

HOT SPOT

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

 **Sunnybrook**
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner



Volume 19, Issue 1, February 2017

Editorial

By May N. Tsao, MD, FRCP(C)

It is a pleasure to introduce this edition of *Hot Spot*. Doctors Yoo-Joung Ko and Ana Abrahao provide a useful summary on second-line treatment options for advanced pancreatic adenocarcinoma. The importance of primary care physician

roles in providing survivorship care for oncology patients is highlighted by Dr. Toni Barnes. The significance of practical skills needed in healthcare for “cultural competency” is discussed by Dr. Blair Henry, our senior ethicist, and

Dr. Margaret Fitch provides a summary on care for the older patient with cancer. Also, the CME activities are included. On behalf of the editorial team, we thank our contributors and we hope you find these articles interesting.

Primary care physician role in providing survivorship care for oncology patients

By Toni Barnes, MD, FRCPC, Department of Radiation Oncology, Sunnybrook Odette Cancer Centre, University of Toronto

Communication between physicians is important to ensure patient information is relayed during the workup, treatment, follow-up and subsequent transition of patient care. Palliative care and symptom control for patients are often provided by the primary care physician (PCP) during and after cancer treatment. Survivorship care is now being appreciated as an important component of patient care, and one often provided by the PCP.

Traditionally, three patterns of medical care representing increasing levels of involvement by the PCP have been identified: (1) sequential care where the patient receives all medical care from the oncologist after diagnosis; (2) parallel care where the oncologist is responsible for cancer care and the PCP manages other medical issues; and (3) shared care where the PCP and specialist are both involved in cancer care. Shared or parallel care can help ease the transition of primary care from oncologist back to the PCP.

It is important for patients to maintain continuity of care with their PCP while being seen at the cancer centre. The PCP has often been involved in the patients’

care for a number of years, and there is often easier access, less travelling time, and more personalized care than a busy cancer centre. Cancer patients also value their PCP for emotional support, primary medical care, and for coordinating care with other healthcare providers. However, PCPs have identified lack of communication with the oncologist as a major concern in caring for cancer patients.

Survivorship care

The National Cancer Institutes’ definition of a cancer survivor is “from the time of diagnosis, through the balance of his or her life”. There has been a dramatic increase in the number of cancer survivors in the United States, due to rising incidence rates (from the aging population), earlier detection and better cancer treatment. At least half of survivors experience some late effects of cancer treatment. Depression, pain and fatigue are the most commonly reported symptoms. There are often significant psychosocial effects from the cancer diagnosis and treatment. Distress

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can result from the fear of recurrence or death. Returning to work, finances, issues regarding sexuality and fertility are also important issues that need to be addressed. Often overlooked and of importance for long-term survivors is the higher incidence of second primary cancers.

With the increased volume of cancer survivors, a higher proportion of care will be performed by the PCP. PCPs manage other chronic patient conditions and, so, are well equipped to assume routine follow-up care for cancer survivors. PCPs can also facilitate screening and encourage lifestyle modifications to reduce the risk of second primary cancers.

Surveys of PCPs have found they are willing to assume follow-up of cancer patients, and many feel they are better able to provide patients with psychosocial support. However, patient surveys have reported that survivors want their oncologist involved in their follow-up care; often citing the belief their PCP lacked the expertise to deal with their cancer-related issues. Physician surveys have also reported the belief that patients would rather go to their oncologist for routine cancer care. Two randomized trials in breast and colorectal patients found no difference in disease-related outcomes, including survival, for survivorship care administered by PCPs compared to oncologists.

A survey of Canadian PCPs was conducted to assess willingness and time from completion of active treatment that they would prefer to assume exclusive follow-up care of cancer survivors (breast, prostate, colon and lymphoma). This study reported that many PCPs already provide exclusive care to well cancer survivors, especially beyond five years of diagnosis. Two-thirds of PCPs were willing to assume exclusive follow-up care earlier, approximately 2.5 to 3.5 years after completion of active treatment. The most useful modalities to facilitate care included: (1) a patient-specific letter from the specialist; (2) printed guidelines; and (3) expedited routes of re-referral, and expedited access to investigations for suspected recurrence.

Palliative care

Patients with non-curable disease, and treated with palliative intent for symptom management have somewhat different survivorship needs. These focus on pain and symptom management for themselves and their families. The PCP can play an important role in providing end-of-life

care and, again, excellent physician communication and collaboration is vital in ensuring optimal patient care.

PCPs can maintain continuity of care with their patients through a model of shared or parallel care, as patients pass through the cancer system. For the population at the end of life, emergency room visits and hospital deaths have been shown to decrease for cancer patients maintaining higher continuity of care with their PCP. While most PCPs are willing to care for cancer patients at the end of life, a proportion may not want to, or feel comfortable with providing palliative care. A palliative care team should then be consulted to assist with pain and symptom management. In 2012, the American Society of Clinical Oncology (ASCO) released a Provisional Clinical Opinion recommending consideration of combined standard oncology care and palliative care early in the course of illness for any patient with metastatic cancer and/or high symptom burden to improve quality of life for both patients and caregivers.

Reports have shown that cancer patients experience a high symptom burden throughout their disease trajectory. Symptoms and needs were not routinely screened for and managed in cancer patients attending cancer clinic visits in the past. Therefore, in 2006, Ontario implemented Edmonton Symptom Assessment System (ESAS) symptom screening for all outpatient visits to Regional Cancer Centres. The goal was to prompt earlier identification, documentation and communication of patients' symptoms to improve the patients' experience across the cancer journey. In a 2013 survey of 3,660 patients, 92% "strongly agreed" or "agreed" that the ESAS was important, as it helped their healthcare team to know their symptoms and severity.

Conclusions

Collaboration and communication between oncologists and PCPs helps provide optimal care throughout a patient's cancer journey. PCPs will play an important role in providing care for the growing population of cancer survivors. Providing physician education and survivorship care plans for patients can aid in transition of medical care back to the PCP upon discharge from the cancer centre. For patients at the end of life, palliative care needs may be provided by the PCP and/or in consultation with a palliative care team.

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A case for enhanced cultural competency in a post-multicultural world

By Blair Henry, D. Bioethics, Senior Ethicist, Sunnybrook Health Sciences Centre; Assistant Professor, University of Toronto

In the mid-twentieth century, multiculturalism, as a social policy in North America began to flourish. It was primarily enabled in our modern era as a result of two key ideological and historical events: the ending of the Second World War (1945), and the African-American civil rights movement in the 1950–60s.¹ For a time, the ideals of multiculturalism meant enhanced tolerance and acceptance for racial and ethnic equality.²

However, by the turn of the twenty-first century two critical changes began happening that altered how multiculturalism is being perceived.³ Some report that multiculturalism is in a state of retreat in certain parts of the world—some fearing diversity has gone too far and is threatening “our way of life”—seeing the rise of populist right wing groups and ideologies. Not unlike those being expressed south of the border by Trump supporters in the recent presidential election.

Some critique multiculturalism as just being a “feel good” construct that enables to us to celebrate diversity and ethno-cultural expressions with little socio-economic integration. One British critic feels that we have devolved into what he calls a “3-S model of multiculturalism: samosas, steel drums and saris!”, i.e., putting culture on display without substance to support it in social policy, ultimately leading to greater unemployment, marginalization, and the fostering of a perception of minorities as ‘other’.

These changes were seen to herald, by some sociologists and anthropologists, a new post-multicultural era. What this really means for the future of cultural diversity remains untested. However, we now can see that the coexistence of multiple cultures within some countries is at the same time a source of enrichment, stress and potential conflict.²

Within this new domain being called post-multiculturalism, some have come to see that in the past 15 years a new and stronger political form of multiculturalism (citizenship) has arisen to redress systemic inequalities in healthcare. New programs now aim to promote quality care for ethnic and racial minorities by bringing attention to health disparities, fostering more representative work force diversity, and increasing education and training in cultural competence.⁴

Canada—a country of immigrants

Cultural diversity has played an important role in Canadian history. International immigration and demographic shifts have rendered Canada as one of the most successful, socially diverse societies in the world. Canada is not a cultural “melting pot”, but a place

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Table 1: Canadian Statistics on Cultural Diversity 2011

<p>Immigration In 2011, many of the 6.8 million foreign-born individuals have lived in Canada. Around 1,162,900 foreign-born people arrived in Canada between 2006 and 2011. These recent immigrants made up 17.2% of the total foreign-born population and 3.5% of the total population in Canada. Among the G8 countries, Canada had the highest proportion of foreign-born population (20.6%).</p> <p>Among the recent immigrants who arrived between 2006 and 2011, the largest share, 56.9% or about 661,600 individuals, came from Asia (including the Middle East). Just over 6 in 10 (62.5%) of these recent immigrants chose to settle in the three largest CMAs—Toronto, Montréal and Vancouver.</p>	<p>Ethnic origin Ethnic origin is another aspect of the nation’s ethno cultural diversity. Ethnic origin refers to the ethnic or cultural origins of the respondent’s ancestors. The ethnic origin most often reported was Canadian, cited by about 10,563,800 people, either alone or with other origins. It was followed by English, French, Scottish, Irish and German. The other ethnic origins that surpassed the 1-million mark were: Italian, Chinese, First Nations (North American Indian), Ukrainian, East Indian, Dutch and Polish. Just over 1,369,100 people reported a First Nations (North American Indian) ancestry, alone or with other origins, while around 447,700 people reported Métis ancestry, alone or with other origins, and around 72,600 people reported Inuit ancestry, alone or with other origins.</p>
<p>Visible minority population In 2011, nearly 6,264,800 people identified themselves as a member of the visible minority population. They represented 19.1% of Canada’s total population. Combined, the three largest visible minority groups—South Asians, Chinese and Blacks—accounted for 61.3% of the visible minority population. They were followed by Filipinos, Latin Americans, Arabs, Southeast Asians, West Asians, Koreans and Japanese.</p> <p>In 2011, 1,567,400 individuals identified themselves as South Asian, the largest visible minority group. They represented one-quarter (25.0%) of the total visible minority population. The second largest group was Chinese, who numbered just over 1,324,700. They made up 21.1% of the visible minority population. Just under 945,700 individuals identified themselves as Blacks, the third largest group. They made up 15.1% of the visible minority population.</p>	<p>Knowledge of languages Most (93.5%) of the foreign-born population was able to converse in English and/or French.</p> <p>Among all immigrants, 61.2% were able to converse in English or French and one or more non-official language(s).</p> <p>Religions in Canada The NHS collected information on religious affiliation, regardless of whether respondents practised their religion. The largest faith in Canada was Christianity, about two-thirds of Canada’s population (67.3%), of which Roman Catholics were the largest group, representing 38.7% of Canada’s. Nearly one-quarter of Canada’s population (23.9%), had no religious affiliation.</p> <p>In 2011, about 7.2% of Canada’s population: people who identified themselves as Muslim made up 3.2% of the population, Hindu 1.5%, Sikh 1.4%, Buddhist 1.1% and Jewish 1.0%.</p>
<p>Citizenship More than three-quarters (78.3%) of the total population were Canadian citizens by birth. Another 15.8% were Canadian by naturalization (that is, the process through which immigrants acquire Canadian citizenship), while the remaining 6.0% did not have Canadian citizenship.</p>	<p>Second generation: Canadian-born children of immigrants In 2011, 17.4% of the total population would consider themselves to be second generation (described as having one or more parent born outside Canada and over half 54.8% of the group had both parents born outside of Canada).</p>

A case for enhanced cultural competency in a post-multicultural world

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where people are encouraged to retain their cultural, linguistic and religious heritage.^{5,6}

Table 1 provides an overview of Canadian diversity based on the 2011 Statistics Canada census report. This trend shows no sign of changing; in fact, the numbers are increasing. In 2012, Canada welcomed a record number of immigrants for its seventh consecutive year, with 257,515 newcomers entering the country. In opening its doors to immigration, Canada has created a society of mixed languages, cultures and religions.⁷

What is missing from the census data presented are the unique statistics of the LGBTQ community, as well as the First Nations and Inuit people. Cultural sensitivity and competency needs are equally important in the provision of healthcare to these communities as any other.

Why is culture (and cultural competency) important in oncology

We lack a good working definition for the term culture. In fact, confusion persists about terms such as race, ethnicity and culture.⁸ Similarly, our individual and collectivist understanding of the relationship between culture, health, and illness are poorly understood. This can be especially problematic in the field of oncology, where patients and healthcare providers deal with such a challenging and potentially stigmatizing (culturally) illness such as cancer.²

Cultural sensitivity and awareness directly impacts health disparities. By example, a study published in 2009 identified that subconscious racial biases exist among physicians, leading to discriminatory attitudes, primarily with regard to communication with patients and families of different skin colour or culture.⁹

Evidence also supports findings that suggest cultural differences, compounded with socioeconomic factors, are a major determinant of unequal access to cancer prevention, screening, optimal standard care, enrolment in clinical trials, effective pain control, and adequate supportive end-of-life care.¹⁰⁻¹²

Cultural beliefs and attitudes impact healthcare professionals and healthcare systems when encountering issues related to health, illness, and death. “We live embedded in our own culture and its prejudices, and we practise in a specific culture of medicine, which in western countries is largely on the basis of a biomedical notion of disease, as opposed to a holistic one of illness”.² This points to a need for enhanced self-awareness and knowledge of one’s own cultural biases as key elements to consider in cross-cultural medical encounters.²

What is cultural competency?

The seminal definition for cultural competence delineates it as a set of “congruent behaviors, attitudes, and policies that come together in a system, agency, or among professionals that enables the system or professionals to work effectively in cross-cultural

situations.¹³ See Figure 1 for a representation of the process components to cultural competency.¹⁴

However, the notion of cultural competence—as being merely a set of practical skills needed to properly deal with patients and families belonging to different cultures—is evolving. Cultural competence is increasingly considered a key factor, both at individual and system levels, that may contribute to our efforts to eliminate disparities in healthcare and reduce the burden of unequal cancer treatment in our community.^{15,16}

Evidence supporting cultural competency

Several systematic reviews on the application of cultural competency in healthcare settings have reported positive effects on care and overall patient satisfaction. In summary the following findings have been noted:

- Improves the knowledge of health professionals (17 of 19 studies demonstrated a beneficial effect)¹⁷
- Improved the attitudes and skills of health professionals (21 of 25 studies evaluating attitudes demonstrated a beneficial effect and 14 of 14 studies evaluating skills demonstrated a beneficial effect)^{17,18}
- Impacts patient satisfaction (3 of 3 studies demonstrated a beneficial effect)¹⁷
- Poor evidence that cultural competence training impacts patient adherence (although the one study designed to do this demonstrated a beneficial effect)¹⁷
- No studies that have evaluated patient health status outcomes¹⁸

Conclusion

The context of cultural competency is changing. However, its primary aim of accommodating diversity remains central. More work at both the individual and system level is needed to address this key element to successful patient- and family-centred care.

REFERENCES

References available upon request

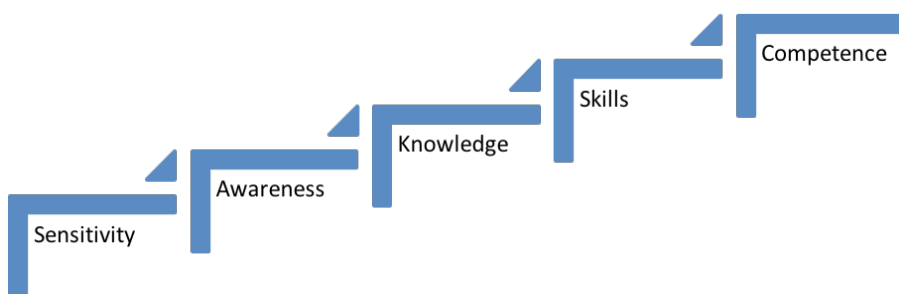


Figure 1: Cultural competence as a process

Focusing on care for the older adult with cancer

By Margaret Fitch, RN, PhD

Cancer is predominantly a disease of older adults. The majority of cancers are diagnosed in individuals over the age of 65.¹ With the growing population of older adults in Canada, there is an increased interest in older adults with cancer and understanding their care requirements both from disease-oriented and psychosocial perspectives.

The older adult population is heterogeneous; their health status ranges from fit to frail and is not necessarily related to chronological age. However, older adults are not well represented in clinical trials designed to find new treatments or studies to document supportive care needs. As a result, there are gaps in understanding about best treatment approaches and ways to support older adults during and after treatment. Collaboration between oncology and gerontology specialties is recommended to improve care delivery to this group of individuals.

Three recent studies have added interesting perspectives to the dialogue about improving care for this population. The first is an evidence synthesis completed under the auspices of the Canadian Partnership Against Cancer (2016).² This review was completed to understand the current state of oncology care for older adults in three areas: treatment and research for older adults with cancer, training of healthcare providers, and policies and programs for older adults. The review affirmed that:

- Older adults are under-represented in clinical trials and significant gaps do exist in our knowledge about how cancer and cancer treatment affects them. Barriers need to be reduced that limit their participation in future trials.
- Given the heterogeneous nature of the population, it is critically important that clinicians assess these differences in order to provide individualized care. Many studies support the use of comprehensive geriatric assessments (CGAs) to help clinicians identify underlying, undetected issues that might affect treatment and classify patients as fit, vulnerable or frail.³⁻⁶
- CGAs can be used to plan interventions to mitigate effects of treatment, and plan further investigations and assessments of possible deficits. The domains

included for assessment are functional status, cognition, social support, objective physical performance, psychological status (anxiety and depression), nutrition, comorbidity, and polypharmacy.⁴

- With regard to social support, an integral part of the assessment of the older adults, attention ought to include caregiver burden and evidence of actual social support in the past. Recommendations for care processes include referral to social work, transportation assistance, nursing/home health, caregiver management, home safety evaluation, support groups, referral to psychology/psychiatry, and spiritual care.⁴
- There is no one model for organizing care of older adults; two existing Canadian Centres of Excellence include:
 - Segal Cancer Centre, Jewish General Hospital, Quebec. Oncology and Aging Program /Geriatric Oncology Clinic
 - University Health Network, Toronto/General Internal Medicine (GIM) and Geriatrics.

The second study by Puts et al. (2016)⁷ explored the perspectives of older adults regarding their participation in clinical trials. Sixty older adults attended a public meeting and 55 attended an in-depth focus group session to discuss this topic. The participants stated clearly that older adults ought to be involved in research to ensure clear understanding about the most effective interventions required for their care. Somewhat contrary to expectations, they also expressed interest in becoming research team members and being involved in the research process if this could benefit them, other patients, and families. Participants identified several factors that would facilitate their participation on research teams: flexibility in time and location, accessibility to computer technology, transportation support, material translation, short training sessions, and opportunities for peer support. Their preference was to have meetings with the research team in face-to-face situations.

Finally, the third study of interest was conducted to understand more about the influences on older adults when making

their decision to undergo a course of chemotherapy.⁸ Semi-structured interviews were held with 29 adults aged 70 and older with advanced prostate, breast, colorectal, or lung cancer and 24 of their family members. The sample was stratified by age (70–79, 80+) and all interviews were analyzed using thematic analysis. There was no difference in the treatment decision-making influences based on age. Most older adults in this study thought they ought to have the final say in the treatment decision, but strongly valued the view of their oncologist. ‘Trust in my oncologist’ and ‘chemotherapy as the last resort to prolong life’ were the most important reasons to accept treatment. Family members indicated the need to improve communication between them, the patient and healthcare providers, especially around the goals of treatment. Co-morbidity and potential side effects did not play a major role in the decision-making.

We have a great deal to learn about providing person-centred care to older adults with cancer. But beginning steps can be taken at the point of care by careful listening and understanding the perspectives of those under our care. Suggestions for improving care offered by older adults⁷ who have been cancer patients include:

- More discussion about what is to happen next (i.e., appointments, transportation, financial costs) and allow time for them to arrange to bring someone with them
- More time during appointments to allow for questions to be asked
- Clarification about medication terms
- Nurses taking more time to talk and be able to provide support
- Assign a consistent person to help navigate the complex and confusing system, especially for those who do not speak English
- More continuity in staff support (i.e., same person on various office/clinic visits)
- Clearly identified numbers to call for help when necessary; someone on the telephone line to answer questions or respond to concerns.

REFERENCES

References available upon request

Continuing Medical Education

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

- **March 16–18, 2017.** 6th ICHNO: International Conference on Innovative Approaches in Head & Neck Cancer. Barcelona, Spain. <http://www.esmo.org/Conferences/ICHNO-2017-Head-Neck-Cancer>
- **March 28–31, 2017.** Oncology Opinion Series in GI Cancer with Dr. Marc Peeters: Left vs Right-Sided Colorectal Tumours: Does Location of the Primary Impact Clinical Practice? Various Canadian Cities. <http://www.oncologyeducation.com/events/upcoming-events/oncology-opinions-gi-cancer-featuring-dr.-marc-peeters/>
- **April 7, 2017.** Best of GU and GI Cancers Summit Canada 2017. Parkview Manor, Toronto, Ontario. <http://www.oncologyeducation.com/events/upcoming-events/best-of-gu-gi-summit-2017/conference-home-2017/>
- **May 8–9, 2017.** World Health Summit (WHS) Regional Meeting—North America. Montreal, Palais des congrès de Montréal, Montréal, Québec, Canada. Institut de recherches cliniques de Montréal (IRCM) / Montreal Clinical Research Institute + Université de Montréal. <https://www.ircm.qc.ca/>
- **May 18–20, 2017.** EAPC 2017, 15th World Congress of the European Association for Palliative Care, Progressing Palliative Care. Madrid, Spain. <http://www.eapc-2017.org/> <http://eapc2017congress.org>
- **May 26–27, 2017.** BCHPCA's Conference 2017, British Columbia Hospice and Palliative Care Association, Extending the Circle of Compassion. Radisson Vancouver Airport Hotel, Richmond, British Columbia. <https://bchpca.org/>
- **June 2–6, 2017.** ASCO Annual Meeting, American Society of Clinical Oncology. American Society of Clinical Oncology McCormick Place, Chicago, Illinois. <https://am.asco.org/>

- **June 16, 2017.** Best of ASCO Toronto 2017. Toronto, Ontario. <http://www.oncologyeducation.com/events/upcoming-events/best-of-asco-toronto-2017/>
- **June 22–24, 2017.** MASCC/ISOO Annual Meeting on Supportive Care in Cancer. Washington DC, USA. <http://mascc2017.com/>
- **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, Canada. <http://palliativemanitoba.ca/events/conference/>
- **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.gi>
- **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>

CME COURSES

NEW ACCREDITED COURSE AVAILABLE: Optimizing Outcomes in Advanced Prostate Cancer

This course will review the clinical implications of prostate cancer heterogeneity, data on sequencing drugs in mCRPC, and will also focus on recent

CRPC guidelines and advanced hormone-sensitive disease. *This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada. This activity was approved by the Canadian Society of Internal Medicine for a maximum of 1.5 hours.* 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 course is accredited until June 15, 2017.** <http://www.oncologyeducation.com/events/cmecourses/currently-accredited-courses/optimizing-outcomes-in-advanced-prostate-cancer/>

NEW ACCREDITED COURSE AVAILABLE: Targeted Therapies in the Management of Non-Small Cell Lung Cancer: A Multi-Disciplinary Approach

The multi-disciplinary approach to this course provides discussion on an array of topics and perspectives related to NSCLC management including diagnosis, various treatment options and pertinent case studies. As a result, this course is relevant to a variety of oncology healthcare providers. *This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada. This activity was approved by the Canadian Society of Internal Medicine for a maximum of 2 hours.* 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 course is accredited until May 11, 2017.** <http://www.oncologyeducation.com/events/cmecourses/currently-accredited-courses/targeted-therapies-in-the-management-of-non-small-cell-lung-cancer/>

Second-line treatment options for advanced Pancreatic Adenocarcinoma

HOT SPOT

By Dr. Ana Abrahao and Dr. Yoo-Joung Ko, Sunnybrook Odette Cancer Centre, University of Toronto

Background

- Pancreatic adenocarcinoma is the fourth leading cause of cancer death in North America, with a five-year survival rate less than 5%.¹
- Surgery remains the only chance of cure, but fewer than 20% of patients present with resectable disease.²
- Systemic therapy remains the mainstay of treatment for locally advanced or metastatic disease.
- FOLFIRINOX (folinic acid, irinotecan, oxaliplatin and 5-fluorouracil) and Gemcitabine + nab-paclitaxel have emerged as new first-line treatment options for those with a good performance status:
 - The PRODIGE³ trial showed a median overall survival of 11.1 months with FOLFIRINOX versus 6.8 months with gemcitabine.
 - The MPACT⁴ trial demonstrated a median overall survival of 8.5 months for the combination of gemcitabine with nab-paclitaxel.

- Despite new treatments, disease progression on first-line therapy is inevitable and no second-line therapy has yet been widely accepted as standard therapy, although currently, gemcitabine-based or fluoropyrimidine-based chemotherapy are often used.
- As many as 40% of patients may be well enough to receive additional lines of therapy.

Second-line clinical trials in advanced pancreatic cancer after failure to first-line treatment with Gemcitabine OFF regimen studies

- In 2009, a single-arm phase II study investigated the efficacy and safety of the OFF regimen. The OFF regimen consisted of a six-week cycle of folinic acid plus 5-fluorouracil (2 g/m² infusion in 24h) administered in days 1, 8, 15 and 22 plus oxaliplatin (85mg/m²) administered in days 15 and 22.
- 37 patients were included and the study showed overall survival of 22 weeks and PFS of 12 weeks with an acceptable toxicity profile.⁵
- The German CONKO-study group published a phase III trial. 46 patients with metastatic pancreatic adenocarcinoma gemcitabine refractory were randomized (1:1) to receive OFF regimen versus best supportive care (BSC).
- Although the patient cohort was small due to the premature closure (lack of acceptance of BSC by the patients and physicians), the trial demonstrated advantage

in OS with second-line chemotherapy over BSC (4.8 months versus 2.3 months p=0.0008).⁶

- In the phase III CONKO-3 trial, 168 patients were randomized (1:1) to receive OFF regimen versus active control arm with 5-fluorouracil single agent (FF) in patients with metastatic pancreatic adenocarcinoma refractory to gemcitabine therapy.
- Improvement in overall OS with OFF regimen compared with FF (5.9 months versus 3.3 months p = 0.010), as well as improvement in progression-free survival (2.9 months versus 2.0 months p= 0.019).
- Toxicity rates were similar between arms, however neuropathy grades 1 and 2 were reported in 38.2% and 6.7% in the OFF and FF regimens, respectively (p <0.001).⁷

Phase III study of mFOLFOX: PANCREOX

- 108 patients were randomized (1:1) to receive modified FOLFOX 6 regimen (leucovorin, oxaliplatin and 5-fluorouracil in 46h infusion) every two weeks or biweekly infusional leucovorin and 5-Fluorouracil (46h infusion).
- The trial showed detrimental effect of oxaliplatin in patients with gemcitabine refractory disease in overall survival (6.1 months versus 9.9 months p=0.02) and quality of life.⁸
- Increased toxicity was observed with the addition of oxaliplatin, with grade 3/4 adverse events occurring in 63% of patients who received mFOLFOX6 and

11% of those who received FU/LV. More patients in the mFOLFOX 6 arm withdrew from the study due to AEs than from the FU/LV arm (20% versus 2%).

- Use of postprogression therapy was significantly higher in the FU/LV arm (25% versus 7%; p = .015).
- No significant differences were observed in time to deterioration on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 global health scale.

Phase III study of liposomal irinotecan: NAPOLI

- Irinotecan has shown activity as a single agent or in combination with other drugs in patients with refractory pancreatic adenocarcinoma in previous small studies.
- Nanoliposomal irinotecan comprises irinotecan free-base encapsulated in liposome nanoparticles. The liposome keeps longer the active irinotecan metabolite in the circulation, prolonging the intratumoral level.
- The NAPOLI trial was initially started as a randomized two-arm study, but evolved to a three-arm study with the addition of a combined liposomal irinotecan with infusional 5-FU. Eligible patients had to have progressed on prior gemcitabine or gemcitabine-based therapy. The study randomized 417 patients (1:1:1) to receive either nanoliposomal irinotecan plus 5-fluorouracil and folic acid (Nano-Irino + FF), nanoliposomal irinotecan monotherapy (Nano-Irino) or 5-fluorouracil and folic acid (FF).⁹

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Table 1: Napoli Trial outcomes: PFS (progression-free survival), OS (overall survival) and ORR (overall response rate)

	Nano-Irino + FF (N = 117)	Nano-Irino (N = 151)	FF (N = 149)	HR
PFS (month)	3.1	2.7	1.5	0.67 (p=0.012)
OS (month)	6.1	4.9	4.2	0.56 (p=0.0001)
ORR (%)	19%*	1%*	6%*	

* Nano-Irino + FF vs. Nano-Irino (difference 15.4 percentage points, 95% CI 8.5–22.3; p<0.0001)
 Nano-Irino vs. FF (difference 5.3 percentage points, 95% CI 1.3–9.3; p=0.02)

- The most frequent Grade ≥ 3 adverse events included neutropenia, fatigue and gastrointestinal side effects including nausea and vomiting.
- Onivyde® was approved by the FDA in October 2015 and is currently under review by Health Canada.

Other studies with target therapy including JANUS-1

- The efficacy of drugs targeting different pathways has been evaluated, including targets in angiogenesis (bevacizumab), MEK1/2 (selumetinib), JAK-STAT (ruxolitinib) and EGFR (gefitinib and erlotinib), and failure to improve outcomes.
- The only target treatment approved by FDA is erlotinib. It produces a small benefit in OS in first-line setting combined with gemcitabine¹⁰ and also demonstrated activity in second-line treatment with OS of 4.1 months.¹¹
- In the phase II JANUS-1 Trial,¹² Ruxolitinib achieved promising outcomes, but the subsequent phase III trial was closed prematurely due to lack of superiority.
- Other promising studies are evaluating the use of olaparib (a poli ADP-ribose polymerase inhibitor) in BRCA1 and BRCA2 mutated patients in second line scenario.¹³

Second-line clinical trials in advanced pancreatic cancer after failure to first-line treatment with FOLFIRINOX

- Fewer studies have addressed therapies after treatment failure to first-line FOLFIRINOX and the optimal therapy has not been established yet. Most of the studies in this scenario are small and non-prospective including gemcitabine-based treatment as a single-agent therapy or in combination with nab-paclitaxel.
- The AGEO Trial, a single-arm, prospective study, enrolled 47 patients to receive gemcitabine plus nab-paclitaxel after disease progression to FOLFIRINOX. The trial exhibited an OS and PFS of 8.8 months and 5.1 months respectively with manageable side effects. Since the start of first-line chemotherapy OS was 18 months.

Immunotherapy

- A variety of strategies have been studied for immunotherapy and gastrointestinal malignances: vaccines, immune checkpoint blockade, anti-CTL4, anti-PD1, and anti-PDL1 inhibitors and no encouraging outcomes have been obtained so far.^{14,15}

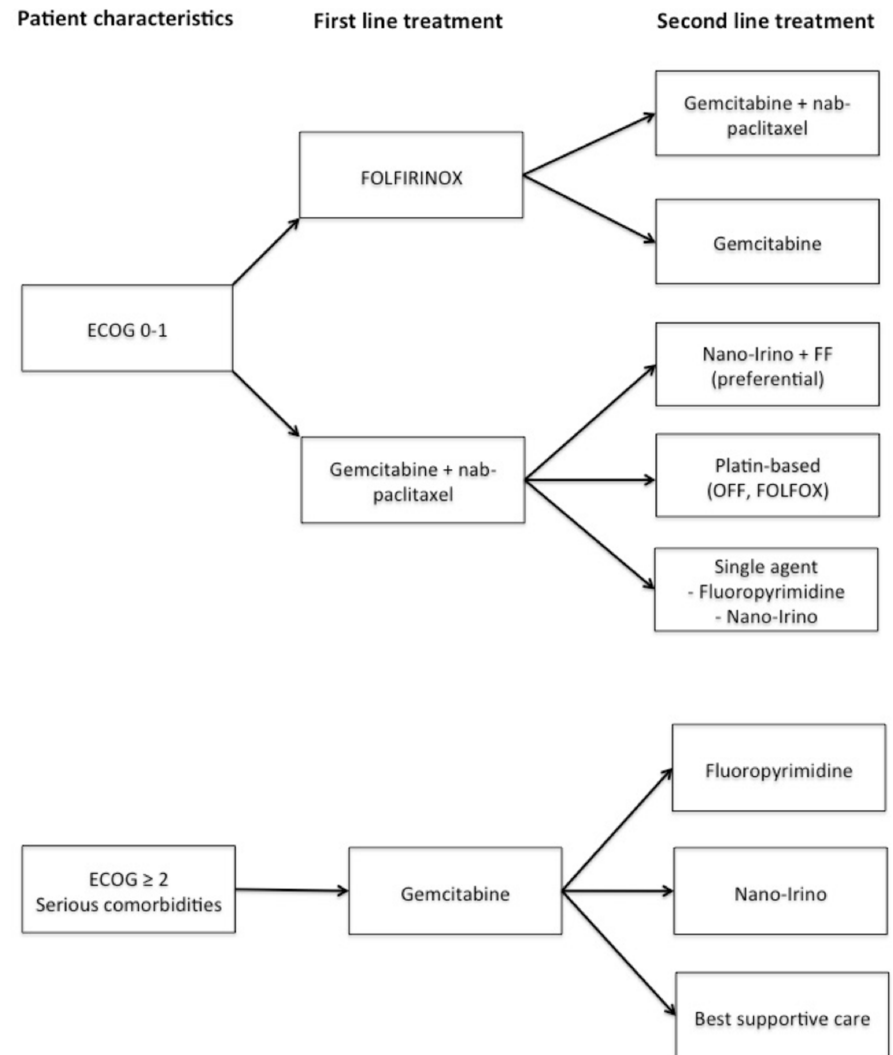


Figure 1: Proposed algorithm of pancreatic cancer therapy