HOT SPOT

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

Sunnybrook
HEALTH SCIENCES CENTRE

Volume 8, Issue 2, May 2006

Editor's corner

By Dr. Cyril Danjoux, MD, DMRT, FRCPC

Our readers like the expanded format of **Hot Spot** and the addition of new contributors introduced by Dr. Edward Chow, our new editor. This issue brings you an insert on "Radioimmunotherapy for salvage treatment of Lymphoma", written by Dr. Rena Buckstein, Department of Medical Oncology, Toronto Sunnybrook Regional Cancer Centre.

Dr. Larry Librach's article provides an update on the national project to develop competencies in palliative and end-of-life care for all medical undergraduates and postgraduates by 2008.

As health care professionals, we feel obliged to help our patients. However, not all patients want our help as Dr. Marg Fitch's research revealed in her interesting article "No help wanted?"

Dr. Monica Branigan reminds us in her article on "Truth-telling at the end of life" that truth is more than evidence-based facts. Understanding which truth needs to be addressed may improve our communication and strengthen the relation we have with our patients.

Dr. Adam Rapoport, the chief resident at the Hospital for Sick Children, has a particular interest in pediatric palliative care and bioethics. His article addresses the issue of whether it is ever justified to forgo nutrition and hydration in children at the end of life. It explores the fine balance between our medical, ethical and legally-sound options. The full article is available on the Temmy Latner Centre for Palliative Care's website, **http://www.tlcpc.org/**

At a research planning retreat in January 2006 at the Vaughan Estates, participants from TSRCC, Sunnybrook and Temmy Latner identified five main themes of interest for their research: symptom management, health services, translational research, education and communication. In this issue, Dr Amna Husain, research physician at the Temmy Latner, explores the challenges of symptom clusters and their relevance to patient care.

Our research students have been a valuable resource to our research and educational program. We are pleased that Hannah Chiu reviewed and summarized their experience in her article "What students think: Undergraduate students in a palliative health care setting".

Dr. Ewa Szumacher, Director of Education, Radiation Program at Toronto Sunnybrook Regional Cancer Centre, provides a list of Canadian CME activities in palliative medicine that is of interest to our readers. If you are organizing a CME event or are aware of one that we missed, please forward the detail to **ewa.szumacher@sunnybrook.ca**.

The new Sunnybrook Health Sciences Centre announced on March 30, 2006, a change in name, which also includes changes to the website, which is now **http://www.sunnybrook.ca** and e-mail addresses. Past issues of **Hot Spot** are located at **http://www.sunnybrook.ca/programs/tsrcc/treatmentprevention/rapidresponse**

Sunnybrook is the first hospital in Canada to put into action a multimedia webcasting system. We plan to webcast our palliative educational rounds so those outside our campus can choose to participate. If you are interested in receiving the notice for those rounds, please contact **melissa.frost@sunnybrook.ca**.

In this issue of HOT SPOT:

Temmy Latner Centre Update on Palliative Care

The Educating Future Physicians for Palliative and End-of-Life Care project (EFPPEC): Developing competencies in medical undergraduates and postgraduates

By Larry Librach, MD, CCFP, FCFP, W. Gifford Jones Professor Pain Control and Palliative Care, University of Toronto, Physician Leader EFPPEC Project

In 2004, a national project was funded by Health Canada and sponsored by the Association of Faculties of Medicine of Canada and the Canadian Hospice Palliative Care Association with the goal that by 2008 all medical undergraduate and postgraduate students will graduate with competencies in palliative and end-of-life care. The Educating Future Physicians for Palliative and End-of-Life Care Project (EFPPEC) has a core leadership team and an interprofessional management committee supervising its operations.

EFPPEC has had a number of successes so far and is well on its way to the goals set for it:

1. Local EFPPEC teams have been established at each of Canada's 17 medical faculties. These interprofessional teams are responsible for analysing local curricula in end-of-life care and helping to integrate curriculum in end-of-life care competencies into undergraduate and postgraduate studies.
2. Core and enabling competencies for medical undergraduates have been established and have gone through a unique national consensus process. A curriculum process defining specific undergraduate objectives and the best teaching and evaluation methods will be complete in April 2006.
3. Core and enabling competencies have been established for family medicine residents and these have undergone a national consensus process as well. A group of family medicine and palliative medicine educators in Toronto is spearheading a national effort to identify how best these competencies can be integrated and taught within family medicine residency programs.
4. A similar effort is underway to identify core and enabling competencies in palliative and end-of-life care for core specialty training in Royal College of Physicians and Surgeons of Canada residency programs. National consensus on these will be sought.
5. An annual interprofessional symposium on palliative and end-of-life care education has been established. The first one was held in April 2005, and the next will be held in London, Ontario, in association with the Canadian Association of Medical Education annual conference.
6. A unique online resource of education materials and programs, the Learning Commons, has been developed and is scheduled for launch by June 2006.
7. Presentations on the project have been done at many national and international conferences.

The unique EFPPEC project has also served as a model for the development of similar educational initiatives in nursing, social work and pharmacy. Please visit our website at **www.efppec.ca**

Truth-telling at the end of life

By Monica Branigan, MD, MHSc (Bioethics)

In our work caring for people with a terminal illness, we are often challenged by the issue of truth-telling. One of the first hurdles we encounter is what we mean by truth. Vaclav Havel reminds us, "Truth is not merely what we are thinking, but also why, to whom and under what circumstances." Often as health care professionals, we confuse truth with information, statistics, risks and benefits. But truth often cannot be nailed down and limited to the objective. Often, our most important truths are personal.

This concept was made evident for me when I recently visited a patient at home with widely metastatic cancer on an experimental chemotherapy protocol. The patient had begun this protocol with great enthusiasm and hope, and had experienced an initial improvement. However, over the past few weeks, she and her husband had been calling our service on almost a daily basis for a myriad of physical symptom issues. I began my visit in an open-ended way and the patient commenced to itemize all her concerns. I realized that I had a choice here: deal with each issue individually, or search for a deeper truth. When I asked the patient to step back and tell me how she was really doing, we opened a whole conversation about her personal suffering, her suffering that was as individual as she was. Once this truth was in the open, we clarified her goal of care: "Quality, but not this quality." This allowed a consideration of whether chemotherapy was meeting this goal, or would likely meet this goal in the future.

Truth-telling has often been conceived in terms of whether or not to withhold certain information. Perhaps this is too limited a view. Perhaps truth-telling is more about creating an opportunity for patients to access their own truth. What information do I need? What am I ready to hear right now? What is the truth of my own experience? How do I use my own truth to make decisions? How do I know when I've had enough?

So there is the challenge: how does one create an opportunity for the truth to be revealed. For me, it begins with a willingness to see a patient as a whole human being, and not as a compilation of diagnoses and symptoms to be managed. I also have to have a willingness to allow the anxiety and fear that naturally arise as we approach the truth. I know things will be revealed that I cannot fix and the limits of my ability to help will be revealed as well. Sometimes, the truth is that we simply don't know what the future holds, and yet decisions must be made.

With all the uncertainty that exists, there is one truth that remains. Today, I am the physician, but one day I will be the patient. Maybe we can use this truth to see our patients and ourselves with compassion. Maybe compassion is the real purpose of truth-telling.

Dr. Branigan is a palliative care physician and a member of the St. Joseph's Health Centre Palliative and Supportive Care team. She is also the Theme Coordinator for Ethics and Professionalism for undergraduate medical students.

What students think: Undergraduate students in a palliative health care setting

By Hannah H. Chiu, BSc(C)

Despite national shortages, entry into medical schools and other professions' programs has become increasingly competitive. Therefore, undergraduate students who wish to pursue a career in medicine often have to possess experiences in different health care settings in order to have a leading edge over their peers. The impact of students' involvement on health care settings is under-reported in literature, especially in light of the growing sector of undergraduate students who work in the field.

The undergraduate students employed in the Rapid Response Radiotherapy Program (RRRP) are a success story. The palliative care setting provides a unique perspective on health care, and experience in this area complements the growing interest in palliative care among health care professionals.

We carried out a qualitative survey of the 10 students who have worked in the RRRP. Several recurring themes emerged with the two most notable being:

The value of patient interaction in inspiring students to pursue medical careers: Most RRRP students described that prior to the position, while they thought that medicine was interesting, they were not necessarily motivated to pursue it as their career. For many of them, this was their first time encountering palliative patients and, although they found it stressful and traumatic at times, the overall experience was highly positive.

A student who has worked in research about health issues before without directly interacting with patients described the position to be much more rewarding and inspirational.

"Before this job, I felt that medicine was a maybe, maybe not thing. I didn't think that I had sufficient interest to go through all the schooling. But after working here, I found that I really liked working with patients. I felt that I could make a huge difference in patients' lives by just listening to them… the atmosphere working here with the health care professionals is very encouraging."

Another student described that while health care professionals are very inspirational role models, it is the patients who have been the motivation to pursue a career as a doctor.

"Working with the patients has been very inspiring to me… it is very moving also to see the improvement in their quality of life from being in a lot of pain to feeling fine. I really hope that as a doctor, I would be able to facilitate the same sort of change."

The changed attitude towards palliative care and clinical research: Many students had preconceptions that dealing with palliative patients would be like looking after those who are basically dying. They were surprised to find that many of them actually looked quite well and were high-functioning.

They also worried that palliative care would be very depressing but, on the contrary, they found that many patients who have accepted their conditions remain in an optimistic and hopeful attitude. A student explains that the experience was far from being filled with hopelessness.

"There was a different kind of hope among the patients. It was not necessarily a hope to live as long as possible, but rather a hope to live a very dignified and meaningful life. And I found that hope was more real than just hoping for a long life, because even me, I wouldn't know what would happen to me tomorrow."

For all the students, this was their first position as a clinical research assistant and many of them started working with vague ideas of what it entailed.

"I perceived clinical research as almost bothersome and so, initially, I was quite nervous to interview patients because I did not want to upset them. On the contrary, I found that patients are often happy to share their experiences with someone who is willing to listen patiently.

"I didn't really think clinical research was significant. But after working here, I realized that it could translate to very direct and useful information for patient care, and so, while it may not cure patients in the future, it would help them with quality of life, which is equally important in palliative care."

Working as a research assistant is more than "just a job" for these students. They consistently reported that they gained skills and knowledge that would be inaccessible within the classroom. This experiential learning is crucial in shaping the character of a future clinician or researcher.

The experience as a clinical research assistant is highly beneficial because students learn to combine research initiatives in clinical trials and develop a receptive and empathetic attitude towards the patients during interviews. Furthermore, their interactions are not concurrently burdened with treatments and required textbook knowledge as in the case of medical students.

Help not wanted?

By Margaret I. Fitch, RN, PhD

Cancer and its treatment have more than a physical impact. There are social, emotional, psychological, spiritual, and practical consequences that emerge as well. However, no two individuals will experience exactly the same impact. Each will have his or her own perspective on the situation and ideas about how to best cope with any change. Some individuals will mobilize their own social support networks while others will require assistance in dealing with the difficulties they experience.

Part of the challenge facing health care professionals is to identify who will benefit from psychosocial and practical assistance and which service is most appropriate for them. All cancer patients require basic emotional support, relevant information, astute symptom control, and effective communication exchange with their cancer care team. The structures and processes in our care facilities ought to be organized to provide that standard of care.

However, some individuals will require additional coaching or encouragement to seek assistance and approximately 35% to 40% of cancer patients will benefit from referral to a psychosocial care provider (although the actual proportion will vary with palliative care patients or survivors who have no clinical evidence of disease). Between 10% and 15% of cancer patients would benefit from referral to psychiatry.

There is a growing impetus in Canada to have psychosocial distress and pain considered "vital signs" and measured, using a standardized tool, on each visit with a health care provider. This approach would mean that psychosocial distress and pain could be documented easily on a regular basis and referrals could be made more proactively.

Recent investigations at Toronto Sunnybrook Regional Cancer Centre have provided additional insight about patients' perspectives on their desire for assistance. These perspectives need to be taken into

If symptom clusters exist, how are they relevant to patient care?

By Amna Husain, MD, CCFP, MPH

At a research planning retreat held in January 2006 at Sunnybrook, a multidisciplinary research group from multiple care settings at Sunnybrook and from the Temmy Latner Centre for Palliative Care at Mount Sinai Hospital examined the emerging area of symptom cluster research. The researchers felt that research in the area of symptom clusters is likely to make a significant contribution to scientific knowledge and is likely to have broad impact for patients. This article reports on the group's deliberations, primarily related to the clinical significance of symptom cluster work.

Although a definition of symptom clusters has been proposed by Dodd, Miaskowski and Paul (2001), the definition has yet to be tested, and our conceptual understanding of symptom clustering has to be developed. The definition states (Miaskowski, Dodd, & Lee, 2004):

- Symptom clusters are three or more concurrent symptoms that are related to each other. The suggested strength of those relationships has not been specified.
- Symptoms within the cluster are not required to have the same etiology.
- The amount of time that all the symptoms within the cluster need to be present to be considered a "cluster" has not been specified.
- Symptom clusters have an adverse effect on patient outcomes and may have a synergistic effect as a predictor of patient morbidity.

Some early work has identified, for example, fatigue, sleep disturbance and pain as a cluster in cancer patients (Dodd, Miaskowski & Paul, 2001), but the evidence for the prevalence and significance of this cluster and the identification of other clusters remains, in large part, to be studied.

What is encouraging is that the idea of symptom clustering resonates with our clinical experience. It is rare that our patients present with a single symptom. Furthermore, it is clinically credible that the interaction or relationship between some symptoms is relevant to patient outcomes and to planning preventive, assessment, and management strategies for patients. However, experienced clinicians have been intuitively assessing, managing and monitoring multiple symptoms simultaneously based on comprehensive clinical assessments in their practices. In view of this, is there any clinical utility to expanding our knowledge of symptom clustering?

In relation to research utility, it is easy to envision how symptom cluster work will improve symptom management for patients. Understanding symptom clusters will allow the design of interventions and outcome measures in trials that more closely reflect patients' experiences. Improving our conceptual understanding of symptom clustering will provide the evidence-based knowledge to our experiential knowledge of the interaction and impact of multiple symptoms in our patients. This knowledge will improve clinical practice and the education of new generations of health care providers.

The direct clinical utility of symptom cluster work is that it will inform the timing and choice of therapeutic strategies when faced with patients with multiple symptoms. For example, in treating a patient with the hypothetical symptom cluster of fatigue, pain and existential distress, we will be able to answer questions such as: Should medications for pain be started alone or in combination with medications for fatigue (e.g., psychostimulant)? Should specialized resources be devoted to existential distress from the beginning or will treating pain and fatigue result in improvement in existential distress? Will interventions for existential distress result in improvement in fatigue and pain? Will pharmacotherapy for pain and fatigue have any adverse effects on existential distress and sense of well-being? Thus, symptom cluster work will make it possible to explore the complex set of clinical questions that clinicians face when caring for patients.

The challenges facing researchers in symptom clusters are many. There are issues in conceptualization, design, measurement and analysis that have yet to be worked out (Barsevick, Whitmer, Nail, Beck & Dudley, 2006). Patients present with, on average, 11 symptoms at a time (Osse, Vernooij-Dassen, Schade, & Grol, 2005). Although optimal, it is not feasible to measure each symptom with a multidimensional measure. The burden on patients is even greater with longitudinal studies. Thus, we are confined to using symptom inventories that, in large part, measure the domain of symptom severity. It is important to do so being aware that the domain of symptom severity may not be the relevant domain in which symptoms are related to each other in a cluster, and that symptom burden may not be related to symptom severity (Walke, Byers, McCorkle, & Fried, 2006). For the symptom measured, clinically relevant cutoffs have yet to be determined by comparison to patient outcomes. Although a number of analytic approaches such as factor analysis, cluster analysis, regression techniques and path models have been used to examine symptom clusters, the best approach has yet to be established (Barsevick et al., 2006). The clinical relevance of the work makes the significant challenges of symptom cluster research worth tackling.

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account during the patient referral process for psychosocial distress needs. Investigations have been conducted with patients attending the Rapid Response Radiation Program, the Lung Cancer Clinic, and the Gynecologic Cancer Clinic to document patient needs, distress associated with unmet needs, and whether or not the patients wanted assistance for any unmet needs. Across all study groups, patients indicated they did not necessarily want help for concerns they had. As many as 50% of the individuals with a concern indicated they did not want help for the concern at the time they completed the survey.

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Forgoing nutrition and hydration in children at the end of life: Is it ever justified?

By Adam Rapoport, MD

When a child's care plan shifts from curative to palliative the alteration of treatment goals requires one to carefully examine the benefits and burdens associated with the patient's current management. While most dying children continue to experience the pleasure of eating and drinking, for some these acts don't provide that enjoyment and may, in fact, potentially lead to increased suffering. Broadly speaking, there are three categories of pediatric patients for whom withholding or withdrawal of nutrition and hydration (N&H) may be considered – neurologic devastation, irreversible total intestinal failure, and proximate death from any pathologic cause (Nelson, Rushton, Cranford, et al., 1995).

In situations of irreversible, profound neurologic impairment or total intestinal failure, patients are invariably dependent on artificial means, such as enteral or intravenous tubes, for the delivery of sustenance. Although capable of supporting biological existence, artificial N&H should be viewed as a medical intervention, requiring trained individuals to insert devices by means of technical procedures, and capable of causing various complications that could significantly impact a dying child's quality of life (Slomka, 2003; Fletcher & Templeton, 1993). In their paper, Carter and Leuthner (2003) describe the findings of a recent review on the benefits and burdens of nutritional support near end of life. Parenteral nutrition had a complication rate of at least 15%. The rate for enteral feedings was 76%. The review also concluded "that clinical benefits of nutritional support fail to be demonstrated in study after study of patients at or near the end of life".

The comfort and pleasure derived from eating and drinking may be experienced very differently by those nourished through artificial means, or perhaps not experienced at all. The sensations of taste, smell and experiencing different textures, which normally contribute to the enjoyment of a meal, are bypassed in this population.

Denying the right of orally provided N&H to any infant or child who demonstrates a desire and who can do so safely, is ethically and legally wrong under any circumstances. However, occasionally pediatric patients who may be physically capable of eating or drinking on their own no longer feel compelled to do so near the end of life. Forced-feeding or medically administered N&H have no proven benefit in the dying child (apart from perhaps a psychological benefit to caregivers) while potentially causing increased suffering and prolonging death.

While medical evidence supports the option to forgo N&H in specific circumstances, the literature suggests that among pediatricians, the prevailing attitude is that it should be continued despite its futility and potential harms (Solomon, Sellers, Heller, et al., 2005). In one large study examining the attitudes of pediatric doctors and nurses towards end-of-life care, respondents were asked to comment on the statement: "Even if life support such as mechanical ventilation and dialysis are stopped, medically supplied food and water should always be continued". Fewer than 50% of all those questioned disagreed with this statement. Among trainees, the trend is similar. Regarding the care of permanently unconscious children whose parents wished no treatment at all, while more than 95% of third-year pediatric residents questioned stated they would forgo vasoactive agents, CPR or assisted ventilation, only 45% indicated a willingness to withdraw N&H (Rubinstein, Unti, & Winter, 1994).

Why does such a discrepancy exist between what the literature suggests is permissible and what is practiced? Psychological forces largely account for this phenomenon. For most of us, there is a feeling that we are obliged to feed those who cannot feed themselves; providing food and fluids is symbolic of care and compassion. Nonetheless, after weighing the potential benefits and burdens of N&H in specific palliative circumstances, there are occasions where greater care and compassion may be achieved by forgoing this life-sustaining provision.

While it is evident that forgoing N&H is a medically, ethically and legally sound option for some pediatric patients at the end of life, it should be emphasized that this decision is very personal and must be made within the framework of one's values. Forgoing N&H is never an obligation. Just as we should respect the decision to withhold or withdraw N&H in specific situations, we must also uphold a caregiver's right to request such treatments be continued.

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Help not wanted?

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Subsequent qualitative inquiry revealed that the reasons patients indicated they did not want help varied widely. These reasons included, among others, not knowing what services were available, being told something was "normal" with cancer treatment, thinking care providers were too busy to deal with the specific concern, and feeling care providers were not interested in some types of concerns. Clearly there is room to influence these perspectives and improve the quality of care.

The implications for practice from these investigations lie in communication with patients. As health care providers, we must find ways to have meaningful discussions with patients about their concerns and the type of assistance they would like at a point in time. We need to understand their particular perspectives and desire for assistance in order to tailor the subsequent care plan to the individual's situation. A triage or screening approach needs to be linked to a process for dialogue and mutual decision-making with the patients.

Continuing Medical Education

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 and starting in 2006, **Hot Spot** will list the Canadian CME activities in palliative medicine that are of interest to our readers. Please kindly forward details of the CME activities to: **ewa.szumacher@sunnybrook.ca**

- May 18-20, 2006 – **"Turning the Wheel: Henri Nouwen and Our Search for God"** at The University of St. Michael's College, Toronto, ON Contact: Colette Halferty at **Colette@halferty.ca** or **www.utoronto.ca/stmikes/nouwen/conference**
- May 25-27, 2006 – **The Transforming Power of Spirituality: Breaking Barriers and Creating Common Ground** at the Rension College, University of Waterloo, Waterloo, ON **http://people.stu.ca/~jcoates/cnssw/overview2006.html**
- May 26-28, 2006 – **BC Hospice Palliative Care Association Conference "Bold Steps: Becoming our Best"** in Vancouver, BC **www.hospicebc.org**
- May 27, 2006 – **University of Toronto Department of Radiation Oncology presents the Third Annual Toronto Radiation Medicine Conference – Accelerating Interprofessional Practice** at the Kingsbridge Centre. Contact: Mary Hooey at (416) 946-4457 or **mary.hooey@uhn.on.ca**
- June 14-17, 2006 – **2006 CPS Conference "Pain Unraveling the Puzzle"** at the Westin Edmonton Hotel, Edmonton, AB **www.canadianpainsociety.ca**
- June 22-24, 2006 – **MASCC/ISOO – 18th International Symposium of Supportive Care in Cancer** at the Toronto Sheraton Centre, Toronto, ON. **www.mascc.org**
- June 23, 2006 – **Philosophy and History of Hospice Palliative Care** (online course) Humber College School of Health Sciences. Contact: Pamela Mckintuck at (416) 675-6622 ext 4637 or **pamela.mckintuck@humber.ca**
- August 13-18, 2006 – **XIV International AIDS Conference** at the Metro Toronto Convention Centre **www.aids2006.org**
- September 26-29, 2006 – **16th International Congress on Care of the Terminally Ill** at the Palais des Congrès, Montreal, QC. **www.pal2006.com**
- September 14-15, 2006 – **16th Annual Provincial Hospice Palliative Care Conference – Advancing Leadership in Palliative Care,** Winnipeg Convention Centre, Winnipeg, MB. For more information: Hospice and Palliative Care Manitoba, 2109 Portage Ave., Winnipeg, MB R3J 0L3 Phone: (204) 889-8525 or 1-800-539-0295 (within Manitoba), Fax: (204) 888-8874 E-mail: **stapper@manitobahospice.mb**, **www.manitobahospice.mb.ca**
- September 13-16, 2006 – **CARO Canadian Association of Radiation Oncology Annual Meeting,** Calgary, AB 20th Annual Meeting. Contact Mary Hooey, **Mary.Hooey@uhn.on.ca**
- September 15 & 17, 2006 – **Hospice Association of Ontario 16th Annual Conference,** Alliston, ON. For more information, phone: 1-800-349-3111 or (416) 304-1477, fax: (416) 304-1479 E-mail: **denise.larocque@hospice.on.ca**, **www.hospice.on.ca**
- September 27-October 1, 2006 – **14th International Conference on Cancer Nursing Cancer Nursing – Reaching New Heights Together** The Sheraton Centre, Toronto, ON For more information, phone: +44 (0) 116 270 3309, fax: +44 (0) 116 270 3673 E-mail: **conference@isncc.org**
- October 2-6, 2006 – **6th Princess Margaret Hospital Conference** Toronto, ON
- November 1-3, 2006 – **Centre for Education and Research on Aging and Health Palliative Care Institute 2006** Travelodge Airlane Hotel, Thunder Bay, ON. For more information: Lakehead University, CERAH, 955 Oliver Road, Thunder Bay, ON P7B 5E1 Phone: (807) 343-2126 E-mail: **cerah@lakeheadu.ca**, **http://cerah.lakeheadu.ca**
- November 5-9, 2006 – **American Society for Therapeutic Radiology and Oncology (ASTRO) Annual Meeting** Philadelphia, PA, United States

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

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AstraZeneca

Amgen

Boehringer Ingelheim

GlaxoSmithKline

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Vol. 8, Issue 2, May 2006

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

Radioimmunotherapies

By Dr. Rena Buckstein, MD, FRCPC, Hematologist, Head, Hematology Site Group, Toronto Sunnybrook Regional Cancer Centre

HOT SPOT

Background

- In Canada, non-Hodgkin's lymphoma (NHL) represents the fifth most common cancer. In 2005, 6,400 new cases were diagnosed and NHL accounted for 3,000 deaths
- B-cell lymphomas account for 90% to 95% of all lymphomas and 90% express the CD20 cell surface antigen in high density
- Indolent lymphomas comprise roughly 30% of all lymphomas and are characterized by median survivals of eight to 10 years, incurability with standard chemotherapy and relapsing/remitting courses
- While the mainstay of treatment for lymphomas has been chemotherapy and radiation, the advent of Rituximab, a humanized monoclonal antibody against the CD20 antigen has revolutionized the management of B cell lymphomas
- Standard treatment for most B-cell (CD20+) lymphomas today is to combine chemotherapy with Rituximab, or to use Rituximab as monotherapy. This approach has improved overall survival in many types of B-cell lymphomas
- Anti-CD20 antibodies kill lymphoma cells by antibody-dependent or complement-mediated cytotoxicity and apoptosis
- Despite this, many patients are either refractory to or relapse following Rituximab-chemotherapy regimens and are in need of alternative 'non-toxic' treatments

What are radioimmunotherapies (RITs)?

- These are radiolabeled antibodies against CD20 that deliver targeted radiation to lymphoma cells by a 'guided missile' approach. This limits the toxicity to surrounding normal tissues, and capitalizes on the inherent radiosensitivity of most indolent lymphomas.
- There are two radiolabeled anti-CD20 monoclonal antibodies currently approved by the US FDA and Health Canada for use in patients with recurrent low-grade or transformed low-grade lymphomas: yttrium-90 ibritumomab tiuxetan (Zevalin™) and iodine-131 tositumomab (Bexxar™)

How do they work?

- In addition to their antibody mediated anti-lymphoma effects (similar to Rituximab), they deliver targeted radiation to B-cells and their immediate vicinity
- The radiation works to kill the lymphoma cells by both bystander and cross-fire effects
- Cross-fire radiation can kill cells in the proximate environment that are not accessible to the monoclonal antibody, that may not express CD20 and/or that may be resistant to the immune-mediated or direct apoptotic effects of the unlabeled antibody

Supported by an educational grant from GlaxoSmithKline

What are their similarities?

(See Tables One and Two)

- Both treatments are well-tolerated, generally outpatient procedures
- Treatment is short – completed by eight to 14 days
- Both require threshold platelet counts (> 100,000 x 10^9/L) and minimal bone marrow infiltration (< 25%) before they can be administered. The radiation dose is attenuated for patients with platelet counts < 150,000 x 10^9/L
- Both must receive naked 'cold' antibody one week prior to 'hot' therapeutic dosing in order to clear circulating CD20+ B lymphocytes, thus optimizing the biodistribution and tumour uptake of the radiolabeled antibody
- Both may provide durable multi-year responses even in patients with disease that is resistant to chemotherapy
- Roughly one-third of patients will achieve remissions of > 12 months. These durable responders may enjoy remission durations ranging from 28 to 46 months
- These drugs may be effective in Rituximab-refractory patients, with some patients having remissions for several years, despite prior short responsiveness or unresponsiveness to previous unlabeled anti-CD20 therapy
- In heavily pretreated patients, RITs may provide remission durations that exceed the immediately preceding one. This is an uncommon occurrence in indolent lymphomas, where remissions typically progressively shorten, not lengthen

What are their differences?

(See Table One)

- Bexxar™ emits both beta and gamma irradiation. The beta particle wavelength is shorter, but its half-life is longer compared with Zevalin™
- Patients administered Bexxar™ must undergo dosimetry and clearance measurements for calculating the therapeutic dose individualized for them
- Patients treated with Bexxar™ must undergo shielding and isolation from others for periods ranging from five to 10 days because of the gamma radiation and must take free oral or intravenous iodine to protect their thyroid glands from the potential damaging effects of free radioactive iodine
- Zevalin™ emits only beta irradiation and does not require dosimetry
- The longer beta particle wavelength of Zevalin™ may make it more suitable for patients with bulkier tumours
- Patients who receive Zevalin™ are not restricted in their daily activities or in their contact with others

What are their chief toxicities?

- Principal side effects are hematologic and occur approximately four to eight weeks after treatment, presumably due to radiation effects on the bone marrow
- Despite this, the incidence of neutropenic fever and transfusion support is low
- Other side effects may include mild nausea (25%-30%), asthenia (32%%-43%), fever (17%-22%), throat irritation (6%-10%) and rash (8%-10%)
- Approximately 10% of patients who receive Bexxar™ will become hypothyroid
- The annualized incidence of treatment-related myelodysplastic syndromes or acute myeloid leukemia following RITs is 1.1%/year. This is not different from that expected in patients treated with chemotherapy alone and depends on the degree of prior exposure to alkylating agents

In whom should radioimmunoconjugates be used?

- In Canada, Zevalin™ is approved for the treatment of patients with relapsed or refractory low-grade or follicular, CD20+, B-cell non-Hodgkin's lymphoma, including

Table One

	I-131 Tositumomab (Bexxar™)	Y-90 Ibritumomab Tiuxetan (Zevalin™)
Monoclonal antibody	Mouse anti-CD20	Mouse anti-CD20
Linker	None	Tiuxetan
Imaging isotope	Iodine-131	Indium-111 (if dosimetry used)
Therapeutic isotope	Iodine-131	Yttrium-90
Isotope radiation decay	Gamma and beta	Beta
Beta particle path length, mm	0.8	5.3
Half-life radioisotope, days	8.0	2.6
Isotope uptake in normal tissues	free iodine, thyroid and stomach	free yttrium in liver and bone
Unlabeled antibody given	mouse tositumomab	rituximab
First dose of 'cold' antibody	450 mg IV day 1	250 mg/m2 day 1
Second dose of cold antibody	450 mg IV day 8 (range: 8-14)	250 mg/m2 day 8 (range: 8-10)
Standard therapeutic dose	0.75 Gy total-body dose on same day (range: days 8-14)	0.4mCi/kg to maximum of 32mCi on same day (range: days 8-10)

* Adapted from Dillman, R. (2002). Radiolabeled Anti-CD20 Monoclonal Antibodies for the Treatment of B-Cell Lymphoma. **Journal of Clinical Oncology, 20**, 3546-3557.

patients with Rituximab-refractory follicular non-Hodgkin's lymphoma (notice of compliance May 10, 2005)
- In Canada, Bexxar™ is approved for the treatment of patients with CD20 positive relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma, including patients with Rituximab-refractory non-Hodgkin's lymphoma (notice of compliance August 18, 2005)
- Neither drug is currently funded in Ontario by the Ministry of Health, but may be available on several clinical trials
- See Table Two for summary of activity of both RITs

What is ongoing research and the future of radioimmunoconjugates in NHL?

- In addition to indolent lymphomas, both Zevalin™ and Bexxar™ are currently under evaluation in diffuse large cell B-cell lymphoma (DLBCL) and mantle cell lymphoma
- These RITs are being tested as monotherapy upfront, in combination with chemotherapy upfront, as consolidation or as components of conditioning treatment in autologous stem cell transplants
- RITs used upfront or earlier in the disease course of patients with CD20+ indolent NHL may provide better remission depths and durations. For example:
  - Single agent Bexxar™ used initially upfront in 76 patients with advanced stage follicular lymphoma achieved overall responses of 95% (75% complete) and 80% molecular remission in Bcl-2 PCR positive patients. At a median follow-up of five years, the progression-free survival was 6.1 years
  - In a SWOG study, single agent Bexxar™ following CHOP chemotherapy improved two-year PFS (81% versus 65%) and OS (97% versus 91%) in comparison to historic controls
- SWOG and CALGB are comparing CHOP + Rituximab versus CHOP followed by Bexxar™ in a multi-centre randomized controlled trial as initial therapy for follicular lymphoma
- Bexxar™ and Zevalin™ are currently being compared in a randomized controlled trial for toxicity and response in patients with follicular lymphoma
- Zevalin™ has significant activity (ORR 58%) in patients with relapsed DLBCL who have not previously received Rituximab

Table Two: Combined analyses of clinical studies for Bexxar and Zevalin

	BEXXAR™ n=250	**ZEVALIN™ n=211**
Data Source	5 combined clinical trials	4 combined clinical trials used for registration in USA
Patient Population	Low grade +/- transformation, follicular large cell, follicular +/— transformation Relapsed/refractory to chemo or Rituximab Patient specific dosing 65 or 75 cGy total body irradiation dose based on platelet count	Low or intermediate grade NHL, Mantle cell, follicular or transformed low-grade Relapsed/refractory to chemo or Ritux Dose ranged from 0.2-0.4 mCi/kg
Overall response	56% (n=141)	73-83%
Median Duration of response	12.9 mos (10.6-17.3)*	6.4-13.9 mos
Time to progression or death Median In responders	 6.4 mos (5.9-9.4)* 15 mos (12.2-19.2)*	 6.4-13.9+ mos -
Complete response	30% (n=75)	15-51%
Duration of complete response, Median	58.4 mos (28.3-NR)*	31 mos (range 12.1-81.5)
Combined analyses of clinical studies for Bexxar and Zevalin – Durable responder patient population: Defined as response duration > 12 mos		
	BEXXAR N=81	ZEVALIN N=78
Demographics	36% did not respond to last Rx 88% had stage 3,4 41 % had bone marrow involvement 49% had bulky disease(>=5cm) 72% follicular	37% did not respond to last Rx 83% stage 3,4 41% had bone marrow involvement 30% had bulky disease(>=5cm) 76% follicular
Median age	52	58
Median # prior regimens	3 (range 1-8)	2 (range 1-9)
Durable Response	31% (81/250)	37% (78/211)
Median Duration of Response	45.8 mos (range 27-NR)	28.1 mos (range 10.5-80.3+)
Median Follow-up	61.2 mos (range 15.5-133.1)	49.8 mos (range 12.7-75.5+)
Median Time to Progression or death	48.5 mos (range 28.5-NR)	29.3 mos (range 12.1-81.5+)
Durable complete responder population (CR with ttp >= 12 months)		
Durable Complete Response	25% (62/250)	24% (51/211)
Median Duration of Durable Complete Response	NR (47.2-NR)	53.9 mos (49-82)

* 95% confidence intervals; NR: not reached; ttp: time to progression; mos: months

Fisher, R.I., Kaminski, M.S., Wahl, R.L., et al. (2005). Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. **Journal of Clinical Oncology, 23,** 7565-7563.

Wiseman, G.A., & Witzig, T.E. (2005). Yttrium-90 (90Y) ibritumomab tiuxetan (Zevalin®) induces long-term durable responses in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. **Cancer Biotherapy & Radiopharmaceuticals, 20**(2), 185-188.