since then, a number of PARP inhibitors have been developed and tested in men with prostate cancer.

The activity of PARP inhibitors in advanced prostate cancer was explored with the phase II TOPARP-A study, published in 2015.[16] The single-arm study included biomarker development, whereby unselected men were treated with olaparib 400 mg twice daily (BD), at the same time that their samples were undergoing next-generation sequencing. The primary endpoint was a composite response definition, including biochemical response based on prostate-specific antigen (PSA) decline, radiographic soft-tissue response and circulating tumour cell (CTC) count conversion. Only men with a baseline CTC $\geq$ 5/7.5 ml blood were enrolled, which is more commonly observed in the pretreated population targeted in the trial;[17] all participants had received at least one chemotherapy agent and a next-generation androgen-receptor axis-targeted (ARAT) therapy. One or more of the response measures was achieved in 16 of the 49 evaluable men, with 14 of these 16 responses occurring in men who had alterations in DDR pathways, giving an overall response rate in biomarker-positive patients of 88%, compared with 2 of 33 (6%) in the biomarker-negative cohort. The impact of the DDR alterations carried through to secondary endpoint measures of radiographic progression-free survival (rPFS), with a median rPFS of 9.8 months in the biomarker-positive group, compared with 2.7 months in the biomarker-negative group ($p < 0.001$), and overall survival (OS; median OS 13.8 months *versus* 7.5 months, $p = 0.05$). Reported toxicity was consistent with the expected profile for olaparib. Anaemia was the most common adverse event, occurring at any grade in 38 (76%) men, with 10 (20%) experiencing at least grade 3 anaemia, a level at which people require transfusion or further intervention. Some element of fatigue was reported in 29 men (58%) with the severest fatigue grading of grade 3 in 6 (12%). Grade 1–2 nausea was reported in 18 men (36%). Approximately one quarter of participants required a dose reduction while on trial.

More recently, initial data from the follow-on TOPARP-B trial were presented, using a similar composite endpoint to define activity.[18] TOPARP-B used DDR alteration as the biomarker to select participants. A total of 711 men were registered in multiple trial centres, with approximately 15% sample failure. A total of 431 men had no mutation identified, leaving 161 men with an eligible biomarker. Of these men, 98 were randomized between the previously tested dose of olaparib and the lower dose of 300 mg BD, as used in treatment of other cancer types. The minimum baseline CTC criterion was removed for TOPARP-B and the composite response endpoint was lower in consequence, achieved in 43 of the 92 evaluable men [47%; 95% confidence interval (CI) 36.3–57.4%]. Radiographic or PSA responses were observed in 32 of these men. Responses were seen in both dose cohorts, but the higher-dose level appeared more active. When looking at the DDR alterations, the highest activity was observed in men with BRCA1/2 (composite endpoint achieved in 25 of 30 men; 83%), with the lowest activity reported in the cohort with disparate 'other' DDR alterations (composite endpoint achieved in 4/20; 20%). This raises the hypothesis that some points in the DDR pathway may be much more sensitive to PARP-inhibitor targeting. The ideal patient population for this treatment strategy remains uncertain.

Thus far, the other presented data for single-agent PARP inhibitors are from the TRITON2 trial of rucaparib (Rubraca, Clovis Oncology) [ClinicalTrials.gov identifier: NCT02952534], in a similarly pretreated (post-ARAT and postchemotherapy) patient population. Although the trial is ongoing, 'early look' activity data were presented at the European Society for Medical Oncology conference in 2018, including 83 patients.[19] Of the men with a BRCA1/2 alteration, ⩾50% PSA decline was observed in 23 of the 45 patients, with confirmed soft-tissue responses in 11 of the 25 BRCA patients with evaluable disease. Little activity was seen in men with ATM or other DDR alterations.

While the activity data presented look encouraging, advanced prostate cancer is notorious for the unreliability of surrogate endpoints, and many clinicians still regard OS as the only meaningful measure. PARP inhibitors have not yet been proven to extend OS compared with other standard-of-care treatments and must still be regarded as experimental. The first phase III data are likely to come from the PROfound trial of olaparib *versus* abiraterone/enzalutamide [ClinicalTrials.gov identifier: NCT02987543], expected to be presented in 2019. Maintenance and neoadjuvant treatment strategies are also in clinical testing, with activity data awaited.

Combination PARP inhibitors in prostate cancer

Following quickly on from the initial reports of monotherapy activity, PARP-inhibitor combinations commenced clinical testing, as summarized in Table 1. The goals of combination testing were to identify therapeutic synergy that could deepen response/delay progression, and to broaden the patient population beyond the important minority of men with DDR alterations. While all strategies followed rationales provided by preclinical data or modelled successful strategies in other cancers, the rocky path of prostate cancer drug development has already claimed some victims.

Strategies that have not resulted in positive clinical trials

DNA-damaging agents

Temozolomide (Temdol, MSD) is an alkylating agent that causes DNA damage. As a monotherapy, the very modest activity observed in prostate cancer was described by the investigators as 'rather discouraging'.[20] In contrast, temozolomide has an established role in the treatment of cancers such as glioblastoma multiforme. Preclinical studies in a number of cell lines (including prostate cancer) suggested enhanced sensitivity to the combination of temozolomide and olaparib.[21–23] However, this synergy was not observed in a combination trial of low-dose veliparib (40 mg BD, compared with a monotherapy dose of 400 mg BD) and temozolomide in 26 men with advanced prostate cancer.[24] Although the veliparib dose may have been insufficient, the data were generally underwhelming. However, this strategy has not been completely abandoned, with a phase I/II trial of temozolomide and talazoparib (Talzenna, Pfizer) currently recruiting men with advanced prostate cancer without known DDR alterations [ClinicalTrials.gov identifier: NCT04019327].

Targeting ETS-fusions

Erythroblast transformation-specific (ETS) fusion genes are common in prostate cancer, potentially

Table 1. PARP-inhibitor combination treatments in clinical development.

Combination strategy	Agents	Trial phase	ClinicalTrials.gov identifier	Preclinical rationale	Clinical activity data	Patient population
Akt inhibition	Ipatasertib + rucaparib	I/II	NCT03840200	PARP inhibition activates Akt to promote cell survival	–	mCRPC, post-ARAT
Antiangiogenic agents	Cediranib + olaparib	II	NCT02893917	Reduced DDR gene expression with hypoxia/cediranib	–	At least second-line mCRPC
AR targeting	Enzalutamide + talazoparib	III	NCT03395197	Reduced DDR gene expression with antiandrogen therapies	Negative: veliparib Positive for PFS: olaparib	First-line mCRPC
	Abiraterone + olaparib	III	NCT03732820			First-line mCRPC
	Abiraterone + niraparib	III	NCT03748641			First-line mCRPC; biomarker stratified
	Abiraterone + olaparib	II	NCT03012321			First-line mCRPC + DDR alteration
DNA-damaging agents	Temozolomide + talazoparib	I/II	NCT04019327	Enhanced DNA damage	Negative: veliparib	mCRPC post-ARAT
DNA-repair combinations	AZD6738 + olaparib	II	NCT03787680	Synergy in cell lines lacking ATM-mediated survival pathways	–	Second-line mCRPC; stratified for DDR alterations
Immunotherapy	Durvalumab + olaparib	II	NCT03810105	Enhanced immunogenicity in combination	Positive for response: durvalumab Phase I activity: pembrolizumab	Biochemical recurrence postprostatectomy + DDR alteration
	Pembrolizumab + olaparib	III	NCT03834519			mCRPC post-ARAT ± taxane chemotherapy
	Nivolumab + rucaparib	II	NCT03338790			mCRPC
	JNJ-63723283 + niraparib	I/II	NCT03431350			mCRPC post-1–2 ARAT
	Nivolumab + rucaparib	I/II	NCT03572478			mCRPC, at least post-ARAT
Radionuclides	Ra-223 + niraparib	IB	NCT03076203	Increased DNA damage	–	Bone-metastatic CRPC, at least post-ARAT
	Ra-223 + olaparib	I/II	NCT03317392			Bone-metastatic CRPC
	^{177}Lu-PSMA + olaparib	I	NCT03874884			mCRPC post-ARAT + taxane chemotherapy
Radiotherapy	IMRT, GnRH agonist + niraparib	II	NCT04037254	Increased DNA damage	–	High-risk localized prostate cancer
Testosterone	Bipolar testosterone enanthate/cypionate + olaparib	II	NCT03516812	DNA damage with bipolar androgen therapy	–	mCRPC post-ARAT; enriched for DDR alterations

^{177}Lu-PSMA, ^{177}lutetium-prostate-specific membrane antigen; Akt, protein kinase B; AR, androgen receptor; ARAT, androgen-receptor axis-targeted therapy; ATM, ataxia–telangiectasia mutated; DDR, DNA-damage repair; DNA, deoxyribonucleic acid; GnRH, gonadotropin-releasing hormone; IMRT, intensity-modulated radiation therapy; mCRPC, metastatic castration-resistant prostate cancer; PARP, polyadenosine-diphosphate-ribose polymerase; PFS, progression-free survival; Ra-223, radium-223 dichloride.

resulting in transcription driven by AR signalling.[25] Preclinical data suggested that PARP inhibition using olaparib was able to inhibit growth in an ETS-mutant cell-line model.[26] However, this did not translate into clinical benefit. The combination of abiraterone acetate (Zytiga, Janssen) with veliparib (ABT-888, AbbVie) did not appear better than abiraterone in a population of men selected on the basis of providing a biopsy for ETS status.[27] A total of 148 men were enrolled and treated, either with abiraterone and prednisone alone, or with the addition of veliparib. The primary endpoint for the study was activity as judged by PSA response rate, defined as a reduction from baseline $\geqslant 50\%$. The combination failed to improve PSA response (63.9% abiraterone *versus* 72.4% combination, $p = 0.27$) and also demonstrated similar PFS (10.1 months *versus* 11 months, respectively, $p = 0.99$). A subset of 80 patients underwent tumour sequencing, with DDR alterations identified in 25%. ETS fusion was not associated with treatment response, but the presence of DDR alterations appeared to associate with treatment response to either form of abiraterone-containing treatment.

Strategies with promising clinical data

Thus far, the data presented on PARP inhibitor combinations have been from phase I/II trials and are therefore regarded as preliminary rather than definitive. The population of men studied in the trials has varied in the enrichment for men with known DDR alterations.

AR targeting

There are clear preclinical data to support the use AR targeting in combination with PARP inhibition. In both AR-responsive and -independent cell lines, the use of enzalutamide (Xtandi, Astellas) reduced the expression of HR genes, including BRCA1.[28] The combination of enzalutamide and olaparib was synergistic in cell-line and orthotopic xenograft models, with an alternating treatment approach proving most active. Extrapolation of these effects to encompass other antiandrogen treatments is supported by data using the first-generation AR antagonist bicalutamide.[29]

Clinically, the combination of olaparib with abiraterone was compared with abiraterone in a randomized phase II trial, presented and published in 2018.[30] This trial randomized 142 men equally between abiraterone with prednisone, or abiraterone/prednisone and olaparib, using a primary endpoint of PFS. The trial met the primary endpoint, with a median PFS of 13.8 months (95% CI 10.8–30.4) in the combination arm, compared with 8.2 months (95% CI 5.5–9.7, $p = 0.034$) in men receiving abiraterone alone. No difference was observed in the secondary endpoint of OS. There was an approximately 25% increase in the incidence of grade 3–4 adverse events in the combination arm, largely due to anaemia, as well as increased pneumonia and myocardial infarction events. Due to collection and testing issues, only a minority of patients were fully characterized for DDR alterations, so it is not possible to address the prevalence or balance of DDR alterations within the arms. While encouraging, false-positive results are common in randomized phase II trials, and the negative trial of abiraterone with veliparib is concerning. Validation will be required from the phase III PROpel trial of abiraterone/prednisone ± olaparib [ClinicalTrials.gov identifier: NCT03732820] currently enrolling men requiring prechemotherapy-ARAT therapy for CRPC.

Further trials testing next-generation ARAT and PARP inhibitors include the phase III trial of enzalutamide and talazoparib [ClinicalTrials.gov identifier: NCT03395197]. There are also a number of trials combining a PARP inhibitor with abiraterone and prednisone that will provide data in this space (see Table 1 for additional detail).

Immunotherapy

Immunotherapy continues as a major research focus in prostate cancer, despite mixed clinical results from monotherapy strategies. Identifying men with DDR alterations may select a cohort more likely to respond to immunotherapy, as tumours have a higher mutational burden and increased neoantigens.[31] Preclinical synergy has been demonstrated with cytotoxic T-lymphocyte-associated protein 4 (CTLA4) blockade and PARP inhibition in BRCA-deficient ovarian tumour models,[32] while improved programmed cell-death protein 1 (PD-1) targeting has been shown both in the absence and presence of BRCA function.[33]

The combination of olaparib with the programmed death-ligand 1 (PD-L1) inhibitor durvalumab (Imfinzi, Medimmune/AstraZeneca) was tested in men previously treated with next-generation ARAT, in a cohort enriched for men with DDR

alterations.[34] Of the 17 evaluable men, 9 had a confirmed PSA or soft-tissue response on treatment. The median rPFS for the cohort was 16.1 months (95% CI 4.5–16.1). The presence of a DDR alteration was associated with higher response.

Further early data of immunotherapy combinations includes phase I data on olaparib and pembrolizumab (Keytruda, MSD) from the KEYNOTE-365 umbrella trial (clinicaltrials.gov ID NCT02861573), presented at the ASCO-GU Symposium in 2019.[35] Men were post-docetaxel and post-ARAT, and none had identified DDR alterations. Of the 39 men evaluable for the primary activity endpoint of PSA decline, only five (13%) had a response – possibly reflecting the non-AR activity of both agents. The median rPFS was 5 months (95% CI 4–8 months) and median OS was 14 months. The safety profile reflected the expected toxicities of each agent. This combination will now be formally evaluated against abiraterone/enzalutamide in the phase III KEYLYNK-010 study [ClinicalTrials.gov identifier: NCT03834519].

Other combination immunotherapy studies are underway, including a number of PD-1 and PD-L1 inhibitors. It is not yet clear whether immunotherapy-PARP-targeting combinations will be best placed to enhance monotherapy responses in men with identified DDR alterations, or as a novel strategy in broader patient populations.

Further strategies undergoing clinical testing

A number of other combination strategies are in early clinical testing. Many of these have good preclinical rationale across the cancer field, but the utility in prostate cancer is unknown.

Angiogenesis

Cediranib (Recentin, AstraZeneca) is an oral small-molecule inhibitor of angiogenesis, targeting vascular endothelial growth factor receptors, platelet-derived growth factor receptor and c-kit. Cediranib treatment leads to decreased perfusion and increased hypoxia within tumours.[36] As a single agent, cediranib showed only modest activity in a cohort of men with previously treated advanced prostate cancer, including median PFS of 3.7 months and median OS of 10.1 months.[37] The combination of cediranib and olaparib showed promise in a randomized phase II clinical trial in women with relapsed ovarian cancer, improving PFS compared with olaparib alone.[38] The mechanism for this synergy has been explored in preclinical ovarian and breast cancer models and appears to be due to the downregulation of DDR genes in response to hypoxia[39] and cediranib,[40,41] as well as a direct suppression effect.[42] The value of this effect will now be tested in unselected men with previously treated CRPC, in combination with olaparib [ClinicalTrials.gov identifier: NCT02893917].

Akt inhibition

Phosphatase and tensin homolog (PTEN) is commonly deleted in prostate cancer, resulting in hyperactivation of the phosphoinositide 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway. Ipatasertib (Roche) is a potent inhibitor of Akt that has been tested in a phase II trial in combination with abiraterone. In a randomized phase II trial, the addition of ipatasertib improved rPFS compared with abiraterone, particularly in men with PTEN-deficient tumours.[43] This combination has been further tested in a phase III trial [ClinicalTrials.gov identifier: NCT03072238]. In preclinical studies, PARP inhibition results in activation of Akt as a cytoprotective response.[44] Akt inhibition is being tested in a phase I trial alongside rucaparib, including men with CRPC previously treated with ARAT agents [ClinicalTrials.gov identifier: NCT03840200].

DNA repair

The first combination of PARP inhibition with another agent targeting DDR is underway, using the ataxia–telangiectasia-and-rad3-related (ATR) kinase inhibitor AZD6738, following *in vitro* demonstrations of synergy in ATM-deficient tumour cells.[45,46] This combination is currently in phase II testing in men with CRPC, stratified by presence of DDR alterations [ClinicalTrials.gov identifier: NCT03787680].

Radionuclides

There are preclinical data in neuroendocrine cell lines demonstrating the increased sensitivity to radionuclide therapy following PARP inhibition.[47] Radium-223 dichloride (Ra-223; Xofigo, Bayer) is an alpha emitter that causes double-stranded DNA breaks[48] and has proven efficacy in men with advanced prostate cancer.[49] In a small cohort of men treated with Ra-223, the presence of DDR alterations was associated with

improved and prolonged reduction in alkaline phosphatase,[50] suggesting increased sensitivity in this cohort. The combination of Ra-223 and PARP inhibitors is now being tested in phase I/II trials in men with CRPC and bone-predominant metastases [niraparib (Zejula, GSK) and olaparib] [ClinicalTrials.gov identifiers: NCT03076203 and NCT03317392, respectively].

Prostate-specific membrane antigen (PSMA) can be targeted using lutetium Lu 177 dotatate (^{177}Lu), a strategy that appears promising in men with advanced prostate cancer.[51] ^{177}Lu is a beta emitter that causes a majority of single-stranded DNA damage. The theory that PARP inhibitors can promote double-stranded breaks and enhance activity will be tested in a phase II trial in men with CRPC suitable for PSMA-targeted treatment [ClinicalTrials.gov identifier: NCT03874884].

Radiotherapy

Like radionuclides, radiotherapy exerts a cancer effect by causing DNA strand breaks. The ability of PARP inhibitors to increase radiosensitivity has been demonstrated in a number of preclinical cell-line and xenograft models, including prostate cancer.[52,53] This strategy is now being explored in a phase II trial for men with high-risk nonmetastatic prostate cancer undergoing radiotherapy and androgen-deprivation therapy [ClinicalTrials.gov identifier: NCT04037254]. Importantly, testing PARP inhibition in radical-intent combinations may provide critical data about the potential to improve long-term disease control at the premetastatic stage.

Testosterone

Alternating between castration and supraphysiologic testosterone, so called bipolar androgen therapy, has been shown to cause double-stranded DNA breaks in preclinical settings.[54,55] Clinically, bipolar androgen therapy has provided intriguing preliminary data[56,57] and there are reports of increased sensitivity in men with DDR alterations.[58] This novel strategy will now be tested alongside olaparib in a cohort of men with CRPC post-ARAT, enriched for DDR alterations [ClinicalTrials.gov identifier: NCT03516812].

Conclusion

Data supporting the use of PARP inhibitors in men with prostate cancer are still early, but already, the field is moving on to combination therapies. The strategy for developing combination treatments is currently focused on increasing the utility beyond those with DDR alterations, although strategies to increase the depth and duration of response in men with DDR alterations will also be needed. Removing the requirement for pretreatment testing will remove the barriers posed by technical failures and testing delays; however, treatment effects may be diluted in consequence. There is no doubt that combination treatments will bring increased toxicities and increased costs, so robust clinical trials and meaningful endpoints will be necessary to ultimately justify both the combination and the target population.

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