Rapidly changing landscape of systemic therapy for castration-resistant prostate cancer

HOT SPOT

By Urban Emmenegger, MD, Medical Oncologist and Clinician Scientist,
Sunnybrook Odette Cancer Centre and Research Institute, University of Toronto

Castration-resistant prostate cancer (CRPC)

Prostate cancer is commonly diagnosed at a localized stage. However, despite curative treatment attempts (i.e., surgery, radiation therapy ± [neo]adjuvant androgen deprivation therapy), around 25% of patients will develop recurrent disease and subsequent metastasis, especially to bones. The latter is a major contributing factor in CRPC-associated morbidity. While initially almost all patients with advanced prostate cancer benefit from androgen deprivation therapy, resistance to such treatment (i.e., CRPC) will eventually develop in most cases. Prior to 2010, evidence-based therapies of CRPC were severely limited (Table 1).

Treatment options for chemotherapy-naïve CRPC

- Various **second-line hormonal therapies** (e.g., antiandrogens, corticosteroids, ketoconazole and estrogens) can palliate CRPC-associated symptoms and induce transient responses that usually last a few months in a subgroup of patients. However, there is a lack of definitive data showing the impact of such therapies on overall survival.
- Novel hormonal agents such as abiraterone (an androgen synthesis inhibitor) and MDV3100 (a high-affinity antiandrogen) are currently being tested in randomized phase III trials to assess their impact on overall survival in chemotherapy-naïve CRPC (Table 2).
- **Sipuleucel-T** is a preparation of peripheral blood mononuclear cells activated with a fusion-protein of prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor. This autologous cellular immunotherapy prolonged the median overall survival of mostly chemotherapy-naïve CRPC patients by 4.1 months, despite it having no impact on progression-free survival (Kantoff et al., 2010). Aside from infusion-associated adverse effects such as chills, pyrexia and headache, sipuleucel-T is generally very well tolerated. On April 29, 2010, the U.S. FDA approved sipuleucel-T for the treatment of asymptomatic or minimally symptomatic metastatic CRPC. However, sipuleucel-T is not yet approved in Canada.

Therapies for bone-metastatic CRPC

- Compared to placebo, intravenous **zoledronic acid** administration has been shown to significantly reduce the number of skeletal-related events (SRE; 38% versus 49%), and to delay the median time to first SRE (488 versus 321 days), in asymptomatic or mildly symptomatic CRPC patients with bone metastases (Saad et al., 2004).
- **Denosumab** is a neutralizing antibody against receptor activator of nuclear factor kappa B ligand (RANKL), a central mediator of osteoclast formation and function. This subcutaneously administered agent significantly reduced the rate of SRE (by 18%) and increased the median time to first SRE (20.7 versus 17.1 months) compared to zoledronic acid treatment, as recently reported at the 2010 ASCO Annual Conference. The U.S. FDA approved denosumab for the prevention of SRE in patients with bone metastases from solid tumours, including CRPC, on November 18, 2010.

First-line chemotherapy of CRPC

Numerous chemotherapeutic agents of different functional classes have been evaluated in CRPC. Mitoxantrone (combined with prednisone) was approved for the treatment of CRPC due to superior symptom palliation compared to prednisone alone, but without improving overall survival.

- **Docetaxel** (75 mg/m^2 IV every three weeks) was the first chemotherapeutic agent shown to provide an overall survival benefit in CRPC (19.2 months versus 16.3 months in patients receiving mitoxantrone) (Berthold et al., 2008). Docetaxel plus prednisone was also superior to mitoxantrone with respect to pain responses and to improvements in quality of life (seen in >30% and >20% of patients, respectively). Docetaxel has become the first-line chemotherapy standard of care for CRPC. Toxicities include neutropenia (32% grade 3/4, 3% febrile neutropenia), fatigue (53%), nausea/vomiting (42%) and neuropathy (30%).
- Weekly administration of docetaxel reduces the risk of neutropenia (2% grade 3/4) without compromising palliation. However, the weekly docetaxel regimen does not provide a significant survival benefit compared to mitoxantrone.

Table 1. Approved therapies for castration-resistant prostate cancer (CRPC)

Agent	Year of approval	Basis for approval
Mitoxantrone (Novantrone®)	1996	superior palliation of symptomatic CRPC compared to prednisone alone
Zoledronic acid (Zometa®)	2002	reduction and delay of skeletal-related events in asymptomatic or minimally symptomatic, bone-metastatic CRPC
Docetaxel (Taxotere®)	2004	survival benefit in CRPC
Sipuleucel-T (Provenge®)	2010	survival benefit in asymptomatic or minimally symptomatic metastatic CRPC*
Cabazitaxel (Jevtana®)	2010	survival benefit in CRPC previously treated with docetaxel*
Denosumab (Xgeva®)	2010	reduction and delay of skeletal-related events in CRPC*

**U.S. FDA approved, Health Canada approval pending*

Table 2. Phase III clinical trials of metastatic CRPC

Expected reporting	Pre-chemotherapy	First-line therapy	Second-line therapy
2012		Zibotentan* Aflibercept* Dasatinib*	MDV3100 Ipilimumab
2013		Lenalidomide* Radium-223*	Custirsen* Orteronel
2014	Abiraterone MDV3100 Orteronel	Atrasentan* Custirsen*	
2015	Ipilimumab	Cabazitaxel**	Cabazitaxel**

** plus docetaxel versus docetaxel monotherapy; ** 20 mg/m^2 and 25 mg/m^2 treatment arms*

- Docetaxel chemotherapy is usually reserved for the treatment of patients with high disease burden, with signs of rapid disease progression, and/or with CRPC-associated symptoms.
- Attempts at combining docetaxel with other cytotoxic agents, or with targeted agents, have thus far failed to show a benefit in terms of overall survival or of palliation.

Post-docetaxel CRPC therapies

While it is a common practice to interrupt docetaxel chemotherapy after 10 cycles to limit chronic toxicities such as neuropathy, selected patients (e.g., those with prior response to docetaxel that remain progression-free for > 3 months following docetaxel therapy) may benefit from **retreatment with docetaxel**. Alternatively, a number of cytotoxic (e.g., mitoxantrone) and hormonal agents have been evaluated in CRPC patients with docetaxel-refractory CRPC, or in patients with docetaxel intolerance. However, positive phase III trial data for the treatment of post-docetaxel CRPC have become available only with the recent publication in *The Lancet* of the findings of the TROPIC trial (de Bono et al., 2010), and the presentation of the results of the post-docetaxel use of abiraterone during the 2010 ESMO Annual Conference.

Cabazitaxel: Second-line chemotherapy of CRPC

- In the TROPIC trial, 755 men with progressive CRPC after docetaxel-based first-line chemotherapy were 1:1 randomized to receive either cabazitaxel (25 mg/m^2 IV) or mitoxantrone every three weeks, each combined with prednisone.
- Cabazitaxel was significantly superior to mitoxantrone with respect to median overall survival (15.1 versus 12.7 months, hazard ratio 0.7, p<0.0001), progression-free survival (2.8 versus 1.4 months, hazard ratio 0.74, p<0.0001), PSA response rate (39.2% versus 17.8%) and tumour response rate (14.4% versus 4.4%).
- The pain response rate was 9.2% in the cabazitaxel arm compared to 7.7% in mitoxantrone treated patients. Thus, it appears that the palliative impact of second-line chemotherapy is generally inferior compared to the first-line treatment setting.
- The most common grade 3/4 side effects of cabazitaxel were hematological (neutropenia rate 82%) and diarrhea (6%). This may explain the febrile neutropenia rate of 8%, a major contributor to treatment-associated mortality (cabazitaxel 5% versus mitoxantrone 2%).
- The TROPIC trial showed for the first time a clinically meaningful survival benefit in second-line therapy of CRPC. In addition, this study also provided phase III trial evidence for the limited activity of second-line mitoxantrone therapy.
- On June 17, 2010, the U.S. FDA approved cabazitaxel for the treatment of post-docetaxel CRPC, mandating the initiation of post-marketing phase III trials of first-line cabazitaxel versus docetaxel, and of two cabazitaxel dose-levels (20 mg/m^2 versus 25 mg/m^2) in the post-docetaxel CRPC setting.
- Studies combining cabazitaxel with abiraterone or with MDV3100 are under consideration.
- Pending approval by Health Canada, cabazitaxel is being made available through early access programs (NCT01254279).
- Close monitoring of the occurrence of neutropenia is recommended in order to guide potential G-CSF use and/or cabazitaxel dose modifications. Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features such as age > 65, poor performance status and extensive prior radiation (US product monograph).

Abiraterone: Hormonal therapy of post-docetaxel CRPC

- Abiraterone is an inhibitor of CYP17 (also known as 17α-hydroxylase/17,20-lyase), a central enzyme in the testosterone/androgen synthesis pathway.
- In the COU-AA-301 study, 1,195 men that had failed one or two chemotherapy regimens for CRPC were randomized 2:1 to receive either abiraterone acetate (1000 mg po od, combined with prednisone 5 mg po bid), or placebo and prednisone.
- In August 2010, the Independent Data Monitoring Committee recommended the unblinding of the study based on the results of the pre-planned interim analysis.
- Compared to placebo, abiraterone significantly improved overall survival (14.8 versus 10.9 months, hazard ratio 0.646, p<0.0001), PSA (10.2 versus 6.6 months), as well as radiological (5.6 versus 3.6 months) progression-free survival, and PSA responses (29.1% versus 5.5%).
- Abiraterone is generally well tolerated. Grade 3/4 abiraterone-associated side-effects (all <5%) involve fluid retention, hypokalemia, hepatotoxicity, arterial hypertension and unspecified cardiac complications.
- Approval of abiraterone by the U.S. FDA is expected in 2011.

Both the TROPIC and COU-AA-301 trial are considered practice-changing studies for the treatment of post-docetaxel CRPC. In the absence of predictive markers of response to cabazitaxel and abiraterone, patient characteristics and patients' preferences will determine the extent and manner by which the results of these two trials will be incorporated into current CRPC treatment patterns. In addition, drug accessibility and funding are expected to impact on the use of these agents in Canada.

Outlook

The number of approved agents for the treatment of CRPC has doubled in the last few months (Table 1). Aside from clinical trials of cabazitaxel and abiraterone in indications other than post-docetaxel CRPC, a number of promising agents are in advanced clinical testing for various CRPC disease stages (Table 2). They include MDV3100, the novel androgen synthesis inhibitor orteronel, endothelin receptor antagonists (atrasentan, zibotentan), the SRC inhibitor dasatinib, antiangiogenic and/or immunomodulating molecules (aflibercept, lenalidomide, ipilimumab), custirsen (antisense oligonucleotide targeting the heat-shock protein clusterin), and a novel radioisotope (radium-223) (Di Lorenzo et al., 2010).

The sequential or combinatorial use of the growing number of available anti-CRPC agents is expected to significantly improve the life expectancy of CRPC patients. Some of these drugs are also likely to be evaluated for their curative potential in early prostate cancer. Overall, the recently approved agents represent a significant step forward. Indeed, a couple of years ago few would have predicted that we soon might have an embarrassment of riches in terms of agents at hand for the treatment of CRPC.

References

Berthold, D.R., Pond, G.R., Soban, F., de Wit, R., Eisenberger, M., & Tannock, I.F. (2008). Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: Updated survival in the TAX 327 study. *J Clin Oncol., 26*, 242–5.

de Bono, J.S., Oudard, S., Ozguroglu, M., et al. (2010). Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. *Lancet, 376*, 1147–54.

Di Lorenzo, G., Buonerba, C., Autorino, R., De Placido, S., & Sternberg, C.N. (2010). Castration-resistant prostate cancer: Current and emerging treatment strategies. *Drugs, 70*, 983–1000.

Kantoff, P.W., Higano, C.S., Shore, N.D., et al. (2010). Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med., 363*, 411–22.

Saad, F., Gleason, D.M., Murray, R., et al. (2004). Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst., 96*, 879–82.

Generously supported by an unrestricted educational grant from Sanofi-Aventis

sanofi aventis

Because health matters