

HOT SPOT

The Newsletter of the Rapid Response Radiotherapy Program
of the Odette Cancer Centre



Volume 12, Issue 1, February 2010

Editorial

By May Tsao, MD, FRCP(C)

The RRRP has been fortunate to have worked with talented research students, many of whom have won many awards and have gone on to pursue careers in medicine and medical research. This year, we have had the honour of congratulating one of our RRRP students, Ms. Roseanna Presutti, with the prestigious University of Waterloo 2009 Applied Health Sciences Co-op Student of the Year Award and the Marion J. Todd Award in Clinical Epidemiology! Ms. Roseanna Presutti has also written this edition of **Hot Spot's** research article along with Dr. Elizabeth Barnes on "Projected referral for health care services in an outpatient palliative radiotherapy clinic".

Ms. Karen Faith, in her article, discusses "Caring and moral distress:

Why do I feel so bad?" This edition of **Hot Spot** also highlights a summary of the Patient and Family Support Program at Odette Cancer Centre during the first year, written by Drs. Jeff Myers, Margaret Fitch and Ms. Pat Brown. Another article regarding the concept of a "good death" is provided by Mr. Stephen Jenkinson. Dr. Carlo DeAngelis gives advice important for the care of our palliative patients in his article, "Breakthrough pain—A thorn by any other name would be as sharp". Dr. Ewa Szumacher again informs us of the educational activities.

Our **Hot Spot** insert topics include exercise and breast cancer by Dr. Teresa Petrella, targeting RANK-ligands in the treatment of bone metastases by Dr.

Christine Simmons and treatment of chronic lymphocytic leukemia (CLL) in the untreated patient by Dr. Martina Trinkaus.

The editorial board would like to thank all our contributing authors and we hope you find this edition of **Hot Spot** interesting and useful.

Projected referral for health care services in an outpatient palliative radiotherapy clinic

By Roseanna Presutti, BSc(C), and Elizabeth Toni Barnes, MD, FRCPC, Rapid Response Radiotherapy Program, Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto

Patients with advanced cancer often present with multiple symptoms, impacting both physical and psychosocial well-being. In the palliative setting, maintaining patient quality of life and functional status are vital end points to consider, and are emphasized by the World Health

Organization stating, "The goal of palliative care is achievement of the best possible quality of life for patients and their families". One way to reach this goal is to ensure sufficient symptom management.

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Caring and moral distress: Why do I feel so bad?

By Karen Faith, MEd, MSc, RSW, Bioethicist, Consultant and Educator

I remember the meeting as if it were yesterday. The patient's treatment team and family could not agree about care options for a terribly ill and incapable patient. For the family, the "war" with the treatment team was more significant than coming to agreement about care. It was all about winning, about anger and, ultimately, about fear. The treatment team was divided, exhausted and frustrated. The arguing was going nowhere. As an ethics consultant, it was my role to help discuss ethical considerations and obligations and to assist in reaching an agreement on appropriate treatment. I knew what I needed to do, but the intensity of the

conflict was a huge barrier. I experienced that awful "yuk" feeling in the pit of my stomach. This visceral sensation is often the first sign of moral distress.

Moral distress has been described as occurring when there is incoherence between what one sincerely believes to be right, what one actually does, and what eventually transpires (Webster, 2000).

Moral distress is an unavoidable part of working in health care. Given the current conditions in medicine, both social and cultural influences, as well as resource and staffing challenges, moral distress is likely to increase. The effects of moral distress can be

cumulative and, if left unaddressed, can lead to symptoms of burnout or compassion fatigue.

Is moral distress all bad? Moral distress is unavoidable and an uncomfortable experience, but it is a necessary part of moral development. Deeply caring about patients, their families and colleagues, as well as professional and organizational values often means we will feel bad when the "right thing" is not being done. Moral distress can teach us how important it is to understand key ethical obligations and to uphold these when facing a challenge.

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Projected referral for health care services in an outpatient palliative radiotherapy clinic

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In Ontario, there are several ongoing projects aimed at improving the delivery of care for cancer patients. Particularly, Cancer Care Ontario (CCO) implemented the Provincial Palliative Care Integration Project (PPCIP) in 2006, with the aim of improving quality of care through evidence-based symptom screening and collaborative care plans. The PPCIP uses the Edmonton Symptom Assessment System (ESAS) as a screening tool in which patients rate the severity of nine symptoms—pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, sense of well being and dyspnea—on a scale of zero (no symptom severity) to 10 (maximum symptom severity). A total distress score is obtained by adding the scores for each of the nine symptoms.

The Odette Cancer Centre (OCC) is one of the regional cancer centres participating in the PPCIP. The OCC established the Rapid Response Radiotherapy Program (RRRP) in 1996

to provide expedited consultation, planning and delivery of radiotherapy (RT) to patients with metastatic cancer. Using the ESAS scores of patients referred to the RRRP, the potential for referrals to other health care professionals was determined. The numeric scale of the ESAS was converted into a categorical scale of none (score 0), mild (scores 1 to 4), moderate (scores 5 to 6) and severe (scores 7 to 10) for each item. Patients categorized as having moderate or severe symptom distress for pain, anxiety or depression, and lack of appetite were identified as potential referrals to other health care disciplines for symptom management.

Our study evaluated the ESAS scores of 588 patients. Fatigue, impaired well-being and pain were the most distressing symptoms with a mean \pm SD score of 4.79 ± 3.18 , 4.69 ± 2.83 and 4.09 ± 3.43 , respectively. Nausea (1.13 ± 2.42) was the least distressing symptom reported. Similar to the numeric scale, fatigue, impaired well-being and pain had the highest reports

of symptom intensity when evaluated using the categorical scale with 57%, 57% and 49% of patients, respectively, being categorized as having moderate or severe symptom distress. Furthermore, moderate to severe distress was reported in 45% of patients for appetite, 33% for anxiety and 24% for depression.

Alleviating symptom distress in palliative settings is vital for maintaining quality of life. Individuals reporting moderate to severe distress on the ESAS require adequate symptom management, and should be considered for referral to other health care professionals. Based on our findings, approximately 50% of patients would be referred for pain management or nutritional counselling, with roughly 30% for psychosocial intervention. In the RRRP alone, the demand for services from other health care disciplines is quite substantial. Due to the nature of this patient population, it is essential that symptom distress is managed in a timely fashion to maximize quality of life at the end of life.

The moral distress I experienced in that moment highlighted for me the key ethical obligation. The patient was ill, incapable and very vulnerable—he needed those responsible to make crucial decisions about his health and his care. Eventually, I intervened by asking the family to describe their brother’s life. They saw him as a fighter, someone whose health had always been a struggle, a person who suffered an irreversible disability because of previous medical error. Aside from their brother’s resultant disability, trust had been the biggest casualty. The compassionate response from the care team was the beginning of a respectful discussion that, ultimately, led to agreement.

What can be done about moral distress? Moral distress is inherent in health care and may be a necessary part of our moral development. It reflects the depth of our commitment, our caring and concern for patients and the complex challenges that are found in most health care settings. Although a difficult experience, moral distress can precipitate greater insight and enhance practice. It can motivate a health care provider to reflect on challenging patient care situations, raise important questions to be discussed with colleagues and can help to identify a need for enhanced skills or knowledge. Such responses to moral distress are consistent with reflective practice

guidelines found in most professional codes of ethics. Healthcare providers are encouraged to discuss the situations and circumstances that lead to moral distress with trusted colleagues who understand the unique nature of the work and the work setting. Health care teams can use their shared experience of moral distress as a catalyst for implementing constructive strategies like enhanced communication and decision-making. For more information about moral distress, ethics resources and consultative support offered through the Ethics Centre at Sunnybrook, please call ext. 4818. For questions or comments about this article, contact: kefaith@rogers.com

Patient and Family Support Program: The first year

By Jeff Myers, MD, CCFP, MSED, Margaret I. Fitch, RN, PhD, and Pat Brown, RN

We are thrilled to bring you the first of what is to be a regular **Hot Spot** contribution by the Odette Cancer Centre’s Patient and Family Support Program. The incredibly dedicated staff and clinicians of our program strive to provide excellent psychosocial, supportive and palliative care to patients both in the hospital and the community, from all disease sites and at any point in their cancer journey.

The Patient and Family Support (PFS) Program was officially launched in May 2008, and our first retreat was held in November of last year. The personal insights and strategic ideas of individuals within and connected to the program led to the identification of four key priorities for our program’s first year. Working groups for each were formed and we are pleased to give you a review of the past year’s activities.

Individuals within the PFS Program often hear from patients and families, “I wish I had known about you sooner”. One of the four key priorities identified was to achieve both a wider awareness and understanding of the services provided by each profession, and educating our colleagues as to

which patients could most benefit from the skills of our clinicians. Over the past year, the PFS Increasing Visibility and Profile Working Group has done an excellent job to put our program on the map.

Because of the diverse physical and psychosocial needs of patients with cancer and the multitude of community-based organizations serving cancer patients, building on partnerships was also identified as a priority focus for the first year of the PFS Program. To ensure OCC patients have access to the full range of support services wherever they are in their cancer journey, the working group for this priority has taken on the substantial task of developing a process that will lead to the cultivation of successful partnerships between our program and the many fantastic community-based agencies offering care.

Cancer Care Ontario has set as a goal “to improve the patient experience along every step of the cancer journey”. A key initiative supporting this goal is the Ontario Cancer Symptom Management Collaborative (OCSMC). PFS Program professionals will be providing key clinical support in

response to the routine screening of common symptoms experienced by patients with cancer. Over the next year, this initiative, a key priority for the PFS Program, will be rolling out across the OCC and is certain to identify and impact those patients in need of excellent physical and psychosocial symptom management.

Given the academic mission and remarkable scholarly contribution of so many clinicians at the OCC, emerging as a clear priority was the provision of guidance and support to professionals within the PFS Program wishing to pursue academic interests. In addition to some incredible teaching and research currently underway, a growing cadre of PFS professionals possess a strong desire to participate in research and education-related activities.

In future issues of **Hot Spot**, we are excited to be profiling the individual professions within the Patient and Family Support Program and to update you on the progress of the working groups. Dr. Marg Fitch, Dr. Jeff Myers and Ms. Pat Brown are honoured to provide leadership to this remarkable group of individuals.

An *N* of one at a time: A little national survey on good death

By Stephen Jenkinson, MTS, MSW, RSW

I have crossed Canada four times in the last two years on teaching tours for audiences of mental health practitioners and palliative care providers. Often these tour stops have included public screenings of **Griefwalker**, the National Film Board documentary project about some of my work and ideas. In the discussions that follow, there are always people who want to tell stories of the dying that they have seen. Usually these are horror stories of a kind that feature inflexible hospital protocols and sometimes emotionally remote staff people. There are others who want to tell hagiographic stories of the calmer, quieter, usually quicker death of a loved one. These usually include compassionate, informed caregivers, and they are usually told in a tone of having triumphed against considerable odds. Most people want to know if there are cultures somewhere in the world that have saner ways of dying than we do. Just about everyone in these movie theatres and town halls across the country has found some halting, uncertain way of asking me whether there is such a thing as a good death, whether there could be, whether there will ever be.

It seems that for most of these people, the question isn't rhetorical. They clearly can't imagine such a thing, even when they want to, or need to. When your culture is death phobic, when your dying is not the proper, justifying outcome of your life but, instead, an interruption of your plans and your entitlements, then a good death is a barely tolerable, barely thinkable thought. When there is no good that comes in your dying but that it ends, then the best death is the least death: the quickest, the least obtrusive, the least known. *What good does it do you to know that you're dying?* In a death-phobic culture, **this** is a rhetorical question. The resounding answer I have heard in my travels is: it's best when it's sudden, when it's unknown. Otherwise,



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dying gets worse with every passing day, with every incremental realization that dying is what is happening.

For the last 30 years, or so, psychosocial palliative care has become more and more “psycho”, more persuaded by the idea that dying is mainly a private, interior event, more a consumer and a purveyor both of the idea that each person decides what dying means to them, as they go through the usually protracted process of palliative treatment. But my clinical experience persuaded me long ago that what most people “decide” dying means comes to them by default. These meanings are usually inherited, not decided, and they usually have this death phobia somewhere in them.

The only time I have heard the social or cultural origins of the meaning of dying seriously discussed in a clinical context—not a workshop—is when there is a difference in culture between the provider and the recipient of palliative care. When the culture is one held in common, the culture and its teaching

about dying almost never surfaces. As our cultural alertness has more and more gone into eclipse in favour of psychology, competence and autonomy, psychosocial palliative care has grown more and more into a specialization in what to do about dying, and what to do about the dying person, instead of a specialization in dying. Partly because of that, the culture that palliative care is there to serve tastes its own poverty of meaning and poverty of options each time someone dies. We would do well in the coming years to rethink our debt to the culture that employs us and, in so doing, to work hard at making a bigger, deeper, more culturally redeeming answer to what, for now, seems to be a thin, haunted question: is there such a thing as a good death? What does it ask of us all?

Stephen Jenkinson, MTS, MSW, RSW

To learn more about my upcoming events, and to sign up for the Orphan Wisdom newsletter, visit <http://www.orphanwisdom.com>

Breakthrough pain—A thorn by any other name would be as sharp

By Carlo DeAngelis, PharmD, Clinical Pharmacy Coordinator—Oncology,
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Breakthrough pain is a cause of significant morbidity in cancer patients and is associated with decreased satisfaction in overall pain control and reduced quality of life (Zeppetella, O'Doherty, & Collins, 2000; Davies, Dickman, Reid, et al., 2009; Green, Montague, & Hart-Johnson, 2009).

The term breakthrough pain is used to describe various clinical scenarios where the patient experiences an increase in their level of pain. The lack of a standardized definition for breakthrough pain has impeded progress in the development of effective strategies to manage it.

Recently, the Association for Palliative Medicine of Great Britain and Ireland convened a task force to develop updated, evidence-based and practical recommendations for the management of cancer-related breakthrough pain. They define breakthrough pain as “a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain” (Davies, Dickman, Reid, et al., 2009). The key elements of this definition are:

- The increase in pain is transient and is either spontaneous or associated with a trigger.
- Background pain is adequately controlled, thus pain that occurs during the titration phase of pain management would not be considered breakthrough pain.
- The occurrence of an end-of-dosing interval increase in pain is not considered breakthrough pain, since this phenomenon suggests that the patient requires additional adjustment to the around-the-clock analgesic medication requirements to improve control of their background pain.

Furthermore, breakthrough pain can be categorized as either “spontaneous”, where it is unpredictable with no identifiable trigger, or “incident” with a clear trigger that can be either the result of a voluntary or non-voluntary act (e.g., activity-related versus coughing)

or procedural (e.g., wound care). Clinically, breakthrough pain is characterized as being sudden in onset, moderate to severe in intensity and short in duration (Davies, Dickman, Reid et al., 2009; Svendsen, Andersen, Arnason, et al., 2005).

Having a universally accepted definition and means to categorize breakthrough pain is critical to progress being made in managing it. However, an additional layer of complexity, which is poorly understood or appreciated, is the role that the pathophysiology of breakthrough pain plays in the benefit or lack thereof a patient gains from a particular intervention. Breakthrough pain is not a single entity (it may lie anywhere along a continuum of purely nociceptive to purely neuropathic pain in nature) and not only varies from individual to individual, but also within the same individual over time.

Traditionally, breakthrough pain is managed by the use of supplemental doses of opioid medication without regard to its nature or cause. In order for true progress to be made in the development of new agents for the management of breakthrough pain, a deeper understanding of its pathophysiology is necessary. The ideal agent would:

- Address the pathophysiology of the breakthrough pain
- Have a rapid onset of action (several minutes)
- Have a short duration of action (the typical duration of a breakthrough pain episode has been reported to be less than 30 minutes [Zeppetella, O'Doherty, & Collins, 2000; Svendsen, Andersen, Arnason, et al., 2005])
- Be available in a formulation that is easy and convenient to administer
- Have minimal side effects.

Until such an agent is available, opioids remain the backbone of any management strategy for breakthrough pain. The opioid used should, if possible, be the same as that being used for the control of background pain and

of a formulation that is rapid in release. The route of administration used is dependent on the patient's clinical situation, but should deliver the medication as rapidly as possible. There is much controversy as to the appropriate dose to be used, but a widely used and clinically accepted strategy is to use 10% to 20% of the total daily opioid dose every four hours (Gammaitoni, Fine, Alvarez, et al., 2003). If the breakthrough pain is predictable (patient going out for a walk or scheduled for a dressing change), the breakthrough dose should be taken in advance with enough time for the opioid to take effect (typically 15 to 20 minutes for morphine and hydromorphone). The patient's breakthrough pain and the benefit of the management strategy in place should be reassessed regularly.

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Continuing Medical Education 2010

By Ewa Szumacher, MD, MEd, 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

- **January 24–February 8, 2010**
Tour: Care of the Elderly and Palliative Care in South India, India (various sites)
www.jonbainestours.co.uk/indiapal/
- **February 3, 2010**
Care at the end of life: The role of the primary healthcare team, London, U.K. Contact name: Nicole Leida
Website: www.rsm.ac.uk/academ/gpj102.php
- **February 11–14, 2010**
IXVII International Conference of Palliative Care of IAPC, Trichirappalli, Tamilnadu; India. Contact: Dr. T. Mohanasundaram
E-mail: drmohs.trichy@hotmail.com
- **February 24–25, 2010**
When Loss and Grief Come to School, Workshop Leader Dr. Alan Wolfelt, Winnipeg, MB
www.manitobahospice.mb.ca
- **March 4–7, 2010**
Leading Together 2010, The 6th Annual HIV/AIDS Skills Building Symposium, Montreal, QC
www.cdn aids.ca
- **March 15–18, 2010**
V5h Latin-American Congress on Palliative Care, Buenos Aires, Argentina
www.vcongresoalcp.org
- **April 17–20, 2010**
OPCA/HAO Joint Conference, Toronto, ON
- **April 23, 2010**
Caring for Persons with Terminal Illness: Living with the Dying in Multicultural Canada, Toronto, ON. Contact name: Calista Anne Mervis
Website: www.careconferences.com
- **April 29, 2010**
Terminal Illnesses and Dying in Multicultural Canada: An Interdisciplinary Approach
www.careconferences.com
- **May 2, 2010**
Hike for Hospice Palliative Care (Canada)
www.chpca.net
- **May 2–8, 2010**
National Hospice Palliative Care Week (Canada)
www.chpca.net
- **May 10–11, 2010**
The 20th Annual Conference of the Réseau de soins palliatifs du Québec — La force de l'héritage: Source de dépassement, Quebec City, QC
www.reseaupalliatif.org
- **May 31–June 1, 2010**
2010 Provincial Palliative Care Conference, Regina, SK
www.saskpalliativecare.org
- **June 2–3, 2010**
9th Annual Kaleidoscope International Palliative Care Conference, Dublin, Ireland. Contact name: Donna Reddy
Website: www.stfranchishospice.ie/education/kaleidoscope.htm
- **September 23–24, 2010**
The Changing Landscape of Palliative Care—19th Annual Provincial Conference, Winnipeg, MB
www.manitobahospice.mb.ca
- **October 5–8, 2010**
18th International Congress on Palliative Care, Montreal, QC
www.pal2010.com
- **October 27–30, 2010**
2nd Conference on Positive Aging: An Interdisciplinary Team Approach for Health Professionals, Vancouver, BC
www.interprofessional.ubc.ca
- **October 28–31, 2010**
World Society of Pain Clinicians Congress (WSPC 2010), Beijing, China
Website: www.kenes.com/WSPC

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Exercise and breast cancer

By Teresa Petrella, MD, MSc, FRCPC, Medical Oncologist, Odette Cancer Centre



Breast cancer is a prevalent disease with more than 22,000 cases diagnosed this year in Canada (Canadian Cancer Society, 2009). Many of these women will undergo surgery followed by adjuvant therapy. With the advent of new and more effective adjuvant therapies for breast cancer, treatment is becoming more complex and prolonged, and may last many years. As a result of their treatment, many women will face long-term consequences such as early menopause, compromise in cardiopulmonary and functional capacity and weight gain. In addition, decreased function, fatigue and weight gain has a significant negative impact on the quality of life of these breast cancer patients (Galalae, Michel, Siebmann, Kuchler, Eilf, & Kimmig, 2005).

Physical activity is a modifiable risk factor for many diseases. These include cardiovascular disease, diabetes, osteoporosis, hypertension, depression and cancer; specifically breast cancer. Evidence suggests that 1/3 of the more than 500,000 cancer deaths that occur in the U.S. each year can be attributed to diet and physical activity habits (Kushi, Byers, Doyle, Bandera, McCullough, Gansler, et al., and the American Cancer Society 2006 Nutrition and Physical Activity Guidelines Advisory Committee). Despite this, the relative acceptance that exists within other medical and scientific communities of the benefits of exercise has not translated to active promotion of physical activity in cancer care.

Primary prevention

- Routine physical activity is associated with reductions in the risk of breast cancer
- Data from epidemiologic studies shows that physically active women have a 20% to 30% reduction in the relative risk of breast cancer compared with their inactive counterparts (Lee, 2003)
- Also, there is consistent evidence that increased body weight or weight gain in adulthood is associated with increased risk of breast cancer (Ballard-Barbash et al.,

2009); exercise can be beneficial in maintaining a healthy weight

- American Cancer Society (ACS) (Kushi, Byers, Doyle, Bandera, McCullough, Gansler, et al., 2006), has published guidelines on nutrition and physical activity for cancer prevention
- ACS recommends adopting a physically active lifestyle: at least 30 minutes of moderate to vigorous physical activity on five or more days of the week. Some examples of moderate and vigorous activities are listed in Table One.

Secondary prevention

- A recent Canadian Community Health Survey revealed that fewer than 22% of Canadian cancer survivors (16.6% of breast cancer survivors) were physically active and more than 18% were obese (Courneya, Katzmarzyk, & Bacon, 2008)
- A Nurses Health Study (Holmes, 2005) suggested improvement in survival with physical exercise post-breast cancer diagnosis:
 - breast cancer survivors who reported higher levels of physical activity had a

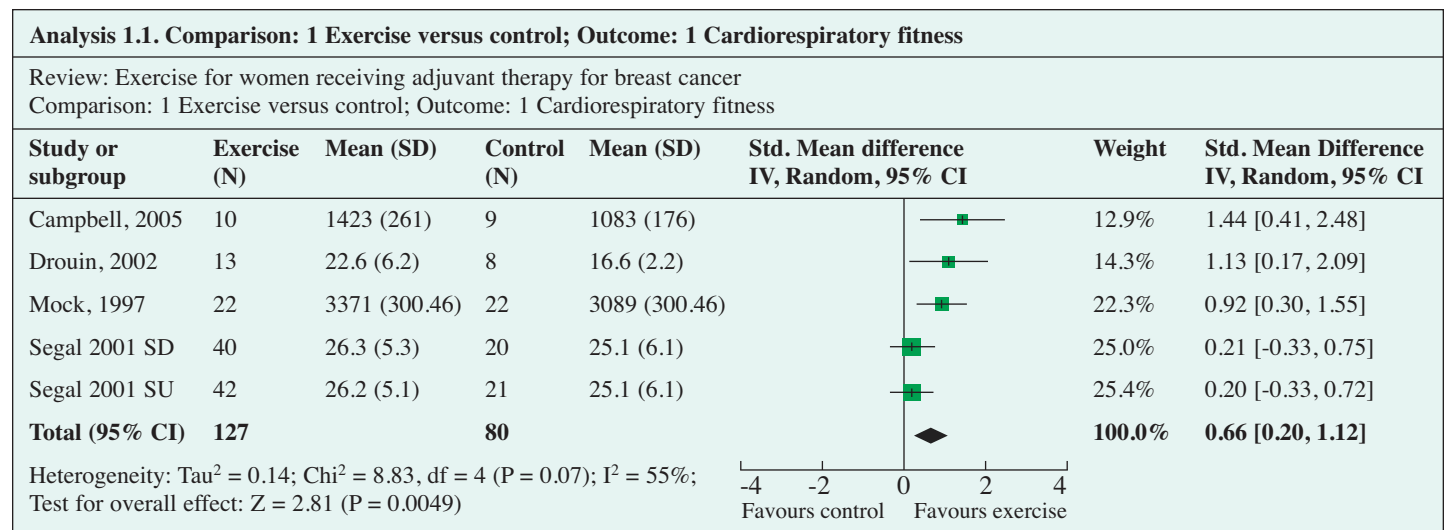
reduced risk of disease recurrence, a decrease in cancer-specific mortality and all-cause mortality

- those who engaged in moderate exercise had an adjusted RR of 0.50 (95% CI 0.31–0.82) with a five-year survival 97% versus 93% compared to those less active, and a 10-year survival of 92% versus 86%.

Benefits of exercise

- The majority of breast cancers are diagnosed at an early stage and treatment is, therefore, focused on cure and prevention of relapse due to micrometastatic disease
- The mainstay of treatment consists of surgery with or without radiation, along with systemic adjuvant therapy that includes chemotherapy, endocrine therapy, or a combination

	Moderate intensity activities	Vigorous intensity activities
Exercise and leisure	Walking, dancing, leisurely bicycling, ice and roller skating, horseback riding, canoeing, yoga	Jogging or running, fast bicycling, circuit weight training, aerobic dance, martial arts, jumping rope, swimming
Sports	Volleyball, golfing, softball, baseball, badminton, doubles tennis, downhill skiing	Soccer, field or ice hockey, lacrosse, singles tennis, racquetball, basketball, cross-country skiing
Home activities	Mowing the lawn, general yard and garden maintenance	Digging, carrying and hauling, masonry, carpentry
Occupational activity	Walking and lifting as part of the job (custodial work, farming, auto or machine repair)	Heavy manual labour (forestry, construction, firefighting)



- The side effects from these therapies can have a significant effect on QOL, as well as physical function and mood
- Lack of physical activity may also result in severe deconditioning and reduced physical function, which may prolong recovery
- Several randomized and non-randomized trials have examined exercise as a supportive intervention
- A recent meta-analysis of 14 breast cancer exercise trials showed significant improvements in QOL, physical functioning and fatigue (McNeely et al., 2006)
- Weight gain is also common and very distressing for breast cancer patients; exercise may aid in maintaining a healthy weight
- A recently published Cochrane review of exercise for women receiving adjuvant therapy also suggests that exercise improves cardiorespiratory fitness (Analysis 1.1 table), fatigue and helps control weight gain (Analysis 1.4 table) while on adjuvant therapy (Markes, Brockow, & Resch, 2009).

Recommendations

- Both the Canadian Cancer Society and the American Cancer Society provide information for cancer patients on exercise
- Wellspring also has an exercise program that is available to cancer patients

- Patients should check with their doctors before starting any exercise program
- Consult with a cancer exercise specialist if one is available
- Combination of both aerobic and resistance training exercises is ideal
- Engage in at least 30 minutes of moderate or vigorous exercise three to five times per week along with a healthy diet.

Summary

In summary, regular physical activity appears to confer a benefit both in prevention, management of side effects from therapy and in secondary prevention of breast cancer. Results from a recent survey show that Canadian cancer survivors have a low level of physical activity and many are overweight. This may place them at higher risk of recurrence and death from their disease, as well as worse supportive care outcomes. Receiving adjuvant therapy should no longer be thought of as a contraindication to exercise. Instead, it should be regarded as a feasible, safe and beneficial supportive care measure. Those at risk for breast cancer and breast cancer patients should be encouraged to exercise during, as well as post-treatment as part of a healthy lifestyle change. The challenge will be in instituting a behaviour change amongst patients and physicians. For behaviour

change to occur, exercise programs will need to focus on the barriers that prevent a healthy lifestyle change, as well as the underlying principles of behaviour theories.

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Analysis 1.4. Comparison: 1 Exercise versus control; Outcome 4 Weight change							
Review: Exercise for women receiving adjuvant therapy for breast cancer; Comparison: 1 Exercise versus control; Outcome: 1 Weight change							
Study or subgroup	Exercise (N)	Mean (SD)	Control (N)	Mean (SD)	Std. Mean difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
MacVicar, 1989	12	0.82 (2.1)	12	1.99 (2.1)		63.0%	-1.17 [-2.85, 0.51]
Segal, 2001 SD	40	0.4 (3.71)	20	0.6 (6.21)		20.4%	-0.20 [-3.15, 2.75]
Segal, 2001 SU	42	-1.4 (6.28)	21	0.6 (6.21)		16.7%	-2.00 [-5.27, 1.27]
Total (95% CI)	94		53			100.0%	-1.11 [-2.44, 0.22]
Heterogeneity: Tau ² = 0.0; Chi ² = 0.65, df = 2 (P = 0.72); I ² = 0.0%; Test for overall effect: Z = 1.63 (P = 0.10)							

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Targeting RANK-ligand in the treatment of bone metastasis

HOT SPOT

By Christine Simmons, MD, FRCP(C), Medical Oncologist, University of Toronto

- Bone is the most common site of metastases for many solid malignancies. Roughly 75% of metastatic breast cancer patients will develop bone metastases at some point in the course of their disease (Coleman, 1997).
- Bone metastases can result in skeletal complications, which may include any of the following:
 - pathological fracture
 - spinal cord compression
 - pain requiring radiation or surgery
 - hypercalcemia.
- These four complications are referred to as skeletal related events (SREs).
- Treatment of bone metastases with bisphosphonates in addition to antineoplastic therapy has been shown to reduce and delay the onset of skeletal-related events in this population (Petrucci et al., 2008). However, many patients still suffer at least one SRE during the course of their disease (Trinkaus et al., 2010).
- Bisphosphonates are synthetic analogs of pyrophosphate and inhibit osteoclasts. First generation bisphosphonates (clodronate) are 100-fold less potent than second generation (pamidronate) and 10,000-fold less potent than third generation bisphosphonates (zoledronic acid) (Simmons et al., 2009). While there may be some utility to considering a switch to a more potent bisphosphonate at the time of progression of bone disease (Clemons et al., 2006), there is evidence that progressive bone disease still may occur despite low levels of osteoclasts within an area of bone involved with cancer (Trinkaus et al., 2009).
- New developments in the understanding of the role of receptor activator of nuclear factor kappa B ligand (RANKL) in the development of bone metastases have allowed the development of novel targeted therapy in the treatment of bone metastases.
- RANKL is a mediator of osteoclast differentiation, function and survival. It is released from osteoblasts and stromal cells in the bone microenvironment and stimulates precursor and mature osteoclasts to differentiate and induce bone resorption. Factors released from the destruction of bone further stimulate tumour growth. Tumour cells further stimulate osteoblasts and stromal cells to release RANKL and, thus, the vicious cycle continues (Terpos et al., 2009).
- Denosumab is a fully human monoclonal antibody with high affinity and specificity to RANKL. Denosumab subsequently binds to and neutralizes RANKL, thus arresting the vicious cycle of bone metastases (Santini et al., 2009).
- It has been shown to increase bone mineral density and reduce fractures in postmenopausal women with low bone mass (Cummings et al., 2009).
- Results of a large phase III randomized controlled trial of denosumab versus Zometa for the treatment of bone metastases in breast cancer patients has recently been reported, and updated results were presented at the San Antonio Breast Cancer Symposium December 10, 2009 (Stopeck et al., 2009).
 - This study enrolled 2,046 women with breast cancer and bone metastases who had not received IV bisphosphonate therapy. They were randomized in a 1:1 non-inferiority study design to receive SC denosumab at 120mg and IV placebo OR IV zoledronic acid at 4 mg and SC placebo every four weeks.
- In this way investigators were able to ensure patients, clinicians and investigators were blinded.
- Daily calcium and vitamin D were encouraged but not mandated.
- The primary endpoint of this study was time to first on study SRE:
- This was found to be prolonged in the denosumab arm compared to Zometa with a hazard ratio of 0.82 (95% CI 0.71-0.95, P < 0.0001 for non-inferiority)
- Of note, the statistical analysis was also able to determine superiority of denosumab over zoledronic acid with a P = 0.01 for superiority.
- The secondary endpoints of this study were also met and are summarized in Table 1 (next page).
- Overall, denosumab was superior to zoledronic acid in reducing and delaying the onset of skeletal related events.
- Adverse effects reported higher rates of pyrexia, chills and arthralgia in the zoledronic acid arm of the study compared to denosumab arm. The rate of renal toxicity was found to be 8.5%

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in the zoledronic acid arm compared to 4.9% in the denosumab arm, and the rates of osteonecrosis of the jaw were similarly low in both arms at a rate of 1.4% and 2.0% (p=0.39) in the zoledronic acid and denosumab arms respectively. Denosumab did result in a higher reported rate of toothache and hypocalcemia (Stopeck et al., 2009).

- These results are interesting but, even more importantly, these studies demonstrate the importance of further work on the treatment and prevention of bone metastases, as these lesions can have such a significant impact on a patients' quality of life.

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Table 1: Secondary endpoints of Denosumab vs. Zometa study

Endpoint	Result	95% CI	P value
Time to first and subsequent on study SRE	HR 0.77	0.66, 0.89	0.001
Time to first radiation to bone	HR 0.74	0.59, 0.94	0.01
First on study SRE or Hypercalcemia of malignancy	HR 0.82	0.70, 0.95	0.007
Skeletal morbidity rate (number of SREs per year)	SMR 0.45 vs 0.58		0.004
Proportion of patients with at least one SRE	30.7% vs. 36.5%		

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Chronic lymphocytic leukemia is an indolent B cell lymphoma with an incidence of two to six cases per 100,000 patients per year. In the Western world, it is the most common adult leukemia, making up 30% of all leukemias with a female to male ratio of 1.7:1. According to SEER data, the median age at diagnosis is 72. However, the majority of patients are diagnosed between the ages of 75–84 (Horner, Ries, Krapcho, et al., 2006).

The 2008 World Health Organization guidelines for the diagnosis of chronic lymphocytic leukemia (CLL) include (Swerdlow, Campo, Harris, et al., 2008):

1. Peripheral blood monoclonal B cell lymphocytosis of $> 5.0 \times 10^9/L$ with a CLL phenotype present for a minimum of three months.
2. Cytopenias with a typical bone marrow infiltrate of CLL, and typical CLL immunophenotype.

The characteristic immunophenotype of CLL consists of clonal B lymphocytes being positive for CD5, CD19, and CD23 with light chain restriction. Often, there is a weak expression of surface immunoglobulin, CD20,

and CD79b. Notably, CLL does not include the molecular translocation t(11;14), which is associated with mantle cell lymphoma.

Prognostic factors

CLL is an incurable disease outside of allogeneic stem cell transplant. Specific prognostic markers have been developed allowing for the early identification of patients at risk of clinical progression. These markers include:

- Clinical stage (see Table 1). Please note the Binet Staging system is not presented
- Interphase Fluorescence In Situ Hybridization (FISH) analysis (see Table 2)
- Lymphocyte doubling time (LDT)
- $> 30\%$ CD38 expression
- Unmutated immunoglobulin variable heavy chain (IgVH). Patients with $> 2\%$ mutated IgVH are considered low risk
- Zeta associated protein-70 (ZAP70) expression (currently not available in Ontario)
- Increased Beta-2 microglobulin
- Micro-RNA expression profiles (currently not available in Ontario).

Indications for treatment

CLL is typically an indolent lymphoma, with treatment recommended in the following settings, as per the CLLWG Guidelines (Hallek, Cheson, Catovsky, et al., 2008):

- Progressive bone marrow failure with cytopenias
- Massive splenomegaly (> 6 cm below costal margin), or progressive or symptomatic splenomegaly
- B symptoms or fall in ECOG performance status. This includes an unintentional loss of $> 10\%$ weight in the past six months, ECOG > 2 , unexplained fevers for > 2 weeks, or night sweats of > 1 month without evidence of infection
- Massive (> 10 cm), progressive, or symptomatic lymphadenopathy
- Progressive lymphocytosis ($> 50\%$ increase over two months or a LDT < 6 months). Notably, in patients with a lymphocyte count of $< 20 \times 10^9/L$, LDT should not be used as a single parameter for treatment initiation
- AIHA unresponsive to steroids or ITP refractory to standard care.

Treatment of the CLL naïve patient

The standard of care in the newly diagnosed CLL patient is a watch-and-wait

approach, as previous randomized controlled trials show no benefit to early chemotherapeutic intervention. Once treatment is required (see Indications for treatment), several options exist with numerous clinical trials ongoing in identifying an optimal treatment strategy. Treatments are often dictated by stage, ECOG status, co-morbid status, age and, more recently, by FISH cytogenetics. For example, older treatments such as Chlorambucil are often given to the increasingly frail patient because of better tolerability, but at the expense of durable treatment response. On the contrary, asymptomatic patients with high-risk cytogenetics (i.e. del(17p)) should be referred early for clinical trial, as this group of patients is often refractory to standard treatment, and may be candidates for allogeneic stem cell transplant. Over the past decade, several agents have emerged for the initial treatment of the CLL patient, either as a single agent or in combination in clinical trials. These include, but are not all encompassing: Fludarabine, Cyclophosphamide, Pentostatin, Alemtuzumab, Bendamustine, and Lenalidomide.

Most studies now support the use of Fludarabine, a purine analogue, alone or in combination as first-line treatment in patients with CLL. Three randomized trials have shown the improved response rates with Fludarabine and Cyclophosphamide (FC) chemotherapy compared to Fludarabine (F) alone. The CLL4 trial (Catovsky, Richards, Matutes, et al., 2007) was the largest of such trials, comparing F to FC to chlorambucil (C) in newly diagnosed patients. Notably, FC resulted in a superior progression-free survival (PFS) of 43 months compared to 23 months with F alone, and a complete response (CR) rate of 38% (FC) versus 15% (F) versus 7% (C). For most centres, FC-based treatment is the standard of care for newly treated patients, up until the recently

Stage	Characteristics	Modified RAI	Prognosis (months)
0	Absolute lymphocytosis in blood of $> 15 \times 10^9/L$, without lymphadenopathy, hepatosplenomegaly, anemia, or thrombocytopenia	Low	140
1	Absolute lymphocytosis (Stage 0) with lymphadenopathy, without hepatosplenomegaly, anemia or thrombocytopenia	Intermediate	100
2	Stage 0 with hepatomegaly or splenomegaly with or without lymphadenopathy	Intermediate	70
3	Stage 0 with anemia (Hb < 11 g/L); not due to AIHA	High	20
4	Stage 0 with platelets $< 100 \times 10^9/L$; not due to ITP	High	20

FISH Cytogenetics	Median Overall Survival
Deletion 17p (p12.1)	32 months
Deletion 11q(q22.3)	79 months
Normal	111 months
Trisomy 12	114 months
Deletion 13q (q14)	133 months

anticipated results of the CLL8 Trial (Hallek, Fingerle-Rowson, Fink, et al., 2009) were presented at the American Society of Hematology meeting in December 2009. This is the first randomized controlled trial to profile whether adding Rituximab to FC can improve patient outcome. Rituximab is a chimeric monoclonal antibody, targeting CD20 and traditionally has been used in lymphomas with higher CD20 expression.

The CLL8 trial

In the CLL8 trial, patients were randomized to six 28 day cycles of Fludarabine 25 mg/m² iv days 1-3 and cyclophosphamide 250 mg/m² iv days 1-3 with or without Rituximab 375 mg/m² on day 0 cycle 1 followed by 500 mg/m² on day one of cycles 2-6. Groups were similar in terms of stage, age and FISH cytogenetics. However, there was a statistically higher proportion of patients with B symptoms in the FC-alone group (48% versus 41%). In total, 817 patients were subsequently followed with the primary endpoint of progression-free survival (PFS) and secondary endpoints of overall survival (OS), response (ORR), and safety.

In terms of primary endpoint, after a median follow-up of 37.7 months, PFS was in favour of the FCR group at 51.8 months versus 32.8 months (FC) in 790 patients (p<0.001). Secondary endpoint results showed a statistically significant achievement of complete response (CR) with FCR versus FC arm at 44.1% versus 21.8% respectively (p<0.01). Overall response rate, as well, was significant in favour of FCR at 95.1% versus 88.4%. In subgroup analysis, patients with 13q-, 11q- or trisomy 12 had a statistically significant higher proportion of CR when given the FCR regimen. Notably, patients with 17p deletion had the worst OS in the FCR versus FC arms at 38.1% and 36.5% respectively (see Figure 1). In addition to del(17p), B2M levels > 3.5 mg/dl were also associated with an overall poor PFS (HR 1.45, P=0.005) and OS (HR 2.287, P< 0.001). Overall survival three years post-randomization was 87.2% in the FCR versus 82.5% in the FC arm (p=0.012), and maturing data will be ongoing to ensure this statistical significance with OS persists.

Despite the advantage of adding Rituximab to FC-based therapy, it does result in a higher degree of statistically significant adverse events. Specifically, ≥ grade 3 or 4 neutropenia was reported at 33.7% versus 21.0% (p< 0.0001) and leukocytopenia reported at 24.0% versus 12.1% (p<0.0001) in the FCR versus FC groups. There was no difference in anemia, infection, or tumour lysis syndrome between both groups. Treatment-related mortality was 2% for both arms.

The CLL8 trial is the first randomized controlled trial to prove the improved PFS and ORR with immunotherapy-based treatment in conjunction with FC. Several other trials are ongoing using immunotherapy-based regimens including Ofatumumab (anti-CD20) and Alemtuzumab (anti-CD52), thereby highlighting the potential of superior treatments in the future for the untreated CLL patient.

Summary

1. The CLL8 trial supports the efficacy of adding Rituximab to Fludarabine and Cyclophosphamide in first-line treatment CLL naïve patients, particularly in patients with del (11q), del(13q), and trisomy 12.
2. FCR results in an improved PFS, OS, and response rates compared to FC chemotherapy.
3. Patients with del (17p) should be referred for clinical trial, as patients show a limited response to FC or FCR.
4. Future trials are ongoing to evaluate the efficacy of immune-based strategies in treating CLL.

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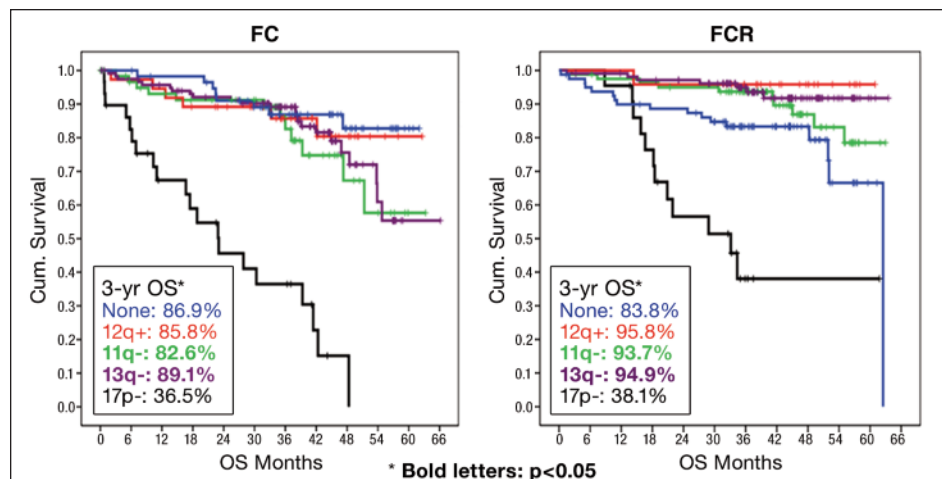


Figure 1: Overall survival and cytogenetic abnormalities according to the hierarchical model

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