Dear Hotspot readers,

This issue of Hotspot brings a diverse spectrum of topics from our expert contributors. Special thanks to Dr. Philip Hébert on medical ethicists and cancer, Dr. Leah Steinberg et al. on the HeartFull Model: Caring for patients with advanced heart failure in the home, Dr. Michele Chaban on compassion informed care, Rev. Bill Ford on spiritual and emotional support to cancer patients and their families, Leslie Gibson on occupational therapy and oncology: Enabling function, optimizing quality of life, Dr. Ewa Szumacher on CME listing events, and Kelly Lien who, with Dr. Urban Emmenegger, has provided a useful summary on the treatment of castration-resistant prostate cancer.

On behalf of the editorial board and contributors, we thank you for your interest in our Hotspot issues and we hope you will continue to find them interesting and informative.

As we know, anyone, anytime, anywhere can get cancer. Politicians, celebrities, health care professionals, we are all susceptible. Malignant disease, the great leveller, is a grim reminder that we are all equal when it comes to facing the limits of human existence. Does being a consultant in medical ethics have an impact on being a person with cancer? Are there special lessons that ethicists who have had cancer can bring to others? A recent book\(^1\) considers these questions from the perspective of seven ethicists, some physicians, some not, who have or have had cancer, or who looked after spouses with cancer. Their stories highlight the heterogeneity of the experience of cancer.

For some people cancer may be a simple and resectable condition. For others it is a protracted illness with many stages of the disease and its subsequent treatment. “We describe not only what cancer taught us about medical care, but also what cancer taught us about ourselves.” (p. 5) The book is at once professional and personal. The intent was to try to keep ethics at the forefront of the stories. The experience of cancer was a crash course in “real-world ethics”—ethics from “the patient’s point of view.” The topics examined include uncertainty, medical error, truth-telling, consent to research, and everyday topics such as survivorship and stereotypes of cancer.

Norman Fost, a pediatrician and ethicist, explains how, presenting with his nth episode of renal colic, his early stage renal cancer was picked up serendipitously when he went along with an “unnecessary” CAT scan of his abdomen. And, subsequently, he had serious treatable conditions also picked up by other “routine” tests. He admits he is a lucky man, but also wonders about the value of routine expensive testing. Fost notes that a U.S. colleague whose wife was on dialysis was very happy that she was able to obtain this therapy. But, observing that society could not afford to pay for every patient’s dialysis, his colleague thought the resources “going to help his wife would be better spent on other things.” (p. 21) The late philosopher Bernard Williams would say Fost’s colleague, and so Fost, had “one thought too many.”\(^2\) One should not second-guess good luck, especially when it favours oneself or someone close.

John Robertson, a lawyer and ethicist, writes of the experience of his wife’s diagnosis of late stage, ultimately fatal prostate cancer: Advances and new challenges

continued on page 2...
Medical ethicists and cancer

...continued from page 1

... ovarian cancer. He expresses anger over the GP who let him and his wife go on a holiday before disclosing the diagnosis he had to hand. He acknowledges “it was probably beyond his expertise to tell his patient about a massive and serious cancer.” (p. 31) He is also angered over the delay in her treatment and frustrated over the lack of continuity in care providers. Anger is admitted, too, over the denial he and his wife engaged in before her diagnosis. The brutality of truth-telling by professionals is noted and serves as another source of bitterness: Not long after diagnosis, Robertson’s wife is bluntly told in the ER, “You have terminal cancer.” This came as a shock to them, “because we hadn’t thought of that way.” (p. 33) Doctors have to disclose bad news, but “not every doctor knows how to do this very well.” (p. 34)

Dan Brock, a non-MD ethicist, is found to have an elevated PSA and struggles over the treatment options available to him. “Although I had... taught... about uncertainty... before I faced serious illness, I did not fully appreciate the problems uncertainty presents for patients.” (p. 51) As a result, he writes, “shared decision-making imposes burdens on patients.” (p. 53) Ultimately, he opts for a prostatectomy, which results in incontinence and impotence. Regarding the seriousness of these side effects, he feels, he had not been sufficiently cautioned.

Patricia Marshall, a bioethics professor, writes of her husband’s harrowing death from lymphoma at a time when she is struggling with breast cancer. Though in her case it has not recurred, her experiences leave her scarred psychologically. She is never free from the cancer world. “I don’t want pity, but I do want people to recognize what I have been through.” (p. 98) She finds comfort in the notion of resilience, rising renewed from a dramatic wound.

And so it goes. Others have similar stories. The authors note the importance and succour that came from having friends and relatives. “Cancer is an occasion for real human contact.” (p. 164) Indeed, I would say this is one important message of this book. We all must depend on others—health care professionals, families, and acquaintances—for their encouragements. Ethicists have no special protection from terrible events. They, as we all do, have limits and frailties.

Despite this, I’m not convinced that this book fulfills one of its goals: to reveal that ethicists confronting cancer have special lessons for other patients. The cancer experience revealed the day-to-day horrors and indignities that all patients must encounter. These were instructive to the ethicists. “Making treatment decisions was much more difficult than we had expected,” observed the editor. “[W]e were surprised at how much we depended on doctors to help us make treatment decisions.”

This dependence on others could only be a surprise to those who either overrate the importance of patient autonomy or who have not had to make medical decisions for people with serious illnesses. Franz Ingelfinger, who died of cancer in 1980 and had been editor of the New England Journal of Medicine, wrote in his well-known paper, Arrogance, that, “a certain amount of authoritarianism, paternalism, and domination are the essence of the physician’s effectiveness.” Indeed, he went on to write, “A physician who merely spreads an array of vendibles in front of the patient and then says, ‘Go ahead and choose, it’s your life,’ is guilty of shirking his duty...”

There is more than a whiff of paternalism in Ingelfinger’s view. That makes it a challenge to those who would see autonomy as the core principle in medical decision-making. The tragedy of cancer can be its relentless and unspiring choice of its sufferers. We depend on the wisdom of others in helping us manage cancer when it affects us. “Our own bodies were out of control,” writes Rebecca Dresser, the editor, a professor of law and ethics. (p. 228) Faced with cancer, “even the boldest among us became meek.” (p. 228) She goes on to say, “We wanted [the doctors and nurses] to tell us what to do.” (p. 228, her emphasis)

Is it wrong to discover one’s cancer at a curable stage by “inappropriate” testing? Or wrong to feel guilty about being a survivor? Or wrong to accept direction and advice from a capable physician? Likely not. Ethics is important, but not the only determinant of right action. The stories in this book are, at times, agonizing and heart wrenching. They may even be considered “not right” on some simple accounts of ethics. Ingelfinger would have agreed and approved. But so much for the primacy of autonomy—and perhaps ethics, as well.

References

Occupational therapy and oncology: Enabling function, optimizing quality of life

By Leslie Gibson, OT Reg(Ont), Occupational Therapist, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Lecturer, Department of Occupational Science and Occupational Therapy, Faculty of Medicine, University of Toronto

A diagnosis of cancer and its subsequent treatments including surgery, radiation and chemotherapy, can significantly impact both an individual’s daily function and quality of life. Symptoms such as fatigue, brain fog, pain, loss of strength, and disrupted sleep, coupled with feelings of anxiety and depression, become barriers to an individual’s ability to engage in their day-to-day activities. If the cancer progresses, patients can experience more challenges and even simple tasks like getting out of bed can become more problematic.

What is Occupational Therapy? The concept of occupation, which is the core domain of the profession, is much more encompassing than strictly paid employment. Occupation is described as everything we do during everyday living and/or anything that occupies our time. An individual living with cancer may experience difficulty managing self-care activities such as bathing, getting dressed, and toileting. Being able to carry out the responsibilities of work, volunteering, caring for family and managing household tasks can become more physically and mentally taxing. Leisure activities like exercise and socializing with friends are often abandoned. Occupation essentially includes the activities we WANT to do, NEED to do, or are EXPECTED to do.

How can Occupational Therapy help? Occupational Therapists take a holistic approach when working with patients. In addition to focusing on the physical, cognitive and affective components of health, Occupational Therapists also assess the environments in which occupations take place. Often a disease like cancer results in a poor fit between the person, their occupation(s) and the environment.

continued on page 3…

HOT SPOT
Occupational therapy and oncology: Enabling function, optimizing quality of life

...continued from page 2

Occupational Therapists collaborate with their patients to problem-solve strategies to achieve a better fit, which, ultimately, has a positive impact on both function and quality of life. Examples of common interventions Occupational Therapists utilize include home safety assessments and recommendations for modifications, prescription of assistive devices and mobility aids, education on energy conservation, cancer-related fatigue and sleep hygiene, cognitive assessments and subsequent compensatory strategies, stress and anxiety management, and return to work planning.

When meeting with patients and reviewing their Edmonton Symptom Assessment System (ESAS) scores together, examples of concerns raised by patients that are triggers to making a referral to Occupational Therapy include:
- “I’m having trouble managing what I need to do at home.”
- “I can’t remember things. My memory isn’t like it was before having chemo.”
- “I feel so tired all the time and have no energy.”
- “I want to return to work, but am not sure I can handle it.”

Occupational Therapy is a profession that can be of benefit to individuals at any point in their cancer journey and compliments interprofessional oncology care. During the treatment phase, optimizing function in daily living is often the priority for the patient. When patients are palliative, Occupational Therapy can also play an important role in enabling individuals to continue participation in activities that bring meaning and optimize quality of life. Occupational Therapy works and provides patients with “skills for the job of living.” Consider making a referral today.

The HeartFull Model: Caring for patients with advanced heart failure in the home

By Leah Steinberg, Temmy Latner Centre for Palliative Care, Mount Sinai Hospital, Toronto, Susanna Mak, Anna Prosser, Heart Function Clinic, Mount Sinai Hospital, Toronto, Jennifer Arvanitis, Russell Goldman, Meghan White, and Anna Husain, Temmy Latner Centre for Palliative Care, Mount Sinai Hospital, Toronto

Patients with advanced heart failure (HF) represent a population that is significant in number, health system utilization, and symptom burden. In 2000, patients with HF accounted for the second highest number of hospital days in Canada. Over a three-year span in Ontario, there were 78,642 emergency department (ED) visits for HF, of which 27,184 were repeat visits.

The condition is responsible for a high burden of hospitalization for symptoms that are currently difficult to manage in the ambulatory setting, and are associated with high mortality. To address patient symptoms and caregiver and system burden, we are developing a collaborative model of symptom management and home-based care for patients with advanced heart failure. The ‘HeartFull’ model integrates specialist cardiology care, primary care, and specialist home-based interdisciplinary teams. Using collaborative toolkits, care pathways, communication tools, therapeutic guidelines, education, and real-time support and mentoring, the collaborative model will engage and support the care of patients with advanced HF. During initial implementation, the HeartFull model is being evaluated based on outcomes for patients and their caregivers, including quality of life, symptom scores, number of goals of care discussions, caregiver burden scores, continuity of care, and costs.

Although, the collaborative model is in the heart failure population, we are learning about factors that influence effective team behaviour that are applicable to other areas of complex care such as cancer care.

Preliminary work on this project has included a retrospective chart audit of eligible heart failure patients in the heart function clinic. Data analysis shows that documented goals of care and advanced directive discussions, as well as referrals to palliative medicine, are occurring in less than 5% of patients with NYHA stage III or IV heart function. This applies to patients identified by cardiologists as appropriate for palliative care involvement. This is an important baseline for comparison. We predict that these numbers will increase with the implementation of the collaborative model.

As part of the program development, we have created and piloted a home diuresis protocol with guidelines for escalation of oral and/or intravenous diuretic therapy; an overview of how to assess and manage common symptoms in patients with advanced heart failure; and guidelines for rational withdrawal of cardiac medications. Both patients and physicians participating in the piloting of this tool report a perceived symptom improvement, avoided hospitalizations, and an improved patient experience.

We are currently conducting recruitment and data collection for the implementation and evaluation phase of the HeartFull model. To date, five patients and three caregivers have consented to participate in the evaluation of the program. Ongoing, iterative analysis will be done throughout recruitment and data collection in order to refine the program.

Home-based care of patients with advanced heart failure that includes optimizing diuresis can lead to improved symptom management and a decreased number of hospitalizations. In turn, we hope it can reduce both patient and system burden and result in greater health-related quality of life for patients with advanced heart failure.

References
Can compassion be taught or is it something we are born with? Research is telling us it is a bit of both.

Dr. Paul Gilbert, a clinical psychologist, suggests that were it not for compassion, we would not have survived, as a species. Gilbert says that human babies are not born “good to go”, they need the tending and caring of others in order for them to survive in the world. If we did not feel compassion for our babies and their needs, those babies and our species would not survive.1

A similar kind of tending has been an integral part of interprofessional health care of patients and families. If we did not have the drive to care for the vulnerable in need, health care would become a series of tasks and tests done, data collected and analyzed.

If compassion is something we come by naturally, is it something we, or experience sustains? Is there something that degrades our compassion responses towards others, over time?

One suggestion is that compassion is eroded by our approach to education. For example, a recent Harvard study showed that young people are prioritizing success—achievement and happiness—above caring for others.2 In our competitive world, this is not surprising. Professor Rick Weissbourd, Co-director of Harvard’s project: “Making Caring Common Project”, says that “[the] challenge [before us societally] is to help parents and educators show that they prioritize caring and goodness [over academic achievement and/or happiness] and [thereby] give our youth an opportunity to build their moral muscle”.3 In other words, messaging of what is important in life has to come from parents and teachers, to our young from the elders in society.

We need to encourage and integrate an understanding that success includes academic achievement and a moral mind, which gives primacy to caring for others. The very existence of a caring project at Harvard suggests caring and compassion can be taught and that it is something important to be cultivated.

What, then, has to change in what we do? Historically, educational curriculum has emphasized reading, writing and arithmetic. To master these 3 Rs is to master higher education. We know from Dr. Dan Siegel, a UCLA psychiatrist and researcher, that a data-driven brain trained in these 3 Rs often excludes or places less value on 3 more Rs: relationship, reflection and resiliency. In order to train the whole brain and a whole person, a concerted effort must be made to exercise the 6 Rs. This means our focus in any form of education has to shift to include all 6 Rs. Watching Siegel’s TEDMED talk, it is clear he is suggesting the moral muscle can be developed by consistent exposure to the full 6 Rs.4

If, as Siegel suggests, a steady diet of data-driven brains degrades one’s ability to develop and/or exercise one’s moral muscle, then compassion training would be an essential knowledge and skill base in how we educate our young. It would also be essential in how we educate interprofessionals health caregivers, which historically relies heavily on the first three Rs that are data driven or informational by nature.

If prominent researchers such as Drs. Christopher Germer, Kristen Neff and Paul Gilbert give us assurances that compassion is teachable, then how does one go about this mentorship? Harvard’s study focuses on compassion being taught as a form of social and emotional intelligence. Other similar methods of teaching compassion include teaching mindfulness, mindfulness meditation, metta or loving kindness.

A spectrum of change is upon us in how we teach our young to have moral sense. Harvard, Stanford and Emory offer training in compassion and self-compassion. To support our young in the broader definition of success, of developing resiliency and compassion, University of Toronto began a campus-wide mindfulness meditation program to encourage a stress-monitored, stress-managed, healthy environment for their students. The meditation program known as Mindful Moments5 offers campus-wide meditation or mind-body exercising three times a day: morning, noon and evening. First reports suggest that, despite the busy schedules of the U of T learners, Mindful Moments is well attended.

Compassion-based training is also being taught in K-grade 12. In response to a large study conducted by the Toronto District School Board, which identified high levels of student stress, the Ontario Ministry of Education (K-grade 12) changed its curriculum this year so as to integrate health and wellness as an essential component of learning.6 Health and wellness in education will include the teaching of mindfulness and mindfulness meditation in our school systems.

Critics of compassion training are concerned that too much feeling might cloud our judgment rather than inform it. Will teaching compassion to our young take away the competitive edge that we have come to value in society? In the West we have been raised on a steady practice of criticism, judgment and problem-based thinking. Research shows that this steady diet of problem-based thinking leads to a negative bias and ruminations that our minds love to catch and mull over.7

Using the metaphor of a car as our mind, how we drive ourselves and our energy determines where we go, how we get there and what we are once we arrive. Learning how to drive our energy includes learning how to use our accelerator or our brake. Fear-based motivators that strive for success may mobilize us. In fact, a little bit of stress can help all of us in our learning. However, if fear is the primary motivation for doing anything, we activate a stress response of: fight, flight, freeze or faint. Over time, a steady diet of stress wears away at us.

Becoming aware of the risk involved in being motivated by the stress response, mindfulness, mindfulness meditation and compassion-informed practices help us develop skills to monitor and manage ourselves and our efforts of doing. The attention plus intention of mindfulness can become self-regulation. Research suggests this approach to self-regulation promotes resiliency in us. The key is to find what works for you.

Compassion-informed care is being integrated into approaches to care such as: mindfulness-based trauma counselling, cognitive-behavioural therapy and as a support to those who suffer from pain and chronic illness. In January 2015, University of Toronto begins compassion-based training in end-of-life care.8

The possibility that with practice and training we can develop and enhance our compassionate minds offers benefit to all: our patients, our families, our teams, our organizations and society, as a whole. Perhaps most importantly, we can learn how to practise self-compassion, continued on page 5...
which finds us being less judgmental, critical of our own selves and, thereby, others.9

It is our choice how we want to practise health care, how we want to be in health care. The health care system that I know asks me to be more than a source of information, or an enskulled brain. Can we recognize the essential importance of compassion? Can we value and cultivate compassionately educated minds and professionals who are whole brains, whole people, embodied rather than enskulled?

With compassion-informed health care, every thought, word and deed, every encounter and interaction integrates compassion. If at first you fail at this, then you have only to try again next time. With practice, you will notice (non-judgmentally we hope) that you fell short of your intention, and you can try again by having a second response to a situation or by trying anew when you meet a similar situation. Failure itself becomes our teacher. With every effort, you lay down the neurological and embodied tracks of compassion. We can integrate compassion simply by changing our minds about what we put our attention to.10

The compassion research is captured within a popular and often-told Aboriginal wisdom tale. It speaks about a grand daughter/son walking with his or her grandmother/father. The child reflects on the trials of life to the trusted elder saying: “I am struggling. I have a heart that feels rage and resentment, hatred and bitterness. Then there is another part of me that feels compassion and wants to do good for others, wants to be kind. I am torn apart by the constant battle between both.” The elder turns to the child and says: “Those are the two wolves of your heart and the one who wins will be the one you feed.”

Imagine we have the ability and power, as we go through our busy day, to exercise our brains and create a mind that will promote our own health and wellness, as well as that of our peers, patients and families. Imagine, as we meet every moment of every day, we have an opportunity to care for ourselves and others with compassion. Imagine, as we care for ourselves through this practice, that we will have an abundance of compassion to share with others, and compassion-informed care will be what we all experience as a norm, not an exception.

About the author
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References

Spiritual and emotional support to cancer patients and their families
By Rev. Bill Ford, BA, MDiv, Certified Specialist in Spiritual Care (CASC), Odette Cancer Centre, Sunnybrook Health Sciences Centre

As a chaplain, I am a member of the Patient and Family Support Program and interprofessional health care team at the Odette Cancer Centre. My role in this program is to provide spiritual and emotional support to patients, their family members and staff. Primarily, I explore with patients their beliefs and values in order to help them make meaning and find purpose in living with cancer. I listen deeply to persons. Patients often want and need to talk of the challenges they face because of their illness, how it is disruptive to their lives and its impact on their relationships with families, friends and their everyday life. To assist them in moving forward, I invite them to speak of what they feel are the significant contributions they have made in life, especially in terms of their relationships and choices, and the legacy they would like to have.

Other important aspects for listening deeply are to help them in reconciling losses, and to articulate whom and what they cherish—what makes life worth living for them. Therefore, my role is to see well beyond the medical issues that have brought patients to hospital in the first place. I help persons widen their perception and understanding of how their life stories, their current situations and illness impact their lives. I especially concentrate my conversations with them in how their relationships with their families and their interactions with their health care team effect meaning in their lives. In listening to the stories of both patients and their family members, I am not only keenly aware of the effect that a diagnosis of cancer has on the person, I am also attentive to the ripple effect it has on their family and caregivers.

We focus attention on the need to support and up-lift the spiritual well-being of others and ourselves amid times of both ease and challenge. Chaplains seek to be present, mindful, compassionate, and attuned to the spiritual distress of others. Chaplains strive to ensure that their actions and interventions have an impact on both the lives of others and themselves. It must be remembered that spiritual well-being is all-encompassing and may include transcendence, meaning and purpose, reconnecting and renewing, service to others, and helping persons to discover strength, hope, creativity, gratitude and connection that they may long for in the midst of pain and suffering. It is important to examine the relationships among spirituality, religion and health and their impacts on physical and psycho-social well-being.
Continuing Medical Education 2015
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 13–15, 2015.** IAPCON 2015, 22nd International Conference of Indian Association of Palliative Care, Hyderabad, India.


- **March 5–7, 2015.** 16th World Congress of Pain Clinicians, Miami, Florida, USA.

- **April 16–18, 2015.** Champions Palliative Care EAPC Palliative Course, Palermo, Italy, Mondello Palace Hotel. [http://www.eapcnet.eu/linkClick.aspx?fileticket=b4DIK5DD1EA53d](http://www.eapcnet.eu/linkClick.aspx?fileticket=b4DIK5DD1EA53d)


- **April 30–May 2, 2015.** Management and Leadership Conference, 30th National Hospice and Palliative Care Organizations (NHPCO), National Harbor, MD.

- **April 30–May 3, 2015.** Transforming Palliative Care, Asia Pacific Hospice Conference, 2015, Taipei, Taiwan.


- **June 25–28, 2015.** MASCC/ISOO 2015, Medical, Oncology, Health, Healthcare, Supportive Care In Cancer, Medicine, Cancer, Health Care, 5 Center Boulevard Copenhagen Denmark. [http://www.mascc.org](http://www.mascc.org)

- **September 9–12, 2015.** CARO, Delta Grand Okanagan, Kelowna, BC

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Recent advances

Prostate cancer is the third leading cause of death from cancer in Canadian men (www.cancer.ca). Most prostate cancer-related deaths can be attributed to metastatic, castration-resistant prostate cancer (mCRPC).

- Docetaxel chemotherapy was approved in 2004 as the first treatment with documented survival benefit in patients with mCRPC.¹
- This approval created three artificial mCRPC disease stages (i.e., pre-docetaxel, docetaxel and post-docetaxel), which have significantly influenced drug development and regulatory approval over the last 10 years (Figure 1):
  - Whereas cabazitaxel (Jevtana®) was approved as a 2nd line (i.e., post-docetaxel) chemotherapy option, new hormonal drugs such as abiraterone (Zytiga®) and enzalutamide (Xtandi®) have been shown to benefit both pre- and post-docetaxel mCRPC patients.²⁻⁶
- In contrast, nine agents with distinct mechanisms of action did not enhance docetaxel chemotherapy compared to docetaxel alone.
- Two novel compounds were successfully studied in selected mCRPC patient groups, i.e., early mCRPC (sipuleucel-T; Provenge®), and bone-metastatic CRPC (alpharadin/ radium-223; Xofigo®).⁷⁻⁸
- These five new agents not only improve survival, but also palliate mCRPC-associated symptoms.

New challenges

However, the successful side-by-side development of these mCRPC therapeutics also created a number of challenges:

- None of the new agents have been compared to docetaxel or to each other in randomized phase III trials; and cross-trial comparisons are challenging due to the different control arms used and the varied patient populations studied, amongst other reasons.
- While abiraterone and enzalutamide are beneficial over the entire mCRPC disease spectrum, there is no high-level evidence on how to best use them with respect to docetaxel and cabazitaxel, including how to sequence them, if at all.
- The presence of androgen receptor splice variants such as AR-V7 (measured in circulating prostate cancer cells) may predict resistance to abiraterone and enzalutamide, but the exciting preliminary AR-V7 findings await validation.⁹
- Although docetaxel has been the mainstay of mCRC therapy for one decade, when/whether to use docetaxel is emerging as a new challenge, especially since the recent presentation of the results of the CHAARTED trial (ECOG 3805): the addition of docetaxel to androgen deprivation therapy compared to androgen deprivation therapy alone substantially improved survival in patients with metastatic, hormone-sensitive prostate cancer (median survival 57.6 versus 44.0 months).¹⁰

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patients, but daily oral intake and complex drug metabolism expose patients to an increased risk of drug-drug interactions compared to intermittently administered docetaxel.

* Furthermore, treatment adherence is known to be more challenging with oral versus parenteral anticancer agents.

* Finally, the new therapies are expensive compared to first generation agents (e.g., abiraterone versus ketoconazole; enzalutamide versus bicalutamide), yet the latter have not been formally tested regarding overall survival benefit in adequately powered phase III trials.11

**Contemporary therapeutics**

To date, the choice of mCRPC therapies in a given patient is informed by Health Canada approval status and provincial funding criteria, patient preference, co-morbidities and drug safety profiles as outlined below:

**Docetaxel**

- Microtubule inhibitor (p-glycoprotein substrate)
- Seminal trial: TAX 3271 - 1006 mCRPC patients randomized 1:1:1 to prednisone (5 mg bid) and q3w docetaxel (75/m²), weekly docetaxel (30 mg/m², 5 of 6 weeks), or q3w mitoxantrone (12 mg/m²); OS: 18.9 vs. 17.4 vs 16.5 months, HR 0.76/P = 0.009 for q3w, HR 0.91/P = 0.36 for weekly docetaxel vs. mitoxantrone
- Seminal trials: COU-XX-301, COU-XX-302:
  - COU-XX-301 – 1195 post-docetaxel mCRPC patients randomized 2:1 to abiraterone (1000 mg/day) plus prednisone (5 mg bid) vs. prednisone alone; OS: 14.8 vs. 10.9 months, HR 0.65/P < 0.001
  - COU-XX-302 – 1088 pre-docetaxel mCRPC patients randomized 1:1 to abiraterone (1000 mg/day) plus prednisone (5 mg bid) vs. prednisone alone; OS: not reached vs. 27.2 months, HR 0.75/P = 0.01 (did not reach efficacy boundary); significant delay of radiological progression-free survival and time to chemotherapy
- Seminal trials: TROPIC2 – 755 post-docetaxel mCRPC patients randomized 1:1 to prednisone (5 mg bid) and q3w cabazitaxel (25/m²) or mitoxantrone (12 mg/m²); OS: 15.1 vs. 12.7 months, HR 0.70/P < 0.001
- Provincially funded indication: for mCRPC previously treated with a docetaxel-containing regimen (funding mutually exclusive with abiraterone and enzalutamide)
- Notable side effects: myelosuppression, diarrhea

**Abiraterone**

- Inhibitor of cytochrome P-450c17, a critical enzyme in androgen synthesis
- Seminal trials: COU-XX-301, COU-XX-302:
  - COU-XX-301 – 1195 post-docetaxel mCRPC patients randomized 2:1 to abiraterone (1000 mg/day) plus prednisone (5 mg bid) vs. prednisone alone; OS: 14.8 vs. 10.9 months, HR 0.65/P < 0.001
  - COU-XX-302 – 1088 pre-docetaxel mCRPC patients randomized 1:1 to abiraterone (1000 mg/day) plus prednisone (5 mg bid) vs. prednisone alone; OS: not reached vs. 27.2 months, HR 0.75/P = 0.01 (did not reach efficacy boundary); significant delay of radiological progression-free survival and time to chemotherapy
- Provincially funded indication: for post-docetaxel mCRPC
- Notable side effects: fatigue, seizures (<1%, usually in patients with risk factors, including brain metastases)

**Enzalutamide**

- Androgen receptor antagonist without partial agonistic activity, interfering at multiple levels of androgen receptor signalling
- Seminal trials: AFFIRM4, PREVAIL5:
  - AFFIRM - 1199 post-docetaxel mCRPC patients randomized 2:1 to enzalutamide (160 mg/day) vs. placebo; OS: 18.4 vs. 13.6 months, HR 0.63/P < 0.001
  - PREVAIL – 1717 pre-docetaxel mCRPC patients randomized 1:1 to enzalutamide (160 mg/day) vs. placebo; OS: 32.4 vs. 30.2 months, HR 0.71/P < 0.001; significant delay of radiological progression free survival and time to chemotherapy
- Provincially funded indication: for post-docetaxel mCRPC
- Notable side effects: fatigue, seizures (<1%, usually in patients with risk factors, including brain metastases)

**Alpharadin/radium-223**

- α particle emitting radium isotope that targets mCRPC bone metastases
- Seminal trial: ALSYMPCA6 – 809 mCRPC patients (43% docetaxel-naïve or not considered for docetaxel; 57% post-docetaxel) randomized 2:1 to alpharadin (50 kBq/kg, q4w, 6 treatments) vs. placebo; OS: 14.9 vs. 11.3 months, HR 0.70/P < 0.001
- Provincially funded indication: pending
- Notable side effects: mild myelosuppression, gastrointestinal

**Outlook**

- Over the last few years, the life expectancy of patients with mCPRC has almost doubled from around 1.5 to near 3 years
- Despite these unprecedented advances, further efforts are needed

Numerous clinical trials study the role of combinations of the recently approved new agents, whereas other clinical trials are testing these novel drugs in earlier prostate cancer stages (i.e., localized or hormone-sensitive metastatic prostate cancer, non-metastatic CRPC)

It remains to be seen if ARN-509 or ODM-201 (novel androgen receptor antagonists), or galeterone (androgen synthesis inhibitor with androgen receptor antagonistic/degrading properties) will result in substantial clinical improvements over abiraterone or enzalutamide

A number of immunotherapeutic agents are in advanced clinical testing (e.g., ipilimumab, PROSTVAC-V/F)

Modern molecular biology technologies are expected to reveal novel therapeutic targets other than the androgen signalling pathway and microtubules

**References**