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Sequences and Combinations of Multifaceted Therapy In Advanced Prostate Cancer

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Abstract

Purpose of Review—Multiple agents with very distinct mechanisms of actions and unique toxicities and efficacies have become available for use in advanced prostate cancer. The next wave of investigations is focused on development of combinations and optimal sequences of the currently available agents. The focus of this review paper is to provide an update on clinical developments in advanced prostate cancer occurring within the past year, and to highlight the ongoing investigations of promising novel targets and compounds.

Recent Findings—The clinical use of enzalutamide prior to chemotherapy, demonstrated improvement in progression free survival (PFS) and overall survival (OS) as compared to placebo in metastatic castrate resistant prostate cancer (CRPC). This report of the PREVAIL trial led to the FDA approval of this agent. Novel agents such as cabozantinib and custirsen that had shown promising results in phase II trials, revealed disappointing results in the phase III setting. The breakthrough report, of the ability of the ARV-7 mutation, detected in circulating tumor cells, to predict lack of response to abiraterone or enzalutamide, and the remarkable responses of poly ADP ribose polymerase (PARP) inhibitors in prostate cancer with BRCA1/2 mutations, have elevated hopes of a bright future in the biomarker driven therapeutic arena.

Summary—As the clinical application of the recently approved multifaceted therapies widens, trials addressing optimal sequences and combinations are gaining importance. In addition, exploring the utility of therapies in the hormone naïve or non-metastatic settings is an area of active investigation. Early use of available agents, optimal sequencing and aid of biomarkers to guide therapeutic choices will make the achievement of lifetime remissions in advanced prostate cancer a reachable goal.

Keywords

Prostate cancer; metastatic; castrate resistant; ARV-7; PARP inhibitors; BRCA-1/2 mutations

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Introduction

Recent advances in systemic therapy have altered the landscape of metastatic prostate cancer. New paradigms of therapy have emerged and as a result, the natural history of prostate cancer is undergoing rapid transformation. The spectrum of presentation of metastatic prostate cancer has broadened considerably. For instance, a patient with prostate specific antigen (PSA) level of 2.0 post radical prostatectomy, with a 1.2 cm supraclavicular lymph node detected on choline PET scan, and a patient presenting with spinal cord compression or urinary obstruction with diffuse metastases, are both similarly categorized as metastatic/ prostate cancer. Most patients with recurrent prostate cancer already are castrate resistant at the time of presentation of metastatic disease, mainly due to use of androgen suppression therapy in the non metastatic disease setting. Symptomatic metastases at presentation are markers of worse prognosis. Early intervention with docetaxel has demonstrated overall survival benefit of a large magnitude [1], especially in the extensive disease patient population. Would the same principle of early intervention be applicable to other therapies such as enzalutamide or abiraterone? Randomized trials are addressing this question. In addition there are other androgen receptor inhibitors such as ARN-509 and ODM-201 that are being evaluated in placebo controlled randomized trials in castrate resistant non metastatic prostate cancer. With the wide range of palliative therapeutic options, the management of prostate cancer has become extremely complex and no evidence is currently available to guide selection of therapy. This has created a dire need for biomarkers to improve the efficiency of the therapeutic sequence, without relying solely on subjective clinical judgement.

Multiple agents with very distinct mechanisms of actions and unique toxicities and efficacies have made the field particularly overwhelming [2-11]. A lot of these changes have also occurred in a very short time interval of the last 3-5 years. Even the multiple reviews written in the last few years are rapidly outdated as more trials get reported. The focus of this review paper is to give a summary of the current clinical perspectives on the indications, pros and cons of the currently approved regimens and delve into future investigations of novel therapies and biomarker testing.

Advances in Chemotherapy

Docetaxel and prednisone is likely to be well established and used in the future in the hormone naïve setting in metastatic prostate cancer [1]. Combination therapies with the addition of novel agents to docetaxel has no proven incremental benefit. A recent report of a phase III trial of the src-1 inhibitor dasatinib or the Southwest oncology Group (SWOG) study 0421 with addition of atrasentan, added to docetaxel revealed no benefit, and comprise some of the many combinations that have failed to demonstrate overall survival (OS) advantage [12-14] (Table 1). Cabazitaxel will most likely be the default front line chemotherapy in the metastatic castrate resistant prostate cancer (mCRPC) setting. The results of the randomized trial comparing every 21 day administration of either cabazitaxel 20mg/m² or 25mg/m² or docetaxel 75mg/m² are awaited. The study will shed light on the relative toxicities and efficacy of two chemotherapy agents; cabazitaxel and docetaxel, currently approved by the Food and Drug administration (FDA) in mCRPC. Combination

studies of cabazitaxel with carboplatin, or custirsen are ongoing. Overcoming chemotherapy resistance has been another area of active research. Clusterin overexpression was reported to be an important mechanism of chemoresistance in metastatic prostate cancer [15]. OGX-011, an antisense inhibitor of clusterin initially demonstrated promising efficacy in combination with docetaxel based chemotherapy. A phase II randomized trial revealed median OS of 23.8 months with the addition of OGX-011 to docetaxel therapy as compared to 16.9 months with docetaxel alone (Table 1) [16]. Phase III trials of docetaxel and cabazitaxel with/without OGX-011 have now completed accrual. The results of the docetaxel based study revealed a disappointing lack of OS benefit (Median OS 23.4 with custirsen arm vs 22.2 months) but the results of the cabazitaxel based study are pending [<http://ir.oncogenex.com/releasedetail.cfm?ReleaseID=842949>].

Immunotherapy

Sipuleucel T has demonstrated OS benefit in the patients with minimally symptomatic/asymptomatic patients with metastatic CRPC [4]. The registration trial randomized mCRPC patients with asymptomatic/minimally disease, to placebo or sipuleucel T. The results revealed an OS benefit favoring the immune therapy (Median OS 25.8months versus 21.7 months) The patients with a PSA of 22ng/ml or less had a prolonged median OS of 41.2 months as compared to that in the placebo arm of 28.3 months. Sipuleucel T is best applied to patients in the early or slowly progressing phases of mCRPC. Other vaccine therapies are being investigated in placebo controlled trials.

Prostavac, a novel immunotherapy, is a PSA-targeted poxviral-based vaccine, administered with three costimulatory molecules (known as TRI-COM) to increase PSA-specific immune responses [17]. The phase I data showed PSA stabilization in 40% of patients. The phase II randomized study enrolled 125 patients and the primary endpoint of progression free survival was similar within both arms. However a 8.5-month improvement in median OS (25.1 months versus 16.6 months) and a 44% reduction in the death rate (HR 0.56, $P = 0.0061$) was noted. Men with visceral metastases, cancer-related pain requiring narcotics, prior chemotherapy or PSA > 7 were excluded. In both the phase I and II studies limited toxicity was noted. A randomized placebo-controlled multicenter phase III trial (PROSPECT) is currently ongoing and will evaluate three arms: ProstVac-VF plus adjuvant GM-CSF, ProstVac-VF plus placebo and placebo-only [ClinicalTrials.gov identifier: NCT01322490]. The primary endpoint of the ongoing study is OS which is appropriate for an immune therapy but will require prolonged follow up and maybe confounded by subsequent treatments.

Immune checkpoint blockade with CTLA-4 inhibition has also demonstrated preclinical efficacy in prostate cancer. Synergistic activity was observed with the combination of radiation therapy and ipilimumab, a CTLA-4 antibody (Table 1). Phase I/II study [18] revealed clinical activity, but the randomized clinical trial demonstrated a large magnitude of increase in toxicity (predominantly diarrhea and fatigue), but did not show any difference in efficacy when compared to the control arm of radiation alone [18]. ADXS-PSA (Advaixis Inc.) is an immunotherapy that delivers PSA antigen to the antigen presenting cells via a live attenuated gram positive bacterial vector. The agent has commenced clinical trials in

combination with a programmed death 1 (PD-1) inhibitor pembrolizumab [<http://www.onclive.com/web-exclusives/Pembrolizumab-Combination-Planned-in-Prostate-Cancer>]. The combination of vaccines with an immune checkpoint inhibitor has strong rationale to enhance efficacy.

Androgen targeted Therapy

Both abiraterone and enzalutamide [8,9] have resulted in a markedly improved radiologic progression free survival (PFS), and a trend towards OS benefit in untreated metastatic castrate resistant prostate cancer. Both these agents attack the androgen-receptor interaction pathway, and demonstrate robust efficacy in advanced prostate cancer. Abiraterone is a CYP-17 inhibitor that suppresses adrenal and tumor microenvironment androgen production and enzalutamide is a competitive antagonist of the androgen receptor. In a placebo controlled double blind randomized trial, 1088 asymptomatic/minimally symptomatic metastatic CRPC patients were treated with either prednisone 5 mg twice daily with or without abiraterone 1000 mg orally daily. Abiraterone therapy doubled the median radiologic PFS to 16.5 months as compared to 8.3 months with patients treated with prednisone [8]. OS also improved with hazard ratio of 0.75 (95% CI, 0.61 to 0.93, $P = 0.01$) leading to the FDA approval of abiraterone, in the pre chemotherapy setting of metastatic CRPC. The results of COU-302 study were updated at the ESMO meeting in September 2014 and the median OS in patients receiving abiraterone and prednisone was 34.7 months as compared to 30.3 months in the placebo and prednisone arm [19]. In October 2013, the results of a similar trial comparing enzalutamide versus placebo, were released [9]. The study, consisting of 1715 randomized patients, was halted early by the independent data and safety reporting committee due to results overwhelmingly favoring the enzalutamide arm. The therapy resulted in a 30% reduction in the risk of death, (hazard ratio=0.70, $p < 0.0001$) and 81% reduction in the risk of radiographic progression (Hazard Ratio=0.19 $p < 0.0001$) [9]. Treatment with enzalutamide resulted in a calculated point estimate for median overall survival of 32.4 months (95% confidence interval, 31.5 months-upper limit not yet reached) versus 30.2 months (95% confidence interval, 28.0 months-upper limit not yet reached) for patients receiving placebo. The promising results and favorable toxicity profiles of both abiraterone and enzalutamide make a strong clinical case for considering either of these medications in the front line treatment of metastatic CRPC. However, the rosy outcomes noted above can also be attributed to the stringent patient selection criteria required on both the trials discussed above. The eligibility consisted of asymptomatic to minimally symptomatic patients, with good/excellent performance status. The abiraterone study did not permit inclusion of patients with visceral metastases whereas the enzalutamide study allowed this. It is noteworthy that this patient population even with metastatic CRPC, was able to stay on therapy with prednisone alone without progression for a median duration of 8.3 months. Chemotherapy would most likely have a similar OS outcome, but with an increased risk of toxicities. The practice of early use of enzalutamide or abiraterone and prednisone has become routine in mCRPC.

An attractive option at present is to sequentially use abiraterone and enzalutamide with the hope of delaying chemotherapy in metastatic CRPC. Unfortunately it appears that these 2 agents used in immediate sequence provide minimal benefit. In addition the potential threat

of encountering neuroendocrine prostate cancer at progression on any of these agents is extremely worrisome. Post docetaxel; the beneficial effects of either abiraterone or enzalutamide are attenuated and with the adoption of chemotherapy in hormone naïve prostate cancer, that is a very likely future scenario in majority of mCRPC patients. This fact underlines the importance of clinical trials of abiraterone and enzalutamide prior to the emergence of castrate resistance. Studies are being conducted to utilize treatments affecting the androgen pathway in the setting of non metastatic disease. This disease state remains an unmet need in prostate cancer and no systemic therapy has shown level 1 evidence of benefit. ARN-509 and ODM-201 are the androgen receptor inhibitors that have ongoing placebo controlled double blind trials.

TAK-700/ Orteronel is an oral, non-steroidal, selective inhibitor of 17,20-lyase, a key enzyme in the production of steroidal hormones [20]. Phase 3 study (C21005) of orteronel plus prednisone compared to placebo plus prednisone in patients with metastatic CRPC following chemotherapy was halted after a pre-specified interim analysis indicating that orteronel plus prednisone was not likely to meet the primary endpoint of improved OS when compared to the control arm (HR 0.894, $p=0.226$). The interim analysis did show an advantage for orteronel plus prednisone for the secondary endpoint of radiographic progression-free survival and no toxicity concerns were seen. (HR 0.755, $p=0.00029$). It is likely that the OS benefit noted was blunted due to crossover of the placebo patients to abiraterone therapy which has a similar mechanism of action or to enzalutamide therapy which also affects the androgen- receptor interaction axis, as both these agents received FDA approval during the trial. Phase III trials are ongoing in hormone sensitive disease (SWOG 1216) and in chemotherapy naïve metastatic CRPC (ELM-PC4). SWOG1014 is a study that evaluates the use of abiraterone and prednisone in the patient population that does not achieve a PSA nadir of 4ng/ml or less on androgen suppression therapy.

Advances in Radiation therapy

External beam radiation therapy has been used for decades for treatment of neuropathic compression and for pain palliation in metastatic prostate cancer. Due to the extensive bone involvement in advanced prostate cancer, radiopharmaceuticals such as strontium-89 and sumarium-43 were introduced to rapidly control multiple sites of pain. However the severe myelosuppressive effects of these agents limited their clinical application. Radium-223 is a therapy that mimics calcium and has selective uptake in the bones. It utilizes alpha particles to decrease the penetration into the marrow and limits the incidence and extent of cytopenias. Alpharadin or radium-223 was evaluated in a placebo controlled phase III trial in docetaxel pretreated or chemotherapy ineligible mCRPC patients [10]. An OS benefit was noted favoring the radium-223 treatment and minimal neutropenia and thrombocytopenias (Grade 3 and 4 incidence of 2% and 6% respectively) were noted. Combination studies of Radium-223 with abiraterone and enzalutamide are ongoing. A global three arm randomized trial evaluating Radium-223 at higher doses (80 Becquerel units/kg as compared to 50 becquerel units/kg) or prolonger administration (12 months versus 6 months) is ongoing.

Therapeutic Options in Untreated Metastatic Prostate Cancer

Conventional androgen suppression therapy remains the mainstay of systemic front line therapies in metastatic prostate cancer. In metastatic prostate cancer, orchiectomy has gradually been replaced by chemical castration methods with LHRH analogue or LHRH antagonists. Interestingly although the addition of anti- androgens to orchiectomy did not seem to add any benefit, combined androgen blockade (addition of anti-androgen) remains superior to LHRH analogue therapy alone.

The final results of the Southwest Oncology Group trial 9346 [21], were reported in 2013. The study randomized metastatic prostate cancer patients to receive either continuous or intermittent androgen suppression therapy. Of the 3040 patients enrolled, 1535 patients (50.4%) were randomized to either continuous (759) or intermittent therapy (770). The hazard ratio of 1.1 (90% confidence interval 0.99, 1.23) revealed that intermittent therapy was not considered non inferior to continuous androgen deprivation therapy. Median survival were 5.8 years and 5.1 years in continuous and intermittent arms respectively. Median OS of extensive disease patients in the intermittent arm was 4.9 years compared with 4.4 years in the continuous arm (HR: 1.02 95% CI (0.85, 1.22). Median OS of minimal disease patients treated intermittently was 5.4 years as compared with 6.9 years for continuously treated patients (HR: 1.19, 95% CI (0.98, 1.43). 1505 patients who were not randomized due to an inability to achieve a nadir PSA of 4 or less, demonstrated a poor clinical outcome with median survival of 1.7 years. This high risk patient population should strongly be considered for early use of docetaxel chemotherapy and for development of novel agents.

The results of the ECOG 3805 (CHAARTED) [1] will drastically change therapeutic sequencing in metastatic prostate cancer. The study evaluated the overall survival benefit of adding docetaxel based chemotherapy to androgen deprivation therapy in metastatic hormone sensitive prostate cancer. The study randomized 790 men with metastatic prostate cancer to receive androgen deprivation therapy +/- 6 cycles of docetaxel chemotherapy. A recent interim analysis of the study revealed that the addition of chemotherapy improved survival outcome, with 3 year OS of 69% with the combination, and 52.5 % with androgen deprivation therapy. Men with extensively metastatic disease (4 or more sites of bone metastases or the presence of liver metastases) were the most likely to benefit from the addition of chemotherapy. The results of this randomized trial will lead us to consider early use of systemic therapies to improve life expectancy. A number of other effective therapies are now being tested in the hormone sensitive metastatic setting. SWOG 1216 is a randomized trial of androgen deprivation +/- TAK-700 in metastatic hormone sensitive prostate cancer. A multicenter phase II study, with the primary endpoint of PSA remission at 7 months is led by our group at Wayne State University. The trial is ongoing with 1:1 randomization to either LHRH analogue + bicalutamide or LHRH analogue + enzalutamide in metastatic hormone sensitive prostate cancer.

Novel Agents with Promising Efficacy in CRPC

Cabozantinib has dual VEGF and c-Met inhibition properties that uniquely fit the current need to delay development of resistance and maintain VEGF inhibition in advanced prostate

cancer. The agent demonstrates the unique phenomenon of effecting complete responses or normalizations of bone scans in metastatic prostate cancer. In the Phase 2 randomized discontinuation study [22], cabozantinib demonstrated exciting clinical activity in men with CRPC. An increase in PFS was observed in the cabozantinib arm compared with placebo (median PFS 23.9 vs 5.9 weeks) with a bone scan response seen in 67% of the patients treated. The results of the phase III trials (COMET-1 and COMET-2) however showed no difference in OS in the pretreated patient population and ended the future development of cabozantinib in prostate cancer [<http://www.exelixis.com/investors-media/press-releases>] (Table 1). Whether biomarkers such as c-MET would be helpful in patient selection and potential benefit from this agent is unknown but needs to be explored.

ARN-509 is a competitive AR inhibitor that is thought to be more potent than Enzalutamide [23]. A phase II study showed that ARN-509 has a very high PSA response rate in treatment naïve CRPC (88%) and it appeared to retain activity in abiraterone pretreated mCRPC with a PSA response rate of 29%. No seizures were reported [23]. The agent is being evaluated in the setting of non-metastatic CRPC, in a double blind placebo controlled randomized trial.

The acceptance of systemic therapy in advanced CRPC is expanding, and the pendulum is shifting towards earlier therapy. The bar is higher and has raised the stakes of our ability to detect an efficacy benefit in an unselected population. Some of the promising novel therapies such as custirsen and cabozantinib have failed to demonstrate an advantage. Combinations of the currently available agents are in clinical trial testing. Alliance trial of abiraterone +/- enzalutamide in metastatic CRPC is rapidly accruing. Numerous trials of combinations with docetaxel continue to be unsuccessful in demonstrating any OS benefit. Targeted therapies, such as atrasentan, aflibercept, and dasatinib [12-14] when combined with docetaxel were associated with no improvement in survival. Multiple other combinations were reported with either no clinical benefit or even an inferior outcome.

Predictive and prognostic Biomarkers

An AR splice variant (ARV-7) was detected to be a reliable marker in metastatic CRPC to predict for lack of response to abiraterone or enzalutamide [24]. ARV-7 detection in circulating tumor cells from men with mCRPC was noted to be associated with resistance to enzalutamide and abiraterone. The presence or acquisition of the ARV-7 mutation was associated with the resistance. The study was conducted in only 31 patients each treated with abiraterone or enzalutamide and needs validation in a larger cohort. In addition the reproducibility of the test needs to be determined and multicenter clinical trial testing is required. BRCA1 or 2 mutations are also known to be predictors of worse prognosis, high grade disease and rapid progression to visceral disease [25]. Conventional chemotherapy is used however the outcome is dismal. In this frustrating disease state, PARP inhibitors [26] have made a major impact with remarkable clinical responses and molecular testing for the BRCA 1 or 2 germline mutation has therapeutic advantage. Olaparib monotherapy demonstrated responses in 4 of 8 patients with mCRPC and was well tolerated with adverse effects of nausea and fatigue. PTEN negativity, c-MET expression, aurora kinase receptors and neuroendocrine markers maybe future targets to be explored.

Conclusions

A number of distinct therapies are now available in management of metastatic CRPC (Figure 1). Since each of these agents were developed in parallel, no comparison trials exist. The cumulative effect of using multiple therapies in sequence is likely to be attenuated and results similar to those seen in clinic trials cannot be realistically expected. The early use of docetaxel is expected to have an impact on the efficacy of abiraterone and/or enzalutamide. Improvement in efficiency of this therapy with use of predictive biomarkers will go a long way towards improving outcomes and reducing cost and decreasing toxicities. Figure 1 summarizes the potential future treatment algorithm for metastatic prostate cancer. Significant strides have been made with a clinically relevant impact on the morbidity and mortality of advanced prostate cancer. The last few years have demonstrated a switch from chemotherapy based regimens to non-chemotherapy options in metastatic CRPC. This has made systemic therapies widely applicable and feasible since even the elderly patients, or those with significant co morbidities can tolerate the treatments. The interspersing and sequencing of the numerous agents now approved for metastatic CRPC requires further study. Development of predictive biomarkers for each of the therapies currently available will reduce costs, enhance outcomes and optimize toxicities.

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Summary

- Multifaceted therapeutic paradigms have emerged as new standards in advanced CRPC.
- Level 1 evidence from a randomized trial (ECOG 3805) suggests that early consideration of docetaxel based chemotherapy in extensive metastatic disease is indicated.
- Without careful patient selection based on a molecular target, future success of novel therapies in mCRPC seems to be in jeopardy.
- Combinations and sequences of existing agents to optimize therapy is an area of active investigation.
- Novel targets and agents continue to be evaluated in this incurable, terminal prognosis disease. Success of PARP inhibitors in BRCA-1 and 2 mutated prostate cancer is a stellar example of the application of genomic testing as a therapeutic guide.

Figure 1.
Contemporary Therapeutic Decision Making in Metastatic Prostate Cancer

Table 1

Results of phase III Clinical trials reported in 2013-2014

Study [Ref]	No of patients	Therapy arms	Endpoint	Hazard ratio (HR)	P value
VENICE [12]	1224	Docetaxel+ prednisone+ aflibercept Vs Docetaxel+ prednisone	Med OS 22.1 mths 21.2 mths	0.94	P=0.38
READY [14]	1522	Docetaxel+ prednisone+ Dasatinib Vs Docetaxel+ prednisone+ placebo	Med OS 21.5 mths vs 21.2 mths	0.99	P= 0.9
SYNERGY [16]	1022	Docetaxel+ prednisone+ custirsen Vs Docetaxel+ prednisone	Med OS 23.4 mths Vs 22.2 mths	0.93	P=0.207
RT+/- ipilimumab [18]	799	SFRT 8Gy Vs SFRT +Ipilimumabx4	Median OS 10 mths Vs 11.2 mths	0.85	P=0.053
COMET-1	950 patients pretreated with docetaxel and abiraterone/ enzalutamide	Cabozantinib Vs prednisone	Med PFS 5.5 mths Med OS 11.0 mths Vs Med PFS 2.8 mths Med OS 9.8 mths	PFS HR 0.5 OS HR 0.9	PFS P<0.0001 and OS P=0.212
COMET-2	119 enrolled out of 246 planned.	Cabozantinib+ prednisone Vs Mitoxantrone+ prednisone	6 and 12 wk Pain response 15% 17%	Not reported	Not reported