

# HOT SPOT

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



Volume 9, Issue 1, February 2007

## Guest editor's corner

By Lisa Barbera, BSc, MD, MPA, FRCPC

Happy New Year and welcome to the first issue of the **Hot Spot** for 2007! You can expect our team to continue to bring you current palliative care news, research and reflection in the upcoming year.

In this issue, the psychosocial contribution is from Dr. Mary Vachon. She discusses the alchemy of healing and how both providers and patients can be transformed as a result of their interactions with each other.

Dr. Deborah Dudgeon and Raquel Shaw Moxam provide an overview of a new large-scale initiative being undertaken by Cancer Care Ontario and the Ministry of Health and Long-Term Care. The Provincial Palliative Care Integration Project (PPCIP) represents an exciting new innovation in the delivery of palliative care in Ontario.

Erica Moran and Dr. Amna Husain provide the research contribution. They

discuss the complexity of measuring and managing dyspnea and describe a new project underway at the Temmy Latner Centre for Palliative Care (TLCPC) to address this difficult clinical problem.

Drs. Christopher Church, Justin Baker and Pamela Hinds provide the pediatric palliative care contribution in this issue. They discuss the importance of redirecting a parent's hope and provide six tips for facilitating communication with parents to foster and maintain a trusting relationship.

The ethics contribution is from Blair Henry who provides a list of the 10 most common myths that clinicians hold about decision-making capacity.

Dr. Albert Kirshen describes the trials and tribulations of instituting a new electronic patient record at the TLCPC and provides some useful tips for surviving the transition.

The insert this month is provided by Drs. Buckstein and Wells. They describe the management of iron overload, which is an inevitable consequence of transfusion therapy commonly used for myelodysplastic syndromes.

The team at **Hot Spot** would like to thank you for your continued interest and wish you health and happiness in the New Year.

## The alchemy of healing: Are we wired for compassion?

By Mary L.S. Vachon, RN, PhD

In a recent book, **When Professionals Weep: Emotional and Countertransference Responses in End-of-Life Care** (New York: Routledge, 2006), Dr. Renee Katz and Therese Johnson (Eds.), examine the psychiatric concept of countertransference and how it applies to end-of-life care. They define countertransference as "...an 'abbreviation' for the totality

of our responses to our work – emotional, cognitive and behavioural – whether prompted by our patients, by the dynamics incumbent to our helping relationships, or by our own inevitable life experiences". End-of-life care professionals of all disciplines and levels of experience, not just therapists, are subject to powerful reactions to their

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### In this issue of HOT SPOT:

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## Provincial Palliative Care Integration Project (PPCIP): Enhancing the quality of palliative care services

By Deborah Dudgeon, MD, FRCPC, Provincial Program Head in Palliative Care, Cancer Care Ontario (CCO), Professor of Palliative Care Medicine, Queen's University, and Raquel Shaw Moxam, MSc, Program Manager Nursing, Psychosocial Oncology and Palliative Care, Cancer Care Ontario

The Provincial Palliative Care Integration Project (PPCIP) is a quality improvement project that aims to improve access and delivery of palliative care services across multiple sectors, conducted under the guidance of Cancer Care Ontario (CCO) and jointly funded by CCO and the Ministry of Health and Long-Term Care.

Based on a successful and proven palliative care integration initiative that was introduced in the South East LHIN, the project emphasizes the use of evidence-based tools for assessment and delivery of palliative care services across the continuum of care.

Currently being rolled out in phases throughout the province, the PPCIP links Community Care Access Centres, home care agencies and Regional Cancer programs within the Regional End-of-Life Care Networks. The

Toronto Sunnybrook Regional Cancer Centre is one of the sites participating in the project. While there are plans to expand the program across all disease sites, the program currently focuses on lung and palliative care patients from regional cancer centres and cancer patients receiving home care. There are three main improvement aims: improved symptom screening and assessment, improved symptom control and coordinated palliative support.

Evidence-based practice is at the heart of the PPCIP. Standardized assessment tools such as the Palliative Performance Scale (PPS), and the Edmonton Symptom Assessment System (ESAS), collaborative care plans, and symptom management guidelines are key project components. The PPCIP allows treatment decisions to be informed by “real-time” data, and provides the health care team

with information to regularly assess the intensity of symptoms and the timeliness and effectiveness of interventions. Technology is used as an enabler for screening and monitoring of symptoms. Touch screen ESAS kiosks at the regional cancer centre and a web-based ESAS tool for patients to enter their own data at home are being implemented in five regions (including the Toronto Sunnybrook Regional Cancer Centre). This system also includes a notification system for symptom severity scores (e.g. pain, dyspnea and depression) to notify the patient's care team of scores that fall outside a predetermined threshold.

While the PPCIP is focused on integration in the palliative care context, there is potential to adapt the project frameworks, approaches and tools for use in other areas, including prevention and disease management.

## The alchemy of healing

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work. These reactions are seen as being far more diverse than “compassion fatigue” or “vicarious traumatization”.

Drawing on the quantum physics concepts that the whole is greater than the sum of its parts, similarly to the work of hospice physician, Dr. Michael Kearney's **A Place of Healing: Working with Suffering in Living and Dying** (Oxford: Oxford University Press, 2000), they speak of objectivity and subjectivity in relationships between healers and clients. An alchemical reaction occurs when two individuals engage together at the most vulnerable time in human existence – the end of life. Alchemy is “that space” that takes its own place in the poignant relationship between helper and patient. Through the experience, both can be transformed.

Personally, I can never hear the word alchemy without thinking of a conversation that occurred with the late Dr. Veronique Benk, a radiation oncologist at TSRCC, Dr. Monica Branigan and Reverend Doctor Tim Elliott. It was 2004; we were preparing a presentation for the Humber College Palliative Care Meeting in which the four of us would address how our experiences with personal and family illness had transformed us as professionals. As we struggled for a title, Dr. Benk, who had recently recovered from breast cancer, suggested, *The Alchemy of Healing* – how lead can be transformed into gold, how challenges can be transformed into opportunities for growth, or even blessings. We had this meeting on a Friday. On Monday, Dr. Benk was diagnosed with Acute Myelogenous

Leukemia (AML). The experience transformed her and those of us who were privileged to accompany her on her journey.

Perhaps an explanation for the alchemy that occurs within relationships can be explained by findings contained in Daniel Goleman's new book **Social Intelligence: The New Science of Human Relationships** (New York: Bantam Dell, 2006). Goleman says that our brains have evolved to push us to act to ease the pain of others. Science is now telling us there is a net of neurons in the brain with the sole task of attuning us to the inner state of the person we're with. The human brain has multiple neuron systems – not just for mimicking actions, but also for reading other people's intentions and emotions. These mirror neurons are part of a neural network called the social brain, which is

## Research Corner

# Issues in the measurement and management of dyspnea in home palliative care patients: Who might benefit from oxygen therapy and how should they qualify?

By Erica Moran, BSc, and Amna Husain, MD, CCFP, MPH

Dyspnea, or shortness of breath, has a significant effect on many of our patients, with reported prevalence in 20% to 80% of patients. One reason for this wide variation in prevalence is the complexity of measuring a complex, multifaceted subjective symptom that has physical, physiological, emotional, psychological and social aspects.

Capturing these aspects in a measurement tool has proved difficult, so that a number of tools exist, each addressing only some aspects of dyspnea: Modified Medical Research Council Scale, Baseline Dyspnea Index, Transition Dyspnea Index, Verbal Rating Scale Dyspnea, Dyspnea Visual Analog Scale (DVAS), Cancer Dyspnea Index, six-minute walk, and Borg Scale. The six-minute walk and Borg scales have been widely used, but are not applicable for most home palliative care patients. These and many other tools are not applicable because they use “activities

of daily living” that are already beyond the scope of most palliative care patients. Some tools are too lengthy or difficult to complete. From an intervention perspective, some tools are suboptimal, having too few categories to be sensitive to treatment effects, unless the effect is a very large one.

Fatigue and hypoxemia are two significant factors that can cause or exacerbate dyspnea. Generalized fatigue or fatigue of the specific muscles that support breathing can lead to physiological changes that result in the sensation of dyspnea.

Hypoxemia, or low blood oxygen, also leads to physiological effects and dyspnea, but it is more easily measured (via blood gas) and remedied (via oxygen therapy). Routine in-hospital measurement of blood gas levels has been supplanted by pulse oximetry, a quickly administered, non-invasive measurement that is easily done in the

home. The published criteria for hypoxemia vary. For COPD, mild to moderate hypoxemia is SaO<sub>2</sub> 88-90%. For exercise-induced hypoxemia, the criteria are mild: 93-95%; moderate: 88-93%; and severe: <88%. Thus, Ontario Ministry of Health (MOH) guidelines based on COPD or on the six-minute walk stipulate that patients who have SaO<sub>2</sub><88% qualify for oxygen therapy funding, as is true in New Brunswick, Britain and the United States.

When the MOH criteria are applied to palliative care patients, they may fail to meet the MOH criteria, and yet be in distress and dyspneic based on qualitative clinical or subjective measures. Since palliative care practitioners do not have definitive criteria to predict the benefit of oxygen therapy, a clinical assessment of each patient to measure the effect of oxygen versus air has been suggested, but this may have feasibility issues because each assessment takes 90 minutes. At present, physicians seeking funding for their patients whose SaO<sub>2</sub> is >88% must recommend oxygen therapy under the “palliative care” provision (three months, one-time only, no oxygen criteria), or ask for “special” funding.

To summarize, evaluating the need for, or benefit of oxygen therapy in our patients is exceedingly difficult, except in cases of severe hypoxemia, and existing government criteria need to be improved to address our patients’ needs. A study of hypoxemia and dyspnea in home palliative care patients would be valuable to policy-makers, oxygen suppliers, clinicians and patients.

At The Temmy Latner Centre for Palliative Care, we have started a study to determine the prevalence and relationship of dyspnea and hypoxemia in our home palliative care population. Additionally, we will assess the suitability of the Cancer Dyspnea Index, DVAS, and Borg Scale in home palliative patients.

designed to connect us to the person we are with in a very intimate way. A brain-to-brain bridge puts us on the same wavelength, not just metaphorically, but actually, so that our brain constructs a representation of what is going on inside the other person and melds our moods and emotions. When we are with someone in distress our motor neurons make us want to act. The social brain prepares us to act appropriately – and the appropriate reaction to someone in dire distress is to help. We are wired to be compassionate and to help, but that help can go both ways, which might be part of the alchemy.

Barnard et al. (**Crossing Over: Narratives of Palliative Care**, New York: Oxford, 2000) described palliative care as whole-person care not only in the sense that the whole person of the patient (body, mind, and spirit) is

the object of the care, but also in that the whole person of the caregiver is involved.

Goleman quotes Strazdins (2002) who found that nurses whose work made them more distressed lost track of their mission, had poorer physical health and most strongly wanted to leave their jobs. However, if a nurse had nourishing relationships with patients and frequently left feeling that she had improved their moods, she herself benefited emotionally.

To honour the memory of Dr. Benk and to facilitate the process of alchemical transformation within the health care system, a conference is being planned for the fall of 2007 on *Healing within the Health Care Environment* to be held on the anniversary of both her diagnosis and death, October 4.

# Redirecting hope

By Christopher Church, PhD, Justin Baker, MD, and Pamela Hinds, PhD, RN, CS

Clinicians don't like to differ with parents over the likelihood of a gravely ill child's survival. Clinicians' training and past experience allows for prognosis. What parents know is their present experience of the child's illness as it gradually unfolds. The tensions inherent in these two perspectives can lead to distress for parents and clinical staff as each tries to live true to their unique responsibilities.

Staff sometimes uses the labels of "false" and "unrealistic" hope. These are not the language of terrified parents. For parents, to talk frankly about and to entertain a poor prognosis for their child is experienced as an attack on their fundamental parental role, i.e. protecting and nurturing their child (Rando, 1984). For parents, abandoning hope for their child is what is false and unrealistic.

Redirecting hope does not insist on denying an expressed hope or on refining it with expert prognostics. Instead, it implies respecting the expressed hope – perhaps even voicing a wish for the same end (the child's cure) while also aligning with the parents to add other hopes. As a film director calls for the camera to pan out to capture all the audience needs to see, clinicians can help position parents to see with a wider lens that takes in other possible hopes.

Redirecting hope begins with clinicians sharing that they, too, are worried and also wish for the child's survival. Redirecting simultaneously addresses responsibility to not allowing parents or child to be taken by surprise – and, thus, the need for honest discussions including more than hope for cure. This allows the clinician to place the hope to avoid unnecessary harm/suffering on the same playing field already occupied by the hope for cure.

Clinicians' tasks include supporting and designing effective communication that facilitates parents' shift from hope only for a cure to hope for readily attainable clinical goals as well. Parents may not be able to tolerate prolonged discussions about their child's unrealistic chance for cure and, in a few situations, certain parents may not be able to acknowledge that their child is dying until the very end. Staff can facilitate communication across the continuum of care by:

- **Maintaining open communication channels.** Frequent meetings with family members from point of diagnosis to avoid escalation of miscommunication, mistrust and related problems. Parents should perceive staff as approachable, committed to their child's welfare, appreciative of their special burden as parents, and respectful of their unique role in the child's life.
- **Repeating information.** Parents of children with catastrophic diseases face obstacles in assimilation of information, including shock, disbelief, sleep deprivation, and fear. Parents may benefit from receiving important information verbally, in written form and depicted pictorially as guided by the parents' preference.
- **Calling parents' attention to what is readily observable.** Parents rely heavily on their own assessment of their child's shifting condition. Staff may assist parents by inviting them to identify changes they have noted.
- **Asking parents open-ended questions and being open to follow-up on uncertainties expressed (and unexpressed).** "Empathetic presence," to sit and listen when nothing is spoken, demonstrates willingness to walk alongside the patient and family throughout the disease experience.

- **Coordinating a consistent message to parents focused on the child's overall condition rather than small variations in organ system functioning.** Since parents search for reasons to build on their hope, staff should avoid misleading communications about any slight improvement when overall prognosis is unchanged.
- **Clarifying the limits of what staff can in good conscience do.** In rare cases, parents' exclusive demands for "curative" interventions may expose a child to undue burdens and loss of opportunities at end of life. Here, staff's reply, "Not by my hand," is itself a show of fidelity to the child patient.

Clinician-initiated strategies aimed at redirecting hope are intended to maintain a supportive and effective clinician-family trust relationship, preparing patients and family members, providing them with preferred times to the extent possible, and avoiding unnecessary harm, but are not aimed at removing parental insistence on a cure. Chaplain Brent Powell observes that parents of a dying child likely vacillate between acknowledging and refuting their child's condition until living with their child's progressive illness eventually wears them down and places the child's sure dying into their focus.

## About the authors

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## Capacity and consent: Separating fact from fiction

By Blair Henry, Senior Clinical Ethics Fellow, Clinical Ethics Centre and Research Ethics Board, Sunnybrook

That we have an ethical and legal obligation to ensure our patients are informed about and allowed to participate in their health care decisions goes without argument. However, the degree to which a patient can be involved in making decisions ultimately depends on whether we deem them capable to do so, and this, ultimately, hinges on our skills for assessing capacity.

A recent study conducted by the National Ethics Committee of the Veterans Health Administration (Ganzini, Volicer, Nelson, Fox & Derse, 2005) in the United States, identified the following 10 common myths that clinicians hold about decision-making capacity and how it is assessed: (1) Decision-making capacity and competence are the same; (2) lack of decision-making capacity can be

presumed when patients go against medical advice; (3) there is no need to access decision-making capacity unless patients go against medical advice; (4) decision-making capacity is an “all or nothing” phenomenon; (5) cognitive impairment equals lack of decision-making capacity; (6) lack of decision-making capacity is a permanent condition; (7) patients who have not been given relevant and consistent information about their treatment lack decision-making capacity; (8) all patients with certain psychiatric disorders lack decision-making capacity; (9) patients who are voluntarily committed lack decision-making capacity; and (10) only mental health experts can assess decision-making capacity.

To truly respect the autonomous choices our patients make, it entails that

we support their participation in the decision-making to the greatest degree possible. Perhaps, in the time of leading up to accreditation and in the culture of promoting ethical health care practices, the above list of commonly held misconceptions can act as a catalyst for further education and discussion about the assessment of capacity. Preventative ethics would suggest that we minimize potential errors from occurring in the clinical assessment of decision-making capacity – and debunking these common misconceptions would be a good place to start!

### Reference

Ganzini, L., Volicer, L., Nelson, W.A., Fox, E., & Derse, A.R. (2005). Ten myths about decision-making capacity. *Journal of the American Medical Directors Association, 6(3 Suppl.), S100-4.*

## Temmy Latner Centre Update on Palliative Care

### Computerization in palliative care

By Albert J. Kirshen, MD, FRCPC, Cert Spec Comp Ger Med, FACP, MsC, Palliative Care Physician

As I grow older, it gets more difficult to remember all the small details I once easily recalled about each patient or disease. All the notes that I wrote into those little binders or cards I used to carry in my lab coat. All that information we now call data. Thanks to the advent of computers – the variety that sit on the desk or in my pocket – I now have all those data easily at my fingertips. But our purpose as health professionals is to use those data to improve patient care.

Our own database at the Temmy Latner Centre has gone from a billing program to one used for electronic problem lists and, shortly, we hope, to a full electronic record. In order to properly protect patient confidentiality and yet promote access, we have learned

about security programs and personal digital assistants (PDA), Virtual Private Networks (VPN), enabling all transfer of data to be fully encrypted between the user and the office, data backup routines, hardware needs, and even how to air condition our computer room. All this has taken a substantial investment of time and dollars. Thanks to our staff and our donors.

We now have a system that allows us to communicate effectively and simply about our program’s 650-plus patients, as well as perform an ongoing review of patient demographics, ICD-9 coded problem lists and medication lists, as well as data on death or discharge.

For anyone interested in replicating our experience, I would strongly suggest a stiff drink of tomato juice, a good

night’s sleep, and a talk with your friendly psychosocial support staff before moving forward. If, in the end, you do decide to replicate part or all of our experience, get professional help and pay for it. Know your limitations, personal and financial, and have a clear idea of the end product you need. Insist on a system that will almost do it your way, but that allows you to improve your processes where indicated. Include more time than you think it will take. Be prepared to learn more about the hardware and software than you want to know just so that you can properly understand what the computer professionals are telling you. Most of all, be prepared to replace your system when it no longer meets your needs and go through this process all over again.

# 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 lists 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@sw.ca](mailto:ewa.szumacher@sw.ca)

- February 12, 2007 – **Canadian Cochrane Symposium: Knowledge for Health**, Ottawa, ON [www.conferencealerts.com](http://www.conferencealerts.com)
- February 14-17, 2007 – **Annual Assembly of the American Academy of Hospice & Palliative Medicine and Hospice and Palliative Nurses Association**, Salt Lake City, UT [www.aahpm.org](http://www.aahpm.org)
- March 14-16, 2007 – **Supportive Care Hematology and Oncology Tours**, France [www.grasspho.org](http://www.grasspho.org)
- March 24-27, 2007 – **American Society for Pain Management Nursing (ASPMN): 2007 National Conference**, InterContinental Dallas Hotel, Addison, TX [www.aspmn.org](http://www.aspmn.org)
- April 19-22, 2007 – **ASRA 2007 Annual Pain Medicine Meeting**, Vancouver, BC [www.asra.com](http://www.asra.com)
- April 20-21, 2007 – **4th Annual Toronto Radiation Medicine Conference**  
Contact: [Kathleen.Conway@rmp.uhn.on.ca](mailto:Kathleen.Conway@rmp.uhn.on.ca)
- May 3-5, 2007 – **26th Annual Scientific Meeting of the American Pain Society**, Washington Convention Center, Washington, DC [www.ampainsoc.org](http://www.ampainsoc.org)
- May 23-26, 2007 – **CPS Annual Conference**, Ottawa, ON [www.canadianpainsociety.ca](http://www.canadianpainsociety.ca)
- May 30, 2007 – **6th Annual Kaleidoscope Palliative Care Conference**, Dublin, Ireland [www.stfrancishospice.ie/education/kaleidoscope.htm](http://www.stfrancishospice.ie/education/kaleidoscope.htm)
- May 30-June 3, 2007 – **18th Canadian Bioethics Society Conference and the 3rd International Conference on Clinical Ethics and Consultation – Ethics Matters**, Toronto Marriott Downtown, Eaton Centre, Toronto, ON [www.utoronto.ca/jcb/ethicsmatters/en/index.html](http://www.utoronto.ca/jcb/ethicsmatters/en/index.html)
- June 20-21, 2007 – **Spiritual Practices for Conflict Resolution**, Waterloo, ON <http://grebel.uwaterloo.ca/certificate>
- June 21-23, 2007 – **American Alliance of Cancer Pain Initiatives (AACPI): 18th Annual Meeting**, The Radisson Hotel Boston, Boston, MA [www.aacpi.wisc.edu/](http://www.aacpi.wisc.edu/)
- August 28-31, 2007 – **9th Australian Palliative Care Conference**, Melbourne, Australia [www.pallcare.org.au](http://www.pallcare.org.au) or [info@pallcarevic.asn.au](mailto:info@pallcarevic.asn.au)
- September 6-9, 2007 – **Pain Educators Forum 2007**, Las Vegas, NV [www.paineducators.org](http://www.paineducators.org) or [dw@paineducators.org](mailto:dw@paineducators.org)
- September 12-14, 2007 – **ELNEC – Oncology**, Pasadena, CA [www.aacn.nche.edu/ELNEC](http://www.aacn.nche.edu/ELNEC)
- September 25, 2007 – **4th World Congress: World Institute of Pain (WIP)**, Budapest, Hungary [www.kenes.com/wip/](http://www.kenes.com/wip/)
- November 4-7, 2007 – **2007 Canadian Hospice Palliative Care Conference – “Hospice Palliative Care: At a Crossroads”**, Toronto, ON [www.chpca.net](http://www.chpca.net)
- November 17-18, 2007 – **ESMO Course on Palliative Care in Oncology**, Ankara, Turkey [www.serenas.com.tr/english/](http://www.serenas.com.tr/english/) or [skayaci@serenas.com.tr](mailto:skayaci@serenas.com.tr)

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

	<b>Abbott Laboratories, Ltd</b>
	<b>AstraZeneca</b>
	<b>Amgen</b>
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## Vol. 9, Issue 1, February 2007

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Produced by Pappin Communications, Pembroke, Ontario [www.pappin.com](http://www.pappin.com)

# Advances in iron chelation for myelodysplastic syndromes

By Rena Buckstein, MD, FRCPC, and Dick Wells, MD, DPhil, FRCPC, Directors, Sunnybrook Myelodysplastic Syndromes Program

## MDS Background

- The myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic disorders affecting predominantly older adults (median age 69). The incidence increases with age and is > 30/100,000 in patients older than 70
- Patients develop cytopenias due to ineffective hematopoiesis and approximately 1/3 of patients will develop acute leukemia
- Cytopenias may lead to bleeding, infection and symptomatic anemia
- The prognosis of MDS is based on the International Prognostic Scoring System (IPSS), a weighted score dependent on the number of cytopenias, the cytogenetic abnormalities and the

**Table One: Survival in MDS risk categories as defined by IPSS**

IPSS Score	Median Survival
Low	5.7 years
Intermediate-1	3.5 years
Intermediate-2	1.2 years
High	0.4 years

per cent of immature precursor cells in the bone marrow at diagnosis (blast count)

## Iron overload in MDS

- 90% of MDS patients become anemic and require blood transfusions
- Iron overload is an inevitable consequence of transfusion therapy
  - every unit of transfused blood contains ~ 200 mg to 250 mg of iron
  - natural iron losses are 1 mg/day
  - no physiological mechanisms exist for excreting excess iron
- Clinical consequences of iron overload occur when total body iron stores exceed 20 to 25 grams
  - in MDS patients there may be excess iron stores even prior to the initiation of transfusion therapy because ineffective hematopoiesis stimulates intestinal iron absorption
  - thus, iron overload may be seen after transfusion of as few as 20 to 50 units of blood
- Iron toxicity occurs when the capacity of serum transferrin to bind iron is exceeded
  - this leads to toxic non-transferrin bound iron (NTBI) circulating in the plasma

- NTBI promotes the generation of free hydroxyl radicals that propagate oxygen-related tissue damage
- Insoluble iron complexes (hemosiderins) deposit in body tissues and promote end-organ toxicity
- Untreated or inadequately managed transfusion-associated iron overload in patients with MDS is associated with damage to multiple systems
  - cardiac: CHF, arrhythmias
  - hepatic: cirrhosis, liver failure
  - endocrine: diabetes, gonadal dysfunction
- Transfusion-dependent MDS patients with iron overload have shorter survival and an increased propensity to develop leukemia

## Iron chelation in MDS

- There is overwhelming evidence that iron chelation has improved the life expectancy of patients with hereditary or acquired childhood anemias including thalassemia, sickle cell anemia and Fanconi anemia
  - similar evidence for impact on survival in the MDS patient population has been lacking until recently
- A recent retrospective audit conducted in British Columbia suggests that low-risk MDS patients

- chelated for iron overload have superior overall survival to similarly matched patients who were not chelated
- The goals of iron chelation in MDS are to prevent or ameliorate iron-related organ damage and to prolong life

## When to chelate

- It is appropriate to chelate iron overloaded patients with MDS whose life expectancy is > 1 year
  - patients with shorter life expectancy are unlikely to benefit from chelation
- Non-invasive determination of hepatic and cardiac iron burden is possible by MRI, but this technique is not yet widely available
- Incipient iron overload is diagnosed on the basis of transfusion history and serum ferritin concentration

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- most clinicians initiate chelation after more than 20 to 25 units have been transfused if it is expected the patient will survive to receive an additional 25 units of blood
- the initiation of chelation therapy should also be considered in MDS patients when serum ferritin levels reach 1000-2000 mg/L
- Chelation should be considered in patients with poor-prognosis MDS if they are candidates for allogeneic stem cell transplantation

### Types of chelators

Three iron chelating agents are currently available: deferoxamine, deferiprone and deferasirox.

#### Deferoxamine (Desferal™)

- The current reference standard therapy
- A hexadente iron chelator that binds iron in a 1:1 ratio and forms a stable complex that is excreted in the bile or urine
- Poor oral bioavailability and a very short plasma half life
  - administered by intravenous or subcutaneous infusion CADD pump over long periods (eight to 12 hours, five to seven times per week)

- Adverse effects are frequent and include local reactions at the infusion site, retinal toxicity, and ototoxicity
- The unfavourable adverse effect profile and inconvenience of administration of deferoxamine limits its utility in elderly MDS patients

#### Deferiprone (Ferriprox™)

- Bidentate oral chelator; binds iron in a 3:1 ratio before being excreted in the urine
  - less iron-specific than deferoxamine
- Licensed by the European Medicines Agency for the treatment of iron overload in thalassaemia patients when deferoxamine is contraindicated or inadequate
- It has not been approved for use by the FDA or Health Canada due to reports of serious toxicities including agranulocytosis (0.5% of patients)

#### Deferasirox (Exjade™)

- Tridente chelator; binds iron in a 2:1 ratio before being excreted in the bile
- Administered as an oral dispersible tablet in water once daily
- Most common adverse events are transient and mild: rashes, nausea, and diarrhea
- Generates a dose-dependent net negative iron balance in thalassemic patients

- Clinical trials to date have involved more than 1,000 patients in 12 countries and are currently ongoing
- Phase II and III clinical trials with once-daily oral administration of Deferasirox demonstrate that:
  - doses of 20 and 30 mg/Kg produced decreases in liver iron content comparable to deferoxamine
  - was well-tolerated in adults and children as young as two years
  - produced none of the serious side-effects associated with other oral iron chelation therapy (e.g. agranulocytosis)
- Deferasirox received Health Canada approval on October 19, 2006, for the following indications:
  - the management of chronic iron overload in patients with transfusion-dependent anemias aged six years and older
  - the management of chronic iron overload in patients aged two to five with transfusion-dependent anemias that cannot be adequately treated with deferoxamine

- Phase II trial is currently accruing patients: Open label safety and tolerability study of deferasirox in MDS patients using serum ferritin monitoring
  - international multicentre trial; six Canadian sites (including TSRCC)
  - inclusion criteria: IPSS Low or Int-1, > 20u PRBC transfused, life expectancy > 6 months, ferritin >1000 µg/L
- Deferasirox can be prescribed off-study. Novartis has initiated an Exjade Patient Support Program (phone: 1-866-395-2334). This program will offer reimbursement assistance, which means looking at all possible avenues for each individual patient. It will also offer some financial assistance for patients who cannot afford the full amount of their share of the costs. This program will also offer support to the patient in terms of adherence to the treatment by providing the patient with educational material and a refill service.

Because of its demonstrated efficacy, tolerability, and convenience of use, deferasirox is considered the preferable first-line iron chelating agent for transfusional iron overload in MDS.