The winter issue of *Hot Spot* has many interesting educational articles by our team of experts.

Dr. Marg Fitch details one of the concerns of cancer survivors in her article “A topic of concern to cancer survivors: Sexuality”. This article reminds us that our patients deal with a number of issues. Dr. Fitch tells us that we, as health care professionals, should provide our patients with the opportunity to talk about their concerns as they relate to sexuality, or refer them to a colleague who can address these concerns.

Do adults in mid-life help or hinder the development of adolescence? Michele Chaban details the findings of new research in brain development.

Blood transfusions are often required for many of our palliative patients. Blair Henry’s ethics perspective on “Blood transfusions at the end of life: Pragmatic considerations” is a very interesting read. He details the considerations required by health care professionals who deal with end-of-life cases where patients require continued use of blood products.

To meet our continued educational needs Dr. Ewa Szumacher provides a list of CME conferences for *Hot Spot* readers.

This issue has two inserts. The one by Drs. Urban Emmenegger and Edward Chow is an overview of contemporary treatment of bone metastases from castration-resistant prostate cancer. Dr. Sonal Gandhi’s insert highlights the key presentations and implications of practice from the San Antonio Breast Cancer Symposium. This is part one of two and we look forward to reading about neoadjuvant therapy in the next *Hot Spot* issue.

In this issue, we also congratulate Dr. Calvin Law on his appointment to the position of Chief of the Edmond Odette Cancer Centre, Sunnybrook Health Sciences Centre, and Regional Vice President, Cancer Services, Toronto Central (North) Regional Cancer Program, Cancer Care Ontario. We hope that you enjoy the content of this *Hot Spot* issue.
A topic of concern to cancer survivors: Sexuality

Margaret Fitch, RN, PhD, Head of Oncology Nursing & Director of Patient and Family Support, Sunnybrook Odette Cancer Centre

The growing number of survivors provides us with the opportunity to learn about the experiences of being diagnosed with cancer, being treated, and living with the resultant impact of the disease and treatment. There is also an expanding opportunity to learn about what can be done to improve the experience throughout this journey and to make a meaningful difference in quality of life.

One aspect of care that cancer survivors indicate could be improved significantly is the attention to the impact of cancer treatment on sexuality. There is a growing recognition that all modes of treatment have the potential to influence sexuality1 and that the impact may be felt at any point along the cancer journey.2 Sexual concerns have been associated with higher symptom distress3-4 and have been reported by 10% to 90% of cancer survivors at some point during or following treatment, depending upon the disease site, gender, treatment type.5 Given this reality, health care providers caring for patients with all types of cancer ought to consider issues of sexuality in their daily practice.

We investigated perspectives of cancer survivors6 and health care professionals7 about their experiences having conversations about sexuality. Thirty survivors and 35 health care professionals working at the Odette Cancer Centre were interviewed.

Without exception, all participants expressed the perspective that having conversations about sexuality was difficult. The topic is hard to talk about for a variety of reasons. The factors contributing to the perceived difficulty include both personal and environmental ones. Participants cited age, culture, gender, language, sexual preference, the existing relationship with a partner, and personal comfort with the topic as personal factors influencing whether or not the conversation takes place. The busy nature of the ambulatory clinic and the desire for these conversations to be private and personally focused were environmental factors that added to the challenge of having a meaningful conversation.

Patients also expressed the view that being overwhelmed with the entire cancer experience, having a level of trust and rapport with the health care provider, and feeling there is enough time for a sensitive conversation were important considerations regarding whether or not they chose to raise sexuality as a topic of conversation with physicians or nurses. Additionally, for many, they had questions related to sexuality, but were reluctant to ask them because of a perception that the topic would not be a concern for health care professionals focused on cancer. In the words of one patient, “I thought if they were interested in my sexuality concerns, or thought it was important to talk about, they would have asked about it.”

Meanwhile, health care professionals described having conversations about side effects of treatment that could influence sexuality (i.e., treatment-induced menopause, impotence), as part of the treatment decision-making stage or informed consent exchange prior to surgery. But many expressed the view they did not discuss the impact of those changes on personal relationships, body image, or quality of life in detail. They waited for the patient to ask questions about these more personal areas.

The challenges, evident from these two studies, leave us with practice implications. Patients recommended that health care professionals need to provide the opportunity to talk about their concerns related to sexuality and to signal that the topic is important at the onset of treatment. If the health care professional is not personally comfortable, even raising the topic and referring the patients to another colleague with greater comfort was considered acceptable if the patient wanted to have a deeper conversation. Patients also thought it would be helpful to have education material available for them and offered, so that they would know it was easily available. Finally, they also suggested that, as health care professionals, we “check in” with them during and after treatment about whether they want to talk or want additional information. Arrangements for the more in-depth conversation could be made for a time outside of the clinic appointment in a more private and relaxed setting.

Health care professionals indicated that general education about sexuality and treatment impact would be helpful to them in their daily practice. Knowing what resources are available in their areas would facilitate easy referral for patients should the need arise. A resource that health care professionals have found useful in their practice is the Canadian Cancer Society’s publication entitled Sexuality and Cancer. This booklet is available through the Cancer Information Service (1-888-939-3333) and is useful for both cancer survivors and health professionals.

References
Blood transfusions at the end of life: Pragmatic considerations

By Blair Henry, Ethicist, Sunnybrook Health Sciences Centre

The Ethic Centre at Sunnybrook typically gets two to four consult requests per year from staff wanting support in end-of-life cases where either the patient or a family member is insisting on continued use of blood products against the judgment of the clinical team who feel this intervention is no longer beneficial. These cases involve considerable moral distress for staff and emotional stress for patients and their families who may be grasping onto last hopes.

That being said, it was with great interest that I read a recently published systematic review of transfusion practices in palliative cancer patients, undertaken by a group of clinicians from Spain. Regrettably their search of the literature did not uncover robust new clinical trial data, clinical practice guidelines, or even consensus-based conference recommendations on the appropriate use of blood transfusions in palliative cancer patients. What the study did identify was that decision making on the use of blood transfusions required the consideration of a multi-factorial set of conditions, identified in Figure 1 as Clinical, Infrastructural, Ethical and Cultural/Contextual.

Good ethics depends on good data! So it might be helpful to understand what information this review might provide clinicians when faced with this challenging dilemma. In oncology, blood transfusions are often used to address symptoms associated with cytopenias and coagulation disorders. This study noted anemia as being cited as the most prevalent occurring cytopenia (occurring in 50% to 70% of the reported cases—more prevalent in those closer to death). Some of the more noteworthy, high-level, clinical summaries that could be considered in decision making are presented in Table 1. Though not representative of a meta-analysis of the data, these general observations should inform (only) potential considerations related to the use of transfusions in this setting. Though steeped in considerable vagueness on strong clinical markers, the authors strongly advised that any decision to offer or withhold transfusions needed to be made based on the actual patient in the bed, and that generalities based on existing data cannot be supported with the current evidence.

Infrastructural considerations for the use of blood transfusions often play into the decision-making process in subtle, but important ways, which may bias opinions of some key stakeholders. The study under consideration identified incidences of “costly and unnecessary” hospital admission due to transfusions at upwards to 40%. In Toronto, the Community Care Access Centres do not support home-based blood transfusions and outpatient services may not be accessible for seriously ill patients unable to ambulate—forcing many patients wanting or needing blood transfusions to be admitted. In many hospices and palliative care units, the use of blood transfusions is typically not part of the standard treatment offerings, and would only be considered on a rare, case-by-case basis with clear limits placed on its use. Acute palliative care units are a rarity in most centres and, typically, end-of-life patients requiring transfusions must occupy a hospital bed in an acute ward, which creates administrative pressures on staff towards discharge or alternate dispositions. In addition, the on-hand institutional supply of blood products will vary depending on the level of acuity and transfusions rates of the normal population served by the hospital (i.e., trauma centre), which may, at times, necessitate partial rationing at some centres, and palliative patients may be considered an easy supply to withhold.

Infrastructural issues of the type described above typically belie a concern that moral distress over blood transfusions may be more related to so-called inappropriate use of a medical resource rather than simply a question of medical futility.

Culture and context play an important role when considering the use of blood transfusions in palliative patients. The patient’s age, life expectancy, religion, culture and their perception of the role blood transfusion has in maintaining their health will all be important considerations in their requesting this service be continued.

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Table 1: Clinically relevant finding from the systematic review

<table>
<thead>
<tr>
<th>Summary of key clinically relevant findings</th>
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<tr>
<td>• The rate of red blood cell (RBC) transfusion was relatively low in the palliative patient population (5% to 17%), with a majority needing less than two sessions, and the average number of units transfused overall was less than three</td>
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<tr>
<td>• 60% to 78% of patients report, “feeling a benefit” after receiving an RBC transfusion</td>
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<tr>
<td>• The sense of “feeling better” was typically reported two days after the transfusion and would not be sustained 15 to 21 weeks after</td>
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<tr>
<td>• Use of platelet transfusion was not indicated for prophylactic use, but only when bleeding episode occurred</td>
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<td>• In making decisions to transfuse palliative patients, do not let Hb levels be the only indicator for decision making</td>
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<tr>
<td>• The risks and frequency of adverse event reporting were deemed so rare that not to be recommended as a valid reason to not offer transfusions in organizational policies</td>
</tr>
<tr>
<td>• Studies stated that 50% of transfusions occurred in the last five weeks of life and 13.2% in the last week</td>
</tr>
<tr>
<td>• The absence of improvement in symptoms related to anemia after transfusions was associated with a nearer proximity to death</td>
</tr>
<tr>
<td>• Culture impacts decision-making preferences from both the patient’s and the HCP perspective</td>
</tr>
</tbody>
</table>

Table 2: Sampler: Stopping transfusions of blood or blood products in palliative patients

<table>
<thead>
<tr>
<th>Transfusions are discontinued when the following parameters related to goals are no longer being met:</th>
</tr>
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<tbody>
<tr>
<td>1. The physiologic or medical parameters, which will dictate the end-point of transfusing blood products, include:</td>
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<tr>
<td>• Blood loss exceeding possible replacement (such as a carotid artery erosion from tumour)</td>
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<tr>
<td>• Inability to obtain venous access</td>
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<tr>
<td>• Inability to match the blood product due to antibodies</td>
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<tr>
<td>2. Subjective or experiential parameters determining the futility of ongoing transfusions include:</td>
</tr>
<tr>
<td>• Failure of the transfusion to achieve the hoped-for goals of improved energy, strength, dyspnea</td>
</tr>
</tbody>
</table>
Balanced or ethical care typically involves a weighing of the potential benefits (that a blood transfusion will result in improved quality of life for the patient) against risks of harm and infrastructural limitations and costs associated with this treatment.

Quality of life considerations are a central part of good palliative care. However, the symptoms related to anemia are diverse and very subjective (between patients, family and staff) and, regrettably, the tools used to measure these symptoms are equally diverse and not easily comparable to each other, making the task of assessing quality of life more challenging.

Decisions related to forgoing or stopping blood transfusions is a challenge. A complex calculus of harms and benefits can be mined with poorly articulated psychological benefits and the negation of temporal harms when faced with imminent death. Having some general guidelines can assist teams from bias or pressures that extend beyond the immediate clinical event. Table 2 outlines a sampler of parameters for stopping transfusions that might provide some measure of objectivity and could be a starting point for further consideration to help clinical staff faced with these challenges.3

Mental health in families: When adolescence meets middle-essence

By Michele Chaban, MSW, RSW, PhD

New research in brain development is changing the way we view adolescents, as well as suggesting how adults or those in mid-life or middle-essence can either support or be a barrier to the developmental purposes of adolescence.

Dan J. Siegel, MD, a clinical professor of psychiatry at UCLA School of Medicine, has gathered a poly-scholarled or confluent view on adolescents. Dr. Siegel is the Co-Director of the Mindful Awareness Project at UCLA and Executive Director of the Mindsight Institute. He is on the faculty of the Center for Culture, Brain and Development, and a champion of research and knowledge that promotes insight, compassion and empathy in individuals, families, institutions and communities.

In January 2014, Dr. Siegel will publish a book titled Brainstorm: The Power and Purpose of the Emerging Adolescent Brain. The book’s knowledge and research is made easily accessible to the reader and will likely change how the world views adolescents, as well as how adolescents view themselves.

Brainstorm offers a positive perspective on the adolescent brain. This in itself is a unique approach, as we often pathologize adolescents and what they put the adult world through. In turn, adolescents often counter with labels or attributions that can poorly portray adults. To help those who encounter adolescents, such as parents, teachers, principals, coaches, therapists, community and criminal justice workers, Siegel encourages all of us to embrace adolescence as one of the most positive periods of growth, change and experimentation in life.

Siegel confirms what we know—that adolescence is a time of increased risk-taking with a statistically demonstrated increase in the chance of harm during this period of life. It is also a time when adolescents push away from their family of origin, and begin the launch of their own life. Dr. Siegel says that this is but one view, but an incomplete understanding. Adolescents have a positive side, a purpose and wisdom.

Historically, the period of time now known as adolescence did not exist in the human life cycle. Adolescence is a social by-product of the Industrial Revolution. During this transition, economies changed from agrarian (farming) to manufacturing, from rural to urban, young people migrated to city factories and the trades that supported manufacturing. Economic mobility meant that, as a worker, you found a tradesperson to intern with. Hands-on training was supported by reading and writing to enhance communication and teaching in manufacturing. Adolescence gradually became a time you sought education and employment to sustain your adult life. Progressively, sociological determinants of health displaced our biological markers. Pre-Industrial Revolution, those biological markers were the signifiers that a child was leaving behind his or her childhood to become an adult. The biological markers would signal it was time for the young person to begin their journey away from the family of origin, towards others who would be their peer group. Through and amongst the peer group, one might find a partner and, in time, begin a family of his or her own. Partnering and parenting signified the biological shift from childhood to adulthood.

Despite changes in our educational and employment histories, those biological markers have not essentially changed for our young people. However, the primacy of these biological markers has assumed second place, being displaced by the social determinants of health: assuring education and employment for our young.

In contemporary society, when those biological markers become active in adolescents, much of adult society tries to ignore, dismiss, or channel adolescent stirrings away from those biological impulses. It can be a time of strife, struggle and conflict within the adolescent and between adolescents and adults. Imagine the tension between those biological impulses and the social determinants that insist that our young stay in school, study, and socialize less with their peers so you can achieve good grades and future success. Perhaps this sounds familiar, as a lived experience.

Based on this understanding, one of the first changes we will notice, as our children become adolescents, is that they are torn between biological and sociological determinants. Or simply put, there is a tension between our biological drives and our social drives. The adult world that supports the adolescent may be very determined to keep adolescent attention on building future capacities through education. The adolescent may simply wish to do what their biology is asking of them—go out and find someone to be with, other than your family.

References

Mental health in families: When adolescence meets middle-essence

...continued from page 4

Not so long ago, it was believed that the brain you were born with was the brain you were stuck with. In the last two decades or so, the imaging of fMRIs has shown us that the brain is not a static entity. Imaging has shown us that the human brain is changing from birth to death through neuroplasticity. We also have discovered that there are times when the brain prunes itself or changes to prepare for our next stage in life. Adolescence is one of those times of brain pruning. Adolescents may view it as a time to explore and develop a self. Adults may wonder what has happened to their child; view some of the problem as the adolescent’s new interest in their peer group, and the diminishment of parental influence. Rightly so that adults view adolescence as a time of great risk and chaos and respond by trying to control the adolescent in their midst. Conflict and resistance can ensue.

Dr. Siegel views adolescence as a distinct time in the life cycle. He identifies it as the second 12 years of our life developmentally, ages 12–24 years. Dr. Siegel suggests that the emotional intensity, social engagement, novelty-seeking and creative explorations that accompany adolescents are not aspects of an “immature” stage of development to be pathologized, but, rather, can be seen as a necessary transition and transformation that produces a set of characteristics that are essential for the individual’s development and for the health and adaptation of all humans. In other words, adolescence primes us for adult life.

Dr. Siegel writes that the features of the teenage brain set the stage for changes that not only shape our life as adolescents, but also can be seen as essential to thriving in adulthood. Dr. Siegel suggests ways for both adolescents and the rest of us to navigate these important years together by developing an understanding and wisdom that supports and encourages adolescents in their ripening, rather than projecting negative attributions onto the biological transitions taking place within our young.

Coming from the new sciences, which view us and the universe in relationship to all that is about us, combined with the evidence from fMRI studies, qualitative and quantitative research, we are learning that the brain creates mind and interpersonal connections. In other words, relationships are the foundations of so much of who we are and what we do.

In the first 12 years of our life, we are in relationship to our parents, siblings and extended family members. The second set of 12 years, we turn our gaze outward to our peer group, and begin to separate and individuate from our family of origin. Our brain prunes itself and begins to establish new attachments to others beyond our nuclear or extended family. To do so, adolescents have to be inquisitive and, perhaps, begin taking risks to step beyond familiar territory or “their village”. It is this very act that parents may view as being dangerous. Siegel suggests the behaviours that accompany adolescents have had a purpose developmentally, socially and genetically to help sustain our species.

What purpose could there be if an adolescent is leaving home to explore new horizons both within and beyond his or her self? If reproductive biology is driving behaviour, it would be to seek a partner and reproduce—but it would be wise to have a partner from another family, village or gene pool. Diversity of genes, rather than drawing from the same gene pool, promotes resiliency in future generations.

Sociologically, according to the Social Determinants of Health (Health Canada, WHO), education leads to occupational success and sustainability. Education and occupational employment are two essential social determinants of health. A third essential and increasingly important social determinant is the quality of our social networks. As we and the adolescents in our lives age, it is important to nurture and sustain social networks or relationships that will see us through our lives.

As a family therapist, I have never met a parent who scolded their child for too much studying. Nor do I remember hearing a parent tell their child to give up their studying and socialize more. A study done at Harvard Business School proposes that the number one skill in the next 100 years will be social and emotional intelligence. Social and emotional intelligence can be taught to adolescents through programs such as Mindfulness without Borders. Where else do people get social and emotional intelligence, but through socializing with others? Spending hours before an LD screen with computer games may develop hand-eye co-ordination in our young, but it is not likely our children will develop S/E Q by spending hours with computer games.

Perhaps those of us in middle-essence need to be concerned with how we and the adolescents in our lives build and broaden social-neural networks, how they attend to their social networks with authenticity and integrity, rather than the too often dominant focus on academic performance and outcomes alone. It is less about bringing a balance to one’s work and play and more about the integration of both.

Success and health can be measured in so many ways—and there is an increasing recognition that one of the primary purposes of our brain is to socialize, rather than process data. The building and broadening of social and emotional intelligence may be the foundations of future healthy relationships both personally and professionally. At work, at home, at play—we benefit from healthy relationships that emphasize connection rather than correction, co-operation rather than competition, responding rather than reacting.

Dan Siegel’s book Brainstorm inspires us to value adolescents and our relationship with adolescents as a key to their future success and health. How adults see adolescents will help support adolescents to consider change within their own brain, body and mind, as a normal part of how life prepares them to do what they must do and, more importantly, who they will be, as adults. Who we and they are will make up the society and world we live in. Let those of us who are in our middle age, and encountering young people as adolescents, try to shift our lens and view adolescence as a time of developing our minds rather than losing them.

For more information on Dr. Siegel’s book Brainstorm: The Power and Potential of the Emerging Adolescent Brain or his other writings, please see DanSiegel.com. You may order the book, sign up for Dr. Siegel’s monthly newsletter or his blog.

A live webinar by Dr. Siegel on Brainstorm will be available for a limited time on the Factor-Inwentash Faculty of Social Work website after January 9.

About the author
Michele Chaban, MSW, RSW, PhD, is Director of the Applied Mindfulness Meditation Certificate Program at University of Toronto, Factor-Inwentash School of Social Work, the largest program of its kind in Canada. Michele has a 30-year history of working with families in end-of-life care and a 20-year history of employing mindfulness and mindfulness meditation clinically and educationally.

http://www.socialwork.utoronto.ca/content/certificate/MINd.htm

References available upon request
Continuing Medical Education 2014

By Ewa Szumacher, MD, FRCP(C)

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

- **February 6–9, 2014.** GOG Semi-Annual Meeting, San Diego, CA USA, [www.gog.org/meetinginformation.html](http://www.gog.org/meetinginformation.html)
- **March 4–5, 2014.** Cardiff University, postgraduate courses in palliative medicine/palliative care, UK, Wales. Call Diploma Office on 02920 196111 or email fionrawlinson@wales.nhs.uk or melanie.findlay@wales.nhs.uk
- **March 27–28, 2014.** The Sharp End of Pain Control (Course), London, UK. [www.stchristophers.org.uk/education/course/the-sharp-end-of-pain-control](http://www.stchristophers.org.uk/education/course/the-sharp-end-of-pain-control)
- **April 3–4, 2014.** Ethics and Evidence in End of Life decision making: Interdisciplinary perspectives, Bochum, Germany. [www.ruhr-uni-bochum.de/malakov/institut/ethics_evidence.html](http://www.ruhr-uni-bochum.de/malakov/institut/ethics_evidence.html)
- **August 25–28, 2014.** CARO 2014 ASM Outcomes: Clinical and Professional Success for our Patients and Ourselves. St. John’s, NL, Canada. [www.caracro.ca/Meetings__Education/Annual_Scientific_Meetings/28th_CARO_Annual_Scientific_Meeting_August_25-28__2014__St__John_s_NL.htm](http://www.caracro.ca/Meetings__Education/Annual_Scientific_Meetings/28th_CARO_Annual_Scientific_Meeting_August_25-28__2014__St__John_s_NL.htm)
- **September 9–12, 2014.** 20th International Congress on Palliative Care, Montreal, Canada. [www.palliativecare.ca/](http://www.palliativecare.ca/)

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Adjuvant breast cancer

1. Bisphosphonates (BP)

**Background:** Previous studies have provided variable results on the impact of adjuvant BPs on breast cancer outcomes, with evidence that benefit is likely restricted to menopausal patients.1,2

**New data:** The EBCTCG Meta-analysis (Oxford Overview) reviewed data on more than 17,700 patients from 22 RCTs comparing BPs to placebo. In post-menopausal women, the absolute 10-year improvement in breast cancer mortality was 3.1%, with a decrease in bone-recurrence of 2.9%. This benefit was seen irrespective of age, ER status, nodal involvement, type or schedule of BP, or chemotherapy use. There was no impact on non-breast disease recurrence. There was no benefit in breast cancer outcomes for premenopausal women.3 BPs improved bone density in both groups.

**Implications for practice:** The use of BP therapy (ideally high-potency aminobisphosphonates) should be considered for post-menopausal in the adjuvant setting to decrease in-breast disease recurrence and improve breast cancer survival. The maximum duration of therapy in the evaluated studies was five years. Patient preference and resource availability should be taken into account when choosing the BP.

**Note:** The majority of BPs studied in the meta-analysis were aminobisphosphonates (zoledronic acid: 11,575 patients, oral ibandronate: 4,273 patients, oral pamidronate:1,424 patients). Oral clodronate was used in approximately 5,174 patients, and was equally effective as the aminobisphosphonates in decreasing in-breast recurrences.2 Less potent-aminobisphosphonates commonly used for osteoporosis (risedronate and alendronate) were evaluated in very few studies and, therefore, their utility in this setting is not clearly established. These data also cannot be extrapolated to the RANK-ligand inhibitor, denosumab.

2. Targeted therapy – Bevacizumab

**Background:** The VEGF inhibitor Bevacizumab has shown only modest effects in metastatic breast cancer (MBC), and an overall survival benefit has not been demonstrated with the addition of this agent to chemotherapy in the MBC setting. In addition, magnitudes of PFS benefits have been variable and toxicities can be significant.4 Research has been ongoing in attempts to identify subgroups of patients that may benefit from this targeted agent in various treatment settings. As VEGF is downstream to the HER-2 receptor and often up-regulated in HER-2 positive breast cancers, the addition of bevacizumab to standard adjuvant HER-2 positive breast cancer therapy was evaluated.

**New data:** In the phase 3 BETH study, Bevacizumab did not prolong disease-free survival when combined with chemotherapy plus trastuzumab in the adjuvant setting for patients with HER2-positive early breast cancer. No clear markers for bevaczumab efficacy were found.5

**Implications for Practice:** Bevacizumab should not be added to adjuvant chemotherapy and trastuzumab for HER-2 positive breast cancer. This study does further support the use of taxotere/carboplatin/trastuzumab as a reasonable HER-2 positive adjuvant therapy option (as evaluated initially in the BCRG 006 trial).6

Metastatic breast cancer (MBC)

1. Hormone receptor positive – Dasatanib

**Background:** c-Src is a non-receptor tyrosine kinase that has been shown to drive breast cancer proliferation and survival, and can be involved in development of resistance to endocrine therapy.7,8,9 It also regulates bone-turnover, and is postulated to contribute to the development of bone metastases in hormone receptor (HR) positive breast cancer. Dasatinib is an oral tyrosine kinase inhibitor that targets several receptors, including c-Src. It has long been in use for chronic myeloid leukemia.10 It has anabolic and anti-resorptive effects, and may have greater anti-tumour activity when combined with inhibition of the aromatase enzyme.8,11,12

**New data:** A randomized phase II study evaluated first line letrozole in combination with dasatinib at 100mg daily, compared to letrozole alone. There was no difference in the primary endpoint of clinical benefit rate (71% versus 66%). However, PFS was improved with the combination (20.1 versus 9.9 months).13

**Implications for practice:** Dasatanib 100mg po od is well tolerated in combination with letrozole for the first line treatment of HR positive metastatic breast cancer, and may decrease resistance to AI therapy. It may also counteract AI-associated osteopenia. However, further study is required to evaluate the benefits of this treatment strategy, subgroups that may preferentially benefit from it, and how it may be best sequenced with other combinations of targeted therapy for HR positive MBC.

2. Hormone receptor positive–Everolimus

**Background:** mTOR/PI3K pathway

**Updated data:** In Bolero-2, the secondary endpoints of overall response rate and duration of response were found to be superior in the everolimus arm; greater than 2/3 of patients on this arm achieved a response, including those whose last treatment before study enrolment was neo/adjuvant therapy, and those with visceral metastases.16 A meta-analysis of MBC trials evaluating everolimus found a small but statistically significant increase in treatment-related mortality with everolimus (0.8% versus 0.4%, p=0.034).19 Safety data from Bolero-3 showed manageable toxicities from the everolimus arm; however, 3.6% of the everolimus-treated patients had to discontinue therapy due to decreased left ventricular function (LVF), compared to 0.4% in the control arm. Five out of 10 patients had improvement in their LVF after treatment discontinuation.20

**New data:** A randomized phase II study evaluated everolimus with vinorelbine and trastuzumab in patients who had progressed on a taxane and trastuzumab therapy. Compared to vinorelbine and trastuzumab alone, the everolimus arm had a PFS of seven months compared with 5.78 months.17

**Implications for practice:** The mTOR/P13K pathway is often dysregulated in breast cancer and has been shown to confer resistance to endocrine therapy and trastuzumab.14 The Bolero-2 study demonstrated improved PFS with the combination of the mTOR-inhibitor everolimus and exemestane in the second line treatment of HR positive MBC, compared to exemestane alone (11 versus 4 months by central review at 18 month follow-up).15 Longer follow up from Bolero-2 demonstrates ongoing PFS benefit (15.2 months versus 4.2 months, central assessment), along with maintenance of health-related quality of life (median time to definitive deterioration in global health status 11 months versus 7 months).21 The Bolero-3 study evaluated everolimus with vinorelbine and trastuzumab in patients who had progressed on a taxane and trastuzumab therapy.
Implications for practice: Everolimus in combination with exemestane remains a reasonable second-line strategy to improve PFS and tumour response rate in HR positive MBC, after progression on non-steroidal AI monotherapy. Overall survival data are still not mature. For HER-2 positive patients, there is a small improvement in PFS with the addition of everolimus to second-line trastuzumab and vinorelbine. This likely comes at the expense of increased cardiac toxicity. In addition, the utility of this strategy in light of other efficacious HER-2 directed treatment approaches (after first line pertuzumab/trastuzumab/taxane, and compared to second line TDM1) is uncertain.

3. Surgery for in-situ primary

Background: Surgical resection of in-situ breast primaries in the setting of metastatic disease has yielded conflicting results; in addition, these data have been largely retrospective.21-28 New data: Two randomized prospective studies evaluated surgical excision of in-situ breast primaries in patients with metastatic disease. One study randomized patients who achieved an objective tumour response after six cycles of chemotherapy to local-regional management or not. There was no difference in survival between the two arms, and there was evidence that distant metastatic disease was worsened by surgery.29 The second trial randomized patients upfront to surgery versus none, followed by chemotherapy. There was also no survival benefit found from the addition of surgery. However, patients with oligometastatic bone disease appeared to benefit on subgroup analysis.30

Implications for practice: This evidence does not support surgical management of in-situ breast cancer primaries in the setting of metastatic disease either upfront or after achieving a response to chemotherapy. In fact, there is possibility of worsening distant disease burden, and this is supported by some pre-clinical models as well.31 Whether certain subgroups of patients may benefit from surgery (such as solitary bone metastases) needs further evaluation.

Neoadjuvant therapy

...Coming soon in the May 2014 Hot Spot.

References

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30. Soran A et al. Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01). Program and abstracts from the 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, Texas. Abstract S203.
Bone metastases in CRPC
- In recent studies of advanced CRPC, around 90% of patients present with bone metastases, 60% with nodal metastases and 30% with visceral metastases.1,4
- Bone metastases are an early metastatic site and the primary source of CRPC-associated morbidity, as well as decreased quality of life.

The vicious cycle of bone metastasis
- Complex interactions between three cellular compartments drive the bone metastatic process: tumour cells, osteoblasts and osteoclasts.5
- Prostate cancer-associated bone metastases are usually osteoblastic.
- Until recently, osteoclast targeting with agents such as zoledronic acid (aminobisphosphonate) and denosumab (RANKL neutralizing monoclonal antibody) has been the most successful approach to minimize the negative impact of bone metastases on the quality of life of CRPC patients.
- Aside from complications related to bone metastases, prostate cancer patients are also at increased risk for osteoporosis and its associated complications, including fragility fractures.

Bone metastases monitoring and treatment response assessment
- The radiological monitoring of bone metastases is challenging. Despite their limitations, the criteria of the Prostate Cancer Clinical Trials Working Group (PCWG2) and variations thereof have been widely adopted for clinical trial purposes.6
- Radionuclide bone scans and CT scans are most commonly used for routine response assessment; MRI and PET are less-established alternatives.
- Skeletal-related events (SRE) comprise palliative radiation therapy to bone, pathological fractures, spinal cord compression, and surgery to bone.
- The concept of SRE has been instrumental for the study of bone-targeted agents.
- More recently, SRE-related outcome measures (e.g., SRE rates, time to first and subsequent SRE) have also been increasingly used as secondary endpoints in phase III CRPC trials studying a broad range of novel agents. However, SRE definitions and assessment vary across studies.

Management of bone metastases from CRPC
Approved bone-targeted agents: Zoledronic acid and denosumab
- Zoledronic acid and denosumab have been shown to delay SRE in CRPC patients by several months (Figure 1), but they do not impact on overall survival.7,9
- Both agents are generally well tolerated: (1) asymptomatic hypocalcemia is common, the risk can be reduced by vitamin D and calcium supplementation; (2) with appropriate patient selection (preventive dentistry as indicated) osteonecrosis of the jaw is a rare complication; (3) neither zoledronic acid nor denosumab have been widely tested in patients with poor kidney function (creatinine clearance < 30 mL/min); renal insufficiency increases the risk of hypocalcemia; zoledronic acid associated nephrotoxicity may require dose adjustments or treatment interruptions.
- Zoledronic acid is administered intravenously, denosumab is given subcutaneously. In Ontario, both agents are funded for use in bone metastatic CRPC.

Endothelin A receptor antagonists
- Endothelin-1 belongs to the factors secreted by CRPC cells that support osteoblastic bone remodelling.10
- Osteoblasts express endothelin receptor A, the activity of which can be targeted by agents such as atrasentan and zibotentan.
- However, both of these endothelin A receptor antagonists have failed to show clinical benefit in phase III trials of different stages of CRPC, either used alone or in combination with docetaxel chemotherapy.

Src inhibitor therapy
- Kinases of the Src family are involved in prostate cancer growth, invasion and metastasis; they also regulate bone resorption by osteoclasts.10
- When combined with docetaxel chemotherapy, the Src inhibitor dasatinib was well tolerated, but did not improve the overall survival of CRPC patients: HR (95% CI) - 0.99 (0.87–1.13).11
- Furthermore, the time to first SRE was not significantly delayed: HR (95%CI) - 0.81 (0.64–1.02).

Reduced SRE as a “side-effect” of established CRPC therapies
- The concept of the vicious cycle suggests that targeting CRPC cells directly could also have a positive impact on bone metastases.3
- While docetaxel chemotherapy has been shown to improve the outcome of CRPC patients, including their quality of life, its impact on SRE is not known.

This educational work is sponsored by Bayer Inc.

Figure 1: Time to first SRE in the zoledronic acid and denosumab registration trials
• In contrast, abiraterone (androgen synthesis inhibitor) and enzalutamide (androgen receptor signaling inhibitor) not only improve the outcome of CRPC patients that have undergone docetaxel chemotherapy, or of docetaxel naïve CPRP patients, but both agents also significantly reduce the time to first SRE on their own (Table 1).

Radium-223/Alpharadin dichloride: A new era in the treatment of bone metastases from CRPC

• Radium-223 is a bone-targeted alpha emitter that selectively binds to areas of increased bone turnover; it emits high-energy alpha particles of short range (<100 μm) and binds into osteoblastic metastases.

• Radium-223 induces mainly double-stranded DNA breaks; the short path of alpha particles is minimizing toxic effects on normal tissues.

• Phase I and II studies showed pain reduction, improvement of bone alkaline phosphatase and prostate-specific antigen (PSA), and minimal myelotoxicity.

• The phase III Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study comprised patients with progressive castration-resistant prostate cancer and ≥2 bone metastases on bone scan/no visceral metastases; patient had undergone docetaxel chemotherapy, or were not healthy enough or declined docetaxel; PSA ≥5μg/L, ECOG performance status 0-2, life expectancy ≥6 months.

• Patients were randomly assigned in a 2:1 ratio to six IV injections of radium-223 (50 kBq/kg of body weight) every four weeks, or placebo.

• In the interim analysis of 809 patients, radium-223 significantly improved overall survival (median 14.0 versus 11.2 months, p=0.002); in the updated analysis with 921 patients the median overall survival was 14.9 versus 11.3 months (p=0.001)

• Secondary endpoints: radium-223 significantly prolonged the time to the first symptomatic SRE (median 15.6 versus 9.8 months, p<0.001), the time to an increase in the total alkaline phosphatase (p=0.001), and the time to an increase in the PSA level (p<0.001).

• Radium-223 treatment was associated with low myelosuppression rates and few adverse events such as diarrhea.

• Radium-223 resulted in a meaningful improvement in quality of life assessed with the FACT-P questionnaire (p=0.02).

• Overall, radium-223 is the first bone-targeted agent to show an overall survival impact in CRPC; it has been approved by Health Canada, but funding approval in Ontario is pending.

What the future might hold: Cabozantinib

• Cabozantinib is a small molecule inhibitor of the vascular endothelial growth factor receptor 2 and the hepatocyte growth factor receptor (c-Met); both receptors have been implicated in CRPC progression and bone metastasis.

• In a phase II randomized discontinuation study in 171 patients cabozantinib resulted in 5% confirmed responses and 75% disease stabilizations. In the group of patients with stable disease who were randomized to cabozantinib versus placebo, the progression-free survival was significantly prolonged (23.9 weeks versus 5.9 weeks).

• Bone lesions decreased in 68% of CRPC patients, with complete responses seen in 12%; bone pain improved in 67% of patients.

• In a separate non-randomized phase II study of cabozantinib in CRPC patients that had undergone docetaxel chemotherapy there was an association between overall survival, decrease of bone scan lesions and reduction in pain.

• Cabozantinib is currently being studied in two randomized phase III trials (COMET-1, COMET-2).

Conclusions

• There is an increasing number of agents that positively affect prostate cancer bone metastases via different mechanisms.

• The results of the ALSYMPCA study demonstrate that in patients with bone-dominant metastatic CRPC bone-targeted therapy can result in improved overall survival.

• It remains to be studied how the different SRE-affecting agents need to be combined to optimize patient benefit.