**Editorial**

By Cyril Danjoux, MD, FRCPC

After a bitter, unusually cold winter for Toronto, we hope for an early spring and some warmth. This issue of *Hot Spot* contains interesting articles by our colleagues. We congratulate Dr. Jeff Myers (Division of Palliative Care, Department of Family and Community Medicine, University of Toronto), who received the OMA Section of Palliative Medicine’s prestigious Award of Excellence, which was presented by Dr. Sandy Buchman on Sunday, April 27, 2014, at the Section’s AGM at the HPCO Conference.

Dr. Monica Branigan’s excellent ethics article, “Responding to patient request to hasten death” provides useful reminders about the complexity of this request and how to respond compassionately and effectively.

In his advice from a pharmacist article, “Cardiotoxicity of chemotherapy”, Mark Pasetka provides a practical summary of offending agents, risk factors and recommendations for monitoring and management.

Mary Vachon discusses “What’s new in staff stress and what can help”. Some things are as they were 40 years ago while others have added to our understanding about burnout and the high risk of psychotic disturbance among cancer care workers. This article includes factors that may help and refers to a free eBook by Singer on Compassion Empathy.

Dr. Ewa Szumacher’s list of upcoming conferences provides us with educational options to choose from for this year.

In our first insert Dr. Sonal Gandhi provides an excellent summary of the Post-San Antonio Breast Cancer Symposium 2013 on the role of neoadjuvant chemotherapy for breast cancer.

The drug-drug interaction insert by Ronak Saluja, Drs. Carlo DeAngelis and Urban Emmenegger addresses the challenges of contemporary treatment of castrate-resistant prostate cancer. The increasing number of effective drugs with proven survival advantage when used in combination poses a risk of side effects or reduced drug benefit and calls for close collaboration between physicians and pharmacists.

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**Ethics**

**Responding to a request to hasten death**

By Monica Branigan, MD, MHSc(Bioethics), Professional Development Lead, Division of Palliative Care

As health care providers, our options in responding to suffering at the end of life are changing. On one hand, we are seeing efforts to introduce palliative care earlier, provide the necessary systems and support to die at home, and quality improvement projects looking at the dying process. On the other hand, physician-assisted death (PAD) is becoming more of a possibility—and many would say probability—in Canada.

Regardless of whether PAD is legally available or not, patients will, at times, request assistance to hasten their death. These “so-called” requests exist on a continuum: wondering about death and hoping it will be quick, expressions of readiness to die, actual desire to die, and others.

In this issue of Hot Spot:

- **Ethics**
  - Responding to a request to hasten death

- **Cardiotoxicity of chemotherapy**

- **What’s new in staff stress and what can help?**

- **Continuing Medical Education 2014**

- **Inserts**
  - Post-San Antonio Breast Cancer Symposium 2013 Update, PART 2
  - Drug-drug interactions: An emerging challenge in the contemporary treatment of castration-resistant prostate cancer

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Responding to a request to hasten death

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wish to hasten death, suicidal thoughts or plans, requests for physician-assisted suicide or euthanasia. I use the term “so-called” intentionally. We may accept these requests at face value, forgetting that they are extremely variable: over time, with change in the illness trajectory, with disease burden and with support or lack of. Chochinov has estimated that up to 45% of patients will make such a request at some time in their cancer illness.¹ Perhaps up to 2% of PCU patients may have a persistent request. In countries where euthanasia is available (Netherlands, Belgium, Luxembourg) the percent of all deaths by euthanasia and physician-assisted suicide varies from 0.1% to more than 2%.

So what might lead to a request from a patient to hasten their death? Rodin et al.² have described hopelessness and depression as separate, but mutually reinforcing pathways of distress that result in a request. This suffering may be mediated by illness related factors: symptoms, function, pain, etc. Individual factors are also at play. Attachment security is important—how easy is it for a patient to be alone and to be close to another person—because this impacts on the ability to accept care. Other individual factors mediating hopelessness and depression include self-esteem, spiritual well-being, age, and gender.

Clearly there are many complex factors behind a desire to hasten death. But do patients always mean they want to die? Nissim et al.³ followed 27 patients with advanced lung and GI cancer and monitored their desire to hasten death (DHD). Through this process, three distinct categories of desire to hasten death were identified: as a hypothetical exit plan, as an expression of despair, and as a way of letting go. DHD, as a hypothetical plan, may be an adaptive response to gain a sense of mastery and control. This was more likely to be a fairly consistent desire, but one that was seldom discussed due to fears, in a Canadian context, that it is illegal. Patients with this desire often had a strong desire to live, but wished to avoid the dying process for themselves and to relieve their family of a perceived burden. When DHD was experienced as a reaction to despair, it was more often transient. Individuals were seen to have different “breaking points” where they experienced this desire, and many of the factors that contributed to the wish were remediable. Finally, researchers described a third possibility seen in patients in the final weeks of life—simply a desire to let go, to have this dying process be over.

As a health care provider, we may be asked by a patient to hasten their death. We need to sensitively explore this with the patient. This is not always so easy. These conversations may elicit strong feelings. We may feel guilty or depressed about forcing patients to continue an unwanted existence. This may trigger feelings of failure, sadness and self-blame. On a deeper level, this may trigger fear of our own death. Given this potential discomfort, we may avoid or pretend that we did not hear. It may be tempting to shut down the conversation with “We can’t talk about that—it’s illegal!” Offering premature closure and false assurance may be another way to avoid a conversation.

There are ways to respond compassionately and effectively to such a request. Hudson et al.⁴ emphasizes the importance of first acknowledging that you have heard the request. Simple statements such as: “We haven’t talked about this before. Please tell me more.” “What is the worst part of your condition right now for you?” “What would make life worth living?” “What can we do to help?” If this is not something you feel you can do, there are many colleagues who can help—psychiatry, spiritual care, palliative care and ethics. I actually feel that it is an honour if a patient trusts me enough to share this with me. So, if this is not a conversation you personally are comfortable having, you could say, “Thank you so much for sharing this with me. This is very important. I would like to ask a colleague to meet with you to discuss this. Is that okay?”

If we do not respond mindfully to a patient’s request to hasten their death, they will continue to suffer and feel isolated and without options. This situation is even more likely to reinforce their wish to hasten death. If we treat a request to hasten death only at face value, we may miss an important opportunity to respond to the underlying suffering. If, or when physician-assisted death becomes available, the result of this avoidance to engage with the patient could be a premature death.

REFERENCES

Chemotherapy used for the treatment of cancer carries several significant side effects, but perhaps one of the most notable is cardiac toxicity. There are several different types of cardiotoxicity (CTox) that may occur with a given treatment, and may include heart failure (HF), myocardial ischemia, thromboembolism, hypertension, left ventricular dysfunction (LVD), arrhythmias, and others. The myocardium is known to have limited capacity to regenerate in comparison to some other tissues such as the gastrointestinal tract and subsequent damage from chemotherapy may be more pronounced or permanent in this case. However, some treatments are known to cause only transient and reversible toxicity.1

There are several treatments that have been shown to be associated with CTox (Table 1) and are typically assigned to one of two categories based on the potential for irreversible or reversible toxicity—Type I (irreversible) and Type II (reversible).2 Traditional chemotherapies are most commonly identified as Type I agents, and the newer monoclonal antibodies and targeted treatments as Type II. However, there are instances where Type I agents cause reversible effects and Type II agents irreversible damage.3

The most commonly cited group of agents causing CTox are the anthracyclines, in particular doxorubicin. Though the popular theory for the development of toxicity with anthracyclines is thought to be the creation of reactive oxygen species (ROS) leading to cardiomyocyte damage, new research suggests pathways that include cardiomyocyte apoptosis or necrosis, impairment of cellular ability to produce adequate contraction, and modification of mitochondrial function may be involved.3,4

In the setting of concurrent radiation and chemotherapy treatment, agents commonly associated with cardiotoxic effects include the antimitabolites (5-fluorouracil and capecitabine) and the alkylating agents (mitomycin and cisplatin). The latter of these, though uncommonly associated with direct cardiotoxic effects, has been noted to produce more myocardial ischemia when given in combination with 5-FU.1,5,6

The antimetabolites, 5-fluorouracil (5-FU) and the pro-drug capecitabine, have been associated with cardiac ischemic effects that manifest as symptoms of angina.1,5,7,8 The incidence has been noted broadly in the literature with 5-FU (1-68%), and most often occurs within five days of initial administration. However, development of cardiac symptoms can occur in subsequent cycles of treatment, as well as on rechallenge.1,5 Several other cardiac abnormalities have been reported in patients who have received 5-FU and include precordial chest pain, which may be anginal or non-cardiac in nature; additionally, there may or may not be changes in EKG parameters, and myocardial enzymes may also appear normal.1 Although not definitively known, coronary artery thrombosis, coronary vasospasm, and angiogenesis inhibitors have also been suggested as potential cardiac adverse events when used concomitantly with 5-FU.1

### Table 1: Potential cardiovascular effects of chemotherapies [Please note this is not a complete list].1,4,6,10-12

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Left Ventricular Dysfunction</th>
<th>Arrhythmias</th>
<th>Ischemia</th>
<th>Thromboembolism</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiogenesis Inhibitors</td>
<td></td>
<td>Thalidomide</td>
<td>Thalidomide</td>
<td>Lenalidomide</td>
<td>Thalidomide</td>
</tr>
<tr>
<td>Alkylating Agents</td>
<td>Cyclophosphamide, Ifosfamide</td>
<td>Cyclophosphamide, Ifosfamide, Melphalan</td>
<td>Cisplatin</td>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Doxorubicin, Liposomal Doxorubicin, Epirubicin, Idarubicin</td>
<td>Doxorubicin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthraquinones</td>
<td>Mitoxantrone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Clofarabine</td>
<td>Cepacitabine, S-Fluorouracil, Gemcitabine</td>
<td>S-Fluorouracil</td>
<td>Cepacitabine</td>
<td></td>
</tr>
<tr>
<td>Anti-tumour Antibiotic</td>
<td>Mitomycin C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histone Deacetylase Inhibitors</td>
<td></td>
<td>Vorinostat</td>
<td>Vorinostat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td>Bevacizumab, Pertuzumab, Trastuzumab</td>
<td>Alemtuzumab, Cetuximab, Rituximab, Trastuzumab</td>
<td>Bevacizumab</td>
<td>Bevacizumab</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Proteasome Inhibitor</td>
<td>Bortezomib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small Molecule Tyrosine Kinase Inhibitors</td>
<td>Dasatinib, Imatinib, Lapatinib, Sunitinib</td>
<td>Dasatinib, Imatinib, Lapatinib, Nilotinib, Pazopanib, Sorafenib, Sunitinib, Vandetinib</td>
<td>Erlotinib, Sorafenib</td>
<td>Erlotinib</td>
<td>Regorafenib, Sorafenib, Sunitinib</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Docetaxel, Paclitaxel</td>
<td>Paclitaxel</td>
<td>Docetaxel, Paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Amsacrine, Arsenic Trioxide</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

continued on page 4...
coronary arteritis, autoimmune responses, apoptosis of myocardial cells, and direct toxicity have been proposed as possible mechanisms.\(^1,5,8\)

A recent systematic review by Polk et al. examined antimitabolite-induced cardiotoxicity and identified the incidence of symptomatic cardiac effects in both 5-FU and capecitabine-treated patients to be 0-20% and 3-35%, respectively.\(^6\) Pulitations, chest pain, dyspnea, and hypotension were frequently reported, while heart failure was uncommon. More serious events such as myocardial infarction (MI), cardiogenic shock, and cardiac arrest occurred in up to two per cent of patients.\(^6\) Risk factors for the development of cardiac symptoms varied between the included studies. For instance, four studies identified cardiovascular co-morbidities to be a risk factor whereas four others did not.\(^6\) Additionally, three of four studies identified continuous 5-FU infusion versus bolus dosing to be associated with a higher incidence of cardiotoxicity, suggesting that continued exposure may predict an increased incidence of cardiac effects.\(^6\)

Mitomycin C (MMC), an alkylating agent commonly used in the treatment of anal cancer, has been associated with an incidence of developing HF\(^1\) ranging from 3-16%.\(^8\) The risk for this effect is thought to occur when patients receive cumulative doses of MMC >30 mg/m\(^2\), as well as having received a prior or concurrent anthracycline.\(^1,9,10\) Interestingly, it resembles the presentation of radiation-induced cardiac injury.\(^1\)

The European Society of Medical Oncology (ESMO) created guidelines for the management of cardiotoxicity in cancer patients. Recommendations for monitoring and management are summarized in Table 3.\(^2\)

### References


### Table 2: Risk factors for the development of cardiotoxicity with chemo and radiation therapy\(^2,5\)

<table>
<thead>
<tr>
<th>Treatment Dependent</th>
<th>Patient Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td><strong>Chemotherapy</strong></td>
</tr>
<tr>
<td>Type of chemotherapy</td>
<td>Age</td>
</tr>
<tr>
<td>Dose of chemotherapy administered during each cycle</td>
<td>Presence of cardiovascular (CV) risk factors</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>Prior cardiovascular disease (CVD)</td>
</tr>
<tr>
<td>Schedule of administration</td>
<td>Prior mediastinal radiation therapy</td>
</tr>
<tr>
<td>Route of administration</td>
<td></td>
</tr>
<tr>
<td>Combination of other cardiotoxic drugs or association with radiotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
<td><strong>Radiation</strong></td>
</tr>
<tr>
<td>Dose &gt;30-35 Gy</td>
<td>Younger age at exposure</td>
</tr>
<tr>
<td>Dose per fraction &gt;2 Gy</td>
<td>Presence of CV risk factors</td>
</tr>
<tr>
<td>Large volume of irradiated heart</td>
<td></td>
</tr>
<tr>
<td>Longer time since exposure</td>
<td></td>
</tr>
<tr>
<td>Use of cytotoxic chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Endotherapy or trastuzumab</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Summarized ESMO recommendations for the monitoring and management of cardiotoxicity (CTox)\(^1\)

<table>
<thead>
<tr>
<th>Baseline Evaluation for Patients Receiving Chemotherapy</th>
<th>Cardiac Monitoring During Treatment with Chemotherapy</th>
<th>Treatment of LVD Induced by Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Baseline evaluation for CV risk factors and comorbidities and optimized management of these is essential</td>
<td>• Monitoring of cardiac function at baseline, three, six, and nine months (during treatment) and 12 and 18 months following treatment initiation should occur for patients receiving anthracyclines and/or trastuzumab</td>
<td>• In subclinical CTox induced by Type I agents, an ACE Inhibitor (enalapril) may prevent LVEF decrease and associated cardiac issues</td>
</tr>
<tr>
<td>• Patients who have received cumulative doses of anthracyclines or mitoxantrone should be considered to be at risk for CTox</td>
<td>• Cardiac function evaluation at four and 10 years should occur in patients who have achieved cumulative doses of doxorubicin (&gt;240 mg/m(^2)) and epirubicin (&gt;360 mg/m(^2))</td>
<td>• Observation is indicated for patients who have developed asymptomatic CTox, with a LVEF ≥40% whilst on Type II agents (Trastuzumab) and have not received an anthracycline; persistence or worsening of status indicates treatment of LVD</td>
</tr>
<tr>
<td>• Evaluation of LVEF, EKG status (including QT Time), cardiac function via echocardiography (or MUGA, or MRI), and diastolic function using US</td>
<td>• Depending on the reduction in LVEF whilst receiving anthracyclines or trastuzumab, require reassessment in three weeks; for more significant decreases in LVEF (i.e., to &lt;40%), cessation of therapy, consideration of alternatives (if applicable), and treatment for LVD is indicated</td>
<td>• Treatment of LVD is as per standard HF guidelines</td>
</tr>
</tbody>
</table>
The sources of staff stress in oncology and palliative care have not changed a huge amount since my colleagues and I started our research in the early 1970s at Princess Margaret Hospital, and later when the Royal Victoria Hospital opened its palliative care unit in 1974. Difficulties in oncology with work overload, the work environment, staff communication issues, and problems communicating with some patients and families were mentioned as often as were difficulties watching patients suffer and die.

Comparing the stress of those in oncology and palliative care, in general, oncology staff have more difficulty than palliative care staff, although there have been some instances indicating the opposite more recently. A summary of 20 studies found psychiatric disturbance in oncology and palliative care staff ranged from a low of 9.5% of support staff and 10.5% of allied health staff in Ontario cancer centres to between a quarter and one-third of the sample in the other studies of oncologists and palliative care specialists. Unpublished, preliminary data of approximately 7,000 physicians found medical oncologists more likely to experience symptoms of depression than other internal medicine physicians (47.1% vs. 37.9%). Reviewing the literature of studies of burnout among oncology-focused specialties, they found a point prevalence of 25% to 35% among medical oncologists, 38% among radiation oncologists, and 28% to 36% among surgical oncologists, similar to the norms. Vachon (2010) found the highest rate of EE (53.3%) in physicians working in Cancer Care Ontario. About half of Ontario oncologists and allied health professionals and Japanese palliative care physicians and 65% of oncologists reported low personal accomplishment (norms 36%).

Work is being done to better understand what can decrease work stress and build resilience.

McCann et al. (2013) reviewed the literature in five professions: nursing, social work, psychology, counselling, and medicine investigating behavioural and cognitive strategies in personal and professional spheres. Being female and maintaining a work-life balance consistently related to resilience across the five disciplines. Four other factors related to resilience in four of the five disciplines: laughter/humour, self-reflection/insight, beliefs/spirituality, and professional identity.

Recovery from burnout is possible. Prospective studies in medical students and residents suggested that approximately 12-27% recover over the following 12 months. However, recovery requires deliberate and sustained effort to identify and address the factors contributing to burnout. A review of burnout interventions identified 25 relevant studies. Most (80%) programs led to reduced burnout. Person-directed interventions reduced burnout in the short term (six months or less), while a combination of person- and organization-directed interventions had longer-lasting effects (>12 months).

Lise Fillion from Quebec City and her colleagues are conducting exciting major systematic research with meaning-centred interventions combined with mindfulness meditation in palliative care, oncology and intensive care units. The work is based in part on the Being with Dying program earlier developed by Roshi Joan Halifax.

The construct of compassion fatigue actually measures empathic strain. Recent work is distinguishing compassion from empathy, and finding that empathic strain can lead to feelings similar to burnout.

A fascinating free eBook contains the latest research and work in the field of the neuroscience of compassion and empathy. Exciting findings such as the fact that mindfulness meditation may increase telomeres, which may be associated with longer and better quality of life, and interventions that teach compassion to health care providers are extremely promising for our long-term survival, and thriving, as health care professionals dedicated to working with those living with and dying from cancer.

REFERENCES
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

- **September 2–5, 2014.** The Australian and New Zealand Society of Palliative Medicine Gold Coast Australia, Gold Coast, QLD, Australia. www.etouches.com/ehome/65181
- **September 7–11, 2014.** 18th International Conference on Cancer Nursing, Panama City, Panama. www.isncc.org/?page=18th_ICCN
- **September 9–12, 2014.** 20th International Congress on Palliative Care, Montreal, Canada. www.palliativecare.ca/
- **September 15–18, 2014.** HPCA (Hospice Palliative Care Assoc of South Africa), Cape Town, South Africa. delshe@hpc.co.za
- **May 8–10, 2015.** EAPEC, 14th World Congress of the EAPC, Copenhagen, Denmark. eapc2015@interplan.de

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Neoadjuvant chemotherapy

Background
- Neoadjuvant chemotherapy (NAT) is considered the standard of care for unresectable, locally advanced breast cancer (LABC); these include T4 and/or N2/N3 cancers, as well as inflammatory breast cancers.
- These tumours require pre-operative down-staging by chemotherapy.
- NAT has increasingly been used for early, resectable breast cancers as well.
- Benefits to NAT in this population include:
  - Tumour down-staging to allow for breast-conserving therapy
  - In-vivo assessment of chemotherapy response → non-responders would be good candidates for clinical trials and salvage protocols
  - Earlier treatment of micrometastatic disease (particularly in high-risk phenotypes, such as triple negative, and HER-2 positive)
  - Novel therapy and biomarker development

- Thus far, there are no robust, prospective data showing an advantage of NAT over adjuvant chemotherapy in terms of patient survival, so practice tends to be varied for early breast cancer patients.
- Many guidelines suggest NAT can be considered for any breast cancer patient who should receive adjuvant chemotherapy.
- In addition, pathologic complete response (pCR—often defined as no residual invasive disease in the breast or axilla) is known to be a good surrogate for survival, particularly in specific breast cancer phenotypes (triple negative, HER-2 positive). pCR in the nodes is thought to be especially important.
- Therefore, many clinical trials have sought to establish ideal early breast cancer candidates for NAT, and increase pCR rates in specific disease phenotypes by using novel NAT regimens.

New data
1. CALGB/Alliance 4063
- This randomized phase 2 study evaluated the addition of carboplatin (AUC 6 every three weeks x 4) to weekly paclitaxel (80mg/m² weekly x 12), compared to paclitaxel alone in combination with bevacizumab, and to carboplatin, paclitaxel, and bevacizumab in a 2 x 2 trial design. All treatment arms were followed by four cycles of dose-dense AC chemotherapy.¹
- The trial was powered assuming a pCR rate of 34% for triple negative breast cancer, as described in the literature; it was not powered to compare individual treatment arms, nor overall survival.
- pCR in the breast and axilla in the carboplatin arms was 54%, compared to 41% in the non-carboplatin arms (p=0.0029).
- The addition of bevacizumab increased pCR with statistical significance in the breast alone, with only a trend in breast/axilla (p=0.057).
- Select grade 3/4 toxicities were higher with both carboplatin and bevacizumab, compared to chemotherapy alone¹ (Table 1).

Implications for practice:
- The addition of carboplatin to neoadjuvant paclitaxel (followed by dose-dense AC) significantly improves pCR (breast/axilla) compared to chemotherapy alone; however, the optimal dose of carboplatin is unclear.
- In addition, there was more grade 3/4 neutropenia and thrombocytopenia with the addition of carboplatin, and more frequent paclitaxel dose modifications.
- This may be a promising approach for the neoadjuvant treatment of triple negative breast cancer; a larger, randomized study may be required to confirm the ideal strategy for using carboplatin, minimizing toxicity, and evaluating impact on patient survival outcomes.

<table>
<thead>
<tr>
<th>Select Grade ≥3 Toxicities</th>
<th>Chemo</th>
<th>Chemo + Bev</th>
<th>Chemo + Carbo</th>
<th>Chemo + Carbo + Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>22%</td>
<td>27%</td>
<td>56%</td>
<td>67%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4%</td>
<td>3%</td>
<td>20%</td>
<td>26%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7%</td>
<td>9%</td>
<td>12%</td>
<td>24%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2%</td>
<td>12%</td>
<td>0%</td>
<td>10%</td>
</tr>
</tbody>
</table>

¹ This randomized phase 2 study evaluated the addition of carboplatin (AUC 6 every three weeks x 4) to weekly paclitaxel (80mg/m² weekly x 12), compared to paclitaxel alone in combination with bevacizumab, and to carboplatin, paclitaxel, and bevacizumab in a 2 x 2 trial design. All treatment arms were followed by four cycles of dose-dense AC chemotherapy.
• Bevacizumab increased pCR in breast alone compared to non-bevacizumab arms, but significantly increased toxicity and, as such, may not be a feasible strategy to develop further.  

2. I-SPY-2  
• This adaptive neoadjuvant therapeutic trial is comparing the efficacy of novel drugs in combination with standard chemotherapy, to the efficacy of chemotherapy alone. Regimens are linked to molecular biomarker signatures, with the aim to identify more effective treatment strategies early. Regimens that show a high Bayesian predictive probability of being more effective than standard treatment are graduated, and less efficacious regimens are dropped. New drugs will be entered as existing ones graduate or are eliminated.  
• I-SPY 2 experimental arm one evaluated veliparib (a parp-inhibitor, known to be active in triple negative breast cancer), in addition to carboplatin (AUC 6 every three weeks x 4), with weekly paclitaxel, followed by AC. This was compared to paclitaxel alone followed by AC, as the standard arm.  
• All HER-2 negative molecular signatures were evaluated.  
• Although this trial is not meant to establish true comparative pCR rates, the triple negative signature was reported to show a 52% estimated pCR rate compared to chemotherapy alone (26%); the predictive probability that this regimen would succeed in a phase 3 trial is 90%.  
• Grade 3/4 neutropenia was more common in the veliparib/carboplatin arm (37%), compared to chemotherapy alone arm (11%).  

Implications for practice  
• Neoadjuvant veliparib and carboplatin in addition to chemotherapy with weekly paclitaxel, followed by AC, is predicted to be superior to chemotherapy alone in achieving a pCR in triple negative breast cancer, as estimated using Bayesian statistics in this adaptive trial.  
• This regimen has graduated in the I-SPY 2 schema, and a phase 3 study would be required to further establish the role of this combination in the neoadjuvant treatment of triple negative breast cancer.  

Updated Data 1. NeoALLTO  
• This neoadjuvant study in HER-2 positive breast cancer evaluated lapatinib (a small molecule TKI against the HER-2 receptor) in combination with weekly paclitaxel, compared to trastuzumab (a monoclonal antibody against the HER-2 receptor) and paclitaxel, or the combination of lapatinib and trastuzumab with paclitaxel.  
• All arms received FEC chemotherapy post-operatively, and continued maintenance targeted therapy.  
• The primary endpoint of this study (pCR) has already been reported, and the lapatinib + trastuzumab arm was found to be superior (pCR of 51%). This was most pronounced in hormone receptor-negative tumours.  
• This updated analysis evaluated survival outcomes in the three arms and by pCR.  
• The lapatinib + trastuzumab arm had superior three-year event-free survival compared to the other two arms; this was most pronounced in (and appears to be driven by) hormone receptor-negative patients.  
• In addition, the three-year overall survival of patients who received a pCR was superior to those who did not; this was again most pronounced in the hormone-receptor negative patients.  

Implications for practice  
• Dual HER-2 blockade with lapatinib + trastuzumab in combination with chemotherapy appears to be superior for pCR in the neoadjuvant treatment of HER-2 positive breast cancer, compared to chemotherapy and HER-2 blockade with a single targeted agent; this benefit is most apparent in hormone receptor-negative patients.  
• These data further illustrate that HER-2 positive, hormone receptor-negative tumours have disparate disease biology than hormone receptor-positive cancers.  
• Hormone receptor-negative patients who achieved a pCR (particularly with the dual-targeted approach) had improved event-free and overall survival with a median four-year follow-up; this strategy may, therefore, be preferred for this subset of patients.  
• However, given these results are of a randomized phase 2 study and subgroup analyses, further prospective data would be needed in order to establish this as a standard treatment. The toxicity of lapatinib also remains a concern in this setting.  
• Lapatinib is so far not approved in Canada for neoadjuvant treatment of breast cancer.  

References  
Drug-drug interactions: An emerging challenge in the contemporary treatment of castration-resistant prostate cancer

By Ronak Saluja, BSc candidate, Carlo DeAngelis, PharmD, and Urban Emmenegger, MD, Sunnybrook Odette Cancer Centre, University of Toronto

Castration-resistant prostate cancer: Rapidly changing treatment landscape

- Metastatic prostate cancer can be contained for prolonged periods of time by a number of systemic therapies, especially androgen-deprivation therapy. However, castration-resistant prostate cancer (CRPC) develops ultimately.
- Until 2010, docetaxel was the only available CRPC treatment with documented survival benefit. More recently, five new agents have shown to improve survival of patients with CRPC (Health Canada approved unless otherwise indicated):
  1. Sipuleucel –T (prostatic acid phosphatase targeting active immunotherapy; Health Canada approval pending; Provenge®)
  2. Cabazitaxel (second generation taxane chemotherapy; Jevtana®)
  3. Abiraterone (second generation androgen synthesis inhibitor; Zytiga®)
  4. Enzalutamide (second generation androgen receptor signaling inhibitor; Xtandi®)
  5. Alpharadin (bone-seeking, alpha particle emitting radioisotope; Xofta®)
- Despite these unprecedented therapeutic advances, prostate cancer remains the third leading cause of cancer-related mortality in Canadian men, accounting for approximately 3,900 deaths annually (www.cancer.ca). In fact, inherent or acquired therapeutic resistance to these novel agents is common, which usually limits the survival benefit to a few months.

New therapies, new challenges

- The approval of several new agents in a short period of time has also generated a number of challenges:
  1. There is a lack of comparative phase III clinical trial data.
  2. There are no validated predictive markers of response that would help in the optimal sequencing of these agents, and there are no definite clinical trial data available on the safety and benefit of treatment combinations.
  3. Health authorities struggle with funding decisions regarding these expensive agents, affecting drug access, in particular for patients without complementary health plans.
- Abiraterone and enzalutamide are very potent, well-tolerated and patient-friendly CRPC therapeutics with an outstanding therapeutic index.
- However, as convenient as the oral route of administration is, in general, it may be associated with added challenges such as: treatment non-adherence, diet-medication interactions, and the risk of drug-drug interactions (DDI), including interactions with complementary and alternative medicines.
- With respect to abiraterone and enzalutamide therapy specifically, the relevance of treatment compliance on therapeutic resistance and CRPC outcome has not yet been studied. On the other hand, DDI have been raised as a safety concern for both agents, although the true scale of this problem is not known to date.

Abiraterone and enzalutamide-associated drug-drug interactions

Both abiraterone and enzalutamide are administered daily without interruption. In addition, the metabolism of these agents is complex, extensive and involves numerous cytochromes and other classes of metabolic enzymes (Table 1).

| Table 1: Pharmacokinetic Characteristics of Abiraterone and Enzalutamide |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Agent           | PK Parameters   | Special Precautions                      | Enzymes Needed for Metabolism | Enzymes Induced | Enzymes Inhibited |
| Abiraterone     | Half-life: 12±5 hours | Hepatic Impairment: Child-Pugh Class A – no dose adjustment; B – do not use C – do not use | CYP3A4, Esterases, SULT2A1 | Strong: CYP17, CYP1A2, CYP2D6, CYP2C8 |
|                 | Feces: 88% Urine: 5% | Renal Impairment: no dose adjustment | | | |
| Enzalutamide    | Half-life: 5.8 days | Hepatic Impairment: Child-Pugh Class A/B – no dose adjustment; C – do not use | CYP2C8 (major), CYP3A4/5 | Strong: CYP3A4 | Strong: CYP2C8 |
|                 | Feces: 14% Urine: 71% | Renal Impairment: CrCl ≥ 30 mL/min – no dose adjustment; CrCl < 30 – caution, not studied | | Moderate: CYP2C9/C19, UGT1A1, CYP2B6 | Moderate to Weak: CYP2C9, CYP2B6, CYP1A2, CYP2D6, BCRP, MRP2 |

Comments: 
- *primary mechanisms of anti-CRPC activity; *Chi et al. (2013) showed that abiraterone co-administration does not affect circulating levels of the CYP1A2 substrate theophylline; 
- conflicting data.

Data extracted from Zytiga® and Xtandi® product monographs, and from the Cancer Care Ontario Drug Formulary (www.cancercare.on.ca/toolbox/drugs/drugformulary).
Concerns about significant DDI are amplified by the fact that CRPC patients are often elderly and frail, which renders drug prescription more challenging, in general. Furthermore, CRPC patients frequently use numerous co-medications for concurrent health conditions, including medications with a narrow therapeutic range such as warfarin and cardiac medications.

DDI may work in opposite ways: abiraterone and enzalutamide may affect drug levels of medications taken for other health conditions, or concurrent medications could affect circulating levels of abiraterone and enzalutamide, thus increasing the risk of side effects (e.g., enzalutamide associated seizures), or undermining their therapeutic benefit.

Postulated DDI are not restricted to metabolic interference, as evidenced by two examples:
1. Abiraterone treatment increases the risk of mineralocorticoid excess. On the other hand, treatment of symptomatic mineralocorticoid excess with aldosterone-blocking agents such as spironolactone or eplerenone may enhance androgen receptor signalling and, thus, CRPC progression.
2. Corticosteroids are commonly used in CRPC patients for a number of indications, including for their palliative and anti-CRPC effects, and for minimizing the risk of mineralocorticoid excess in patients undergoing treatment with abiraterone. On the other hand, recent preclinical evidence suggests that concurrent use of corticosteroids may contribute to enzalutamide treatment resistance in that glucocorticoid pathway activation may be able to bypass androgen receptor inhibition.

### Approaching the scale of the problem

- Public domain DDI databases (e.g., http://www.epocrates.com) are practical for rapid DDI screens during busy clinics.
- As an example, an Epocrates screen of the top 50 dispensed medications in Canada (http://www.imshealth.com) revealed that the co-administration of abiraterone or enzalutamide with a number of top 50 agents may increase the risk of side effects or reduce drug benefit (Table 2).
- Of note, the threshold for flagging potentially harmful DDI is considered relatively low in such database screens. On the other hand, publications addressing DDI of practical relevance are just emerging (abiraterone), or lacking (enzalutamide).
- Pharmacokinetic studies may confirm postulated DDI (i.e., elevation of dextromethorphan levels by abiraterone-mediated inhibition of CYP2D6), but may also question certain concerns (i.e., abiraterone is a strong inhibitor of CYP1A2, yet abiraterone co-administration does not seem to affect circulating levels of the CYP1A2 substrate theophylline).

### Conclusions

- Ultimately, the safe and efficacious administration of agents such as abiraterone and enzalutamide depends on close collaboration between prescribing physicians and pharmacists.
- Identifying potentially harmful drug combinations is just the first step that needs to be followed by searching for treatment alternatives and/or monitoring strategies for early detection of relevant DDI.
- In addition, concerted efforts between all levels of health care providers are essential to optimize treatment adherence, including the upfront identification of patients at risk of non-adherence.

### REFERENCES

References available upon request

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**Table 2: Postulated drug-drug interactions of abiraterone and enzalutamide with top 50 dispensed medications**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Abiraterone Interactions</th>
<th>Abiraterone Comments</th>
<th>Enzalutamide Interactions</th>
<th>Enzalutamide Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/11</td>
<td>Lipitor/ Apo-Atorvastatin</td>
<td>Atorvastatin</td>
<td>No significant interactions</td>
<td>Avoid/Use alternative</td>
<td>Avoid combo or monitor closely: combo may decr. statin levels, efficacy (hepatic metab. induced)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Teva-Amoxicillin</td>
<td>Amoxicillin</td>
<td>No significant interactions</td>
<td>Caution advised</td>
<td>Combo may incr. risk of seizures (additive effects)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Nexium</td>
<td>Esomeprazole</td>
<td>No significant interactions</td>
<td>Avoid/Use alternative</td>
<td>Combo may decr. esomeprazole levels, efficacy (hepatic metab. induced)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Teva-Venlafaxine XR</td>
<td>Venlafaxine</td>
<td>No significant interactions</td>
<td>Caution advised</td>
<td>Combo may incr. risk of seizures (additive effects)</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Adalat XL</td>
<td>Nifedipine</td>
<td>No significant interactions</td>
<td>Monitor/ Modify therapy</td>
<td>Monitor BP: combo may decr. calcium channel blocker levels, efficacy (hepatic metab. induced)</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Ratio-Oxycocet</td>
<td>Oxycodeone - (acetaminophen)</td>
<td>No significant interactions</td>
<td>Avoid/Use alternative</td>
<td>Avoid combo or consider oxycodone dose adjustment: combo may decr. oxycodone levels, efficacy (hepatic metab. induced)</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Tylenol with Codeine #3</td>
<td>Codeine - (acetaminophen)</td>
<td>Caution advised</td>
<td>Combo may decr. codeine efficacy (hepatic conversion to morphine decr.)</td>
<td>No significant interactions</td>
<td></td>
</tr>
<tr>
<td>33/44</td>
<td>Taro-Warfarin/ Coumadin</td>
<td>Warfarin</td>
<td>No significant interactions</td>
<td>Avoid/Use alternative</td>
<td>Avoid combo or monitor INR: combo may decr. warfarin levels, efficacy (hepatic metab. induced)</td>
<td></td>
</tr>
<tr>
<td>36/48</td>
<td>Teva-Metoprolol/ Apo-Metoprolol</td>
<td>Metoprolol</td>
<td>Caution advised</td>
<td>Combo may incr. metoprolol levels, risk of adverse effects (hepatic metab. inhibited)</td>
<td>No significant interactions</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Flomax CR</td>
<td>Tamsulosin</td>
<td>Caution advised</td>
<td>Combo may incr. tamsulosin levels, risk of adverse effects (hepatic metab. inhibited)</td>
<td>No significant interactions</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>Apo-Prednisone</td>
<td>Prednisone</td>
<td>No significant interactions</td>
<td>Caution advised</td>
<td>Combo may decr. corticosteroid levels, efficacy (hepatic metab. induced)</td>
<td></td>
</tr>
</tbody>
</table>