Chemotherapy for prostate cancer: Clinical practice in Canada

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Abstract

Whereas prostate cancer was once deemed unresponsive to chemotherapy, there is now evidence that patients with metastatic castration-resistant prostate cancer can obtain a survival benefit from both first-line (docetaxel-based) and second-line (cabazitaxel-based) chemotherapy. The side effects of these agents have been shown to be predictable and manageable, particularly in North American centres. However, patient selection remains a key issue, with the aim of delivering each line of treatment at a time when the individual patient remains fit and well enough to tolerate a cytotoxic regimen. Hence, it is increasingly important for urologists and oncologists to work together to ensure timely consideration of the chemotherapeutic approach before it is precluded by a decline in performance status.

Introduction

Prostate cancer is the most common cancer (other than non-melanoma skin cancer) in Canadian men. It is predicted that 26 500 new cases of prostate cancer will be diagnosed in Canada in 2012 (i.e., 121 per 100 000 population) and that 4000 men will die of the disease. The reported incidence of prostate cancer in Canada has risen since 1980, which is probably a reflection of improved diagnosis; however, the rate of death from the disease has been in decline since the mid-1990s. Hormonal manipulation, based on androgen deprivation and anti-androgen therapy, is the initial cornerstone of medical management of locally advanced or metastatic prostate cancer. On disease progression despite hormonal manipulation, the disease is defined as castration-resistant prostate cancer (CRPC; often referred to in earlier literature as hormone-refractory prostate cancer). Most men (90%) with CRPC have metastatic disease (mCRPC), and may or may not have potentially debilitating symptoms.

Less than a decade ago, mCRPC was deemed to be a “chemoresistant” disease, with a poor prognosis. Mitoxantrone, in combination with prednisone or prednisolone, was commonly used, but provided only palliation of symptoms without improvement in survival. Then the landmark TAX327 trial, published in 2004, showed that a course of chemotherapy based on the taxane docetaxel could extend survival for men with mCRPC (versus mitoxantrone-based chemotherapy). With this trial, prostate cancer entered the chemotherapy age. For several years, docetaxel remained the only chemotherapy to offer a survival benefit in this setting. Then, in 2010 it was reported that men with mCRPC who progressed during or after docetaxel could gain a further survival benefit from a second line of chemotherapy, based on another taxane—cabazitaxel. Once again, the palliative chemotherapy agent mitoxantrone was the comparator.

This article considers the evidence base for each of the chemotherapy lines associated with extended survival, and the implications for patient care, with specific reference to clinical practice in Canada.

First-line chemotherapy

Phase III evidence

In TAX327, 1006 men with mCRPC were randomized to prednisone 10 mg/day plus weekly or 3-weekly docetaxel or 3-weekly mitoxantrone (Fig. 1). At updated analysis, median overall survival was 19.2 months with 3-weekly docetaxel, 17.8 months with weekly docetaxel and 16.3 months with mitoxantrone (Fig. 2). Other outcomes are presented in Fig. 3. The most common grade 3/4 adverse event was neutropenia (3-weekly docetaxel, 32%; weekly docetaxel, 2%; mitoxantrone, 22%), but febrile neutropenia was rare (3-weekly docetaxel, 3%; weekly docetaxel, 0%; mitoxantrone, 2%). More docetaxel recipients than mitoxantrone recipients experienced at least one serious adverse event (3-weekly docetaxel, 26%; weekly docetaxel, 29%; mitoxantrone, 20%). Based on their findings, the investi-
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Gators suggested that 3-weekly docetaxel plus prednisone improved survival, prostate-specific antigen (PSA) response, pain response and quality of life versus mitoxantrone plus prednisone.

**Patient selection/referral**

A retrospective analysis of the outcome of docetaxel treatment in 145 patients at a single centre suggested that men with no/minimal pain at the outset of chemotherapy had longer survival times than those with mild or moderate/severe pain.8 Furthermore, it has been reported that once a new lesion is detected on bone scan, an asymptomatic patient with mCRPC is likely to develop symptoms within a median of just 3 months.9 These findings suggest that prompt referral of patients with mCRPC, rather than a policy based on waiting for symptoms, is likely to benefit survival.10

Guidelines from the Canadian Urologic Oncology Group (CUOG) and the Canadian Urological Association (CUA) state that docetaxel plus prednisone is the standard of care for men with mCRPC, and the 3-weekly regimen is recommended for patients with clinical or biochemical evidence of disease progression and evidence of metastases.3 To ensure timely and appropriate initiation of chemotherapy, the guidelines emphasize that patients with advanced prostate cancer should receive an early referral for consideration of docetaxel, and that their outcomes will be optimized through a multidisciplinary approach to their care.

Looking specifically at patients who have mCRPC but, for the time being at least, remain pain free, the CUOG/CUA guidelines recommend an individualized approach, taking into account the patient’s clinical status and preferences.3 Prostate cancer guidelines from the National Comprehensive Cancer Network (NCCN) also stipulate that docetaxel may be considered for asymptomatic men with mCRPC who have signs of rapid progression or soft tissue/visceral metastases.2

**Second-line chemotherapy**

**Early evidence**

Once docetaxel-based chemotherapy became established as the standard of care for mCRPC, several regimens were investigated for their potential in the post-docetaxel setting.
The first to show a survival benefit was cabazitaxel. The selection of another taxane was not entirely expected. Cross-resistance has been shown between different members of this drug class, so disease progression on or shortly after docetaxel treatment is likely to predict a lack of response to a second taxane. However, cabazitaxel has a low affinity for the adenosine triphosphate (ATP) drug efflux pump P-glycoprotein associated with resistance to docetaxel, and the agent was found to be active against cell lines with demonstrated taxane resistance.

Based on these findings, cabazitaxel was selected for clinical investigation. The novel taxane was found to have anti-tumor activity and good tolerability in a phase I trial in 25 patients with solid tumors (including 8 with prostate cancer), and a phase II trial in 71 women with taxane-resistant breast cancer showed a 14% response rate, and a 3% rate of febrile neutropenia.

### Phase III data

The key phase III clinical data on cabazitaxel emerged from the TROPIC trial, conducted in 26 countries in North and South America, Eastern and Western Europe and Asia, and involved 755 patients with mCRPC who had already received docetaxel-based chemotherapy. About one-third of the patient population had already received 2 or more courses of chemotherapy, and two-thirds had developed progressive disease either during or within 3 months of docetaxel treatment. In addition, about half had measurable disease, and 25% had visceral metastases, indicating mCRPC with a poor prognosis.

The patients were randomized to receive cabazitaxel or mitoxantrone, plus prednisone or prednisolone 10 mg/day (Fig. 4). As well as improving overall survival across the study population (cabazitaxel 15.1 months; mitoxantrone 12.7 months; Fig. 5), objective tumor response and PSA response (Fig. 6), subgroup analysis suggested that cabazitaxel was beneficial for older and younger patients (age <65 vs. ≥65 years), and in the presence or absence of pain at baseline. In an updated analysis, published in 2011, it was estimated that the probability of survival at 24 months was 28% in the cabazitaxel group, compared with 17% with mitoxantrone.

The most common (≥5%) grade 3/4 side effects were neutropenia, leucopenia, anemia, febrile neutropenia and diarrhea. Grade 3/4 neutropenia was recorded in 82% of cabazitaxel and 58% of mitoxantrone recipients, with febrile neutropenia in 8% and 1%, respectively. Diarrhea at any
grade was reported in 47% of the cabazitaxel group and 11% of the mitoxantrone recipients (6% vs. <1% at grade 3/4, respectively). Among the cabazitaxel recipients, there were 18 deaths (5%) within 30 days of the last treatment, compared with 9 in the mitoxantrone arm. Neutropenic complications were the most common cause of death associated with cabazitaxel (7 deaths [2%] in cabazitaxel recipients, vs. 1 death [<1%] in the mitoxantrone group). However, all of the deaths occurred early in the trial before investigators were reminded that the protocol required prophylactic use of granulocyte colony-stimulating factor, plus dose modification in the event of febrile neutropenia. 6 Moreover, it was noted, in a commentary published concurrently with the TROPIC trial, that management of febrile neutropenia varied considerably between the various TROPIC centres across the world, a factor that might have contributed to the excess mortality in the cabazitaxel group. 16 Indeed, analysis of the data from the North American centres (n=235) showed that only 1 patient (<1%) in each treatment group died as a result of treatment side effects. 17 The commentary authors recommend that centres offering cabazitaxel should have well-structured plans in place for the management of both diarrhea and febrile neutropenia. (The importance of proactive management of cabazitaxel side effects is discussed by Sperlich and Saad in this supplement on page S18. 18)

In June 2011, based on the findings of the TROPIC trial, 6 Health Canada approved cabazitaxel for the treatment of mCRPC in men previously treated with docetaxel. 19

**Early-access program**

Following the TROPIC trial, an international cabazitaxel early-access program was established to collect data on treatment safety and patients’ quality of life. 20 The participating countries are shown in Fig. 7. 20

Interim data from the UK arm of this study (based on up to 4 treatment cycles), showed improvement in pain control with continuing treatment (Fig. 8), stable scores for anxiety/depression, mobility and self-care, a 4.9% incidence of febrile neutropenia and a 2.4% incidence of diarrhea. 20

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**Fig. 4. TROPIC trial design.** mCRPC: metastatic castration-resistant prostate cancer.

**Fig. 5. TROPIC overall survival.** Patients in both treatment lines also received prednisone or prednisolone. CI: confidence interval.

**Fig. 6. TROPIC data on objective tumor response (in patients with measurable disease, n=405), PSA response (in evaluable patients, n=654) and pain response (evaluated in patients with high scores for pain and/or analgesia use, n=342).** Patients in both treatment lines also received prednisone or prednisolone. PSA: prostate-specific antigen.
Preliminary analysis of data from the Canadian arm of the early-access program (33 patients, median age 65 years, >50% received ≥5 cycles) have shown improvement in pain—the pain subscale of the Functional Assessment Cancer Therapy-Prostate (FACT-P) questionnaire found that pain improved in the first 4 cycles of cabazitaxel, and present pain intensity scores improved despite use of analgesia. The incidence of grade 3/4 diarrhea was 3%, and no treatment-related deaths have been reported.

**Implications for patient care**

The availability of two lines of chemotherapy for mCRPC highlights the importance of an effective multidisciplinary approach to the management of prostate cancer. Where there was initially a need for timely referral for docetaxel (i.e., before the development of any more than minimal pain and while the patient is fit and well), timeliness now needs to encompass potential access to a second line of chemotherapy.

Given the growing list of active agents for mCRPC and the fact that patients will eventually progress on any of the current treatments, it will become crucial that appropriate sequencing of treatment is considered at a time when the patient is still well enough to obtain the potential benefit of multiple therapies. It is therefore essential for specialists in urology and oncology to work together to ensure optimum access to both chemotherapy regimens. (The implications for the treatment pathway of advances in chemotherapy and other developments in the management of mCRPC are discussed by Asselah and Sperlich in this supplement on page S11.)
Conclusion

After many years of apparent “chemoresistance,” mCRPC has emerged into the chemotherapy age, initially with one line of chemotherapy, and now a two-line approach based on docetaxel followed by cabazitaxel, both offering a survival advantage to a population that previously only had access to symptom palliation. Further data are expected soon from the cabazitaxel early-access scheme, which will shed more light on the clinical implications of the two-line chemotherapeutic pathway.

Optimal use of docetaxel and cabazitaxel will depend on a multidisciplinary approach to patient care, with insight from urology and oncology, to facilitate effective patient selection, timely treatment initiation and proactive toxicity management.

Competing interests: Dr. Saad has served as a consultant and has been involved in research with Amgen, Astellas, Janssen, Novartis and Sanofi. Dr. Asselah has participated in advisory boards for Amgen and Sanofi, and has received speaker honoraria from Amgen and Sanofi.

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References


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