From the associate editor’s desk

By Edward Chow, MBBS, MSc, FRCPC

The Rapid Response Radiotherapy Program welcomes Drs. Shun Wong and Mary Gospodarowicz as our new heads in the Department of Radiation Oncology at Toronto Sunnybrook Regional Cancer Centre and at the University of Toronto respectively. Both of them are very supportive of clinical service and research for our patients with advanced cancer. We also welcome our new radiation oncologist, Dr. Juhu Kamra, to the RRRP and the editorial board of Hot Spot.

New chiefs at TSRCC and University of Toronto

By Cyril Danjoux, MD, DMRT, FRCP, and Edward Chow, MBBS, MSc, FRCP

Dr. Shun Wong assumed the position as Head of the Radiation Treatment Program at Toronto Sunnybrook Regional Cancer Centre and Chief of Department of Radiation Oncology at Sunnybrook and Women’s College Health Sciences Centre in February 2002. He is also a senior scientist in the discipline of molecular and cellular biology, and a professor in the departments of radiation oncology and medical biophysics at the University of Toronto.

Dr. Wong’s academic interests are in gastrointestinal and central nervous system neoplasms. He is internationally recognized for his research in the response of the central nervous system (CNS) to ionizing radiation. Dr. Wong will bring his expertise in basic radiobiology and clinical radiation oncology to our centre. He will continue to promote both the clinical and research aspects in the palliative radiotherapy program here at T-SRCC.

Professor Mary Gospodarowicz has been the new Chair of the Department of Radiation Oncology at University of Toronto since July 2001. She is also the Chief of the Radiation Medicine Program at Princess Margaret Hospital/University Health Network. She is world-renowned in the fields of genitourinary cancer and lymphoma. Recently she has been involved internationally in cancer staging and prognostic factors.

Professor Gospodarowicz has led many national and international clinical trials. She has published extensively in her research areas. She will be working in close collaboration with Professor Shun Wong at Toronto Sunnybrook Regional Cancer Centre to foster better patient care and academic research.

We welcome both Professors Wong and Gospodarowicz.
Depression in advanced cancer

By Mary L.S. Vachon, RN, PhD

An expert working group of the research steering committee of the European Association of Palliative Care found that the prevalence of depression in the terminally ill ranges from 3.7 to 58%, depending on the study, the type and stage of disease, setting and population characteristics. Wilson concluded that five to 15% of people with cancer meet the criteria for major depression, and another 10 to 15% present with symptoms that are somewhat less severe. In those with significant levels of physical impairment, at least one-quarter of those with advanced disease experience a clinically relevant and treatable depressive illness. Only a minority of those with depression receive the necessary pharmacological treatment. The reasons for this under-treatment include: the difficulty physicians experience talking with patients about their emotions, the belief that psychiatric intervention may not be helpful, and the belief - even amongst those in the mental health professions - that depression is inevitable in the terminally ill.

Pain and depression often co-exist and influence each other in palliative care. A close correlation between long periods of pain and depressive feelings has been demonstrated, a correlation that may be due to neurotransmitter changes, but also to psychological exhaustion. On the other hand, pain-free periods are known to give patients new strength, and to lower the incidence of mood disturbances and suicidal ideation.

Spiegel et al. reported that major depression was significantly higher among patients with considerable pain (28%) than among those without (10%). However, a history of prior major depression was more prominent in the low pain group, suggesting that pain produces major depression, since, by history alone, the low-pain group should have been more likely to have current depression. The psychiatric symptoms of patients in pain should be considered a consequence of uncontrolled pain. “Acute anxiety, depression with despair (especially when the patient believes the pain means disease progression), agitation, irritability, uncooperative behaviour, anger and inability to sleep may be the emotional or behavioural concomitants or sequel of pain.

Health care professionals are not particularly good at recognizing depression. In a study of depression in 25 ambulatory cancer centres, 21.5% of patients scored in the mild level of depression, 12.5% had moderate depression, and 1.9%, severe depression. When patients were not depressed, the responses of patients and oncologists were concordant 94% of the time. However, when patients had mild to moderate depression, their responses were concordant only 33% of the time, and they were concordant only 13% of the time with severe depression.

Anhedonia (loss of interest or pleasure in life) is an important marker for major depression in the terminally ill. Mermelstein and Lesko suggest focusing on the psychological symptoms of persistent dysphoria, feelings of helplessness and hopelessness, loss of self-esteem, feelings of worthlessness, and wishes to die, as reliable diagnostic indicators of major depression. When these symptoms interfere with functioning or overwhelm the patient, treatment is indicated.

Table One shows a number of risk factors associated with increased risk of depression.

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Table One: Risk factors for depressive disorders among cancer patients

- social isolation
- recent losses
- tendency to pessimism
- socio-economic pressure
- history of mood disorder
- alcohol or substance abuse
- previous suicide attempt(s)
- poorly controlled pain
- depressive side effects of medication
- advanced stage of cancer
- younger age
- older age
- head and neck, or pancreatic cancer

Historical Vignette: Blood and medicine

By Charles Hayter, MA, MD, FRCPC, Radiation Oncologist, TSRCC

The insert in this issue of Hot Spot focuses on the treatment of anemia. As historian Jackie Duffin points out in her History of Medicine: A Scandalously Short Introduction (University of Toronto Press, 1999), blood has always occupied an important place in history because of its visibility and its association with life.

For many centuries, the examination of a patient’s coagulated blood gave clues about imbalances in the “humours” which might cause disease. Doctors often practised bloodletting of patients to reduce fever and agitation (see illustration).

The advances in microscopy of the eighteenth and nineteenth centuries allowed identification of the many constituents of blood, including red cells, various types of white cells, and platelets. The critical role of blood in carrying oxygen to the organs of the body only became established after German physiologists Otto Funke and Felix Hope-Seyler identified the oxygen-carrying red pigment hemoglobin in red cells around 1850. Subsequently, the causes of various types of anemia began to be explored. The 1929 observation that ingestion of raw liver caused improvement in red cell counts in patients with pernicious anemia led to the discovery of vitamin B12.

Because of its life-giving properties, doctors have always had an interest in blood transfusions. In 1829 James Blundell at Guy’s Hospital injected bleeding postpartum mothers with blood taken from junior doctors, and during the Franco-Prussian war direct soldier-to-soldier transfusions were given on the battlefield. Needless to say, the outcome was sometimes fatal. It was not until around 1900 that the problems of incompatibility and clotting of transfused blood began to be solved, and transfusion began to be safe. In 1901, Karl Landsteiner developed the basis of the blood grouping system (ABO) which is still used today.
Hope for a good death

By Monica Branigan, MD

Men come and they go and they trot and they dance, and never a word about death. All well and good. Yet when death does come - to them, their wives, their children, their friends - catching them unawares and unprepared, then what storms of passion overwhelm them, what cries, what fury, what despair!.... Montaigne

As a palliative care physician, I see suffering every day. I am also privileged to see compassion, transcendence and the resilience of families. Much of the suffering that I see is unavoidable - the many losses, and fear of the unknown that inevitably surround death in our culture. Some of the suffering that I see is different, and I believe it is unnecessary and avoidable. It comes when we, as caregivers, hide behind our fear of death and postpone dealing with the reality of dying until it is too late.

This waiting until it is too late manifests in many ways. It lies behind the physician who finds him or herself before the patient, feeling naked, saying, “I’m sorry, there’s nothing more that I can do.” It is the underlying dynamic when a patient becomes too ill to come into the clinic, but is virtually abandoned at home. It is at play when a bewildered family is told that their loved one must be transferred to the palliative care unit, because someone else needs the hospital bed. It is the reason that a palliative care referral may be seen as a death sentence.

When we postpone dealing with the reality of death, we often do it with the best of intentions. We don’t want to take away hope. Somehow, on some level, we believe that hope is a necessary part of our will and our ability to live. We believe that if we take away hope, perhaps by actively planning for death, perhaps by talking about dying, somehow people will give up and die. Usually we assume, without examination, that this is always a bad thing. Maybe what we are really hoping is that our patients don’t need to die. We may not harbour hope for eternal life, but perhaps, hope that the patient won’t die now. If the patient does not die now, then when and how? What about the hope for a good death?

Hope is “a desire accompanied by expectation or belief in fulfillment.” Traditionally, hope is the belief in a cure - if not immediate, then in the future. This may explain why physicians are likely to be overly optimistic when, and if, they discuss prognoses with their patients. This may also explain why many patients and families do not ask, nor want to know, about prognosis and the chance for a cure. A traditional view of hope may be congruent with valuing the goal of care of preserving life above all others. If your goal of care, as physician, is preserving life, then you certainly encounter a conflict when treating people at the end of life. If your idea of hope, or perhaps your unconscious sense of failure, makes it difficult to clarify with the patient what they hope for, then you postpone dealing with the reality of death. A physician may also be in conflict with the goal of care of relieving suffering when preserving life comes first. Symptoms of disease may not be viewed as important and deserving of time and attention. Patients may be reluctant to reveal the extent of their discomfort for fear that it may indicate disease progression. Thus, a traditional view of hope for a cure may itself contribute to suffering.

The concept of hope can be expanded in a more humane way. Daniel Callahan has described the concept of hope for individualized meaning in dying and death. Truth-telling, when permission is given, can be part of fostering hope, and part of truth-telling may be using the label “dying”. “Using the label ‘dying’ indicates to health care professionals that death will occur sooner rather than later. It gives them the permission and the responsibility to provide appropriate palliative care.” It allows the perspective to be expanded from hope for a cure to hope for a good death. Hope for a good death, in turn, allows attention to symptoms, emotions and appropriate support. This is as much about hope for the life that remains, as hope for a good death. As importantly, it permits the opportunity for meaning-making and leave-taking.

This expanded view of hope gives an opportunity for the physician to broaden his or her role. By acknowledging and witnessing the reality of impending death, the patient and family are not isolated and marginalized to dealing with this alone. In receiving the story of the patient’s dying, and living, the physician can set down the burden of working for a cure without abandoning the patient. As physicians, we have not been taught to value this aspect of care because it draws on our innate humanness, and not some highly specialized “medical” skill. It can be a tremendous gift from our patients if we choose to accept it.

References:
1. Merriam-Webster dictionary @ www.m-w.com/dictionary.htm
Depression in advanced cancer

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Asking patients about how their morale is these days, whether or not they have a supportive social network, or about how discouraged they are getting dealing with their disease, gives the opportunity for patients to share their concern and for clinicians to decide whether it is sufficient to simply have a caring discussion about the patient’s current situation, whether referral to a mental health or spiritual counsellor might be helpful and/or whether antidepressants may be indicated.

Caregivers may be hesitant to bring up difficult topics. However, if the clinician acts in a warm, non-judgemental, professional manner, giving the impression that such issues are a part of normal life and not particularly shocking to the caregiver, the patient will generally be willing to discuss these and other difficult issues. Avoiding asking such questions risks missing the opportunity to make a significant difference in patients’ lives.

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Exclusion criteria

1. Brain primary or metastatic disease.
2. Hormone-sensitive malignancies including breast, ovarian, endometrial and prostate cancer.
3. Receiving tube or parenteral feeding, or bowel obstruction.
4. Ascites.
5. Current or planned steroid therapy.
6. Thromboembolic disease.
7. Insulin-dependent diabetes, poorly controlled congestive heart failure or hypertension.

For further information, please contact Dr. Jolie Ringash at Princess Margaret Hospital (416-946-2126) or Dr. Yee Ung at Toronto Sunnybrook Regional Cancer Centre (416-480-4951).

Doctor, I am losing weight, what should I do?

This is one of the most common complaints among our patients with advanced cancer, yet paradoxically, it is the symptom we most frequently would shy away from tackling. One of the reasons for this is the paucity of effective management options that could produce results that have the potential of coming to approximate our patients’ expectations.

A National Institute of Canada Clinical Trials Group study, entitled “Phase III Double-blind placebo-controlled randomized comparison of megestrol acetate (Megace) versus an N-3 Fatty Acid (EPA) enriched nutritional supplement versus both for the treatment of cancer cachexia and anorexia”— SC 18, is now open to accrual to take on this difficult topic head on. This study is currently open across Canada, including both Toronto Sunnybrook Regional Cancer Centre and Princess Margaret Hospital, in addition to many US centres, working in collaboration with the North Central Cancer Treatment Group.

Megace is a progesterational agent that has a defined place already in the clinical management of cancer and AIDS-related anorexia. Eicosapentaenoic acid (EPA), a substance found in fish oils, has been shown in preclinical studies to alleviate inflammatory cytokines which may be acting as mediators of cachexia and anorexia. In addition, early clinical studies have shown promising results in humans. For the purpose of this study, EPA is added to an oral dietary supplement as part of the intervention.

Eligible patients are randomized to one of three arms. Megace (600mg od) with EPA-enriched supplement (1 can bid) vs. megage with supplement placebo vs. megage placebo with EPA-enriched supplement. Both study drugs and supplements are supplied for the duration of the study. Being a pragmatic study, patients will stay on the intervention for as long as MD and patient feel it is beneficial. The primary endpoint of interest is a composite triad of weight loss, rate of weight change, and appetite. Secondary endpoints include overall survival, toxicity and quality of life.

For patients whose weight loss is a dominant clinical complaint, participation in this study represents a concrete step forward for both the patient and the health care team as we strive to identify ways to relieve a major source of physical and emotional distress among patients with advanced cancer.

Inclusion criteria

1. Histologically proven, incurable cancers (most suitable larger patient groups include gastrointestinal and lung cancers).
2. Life expectancy ≥ three months.
3. ECOG 0-2.
4. Ability to take oral medications/supplements.
5. History of losing ≥ five pounds over ≥ two months.
6. Concurrent chemo/radiotherapy is permitted.
Anemia in hematology and medical/radiation oncology

By Dr. Gerard Morton, MD, FRCPI, FRCPC, radiation oncologist, TSRCC; and Dr. Rena Buckstein, MD, FRCPC, clinical hematologist, TSRCC.

Sponsored by an educational grant from Ortho Biotech

Definition of anemia
- Generally defined as a hemoglobin level less than 120 g/l.

Prevalence of anemia
- Up to 60% of patients with cancer will either present with anemia or develop anemia while undergoing chemo or radiotherapy.

Causes of anemia
- Chemotherapy and/or radiotherapy myelosuppression
- Cisplatinum-based agents are toxic to renal tubules, leading to decreased production of erythropoietin
- Anemia of chronic disease: mild to moderate erythroid hypoplasia of the bone marrow, modest decrease in red cell survival, decreased bone marrow reutilization of iron, inappropriately low serum erythropoietin levels for degree of anemia. Likely caused by inflammatory cytokines such as TNF alpha, IL-1 and IFN gamma.
- Tumour infiltration of bone marrow +/- myelofibrosis
- Nutritional deficiencies
- Bleeding from tumour or coagulopathy (including DIC)
- Myelodysplasia: not usually seen until two to five years post chemotherapy, more common with alkylators and topoisomerase-2 inhibitors
- Hypersplenism
- Hemolysis
- Androgen blockade for prostate cancer

Symptoms of anemia
Anemia often gives rise to symptoms such as:
- exhaustion
- fatigue
- weakness
- impaired concentration
- dyspnea
- chest pain

Consequences of anemia
- Linear correlation with decreased quality of life
- Correlates with decreased life expectancy
- Reduced effectiveness of chemo/radiotherapy by impairing tumour oxygenation. Hypoxic tumours are more resistant to the effects of chemo and radiotherapy.

Three possible mechanisms:
- Hypoxia may induce the expression of VEGF, a protein that increases angiogenesis and may itself be a growth factor for some tumours.
- Hypoxia decreases the fixation of free radicals formed by ionizing radiation, thereby decreasing free radical mediated cell death.
- Hypoxia may select for tumour cells resistant to hypoxia and apoptosis, or cells that might overexpress the tumour suppressor gene p53.

Radiation literature to support this
- Hypothesized that correcting the anemia during radiotherapy will lead to an improvement in tumour oxygenation, and improve radiotherapy outcome.
- Supported by experimental animal studies and is consistent with the observed clinical data.
- A recent study of xenografted human tumours in anemic nude mice demonstrated that recombinant human erythropoietin increased the tumour radiosensitivity.
- A multi-institution survey of over 600 women with cervical cancer treated with radical radiotherapy:
  - Baseline hemoglobin level > 120 g/l was associated with an improved local control and disease-free survival.
  - The average weekly nadir hemoglobin level during radiotherapy was found to be a powerful predictor for survival, second only in importance to tumour stage.
  - Best outcome in women whose average weekly nadir hemoglobin levels were > 120 g/l, irrespective of transfusion.

Conclusion: increasing hemoglobin levels above 120 g/l could improve an anemic patient’s prognosis to that of a non-anemic patient.

Several studies of patients with cancers of the head and neck have also shown a strong relationship between a low hemoglobin level during radiotherapy and poorer disease control rates.

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Anemia in hematology and medical/radiation oncology - continued...

Investigation of anemia

The initial work-up of anemia in cancer patients should include:

- A blood film and reticulocyte count (to assess the bone marrow response to the anemia)
- Vitamin B12, RBC folate and ferritin (macrocytosis is commonly seen after cytotoxic chemotherapy, a low ferritin [< 18 ug/L] has high specificity)
- Serum erythropoietin (patients with inappropriately low levels are more likely to respond to supplemental erythropoietin alfa therapy)
- In some instances, a bone marrow is necessary to rule out BM infiltration with cancer or myelodysplasia.

Treatment

- Anemia’s adverse effects on QOL, and perhaps inferior response to treatment, are stimulating earlier intervention than previously.
- Blood transfusions correct anemia, but are associated with risks: nonhemolytic and hemolytic transfusion reactions, reduced immunocompetence and infection.
- A baseline Hgb of 100 g/L or lower (prior to starting chemotherapy) or a drop in Hgb of 10-20 g/L chemotherapy cycle are strong risk factors for blood transfusion while on treatment.
- Transfusion Hgb threshold is now often quite low, leaving patients with untreated anemia. Transfusions are useful for the rapid correction of significant anemia.
- Erythropoietin is a hormone released by the kidney in response to hypoxia - responsible for the differentiation, proliferation and survival of red cell precursors in the bone marrow.
- Eprex (Ortho Biotech Products) is recombinant human erythropoietin - in clinical trials improves or prevents anemia and reduces red cell transfusions.
- Several large prospective multicentre open label clinical trials of Eprex in non myeloid malignancies have demonstrated the safety and efficacy of Eprex for the treatment of anemia in patients undergoing platinum or non platinum based chemotherapy.
- Eprex improves Hgb and decreases by 40% the proportion of patients requiring transfusion (recent meta-analysis).
- Eprex also improves QOL in a matter tightly correlated with increased Hgb.
- An important recently published randomized placebo controlled trial of erythropoietin in 375 cancer patients with solid tumours or non-myeloid hematologic malignancies about to undergo chemotherapy found that:
  - Eprex-treated patients required fewer transfusions (24.7% vs. 39.5% p=0.0057), had increased hemoglobin levels from baseline (2.2 g/dL vs. 0.5 g/dL p<0.001) and significantly improved cancer- and anemia-related QOL domains. These included energy level and ability to do daily activities, and significantly reduced fatigue (seven different scales used).
  - Survival analysis demonstrated a trend in survival favouring epoetin alfa that was not statistically significant.
  - Gabrilove et. al found that erythropoietin may be administered once weekly instead of three times weekly with similar effects.
  - Quirt et. al found that the benefits of epoetin alfa administered to patients with cancer-related anemia for up to 16 weeks also applied to cancer patients not receiving chemotherapy.

Administration guidelines for erythropoietin

- Typical starting doses are 40,000 units SQ once weekly or 150 units/kg SQ three times weekly
- If inadequate hematologic response defined by Hgb increase by 10 gram/L or retic count increase ≥ 40 x 109/L over the baseline values after four weeks, increase dose to 60,000 units SQ weekly or 300 units/kg three times weekly.
- Discontinue therapy after a further four weeks if inadequate response (defined above) to higher dose
- Patients with ferritin < 100ug/L or transferrin saturation < 20% should receive supplemental iron to support epoetin alfa-stimulated erythropoiesis
- Treatment should be continued until target hemoglobin is achieved, and re-evaluated after completion of chemotherapy
- If Hgb rising > 20g/L/month, reduce dose by 25%
- If Hgb exceeds 140 g/L, d/c use until Hgb < 120 g/L, then re-institute with 25% dose reduction

Predictors of response

- Inappropriately low erythropoietin levels for degree of anemia in patients not receiving chemotherapy.
- Patients receiving chemotherapy with erythropoietin levels of > 200 mU/ml are less likely to respond

What to watch for in patients on erythropoietin

- Increased hypertension
- Thrombosis
- Rapidly rising hemoglobin levels

Other potential side effects

- Pain at injection site
- Flu-like symptoms
- Skin rash

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