HOT SPOT

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

10 years

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

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Editorial

By Arjun Sahgal, MD, FRCPC

This issue of **Hot Spot** has a special focus on ethics, and this is an area of great importance in medicine for which we often do not have sufficient training. A provocative piece by Dr. Philip Hébert raises important ethical issues in a scenario format. In particular, he raises our awareness and challenges us to think about possible ethical situations surrounding the real threat of an H1N1 virus pandemic this year. The process for an ethics consult via an on-line request form at Sunnybrook is introduced, and represents an excellent resource to use when faced with tough ethical situations. In this issue, other important aspects with respect to the Canadian health care system are discussed. These include the role of family caregivers by Michele Chaban, and electronic medical record programs, as currently instituted at the Temmy Latner Centre for Palliative Care by Christopher Obwanga.

The colon cancer special insert provides a summary of the role of monoclonal antibodies in colon cancer therapy. Dr. Yoo-Joung Ko provides an excellent brief synopsis of how they are currently used in our health care system. The second insert written by Dr. Christine Simmons provides a detailed summary of symptoms associated with side effects of anti-hormonal therapy in breast cancer survivors, and potential treatments for the resulting estrogen deprivation. Dr. Ewa Szumacher has once again compiled a list of the latest events in continuing medical education. Dr. Carlo DeAngelis continues with Part 4 in his pharmacy column on Opioid Dose Equivalency—Dose Conversion for Transdermal Fentanyl and Methadone. We hope you find the **Hot Spot** resourceful.

A brief primer on scarcity and fairness

By Philip Hébert, MD, PhD, FCFPC

It is sometimes asked whether health care providers have an obligation to provide all care to all patients at all times. Posed in such an extreme fashion, the answer would obviously be, "No." It is not possible to provide all needed care to all patients in a timely way. This may be on account of geography, the nature of the disease, the lack of effective treatment or the scarcity of such. This lack of availability may also be exacerbated during extreme times—for example, large-scale medical emergencies, war, or economic recessions. Combining a pandemic, such as the current H1N1 virus outbreak, with the global recession may result in demands for scarce critical care resources that, seemingly, cannot be met in a non-arbitrary way.

This scenario should concern families and health providers alike. It is difficult enough to meet the physical and mental challenges of critical illness. It would be doubly so should the resources required for life-support be insufficient to meet the needs of all. Where needed resources are in short supply, the needs of some must be prioritized over the needs of others. As one astute writer has observed, prioritizing the needs of some patients means *posteriorizing* the needs of others (Tallis, 2004). Can such discriminations among patients be made in a fair way?

Case

A viral epidemic, due to virus XN, has caused widespread serious illness, with many patients requiring respiratory support. While all age groups are affected and the aged are more likely to be sick, it

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is the youngest who are more likely to be critically ill. Lacking effective treatment for virus XN, treatment is only supportive. Complete respiratory collapse in affected individuals can be sudden and is catastrophic. Your hospital is at 120% capacity. There are 12 beds in the ICU with all patients intubated, and six more beds in a step-down unit, also ventilated. There are 10 patients in the ER awaiting admission, including three patients very ill with virus XN. One of the beds for ventilation has become available. A decision has to be made as to who should get that bed.

Of these three patients, one, a 13-year-old boy with Down's syndrome from a large, caring family, is the sickest. There is a 90% chance he will die in the near future, even with respiratory support and admission to the ICU. If he survives, however, his long-term prognosis is good. The second is an 80-year-old world-renowned pianist with a history of peripheral vascular disease and a serious stroke one year ago. Her short-term prognosis is excellent: with prompt respiratory support, there is a 90% chance she will survive to discharge. However, her long-term prognosis is poor, given her age and co-morbid conditions. The third affected patient, a 35-year-old stockbroker, married with two young children, is now septic and in acute renal failure. His short-term prognosis is poor: he has a 30% chance of survival to discharge.

Of these three patients, who should have priority of access to the ventilator in the ICU?

In the past, scarce medical resources would often have been allocated by social criteria. On that basis, the stockbroker might have been prioritized, as a productive member of society. The aging pianist would come in a close second, as a prior contributor. The boy with Down's would come last, as a past and future non-contributor. If, instead, we used purely medically based criteria, the pianist would be prioritized, as, with treatment, her short-term prognosis is so favourable. The boy with Down's would not be prioritized because his treatment is likely to fail. On the other hand, if increasing age were a factor counting against aggressive care, then the pianist would be the last to receive treatment and the boy would be the first. This is "age-ism" and wrong in some people's eyes. All lives are equally important and a year of life gained at 80 is as important as a year of life gained at age 13.

All such traditional answers to the problem of scarce resource allocation seem to be unfair and cruel. As a result, some would refuse to make choices among ill. Every patient is worthy of treatment and allocation decisions should simply be a matter of mere chance or fate. Treatment priority is a matter decided by a roll of the dice or by who turns up first to be admitted.

A recent paper in the **Annals of Internal Medicine** (White et al. 2009) addressed the problem of fair decision-making during times of scarcity. The authors advocate the use of a mixed set of criteria to arrive at an allocation score to guide decision-makers. Rather than a single principle or perspective, they recommend a numerical scoring system that would reflect three different aspects of a patient's situation: the patient's short-term prognosis, long-term prognosis and, interestingly, the patient's "stage of life". This latter factor would give priority of treatment, other things being equal, to those who have gone through fewer of "life's stages". Short-term prognosis reflects how sick the patient is currently and how likely it is that aggressive treatment will be successful. (The less likely it is that a patient will survive in the short-run is also a measure of an intervention's futility.) Long-term prognosis reflects the presence or absence of co-morbid conditions that impact the likelihood of one-year survival. (Other things being equal, scarce treatment ought to go to the individual likely to benefit the longest.)

This scoring system has the advantage of combining medical prognostic data with the principle of "fair innings". The priority for treatment opportunities goes to those who have yet to experience the diversity that life offers. In other words, everybody is due at least five innings to make it a fair game; anything greater than nine is pure gravy.

Applied to our case scenario, the stockbroker would lose points due to his poor short-term prognosis, but gain some for having gone through only some of the lifecycle and gain some more points, as his initial health is so good. The pianist patient gains points for short-term survival, but loses more as she is more likely to succumb to her co-morbid conditions in the next year and as she has also passed through life's stages. As a result, of the three patients, she would be the last to gain access to the ICU. The boy with Down's, although losing points for short-term prognosis, gains many more back as his long-term prognosis is so good and he has yet to go through many of life's stages. On this scheme, the boy would be prioritized for the one open ICU bed. The stockbroker would come in a close second to the boy. (His access might come first if the boy's immediate survival diminished to a vanishing point making ICU treatment futile.)

The main difficulty with this whole scheme, as the authors acknowledge, is that prognostic scores are notoriously uncertain. The most attractive feature of the proposed prioritization scheme is not the numbers but, rather, its intuitive appeal. Any acceptable, non-arbitrary model for making contentious prioritization decisions ought to reflect the complexity of such decisions. The model these authors offer does so, and should be a reminder that no single principle will apply without exception, and this applies to their model, as well. Using the life-cycle principle, for example, would generally favour treatment of children first. This may be acceptable for everyday practice but, in medical catastrophes, the adult's well being will be required to protect the child's and so the adult with more experience of the life-cycle may be prioritized for treatment. More generally, there must be a place for family and community in this model that does not lead us back into the bad old days of "social worth". Any allocation decision that did not, in part, reflect ties of kith and kin—the interdependence of members of a family, the emotional bonds between them—would be a poor decision indeed. These are mere quibbles, however. The authors' attempt at fairness and clinical usefulness remains.

Finally, the authors recognize that the acceptability of any such access-to-treatment process requires public support through openness and community dialogue, or "meaningful public engagement," something that we have not, as yet, had. But if the experience of Obama's quest for a new health care

system teaches us anything, it is that public engagement is an enterprise fraught with danger and uncertainty. Some public opinions are far from the expansive and altruistic perspective that fair allocation decisions require.

Critical illness may be unfortunate, but the allocation of scarce interventions need not be unfair or arbitrary. An approach to prioritizing access that utilizes a more nuanced view of prognosis and the stages of life does a better job of rationalizing who gets what when.

About the author

*Philip Hébert, MD, PhD, FCFPC, is the author of **Doing Right,** an introduction to medical ethics for all health care providers published by Oxford University, now in its second edition.*

References

Tallis, R. (2004). **Hippocratic oaths: Medicine and its discontents**. London: Atlantic Books.

White, D., Katz, M., Luce, J., & Lo, B. (2009). Who should receive life support during a public health emergency? Using ethical principles to improve allocation decisions. **Ann Intern Med, 150**(2), 132–39.

Are family caregivers an essential component of our health care system?

By Michele Chaban, MSW, RSW, PhD

It is estimated that 80% of all caregivers in our home health care system are family members. The other 20% of caregiving comes from interprofessional health care providers. Depending on your definition of "family caregiver" and the source of your statistics, it is estimated that there are one (end of life), three, five or seven (all family caregivers) million family caregivers in Canada. Even at its lowest denominator, it is a formidable group.

Family caregivers are not only a part of health care, they are an ingredient of health itself. Social networks are considered to be a determinant of health. If we define family as anyone who is emotionally connected by birth or sentiment to the person who is at risk—family caregivers come from our social networks. The National Profile of Family Caregivers in Canada 2002 indicates that the majority of family caregivers are less than 55 years of age. This is an age for maximizing one's earning potential pre-retirement, being the high point or culmination of one's career, as well as caring for the generations both before and after you.

The 1996 Canadian Census indicated that one out of every six adults over 15 years of age provided care for the elderly. If one out of six adults shared a common condition, then this number would constitute a population health issue—an identity that would mobilize supportive resources. It is estimated that the fiscal value for their caregiving work is $20 to $30 billion. They also spend more than $27 billion a year on caregiving resources, making them both a work and economic force. For both these reasons and more, family caregivers' importance is not fully recognized. Consider this: what if family caregivers decided to relinquish their caregiving roles? It is likely that the health care system would collapse under the displaced demands of care.

While a typical family caregiver is a 46-year-old, married and employed woman, men now represent 39% of all caregivers. Male caregivers who provide the same amount of care hours as women feel more burdened by the care, would prefer to work more hours at their job and pay someone else to do the bulk of family caregiving. This runs the risk of marginalizing men as participants in care in their own families.

Even though family caregiving is a highly rewarding commitment, its intensity and duration takes its toll on our health. One in four Canadian workers suffers from caregiver stress. Absenteeism due to caregiver stress costs Canadian business $2 to $3 billion each year ($1 billion in direct costs and $1 to $2 billion in indirect costs). As a society, we are already paying a hidden price for family caregivers who are not adequately supported in their tasks.

The social scaffolding for family caregiving networks needs to be built and managed, as would any community. How to do this effectively and efficiently requires an interprofessional group that is able to translate its expertise into family caregiving capacity for a healthier workforce.

Without doubt, both family and interprofessional health care givers could benefit from enhanced support and respite resources. Amongst all that 20% of us do in health care, we need to remember to mobilize these resources for the other 80% of home health caregivers.

For further information on this subject, contact Donn Fenn or Terry Morgan at the Family Caregiver Network Magazine or navCare, a multi-agency resource committed to the above.

1. Identify, empathize and advocate for family caregivers' needs and networks.
2. Connect family caregivers with appropriate interprofessional resources that will lessen the demands of care, promoting endurance and resiliency over the course of time (i.e., energy conservation [OTs], psycho-educational counselling, mindfulness meditation, resource management and fiscal planning [social work], pain management and ambulatory transferring strategies [nursing, rehabilitation medicine], respite care [CCAC, hospices]).
3. Educate family and professional caregivers in the importance and strategies for building family caregiver networks.
4. Refer family caregivers to resources that will help them develop family caregiver networks through education, coordination, navigation (CCAC, Hospice, navCare, The Family Caregiver Magazine).

About the author

*Michele Chaban, MSW, RSW, PhD is co-founder of Toronto-based Habitat Healing (**habitathealing.com**), a family education and counselling service. Michele is the current Director of the Contemplative End-of-Life Care Program at The Institute of Traditional Medicine in Toronto, a unique national program which joins many forms of scholarship and skills. She is also co-director of the Clinical Mindfulness Program at University of Toronto, Faculty of Social Work. Her work is dedicated to wholism at many levels including humanizing health care systems for patients, families and professional caregivers.*

Ethics Centre launches new on-line consult request on Sunnynet!

By Sally Bean, JD, MA Clinical & Research Ethicist

What?

Do you or your team need to request an ethics consult, education event or debriefing session? The Sunnybrook Ethics Centre has launched a new on-line ethics request form that will allow all staff and volunteers to request ethics support on-line from our dynamic ethics team.

Why?

Our available services and activities are intended to promote ethical decision-making throughout the organization with the ultimate goal of enhancing patient care. We recognize that ethical issues arise outside the typical Monday to Friday 8:30 a.m. to 5:00 p.m. timeframe. Therefore, we have developed a quick and accessible mechanism for Sunnybrook staff and volunteers to request ethics support whenever the need arises.

How?

Access our on-line consult request tool 24 hours a day on the Ethics Centre home page: **http://sunnynet.ca/Default.aspx?cid=104246&lang=1** or by accessing the request tool directly from the intranet: **http://ec/**. We will make every effort to promptly respond to your request during normal business hours, which are Monday to Friday, 8:30 a.m. to 5:00 p.m. If you have any questions or clarifications, please contact the Ethics Centre's administrative assistant at extension 4818.

Improving data capture and standardization in a home palliative care program

By Christopher Obwanga, BSc, Research Coordinator, Temmy Latner Centre for Palliative Care

The Temmy Latner Centre for Palliative care employs an electronic medical record (EMR) program in delivering home-care services. The EMR has accorded the centre the ability to capture real-time data from patients' bedside, creating a new interface between patient care and research initiatives (Porcheret, Hughes, & Evans, 2004). Secondary data analyses of these databases pose a challenge, as most EMRs have been developed to facilitate the provision of care, and not for research purposes (Harpe, 2009). As a result of the EMR offering flexibility as a clinical tool, data capture is inconsistent, limiting the quality of data available for research. Patients' progress notes are mainly captured as free text, which not only affects the accuracy and completeness of data, but also requires more complex data manipulation prior to analysis.

As an attempt to address some of these limitations, the centre has embarked on a continuous quality improvement process of data entry standardization through a working group comprising health care providers (HCPs), administrative and research personnel. Following a survey of users, the group intends to achieve data consistency through the use of templates. An audit of a cohort of patients (n = 64) who died in the month of December 2008 shows CPR as the most commonly documented advance directive with a completion rate of 42% followed by IV hydration (12.5%), artificial nutrition (3.1%) and transfusion (3.1%). Using these completion rates as a baseline, the committee will generate a follow-up visit or "encounter" template to capture the evolving discussion around advanced directives and goals of care using hard coded drop-down menus. Analysis of these fields of interest will compare the completion rates of the data pre-/post-template implementation as the outcome. Through iterative loops in the data standardization process, the committee will put forward a final template for consensus before implementation. Using the template as an intervention for data quality, the goal of improvement would be to double the data capture in these fields, i.e., increase the documentation of discussions around CPR to greater than 80%. Consistent data will vastly aid research initiatives by achieving appropriate coding to represent the outcomes and exposures of interest (Porcheret, Hughes, & Evans, 2004).

Through an iterative process, EMR users will receive feedback on the accuracy and completeness of their patient encounters and, in turn, EMR users will influence the format of the data collection template, thus meeting the needs of a busy clinical practice and research. Data standardization will make the EMR valuable in systematically generating hypotheses for research based on electronic data (Powell & Buchan, 2005). We anticipate accruing data on approximately 2,000 to 2,500 patients per year. A robust clinical database of this size will enable the centre to pursue projects that link our clinical database with administrative databases, hence advancing the centre's ability to monitor the outcomes of home palliative care services. Future projects at the centre involve the development of a set of standardized variables or minimal dataset (MDS) for home palliative care research and program development. This dataset will serve as a framework for promoting standardization of databases across home palliative care programs (Kuziemsky & Lau, 2008).

References

Harpe, S.E. (2009). Using secondary data sources for pharmacoepidemiology and outcomes research. **Pharmacotherapy, 29**(2), 138–53.

Kuziemsky, C.E., & Lau, F. (2008). A comparative analysis of computer-based hospice palliative care datasets in Canada. **BMC Palliat Care, 7**, 6.

Porcheret, M., Hughes, R., Evans, D., et al. (2004). Data quality of general practice electronic health records: The impact of a program of assessments, feedback, and training**. J Am Med Inform Assoc., 11**(1), 78–86.

Powell, J., & Buchan, I. (2005). Electronic health records should support clinical research. **J Med Internet Res., 7**(1), e4.

Opioid dose equivalency: Part 4—Dose conversion for transdermal fentanyl and methadone

By Carlo DeAngelis, PharmD, Clinical Pharmacy Coordinator—Oncology, Department of Pharmacy, Odette Cancer Centre, Sunnybrook Health Sciences Centre

In recent years, there has been an increase in the use of transdermal fentanyl. While there may be several reasons for switching to transdermal fentanyl, a common reason is to facilitate opioid administration in a patient unable to take medication orally. Due to the risk of serious or life-threatening respiratory depression, Health Canada has recently added several contraindications to the fentanyl product monograph including a contraindication on its use in patients who are opioid naïve. This applies even to the 12-microgram patch. In addition, fentanyl administered by the transdermal route poses several challenges with respect to opioid dose equivalency because of the dose used (fentanyl is dosed in micrograms and morphine and other opioids in milligrams), dosage strengths available, how the available transdermal fentanyl is labelled (the patches are labelled based on the micrograms of drug delivered per hour) and disagreement as to the appropriate equianalgesic conversion ratio. A practical approach to this latter issue is offered by Donner, Zenz, Tryba, et al. (1996) who studied the direct conversion of oral morphine to transdermal fentanyl (the most common clinical scenario) in cancer patients. They recommend that the conversion ratio for oral morphine to transdermal fentanyl be 100:1 (100 mg of morphine = 1 mg of fentanyl). Thus, for a patch that delivers 100 micrograms per hour of fentanyl, a patient would receive a dose of 2400 micrograms (or 2.4 mg) of fentanyl in 24 hours. Using the above conversion, an equivalent 24-hour morphine dose would be 240 mg (100 x 2.4 mg). Since, with the exception of the newly available 12-microgram/hour patch, the remaining patch strengths (25, 50 and 75 micrograms/hour) are all multiples of 25, one only needs to remember that the 25 microgram per hour patch delivers the equivalent of 60 mg of morphine administered orally over 24 hours. The 50, 75 and 100 microgram per hour fentanyl patches would, thus, deliver the equivalent of approximately 120 mg, 180 mg and 240 mg (2 x 60 mg, 3 x 60 mg or 4 x 60 mg) respectively of morphine taken in divided doses over 24 hours. While not mathematically precise, the 12 microgram per hour patch of fentanyl could be considered to deliver approximately 30 mg of orally administered morphine taken in divided doses over 24 hours.

A physician wishing to use methadone for pain management must be licensed to do so by Health Canada. A licence to prescribe methadone for opioid addiction (a provincial responsibility) is not valid for this purpose. The conversion of a patient to methadone poses significant challenges (Souter & Fitzgibbon, 2004; Berdine & Nesbit, 2006). There is significant interpatient variability in response to and metabolism of methadone in addition to the fact that the elimination half-life is longer than the duration of analgesic effect requiring careful dosing and follow-up to prevent drug accumulation and side effects. Finally, the conversion ratio for methadone is dose dependent, so that the relative potency of methadone is greater when the patient is on higher doses than when they are on lower doses. In one study, the conversion ratio of oral morphine to oral methadone was 4:1, 8:1 and 12:1 in patients receiving morphine doses of 30 to 90 mg/day, 90 to 300 mg/day and > 300 mg/day respectively (Ripamonti, Groff, Brunelli, et al., 1998). Thus, the conversion of a patient to methadone requires close follow-up for signs of toxicity and should be done by a physician who is experienced in using methadone.

Key points to remember from this series of four pieces on opioid conversion are:

- Dose equivalency ratios are a starting point, interpret the calculated dose with caution always keeping in mind the patient's clinical situation and goals for changing the opioid in mind.
- Ongoing and close follow-up of the patient for response (or lack thereof) and/or side effects is essential.
- Anticipate the need for further dose adjustments (either up or down).
- There may be incomplete cross-tolerance between different opioids and the calculated equianalgesic dose of the new opioid may require adjustment downwards (usually 25%), particularly if the change in opioid is being made to reduce side effects, facilitate the taking of the medication, or if pain control is inadequate, but it is expected that the patient is near the required dose.
- Once the dose of the new opioid analgesic is calculated the final dose to be taken by the patient must take into account the dose strengths available and the ease with which the patient can take the new prescribed regimen.

References

Berdine, H.J., & Nesbit, S.A. (2006). Equianalgesic dosing of opioids. **Journal of Pain and Palliative Care Pharmacotherapy, 20**, 79–84.

Donner, B., Zenz, M., Tryba, M., et al. (1996). Direct conversion from oral morphine to transdermal fentanyl: A multicenter study in patients with cancer pain. **Pain, 64**, 527–534.

Ripamonti, C., Groff, L., Brunelli, C., et al. (1998). Switching from morphine to oral methadone in treating cancer pain. What is the equianalgesic ratio? **Journal of Clinical Oncology, 16**, 3216–3221.

Souter, K.J., & Fitzgibbon, D. (2004). Equianalgesic guidelines for long-term opioid use: Theoretical and practical considerations. **Seminars in Anesthesia Perioperative Medicine and Pain, 23**, 271–280.

Clarification: *In the third installment of this series in the example, the breakthrough dose calculated for the patient was very conservative. The more commonly used approach would be as follows:*

Once again using the rule of thumb for calculating the breakthrough as 10% to 20% of the total daily dose administered in divided doses (usually every four hours). For our patient this would be: 54 mg/24 hours × 0.1 = 5.4 mg in divided doses

Thus, the breakthrough dose would be 5.4 mg (10% of the total daily dose) every four hours. However, hydromorphone regular release formulation is available in 1 mg, 2 mg, 4 mg and 8 mg tablet strengths. Thus, the patient could be given hydromorphone 4 mg and told to take one or two (20% of the total daily dose) tablet(s) every four hours, as needed for breakthrough pain. An alternative strategy, particularly if the pain is poorly controlled and with the aim of encouraging the patient to use breakthrough doses more often, would be to prescribe the 2 mg strength and recommend that she take one or two tablets every two hours, as needed for breakthrough pain.

Continuing Medical Education 2009–2010

By Ewa Szumacher, MD, MEd, FRCP(C)

Continuing Medical Education (CME) can update health care professionals on the latest advances for modifications to their clinical practice. At the request of the CME organizers, Hot Spot lists the national and international CME activities in palliative medicine that are of interest to our readers. Please forward details of the CME activities to: **Ewa.Szumacher@sunnybrook.ca**

- November 1–5, 2009
  51st Annual ASTRO Meeting, McCormick Place; Chicago, Illinois. **http://www.astro.org/meetings/annualmeetings/**

- November 9–13, 2009
  Multi-professional week in palliative care, Education Administrator, St. Christopher's Hospice, London, UK. Tel: +44 (0)20 8768 4656, Fax: +44 (0)20 8776 5838, E-mail: **education@stchristophers.org.uk** **www.stchristophers.org.uk/education**

- November 24–26, 2009
  Help the Hospices Conference 2009; Third multi-disciplinary conference, Harrogate International Conference Centre; London, UK. **http://www.helpthehospices.org.uk/our-services/running-your-hospice/education-training/2009conference/**

- February 11–14, 2010
  IXVII International Conference of Palliative Care of IAPC, Trichirappalli, Tamilnadu; India: Contact: Dr. T. Mohanasundaram, E-mail: **drmohs.trichy@hotmail.com**

- March 7–11, 2010
  16th International Conference on Cancer Nursing (ICCN), Atlanta, Georgia, USA. **www.isncc.org**

- April 29, 2010
  Terminal Illness & Dying in Multicultural Canada: An Interdisciplinary Approach, Toronto, Ontario, Canada **http://www.careconferences.com**

- June 10–12, 2010
  6th Research Forum of the EAPC, Glasgow, UK: Mike Bennett **m.i.bennett@lancaster.ac.uk**

- August 29–September 2, 2010
  13th World Congress on Pain, Montréal, Quebec, Canada **www.iasp-pain.org/Montreal**

- October 5–October 8, 2010
  18th International Congress on Palliative Care, Montréal, Quebec, Canada. E-mail: **info@pal2010.com**, Phone: (450) 292-3456 ext. 227, Fax: (450) 292-3453

- October 28–October 31, 2010
  14th World Society of Pain Clinicians Congress (WSPC 2010), Beijing, China **http://www.kenes.com/WSPC**

- November 13–14, 2010
  13th Annual Interdisciplinary Approach to Symptom Control, Palliative and Hospice Care, Houston, Texas; USA **http://www.conferencealerts.com/seeconf.mv?q=ca1m3maa**

Correction

In the Chronic lymphocytic leukemia (CLL) insert by Dr. Rena Buckstein included in the last issue of Hot Spot, the first bullet point in the conclusion section should have read: Improves PFS by 10 months (*not* Improves PFS by 13 and 10 months respectively). We apologize for the error.

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Anti-epidermal growth factors in colorectal cancer

By Yoo-Joung Ko, MD, MMSc, SM, FRCPC

HOT SPOT

Background

- Colon cancer is the second leading cause of cancer death in Canada
- Biologic therapies including anti-VEGF and anti-EGFR approaches have been approved in advanced colorectal cancer
- The epidermal growth factor receptor (EGFR) is a member of the HER tyrosine kinase cell surface receptors and is important in regulating a diverse range of cellular processes including cellular proliferation, differentiation and survival
- Dysregulation of the epidermal growth factor pathway is important in many cancers including breast, lung and colon cancer
- Two monoclonal antibodies to the EGFR (Erbitux® and Vectibix®) and two small molecule inhibitors (Iressa® and Tarceva®) are in current clinical use in cancer treatment

EGFR and K-ras

- K-*ras* gene encodes a small G protein that links the ligand-induced EGF receptor activation to activation of MAP kinase intracellular pathway
- Mutations in K-*ras* commonly seen in lung, pancreatic and colon cancer (40%–50%)
- Mutations in K-*ras* result in ligand-independent constitutive activation of the EGFR pathway
- Approximately 40% of patients with colorectal cancer have mutations in K-*ras* and 60% express wild-type K-*ras*
- Colorectal cancer patients with somatic mutations in K-*ras* do not benefit from anti-EGFR treatment
- Mutations in B-*raf* have been detected in patients who do not have K-*ras* mutations, but do not benefit from anti-EGFR therapy

K-ras testing

- Most common mutations are in codons 12 and 13 in exon 2, which account for approximately 90% of K-*ras* mutations
- Approved laboratories use a PCR-based kit (DxS®) to detect seven possible mutations in codons 12 and 13
- Tumour tissue can be from biopsies embedded in paraffin or frozen (either metastatic or primary tumour)

Table One.

	Cetuximab (Erbitux®)	Panitumumab (Vectibix®)
Approved Indication	Cetuximab + Irintocan	Panitumumab monotherapy
Backbone	Chimeric	Human
Class	IgG1	IgG2
Loading Dose	Yes: 400mg/m^2 over 120 min	No
Schedule	Weekly: 250mg/m^2 over 60 min	Q2weekly: 6mg/kg over 60 min or 90 min (if >1000mg)
Premedication	Yes: H1 antagonist 30–60 min prior to first infusion	None

EGFR inhibitors in colorectal cancer

(Table One)

- Cetuximab was approved by Health Canada in 2005
- Panitumumab was approved by Health Canada in 2008

Phase III studies of anti-EGFR therapies in colorectal cancer

(Table Two)

- One study of FOLFIRI with or without cetuximab as first-line therapy demonstrated significant improvement in response rate, progression-free survival and respectability for those who received combined therapy
- A recent randomized trial of FOLFOX +/- panitumumab as first-line therapy demonstrated an improved progression-free survival (9.6 versus 8.0 months), but no difference in overall survival or response rate
- In the second-line setting, a study of FOLFIRI +/- cetuximab showed a better response rate (16% versus 4%), progression-free survival and quality of life, but no difference in overall survival (half crossed over to cetuximab at progression)
- A third-line study of panitumumab versus best supportive care demonstrated an improved progression-free survival and response rate, but not in overall survival due to a preplanned crossover
- A third-line study of cetuximab versus best supportive care demonstrated an improvement in overall survival (9.5 versus 4.8 months) in K-*ras* wild-type patients

Table Two. (Statistically significant results in BOLD)

	Study	RR %	Median PFS/TTP (mos)	Median OS (mos)
1st line	**CRYSTAL (FOLFIRI +/- Cetux)**	**59 vs 43**	**9.9 vs 8.7 (HR=0.68)**	**23.5 vs 20.0 (HR=0.80)**
	OPUS (Rand Phase II FOLFOX +/- Cetux)	**61 vs 37**	7.7 vs 7.2 (HR=0.57)	**?**
	PRIME (FOLFOX4 +/- Pmab) 60% WT *K-RAS*	55 vs 48	**9.6 vs 8.0 (HR=0.80)**	Not reached vs 18.8 (HR=0.83)
2nd line	**EPIC (Iri +/- cetux)**	**16 vs 4**	3.98 vs 2.79 (HR=0.77)	10.71 vs 9.99
	Study 188 (FOLFIRI +/- Pmab) 55% WT *K-RAS*	**35 vs 10**	**5.9 vs 3.9 (HR=0.73)**	14.5 vs 12.5 (HR=0.85)
3rd line	**P-mab (Pmab vs BSC)**	**17 vs 0**	**12.3 vs 7.3 Weeks (HR=0.45)**	**Not reported (Crossover)**
	NCIC CO.17 (Cetux vs BSC)	**NR**	**3.8 vs 1.9 Mos (HR=0.40)**	**9.5 vs 4.8 Mos (HR=0.55)**

Anti-epidermal growth factors in colorectal cancer

HOT SPOT

Side effects

- Fatigue, papulopustular rash, and diarrhea most common side effects
- Rash commonly seen on the face, scalp, trunk, usually within two to three weeks of therapy initiation
- Hypomagnesemia uncommon, but often needs replacement therapy
- Cetuximab rarely associated (<4%) with infusion reactions

Skin toxicity management

- Appearance and severity of rash has been associated with tumour response and survival
- Pre-emptive strategy may minimize dose delay or dose reduction given that they are most likely to have clinical benefit
- A randomized study of a pre-emptive strategy decreased the incidence of grade two or higher skin toxicity by more than 50%
- Sun exposure and skin drying products may exacerbate the rash
- 2% topical clindamycin and 1% hydrocortisone in a lotion base for mild to moderate rash
- Oral minocycline 100mg od or doxycycline 100mg od to bid for moderate to severe rash
- For severe painful rash, anti-EGFR therapy may need to be held until improvement

Combination of biologic therapies

- Randomized phase II study of bevacizumab + cetuximab versus bevacizumab + cetuximab + irinotecan demonstrated response rates of 23% and 38% respectively
- PAACE study of oxaliplatin or irinotecan-based chemo + bevacizumb +/- panitumumab had more toxicity in the double biologic arm and decreased PFS
- CAIRO-2 study of XELOX + bevacizumab +/- cetuximab did not demonstrate improved PFS or response rates with double biologics

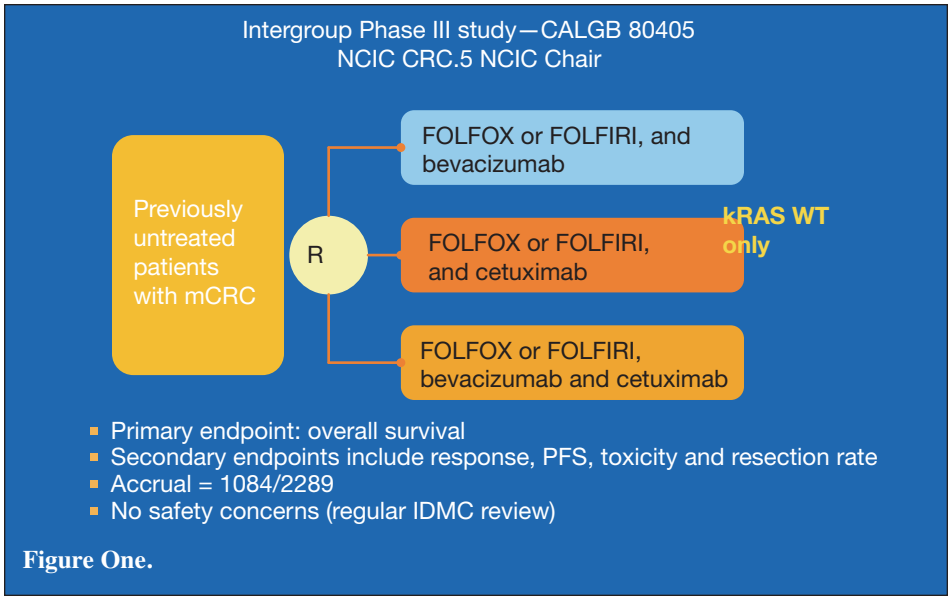

Figure One.

Ongoing studies of anti-EGFR therapies

(Figure One)

- A priority North American trial of chemotherapy (either FOLFOX or FOLFIRI) with cetuximab or bevacizumab has been activated by the National Cancer Institute of Canada
- This study is limited to those with wild-type K-*ras* and the combined biologic arm (cetuximab and bevacizumab with chemotherapy) has been dropped
- This study is powered to assess a survival difference between chemotherapy + bevacizumab and chemotherapy with cetuximab

Conclusion

- Monoclonal antibodies to the epidermal growth factor receptor provide clinical benefit to colorectal cancer patients who have progressed on oxaliplatin and irinotecan-based chemotherapies
- Clinical benefit is limited to those patients who do not have a detectable mutation in K-*ras* (i.e., wild-type)
- K-*ras* testing one tumour tissue must be done prior to initiating therapy
- Two monoclonal antibodies are approved in Canada, one (cetuximab) with irinotecan and the other (panitumumab) as monotherapy
- Rash is a common side effect that can be managed with a pre-emptive strategy
- There is emerging evidence that chemotherapy with an anti-EGFR agent may have a role in the second-line and first-line settings

References

Ciardiello, F., & Tortora, G. (2008). EGFR antagonists in cancer treatment. **N Engl J Med, 358,** 1160–74.

Cutsem, E.V., Kohne, C.H., Hirte, E., et al. (2009). Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. **N Engl J Med, 360,** 1408–17.

Cutsem, E.V., Peeter, M., Siena, S., et al. (2007). Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. **J Clin Oncol, 25,** 1658–1664.

Karapetis, C.S., Khambata-Ford, S., Jonker, D.J., et al. (2008). K-ras mutations and benefit from cetuximab in advanced colorectal cancer. **N Engl J Med, 359,** 1757–65.

Melosky, B., Burkes, R., Rayson, D., et al. (2009). Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. **Current Oncology, 16**(1), 14–24.

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Management of symptomatic side effects of anti-hormonal therapy in breast cancer survivors

HOT SPOT

By Christine Simmons, MD, FRCP(C), Medical Oncologist, Sunnybrook Health Sciences Centre

Breast cancer is a disease that will affect more than 22,000 women in 2009 (Canadian Cancer Society, 2009). That being said, women with early stage disease have a greater than 85% chance of long-term cure. As such, there is a need to pay increased attention to the symptomatic long-term side effects of breast cancer treatments. Some of the most prevalent long-term side effects of therapy are those related to menopausal symptoms. Women with breast cancer are more likely to suffer the effects of menopause for several reasons. These include, but are not limited to the following:

1. Average age of diagnosis is 62
2. Abrupt discontinuation of hormone replacement therapy at the time of diagnosis of breast cancer
3. Therapeutic hormonal manipulation with agents such as Tamoxifen and Aromatase inhibitors
4. Chemotherapy-induced ovarian failure in pre-menopausal women
5. Improved earlier detection of breast cancer resulting in more breast cancer survivors.

Estrogen deprivation causes many symptoms, but the most common are those related to vasomotor effects and urogenital atrophy. Due to the concerns about risk of recurrence or second breast malignancy of hormone replacement therapy, as raised by the HABITS (Brincat, Muscat Baron, & Ciantar, 2004) and Women's Health Initiative studies (Rossouw et al., 2002), systemic hormone replacement is not recommended in breast cancer survivors. Therefore, alternate strategies to minimize or ameliorate these symptoms are required. The remainder of this insert will address this issue.

Vasomotor symptoms

Also known as "hot flushes" or "hot flashes" are the most frequent menopausal symptoms, and are reported at a higher frequency than post-menopausal women without breast cancer (Carpenter et al., 1998). The symptoms are described as a sudden transient sensation of internal heat and redness of the face and upper body, often accompanied by sweating and dizziness, and may be followed by a chill. Objective findings include peripheral vasodilation, tachycardia and large skin conduction changes. Core body temperature is not elevated during the hot flush. Most women tolerate hot flushes and are able to remain active. However, others may find them distressing and some may even consider discontinuing breast cancer therapy. Advising patients as to the non-pharmacological strategies and the pharmacological options for dealing with hot flushes is important in order to ensure that women remain compliant with therapy.

Non-pharmacological strategies for dealing with hot flushes have been shown to improve severity of symptoms significantly. These strategies can also be combined with pharmacological therapy to improve outcome (Table One).

When considering introduction of pharmacological strategies for dealing with hot flushes, it is important for the clinician to consider that multiple placebo-controlled trials have shown a 25% decrease in symptoms with four weeks of placebo therapy alone. This must be considered, especially if the therapy used has only anecdotal evidence. Some of the more extensively studied agents include the SSRIs, Gabapentin, Clonidine, and hormonal agents. Hormone replacement therapy is the most effective pharmacological intervention for the treatment of hot flushes, but due to previous studies, which indicated that there may be an increased risk to breast cancer recurrence, these agents are, for the most part, avoided in breast cancer survivors. To date, the long-term effect of progesterone-only agents or alternate hormone agents such as tibilone are not known in breast cancer survivors. The most commonly studied non-hormonal agents are summarized in Table Two.

Urogenital atrophy

Postmenopausal women are at risk for developing urogenital atrophy, symptoms of which can include vaginal dryness resulting in dyspareunia, vaginal itching, frequency, urgency and recurrent urinary tract infections. This is due to a combination of physiologic aging and the effects of decreased estrogen levels on the urogenital tract. The reasons for symptoms of urogenital atrophy in breast cancer survivors are summarized in Table Three.

These symptoms are heightened by the further estrogen deprivation of the aromatase inhibitors, but, for the most part, the symptoms are under-reported by women. A recent survey study has shown that more than 63% of breast cancer survivors do experience these symptoms, as opposed to the reported

Table One: Non-pharmacological strategies for the treatment of hot flashes in breast cancer survivors

Approach	Description
Environmental	Cool ambient temperature, wear loosely woven cotton fabric, layering clothing so that pieces can be removed (Loprinzi et al., 2001)
Behavioural	Avoiding precipitants (spicy food, coffee, alcohol) (Loprinzi et al., 2001) Paced respiration during hot flash, biofeedback techniques such as progressive muscle relaxation training (Germaine & Freedman, 1984)
Physical	Regular aerobic exercise has been shown to decrease vasomotor symptoms (Ivarsson, Spetz, & Hammar, 1998)
Intervention	Acupuncture has been found to decrease number of hot flushes (Lee, Kim, Choi, & Ernst, 2009)

Table Two: Non-hormonal pharmacological agents to treat hot flushes in breast cancer survivors

Agent	Proposed mechanism	Efficacy
SSRIs (Venlafaxine)	Estrogen withdrawal is associated with decreased levels of serotonin and up-regulation of serotonin receptors in the hypothalamus, which may mediate heat loss. Venlafaxine has been the most extensively studied of this class	40%–60% decrease in number and severity of hot flushes vs. placebo (Loprinzi et al., 2000)
Gabapentin	GABA analogue, possibly due to up-regulation of binding site in hypothalamus due to estrogen withdrawal	20%–30% decrease in number and severity of hot flushes vs. placebo (Pandya et al., 2005)
Clonidine	Antihypertensive agent, centrally active adrenergic agonist that reduces vascular reactivity	20% decrease in number of hot flushes versus placebo (Loprinzi et al., 1994)

incidence of roughly 40% in studies of aromatase inhibitors (Chin et al., 2009).

Non-pharmacological strategies for the treatment of urogenital atrophy include topical vaginal moisturizers. These agents have been shown to substantially reduce vaginal dryness and dyspareunia in breast cancer survivors. In general, the water-soluble lubricants are usually found to be more effective. However, they do not relieve all vaginal symptoms and do not alter urinary symptoms. Some of the most effective non-hormonal agents include, but are not limited to the following:

- Replens
- K-Y Jelly
- Astroglide

Pharmacological treatment of urogenital atrophy has, for the most part, been in the form of hormone replacement therapy. While the systemic route of administration has been studied and demonstrated increase in breast cancer risk, the vaginal route has not. In addition, the vaginal route of administration may be more effective, as it allows delivery directly to the urogenital tissues and avoids the enterohepatic first-pass effect, providing a more rapid local response. To date, there have been no data to assess the risk of vaginal estrogen on breast cancer recurrence, but some data have been reported on the systemic absorption of estradiol, which may act as a surrogate marker for recurrence risk, but this is not yet known. The effects of vaginal estrogenic agents on serum estradiol levels are summarized in Table Four.

Table 3: Results of decreased estrogen on the urogenital tract

Changes resulting in vulvovaginal symptoms	Changes resulting in lower urinary tract symptoms
Vagina shortens and narrows Change in vaginal cytology from superficial cells to parabasal cells • loss of rogation • loss of elasticity • thinning of epithelium Decreased vascularity of vaginal epithelium Decreased vaginal secretions	Change in angle of the urethral meatus pubis form 90–180 degrees Decreased cellular glycogen levels causing decrease in amount of lactobacilli in vagina Increase in vaginal pH predisposes women to UTIs

The bottom line

- Menopausal symptoms are common in breast cancer survivors.
- Having an awareness of the symptoms and providing women with education and strategies to manage these symptoms may improve compliance with endocrine therapy in this population.

References

Brincat, M., Muscat Baron, Y., & Ciantar, E. (2004). Hormone replacement in women with breast cancer: The HABITS Study. **Endocrine, 23**(3), 255–257.

Canadian Cancer Society. (September 24, 2009). **Cancer Statistics 2009.** Retrieved September 24, 2009, from www.cancer.ca

Carpenter, J.S., Andrykowski, M.A., Cordova, M., Cunningham, L., Studts, J., McGrath, P., et al. (1998). Hot flashes in postmenopausal women treated for breast carcinoma: Prevalence, severity, correlates, management and relation to quality of life. **Cancer, 82,** 1682–1691.

Chin, S.N., Trinkaus, M., Simmons, C., Flynn, C., Dranitsaris, G., Bolivar, R., et al. (2009). Prevalence and severity of urogenital symptoms in postmenopausal women receiving endocrine therapy for breast cancer. **Clinical Breast Cancer, 9**(2), 108–117.

Germaine, L.M., & Freedman, R.R. (1984). Behavioural treatment of menopausal hot flashes: Evaluation by objective methods. **Journal of Consultant Clinical Psychology, 52**(6), 1072–1079.

Ivarsson, T., Spetz, A.-C., & Hammar, T. (1998). Physical exercise and vasomotor symptoms in postmenopausal women. **Maturitas, 29**(2), 139–46.

Kendall, A., Dowsett, M., Folderd, E., & Smith, I. (2006). Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. **Annals of Oncology, 17**(4), 584–587.

Lee, M.S., Kim, K.H., Choi, S.M., & Ernst, E. (2009). Acupuncture for treating hot flashes in breast cancer patients: A systematic review. **Breast cancer research and treatment, 115**(3), 497–503.

Loprinzi, A., et al. (2001). Management of hot flushes in breast cancer patients. **Lancet Oncology,** 199–204.

Table 4: Efficacy and systemic absorption of estrogen in vaginal estrogen compounds

Agent	Efficacy (reported in non-breast cancer survivors)	Systemic absorption
Vaginal estrogen tablets (Vagifem)	80%–90% decrease in symptoms or urogenital atrophy	Non-breast cancer survivors have been shown to have rise in estradiol into pre-menopausal range (Notelovitz, Funk, Nanavati, & Mazzeo, 2002) Breast cancer survivors on AI therapy have been shown to have peak rise at week two of administration, but not to pre-menopausal range (Kendall, Dowsett, Folderd, & Smith, 2006)
Estradiol releasing vaginal ring (Estring)	80%–90% decrease in symptoms of urogenital atrophy	(Non-breast cancer survivors have been shown to have no change in levels of estradiol (Weisberg et al., 2005) Breast cancer survivors have been shown to have minimal rise in systemic levels

Loprinzi, C.L., Goldberg, R.M., O'Fallon, J.R., Quella, S.K., Miser, A.W., Mynderse, L.A., et al. (1994). Transdermal clonidine for ameliorating post orchiectomy hot flashes. **Journal of Urology, 151**(3), 634–636.

Loprinzi, C.L., Kugler, J.W., Sloan, J.A., Mailliard, J.A., LaVasseur, B.E., Barton, D.L., et al. (2000). Venlafaxine in management of hot flashes in survivors of breast cancer: A randomized controlled trial. **Lancet, 356**(9247), 2059–2063.

Notelovitz, M., Funk, S., Nanavati, N., & Mazzeo, M. (2002). Estradiol absorption from vaginal tablets in postmenopausal women. **Obstetrics and Gynecology, 99**(4), 556–562.

Pandya, K.J., Morrow, G.R., Roscoe, J.A., Ahao, H., Hickok, J.T., Pajon, E., et al. (2005). Gabapentin for hot flashes in 420 women with breast cancer: A randomised double-blind placebo-controlled trial. **Lancet, 366**(9488), 818–824.

Rossouw, J.E., Anderson, G.L., Prentice, R.L., LaCroix, A.Z., Kooperberg, C., Stefanick, M.L., et al. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. **JAMA, 288**(3), 321–333.

Weisberg, E., Ayton, R., Darling, G., Farrell, E., Murkies, A., O'Neill, S., et al. (2005). Endometrial and vaginal effects of low-dose estrogen delivered by vaginal ring or vaginal tablet. **Climacteric, 8**(1), 556–562.

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