Malignant spinal cord compression (MSCC) is one of the most dreaded complications of metastatic cancer. MSCC can be intradural (intramedullary and leptomeningeal) or extradural (MESCC).\(^1\) Its natural history, if untreated, is usually one of relentless and progressive pain, paralysis, sensory loss, and sphincter dysfunction.

An Ontario population-based study of cancer patients reported that MSCC is fortunately not common; between 1990 and 1995, 2.5% of all cancer patients who died of their disease had at least one admission for MSCC.\(^2\) The incidence of MSCC varied widely by primary cancer site, from 7.9% in patients with myeloma to 0.2% in patients with pancreatic cancer.\(^3\)

Our group has published two previous systematic reviews for the diagnosis and management of MESCC in 1998\(^4\) and in 2005.\(^5\) Recently we updated these systematic reviews and generated clinical practice guidelines.\(^4\) This article summarizes the key findings from that 2012 guideline.

A review and analysis of data published from January 2004 to May 2011 was performed. The systematic literature review included published randomized control trials (RCTs), systematic reviews, meta-analyses, and prospective/retrospective studies. Four RCTs were identified. One was a published article of radiation therapy (RT) with or without decompressive surgery for patients with MESCC of the spinal cord (cauda equina lesions excluded) that had only been referenced in the 2005 systematic review, but only the abstract was available for review.\(^6\) One was a small feasibility study examining two different maintenance doses of dexamethasone.\(^7\) The
other two RCTs examined different dose fractionation comparisons for patients with poor prognosis MESCC (30 Gy in 8 fractions versus 16 Gy in 2 fractions; 16 Gy in 2 fractions versus 8 Gy in 1 fraction).8,9

When recommending treatment, our expert panel felt that it should be individualized to the patient, taking into consideration an estimate of prognosis, goals of therapy, medical comorbidities and distance from the treating surgical or radiation centre. We felt it was critical to achieving a balance between the effectiveness and burden of the treatment regimen.

Simple prognosis scales are available to assist the clinician. Probably the most comprehensive and practical was published by Rades et al. They developed a prognostic scoring system based on the six factors that were found to be independently prognostic. Total scores ranged between 20 and 45 points and patients were divided into five groups. The six-month estimate of overall survival (OS) ranged from 4% to 99% (P<0.001) with median OS estimated to range between two and 62 months from the worst to the best prognostic group. See Tables 1 and 2.

If not medically contraindicated, steroids are recommended for any patient with neurologic deficits suspected or confirmed to have MESCC. Most often an 8 mg to 10 mg loading dose followed by 16 mg/day of dexamethasone (or equivalent) is used; higher doses (up to 100 mg bolus and 96 mg/day maintenance) can be considered for younger, medically well patients with deeper neurologic deficits, but otherwise good prognosis. Surgery should be considered for patients with a good prognosis (prognosis score 36 to 45) who are medically and surgically operable. This was based on the small RCT (n = 101 patients) that showed clinically and statistically significant improvements in pain, ambulatory ability, urinary continence, duration of continence, functional status, and overall survival.6

RT should be given to nonsurgical patients. For those with a poor prognosis (prognosis score 21 to 35), a single fraction of 8 Gy should be given. This was based on the two RCTs described above. The protracted course of therapy (30 Gy in 8 fractions) did not improve ambulation rates, duration of ambulation, bladder function, pain response, in-field failure, nor overall survival (compared to 16 Gy in 2 fractions and this was equivalent in a second RCT to 8 Gy in 1 fraction).9 For those with a good prognosis (score 36 to 45), 30 Gy in 10 fractions could be considered based on retrospective data showing improvements in local control (but no difference in survival or functional outcomes). Patients should be followed up clinically and/or radiographically to determine whether a local relapse develops. Salvage therapies should be introduced before significant neurologic deficits occur.

References
Available upon request.

| Table 1: Prognostic score for malignant epidural spinal cord compression (adapted from Rades et al.)10 |
|---|---|---|
| Prognostic Factor | Category | Score |
| Type of tumour | Myeloma/lymphoma | 9 |
| | Breast cancer | 8 |
| | Prostate cancer | 7 |
| | Other tumours | 4 |
| | Lung cancer | 3 |
| Other Bone Metastases* | No | 8 |
| | Yes | 2 |
| Visceral Metastases* | No | 8 |
| | Yes | 2 |
| Tumour diagnosis to MESCC | > 15 months | 7 |
| | ≤ 15 months | 4 |
| Ambulatory status pre-treatment | Ambulatory | 7 |
| | Non-ambulatory | 3 |
| Time to develop motor deficits before treatment | > 14 days | 8 |
| | 8–14 days | 6 |
| | 1–7 days | 3 |

* At time of radiotherapy

| Table 2: Overall Survival by MESCC prognostic score10 |
|---|---|---|
| Score | 6 month OS | 1 year OS | Median OS (months)* |
| 21–25 | 4% | 0% | 2 |
| 26–30 | 11% | 6% | 5 |
| 31–35 | 48% | 23% | 7 |
| 36–40 | 87% | 70% | 25 |
| 41–45 | 99% | 89% | 62 |

* Estimated; OS: overall survival
Preventative ethics, advanced directives, normalization—and Blairsville
Blair Henry, Ethicist, Sunnybrook Health Sciences Centre

The lack of uptake on the use of advanced directives has always surprised me. I suspect everyone immediately associates it with having to have the “dreaded” end-of-life conversations, and in some cases it does—but in others it can be a rather simple beginning of an important conversation. Let me give you an example!

Ever since a colleague brought back a photo taken of a roadside sign that said: Blairsville 15 miles—I’ve had many opportunities to play around with the idea of such a place existing, but by my design. Here’s how it works vis-à-vis advanced directive.

Did you know that in Blairsville, every patient wanting to receive non-emergency care must answer the following three questions, as part of their intake process (P.S. it’s important that they know every patient is asked this, and not geared just to the really sick ones):

1) Should you ever be in a condition that you could not communicate for yourself, who would you want us to talk with regarding care decisions at that time? Record this information along with contact information in the front of the chart. If this is someone different than the hierarchy for substitute decision makers (SDM) in the health care consent act advise the patient to do a power of attorney for personal care.

2) Have you told them you’d want them to assume this role? Do they know your wishes? Record this in the chart.

3) Can you share with us any specific wishes that are really important to you? Record this in the chart.

Now let’s face it—how can anybody say that these three questions would be particularly challenging to ask? And the word death doesn’t have to come up at all—unless the patients brought it up themselves. If this information was simply and clearly documented for each and every patient, and then retrievable by the health care consent act advise the patient to do a power of attorney for personal care.

Oh—and in Blairsville, anyone undertaking an elective, moderate- to high-risk procedure must fill in a more comprehensive advanced directive outlining what the SDM should know if things subsequent to the procedure didn’t go as planned, given the known risk factors for many surgical procedures.

Every time I purchase a flight on Expedia I am asked if I want to purchase life insurance, and the fact that I get a policy statement outlining in graphic details how much money I might get should I lose various appendages doesn’t dissuade me from enjoying my trip. Perhaps if we “normalized” these conversations as part of our regular health care they would be received with equal ease and expectancy.

What families (and dare I say many health care providers) need to know is that an advanced directive isn’t a menu for how care will be delivered in the future. It is simply a predefined understanding to move forward on when a health care provider decides to offer a treatment to an SDM. At least then, the SDM and the team can see if that option is congruent with what the patient might have wanted.

Addressing smoking cessation with our patients: It is all of our responsibility
By Leslie Gibson, OT Reg. (Ont.)

Tobacco use is a worldwide epidemic and has a significant impact on our health care system. Approximately 17% of Canadians are current smokers. Smoking is responsible for 30% of all cancer deaths and has a direct link to more than 85% of lung cancer cases. Smoking has also been associated with the development of cancers of the mouth, throat, larynx, esophagus, bladder and cervix. The financial burden of tobacco use on direct health care costs is estimated at $4.4 billion annually.

Smoking has a negative impact on health and is the leading preventable cause of disease and death. Smoking is one of the leading causes of hospitalizations and re-hospitalizations. In spite of this, how often do we actually take the time to address smoking with our patients?

Examine your clinical practice and consider the following questions:

• Do you routinely ask your patients if they smoke?
• How often do you encounter a smoker in your practice?
• Do you assess the patient’s smoking history?
• Do you advise your patients to quit smoking?
• Do you consider addressing smoking cessation but because of lack of time, knowledge or confidence, defer it to another health professional?

In 2011, a Joint Position Statement entitled: “The Role of Health Professionals in Tobacco Cessation” was released by the Canadian Associations of Counselling and Psychotherapy, Dental Hygienists, Medicine, Nursing, Occupational Therapy and Physiotherapy. The statement advocates that every Canadian Health Care Professional has a responsibility to address tobacco-use cessation with their patients and clients. Because most Canadians see a health care professional at least once a year, we are well positioned to offer “teachable moments” to our patients and counsel them to quit smoking. In fact, best practice dictates that all clinicians should provide smoking cessation interventions at every encounter. The more frequently a smoker is offered strategic advice on smoking cessation from a variety of health care providers, the greater the chances of quitting increase. The 2008 WHO Report on the Global Tobacco Epidemic states that after immunization, smoking cessation counselling is one of the most cost-effective interventions a clinician can perform.

continued on page 4…
Eighty-five per cent of cancer patients and 71% of oncologists endorse the belief that psychological variables affect cancer progression. Previous life experiences may make people more vulnerable to the development of cancer and may interfere with adaptation to the cancer experience and its treatment, but psychosocial interventions may mitigate some of these experiences and extend survival.

Childhood maltreatment: physical and sexual abuse, neglect, and/or family dysfunction and maternal death have been found to be related to adult chronic health conditions including cancer. Data from a 2005 Canadian Community Health Survey found that childhood physical abuse was associated with 49% higher odds ratio of cancer when adjusting for age, sex, and race.1

In a palliative care audit of 59 families, one of whom was terminally ill or recently deceased, who had direct responsibility for children and young people aged under 20 years old, there was a childhood sexual abuse rate of 33% for women and 10% for men.2 Half of the families had one or more family members who had experienced childhood sexual abuse. A further 9% of adults had experienced severe physical and emotional abuse in childhood and many families had faced multiple trauma.

Depression can also increase the lifetime risk of cancer. In the population-based sample Baltimore Epidemiologic Catchment Area Study, major depression was associated with a higher hazard for overall cancer (HR 1.9, 95% CI 1.2–3.0) and a statistically significant increased hazard for breast cancer (HR 4.4 95% CI 1.08–17.6).3 There was also a positive association between a history of depression and prostate cancer, but confidence bounds included the null. The authors concluded that there was an association between depression and hormonally mediated cancers, which provides support to hypotheses about a common biological pathway between depression and cancer.

What might be the links between stress and cancer? Chronic stress, negative affect and social adversity have been associated with biobehavioural alterations (increased sympathetic nervous system [SNS] signalling, hypothalamic-pituitary-adrenal [HPA] axis dysregulation, inflammation and decreased cellular immunity). These could interact with the tumour microenvironment to promote factors favouring tumour growth (angiogenesis), invasion (tissue remodelling and epithelial-mesenchymal transition), and metastatic signaling (anoki- kis), during and after cancer treatment.4 Cancer diagnosis and treatment induce acute and chronic stress and reduced quality of life, which may affect neuroimmune regulation by promoting inflammatory processes that could contribute to both symptom exacerbation and metastasis.5 Breast cancer patients who recalled one or more form of abuse as children were more likely to experience emotional difficulties two to four days after cancer surgery. Depression is an independent predictor of shorter cancer survival. Women who were abused or neglected as children reported more cancer-related psychological distress, more fatigue and poorer physical, emotional, functional and breast cancer-specific well-being after treatment, partially explained by the fact that breast cancer survivors reported receiving less support as adults.

Women with metastatic breast cancer have flatter than normal diurnal cortisol patterns, and the degree of loss of daily variation in cortisol predicts earlier mortality with breast cancer. Abnormal cortisol patterns, in turn, can affect expression of oncopgenes such as BRCA1 and retard apoptosis of malignantly transformed cells. Abnormal levels of cortisol also may stimulate tumour proliferation via differential gluconeogenesis in normal and tumour tissue, as well as activation of hormone receptors that promote tumour growth.6

Two studies used psychosocial interventions to modulate psychological adaptation. Patients with melanoma receiving intervention had decreased mortality at six-year and 10-year follow-up.7 Women with breast cancer receiving intervention had a lower risk of recurrence (HR 0.55, p = .034) and death from breast cancer (HR=0.44, p=0.016).8

References
References available upon request to:
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As health care providers, what can we do? Smoking cessation best practice advocates the use of the 5A’s:

ADVISE: Encourage your patients to quit or reduce their tobacco use. Hearing this advice from a clinician greatly increases quitting success.

ASK: Explore your patient’s readiness to quit. Is your patient motivated to quit in the next 30 days?

ASSIST: Assist your patient in establishing a quit plan. Work together to set a quit date. Explore challenges and triggers. Explain that both prescribed medications and nicotine replacement therapies can be beneficial adjuncts in quitting smoking.

ARRANGE: Provide your patient with Canadian Cancer Society’s self-help materials. Refer your patient to the Smokers’ Helpline Quit Connection (1-877-513-5333) for online, texting, and telephone support. Encourage your patient to follow up with their pharmacist and physician. Suggest seeking support from members of the Odette Cancer Centre’s Patient and Family Support Program.

Limited time in our busy workday is often cited as a reason why we are unable to address smoking cessation with our patients. Research has shown that even brief interventions lasting less than three minutes can have a positive impact on abstinence.9 In the coming months, a greater emphasis will be placed on addressing smoking cessation with our patients.

Implementation of a new tobacco control strategy has been outlined as a strategic priority by Cancer Care Ontario. A smoking cessation steering committee has been established at Sunnybrook Health Sciences Centre involving key stakeholders to facilitate discussion on how best to implement smoking cessation intervention throughout our facility and across programs. Take the opportunity to discuss smoking with your patients. As health care providers, it is all of our responsibility.
For patients with advanced cancer, treatment intent changes from curative to palliative, making quality of life (QOL) a very important end point. Symptoms arising from cancer itself or treatment have been shown to greatly affect a patient’s QOL. However, it has been less frequently studied to which degree this change is meaningful to patients.

Meaningful change, or minimal clinically important difference (MCID), is often defined as the smallest difference in QOL score that is large enough to have an effect on a patient’s care or treatment. It is the size of change required for patients to determine whether they have improved or deteriorated. Although statistically significant differences in QOL can be appreciated in large-scale clinical trials, whether this amounts to clinically meaningful change is less known and infrequently assessed. Clinicians often determine whether treatment is working by objective measures such as tumour size and number of metastases. They are familiar with these methods and know when these measures are meaningful. QOL change, however, is a measure that is less familiar to health care professionals (HCPs) in terms of what is a meaningful change. Currently, QOL assessments are uncommon in daily clinical practice and are utilized mostly in the research setting. This QOL assessment is important for HCPs to determine how their patients are coping and to which degree the treatments they are receiving have improved or worsened QOL.

There are two methods for determining MCID—the anchor-based model and the distribution-based model. The anchor method links health-related QOL to known indicators that have clinical relevance or patient-derived ratings of change in health such as performance status and global rating of change. The distribution-based method is based on statistical data obtained and the calculated distribution statistics. These conclusions are based on means, standard deviations and effect size. Most often, studies use 0.2SD, 0.5SD and the standard error of measurement. Typically, both the anchor- and distribution-based methods are used in unison.

We conducted a literature review on meaningful change in oncology quality of life instruments from 1996 to January 2012, and we found there were only 26 articles that discussed meaningful change, either through review/commentary or specific meaningful change studies. The majority of studies utilized the FACT-G or the EORTC QLQ-C30.

Most meaningful change studies have used the anchor-based method. However, very few address the appropriateness of the anchor used. The use of the anchor-based method must depend upon the association that anchor has with the target QOL questionnaire. Empirical validation of each anchor should be determined before its use. In most meaningful change studies, the correlation between the anchor and the QOL score is calculated through the Spearman or Pearson correlation coefficient. Other studies have employed a regression line relating changes in QOL scores as a function of changes in the anchor. Both approaches have restrictions: using the correlation coefficient appears more meaningful when the anchor is of a continuous nature, and its use when the anchor is categorical is questionable, while the linear regression approach is restrictive, as the relationship between the anchor and QOL is often non-linear and can be complex.

As there is very little literature on MCID, our group conducted meaningful change studies in the ESAS, EORTC QLQ-C30, EORTC QLQ-C15-Pal, EORTC QLQ-BM22, and the BPI.

For the majority of these studies, patients completed the QOL questionnaire at baseline before treatment and at follow-up one month later. Both anchor- and distribution-based methods were utilized to determine the meaningful change in our studies. Demographic information was summarized through descriptive statistics. In the QLQ-C30, QLQ-BM22 and QLQ-C15-Pal studies, two anchors were used—overall health and overall QOL (rated on a one to seven scale). Due to the natural fluctuation of patient scoring, a change of two units on these QOL and overall health scales were used as the anchors. In the ESAS study, the anchor of overall well-being was used, and in the BPI pain response was utilized as the anchor.

Spearman correlation analysis was conducted between the anchors and item scores at baseline to select symptoms that demonstrated at least moderate correlation with the anchor. Correlations of at least 0.30 were considered moderate, as per Cohen’s rules, and those items that correlated at least moderately were used in further MCID analysis. For each symptom that corresponded with the anchors, the mean change in score was calculated for patients who improved, deteriorated, and were stable. Ninety-five per cent confidence intervals (CI) were used for each anchor and those that did not include zero, suggested statistically significant difference between the mean changes of adjacent categories. Estimations of MCID by the distribution method were calculated using 0.2SD, 0.3SD, 0.5SD and 1 SEM.

In order to be included in the meaningful change assessment, items were required to achieve moderate correlation with the anchor at baseline. It was found that those items that did not achieve significance with the anchor at baseline were often the ones that were scored relatively low by patients.

It was determined that in all studies, the distribution-based estimates were closest to 0.5SD. Meaningful change calculated by the anchor-based method, ranged from 10 to 20 units on 0 to 100 scales (QLQ-C30, QLQ-BM22, QLQ-C15-Pal) and 1 to 2 units on 0 to 10 scales (ESAS, BPI).

One trend seen in the majority of meaningful change studies was that QOL scores required for meaningful improvement were smaller in magnitude than those of meaningful deterioration. This demonstrates that patients often are more aware of small changes in improvement as compared to small changes in deterioration.

This type of study is not without its limitations. The most common limitation to meaningful change studies is the high attrition rates. Many patients are unavailable for follow-up or become too ill to complete the follow-up. Another limitation commonly seen is the response shift. When diagnosed with an illness, patients often change their internal frame of reference in response to QOL, and patients often rank their QOL as better when, in fact, their symptoms have worsened.

Knowledge of meaningful change allows physicians to assess patient change over time, along with evaluating the impact of treatment (or no treatment) on a patient’s QOL. This knowledge gives insight into whether or not the treatment is effective and, ultimately, if it should be continued. Knowledge of MCIDs may also allow clinicians to determine sample size for future clinical trials.

Future meaningful change studies should include one specific subset of the palliative oncology population. They should also employ the use of symptom-specific modules such as the EORTC QLQ-BN20 and the EORTC QLQ-BM22, as they may prove to be a more useful tool in these patient populations than the general questionnaires.

References

References available upon request.
Continuing Medical Education 2012–2013
By Ewa Szumacher, MD, FRCP(C)

Continuing Medical Education (CME) can update health care professionals on the latest advances for modifications to their clinical practice. At the request of the CME organizers, Hot Spot will list the national and international CME activities in palliative medicine that are of interest to our readers. Please forward details of the CME activities to: Ewa.Szumacher@sunnybrook.ca

• November 9–11, 2012
Synergy 2012: A Multidisciplinary Approach to Interventional Oncology
http://cme.med.miami.edu/x88.xml

• November 22–25, 2012
The 2nd International Multidisciplinary Forum on Palliative Care
www.imfpc.org

• November 22–23, 2012
Toronto Cancer 2012
www.torontocancer.ca

• November 28–30, 2012
13th Annual Meeting of the Society of Urologic Oncology in Conjunction with the World Urological Oncology Federation
http://suonet.org/default.aspx

• November 30, 2012
2nd Annual Best of Oncology 2012

• November 30–December 1, 2012
ASCO's Quality Care Symposium
www.asco.org/ASCOv2/Meetings/ASCO%27s+Quality+Care+Symposium

• December 4–8, 2012
35th Annual San Antonio Breast Cancer Symposium
www.sabcs.org

• January 17–18, 2013
5th Breast Gynecological International Cancer Conference
www.bgicc.net

• March 13–16, 2013
13th St. Gallen International Breast Cancer Conference 2013, St. Gallen/Switzerland
www.uicc.org/13th-international-conference-primary-therapy-early-breast-cancer
www.oncoconferences.ch

• March 20–22, 2013
17th Reach to Recovery International Conference, Cape Town, South Africa
www.reachtorecovery2013.org

• April 25–27, 2013
3rd International Public Health & Palliative Care Conference 2013, Limerick, Ireland
www.publichealthpalliativecare.org

• May 9, 2013
14th Annual Mary O’Connor Palliative and Hospice Care Conference, Calgary, AB
www.palliativecareconference.ca

The newsletter of the Rapid Response Radiotherapy Program of the Odette Cancer Centre is published through the support of:

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Scan the QR code with your smartphone to read past issues of Hot Spot
In the November 2011 Hot Spot, we reviewed the latest treatments for men with metastatic castrate-resistant prostate cancer. Since then, more exciting results have been published which add more hope for men with this condition by again offering improvements in overall survival and quality of life. Moreover, two of these treatments are now Health Canada approved and reimbursed in Ontario.

What is CRPC?

Androgen deprivation therapy (ADT) is commonly prescribed for men with recurrent, progressive, or metastatic prostate cancer that is androgen sensitive. 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).1

Patients with CRPC 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 CRPC) and symptomatic metastatic disease (M1s CRPC), as the onset of symptoms usually prompts consideration of systemic chemotherapy.

The goal of treatment for men with CRPC is palliative (i.e., symptom relief or prevention) although many treatments also improve overall survival. In the last review, docetaxel, abiraterone acetate, cabazitaxel, and sipuleucel-T had been shown to improve overall survival in men with M1 CRPC.2 We can now add enzalutamide to the list.3 Whereas abiraterone acetate was shown to benefit patients post-docetaxel,4 a separate study has now been reported which shows that it improves overall survival and radiographic progression-free survival before docetaxel.5

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,6,7 but their review is outside the scope of this paper.

Abiraterone acetate

Abiraterone acetate (AA—Zytiga™) is a synthetic cyp-17 inhibitor that interferes with steroidogenesis. In the last review, the benefits of the pivotal COU-AA-301 study were outlined.4 Patients who progressed after docetaxel were randomized 2:1 to AA 1,000 mg po OD + prednisone 5 mg po BID (n = 797) or placebo + prednisone (n = 398). The final analysis of the study has since been published with similar findings.8 After a median follow-up of 20.8 months, the study’s primary endpoint, overall survival (OS) was greater in patients randomized to the AA arm (median OS 15.8 versus 11.2 months, HR 0.74, p < 0.001). All secondary objectives were also improved in the AA arm including: time to PSA progression (median 8.6 mo versus 6.6 mo, HR 0.63, p < 0.0001); time to radiographic progression (5.6 mo versus 3.6 mo, HR 0.66, p < 0.0001); and PSA response (30% versus 6%, p < 0.0001).

The results from the multinational COU-AA-302 study have recently been reported. 1,088 pts with docetaxel-naïve M1 CRPC were randomized 1:1 to AA (1 g) + prednisone (5 mg BID) or placebo + prednisone. The co-primary endpoints were radiographic progression-free survival (rPFS) and overall survival (OS).5 The Independent Data Monitoring Committee concluded that the OS, rPFS and secondary endpoints all favored the AA arm and unanimously recommended unblinding the study and crossing pts from placebo to AA. With a median follow-up of 22 months, the following outcomes were reported: median overall survival (not reached (NR) vs. 27.2 mo, HR 0.75, p = 0.00097); median rPFS (NR vs. 8.3 mo, HR 0.43, p < 0.0001); time to opiate use (NR vs. 24 mo, HR 0.69, p = 0.0001); time to chemotherapy initiation (25.2 vs. 16.8 mo, HR 0.58, p < 0.0001); time to performance status decline (12.3 vs. 10.9 mo, HR 0.82, p = 0.0053); time to PSA progression (11.1 vs. 5.6 mo, HR 0.49, p < 0.0001).

Grade 3/4 AEs (AA + P, PL + P) (%): hyper-tension 3.9 vs. 3.0; hypokalemia 2.4 vs. 1.9; ALT ↑ 5.4 vs. 0.7; AST ↑ 3.0 vs. 0.9.

Abiraterone acetate is now Health Canada approved for the treatment of men with CRPC post-docetaxel. In addition, it has recently been approved for reimbursement in Ontario after the use of docetaxel, meaning that patients in this and every other province have access to a publicly funded drug.

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. As reviewed last time, patients with disease progression during or after completion of treatment with docetaxel were randomized to receive cabazitaxel (n = 378) or mitoxantrone (n = 377).9 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 vs. 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 vs. 1.4 mo, HR 0.74, p<0.001); time-to tumour-progression (8.8 mo vs. 5.4 mo, HR 0.61, p<0.0001); time-to-PSA-progression (6.4 mo vs. 3.1 mo, HR 0.75, p=0.001); objective tumour response (14% vs. 4%, p=0.0005); and PSA response (39% vs. 18%, p=0.0002). 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 vs. median not reached, HR 0.91, p=0.52) and pain response (9.2% vs. 7.7%, p=0.63).

Significant rates of grade 3/4 toxicities were seen in both arms, but were higher in the cabazitaxel arm: neutropenia (82% vs. 58%); leucopenia (68% vs. 42%); febrile neutropenia (8% vs. 1%) and diarrhea (6% vs. <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 and is reimbursed by the Ontario government. Currently in Ontario, the government will pay for patients to either receive cabazitaxel or abiraterone acetate but not both.

**Enzalutamide**

Enzalutamide (Xtandi™) is a potent oral inhibitor of the androgen receptor signalling pathway. A multinational, phase 3 RCT compared enzalutamide vs. placebo (2:1) in 1,199 M1s CRPC patients previously treated with docetaxel. The study was stopped after a planned interim analysis at the time of 520 deaths. Patients randomized to enzalutamide demonstrated a significant overall survival advantage (median OS, 18.4 vs. 13.6 mo, HR 0.63, p<0.001) as well as improvements in: PSA response rate (54% vs. 2%, p<0.001); soft-tissue response rate (29% vs. 4%, p<0.001); quality-of-life response rate (43% vs. 18%, p<0.001); time to PSA progression (8.3 vs. 3.0 mo, HR 0.25, p<0.001); rPFS (8.3 vs. 2.9 mo, HR 0.40, p<0.001); and time to first skeletal-related event (16.7 vs. 13.3 mo, HR 0.69, p<0.001).

There were no significant differences in serious adverse events or discontinuation due to adverse events. Rates of fatigue, diarrhea, and hot flashes were higher in the enzalutamide group. Seizures were reported in five patients (0.6%) receiving enzalutamide.

Enzalutamide is undergoing Health Canada review and is not publicly funded in Canada. It has recently been approved by the Food and Drug Administration in the U.S.

**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 three agents, life expectancies are approaching 36 months. New agents, combinations of these agents and starting earlier in the disease process holds the hope of even better survival and quality of life.

The challenge we face is that many patients are not getting treated with 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. Options include referral to Medical Oncologists experienced in the use of these drugs as well as educating Urologists and Radiation Oncologists in how to use the oral drugs when the patient is chemotherapy naïve.

**References**


