Novel treatments for castration-resistant prostate cancer

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Abstract

The contemporary management of metastatic castration-resistant prostate cancer (mCRPC) is evolving dramatically. Understanding the biology of this disease, positive phase III studies and approvals for 4 novel agents in the US in 2010 and shortly in Europe have dramatically changed the therapeutic landscape.

Endpoints in mCRPC

The majority of patients with mCRPC have bone metastases and this may be the only site of measurable disease in up to 70%. Response Evaluation Criteria in Solid Tumors (RECIST) criteria are inadequate for measuring response in prostate cancer trials. Bone scans, in particular, are suboptimal in distinguishing response to therapy and tumour progression. For this reason, the Prostate Cancer Clinical Trials Working Group has defined radiological progression as the development of two or more new lesions on bone scan compared with a prior scan and requires additional confirmation on a subsequent scan [1].

In view of the above, overall survival (OS) is the only accepted endpoint for regulatory purposes in phase III trials. To compensate, several ongoing Phase III trials have incorporated circulating tumour cells (CTCs) into their trial design in order to prospectively validate CTCs as surrogates of response and survival. Isolation of CTCs based on epithelial surface markers and quantification using the CellSearch platform was approved by the FDA in 2008. This was based on a study in 231 mCRPC patients who had received a variety of different treatments [2]. Patients with a CTC count >5 detected in 7.5 ml blood had an OS of 11.5 months (unfavourable), compared to an OS of 21.7 months in patients with CTC < 5 (favourable). On serial CTCs, if patients converted from an unfavourable group to a favourable group on therapy, prognosis was better and similar to those patients that started in the favourable risk group. Similarly, if CTC counts converted from <5 to >5, prognosis was worse than in those who maintained a CTC < 5. Prospective clinical trials incorporating molecular analyses using CTCs are ongoing to better understand tumour biology, identify and validate new biomarkers.

Chemotherapy

In the 1990s, the combination of mitoxantrone plus prednisone (MP) demonstrated palliative benefits in two randomised trials. These trials did not, however, reveal a benefit in OS [3,4]. Docetaxel-based chemotherapy has become the standard since 2004 for the management of mCRPC, based on two additional landmark trials, TAX327 and SWOG-9916 [5,6]. On long-term follow-up of the TAX327 trial, docetaxel every 3 weeks plus prednisone (DP) extended median survival OS to approximately 19 months with a 21% improvement in survival as compared to mitoxantrone and prednisone [7]. Since then, several different biologic agents have been studied in combination with docetaxel and prednisone in attempts to improve efficacy of first line therapy (Table 1). After chemotherapy, approximately 50% of patients go on to receive second-line chemotherapy.

Satraplatin

Satraplatin is a third-generation orally available platinum analogue which was evaluated in a phase III placebo-controlled randomised trial of 950 patients called SPARC (Satraplatin and Prednisone Against Refractory Cancer) [15]. Satraplatin demonstrated a 33% improvement in progression-free survival (PFS) in patients with mCRPC following one prior chemotherapy regimen. Beneficial effects on pain and biologic activity with prostate-specific antigen (PSA) declines and objective responses were likewise observed. Unfortunately, satraplatin and prednisone did not extend median survival as compared to placebo and prednisone. OS was 14.3 months in both groups. This analysis may have been confounded by post-study therapy and good survival in the control arm. The

Table 1
New agents and trials for CRPC pre docetaxel, in combination with docetaxel, and post docetaxel

Pre-docetaxel	Docetaxel +/–	Post-docetaxel
Abiraterone	Dasatinib	Abiraterone [8]
MDV3100 [1]	Atrasentan	MDV3100 [1]
TAK-700	Zibotentan	TAK-700
Sipuleucel-T [9]	Aflibercept	Cabazitaxel [10]
Prostvac-VF [11]	Bevacizumab [12]	Ipilimumab
Zibotentan [13]	Lenalidamide	Sunitinib
Tasquinimod	OGX-011 [14]	
Ipilimumab		

composite endpoint used to evaluate PFS was also questioned by the regulatory authorities.

Cabazitaxel

Cabazitaxel, a novel semi-synthetic taxane which stabilises microtubules as potently as docetaxel, has revealed preclinical activity in both docetaxel sensitive and resistant cell lines. In the TROPIC trial, cabazitaxel plus prednisone was compared to MP for progressive mCRPC following prior docetaxel [10]. In this randomised trial, 755 patients who had received prior docetaxel therapy were randomised between either cabazitaxel 25 mg/m^2 intravenously every 3 weeks (n = 378) or mitoxantrone 12 mg/m^2 every 3 weeks (n = 377). Both groups received prednisone 10 mg daily.

Median survival was prolonged by 30% with cabazitaxel plus prednisone compared to MP (15.1 months vs. 12.7 months; hazard ratio 0.70, $P < 0.0001$). Benefit was observed irrespective of performance status, number of prior chemotherapy regimens, time to progression from prior docetaxel and age. Benefit was obtained even in patients who had progressed during docetaxel therapy. Secondary endpoints also demonstrated improvements with cabazitaxel: PFS 2.8 months vs. 1.4 months, $P < 0.001$; measurable tumour response rate 14.4% vs. 4.4%, $P = 0.005$; PSA response rates 39.2% vs. 17.8%, $P = 0.002$; and time to PSA progression 6.4 months vs. 3.1 months, $P = 0.0010$. Pain response was, however, similar (9.2% vs. 7.7%, $P = 0.6286$). This drug has now been approved both in the USA and Europe.

Myelosuppression was significant in this trial and may have been related to the 25 mg/m^2 dose. Grade $\geqslant 3$ toxicities with cabazitaxel were febrile neutropenia (8% vs. 1%), diarrhoea (6% vs. <1%) and fatigue (5% vs. 3%). Deaths due to adverse events occurred in 5% in the cabazitaxel arm, as compared to 2% in the mitoxantrone arm. A randomised trial is comparing cabazitaxel at 20 mg/m^2 and at 25 mg/m^2 every 3 weeks in combination with prednisone for mCRPC patients previously treated with a docetaxel-containing regimen. 1,200 patients are planned, with OS as the primary endpoint and PFS as the secondary endpoint (clinicaltrials.gov.NCT01308580). Another trial is planned which will attempt to demonstrate the superiority of cabazitaxel plus prednisone at 25 mg/m^2 (Arm A) or 20 mg/m^2 (Arm B) versus docetaxel plus prednisone (Arm C) in terms of OS in 1170 patients with mCRPC not previously treated with chemotherapy (clinicaltrials.gov.NCT01308567).

Immunotherapy

Provenge

Sipuleucel-T (Provenge) is cellular immunotherapy consisting of autologous dendritic cells isolated from peripheral blood mononuclear cells obtained by leukapheresis and activated ex vivo with a recombinant fusion protein composed of prostatic acid phosphatase linked to granulocyte-macrophage colony stimulating factor (GM-CSF). Sipuleucel-T is infused every two weeks for a total of 3 infusions, and is thought to activate host antigen-specific T cells. Three phase III trials of Sipuleucel-T compared to placebo were conducted for patients with metastatic asymptomatic or minimally symptomatic CRPC (D9901, D9902, IMPACT) [9,16,17].

Although not the primary endpoint for D9901 or D9002, analysis of all 3 trials demonstrated a survival benefit. This therapy, approved by the FDA in 2010, has become the first vaccine for advanced solid tumours. The Phase III IMPACT study showed that Sipuleucel-T conferred a 4.1 month survival benefit

over placebo in asymptomatic or minimally symptomatic mCRPC patients without visceral metastasis. Although OS was prolonged, the control arm had an unusually poor survival of 21.7 months, and there was no increase in either PSA response rate or PFS. Lack of availability, especially in Europe, complexity of administration, and cost issues have limited the use of Sipuleucel-T.

PROSTVAC-VF

PROSTVAC-VF is a recombinant vaccinia viral expression cassette engineered to express the human PSA gene and co-stimulatory molecules, followed by a fowlpox virus booster. It was designed to enhance and sustain the host's anti-tumour immune response. A randomised phase II trial compared PROSTVAC-VF to placebo but the company had difficulties in completing the trial, which was finalised by the investigators [11]. The trial did not meet its primary endpoint and time to progression (TTP) was 3.9 months versus 3.7 months. However, there was an 8.5 month OS benefit seen with median OS of 25.1 months versus 16.6 months despite 50% patient crossover to active treatment. This discrepancy between PFS and TTP and OS is similar to what was observed with Sipuleucel-T, and highlights the difficulties in measuring biologic and other responses in prostate cancer perhaps more notably with immunotherapy. Similar to the Sipuleucel-T immunotherapy trial, some suggest that this study may overestimate the OS benefit due to the poorer than expected survival seen in the control arm. A confirmatory phase III trial is planned.

Ipilumimab

Ipilumimab is a human monoclonal antibody that blocks CTLA-4, an inducible receptor expressed by T cells. Two phase III trials are ongoing. One is a randomised, double-blind, phase III trial to compare ipilimumab vs placebo in patients with mCRPC who are asymptomatic or minimally symptomatic, and will include 600 patients (clinicaltrials.gov.NCT01057810). The second trial is a randomised, double-blind, phase III trial comparing ipilimumab vs. placebo following radiotherapy in 800 patients with mCRPC who have received prior docetaxel chemotherapy (clinicaltrials.gov.NCT00861614). Both trials have OS as their primary endpoint.

Bone protecting agents

Zoledronic acid

In a placebo-controlled randomised clinical trial, zoledronic acid 4 mg (15-minute iv infusion every 3 weeks for 15 months) reduced the incidence of skeletal-related events (SREs) and has become the standard of care in patients with mCRPC and bone disease [18]. Fewer patients in the zoledronic acid group than in the placebo group had at least one skeletal related event (SRE) (38% versus 49%, difference –11.0%, 95% confidence interval [CI] = –20.2% to –1.3%; $P = 028$), The median time to the first SRE was 488 days for the zoledronic acid group versus 321 days for the placebo group ($P = 0.009$). Compared with placebo, zoledronic acid reduced the ongoing risk of SREs by 36% (risk ratio = 0.64, 95% CI = 0.485 to 0.845; $P = 0.002$).

Denosumab

A large phase III randomised has demonstrated the superiority of denosumab, a RANK-ligand antagonist, compared to zoledronic acid in the prevention of SREs in men with bone metastases and CRPC [19]. In this phase III study, 1904 patients with mCRPC were randomised between 120 mg subcutaneous denosumab plus iv placebo, or 4 mg iv zoledronic acid plus sc placebo, every 4 weeks. Randomisation was stratified by prior SRE, PSA and chemotherapy within 6 weeks before randomisation. Supplemental calcium and vitamin D were recommended. Median time to first on-study SRE was 20.7 months (95% CI 18.8–24.9) with denosumab compared with 17.1 months (15.0–19.4) with zoledronic acid (hazard ratio 0.82, 95% CI 0.71–0.95; $P = 0.0002$ for non-inferiority; $P = 0.008$ for superiority). Adverse events were recorded in 916 patients (97%) on denosumab and 918 patients (97%) on zoledronic acid, and serious adverse events were recorded in 594 patients (63%) on denosumab and 568 patients (60%) on zoledronic acid. More events of hypocalcaemia occurred in the denosumab group (121 [13%]) than in the zoledronic acid group (55 [6%]; $P < 0.0001$). Osteonecrosis of the jaw occurred in 22 patients (2%) vs 12 patients (1%; $P = 0.09$). The study investigators concluded that denosumab was better than zoledronic acid for prevention of SREs, and potentially represents a novel treatment option in men with bone metastases from CRPC.

Dasatinib

Dasatinib is an oral tyrosine kinase inhibitor with potent activity against SRC and SRC family kinases,

BCR-ABL, platelet-derived growth factor receptor, and c-KIT. In experimental models, inhibition of SRC both has antitumor effects, directly on prostate cancer cells (proliferation and metastasis), and decreases bone turnover. Two different dosage schedules were evaluated in a phase II trial and a phase II expansion trial in patients with mCRPC who had not received prior chemotherapy [20,21]. In these studies, activity was most notable in declines in urinary N-telopeptide and bone-specific alkaline phosphatase. A phase III study known as the READY trial (clinicaltrials.gov.NCT00744497) is evaluating docetaxel plus or minus dasatinib in patients with mCRPC. Another phase II study of dasatinib monotherapy in patients who failed prior chemotherapy (clinicaltrials.gov.NCT00570700) has been completed.

Endothelin A inhibitors

ET_AR has a function in the biology of prostate cancer and osteoblastic lesions. Two oral selective ET_AR antagonists (atrasentan and zibotentan) have been studied. Two randomised, placebo-controlled, phase II and phase III trials of atrasentan in mCRPC have demonstrated significant delays in PSA progression or PSA doubling time (PSADT) and progression in bone biochemical markers (i.e. bone alkaline phosphatase). Both failed to show significant improvements in TTP. A phase III trial is being conducted by the Southwestern Oncology Group (SWOG S0421; clinicaltrials.gov.NCT00134056) that will assess OS and PFS with the combination of atrasentan and docetaxal plus prednisone (Table 1).

Zibotentan was evaluated in a randomised phase II study of 312 patients with CRPC and bone metastases who were pain free or mildly symptomatic. At the final analysis, there were no statistical differences in the primary outcome of TTP among groups. Consistent with the previous analyses for OS, hazard ratios (HRs) were in favour of zibotentan 15 mg (HR, 0.76; 80% CI, 0.61–0.94; $P = 0.103$) and 10 mg (HR, 0.83; 80% CI, 0.67–1.02; $P = 0.254$) compared to placebo [13]. Based on the preliminary results from this trial, 3 large phase III trials were initiated with zibotentan. ENTHUSE 33 (clinicaltrials.gov.NCT00570700) NCT00617669) is similar to the SWOG S0421 trial which investigates whether addition of zibotentan to docetaxel plus prednsione can improve OS in patients with bone metastases (Table 1).

Tasquinimod

Tasquinimod, an oral quinoline-3-carboxamide derivative, binds to the S100A9 protein and displays antiangiogenic properties and antitumor activity in prostate cancer models [22].

In a randomised, double blind phase II study of tasquinimod in patients with asymptomatic to minimally symptomatic mCRPC, disease progression was significantly delayed by tasquinimod. Median PFS was 7.6 months with tasquinimod and 3.2 months for patients treated with placebo ($P = 0.0009$). After 6 months of treatment, 66% of patients in the placebo group had progressed as compared to 31% of patients in the tasquinimod group [23]. A phase III trial comparing tasquinimod to placebo in men with asymptomatic or minimally symptomatic mCRPC was launched this year (clinicaltrials.gov.NCT01234311).

Conclusions

Prostate cancer remains an extremely heterogeneous disease with few surrogate endpoints other than OS upon which drug development has been based. There are clearly more options available today for patients with mCRPC with recent approvals of abiraterone acetate, cabazitazel, denosumab and Sipuleucel-T. Patient selection for second-line cabazitaxel or abiraterone is somewhat challenging, given the similar populations enrolled in these trials. In addition to patient preferences, optimal sequencing, combinations and selection of patients must be based on better understanding of the biology of this disease. Clinical trials should remain a priority.

Conflict of interest statement

The author has an interest in relation with one organisation that could be perceived as a possible conflict of interest in the context of the subject of this abstract. Honoraria: Sanofi-Aventis, Amgen.

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