HOT SPOT

SUNNYBROOK & WOMEN'S
Sunnybrook and Women's College Health Sciences Centre

Guest editorial

By May N. Tsao, MD, FRCP(C), Radiation Oncologist

The Rapid Response Radiotherapy Program at the Toronto-Sunnybrook Regional Cancer Centre would like to welcome doctors Lisa Barbera and Yoo-Joung Ko to the editorial board of **Hot Spot.** This edition of **Hot Spot** features several interesting articles including subjects such as "What keeps us going in our work?" by Dr. Vachon, "Research ethics and the importance of determining risk" by K. Faith, and an article which explores terminal sedation and the ethical issues surrounding this topic by Dr. Cellarius. This issue's insert was written by Dr. Ko who summarizes the management of hormone refractory prostate cancer and the role of a prostate bone metastasis multidisciplinary clinic. We hope you will find this issue informative.

What keeps us going in our work?

By Mary L.S. Vachon, RN, PhD

Job engagement (Maslach, Schaufeli & Leiter, 2001) and compassion satisfaction (Stamm, 2002) are two frameworks to understand what keeps workers functioning and enjoying work in difficult situations.

Job engagement is conceptualized as the opposite of burn-out. It involves energy, involvement and efficacy. Engagement involves the individual's relationship with work. It involves a sustainable workload, feelings of choice and control, appropriate recognition and reward, a supportive work community, fairness and justice and meaningful and valued work. Engagement is also characterized by high levels of activation and pleasure. Engagement is defined as a persistent, positive-affective-motivational state of fulfillment in employees that is characterized by vigour, dedication and absorption.

Compassion satisfaction (CS) is satisfaction derived from the work of helping others. It may be the portrayal of efficacy. Compassion satisfaction may be happiness with what one can do to make the world in which one lives a reflection of what one thinks it should be. Caregivers with CS derive pleasure from helping others, like their colleagues, feel good about their ability to help and make a contribution. Stamm describes a balancing act between compassion fatigue, which is associated with the "cost of caring" for others in emotional pain, and compassion satisfaction. Caregivers may be experiencing compassion fatigue, yet they like their work because they feel positive benefits from it. They believe what they are doing is helping others and may even be redemptive. When a person's belief system is well-maintained with positive material, a person's resiliency may be enhanced. What seems to count most for resilience is the opportunity to encounter pain within a context of meaning and to find that one's compassion (one's suffering with) has power. These sustain an underlying belief that the world is good and in order (Young-Eisendrath, 1996).

Stamm suggests that if compassion fatigue and burn-out are combined, there may be no energy available to sustain the vision of a better world in which one could find satisfaction. Burn-out, characterized by exhaustion, seems to

continued on page 2…

HOT SPOT

The Newsletter of the Rapid Response Radiotherapy Program of Toronto Sunnybrook Regional Cancer Centre

Vol. 7, Issue 4, November 2005

Toronto Sunnybrook
Regional Cancer Centre,
2075 Bayview Avenue,
Toronto, Ontario M4N 3M5
Tel: (416) 480-4998,
Fax: (416) 480-6002
E-mail: cyril.danjoux@sw.ca
Website:
http://www.sw.ca/programs/tsrcc/treatmentprevention/rapidresponse

Produced by Pappin Communications, Pembroke, Ontario
www.pappin.com

In this issue: **What keeps us going in our work?; Research ethics and the importance of determining risk; Temmy Latner Centre Update on Palliative Care – Is terminal sedation ethical?; Research Corner – Results of three important randomized studies and their clinical implications**

Insert – Management of hormone refractory prostate cancer; Prostate bone metastasis multidisciplinary clinic

Research ethics and the importance of determining risk

By Karen Faith, Med, MSc, RSW

Clinical research is governed by standards for scientific merit as well as ethical criteria intended to protect the rights of subjects and to ensure that risks to research subjects are both reasonable and justifiable. The goal of research is to improve treatments designed to cure or prevent disease, extend the lifespan of those with incurable illnesses and enhance the comfort as well as activities of daily living for those with chronic conditions. There is reason to be enormously grateful for the skilled science and technology behind these medical innovations as well as for the dedicated scientists behind the research. At the same time, respect must be shown for the courageous individuals who agree to be research subjects in the hope of furthering scientific understanding of disease and the promotion of healing as well as identifying optimum care strategies. The medical innovations that result from such research are rarely discovered in time to benefit the subjects themselves. Understanding of risk, often defined by researchers and identified by research ethics boards, should include the opinions and experiences of research subjects as well.

How much risk or what kinds of risks are acceptable for research subjects whose interests lay at the heart of why research ethics boards were conceived and developed? In lay terms, risks should be reasonable and in proportion to the likely benefits afforded to science, society or future patients with similar conditions. Risks are often measured against those risks associated with more conventional forms of treatment. Some in the bioethics community argue that patients themselves should have more say in how much risk is acceptable or whether patients regarded as too vulnerable to be part of clinical research should, in fact, be given the right to make an informed choice about participating in research trials or qualitative studies (Berry, 2004).

Research ethics boards, scientists and health care professionals, as well as those from the pharmaceutical manufacturing industry, share a common obligation to examine acceptable levels for risks associated with biomedical research. Responsible scientists and professionals, as well as members of research ethics boards have a duty to ensure that the interests and safety of research subjects are not only protected, but also adequately understood from the perspective of subjects themselves. It is, therefore, important that former research subjects and family members whose loved ones participated as research subjects are among the community members that sit on research ethics boards. In addition, former research subjects, or substitute decision-makers can provide valuable insight and speak to such issues in educational forums provided for health care professionals and researchers. In addition, risks should be outlined to subjects in lay terms, with understandable concepts or terminology, in ways that provide as much opportunity as necessary to ensure that subjects are well-informed. We, as a society, owe an enormous debt to the individuals who, by volunteering as research subjects, furthered medical science and provided the research community with many valuable lessons about the protection of the rights and the safety of research subjects.

Vachon

… continued from page 1

make it impossible to envision a world in which one is not overwhelmed by an inability to be efficacious. The lack of efficacy (individual or corporate) likely colours negatively a person's view of his or her fit with a personal belief system.

The compassion of caregivers may catch the attention of others. Dr. Peter Frost was a professor of organizational behaviour. As he was being treated for metastatic melanoma, he observed the nurses of the British Columbia Cancer Agency "whose highly professional and empathic behaviour caught my attention when I was in their care. They sparked my initial interest in exploring the meaning and practice of compassion". Observing and reflecting on the compassion of these nurses led to his book, *Toxic Emotions at Work: How Compassionate Managers Handle Pain and Conflict,* hailed as one of the top management books of 2003. "My illness – a trigger for changes, obviously in my personal life – also set in motion my thinking about the kinds of hidden forces that determine our well-being, even to the point of acquiring disease. And, in particular, how the behaviour of organizations and the people in them can affect the health of certain individuals. … A few months after my surgery, I found myself at a week-long seminar on health and healing. That is where my ideas about emotional pain in organizations, and its effects on people who try to manage that pain for organizations began to crystallize".

Frost draws on the work of Dr. Larry Dossey (*Be Careful What You Pray For,* Harper Collins, 1997) and Daniel Goleman (*Emotional Intelligence,* Bantam, 1995) to understand the power of negative thoughts and the contagion of emotion. He concluded that "…the whole area of pain and suffering – and any attempts to help others – was fraught with danger." Handling emotional toxins can be as hazardous as working with physical toxins.

Within organizations there can be toxic relationships amongst colleagues. Clinicians can be overwhelmed with the tragedies to which we are exposed. Frost suggests that those who handle toxic emotions routinely should create a game plan for self-protection involving breaks, healthy connections with others, a kind of tempered optimism for the task at hand, and a degree of self-compassion for their attempts to heal themselves. He suggests the need for toxin handlers to strengthen their physical capacity, boost their emotional capacity, regenerate their mental capacity and build their spiritual capacity.

References

Maslach, C., Schaufeli, W.B., & Leiter, M.P. (2001). Job burnout. **Annu Rev Psychol, 52,** 397-422.

Stamm, B.H. (2002). Measuring Compassion Satisfaction as Well as Fatigue: Developmental History of the Compassion Fatigue and Satisfaction Test. In C.R. Figley (Ed.) **Treating Compassion Fatigue** (pp. 107-119). New York: Brunner Rutledge.

Young-Eisendrath, P. (1996). **The Resilient Spirit: Transforming Suffering into Insight and Renewal.** Perseus.

Mary L.S. Vachon, RN, PhD, is a psychotherapist in private practice and Professor, Departments of Psychiatry and Public Health Science, University of Toronto. She may be reached at ***maryvachon@sympatico.ca****.*

Temmy Latner Centre Update on Palliative Care

Is terminal sedation ethical?

By Victor Cellarius, MD, CCFP

Given that many of us will, at some point, recognize not abstractly, but directly, the approach of our own death, we may well ask, "How am I to do this, this dying and death?" One answer that has begun to show itself in many countries around the world in one form or another is a type of circumvention. "Dying" is forgone such that the unavoidable end of death is induced, but the period of dying is avoided so far as possible. In the medical field, these answers show up under the heading of "physician-assisted dying" (PAD), which includes euthanasia, assisted suicide and palliative (terminal) sedation. Of the three, I will discuss palliative (terminal) sedation, the only practice with medical sanction in Canada.

Palliative sedation refers broadly to several practices of sedation for symptom control in terminally ill patients, and many of these practices are fairly uncontentious. Reviews of palliative sedation have intimated (though it is difficult to prove) that sedation in imminently dying patients reduces symptoms without hastening death (Sykes & Thorns, 2003). However, controversy remains regarding instances of palliative sedation that are thought to hasten death, and these I refer to here as "terminal sedation".

Terminal sedation is thought to hasten death in two ways. The first way appears as a consequence of terminal sedation but it is not. If we clarify the concepts and clarify our practice accordingly, the problem dissolves. The second way is rare, though it receives much attention in ethical discussion. It finds ethical justification through certain conditions including the "Principle of Double Effect", though we should note that this justification is sometimes challenged. I will remark on both these ethically contentious ways to death, mentioning how the first way can be dissolved and how the second way is typically justified.

One way terminal sedation is thought to cause death is by "stopping everything". By this I mean the simultaneous occurrence of both sedation and the withholding or withdrawal of life-sustaining treatments (e.g. stopping high-dose steroids abruptly or withdrawing parenteral nutrition and hydration). The confusion is to consider all these choices together as being terminal sedation, as an all-or-nothing option. These choices must be distinguished. Withholding and withdrawing life-sustaining therapies are choices, while beginning sedation to control intractable symptoms is yet another distinct choice. First is the question of whether life-sustaining treatments should be forgone, and second is the question of whether sedation is required to control symptoms. By separation, each practice can be ethically and legally justified (or not) on its own terms.

In rare cases, we may expect that the sedation required to control symptoms may in itself hasten death. Justification for proceeding with sedation in such circumstances arises from several sources: 1) that sedation will actually control the symptom, 2) that the patient (or power of attorney) consents to sedation, knowing the possibility of hastened death exists, 3) that proceeding would agree with the definition of terminal sedation, and 4) that proceeding would agree with the principle of double effect.

Condition one is usually fulfilled. Condition two is necessary of any treatment. Condition three entails that: i) the symptom is profoundly distressing to the patient, ii) that no other way exists to palliate this symptom, and iii) that the patient is imminently dying (usually days from death) (Cowan & Walsh, 2001). Condition four requires that the physician intends only symptom control in sedating the patient and that dosing reflects this intention (Boyle, 2001). Intending to hasten death, even as a means to end suffering, is ethically and legally proscribed, falling, in the Criminal Code of Canada, under the description of murder. Intending through treatment to control symptoms, even where such practice may hasten death, is thought to be permitted through common law precedent (though such a case has yet to come to trial in Canada) (Sneiderman, 2002). These conditions of justification receive continuing criticism but, generally, are understood in legal and ethical discussion to permit palliative sedation even in cases of terminal sedation in which the sedation itself is thought likely to hasten death.

References

Boyle, J. (2001). Toward Understanding the Principle of Double Effect. In P.A. Woodward (Ed.), **The Doctrine of Double Effect: Philosophers Debate a Controversial Moral Principle** (pp. 7-20). Notre Dame, IN: University of Notre Dame Press.

Cowan, J.D., & Walsh, D. (2001). Terminal sedation in palliative medicine - Definition and review of the literature. **Supportive Care In Cancer, 9**, 403-407.

Sneiderman, B. (2002). Decision-making at the end of life. In J. Downie, T. Caulfield, & C. Flood (Eds.), **Canadian Health Law and Policy** (pp. 501-531). Markham, ON and Vancouver, BC: Butterworths.

Sykes, N., & Thorns, A. (2003). The use of opioids and sedatives at the end of life. **The Lancet Oncology, 4**, 312-318.

Research corner

Results of three important randomized studies and their clinical implications

By J. Wu, MD, FRCPC

Three large randomized trials of patients with bone metastases were published in the last six months:

1. Neuropathic bone pain study (Radiotherapy & Oncology, Apr 2005, 75, 54-63). Principal investigator: Dr. Daniel Roos, Royal Adelaide Hospital, Australia.

This multicentre study randomized 272 bone mets patients to palliative radiotherapy of either single treatment (8 Gy) or multiple treatments (20 Gy in five fractions). Study design included a specific pain definition of "pain or dysesthesia with a radiating cutaneous [superficial] component in the distribution of one or more spinal nerves or peripheral nerves, often associated with altered sensation along the same distribution".

Patients on this study were different from other randomized trials of "uncomplicated" bone pain (see below). Although the overall pain response did not differ significantly between the two arms (61% versus 53%, p=0.18 favouring 20 Gy), the study did not exclude a potentially inferior response rate of 15% for single fraction treatment. This is a mind twister typically associated with "non-inferiority" trial design.

The bottom line is that multiple fractions of radiation could be significantly better than single treatment. For the good-performance patient with neuropathic pain from bone metastases, a one-week course of treatment is advisable. However, it may be preferable for patients with limited travelling capability to try a single 8 Gy treatment, and re-treat to a similar or higher dose if the initial treatment is ineffective.

2. RTOG 9714: Single versus two-week treatment of palliative radiotherapy for bone metastases (J Nat Cancer Inst, June 2005, 97, 798-804). Principal investigator: Dr. William Hartsell, Advocate Good Samaritan Hospital, Illinois.

This large U.S. multicentre study of 8 Gy versus 30 Gy/10 fractions was designed specifically to answer the question of whether one treatment is as good as a more prolonged course of treatment for ***uncomplicated*** bone pain. A few Canadian cancer centres (including TSRCC) also participated. Only breast and prostate cancer patients were included. Their relatively longer life expectancy might benefit more from a longer course of treatment. 30 Gy/10 fractions is the most common palliative radiotherapy dose given in the U.S.

No significant difference in pain response was found between the two treatment arms for a total of 898 patients randomized. Among the 573 patients evaluated at three months, single 8 Gy and 30 Gy/10# gave overall pain response of 65% and 66% respectively (p=0.6), with 33% of the patients free from narcotic analgesia. Patients treated with single 8 Gy had fewer side effects, but were more likely to be re-irradiated. It is important to note that re-irradiation is not an outcome to compare the two treatment arms for several reasons, including the fact that few oncologists would re-treat an area over the spine after an initial treatment to 30 Gy (investigator bias).

The bottom line is that once again single treatment of 8 Gy appears as effective as longer treatment in alleviating uncomplicated pain due to bone metastases. This is consistent with the results of seven other randomized studies of more or less the same question.

3. Spinal cord compression treated with radiation +/- surgical decompression (The Lancet, 21 Jul 2005). Principal investigator: Dr. Roy Patchell, University of Kentucky Medical Center, Kentucky.

This is another landmark study by Dr. Patchell. It took 10 years to randomize 100 patients presenting with spinal cord compression in varying degrees of ambulatory status (no paraplegia >48 hrs). Except for known diabetics, all patients received 100mg of dexamethasone at diagnosis of cord compression, followed by 24mg q 6 hr until start of radiotherapy or surgery (tapering course thereafter). RT (alone) or surgery (followed by RT within 14 days post-op) would start within 24 hours of diagnosis. All patients received RT to dose of 30 Gy/10 fractions, the most common palliative prescription in the U.S.

A significantly greater proportion of patients were able to walk after surgery+RT (84%) than RT alone (57%). Of the 32 non-ambulatory patients randomized, 10/16 regained the ability to walk after surgery+RT, compared to only 3/16 after RT alone (p=0.03). Those patients who regained walking after RT alone all had surgery as salvage treatment. Failure of fixation/graft and/or post-op wound complications were seen in 12% of patients in the surgery+RT arm.

The bottom line is that spinal cord compression is a structural problem that requires a structural fix (decompression +/- stabilization). Although some selection criteria might make the results less generalizable, it is clear that early surgical intervention provides significantly better ambulatory outcome. It is best to consult with local neurosurgical and/or orthopedic/spine surgery regarding appropriate indications for referral.

These three well-conducted randomized trials highlight the importance of thoughtful evaluation of patients with symptomatic bone metastases. Chronic, gnawing pain exacerbated by activity may be easily palliated with a single treatment of radiation. On the other hand, complex pain symptoms due to nerve root compression (neuropathic) or, in the worst case scenario, spinal cord compression, require more aggressive and, often, multidisciplinary management for better outcomes.

Dr. Wu is a Clinical Associate Professor, Department of Oncology, Tom Baker Cancer Centre, University of Calgary

The newsletter of the Rapid Response Radiotherapy Program of Toronto Sunnybrook Regional Cancer Centre is published through the support of:

Abbott Laboratories, Ltd
AstraZeneca
Amgen
Boehringer Ingelheim
GlaxoSmithKline
Kyphon
Novartis
Ortho Biotech
Pharmascience
Purdue Pharma
Sanofi Aventis
Solvay
Valeant Canada
VitalAire

HOT SPOT

Yoo-Joung Ko, MD, MMSc, SM, FRCPC
Assistant Professor, University of Toronto
Staff Physician, Division of Medical Oncology/Hematology
Toronto Sunnybrook Regional Cancer Centre

Management of hormone refractory prostate cancer

Background

- Most commonly diagnosed non-skin cancer in men
- Lifetime risk 1/7
- In 2005, 20,500 are expected to be diagnosed and 4,300 deaths are expected to occur in Canada
- Almost all those who die from prostate cancer have hormone refractory disease at time of death
- Until recently, chemotherapy did not improve survival

Clinical manifestations

- Asymptomatic patients who have a rising PSA while on LHRH agonists are becoming more common
- Fatigue, anorexia and weight loss are present at later stages of disease
- Skeletal complications including bone pain, pathologic fractures and spinal cord compression
- Urinary obstruction and hematuria are seen in those who have not had a prior prostatectomy

Additional hormonal therapy for HRPC

- Continued LHRH agonist is standard of therapy
- Anti-androgen withdrawal observed in a minority of patients
- High dose ketoconazole and hydrocortisone well-tolerated and effective in some patients

Chemotherapy for HRPC

- Until 2004, mitoxantrone and prednisone (M+P) were the standard of therapy. Palliative benefit is seen in about a third of symptomatic patients, and a large phase III (CALGB 9152) study failed to demonstrate a survival benefit when compared to steroid alone
- Two large phase III studies demonstrated a survival benefit to a docetaxel-based regimen when compared to M+P (see Table One)
- In TAX 327, 1.8-month improvement in overall survival (p=0.03)
- In SWOG 9916, two-month improvement in overall survival (p=0.01)
- Better quality of life in docetaxel arm in TAX 327
- Longer time to progression in SWOG 9916 (six versus three months)

Side effects with docetaxel-based regimens

- Severe toxicity rare
- Fatigue, anemia and grade three neutropenia most common
- Thrombotic risk with estramustine

Supportive therapy

- Bisphosphonates (zoledronic acid) is associated with a significant decreased risk of skeletal-related events (hazard ratio of 0.64)
- Patients who received zoledronic acid had six months longer without complications

Unanswered questions

- It is unclear if those with asymptomatic metastatic disease benefit from early administration of chemotherapy
- Estramustine is associated with increased toxicity, but its added value to docetaxel is unclear
- No clear second-line chemotherapy available

Summary and future directions

- Continue LHRH agonist in HRPC
- In those with asymptomatic progression, discontinue anti-androgen and consider ketoconazole and hydrocortisone
- Enroll on clinical trial if available
- Zoledronic acid in those with asymptomatic or minimally symptomatic bone metastasis
- Docetaxel-based regimen is associated with improved survival, time to progression and quality of life
- Future trials are examining the role of novel targeted therapies (e.g. VEGF) in addition to docetaxel

Table One: Summary of docetaxel studies

Trial	# of Patients	Regimens	Median Survival	P value	PSA response
TAX 327 (2004)	997	1) Docetaxel 75mg/m^2 q3week + pred 5mg bid	18.9 months	0.009	45% (p=0.0005)
		2) Docetaxel 30mg/m^2 qweekly (5 of 6 weeks) + pred 5mg bid	17.4 months	0.3	48% (p<0.0001)
		3) Mito 12mg/m^2 +pred 5mg bid	16.5 months	-	32%
SWOG 9916 (2004)	674	1) Docetaxel 60mg/m^2 + estramustine 280mg tid x 5 days (q3weeks)	17.5 months	0.01	50% (p<0.0001)
		2) Mitox 12mg/m^2 + pred 5mg bid	15.6 months	-	27%

HOT SPOT

Yoo-Joung Ko, MD, MMSc, SM, FRCPC
Assistant Professor, University of Toronto
Staff Physician, Division of Medical Oncology/Hematology
Toronto Sunnybrook Regional Cancer Centre

Prostate bone metastasis multidisciplinary clinic

Prostate cancer cells exhibit a unique tropism for bone and bone marrow and nearly all patients with advanced prostate cancer have bone metastasis during some time in the course of their disease. Bone metastasis remains the single most important cause of morbidity in prostate cancer patients. Skeletal complications can result in pain, pathologic fractures, hypercalcemia and spinal cord compression.

Emerging supportive treatments – including advances in systemic therapy, bisphosphonates, and vertebroplasty – warrant thoughtful integration that is best achieved through a multidisciplinary setting. Many prostate cancer patients who are referred to a comprehensive cancer centre are initially referred for palliative radiation therapy to a painful bony lesion. However, it is unclear how many of these patients have reasonable access to other systemic and interventional therapies. A multidisciplinary prostate bone metastasis clinic will facilitate rapid and convenient access for patients to specialized care.

We are pleased to announce the addition of a prostate-focused effort to the bone metastasis clinic at the Toronto Sunnybrook Regional Cancer Centre (TSRCC) supported by Novartis Pharmaceuticals Canada. The bone metastasis clinic is a research-focused multidisciplinary clinic composed of several specialities including radiation oncology, orthopedic surgery, interventional radiology and palliative care. This clinic has been an integral part of the Rapid Response Radiotherapy Program at TSRCC since 1999. The addition of a prostate cancer fellow and a GU medical oncologist to the multidisciplinary clinic will enhance the mission of the bone metastasis group. The clinic will act to provide care and education for those patients with skeletal complications from their prostate cancer and its treatments. Research will be focused on quality-of-life issues as well as biochemical markers of bone metastasis and novel systemic therapeutic treatments. The clinic will also seek to determine the patterns of care for patients with advanced prostate cancer.

Clinic mission

To provide the state of the art therapy for men with metastatic prostate cancer to bone through patient education and research.

When is the clinic held?

- Twice a month on Friday mornings

Who will be at the clinic?

- Physicians including radiation and medical oncologists, orthopedic surgeons, interventional radiologists, palliative care physicians
- Primary care nurses
- Research assistants

Who can be referred?

- Patients with either asymptomatic or symptomatic bone metastasis
- Patients may have either hormone sensitive or hormone refractory prostate cancer
- Patients requiring palliative radiation therapy to bone
- Patients requiring surgical intervention
- Patients with symptoms refractory to conventional treatment
- Patients requiring systemic therapy e.g. chemotherapy or bisphosphonates

What can patients expect?

- Palliative radiation therapy
- Supportive care
- Systemic therapy including participation in clinical trials of novel agents
- Pain management
- Surgical intervention if required
- Prompt communication with referring physicians

How to refer

- Call new patient referrals at 416-480-4205 and ask for the bone metastasis clinic
- Fax a referral to 416-480-6179

Supported by an educational grant from Novartis

NOVARTIS ONCOLOGY

HOT SPOT

Yoo-Joung Ko, MD, MMSc, SM, FRCPC
Assistant Professor, University of Toronto
Staff Physician, Division of Medical Oncology/Hematology
Toronto Sunnybrook Regional Cancer Centre

Management of hormone refractory prostate cancer

Background

- Most commonly diagnosed non-skin cancer in men
- Lifetime risk 1/7
- In 2005, 20,500 are expected to be diagnosed and 4,300 deaths are expected to occur in Canada
- Almost all those who die from prostate cancer have hormone refractory disease at time of death
- Until recently, chemotherapy did not improve survival

Clinical manifestations

- Asymptomatic patients who have a rising PSA while on LHRH agonists are becoming more common
- Fatigue, anorexia and weight loss are present at later stages of disease
- Skeletal complications including bone pain, pathologic fractures and spinal cord compression
- Urinary obstruction and hematuria are seen in those who have not had a prior prostatectomy

Additional hormonal therapy for HRPC

- Continued LHRH agonist is standard of therapy
- Anti-androgen withdrawal observed in a minority of patients
- High dose ketoconazole and hydrocortisone well-tolerated and effective in some patients

Chemotherapy for HRPC

- Until 2004, mitoxantrone and prednisone (M+P) were the standard of therapy. Palliative benefit is seen in about a third of symptomatic patients, and a large phase III (CALGB 9152) study failed to demonstrate a survival benefit when compared to steroid alone
- Two large phase III studies demonstrated a survival benefit to a docetaxel-based regimen when compared to M+P (see Table One)
- In TAX 327, 1.8-month improvement in overall survival (p=0.03)
- In SWOG 9916, two-month improvement in overall survival (p=0.01)
- Better quality of life in docetaxel arm in TAX 327
- Longer time to progression in SWOG 9916 (six versus three months)

Side effects with docetaxel-based regimens

- Severe toxicity rare
- Fatigue, anemia and grade three neutropenia most common
- Thrombotic risk with estramustine

Supportive therapy

- Bisphosphonates (zoledronic acid) is associated with a significant decreased risk of skeletal-related events (hazard ratio of 0.64)
- Patients who received zoledronic acid had six months longer without complications

Unanswered questions

- It is unclear if those with asymptomatic metastatic disease benefit from early administration of chemotherapy
- Estramustine is associated with increased toxicity, but its added value to docetaxel is unclear
- No clear second-line chemotherapy available

Summary and future directions

- Continue LHRH agonist in HRPC
- In those with asymptomatic progression, discontinue anti-androgen and consider ketoconazole and hydrocortisone
- Enroll on clinical trial if available
- Zoledronic acid in those with asymptomatic or minimally symptomatic bone metastasis
- Docetaxel-based regimen is associated with improved survival, time to progression and quality of life
- Future trials are examining the role of novel targeted therapies (e.g. VEGF) in addition to docetaxel

Table One: Summary of docetaxel studies

Trial	# of Patients	Regimens	Median Survival	P value	PSA response
TAX 327 (2004)	997	1) Docetaxel 75mg/m^2 q3week + pred 5mg bid	18.9 months	0.009	45% (p=0.0005)
		2) Docetaxel 30mg/m^2 qweekly (5 of 6 weeks) + pred 5mg bid	17.4 months	0.3	48% (p<0.0001)
		3) Mito 12mg/m^2 +pred 5mg bid	16.5 months	-	32%
SWOG 9916 (2004)	674	1) Docetaxel 60mg/m^2 + estramustine 280mg tid x 5 days (q3weeks)	17.5 months	0.01	50% (p<0.0001)
		2) Mitox 12mg/m^2 + pred 5mg bid	15.6 months	-	27%

HOT SPOT

Yoo-Joung Ko, MD, MMSc, SM, FRCPC
Assistant Professor, University of Toronto
Staff Physician, Division of Medical Oncology/Hematology
Toronto Sunnybrook Regional Cancer Centre

Prostate bone metastasis multidisciplinary clinic

Prostate cancer cells exhibit a unique tropism for bone and bone marrow and nearly all patients with advanced prostate cancer have bone metastasis during some time in the course of their disease. Bone metastasis remains the single most important cause of morbidity in prostate cancer patients. Skeletal complications can result in pain, pathologic fractures, hypercalcemia and spinal cord compression.

Emerging supportive treatments – including advances in systemic therapy, bisphosphonates, and vertebroplasty – warrant thoughtful integration that is best achieved through a multidisciplinary setting. Many prostate cancer patients who are referred to a comprehensive cancer centre are initially referred for palliative radiation therapy to a painful bony lesion. However, it is unclear how many of these patients have reasonable access to other systemic and interventional therapies. A multidisciplinary prostate bone metastasis clinic will facilitate rapid and convenient access for patients to specialized care.

We are pleased to announce the addition of a prostate-focused effort to the bone metastasis clinic at the Toronto Sunnybrook Regional Cancer Centre (TSRCC) supported by Novartis Pharmaceuticals Canada. The bone metastasis clinic is a research-focused multidisciplinary clinic composed of several specialities including radiation oncology, orthopedic surgery, interventional radiology and palliative care. This clinic has been an integral part of the Rapid Response Radiotherapy Program at TSRCC since 1999. The addition of a prostate cancer fellow and a GU medical oncologist to the multidisciplinary clinic will enhance the mission of the bone metastasis group. The clinic will act to provide care and education for those patients with skeletal complications from their prostate cancer and its treatments. Research will be focused on quality-of-life issues as well as biochemical markers of bone metastasis and novel systemic therapeutic treatments. The clinic will also seek to determine the patterns of care for patients with advanced prostate cancer.

Clinic mission

To provide the state of the art therapy for men with metastatic prostate cancer to bone through patient education and research.

When is the clinic held?

- Twice a month on Friday mornings

Who will be at the clinic?

- Physicians including radiation and medical oncologists, orthopedic surgeons, interventional radiologists, palliative care physicians
- Primary care nurses
- Research assistants

Who can be referred?

- Patients with either asymptomatic or symptomatic bone metastasis
- Patients may have either hormone sensitive or hormone refractory prostate cancer
- Patients requiring palliative radiation therapy to bone
- Patients requiring surgical intervention
- Patients with symptoms refractory to conventional treatment
- Patients requiring systemic therapy e.g. chemotherapy or bisphosphonates

What can patients expect?

- Palliative radiation therapy
- Supportive care
- Systemic therapy including participation in clinical trials of novel agents
- Pain management
- Surgical intervention if required
- Prompt communication with referring physicians

How to refer

- Call new patient referrals at 416-480-4205 and ask for the bone metastasis clinic
- Fax a referral to 416-480-6179

Supported by an educational grant from Novartis

NOVARTIS ONCOLOGY