Dear Hot Spot readers,

It is with sadness that we dedicate this Hot Spot issue to our dear friend and colleague, Dr. Larry Librach. Doctors Danjoux and Law have provided a moving tribute to Dr. Librach, our dedicated palliative care colleague who touched many of our lives. This edition of Hot Spot also features several useful and interesting articles: Chemotherapy-Induced Peripheral Neuropathy by Mark Pasetka, BSc, BScPharm, PharmD, Lessons from the Bedside as a Substitute Decision-Maker by Karen Faith, MEd, MSc, Bioethics Consultant, Tips on Assessment and Management of Distress in the Oncology Clinic by Dr. Janet Ellis and Dr. Eileen La Croix, Psychiatrists, Odette Cancer Centre, and Dr. Madeline Li, Psychiatrist, Princess Margaret Cancer Centre. We have two inserts: Dr. Klotz on the management of metastatic castrate cancer prior to chemotherapy: focus on bone health, and Drs. Ko and Law on gastrointestinal stromal tumour. Dr. Szumacher again provides a useful update on CME activities. We also congratulate Dr. Margaret Fitch on her recent prestigious award.

As the colder season descends upon us, we hope you will find some warmth and enlightenment from our “Hot” Spot articles.

Editorial

By Dr. May Tsao

Congratulations to Dr. Margaret Fitch

Hot Spot congratulates Dr. Margaret Fitch, Head, Oncology Nursing at Sunnybrook Odette Cancer Centre, for the Lifetime Achievement Award from the Dalhousie Alumni Association on October 3, 2013. Each year, the Dalhousie Alumni Association Awards recognizes a number of Dalhousie alumni for their outstanding accomplishments and contributions. The Lifetime Achievement Award recognizes alumni for exceptional accomplishments in career and community service. See the following website for more details on the award. http://www.dal.ca/news/2013/10/04/celebrating-our-outstanding-alumni-.html. Please join us in congratulating Dr. Fitch on this terrific recognition.

Lessons from the bedside as a substitute decision-maker

By Karen Faith, MEd, MSc, Bioethics Consultant

A person’s previously stated capable wishes need to be reconsidered as their health challenges and quality-of-life issues change. On several occasions my Dad stated that he did not wish to receive CPR or become dependent on machines or other devices in order to extend his...

In this issue of Hot Spot:

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Inserts
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Gastrointestinal stromal tumours (GIST)
Chemotherapy-induced peripheral neuropathy
By Mark Pasetka, BSc, BScPharm, PharmD, Clinical Pharmacy Coordinator, Odette Cancer Centre, Sunnybrook Health Sciences Centre

Introduction
Chemotherapy-induced peripheral neuropathy (CIPN) can be defined as damage, degeneration, or inflammation (in any form) of peripheral nerves, as caused by chemotherapeutic medication. Several of these agents are commonly administered to patients concurrently while receiving radiotherapy (RT). CIPN can affect patients directly through clinical manifestations, impact on quality of life and, potentially, treatment outcome. Dose modification, delay in therapy and, ultimately, treatment cessation may occur as a result of CIPN. Despite the presence of several measurement tools, there is no universally accepted method of neuropathy assessment, and few well-studied prevention or management strategies exist. Patient-associated risk factors for developing CIPN include age, diabetes, and alcohol abuse, while those related to the treatment are dose intensity, duration, cumulative dose, and co-administration of other neurotoxic agents. Several types of neural function can be affected and include sensory, motor, autonomic, cranial, and combinations thereof. The incidence with chemotherapies varies broadly.

Mechanism of chemotherapy-induced neuropathy
The development of CIPN is thought to include several processes and different types of neuronal damage.

Exposure: Neurons found in the periphery (afferent motor, sensory) receive greater exposure to chemotherapeutic agents and their damaging effects due to the lack of a protective barrier as seen with central neuronal tissue (i.e., blood brain barrier).

Metabolic interference: Neurons in the periphery (which may be quite long) are sensitive to changes in energy metabolism or axonal transportation. Several chemotherapies target the microtubule structure of mitotic spindle fibres, which may also affect microtubule-axonal transportation and include both taxanes, vinca alkaloids, and epothilones. This type of neuropathy, commonly referred to as “axonal degeneration”, typically appears over weeks to months and the degree of resolution following treatment cessation is dependent on the extent of degeneration.

DNA damage and apoptosis: Insult to DNA caused by chemotherapies can induce programmed cell-death quite exquisitely in neurons. Cell death, usually involving neurons of the dorsal root ganglion (DRG), results in irreversible sensory (predominantly) neuropathies.

Demyelination: Demyelinating neuropathies are considered less common and more agent specific.

Ion-channels: Neuromyotonia and hyperexcitability of motor and sensory neurons are thought to cause oxaliplatin-induced acute neuropathy via involvement of voltage-gated sodium channels.

Presentation
CIPN may present as sensory, motor, autonomic, and cranial neural manifestation, or combinations of these. Typically, a glove and stocking presentation is seen in patients presenting with CIPN with it first noted in the fingers and toes. Several other signs and symptoms are noted in Table 2.

Prevention and treatment
Several agents have been studied in the setting of CIPN to determine their effectiveness in prevention or treatment (Table 3). Two recently published trials describe the use of an antidepressant and mineral supplementation as treatment and preventative strategies, respectively. Duloxetine

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<tr>
<th>Agent</th>
<th>Sensory</th>
<th>Motor</th>
<th>Sensory &amp; Motor</th>
<th>Autonomic</th>
<th>Cranial</th>
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Table 1: Chemotherapeutic agents causing peripheral neuropathies<sup>2,4,5,11,12,13</sup>

HOT SPOT
(Cymbalta®) was studied in a phase III randomized controlled trial (P3RCT) involving patients receiving oxaliplatin, cisplatin, paclitaxel, or docetaxel to determine its effect on chemotherapy-induced peripheral neuropathic pain. Patients receiving duloxetine 60 mg once daily demonstrated a significant reduction in pain score when compared to patients administered placebo. In a recent P3RCT, calcium and magnesium supplementation given concurrently with oxaliplatin to colorectal cancer patients was found to be ineffective in preventing treatment-related sensory neuropathies.

**Considerations**

1. Identify risk factors for the development of CIPN in patients receiving neuropathy-inducing chemotherapies.
2. Attain baseline neuropathy assessments for patients at risk for CIPN.
3. Educate patients on the signs and symptoms of CIPN.
4. Monitor patients regularly for signs and symptoms of CIPN and take appropriate action.
5. Consider other causes for neuropathic symptoms if not congruent with a chemotherapeutic cause.

**References**

10. Loprinzi CL, et al. Phase III randomized, placebo (PL)-controlled, double-blind study of intravenous calcium/magnesium (CaMg) to prevent oxaliplatin-induced sensory neurotoxicity (sNT), N08CB. An alliance for clinical trials in oncology study, American Society of Clinical Oncology (ASCO), iMeeting.

**Table 2: Common signs and symptoms observed in patients with chemotherapy-induced peripheral neuropathies**

<table>
<thead>
<tr>
<th>Type of Neuropathy</th>
<th>Signs &amp; Symptoms</th>
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<tr>
<td>Sensory</td>
<td>Paresthesias; Dysesthesias; Hypoesthesia; Hyperesthesia; Burning; Pain; Sensory Ataxia; Diminished or Absent Proprioception, Vibration Sensation, Cutaneous Sensation, Discrimination between Sharp and Dull</td>
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<tr>
<td>Motor</td>
<td>Muscle Weakness; Balance Disturbance; Gait Disturbance; Fine Motor Skill Impairment</td>
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<tr>
<td>Sensory-Motor</td>
<td>Hypo-, Areflexia</td>
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<td>Autonomic</td>
<td>Constipation; Blood Pressure Alteration; Urinary Retention; Sexual Dysfunction; SIADH; Paralytic Ileus</td>
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<tr>
<td>Cranial</td>
<td>Diplopia; Transient Blindness; Optic Atrophy; Vocal Cord Paralysis; Ocular Motor Nerve Dysfunction</td>
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**Table 3: Medications studied for prevention and treatment of CIPN**

<table>
<thead>
<tr>
<th>Preventative Strategies</th>
<th>Treatment Strategies</th>
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<tbody>
<tr>
<td>Acetyl-L-Carnitine</td>
<td>Acetyl-L-Carnitine</td>
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<tr>
<td>N-Acetyl Cysteine</td>
<td>Acupuncture</td>
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<td>Amifostine</td>
<td>Alpha-lipoic acid</td>
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<td>Calcium &amp; Magnesium</td>
<td>Amitriptyline</td>
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<td>Oxcarbazepine</td>
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<td>Vitamin E</td>
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<td>Valproic acid</td>
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<td>Venlafaxine</td>
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Tips on assessment and management of distress in the oncology clinic

Dr. Janet Ellis, Dr. Eileen La Croix, Psychiatrists, Odette Cancer Centre, and Dr. Madeline Li, Psychiatrist, Princess Margaret Cancer Centre

Emotional distress in our cancer patients is common. There is good evidence that untreated distress is associated with delay in and early discontinuation of treatment, thus affecting outcomes, as well as increased disability post treatment and family distress throughout. Under-treatment of distress partly results from under-detection of distress, but also from our lack of capacity to provide timely access to quality psychosocial specialized care. In view of this, I was asked to provide some practical tips for clinicians faced with patient distress, considering or waiting for a psychosocial oncology appointment.

The main question is whether the distress is due to a psychiatric disorder requiring medication, as well as psychosocial support, or whether the distress is more psychological, social, or spiritual in nature, which may be treated by brief supportive interventions in clinic or psychosocial referral for therapy and/or short-term medications.

Consider the following vignette:

Samantha V. is a 46-year-old female attending clinic accompanied by her mother for treatment planning for a recent recurrence of breast cancer. Within five minutes of the appointment she dissolves into tears and begins sobbing and hyperventilating. Her mother says this has been happening all week, since she met with her surgeon for the biopsy results. Her mother says she is not sleeping.

Oncologists have the difficult job of managing a complex constellation of symptoms in vulnerable patients in the service of administering life-saving or altering treatment. If someone in your office is clearly in an acutely overwhelmed or extremely anxious state lasting days, but there is no safety concern, short-term use of clonazepam 0.25 mg bid (ensure no addiction history) can be helpful whilst the patient adapts and regulates, after which early follow-up, further assessment and, within a few weeks, gradual weaning of the clonazepam should occur. If the patient is not sleeping, consider zopiclone 7.5 mg or trazadone 25-50 mg qhs. If symptoms have persisted longer than several weeks, are worsening and affecting daily function, then initiation of treatment and referral may well be necessary, especially if there is a family or past personal psychiatric history.

Urgent psychiatric referral is indicated for cognitive impairment/mania/psychosis affecting treatment decision-making or resulting in dangerous self-neglect or suicidal or homicidal ideation.

Distress will likely have biopsychosocial or spiritual roots and, in turn, these make up the components of the management. Apart from biological management, it is often very calming and helpful for existential distress to be understood, named, validated and normalized. Death anxiety, living with uncertainty, the importance of meaning in the life led, a strong feeling of connection to those who are important, anticipatory grief, acceptance of cancer/suffering, and spiritual well-being versus existential isolation or despair are all salient areas to identify. Components of support that will help all patients include instillation of hope, validation of feelings and consistent, caring support by the team, as well as encouraging the patient to seek family/spiritual/community/online support. The importance of doctor-patient communication cannot be over-emphasized, particularly around the understanding of diagnosis, prognosis and rationale for treatment, and there is a powerful therapeutic effect if you (the oncology team) simply ask about psychosocial concerns.

If someone is distressed with depressive symptoms, but is still able to enjoy life in between times of extreme distress, tearfulness or sadness, then this may well be an adjustment disorder. It is important not to medicate an adjustment disorder with an antidepressant, as improvement may occur with a few weeks of adaptation, but will then be thought to have responded to the new medication, leaving the patient taking unnecessary medication for the next year. Simple scales may be of help if you are in doubt as to the severity, or wish to track symptoms and can save time in asking about each symptom. Patients can complete them before or after the appointment—the PHQ9 or BDI-II for depression, BAI or HADS for anxiety, MMSE or MOCA for cognition, the Young Mania Rating Scale, the Canadian Problem Checklist to screen for social difficulty, to mention a few.

If a patient seems slowed, dysphoric, and has a restricted, sad affect (does not smile even faintly at any point during the interview with usual social cues) or has neuro-vegetative symptoms of reduced or increased sleep and appetite, impaired concentration and low energy and motivation, along with functional impairment, low mood/loss of enjoyment for several weeks, then you could make a provisional diagnosis of depression. If someone has been a lifelong worrier and this has worsened to cause significant distress and almost constant worrying, they may have generalized anxiety disorder. You would expect worry about little things, as well as big things and for the worry to affect their function, sleep and quality of life. It is not uncommon for people to experience panic attacks at times of stress, if there is an underlying pre-disposition. Panic attacks are characterized by 4-10-minute sudden onset attacks of extreme anxiety with multiple physical symptoms, often leading to a visit to emergency, due to the fear that these are symptoms of a heart attack.

After considering the side effect profile and drug interaction check, usually an SSRI with few drug interactions like citalopram, starting at 10 mg qam, would be first line for definite depression (ensure not bipolar) or an anxiety disorder. If someone is depressed, overweight, hypersonomolent and fatigued, consider a stimulating medication like venlafaxine, starting at 37.5 mg qam, bupropion-XL 150 mg qam (contra-indicated with history of seizure/bulimia) or sertraline starting at 25 mg po qam. However, if someone is not sleeping, has poor appetite, depression and or anxiety, the sedation and appetite stimulation of mirtazepine would be ideal, starting at 7.5 mg (elderly) or 15 mg, increasing after a week to 30 mg qhs in adults. Patients on Tamoxifen should not generally be prescribed medications that significantly affect 2D6, so can be prescribed venlafaxine, starting at 37.5 mg qam (increasing to 75 mg after one week) or citalopram, starting at 10 mg qam, or escitalopram starting at 5 mg qam. Steroid induced psychiatric symptoms can be treated with quetiapine 25-50 mg po qhs (agitation, insomnia) or olanzapine 2.5-5 mg po qhs (mood symptoms and psychosis), along with an urgent referral. A quick shared care phone call or email to psychosocial oncology is also possible and it is wise to have such a link.
...continued from page 1

life. However, while still capable and acutely ill he had consented to receiving oxygen and hydration through artificial means. In the last month of his life when Dad was incapable, I consented to a proposed course of IV hydration to help revitalize him when needed. There were only short periods of sustained benefit from this treatment, and at that point I had to reconsider Dad’s previously stated wishes as they applied to his progressive decline in health. The question I faced was whether Dad had become dependent on a “device” (IV hydration) to extend his life. In consultation with my family and Dad’s physician, it was decided that palliative care would be consistent with Dad’s wishes, and appropriate given his decline in health.

Emotional and psychological difficulties experienced by an SDM can impede the way in which health information is being interpreted and decisions made. I recall an SDM who shared her mother’s love for exercise. The elderly mother was physically disabled and mentally compromised from dementia. Despite the information the SDM received about her mother’s state of diminished health and danger of falling, she persisted in getting her mother out of her wheelchair to walk and exercise. The care team negotiated a safety plan with the SDM and offered resources to help address the difficulties she faced with her mother’s illness. The daughter later became a more capable SDM, better able to judge what was in her mother’s best interests.

People are vulnerable when they lack capacity due to illness or injury, and benefit greatly from having a well-functioning “circle of care”. By circle of care, I mean the working partnership that is formed between an inter-professional treatment team and the patient’s SDM. Here are some suggestions about the role of SDM within this circle of care:

a) Prepare to be an effective advocate for the patient. Ask questions of the care team when you need further clarification about treatment options. Ensure that if you don’t understand the health information or have concerns, you request time for further discussion. In some cases, an SDM may wish to request a second opinion. Mutual respect is crucial to these discussions.

b) Examine whether emotional and/or psychological difficulties are interfering with your ability to fulfill your duties, to face hard facts and engage as a productive member in the circle of care. Get the help and support you may need from professionals, as well as family and friends.

c) Research the actual duties of the SDM beforehand and anticipate the kinds of challenges you are likely to face. If possible, discuss your role, as well as care wishes with the person for whom you will serve as SDM. Confusion or misinformation about your role as an SDM, about the patient’s wishes, or about the duties of the inter-professional team could result in avoidable conflict at a time when a respectful working relationship and a shared sense of compassion are paramount to the patient’s circle of care.

For more information about the role and responsibilities of being an SDM contact the Ethics Centre at 416-480-4818 or follow this link: www.attorneygeneral.jus.gov.on.ca/english/family/pgt/pgtsda.pdf

A tribute to Dr. Larry Librach
Drs. Cyril Danjoux and Calvin Law

There are no adequate words to truly pay tribute to a colleague and dear friend of the Odette Cancer Centre, Dr. Larry Librach. Dr. Librach passed away in August 2013, having lived courageously for 67 years, dedicating his life to the advancement of palliative care—a dedication that will leave a permanent and awesome imprint on medicine forever.

Dr. Larry Librach graduated from the University of Toronto Faculty of Medicine in 1970, where he completed a residency in family medicine. His involvement in palliative care began in 1978. He was the founder of Mount Sinai Hospital’s Temmy Latner Centre for Palliative Care (a position he held for 22 years). He also previously served as the Director of the Joint Centre for Bioethics at U of T. Dr. Librach was the W. Gifford-Jones Professor in Pain Control and Palliative Care at the U of T from 1999 to 2011, as well as Professor in the Department of Family and Community Medicine, where he was also the first head of the division of palliative care from 2007 to 2011. His work in palliative medicine led to major improvements in how health professionals care for dying patients across Canada. Dr. Librach, along with co-pioneer Frank Ferris, built the model for palliative care that has shaped and continues to shape palliative care in Canada. As the physician leader of a national project called Educating Future Physicians for Palliative and End-of-Life Care, Dr. Librach helped introduce curriculum in end-of-life care to Canada’s 17 medical schools. He also authored an educational pain manual—distributed more than 150,000 copies—and co-edited an influential textbook, Palliative Care: Core Skills and Clinical Competencies, which is into its second edition. In 2012, he was awarded the Queen Elizabeth II Diamond Jubilee Medal for his work in palliative care and, in his final months, he received the Balfour Mount Champion Award from the Canadian Hospice Palliative Care Association and the Eduardo Bruera Award in Palliative Medicine by the Canadian Society of Palliative Care Physicians.

At the Sunnybrook Health Sciences Centre and the Odette Cancer Centre, Dr. Librach was the first head of our palliative care program. He initiated many of our current programs. The Rapid Response Radiotherapy Program (RRRP) at the Odette Cancer Centre incorporated one of his visions. In a symposium on palliative radiotherapy in 1996, Dr. Librach suggested, “a separate palliative RT clinic, where access is rapid and patients can be assessed, planned and treated on the same day, would be an excellent way of handling the special needs of those patients”. Today, the RRRP serves with the principles that Dr. Librach laid out 16 years ago.

We are all saddened by the news of his death. He will always be missed as a member of our team, but his impact will echo at this centre and across the nation for all time. We offer our condolences to his family on behalf of Sunnybrook Health Sciences, the Odette Cancer Centre, the RRRP team and our readers.
Continuing Medical Education 2013–2014
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


2014


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

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Management of metastatic castrate resistant prostate cancer prior to chemotherapy: Focus on bone health
Laurence Klotz, MD, Professor of Surgery, Division of Urology, Sunnybrook Health Sciences Centre University of Toronto

Introduction
The treatment of metastatic castrate resistant prostate cancer (mCRPC) has changed dramatically in the last decade.
- Prior to 2004, once patients failed primary androgen deprivation therapy (ADT), they were treated with palliative intent alone
- In that year, pivotal articles by Tannock1 and Petrylak2 demonstrated a survival improvement with docetaxel
- More recently, five additional agents (cabazitaxel, abiraterone acetate, enzalutamide, sipuleucel-T, and alpharadin) that show a survival benefit have been FDA-approved based on randomized clinical trials, with the first three of these agents also approved by Health Canada
- These agents have been tested in a range of “disease states” of CRPC to determine which patients might benefit from each treatment, and to what degree
- Bone-targeted agents (BTAs), particularly zoledronic acid and denosumab, have been shown to improve outcome and reduce morbidity, specifically related to skeletal-related events (SREs)
- Further, the pipeline is full, with more new agents with proven benefit (OGX-011, ODM-201 and ARN 509) working their way through registration trials and approval

Thus, metastatic CRPC has gone from a quiet backwater of oncology, managing patients’ symptoms with modest palliative benefit, to a “hot” disease site with numerous new agents, each associated with a survival benefit. While these drugs are taking their place in routine clinical practice, many questions remain about horizontal and vertical integration (which order, at what point in the disease, and in which combinations), as well as cost and availability.

Treatments options
Androgen Deprivation Therapy
The typical patient with CRPC is elderly, and may have underlying osteoporosis
- ADT induces loss of bone mineral density (BMD)14
- Bone metastases may further put the patient at risk for a fracture
- Thus, maintenance of bone health is a key consideration in this population
- Patients going on long-term ADT should have a DEXA scan of their bone mineral density either at baseline or within the first year of treatment, and BMD should be monitored every two to three years
- Patients on ADT should be placed on Vitamin D, 1,000-1,500 IU per day. The evidence supporting this recommendation is indirect, but these supplements are innocuous. A meta-analysis of randomized studies in 9,000 patients older than 60 reported a 26% reduction in the risk of hip fracture for patients on >700 IU of vitamin D compared to placebo.
- There was no benefit observed at 400 IU/day, the usual multivitamin dose
- Calcium supplementation at a dose of 1,000 mg/day is also recommended, although on its own it does not prevent BMD loss, and has been associated with an increased risk of cardiovascular disease and prostate cancer4
- Alendronate acid (Fosamax)
  - A single dose of 70 mg/week has been shown in two prospective trials, one led by the author,1 to result in an improvement in BMD in men on ADT compared to BMD loss in men on Vitamin D and calcium alone
- Denosumab (Xgeva)
  - A human monoclonal antibody directed against RANK Ligand, which inhibits osteoclast mediated bone destruction
  - Administered subcutaneously monthly
  - In a key randomized trial, patients with minimally symptomatic metastatic CRPC treated with this drug demonstrated a longer time to first skeletal-related event (SRE) compared to zoledronic acid
  - Denosumab resulted in a slightly higher rate of hypocalcemia and the other serious complication is osteonecrosis of the jaw (ONJ). Both of these complications can be minimized by putting patients on calcium supplementation, monitoring serum calcium, and ensuring the patient has no active dental problems prior to starting the drug. Close monitoring of dental health is required
- Zoledronic Acid (Zometa)
  - A rank ligand inhibitor acts to inhibit bone resorption and implantation of bone metastases
  - Administered by infusion every three weeks
  - In a phase III randomized trial; zoledronic acid decreased the incidence of SREs as compared to placebo
  - Longer therapy (up to 24 months) appears to confer continued benefit, even in patients who have experienced one SRE, when compared to placebo
  - The toxicity of this therapy includes a small incidence of ONJ, hypocalcemia and nephrotoxicity9
  - A randomized trial comparing zoledronic acid to denosumab showed that time to first SRE was significantly longer with denosumab, 20.8 versus 17.1 months
  - These data support using denosumab first line for this indication10

Following second line hormonal manipulation, only two agents have demonstrated a survival advantage in the asymptomatic or minimally symptomatic metastatic CRPC patient: docetaxel chemotherapy and sipuleucel-T immunotherapy. Abiraterone acetate plus prednisone has demonstrated progression-free survival benefits. Docetaxel and abiraterone have been approved by Health Canada in metastatic CRPC.
- Abiraterone acetate (Zytiga)
  - An irreversible inhibitor of CYP17A, which has both hydroxylase and lyase enzymatic activity
- In previous reviews, the benefits of the landmark COU-AA-301 study were outlined. Abiraterone, given with prednisone in men failing docetaxel, resulted in a 4.6-month overall survival benefit compared to prednisone alone, which led to Health Canada approval of the product. Median time to occurrence of the first skeletal-related event was significantly longer with abiraterone and prednisone compared with placebo and prednisone (delay: 4.7 mo; p = 0.0001)11,12
- The results from the multinational COU-AA-302 study have also been reported and Health Canada recently approved abiraterone for the use in men with asymptomatic or mildly symptomatic mCRPC prior to chemotherapy. Abiraterone + prednisone prior to chemotherapy showed an improvement in radiographic progression-free survival across all risk groups (16.5 mos AA versus 8.3 mos placebo, HR of 0.53, p value <0.0001). The risk of disease progression was reduced by 47%, an eight-month difference, and the time to opiate use and chemotherapy were also significantly delayed. Overall survival was improved, with a HR of 0.79 and a p value of 0.01; but the pre-specified O’Brien-Fleming boundary value for significance was 0.003, thus this is considered a strong trend for OS12
- A sub-analysis of the data on abiraterone prior to chemotherapy showed that men on the combination of abiraterone and bone-targeted therapies had delayed symptomatic progression compared to patients on abiraterone alone14
- Abiraterone results in an increase in mineralocorticoids upstream of CYP17A, resulting in salt accumulation and hypertension, hypokalemia, peripheral edema and fatigue. These can be prevented in most cases by low-dose glucocorticoids. Prednisone 5 mg bid is used routinely in conjunction with abiraterone for this purpose. In the COU-AA-302 (pre-chemotherapy) study, grade 3 and 4 adverse events were very uncommon13
• Given the strength of the evidence for the benefit of abiraterone when used prior to chemotherapy, this should be considered in patients with coverage or the ability to purchase the drug.

• At the time of this review, the initial recommendation from the pan-Canadian Oncology Drug Review (pCODR) had been made public and summarized that the pCODR Expert Review Committee (pERC) had concluded that there is a net overall clinical benefit to the use of abiraterone acetate in the treatment of asymptomatic or minimally symptomatic mCRPC based on the Phase 3 trial that demonstrated a clinically and statistically significant benefit in radiographic progression-free survival for abiraterone acetate compared with prednisone alone.

Enalutamide (Xtandi)
• Novel androgen receptor signalling inhibitor.
• The AFFIRM trial randomized men with mCRPC post docetaxel between the enalutamide and placebo and resulted in an overall survival that improved significantly with enalutamide, with a four-month median survival benefit.
• The time to first SRE was significantly delayed with enalutamide compared to placebo (delay: 3.4 mo; p = 0.001).
• The drug is currently being evaluated with phase 3 trials in the pre-chemotherapy space, and results should be available within the year.
• Toxicity was mild, related to fatigue, diarrhea, and hot flashes. Five of 800 patients developed seizures.
• Enalutamide is also another active oral agent with minimal toxicity, and was approved by Health Canada in June 2013 for mCRPC patients following chemotherapy.
• It has not yet been approved for funding in Ontario.

On the horizon
Alpharadin (radium-223 chloride)
• A calcium mimic that localizes to the bone and delivers radiation directly to bone metastases by emitting an alpha particle.
• In a recent phase 3 trial in CRPC, radium 223 was administered by infusion monthly for six months resulting in an improved overall survival by 44%, a four-month median survival benefit, and a delay in time to first SRE.
• It is a very well tolerated product; the main adverse event is mild neutropenia and anemia.

• Radium 223 will almost certainly have a role in older and co-morbid patients as an alternative to cytotoxic chemotherapy.
• It has been approved by the FDA, but not yet by Health Canada.

OGX-011
• A novel second-generation inhibitor of the cytoprotective chaperone protein clusterin that may play a role in cell survival and treatment resistance.
• Clusterin is upregulated in tumour cells in response to treatments such as chemotherapy, hormone ablation and radiation.
• A phase 2 study showed that the addition of OGX-011 to docetaxel and prednisone was associated with improved overall survival and a favourable tolerability profile in mCRPC.
• OGX-011 is currently being studied in phase 3 trials.

ARN-509
• A potent selective antagonist of the androgen receptor, similar in action to enalutamide.
• The drug inhibits AR transcriptional activity and prostate cancer cell proliferation.
• In contrast to bicalutamide and other earlier anti-androgens, ARN-509 had no agonist activity in preclinical models.
• In a murine xenograft model of human CRPC, ARN-509 showed greater efficacy than enalutamide.
• In phase 2 studies in CRPC, PSA response rates at 24 weeks were 91%.
• This drug is currently being evaluated in phase 3 studies.

ODM-201
• A new androgen receptor (AR) inhibitor with higher affinity for the AR and better anti-proliferative activity in prostate cancer xenograft models compared to enalutamide.
• ODM-201 and its major metabolite ORM-15341 inhibit AR translocation to the nucleus.
• Results of a phase I/IIa proof-of-concept study in patients with progressive metastatic castration-resistant prostate cancer (mCRPC) were presented recently at ESMO.
• The studies were dose-ranging and stratified patients by whether they had received chemotherapy or a CYP 17 inhibitor (i.e., abiraterone).
• The drug was well tolerated and demonstrated high activity in all patient groups.

Conclusion
The pre-chemotherapy space for men with CRPCs is burgeoning with new, relatively non-toxic and well-tolerated drugs that offer a survival benefit and improved quality of life. Only the bone-targeted agents (Zoledronic acid and Denosomab) are currently funded in Ontario. Abiraterone is funded for patients post docetaxel and for patients who are ineligible for chemotherapy in British Columbia and Quebec. It is likely that within the foreseeable future, Abiraterone and Enalutamide will be funded and available for patients prior to chemotherapy.

Clusterin is upregulated in tumour cells in response to treatments such as chemotherapy, hormone ablation and radiation.

References
Gastrointestinal stromal tumours (GIST)

Drs. Yooj Ko and Calvin Law, Sunnybrook Odette Cancer Centre

1. What is GIST?

GIST stands for gastrointestinal stromal tumours, which are the most common mesenchymal tumours of the gastrointestinal tract. In Canada, approximately 500 new cases are diagnosed each year. The putative cell of origin is the interstitial cells of Cajal (ICC), which are the pacemaker cell for intestinal peristalsis. The majority of tumours are sporadic, but familial cases can occur in those with neurofibromatosis type 1, Carney’s triad and familial GIST syndrome known as Carney-Stratakis syndrome. The stomach is the most common site followed by the small intestine, although rectal and colonic GISTs are relatively uncommon.

2. What are the pathologic features of GIST?

The principal histologic types include spindle cell type (more common), epithelioid or, rarely, mixed. Routine immunohistochemical staining is positive for CD117 (KIT), DOG-1 and CD34 in the majority of cases and are critical in confirming the diagnosis of GIST. In the past two decades, GIST has become an ideal tumour model in the identification of molecular aberrations and the development of corresponding targeted therapies. Nearly 80% of all GIST tumours harbour a KIT gene mutation, which leads to the development of corresponding targeted therapies.

3. When is a GIST operable and not operable in 2013?

Surgery is still the primary modality for cure for GIST tumours. Regardless of the location of the primary GIST tumour, there are some consistent principles for surgical selection. Clearly operable tumours are defined as: (1) isolated primary tumours where there is no evidence of systemic metastases or peritoneal spread; (2) fully resectable with predictable R0 margins; (3) surgery would not result in major functional impact; (4) and that the patient is fit for surgery. Non-operable tumours are defined as: (1) primary with metastatic disease in minimally or asymptomatic patients; (2) surgery would clearly result in a predicted positive margin; (3) a patient who is not able to physiologically tolerate surgery. It becomes more challenging in the situation where: (1) it is difficult to predict margin—may be R1 or R0; (2) the surgery may impact function considerably (example: requires an abdominal-perineal resection that requires a permanent stoma, or a Whipple procedure).

4. What are the current surgical principles for resection?

There are a few main principles for good surgical technique in resection. The most important over-riding principles are that the GIST surgery should be planned using multiphasic CT imaging and that surgery must not rupture the tumour and be completed with a microscopic negative margin (R0). The margin does not have to be large, but general consensus would agree that a minimum 1 cm microscopically negative margin is best. Additional specific principles of surgery would further include: (1) ultra-careful retraction to prevent tumour rupture or rupture of adhesions attached to the tumour; (2) gentle manipulation—pressure must be spread over wide areas of the tumour to prevent a puncture or rupture of the GIST tumour otherwise; (3) adhesions to GIST tumours should never be taken down with blunt dissection, rather they need to be divided sharply and usually contain vascular elements; and (4) lymphadenectomy is not required in GIST resections, so organ preservation should always be considered, when possible. However, suspicious masses not otherwise diagnosed on a pre-operative CT Scan should be considered for simultaneous resection, if safe, for diagnosis.

Table 1: Risk Classification for Primary GIST by mitotic index, size and primary tumour site (adapted from Mitettinen & Lasota, 2006. Seminars in Diagnostic Pathology, 23, 70–83)

<table>
<thead>
<tr>
<th>Tumour Characteristics</th>
<th>Risk of Progressive Disease</th>
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<tbody>
<tr>
<td>Mitotic Index</td>
<td>Size</td>
</tr>
<tr>
<td>≤ 5 per 50 hpf</td>
<td>≤ 2 cm</td>
</tr>
<tr>
<td></td>
<td>&gt;2 ≤ 5 cm</td>
</tr>
<tr>
<td></td>
<td>&gt;5 ≤ 10 cm</td>
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5. What are the current principles for adjuvant therapy?
Surgical resection remains the cornerstone of treatment for non-metastatic GISTs. The prognostic factors include primary tumour site, size of primary tumour, and the mitotic index (see Table 1). Adjuvant imatinib for 12 months following surgical resection of GISTs larger than 3 cm improves recurrence-free survival, as demonstrated by a randomized, placebo-controlled trial by Dematteo et al. Recurrences are often noted in the first few years following discontinuation of adjuvant imatinib. A large randomized study of three years of adjuvant imatinib versus one year of therapy demonstrated an improved relapse-free survival, as well as longer overall survival in favour of three years of therapy. Consequently, the current standard of care in Ontario is three years of adjuvant imatinib for those with either an intermediate or high risk of recurrence according to the modified National Institutes of Health Consensus Criteria.

6. What are the current principles of neoadjuvant therapy for GISTs that are not immediately resectable?
GIST may not be amenable to surgical resection due to either its size or location. The goal of any neoadjuvant therapy is to downsize a borderline resectable tumour and to avoid any mutilating surgery that may compromise organ function such as in rectal GISTs. There are no randomized studies supporting this approach and few single arm phase 2 studies have been reported to date. It is important to obtain histologic diagnosis of GIST prior to initiating treatment with imatinib. Although the optimal duration of preoperative therapy is not yet known, it is generally accepted to treat until maximal response, as demonstrated by no further tumour reduction in two separate scans. Given the results of the three-year adjuvant study, most patients are recommended to complete at least three years of imatinib, including the duration of the preoperative therapy.

7. What are the current principles of therapy for advanced, metastatic GIST patients?
The current standard for patients with metastatic GIST remains imatinib at 400 mg once a day for nearly all patients who are able to tolerate the medication. For those who are known to harbour a mutation in exon 9 and for those who progress on 400 mg, dose escalation to 800 mg a day is advised. The treatment is generally continued until progression, as discontinuation of imatinib is associated with inferior outcomes. When there is progression on 800 mg a day of imatinib, therapy is changed to sunitinib. Plasma imatinib monitoring may be available for those who do not respond to standard doses or for those who are experiencing significant toxicity to require dose modifications. Recently, the results of the GRID study compared a novel tyrosine kinase inhibitor (TKI), regorafenib to placebo for those who have progressed on sunitinib (Figure 1). Based on an improved progression-free survival for those on regorafenib (4.8 versus 0.9 months, Table 2), regorafenib was approved by the FDA in the U.S., and was also recently approved by Health Canada. In terms of toxicity, fewer patients on the regorafenib arm discontinued the study drug, as compared to those receiving placebo. Hand-foot reactions, hypertension and diarrhea were the most common side-effects observed in those receiving regorafenib.

8. What are the future directions for GIST patients?
GIST has been a model for targeted therapy in both solid and hematological tumours. Although several TKIs have been tested against imatinib, none have been found to be superior to date. Masatinib, which, in vivo, has greater activity and selectivity than imatinib against the wild-type c-kit receptor and activated mutant (exon 9 or 11) or secondarily resistant (exon-14) c-kit, has been found to have encouraging survival benefits in comparison to sunitinib in imatinib resistant GIST patients. Ongoing phase 3 studies of masatinib versus imatinib in the first line setting and versus sunitinib in the second line setting are being conducted.