FEATURE

Two decades in review

Progress in the treatment of mCRPC

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ABSTRACT

Between the mid-1990s and now, median overall survival for men with metastatic castrate resistant prostate cancer (CRPC) starting on chemotherapy has risen from 1 year to almost 3 years. This review summarizes progress made over the last 2 decades in the systemic management of patients with CRPC and evolving treatment directions.

Keywords: Metastatic castration-resistant prostate cancer, androgen deprivation therapy, chemotherapy, androgen receptor antagonist, radiopharmaceutical, immunotherapy, bone-targeted therapy, predictive biomarker

INTRODUCTION

In Canada, it is estimated that 4000 men will die of prostate cancer in 2014, making it the third leading cause of cancer-related death among men.1 When metastatic, the backbone of treatment is androgen deprivation therapy (ADT), typically in the form of either surgical castration or medical castration with a gonadotropin-releasing hormone agonist or antagonist (GnRHa). Initially, most patients achieve durable response with ADT; however, the development of castration-resistant prostate cancer (CRPC) inevitably occurs. Patients with CRPC are a heterogeneous group defined as having castrate levels of testosterone plus 1 or more of: radiographic progression of metastases, clinical progression, and rising serum prostate-specific antigen (PSA) levels.2 Numerous negative prognostic factors have been identified, including: poor patient performance status, presence of pain, presence of visceral metastases, elevated alkaline phosphatase, elevated lactate dehydrogenase, anemia and rapid PSA doubling time.2

In the late 1990s, the median overall survival (OS) for patients with metastatic CRPC starting on first-line chemotherapy was approximately 1 year.3-5 By 2012, trials demonstrated median OS approaching 3 years from time of first chemotherapy.5 Such progress reflects a dramatically altered landscape of clinical care for men with CRPC with the introduction of new systemic therapies with proven ability to improve outcomes (see Figure 1). This review summarizes the progress made over the last 2 decades in the systemic management of patients with CRPC.

CHEMOTHERAPY

The first advance in chemotherapy for CRPC focused on symptom control. Recognizing the advanced age and comorbidities of many patients with CRPC, together with the limited antitumour activity of available agents in the 1990s, Tannock et al initiated a randomized trial to assess the impact of mitoxantrone, a well tolerated anthracycline analogue, looking at pain improvement as the primary endpoint.6

One hundred and sixty-one patients with pain/symptomatic disease were randomized to mitoxantrone plus prednisone vs prednisone alone (of note: the study was not blinded). Twenty-nine percent of patients on the mitoxantrone arm achieved a palliative response (reduction in patient-reported pain scores and/or reduction in analgesic consumption) compared with 12% of those who received prednisone alone (p=0.01). Moreover, the pain response was prolonged, with a median duration of 43 weeks in the experimental arm vs 18 weeks in the control group (p<0.0001). No difference in OS was seen between the 2 groups. This lack of survival improvement with mitoxantrone was confirmed in a subsequent study by Kantoff et al, which assessed OS as the primary endpoint.7

It was not until 2004 that a treatment for CRPC was associated with an OS advantage. (Table 1 lists this and other trials showing OS improvements). The TAX 327 multinational trial randomized 1006 patients with mCRPC to mitoxantrone every 3 weeks, the taxane docetaxel every 3 weeks, or docetaxel weekly for 5 weeks out of 6; all patients received prednisone 10 mg daily and OS was the primary endpoint.8 Patients who received docetaxel every 3 weeks experienced a median OS of 18.9 months, compared to 16.5 months for those who received mitoxantrone, which translates into a 24% reduction in risk of death (HR 0.76 [95% CI 0.62–0.94], p=0.009). In addition, a significantly higher number of patients experienced a reduction in pain in the docetaxel arm compared to the mitoxantrone arm (35% vs 22%, respectively; p=0.01). Significant differences in favour of docetaxel were also seen in reduction of PSA ≥50% from baseline and in quality of life (QOL) improvement.9 The survival advantage with docetaxel-based chemotherapy was confirmed with the simultaneous publication of results from the SWOG 99-16 trial.9 This study...

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compared docetaxel with estramustine against mitoxantrone, with a similar survival advantage observed in favour of the docetaxel-based treatment (HR 0.80 [95% CI 0.67–0.97], p=0.02). These landmark studies established docetaxel chemotherapy as the standard first-line treatment for patients with metastatic CRPC.

In 2010, the TROPIC trial demonstrated the efficacy of cabazitaxel as an effective second-line chemotherapy for progression in the post-docetaxel setting. Like docetaxel, cabazitaxel is a taxane that targets microtubules; it was selected for development due to its activity in docetaxel-resistant cell lines. In the TROPIC study, 755 patients were randomized to cabazitaxel or mitoxantrone given every 3 weeks plus daily prednisone. Cabazitaxel was found to confer a survival advantage of 2.4 months over mitoxantrone (15.1 months vs 12.7 months; HR 0.70 [95% CI 0.59–0.83], p<0.001). Disappointingly, the pain response rate was less than 10% in both arms. Also of concern were the significant adverse events observed with cabazitaxel: 82% of patients experienced grade ≥3 neutropenia (vs 58% with mitoxantrone), 6% had grade ≥3 diarrhea (vs <1% with mitoxantrone), 8% experienced febrile neutropenia (vs 1% with mitoxantrone) and 5% patients died within 30 days of the last dose (vs 2% with mitoxantrone). Subsequent analyses of patients enrolled in phase IV expanded access studies suggested a lower incidence of these serious adverse events, highlighting the importance of patient selection and attentive supportive care.

**HORMONE THERAPY**

Androgen deprivation therapy serves as the primary treatment for metastatic prostate cancer. However, castration resistance occurs in the majority of men through a variety of mechanisms, including increased expression of androgen receptors (AR) and the upregulation of androgen biosynthesis enzymes within tumour cells themselves. As such, research efforts over the last decade have focused on the development of drugs that are more potent at inhibiting the peripheral steroidogenesis pathway in an attempt to further suppress both circulating and intratumoural levels of androgens, as well as more potent antagonists of the AR. Two agents have now entered clinical practice: abiraterone acetate, an irreversible steroidal inhibitor of cytochrome P450 c17 (CYP17), and the novel AR antagonist, enzalutamide.

In 2011, the COU-AA-301 study was published, demonstrating the benefits of abiraterone acetate. A total of 1195 patients previously treated with docetaxel were randomized 2:1 to receive abiraterone acetate plus prednisone or placebo plus prednisone, with OS serving as the primary endpoint. A preplanned interim analysis revealed a median OS of 14.8 months for patients who received abiraterone acetate plus prednisone vs 10.9 months for those who received placebo plus prednisone (HR 0.65 [95% CI 0.54–0.77], p<0.001). Given these results, the independent data and safety monitoring committee (IDSMC) recommended unblinding the study. Time to PSA progression, progression-free survival (PFS), and PSA response rate were all significantly superior in the abiraterone acetate plus prednisone arm. Expected side effects of mineralocorticoid excess (hypokalemia, hypertension, fluid retention) were seen more commonly in patients who received abiraterone acetate, but these were predominantly grade 1 and 2. Of note, aminotransferase elevations were also found to occur with abiraterone acetate.

A subsequent study, referred to as COU-AA-302, assessed the impact of abiraterone acetate on the co-primary endpoints of radiographic PFS and OS in 1088 chemotherapy-naive...
CRPC patients with minimal symptoms. Patients were randomized 1:1 to either abiraterone acetate plus prednisone or placebo plus prednisone. The second planned interim analysis revealed a nearly 2-fold relative increase in radiographic PFS in the abiraterone acetate arm (HR 0.53 [95% CI 0.45–0.62], p<0.001). After a median followup of 22.2 months, OS was not reached for those in the abiraterone acetate arm, yielding a 25% relative reduction in risk of death; however, this did not reach the prespecified statistical significance threshold. Nevertheless, the IDSMC recommended unblinding the study. All secondary endpoints were significantly superior for abiraterone plus prednisone, including time to initiation of cytotoxic chemotherapy (25.2 months vs 16.8 months, respectively; p<0.001).

Enzalutamide is a “next-generation” antagonist of the AR, inhibiting signaling via a number of mechanisms. Similar in design to the COU-AA-301 study with abiraterone acetate, the AFFIRM trial enrolled 1199 patients previously treated with docetaxel and randomized them 2:1 to receive enzalutamide or placebo. After a prespecified interim analysis at 520 deaths, enzalutamide was found to improve survival by 4.8 months over placebo (HR 0.63 [95% CI 0.53–0.75], p<0.001), prompting the IDSMC to recommend halting and unblinding the study. Rates of adverse events were similar between the 2 arms although 5 seizures were reported in the enzalutamide arm (vs none in the placebo arm). The occurrence of seizures related to enzalutamide is postulated to be through inhibition of γ-aminobutyric acid (GABA)-gated chloride channels.

Results of the PREVAIL study presented at the 2014 ASCO Genitourinary Cancers Symposium demonstrated the benefits of enzalutamide in chemotherapy-naïve CRPC patients who were asymptomatic or minimally symptomatic. This study randomized 1717 patients 1:1 to receive enzalutamide or placebo, with co-primary endpoints of radiographic PFS and OS. Treatment with enzalutamide demonstrated a 30% reduction in risk of death (HR 0.70 [95% CI 0.59–0.83], p<0.001) and an 81% reduction in risk of radiographic progression or death (HR 0.19 [95% CI 0.15–0.23], p<0.001) as compared to placebo, corresponding to a median OS of 32.4 months (vs 30.2 months for placebo). Median radiographic PFS was not yet reached (vs 3.9 months for placebo). Importantly, enzalutamide also delayed the median time to cytotoxic chemotherapy by 17 months and delayed the median time to QOL deterioration by 5.7 months. Treatment was well tolerated, with adverse event rates similar to placebo. Two patients, 1 in each arm, experienced a seizure during the trial. The incidence of hypertension and fatigue appeared to be increased in the enzalutamide arm.

**IMMUNOTHERAPY**

Enhancing the immune response against cancer cells has been the focus of extensive research in prostate and other cancers. The autologous active cellular immunotherapy sipuleucel-T is the first therapeutic cancer vaccine to demonstrate OS benefit. Sipuleucel-T involves the reintroduction of a patient’s own autologous peripheral-blood mononuclear cells (PBMCs), including antigen-presenting cells (APCs), that have been activated ex vivo with a recombinant fusion protein consisting of prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor. The IMPACT trial enrolled 512 asymptomatic or minimally symptomatic patients with mCRPC and randomized them 2:1 to receive either sipuleucel-T or placebo (untreated PBMCs). Sipuleucel-T therapy was associated with a median 4.1 months improved OS (HR 0.78 [95% CI 0.61–0.98], p=0.03). However, this survival benefit did not translate into any other clinical benefits as responses were rare (one partial radiologic response; PSA decline >50% in 2.6% vs 1.3% with placebo) and there was no difference in terms of time to objective or clinical disease progression compared to placebo.

**RADIOPHARMACEUTICALS**

Bone metastases are a major contributor to both morbidity and mortality in mCRPC, and bone-targeted agents have been the focus of a substantial body of research. Radiotherapeutics are one facet of such treatment, with a variety of radioisotopes studied over the years. One such agent, strontium-89, is a beta-emitting radioisotope that has been evaluated in numerous trials of men with mCRPC metastasized to the bone and has been shown to provide

**TABLE 1. Phase III studies of agents showing OS benefit in patients with metastatic CRPC**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Class</th>
<th>Setting</th>
<th>Agent</th>
<th>Control</th>
<th>mOS improvement (months)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX 327†</td>
<td>chemotherapy</td>
<td>mCRPC, chemo-naive</td>
<td>docetaxel</td>
<td>mitoxantrone</td>
<td>2.4</td>
<td>0.76</td>
</tr>
<tr>
<td>TROPIC</td>
<td>chemotherapy</td>
<td>mCRPC, post-docetaxel</td>
<td>cabazitaxel</td>
<td>mitoxantrone</td>
<td>2.4</td>
<td>0.70</td>
</tr>
<tr>
<td>COU-AA-301</td>
<td>androgen biosynthesis inhibitor</td>
<td>mCRPC, post-docetaxel</td>
<td>abiraterone</td>
<td>prednisone</td>
<td>4.6</td>
<td>0.74</td>
</tr>
<tr>
<td>COU-AA-302</td>
<td>androgen biosynthesis inhibitor</td>
<td>mCRPC, post-docetaxel</td>
<td>abiraterone</td>
<td>prednisone</td>
<td>5.2</td>
<td>0.79</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>androgen receptor signaling inhibitor</td>
<td>mCRPC, post-docetaxel</td>
<td>enzalutamide</td>
<td>placebo</td>
<td>4.8</td>
<td>0.63</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>androgen receptor signaling inhibitor</td>
<td>mCRPC, post-docetaxel</td>
<td>enzalutamide</td>
<td>placebo</td>
<td>2.2</td>
<td>0.70</td>
</tr>
<tr>
<td>IMPACT</td>
<td>immunotherapy</td>
<td>mCRPC, +/- chemo</td>
<td>sipuleucel-T</td>
<td>placebo</td>
<td>4.1</td>
<td>0.78</td>
</tr>
<tr>
<td>ALSYMMA</td>
<td>radiopharmaceutical</td>
<td>mCRPC, +/- chemo</td>
<td>radium-223</td>
<td>placebo</td>
<td>3.6</td>
<td>0.70</td>
</tr>
</tbody>
</table>
symptomatic benefit with no effect on survival.30,34 Recently, the TRAPEZE trial evaluated 757 patients treated with either docetaxel alone or docetaxel with strontium-89, zoledronic acid, or both.35 On multivariate analysis, strontium-89 was found to offer modest improvement on clinical PFS, however no impact on OS was observed. Other agents, such as complexes containing samarium-153, rhenium-186, and rhenium-188, have also been found to provide palliative benefit.24,26,27 Overall, the propensity for causing myelosuppression and the lack of survival benefit with beta-emitting radiopharmaceuticals has resulted in limited enthusiasm for this class of agents.28

Conversely, alpha-emitting radiopharmaceuticals, such as radium-223, are able to deliver high-dose energy over a short range, resulting in a more favourable toxicity profile.29 Radium-223 dichloride was compared to placebo in the ALSYMPCA trial, with 921 men with mCRPC randomized in a 2:1 fashion.30 All patients had symptomatic bone metastases and were docetaxel pretreated or considered docetaxel-ineligible. Presence of visceral metastases or lymph node metastases >3 cm in size were exclusion criteria. Analysis after 528 deaths demonstrated a 3.6-month survival advantage for radium-223 over placebo (HR 0.70 [95% CI 0.58–0.83], p<0.001). All secondary endpoints also favoured radium-223, including time to first symptomatic skeletal event (15.6 vs 9.8 months, respectively; p<0.001). Notably, rates of myelosuppression were acceptable, with grade 3–4 neutropenia and thrombocytopenia occurring in <5% of patients, although there was 1 death from thrombocytopenia. There was also an increased incidence of diarrhoea, as radium-223 is excreted into the intestine, but this was predominantly grade 1 or 2. Numerous ongoing trials are now exploring the use of radium-223 at higher doses, longer durations, and in combination with other agents shown to be effective in prolonging survival in mCRPC. (clinicaltrials.gov identifiers: NCT02023697; NCT01106352; NCT02043678; NCT01934790).

**BONE-TARGETED THERAPY**

Complications of bone metastases in men with mCRPC are a cause of substantial morbidity. Bisphosphonates such as clodronate, pamidronate, and zoledronic acid have been studied extensively in this setting. Clodronate both as a single agent and in combination with mitoxantrone has not been found to offer clear benefit.31,32 Likewise, pamidronate has not demonstrated advantages in terms of improving pain control or decreasing skeletal related events.33

A skeletal-related event (SRE) is a composite endpoint (defined as the development of pathologic fracture, spinal cord compression, or radiotherapy or surgery to bone) used to assess efficacy with bone-targeted agents. The first randomized, phase III trial showing a reduction in SREs with the use of zoledronic acid in patients with mCRPC was reported in 2002.34 Followup analyses 2 years later revealed that significantly fewer patients suffered bone complications after treatment with zoledronic acid and showed an almost 5-month prolongation in time to first SRE. There was also a reduction in the more clinically meaningful endpoint of symptomatic skeletal event rate (defined as a SRE not identified as an incidental finding on routine imaging) in patients receiving 4 mg zoledronic acid compared with placebo (30% vs 41%, respectively; p=0.019).35 Another study found that the cumulative incidence of radiotherapy required for bone pain was decreased significantly by 33% in patients treated with zoledronic acid compared to placebo.36

Denosumab is a humanized monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL), a key mediator in osteoclast-driven bone destruction in the setting of bone metastases. A recent trial in men without prior intravenous bisphosphonate use demonstrated denosumab to be both noninferior and superior to zoledronic acid in delaying time to first SRE (HR 0.82 [95% CI 0.71–0.95], p=0.0002 for noninferiority, p=0.008 for superiority).37 In the nonmetastatic setting, denosumab was shown to extend bone metastasis-free survival by 4.2 months (p=0.028) and median time to first bone metastasis by 3.7 months (p=0.032) compared to placebo.38 However, weighing the degree of benefit against the increased risk of osteonecrosis of the jaw and hypocalcaemia with denosumab, the US Food and Drug Administration (FDA) rejected an expanded indication for denosumab.

**FUTURE DIRECTIONS**

Progress continues on a number of fronts and a large number of clinical trials are underway. Combinations of the newer agents now in use are being evaluated in several studies. In phase III, a combination of enzalutamide and abiraterone is being compared to enzalutamide alone in a study sponsored by the Alliance Cooperative Group (NCT01949437). Another phase III study is comparing abiraterone acetate in combination with radium-223 to abiraterone acetate alone (NCT02043678).

Therapeutics employing novel mechanisms of action are also in phase III testing. Cabozantinib (XL-184) is an inhibitor of multiple receptor tyrosine kinases, including c-MET and vascular endothelial growth factor receptor (VEGFR). Promising phase II results demonstrating cabozantinib effects on decreasing serum markers of bone turnover, bone scan improvements, and pain improvements in patients with CRPC have led to phase III studies evaluating whether cabozantinib imparts a survival advantage (NCT01605227) or leads to improved pain benefits (NCT01522443) in patients previously treated with docetaxel and abiraterone acetate or enzalutamide.39

The oral second-generation quinoline-3-carboxamide analog, tasquinimod, was shown to impede tumour angiogenesis and enhance the efficacy of ADT, radiotherapy and taxanes in prostate cancer animal models. The specific targets within the molecular machinery that it targets, however, remain to be conclusively identified.40 Its possible utility was highlighted in a randomized phase II trial where men with minimally symptomatic mCRPC derived over a 2-fold increase in median PFS and an OS benefit of 33.4 months for tasquinimod vs 30.4 months for placebo (HR 0.87 [95% CI 0.46–1.17], p=0.049). Multivariate analysis further supported a survival benefit in favour of tasquinimod.
(adjusted HR 0.64 [95% CI 0.42–0.97], p=0.034).41,42 Investigation of tasquinimod vs placebo is currently ongoing in a phase III trial (NCT01234311).

A different strategy of immunotherapy is the utilization of virus-based vaccines to enhance the immune response against prostate cancer cells. PROSTVAC-VF is one such agent that contains vaccinia and fowlpox viral vectors leading to the expression of PSA and an immune-stimulating product called TRICOM. In a phase II trial in the mCRPC setting, there was no difference between PROSTVAC-VF and the control arm in the primary endpoint of PFS; however, long-term followup revealed a survival benefit of 8.5 months for those who received the vaccine (HR 0.56 [95% CI 0.37–0.85]).41 A randomized, placebo-controlled phase III trial with PROSTVAC-VF looking at a primary endpoint of OS in asymptomatic or minimally symptomatic men is ongoing (NCT01322490).

Along with investigations into new therapeutics, studies are underway to address the development of predictive markers to help individualize and optimize therapy. Efforts at molecular characterization of mCRPC tissues from biopsies and blood-based markers such as circulating tumour cells or circulating tumour DNA are at an early stage, but have already had some early promising results, showing that the presence of AR gene amplification, splice variants and mutations are correlated with negative treatment outcomes.44-46

CONCLUSION

The management of mCRPC has evolved substantially over the past 20 years (Figure 2). Incremental improvements in survival have been achieved with chemotherapy in the form of docetaxel and cabazitaxel, disruption of androgen receptor signaling with abiraterone acetate and enzalutamide, harnessing the immune response with sipuleucel-T, and targeting bone disease with the radiopharmaceutical radium-223. Morbidity has been improved through a reduction in symptomatic skeletal event rates with zoledronic acid and denosumab.

Without minimizing the importance of any of these advances, it must still be recognized that none of these treatments are curative and not all patients will respond. Also, given the age and comorbidities of the patient population with CRPC, issues of symptom control, side effects and quality of life may be of paramount importance, over and above survival, for many patients. Despite the successes of the past 2 decades, several agents have not met their primary endpoints in phase III trials. In particular, strategies to improve docetaxel efficacy by combining it with a targeted therapy have all been negative in phase III trials.47-54 Nevertheless, several promising new agents directed against key drivers in prostate cancer progression are under investigation.

Practicing clinicians are now challenged to incorporate these therapeutic choices into the management of an individual patient given the diverse mechanisms of action, differing toxicities, and different constellations of demonstrated benefits. Also complicating matters is the fact that many of these agents have been evaluated in relative isolation from each other and compared primarily to placebo. It is not a foregone conclusion that the benefits will be additive or at the very least retained when different therapies are sequenced. Furthermore, the optimal time to start a particular treatment during a patient’s disease course is still not known due to the heterogeneity of the disease. Clinical trials designed to achieve regulatory approval do not always help to answer these questions. For now, practical matters such as patient preference, drug toxicity profile and access will dictate treatment selection and sequencing, but as our ability to molecularly characterize mCRPC tissues advances, we will move closer to precision medicine and a personalized approach.44-46

References:


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