New treatments improve quality of life and survival in castrate-resistant prostate cancer

HOT SPOT

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What is CRPC?

Androgen deprivation therapy (ADT) is commonly prescribed for men with recurrent, progressive, or metastatic prostate cancer that is androgen sensitive. The American Society of Clinical Oncology published recommendations for the management of men in this disease state in 2004 (Loblaw, Mendelson, Talcott, et al., 2004), updating these recommendations in 2007 (Loblaw, Virgo, Nam et al., 2007).

Many men with androgen-sensitive disease on ADT will have biochemical, radiographic and/or symptomatic progression despite castrate levels of testosterone (< 50 ng/ml or < 1.7 nmol/L). This state is now referred to as castrate-resistant prostate cancer (CRPC) (Scher & Heller, 2000). The prevailing theory is that CRPC cells make their own intracellular testosterone, which then drives cell growth (Sharifi, McPhaul, & Auchus, 2010).

Patients can be divided into those with biochemical recurrence and no evidence of metastases (M0 CRPC) and those with metastatic disease (M1 CRPC). One often differentiates the latter group into asymptomatic (M1a CPRC) and symptomatic metastatic disease (M1s CPRC), as the onset of symptoms usually prompts consideration of systemic chemotherapy. Most patients progress sequentially through the CRPC states although depending on the frequency of follow-up, the biology of the patient's disease and the frequency of restaging, a patient on ADT can present in any of these states.

The goal of treatment for men with CRPC is palliative (i.e., symptom relief or prevention) although docetaxel has also been shown to improve overall survival (Petrylak, Tangen, Hussain, et al., 2004; Tannock, de Wit, Berry, et al., 2004) and quality of life (Tannock, de Wit, Berry et al., 2004) in men with M1 CRPC. Abiraterone acetate, cabazitaxel, and sipuleucel-T have all recently been reported to also improve overall survival (de Bono, Logothetis, Molina, et al., 2011; de Bono, Oudard, Ozguroglu, et al., 2010; Kantoff, Higano, Shore, et al., 2010).

An overview is provided here of the management of M1s CRPC. Bone-targeted therapies (such as bisphosphonates and RANK-ligand inhibitors) improve skeletal-related events (SREs) in men with M1 CRPC (Saad, Gleason, Murray, et al., 2004; Fizazi, Carducci, Smith, et al., 2011), but their review is outside the scope of this paper. Alpharedin is a radionucleotide that has been shown to improve survival and SREs in men with M1s CRPC pre- and post-docetaxel, but will be covered in another review (Parker, Heinrich, O'Sullivan et al., 2011).

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Abiraterone acetate

Abiraterone acetate (AA—Zytiga™) is a synthetic cyp-17 inhibitor that interferes with steroidogenesis. The pivotal trial showing the benefit of AA enrolled 1,185 patients from multiple countries with progressive M1s CRPC and at least one course of chemotherapy, which included docetaxel (de Bono, Logothetis, Molina, et al, 2011). Patients were randomized 2:1 to AA 1000 mg po OD + prednisone 5 mg po BID (n = 797) or placebo + prednisone (n = 398).

After a median follow-up of 12.8 months, the study's primary endpoint, overall survival (OS) was greater in patients randomized to the AA arm (median OS 14.8 versus 10.9 months, HR 0.65, $p < 0.001$). All secondary objectives were also improved in the AA arm including: time to PSA progression (median 10.2 mo versus 6.6 mo, HR 0.58, $p < 0.001$); time to radiographic progression (5.6 mo versus 3.6 mo, HR 0.67, $p < 0.001$); PSA response (29% versus 6%, $p < 0.001$); and objective response (14% versus 3%, $p < 0.001$). Exploratory outcomes also favoured of the use of the drug: skeletal-related events (SRE) were also observed in (25% percentile time to SRE: 9.9 mo versus 4.9 mo, HR 0.64), as was global and prostate-specific quality of life. Pain endpoints were more difficult to evaluate due to censoring. Nonetheless, pain palliation and time to pain progression were in favour of abiraterone.

Considering the patients recruited to this study, the drug was generally well tolerated. The main toxicities observed in the AA arm versus placebo arm were: hypokalemia (17% versus 8%), hypertension (10 % versus 8%), peripheral edema (31% versus 22%), abnormal liver function (10% versus 8%) and cardiac disorders (13% versus 11%) (de Bono, Logothetis, Molina, et al, 2011). Overall, withdrawal due to adverse events was lower than placebo randomized patients. Overall, grade 3 and 4 adverse events were similar between both groups (there was no more than 10% G3/4 toxicity reported in both arms).

Abiraterone acetate is now Health Canada approved for the treatment of men with CRPC post-docetaxel. Currently it is being considered for reimbursement through the Ontario Committee to Evaluate Drugs (CED) pathway. In the meantime (until February 1, 2012), Janssen is sponsoring a Zytiga access program where the drug is given free of charge to patients who qualify for the indication. Physicians can contact their local Janssen representative. Patients enrolled in the program will have the drug supplied under the auspices of this program until there is evidence of progressive disease.

Cabazitaxel

Cabazitaxel (Jevtana™) is a compound similar to docetaxel (a microtubule inhibitor in the taxane family of drugs), but was selected for its high cytotoxicity and low affinity for the multidrug resistance protein, p-glycoprotein. The pivotal trial investigating the use of cabazitaxel had the acronym "TROPIC" (de Bono, Oudard, Ozguroglu, et al., 2010). Patients with disease progression during or after completion of treatment with docetaxel were randomized to receive cabazitaxel (n = 378) or mitoxantrone (n = 377). Patients were excluded if they had previous mitoxantrone therapy, radiotherapy to 40% or more of bone marrow, or cancer therapy other than luteinizing-hormone-releasing hormone within four weeks of enrolment.

The primary outcome of the study was OS. After a median follow-up of 12.8 months, there was a significant difference in OS in favour of cabazitaxel compared to mitoxantrone (median, 15.1 mo versus 12.7 mo; HR 0.70, $p < 0.0001$). There were also a number of secondary analyses that favoured cabazitaxel over mitoxantrone: progression-free survival (2.8 mo versus 1.4 mo, HR 0.74, $p < 0.0001$); time-to-tumour-progression (8.8 mo versus 5.4 mo, HR 0.61, $p < 0.0001$); time-to-PSA-progression (6.4 mo versus 3.1 mo, HR 0.75, $p = 0.001$); objective tumour response (14% versus 4%, $p = 0.0005$); and PSA response (39% versus 18%, $p = 0.0002$) (de Bono, Oudard, Ozguroglu, et al., 2010). Quality of life outcomes were not reported by the

authors, but pain scores were recorded. There was no significant difference in time to pain progression (11.1 mo versus median not reached, HR 0.91, p=0.52) and pain response (9.2% versus 7.7%, p=0.63).

The following adverse events (any grade) were reported in more than 10% of patients in either arm: diarrhea (47% versus 11%, cabazitaxel versus mitoxantrone, respectively), fatigue (37% versus 27%), asthenia (20% versus 12%), back pain (16% versus 12%), nausea (34% versus 23%), vomiting (23% versus 10%), hematuria (17% versus 4%), abdominal pain (12% versus 4%), dyspnea (12% versus 5%), constipation (20% versus 15%), pyrexia (12% versus 6%), and arthralgia (11% versus 8%). The following hematological adverse events (any grade) were reported: neutropenia (94% versus. 88%, cabazitaxel versus mitoxantrone, respectively), leucopenia (96% versus 92%), anemia (97% versus 81%), and thrombocytopenia (47% versus 43%) (de Bono, Oudard, Ozguroglu, et al., 2010). Significant rates of grade 3/4 toxicities were seen in both arms, but were higher in the cabazitaxel arm: neutropenia (82% versus 58%); leucopenia (68% versus 42%); febrile neutropenia (8% versus 1%) and diarrhea (6% versus <1%). According to the authors, 5% of patients who received cabazitaxel and 2% of patients who received mitoxantrone died within 30 days of the last infusion.

Cabazitaxel is also now Health Canada approved for the treatment of men with CRPC post-docetaxel. It will soon be considered under the Joint Oncology Drug Review (JODR) process. It is currently only available through private infusion clinics in Ontario.

Sipuleucel-T

Sipuleucel-T (Provenge™) is the first immunotherapy to be effective in treatment of prostate cancer. The treatment involves three visits to a specialized centre—none of these centres are in Canada. At the first visit, the patient's blood is plasmapheresed to isolate the peripheral blood-mononuclear cells including the dendritic cells (the antigen-presenting cells of the immune system). The patient's selected blood cells are incubated with a special protein and activated with colony-stimulating factors, sensitizing the cells to a protein commonly expressed in prostate cancer. The cells are then reinfused into the patient approximately three days later. This process was repeated three times over the subsequent four weeks (days 0, 14 and 28).

There are now two randomized studies supporting the benefit of sipuleucel-T (Kantoff, Higano, Shore, et al., 2010; Small, Schellhammer, Higano, et al., 2006). The trial used for the registration of the product was called "IMPACT" and was a double-blind, placebo-controlled, multicentre, randomized controlled trial. Asymptomatic or minimally symptomatic CPRC patients pre-chemotherapy were randomized 2:1 sipuleucel-T (n=341) versus placebo (n=171). There was an improvement in the primary objective of the study, OS (25.8 mo versus 21.7 mo, HR 0.78, p=0.03) favouring the sipuleucel-T arm. There was no significant difference in objective disease response (3.7 mo versus 3.6 mo, HR 0.95, p=0.63), clinical disease progression (HR 0.92, p=0.40) or PSA response (2.6% versus 1.3%).

The most common side effects observed were immunologic in nature and more frequently reported in the sipuleucel-T arm. These included (all grades, sipuleucel-T versus placebo): chills (54% versus 12%); pyrexia (29% versus 14%); headache (16% versus 5%); myalgia (10% versus 5%); influenza-like illness (10% versus 4%); hypertension (7% versus 4%); hyperhidrosis (5% versus 1%); and groin pain (5% versus 2%). Grade 3 or higher adverse events seen within one day of an infusion occurred in 6.8% versus 1.8% of patients in the sipuleucel-T and placebo arms, respectively.

Sipuleucel-T, however, is not approved by Health Canada and is not available in Canada.

Conclusions

It is really exciting to learn about the promising new agents that have been proven to improve overall survival and quality of life. Before 1994, when docetaxel was first reported to have survival advantage, there was little hope systemic therapies could offer for men with CRPC. At that time, median survival was just over 12 months. Currently, with these last three agents, life expectancies are approaching 30 months. New agents, combinations of these agents and starting earlier in the disease process hold the hope of even better survival and quality of life.

The challenge we face is that many patients are not getting referred for an opinion regarding these agents. There is a sense of hopelessness among patients, their General Practitioners and even among some Medical Oncologists. The result is that fewer than 20% of patients get treatment with any of these drugs (including docetaxel). I believe our men with metastatic prostate cancer deserve better and should be referred to a Medical Oncologist who is knowledgeable about these agents for at least an opinion.

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