

HOT SPOT

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



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Editorial

By Edward Chow, MBBS

In this issue, Dr. Camilla Zimmermann and her team explore caregiver quality of life in advanced cancer. Ms. Bo Angela Wan highlights recent research activities of the Rapid Response Radiotherapy Program. Ms. Laura MacDonald and Ms. Manisha

Gandhi share with us “I am not alone in my cancer journey!” Dr. Patrick Paladino and Toby Rodin provide the information on continuing medical education.

The inserts include a review of medical cannabis in Post-Traumatic Stress Disorder (PTSD) management

from Ms. Shannon Ohearn and her colleagues, and also a Canadian commentary on the British guidelines for the management of adult patients with aplastic anemia from Dr. Richard A. Wells. Hope you find the issue interesting to read.

Exploring caregiver quality of life in advanced cancer

By Runting Cai, BHSc, Ashley Pope, BSc, Julie McDonald, MBChB, Camilla Zimmermann, MD, PhD, Princess Margaret Cancer Centre, University of Toronto

Introduction

Palliative care is oriented towards improving quality of life (QOL) for patients, as well as for their families.¹ Despite the importance of caregivers in the care of advanced cancer patients, domains of caregiver QOL are not well understood. In contrast to the established domains that inform measures of patient QOL in advanced cancer,²⁻⁴ few caregiver QOL measures have been validated.⁵ Previous attempts to conceptualize caregiver QOL have utilized limited areas of functioning (physical, emotional, social, and family) that may not fully capture the experience of caregivers in this setting.⁶⁻⁷

We previously reported on results from a cluster-randomized trial of early palliative care (EPC) compared to standard oncological care in patients with advanced cancer. Patients receiving EPC showed improvement in QOL, symptom control and satisfaction with care,⁸ while

their caregivers demonstrated higher satisfaction with care, but no difference in overall QOL compared with standard care⁹. Following the trial, we conducted qualitative semi-structured interviews with 23 caregivers (14 intervention and nine control), using open-ended questions to explore their thoughts about the future, what they valued and found meaningful, and any changes to their well-being throughout the trial. Our aim was to identify domains of QOL for caregivers of patients in the early stage of advanced cancer, and to characterize potential differences in caregiver QOL between EPC and standard care groups.

Using grounded theory, six major themes of QOL emerged from caregiver interviews: *living in the patient's world* (core category); *burden of illness and caregiving*; *assuming the caregiver role*;

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*renegotiating relationships; confronting mortality; and maintaining resilience.*¹⁰

Living in the patient's world

When asked about what was important to them, caregivers tended to answer in the context of the patients' well-being ("Your life does end up circling around the fact that your husband has cancer."). This core category reflects the caregivers' experience of living a life focused solely on the patient, with their QOL being closely linked to that of the patient. This shift in focus came easily to some caregivers ("She's the patient and I'm here to help her."), but others admitted to struggling with the change ("It's all about him, not me. I have trouble with that."). This experience of living in the patient's world was closely linked to the concerns arising in the five other themes, which together help construct an understanding of the caregivers' overall QOL.

Burden of illness and caregiving

Their role in supportive care impacted caregivers' lives heavily in emotional, physical, social, and financial realms. They experienced significant emotional burden, feeling helpless and strained ("I probably have a level of anxiety that never really goes away."), as well as suffering physical repercussions such as fatigue and loss of energy. Caregivers also experienced social consequences, whether it was a lack of time or desire to socialize, or friends who "don't know what to say or... don't know what to do". Financial concerns also occupied their thoughts, as caregivers tried to balance work and caregiving, and some gave up their jobs to become full-time caregivers.

Assuming the caregiver role

As patients became increasingly dependent, their caregivers described taking on a multifaceted role, completing practical tasks ("changing the bed sheets, doing the laundry, getting the groceries, cooking the meals"), as well as providing emotional support ("I am the receptacle for his emotions."). Caregivers also served as manager and advocate ("I just kind of went into administrative mode...getting

things organized, doing this, doing that."), a role that was described as an important coping mechanism that helped caregivers regain control.

Renegotiating relationships

The illness and increasing dependency of the patient resulted in a considerable change in relationship dynamics between the caregiver and patient, especially when the caregiver was a spouse ("We're not the same couple. He's not the same person and our life is not the same."). A subtheme of increasing emotional closeness emerged as caregivers described the illness as a shared experience that they faced with the patient as a "team". For some, however, the illness was a strain on the relationship, with the patient being "walled away" or emotional ("It's just stressful right now....He yelled. He gets angry.").

Confronting mortality

Caregivers in each trial arm responded differently when asked about how they saw the future. Most caregivers in the control group were avoidant, admitting to "a little bit of deliberate ignorance" and "not looking ahead too far". They described an underlying fear of the future coupled with unfamiliarity with available supports ("I believe he is heading towards the end of his days. I'm terrified of that. What's that going to look like?"). In contrast, caregivers in the intervention group engaged in reframing, balancing hope with realism ("I guess we will be... forever hopeful, but also practical, preparing for the worst, expecting the best: that we're going to be able to make her cozy and comfortable."). They prepared for the future, making sure that "all her papers are in order", including wills, living wills, home hospice care, and funeral arrangements.

Maintaining resilience

The sentiment of needing to "stay strong" was pervasive among caregivers in both groups. Coping mechanisms included spending time with family and friends, taking time alone, and taking control by pursuing disease education. However, the use of professional supports

represented a point of difference between the two groups. Caregivers in the control group expressed a desire for support, but were unsure of how to access these services and were less confident within the role of caregiver ("... I'm not a nurse; I'm not a doctor. What would I do if something happened?"). In the intervention group, caregivers displayed greater confidence in their abilities and were able to access a range of services through the palliative care team ("... you know you've got somebody there that's going to help you deal with it...").

Conclusion

The identification of these six themes of caregiver QOL has significant implications for the future development of caregiver QOL measures in earlier stages of advanced cancer. Existing measures do not fully address the family and carer-related changes in roles and responsibilities in this setting,⁵ nor do they encompass the themes of confronting mortality and maintaining resilience. Our qualitative exploration of these two themes suggests that early palliative care may have an impact on caregivers with respect to preparing for end of life, balancing realism with hope, fostering confidence in their role as caregiver, and accessing a range of professional supports. Our study also demonstrates the importance of including a qualitative component in trials of palliative care interventions, as these benefits were not detected in the quantitative analysis.

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Recent research activities of the Rapid Response Radiotherapy Program

By Bo Angela Wan, MPhil, Rapid Response Radiotherapy Program, Department of Radiation Oncology, Sunnybrook Odette Cancer Centre

The Rapid Radiotherapy Response Program (RRRP) had a variety of research activities in the last quarter. Some recent accomplishments were published in the March 2017 issue of *Annals of Palliative Medicine*, in which four RRRP-authored papers were selected as “recommended articles”. These cover a range of topics and formats, including literature review, meta-analysis, and original studies.

Could time of whole brain radiotherapy delivery impact overall survival in patients with multiple brain metastases?

Stephanie Chan authored a publication that investigated whether delivery time of radiotherapy (chronotherapy) affects survival in 755 patients with metastases to the brain.¹ She identified that males and females had different time-dependent responses to radiotherapy, with overall survival in females being significantly affected by time of radiotherapy delivery. Specifically, longer overall survival was observed in elderly women who were treated between 11 a.m. to 2 p.m. This suggests a role for circadian rhythm and gender in response to radiotherapy.

Correlating symptoms and their changes with survival in patients with brain metastases

Erin Wong led a study investigating how symptoms and changes in symptoms are associated with survival in 1,660 brain metastases patients². In this study, responses from six quality-of-life and symptom questionnaires, including the Edmonton Symptom Assessment Scale (ESAS), Spitzer Quality of Life Index (SQLI), EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30), EORTC QLQ-Core 15 Palliative (QLQ-C15-PAL), EORTC QLQ-Brain Module (QLQ-BN20) and Functional Assessment of Cancer Therapy-Brain Scale (FACT-Br) were evaluated at baseline and follow-up. Multivariate analysis identified that the symptoms of fatigue and appetite loss were significantly associated with poor overall survival. Deterioration in concentration, fatigue, nausea, and worse headaches from baseline to follow-up were also associated with poor overall survival. This study identified symptoms that may

be monitored to enable more effective management of quality of life in patients with advanced cancer.

The impact of psychosocial intervention on survival in cancer: A meta-analysis

Wayne Fu conducted a meta-analysis of 13 clinical trials to summarize the impact of different types of psychosocial interventions on cancer survival.³ A wide range of interventions were analyzed, including cognitive-existential group therapy, supportive-expressive group therapy, psychoeducation, and cognitive-behavioural therapy. Overall, survival was significantly improved in patients who received psychosocial intervention at one and two years, but not at four years. Six studies investigating breast cancer trials underwent independent analysis, and psychosocial intervention was found to produce a significant improvement in overall survival at one year, but not at two or four years. Therefore, while psychosocial interventions likely have short-term survival benefits, their utility for long-term improvement in survival should be further investigated and validated.

Review of the accuracy of clinicians' predictions of survival in advanced cancer

Stephanie Cheon led a literature review to summarize the ability of healthcare professionals to predict survival in cancer patients.⁴ She identified 15 studies that assessed patients with a range of primary cancer types, and identified whether healthcare providers, most commonly physicians, nurses, or radiation therapists, underestimated or overestimated patient survival. Overall, physicians tended to be overly optimistic about their patients' survival, with 12 out of 15 studies reporting this result. There was a large discrepancy between predictions and outcomes, highlighting the difficulty in accurately predicting survival. This study pointed out that survival prediction is important in appropriate and quality care for the patients. Therefore, additional tools to enable improvement in this area are needed.

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Available upon request

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“I am not alone in my cancer journey!” A Patient Story

By Laura MacDonald (patient and Patient and Family Advisor) and edited by Manisha Gandhi, Program Manager of Patient and Family Support at Sunnybrook Odette Cancer Centre

In addition to the life-giving medical care I received, including a long aggressive surgery followed by chemotherapy, I also received expert support that has proven to be profound and integral to my healing from an emotional, spiritual, physical and social perspective.

But first let me introduce myself, and share my cancer story briefly...

My name is Laura MacDonald and I was diagnosed in February 2014, at the age of 49, with high-grade serous ovarian cancer, stage 3C. I am an avid long-distance cyclist. I finished the 2013 cycling season on top of my game, feeling the best I had in years. In fact, I completed my last 125 km race at the end of September 2013 in the best time I had ever accomplished. Training consisted of cycling 200–250 km a week and going to the gym. Needless to say, I was feeling great going into my fifties.

Unfortunately, however, like many women diagnosed with ovarian cancer, I was diagnosed at a late stage. My debulking surgery went much longer than anticipated due to the extent of the disease found once I was on the operating table. I woke up in CRCU and spent four days there, followed by 12 days in the oncology unit. I found out that I was in the hands of two gifted and skilled gyne-oncologists, one started the surgery, and the second finished and closed me up.

My procedure included total abdominal hysterectomy and bilateral salpingo oophorectomy (TAH-BSO), omentectomy, ileostomy, appendectomy, splenectomy, partial pancreatectomy, bilateral diaphragm stripping, resection of pelvic peritoneum, and the removal of 17 lymph nodes. My ileostomy was thankfully reversed months later. What relief and freedom that provided.

I started frontline chemotherapy approximately six weeks after surgery. Within 10 weeks post-surgery, I lost a significant amount of weight. It was surreal watching myself waste away, becoming weak enough to be blown over by a strong wind. I asked my CCAC nurse to set up a visit with an occupational therapist, and I started to walk outside again on my own with a walker eight weeks after surgery. My open wounds healed just before my reversal surgery, seven months post-surgery.

So where does the Patient and Family Supportive Care/Psychosocial Oncology program enter into my cancer journey?

Right from the beginning, as soon as I made contact with the Odette Cancer Centre. Intuitively, I tapped into the resources I felt I needed, when I needed them. I sincerely believe that my healthcare “team” is multidisciplinary and multifaceted. It includes all involved in my surgery and chemo, as well as the psychosocial team members I connected with. I needed each and every one of these professionals on my team.

I developed a relationship with my dietitian from the very start. You see, within the month before surgery, the ascites built up so fast that I was feeling seven to nine months pregnant. The pain started and got progressively more severe. My appetite was low to nil, I stopped eating solid food, and I was losing weight fast and feeling weak. I found myself bedridden because my torso was so fatigued that I couldn’t lift it up and, even worse, I did not have a clue what to do. My sister-in-law, who has a PhD in nutrition, advised me to phone Sunnybrook because she assumed there would be a dietitian on staff to help oncology patients. Well, indeed there was. I phoned a Sunnybrook dietitian for advice on “how to be as healthy as I can be for the surgery”. I followed their advice explicitly. Who knew that I needed 80 grams of protein/day, and I could consume that without eating any solid foods? My dietitian did. My relationship with my dietitian has been constant throughout my cancer journey. We have had telephone conversations all along the way...

- After surgery to maximize calorie and nutrients despite having no appetite.
- Dealing with new diet requirements and minimizing the difficulty with the ileostomy.
- When the ileostomy was reversed, how to transition into real food.
- Within 10 days of the reversal, I had small bowel obstruction. Once it corrected itself, I was scared to death to eat.
- And now, two years in, chatting about this weight gain!

Another service I tapped into relatively early in my journey, was speaking with a chaplain. I distinctly recall waking

up in CRCU, the pain was excruciating (three epidurals hadn’t worked and pain management hadn’t quite figured it out yet). I wasn’t able to move, yet I remember thinking to myself “I’m left here doing the heavy lifting”. I distinctly recall mentioning to the nurse that I could now understand the dialogue around assisted death. I had this experience that I characterize as a spiritual crisis, although some may view it as an existential crisis.

It was then that I requested to speak to a chaplain. Again, an assumption. I have a friend who was a chaplain in a long-term care facility and I just assumed that Sunnybrook, being as big as it is, would have an interfaith chaplain. The chaplain came each day that I was in CRCU, even though I was not capable of talking, having been too drugged and exhausted. He then found me on the oncology unit and I had a 20-minute visit with this very gifted chaplain. Among other things, he was instrumental in putting my pending chemotherapy anxiety into a perspective and context that was meaningful and achievable for me to manage. In that short period of time, he learned I was a cyclist who is familiar with training regimens preparing for long rides or races, and he used that analogy of pre, during, and post training to describe how I may view my chemo treatments. My anxiety was lifted...well ok, a significant portion of it.

I saw the same chaplain by chance (well, I believe in divine intervention) on my last day of chemotherapy, just after the IV Benadryl. I was tired and groggy, yet I had the opportunity to thank him and tell him how successful his suggestion was. I took a course later in the fall that he and a social worker facilitated on “meaning making”. I also took his advice on how I could deepen my spiritual journey using the resources available to me through my own faith community.

As my treatment was drawing to an end, I realized I needed to talk to someone. Although it is supposedly an exciting time and my friends and family were ecstatic that “it’s over”, I was in a state of high anxiety and feeling completely overwhelmed by the prospect of my treatment ending. I had a sense of abandonment... “What do you mean I’ll see you in three months with no

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“I am not alone in my cancer journey!” A Patient Story

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tests being conducted?” It took a while to understand that logic, since my life had been constant appointments, drugs, consultations, blood work, and CT scans until then. I was losing my full-time job of “treatment” and I was losing the team who saved and supported me. We had been “fighting the cancer together”. I really didn’t want to burden my friends and family because I sensed they were happy that I was going to get back to being normal. Well, there is no going back. My life was radically changed.

Luckily, on the last day of chemo in July, my friend saw a notice advertising a seminar called “How to get on with the business of living” when at the end of treatment and when to seek help provided by a psychosocial expert such as a psychiatrist. I attended. It was a discussion I so desperately needed at that exact moment in time. All my thoughts, cares, and worries were validated and, more importantly, it provided hope for tomorrow in my newly found independence. I personally felt a connection with the psychiatrist, so I asked if she would take me on as a patient.

In a single meeting, based on our discussion, her assessment, and identifying my needs, concerns, and desires, we developed a plan for “how to get on with the business of living”. She also suggested exercise classes, a “brain fog” course, and the Healing Journey all offered here at Wellspring. I had found my new full-time job: “getting on with living”. I have also met with a palliative care doctor through Patient and Family Support... Looking at options, planning,

and developing advance care plans. For me, I needed to plan and file it all away to get on with living.

I now continue my exercise once a week at Wellspring, in addition to going to my own gym. I have come a long way from the initial goals I set in September 2014 of “being able to push a grocery cart and grow back the 2 cm I lost from being so hunched over.” I finished five 100 km rides last summer, one was a fundraiser for Wellspring and the other was cycling PEI. Both were accomplished around the time that I heard I was in a recurrence. In fact, I delayed starting up treatment again to complete the Wellspring fundraiser.

I maintained my relationship with my psychiatrist and she was one of my first calls upon receiving the news of a recurrence. I was scrambling. Again, all it took was one meeting. I left relieved. I had a plan and a new perspective. With her support, I have managed the sense of a dual reality... finding ways to enjoy life and fearing that I’ll die much sooner than later. Together, with my healthcare team at Odette, which includes my psychosocial team members, I was able to change my relationship with my fear. I live as full and meaningful of a life as possible. I experience joy daily.

I was fortunate and intuitive enough to find the services that I needed when I needed them. I was resourceful, I took responsibility in my healing process, and I was my own advocate. Sitting in the clinic waiting area, I noticed the diverse demographics of the patients... various languages, various age groups, and various degrees of experience with Ontario’s healthcare system. I wondered how they were navigating through the system and how they were finding the

support services that they (both patient and caregiver) needed.

That is why I joined the Odette Patient and Family Advisory Committee (PFAC). My hope for the future is the sustainable, process-driven integration of supportive care services into the primary care of patients. These are ESSENTIAL SERVICES. I don’t view these services as “support per se”. **Cancer care, for me, is whole person care.**

To accomplish this, my hope is that supportive care experts are incorporated into your overall treatment plans and that you help your patients and caregivers get in touch with these services. Check in to see if they followed up and encourage them again. Unfortunately, we do not always retain all that was said.

You need to routinely promote these services at important transition points: as your patients move through treatment, as the cancer progresses from diagnosis, as the treatment ends, in the event of a recurrence, and at the end of life. I personally found that each stage has its own unique set of trials and issues.

I’m not asking that you become the expert in supportive care, or even to field questions that you may not feel comfortable with addressing. All I am asking is that you point people in the right direction, to the appropriate professional or service. All it takes is a quick “Did you know that we have people who can help with that?”

As patients, we listen so intently to what you say or suggest. Please promote and use the Patient and Family Supportive Care program for all its worth—every one of your patients and the people who love them will thank you from the bottom of their hearts.

Continuing Medical Education

By Toby Rodin, Odette Cancer Centre and Patrick Paladino, PhD, eLearning Manager, Oncology Education.com, elarning@oncologyeducation.com

Continuing Medical Education (CME) can update healthcare 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 activities in palliative medicine that are of interest to our readers. Please forward details of the CME activities to: toby.rodin@sunnybrook.ca

- **September 8–12, 2017.** ESMO Congress, Madrid, Spain. <http://www.esmo.org/Conferences/ESMO-2017-Congress>
- **September 13–16, 2017.** CARO Annual Scientific Meeting, Toronto, ON. <http://www.caro-acro.ca/>
- **September 14–15, 2017.** 26th Annual Provincial Palliative Care Conference, Victoria Inn Hotel and Convention Centre, Winnipeg, Manitoba. <http://palliativemanitoba.ca/events/conference/>
- **September 15, 2017.** Canadian Immuno-Oncology Summit. Parkview Manor, Toronto, Ontario. <http://www.oncologyeducation.com/events/upcoming-events/2017-canadian-immuno-oncology-summit/>
- **September 17–20, 2017.** 5th International Public Health & Palliative Care Conference, Ottawa Conference and Event Centre, 200 Coventry Road, Ottawa, ON, Canada. <http://www.iphpc2017.com/about/>
- **September 18–20, 2017.** National Hospice and Palliative Care Organization, NHPCO's 2017 Interdisciplinary Conference, San Diego Marriott Marquis and Marina, San Diego, CA. <http://nhpco.confex.com/nhpco/fc17/cfp.cgi>
- **September 20–23, 2017.** Canadian Hospice Palliative Care Conference, Ottawa Conference and Event Centre, 200 Coventry Road, Ottawa ON. <http://conference.chpca.net/about-the-conference/>
<http://www.casw-acts.ca/en/2017-canadian-hospice-palliative-care-conference>
- **September 24–27, 2017.** ASTRO's 59th Annual Meeting the Healing Art and Science of Radiation Oncology, San Diego Convention Centre, San Diego, CA. <https://www.astro.org/2017-ASTRO-Annual-Meeting.aspx>
- **October 26–28, 2017.** Controversies in Breast Cancer (CoBrCa) 3rd World Congress on Controversies in Breast Cancer, Tokyo, Japan. <http://congressmed.com/cobrca/wp-content/uploads/2015/10/CoBrCanew.jpg>
- **October 27, 2017.** Best of Lung Cancer Summit. Parkview Manor, Toronto, Ontario. <http://www.oncologyeducation.com/events/upcoming-events/2017-best-of-lung-cancer-summit/>
- **October 27–28, 2017.** Palliative and Supportive Care in Oncology Symposium, Patient-Centered Care Across the Cancer Continuum. San Diego, CA. <https://pallonc.org/>
- **November 1–2, 2017.** 7th World Congress on Breast Cancer, Toronto, ON. <http://breastcancer.alliedacademies.com/>
- **November 17, 2017.** Best of Oncology East Conference. Parkview Manor, Toronto, Ontario. <http://www.oncologyeducation.com/events/upcoming-events/best-of-oncology-east-2017/conference-home/>
- **November 17–18, 2017.** 1st ESTRO Physics Workshop Scottish Exhibition and Conference Centre, Exhibition Way, Glasgow, United Kingdom. <http://estro.org/congresses-meetings/articles/physicsws2017reg>
- **November 26–December 1, 2017.** Radiological Sciences of North America (RSNA) 103rd Scientific Assembly and Annual Meeting, McCormick Place, Chicago, IL. <http://www.rsna.org/Annual-Meeting/>
- **November 30–December 1, 2017.** 5th GEC-ESTRO Workshop, "The Strength of Brachytherapy" Faculty of Medicine and Surgery, A. Gemelli Centro Congressi Europa (Conference Centre) Largo Francesco Vito no. 1, Rome, Italy. <http://estro.org/congresses-meetings/items/5th-gec-estro-workshop>
- **December 5–9, 2017.** San Antonio Breast Cancer Symposium, Henry B. Gonzalez Convention Center, San Antonio, Texas. <http://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=115#.WW-RyvMclUI>
- **February 15–17, 2018.** Multidisciplinary Head and Neck Cancers Symposium, Expanding Treatment Horizons, The Westin Kierland Resort and Spa, Scottsdale, Arizona. <http://headandnecksymposium.org/2018-Head-and-Neck-Symposium/Home/>
- **February 22–25, 2018.** 12th Annual Canadian Melanoma Conference. Fairmont Banff Springs Hotel, Banff, Alberta. <http://www.oncologyeducation.com/events/upcoming-events/12th-canadian-melanoma-conference/>

CME Programs

What I-O Really Means for Your NSCLC Patients. In this video, International guest speaker, Prof. Solange Peters, shares the stage with Dr. Sunil Verma to discuss the latest trends on I-O in NSCLC. Patient advocacy group Lung Cancer Canada also provides invaluable patient perspectives. <http://www.oncologyeducation.com/events/oncologyeducation-events-video-archives/clcco-2017-what-i-o-really-means-for-your-nsclc-patients/>

This program meets the accreditation criteria, as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada, and has been accredited by the Office of Continuing Professional Development, Faculty of Medicine, McGill University, for up to 1 Section 1 credits. Through an agreement between the Royal College of Physicians and Surgeons of Canada and the American Medical Association, physicians may convert Royal College MOC credits to AMA PRA Category 1 Credits™. Information on the process to convert Royal College MOC credit to AMA credit can be found at www.ama-assn.org/go/internationalcme. This program is accredited until March 2018.

A Canadian commentary on the British guidelines for the management of adult patients with aplastic anemia

HOT SPOT

By Shelly Kuang, MD, and Richard A. Wells, MD, DPhil, FRCPC, Sunnybrook Odette Cancer Centre, University of Toronto

Background

- Aplastic anemia is defined as pancytopenia with hypocellular bone marrow, in the absence of an abnormal infiltrate or marrow fibrosis.
- This is a rare disease, with an incidence of ~2 cases per million population per year, and has a bimodal distribution, with peaks at 10–25 years and older than 60 years.
- Although the great majority (70–80% of cases) is idiopathic, examination of drug, occupational exposure and family history may be helpful in discerning an underlying etiology.
- Without appropriate investigation and treatment, aplastic anemia is fatal within months of diagnosis—the most common cause of death is infection.

Here we summarize evidence-based guidelines for management of adults with aplastic anemia recently published by The British Society for Standards in Haematology.¹

This education grant provided by Alexion is gratefully acknowledged.



Diagnosis and initial workup

The diagnosis of aplastic anemia requires demonstration, on a good quality bone marrow aspirate and core biopsy, of marrow hypoplasia (bone marrow cellularity < 25%) and the absence of diagnostic features of myelodysplastic syndrome. It is important to note that the presence of clonal cytogenetic abnormalities does not rule out the possibility of AA.

In addition to the bone marrow examination, the following investigations are essential in the initial workup of AA:

- **Complete blood count:** Patients usually present with pancytopenia although, in the early stages, isolated cytopenia, particularly thrombocytopenia, may occur. The reticulocyte count is low (<20 × 10⁹/l by manual count or <60 × 10⁹/l by automated technologies). The blood film must be examined to exclude presence of dysplastic neutrophils, abnormal platelets, blasts and other abnormal cells.
- **Flow cytometry to detect PNH cells:** GPI-deficient cells can be identified by peripheral blood high-sensitivity flow cytometry in ~50% of patients with AA. Although the PNH cell population is almost always small (<10% of peripheral leukocytes), in about 1/3 of cases the clone grows over time and can necessitate specific treatment.
- **Viral studies:** Hepatitis A/B/C, EBV, CMV, HIV and Parvovirus B19. Liver

function tests should also be performed in all AA cases at the time of diagnosis to detect ongoing hepatitis. AA due to hepatitis is rare, it usually occurs 2–3 months after an acute episode of hepatitis and is more common in young males. In post-hepatic AA, the serology is often negative for the known hepatitis viruses. CMV should be assessed if SCT is being considered. HIV more commonly causes isolated cytopenias, but is a very rare cause of AA. Likewise, parvovirus B19 is more usually associated with pure red aplasia, but has been reported with AA.

- **Tests to exclude rare causes of AA:** Peripheral blood chromosomal breakage analysis (diepoxybutane test) to exclude Fanconi anemia should be performed in younger patients (<50 years), or those who have a family history, and all patients who are candidates for allogeneic stem cell transplant. Vitamin B12 deficiency very rarely causes marrow aplasia, but is easily treated and should be excluded. Pancytopenia in systemic lupus erythematosus may rarely be associated with a hypocellular marrow, and so patients should be screened for anti-nuclear antibody and anti-double stranded DNA.
- **Imaging:** Chest x-ray is useful at presentation to exclude infection and for comparison with subsequent films. X-rays of the hands, forearms and feet may be indicated

if an inherited bone marrow failure syndrome is suspected. If abdominal ultrasound reveals an enlarged spleen and/or lymph nodes, the possibility of a malignant hematological disorder should be considered as the cause of the pancytopenia. In younger patients, abnormal or anatomically displaced kidneys are features of Fanconi anemia.

Other emerging diagnostic tests—peripheral blood leukocyte telomere length, next-generation gene sequencing panels, and single-nucleotide polymorphism array karyotyping—require special technology and are neither routinely available nor considered to be standard of care, but where available may provide useful information in diagnosis and management of AA patients.

Grading the severity of aplastic anemia

- Severity of aplastic anemia should be according to Camitta criteria (Grade 1C)
 - Severe (SAA): marrow cellularity <25%, plus at least 2 of neutrophil <0.5 × 10⁹/L, platelets <20 × 10⁹/L, Reticulocyte <20 × 10⁹/L.
 - Very severe (VSAA): same as severe, except neutrophil <0.2 × 10⁹/L.
 - Cases of AA not meeting criteria for severe or very severe disease are referred to as non-severe AA (NSAA).

AA and PNH

- Small PNH clones can be detected in up to 50% of patients with AA.
- All patients with AA should be tested for PNH at the time of diagnosis.
- Patients who test negative should be retested every six months for two years, then annually unless signs and symptoms appear.
- Patients in who a PNH clone is detected should be retested every three months for two years, after which the monitoring frequency may be reduced only if the clone size is stable.

Treatment of aplastic anemia

All patients with AA require supportive care to ameliorate symptoms and complications caused by cytopenias. However, in all cases of SAA and VSAA, as well as in NSAA associated with significant symptoms or need for blood transfusions, disease-modifying treatment with immunosuppressive therapy (IST) or allogeneic stem cell transplantation (SCT) should be considered.

Supportive care:

- Anemia
 - Transfusions should be given to improve quality of life (Grade 1A).
 - Transfusion threshold should be individualized according to co-morbidities (Grade 1A).
- Thrombocytopenia
 - Only one adult platelet dose is routinely required (Grade 1A).

- Prophylactic platelet transfusions should be given to stable aplastic anemia patients on active treatment, with a transfusion threshold of $10 \times 10^9/L$ (Grade 1B).
- If additional risk factors for bleeding exist, a higher prophylactic transfusion threshold $20 \times 10^9/L$ is recommended (Grade 2C).
- Prophylactic platelet transfusions are not recommended for patients not on active treatment (Grade 2B).
- Neutropenia
 - Prophylactic antibiotics and antifungal therapy are recommended per local policies (Grade 2B).
 - Patients receiving immunosuppressive therapy should receive prophylactic anti-viral agents, but routine prophylaxis against *Pneumocystis jirovecii* is not necessary (Grade 2C).
- Irradiated blood products are recommended for patients undergoing immunosuppressive therapy (Grade 1C) and hematopoietic stem cell transplantation (Grade 1A).
- Cyclosporine therapy is started two weeks after ATG administration and is continued as long as blood counts continue to improve; after a further 12 months of treatment the dose is slowly tapered.
- IST is the recommended first-line treatment for the following groups (Grade 1A):
 - NSAA patients who are transfusion dependent, bleeding, encountering infections or for lifestyle (activities).
 - SAA/VSAA patients in the absence of an HLA-matched sibling.
 - SAA/VSAA patients >35–50 years of age.
- The six-month response rate to a first course of horse ATG is around 70%.
- Five-year OS is age-dependent: 100% for age <20 years, 92% for 20–40 years, 71% for 40–60 years and 56% for >60 years.
- Vaccinations in AA patients
 - There is a risk of relapse of AA following vaccinations in patients who have responded to IST.
 - Vaccination, including influenza, should be avoided in AA patients.
 - An exception is AA patients who have received SCT, who should receive all routine vaccinations.

Immunosuppressive therapy (IST):

- Current standard first line IST is horse antithymocyte globulin (ATG) combined with cyclosporin (Grade 1A).
 - ATG must be given as an in-patient.
 - ATG is a powerful immunosuppressive agent; it should only be used in centres that are familiar with using the drug and with its side effects.

Hematopoietic stem cell transplantation:

- HLA identical sibling donor HST is the treatment of choice for severe disease for young adult patients, but co-morbidities need to be carefully reassessed in patients aged 35–50 (Grade 1B).

- For adult MSD HSCT, the survival is age-dependent, but OS is 70–85% between the ages of 30 and 50 years.
- Matched unrelated donor transplant in adults should be considered as second-line therapy after lack of response to one course of immunosuppressive therapy.
- In patients without response to IST for whom no matched sibling or unrelated donor can be identified, alternative donor HSCT using either cord blood, a haplo-identical family donor or a 9/10-matched UD may be considered.

Treatment of AA in elderly patients:

- Treatment of AA in elderly patients (older than 60 years) is more complex than in younger patients and has worse outcomes due to poorer tolerability of treatment.
- Although older age per se is not a reason to withhold treatment, there is no place for SCT as first-line therapy in patients older than 60 years.
- IST with ATG/cyclosporine or cyclosporine is an option for first-line therapy.
- Patients who are intolerant of, or decline IST should be offered best supportive care.

REFERENCE

1. Killick SB et al. Guidelines for the diagnosis and management of adult aplastic anemia. *British Journal of Haematology*. 2015;175(3):546.

A review of medical cannabis in Post-Traumatic Stress Disorder (PTSD) management

HOT SPOT

By Nicholas Lao, BMSc, Shannon Ohearn, MSc, Alexia Blake, MSc and Carlo DeAngelis, DPharm

1. Mitigation of post-traumatic stress symptoms by Cannabis resin: A review of the clinical and neurobiological evidence

1. Roitman, P., Mechoulam, R., Cooper-Kazaz, R., & Shalev, A. (2014). Preliminary, Open-Label, Pilot Study of Add-On Oral Δ9-Tetrahydrocannabinol in Chronic Post-Traumatic Stress Disorder. *Clinical Drug Investigation*, 34(8), 587–591.

This review shows recent studies of post-traumatic stress disorder (PTSD) patients who may be able to better cope with their condition using cannabis.

Results

- PTSD patients using cannabis may experience dampened strength/emotional impact of traumatic events, making it easier for them to sleep or decreasing their anxiety.

- There is evidence that tetrahydrocannabinol (THC) may act through GABAergic and CRH-mediated mechanisms to modulate anxiolytic effects.
- It has been hypothesized that PTSD is the result of hyperactivity of the amygdala.
- CBD has shown to reduce activation of the left amygdala-hippocampal complex and left posterior cingulate cortex.
- This mechanism for CBD may play a role in extinguishing fear-conditioned responses and reducing anxiety through reduced GABA release in the amygdala.
- Through the endocannabinoid system modulation by cannabis-derived compounds, alteration of fear conditioning, memory systems, general central nervous system arousal, mood, and sleep may be possible for those with PTSD.

2. Medical cannabis and mental health: A guided systematic review

2. Walsh, Z., Gonzalez, R., Crosby, K., Thiessen, M.S., Carroll, C., & Bonn-Miller, M.O. (2017). Medical Cannabis and Mental Health: A Guided Systematic Review. *Clinical Psychology Review*, 51. Elsevier Ltd: 15–29.

This systematic review examines the use of cannabis for therapeutic purposes in areas of interest to mental health professionals. The following results are pertinent to the use of cannabis for those with PTSD:

Results

- Several studies have shown effectiveness of oral THC for improving sleep duration and quality, and reducing nightmares and daytime flashbacks in treatment-resistant patients.
- One study showed a self-reported 75% reduction in self-reported re-experiencing, avoidance, and arousal symptoms of PTSD
- One observational study found worsening PTSD symptoms in those who started cannabis use after discharge from traditional PTSD treatment.
- Patients with PTSD who begin treatment with medical cannabis should be monitored for cannabis use disorders.

3. Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders

3. Belendiuk, K.A., Baldini, L.L., & Bonn-Miller, M.O. (2015). Narrative Review of the Safety and Efficacy of Marijuana for the Treatment of Commonly State-Approved Medical and Psychiatric Disorders. *Addiction Science & Clinical Practice*, 10(1), 10.

This review outlines the safety and efficacy of cannabis for treatment of medical and psychiatric disorders. The following results presented are pertinent to the use of cannabis for those with PTSD.

Results

- The endocannabinoid system plays a significant role in the mechanism behind PTSD.
- Studies have shown cannabis and THC to mitigate many PTSD symptoms through the endocannabinoid system.
- One randomized controlled trial (RCT) has shown Nabilone as potential treatment for nightmares in those with PTSD.

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- Observational studies have shown PTSD is associated with greater odds of cannabis use disorder diagnosis, greater cannabis craving and withdrawal.
- However, no RCT has been conducted using whole-plant extracts.
- There is a strong need for more RCTs examining the efficacy of cannabis for PTSD.

4. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD)

4. Fraser, G.A. (2009). The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). *CNS Neuroscience and Therapeutics*, 15(1), 84–88.

Forty-seven patients with continuing PTSD-related nightmares were reviewed for changes in nightmare incidence, nightmare intensity, incidence of flashbacks, sleep time, and quality of sleep after adjuvant treatment with Nabilone. Patients included in this review did not experience relief from conventional antidepressants and hypnotics.

Study design

- Patients were included in this prospective study if they experienced nightmares due to PTSD at least once per week.

- Nightmares in these patients were considered treatment-resistant when they persisted despite the use of conventional medications for PTSD.
- Patients were given Nabilone at a starting dose of 0.5 mg prior to bedtime.
- Patients titrated to appropriate doses to achieve therapeutic effect.
- Patients used a tracking sheet to record the intensity of their nightmares, the duration of sleep, and quality of sleep.

Results

- Forty-seven patients were included in this study.
- The average effective dose of Nabilone prior to bedtime was 0.5 mg.
- Thirty-four (72%) patients experienced cessation of nightmares or lessening of severity.
- In four patients, discontinuation of Nabilone was successful with nightmares not returning or returning at a reduced level.
- However, other patients experienced recurrence of nightmares after Nabilone withdrawal.
- Thirteen (28%) patients discontinued Nabilone therapy due to side effects.
- Common side effects included light-headedness, forgetfulness, dizziness, and headache.

Conclusion

Nabilone appears to be an efficacious option for the treatment of PTSD nightmares. Further RCTs examining Nabilone in PTSD patients are warranted.

5. A preliminary, open-label, pilot study of add-on oral Δ -tetrahydrocannabinol in chronic post-traumatic stress disorder

5. Roitman, P., Mechoulam, R., Cooper-Kazaz, R., & Shalev, A. (2014). Preliminary, Open-Label, Pilot Study of Add-On Oral Δ 9-Tetrahydrocannabinol in Chronic Post-Traumatic Stress Disorder. *Clinical Drug Investigation*, 34(8), 587–591.

Patients with chronic PTSD received 5 mg of oral Δ 9-THC twice per day. Patients' global symptom severity, sleep quality, frequency of nightmares, and PTSD hyperarousal symptoms were measured using validated tools.

Study design

- Patients from a mental health clinic in Jerusalem, Israel, with chronic PTSD were included in this pilot study.
- Patients received 5 mg of Nabilone twice per day.
- The Clinicians-Administered PTSD Scale (CAPS) and Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) were used to confirm diagnosis of PTSD and assess patient symptom severity scores.
- The Clinical Global Impression Scale (CGI) was used to measure illness severity and global improvement.
- The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality and disturbances.

- The Nightmare Frequency Questionnaire (NFQ) was used to measure the degree of impairment attributed to nightmares.

Results

- Ten patients were included in this study.
- There was a significant decrease in symptom severity in PTSD hyperarousal symptoms.
- Significant decrease in frequency of nightmares and total NES scores.
- Significant increase in sleep quality.
- Four patients reported mild side effects of dry mouth, headache and dizziness.

Conclusion

This study provides preliminary evidence of the safety and tolerability of oral Δ 9-THC for use in chronic PTSD. These results support other studies investigating the efficacy of Δ 9-THC for chronic and acute PTSD.