COLORECTAL CANCER RESEARCH & PRACTICE UPDATES

Colorectal Cancer Canada curates monthly Research & Practice Updates to inform clinicians, patients and their loved ones of new innovations in colorectal cancer care. The following updates extend from March 9th 2020 to April 30th, 2020 inclusive and are intended for informational purposes only.

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Pathological response seen with neoadjuvant immunotherapy in early stage colon cancer
20 April 2020

The ongoing NICHE study is investigating the safety, feasibility, activity and immunological activity of short-term preoperative ipilimumab/nivolumab with or without celecoxib among patients with non-metastatic, localized colon cancers. Primary results from the study have already demonstrated promising pathological responses, i.e. the absence of all signs of cancer in tissue samples, associated with neoadjuvant immunotherapy among patients with mismatch repair (MMR)-deficient and MMR-proficient early stage colon cancer. The researchers noted the impressive 100% response rate among patients with MMR-deficient tumours, a patient group that rarely demonstrates complete or near-complete responses to any treatment. Among all 40 patients with non-metastatic colon cancer treated with neoadjuvant immunotherapy, treatment was well tolerated. The study findings highlight the importance of testing at all stages of colorectal cancer for microsatellite instability high status (MSI-H). When a patient is MMR deficient, the role of immunotherapy could be considered. The NICHE study will continue, involving a greater number of patients in the future and monitoring them for at least 3 years to examine the durability of responses to treatment.

FDA approves Braftovi with Erbitux for metastatic colorectal cancer subset
9 April 2020

The FDA has approved the use of encorafenib in combination with cetuximab for adults with previously treated BRAF-V600E-mutant metastatic colorectal cancer (mCRC). Encorafenib (Braftovi) is an oral small molecule kinase inhibitor that targets BRAF V600E. Cetuximab (Erbitux) is an epidermal growth factor receptor inhibitor. The FDA approval was based on results from the phase III BEACON CRC trial which involved patients with BRAF V600E-mutant mCRC who had progressed after one or two prior treatment regimens. The encorafenib-cetuximab combination achieved significantly longer median overall survival and median progression-free survival compared to the control group. This combination treatment provides a promising option for patients with BRAF mutations, which occur in about 15% of patients with mCRC and result in poor prognosis.

Mature follow-up of BEACON CRC study reports quality-of-life measures and survival outcomes
March 25 2020

Among patients with previously treated metastatic colorectal cancer (mCRC) with BRAF V600E mutations, results from the phase III BEACON CRC study demonstrated the benefit of combining two or three targeted agents compared to the standard of care. With longer-term follow-up, combination treatments have also demonstrated a benefit in maintaining quality of life during treatment. Overall survival for the doublet therapy (encorafenib + cetuximab) improved by about a month at mature
follow-up (thirteen months), with a final median overall survival of 9.3 months for the triplet therapy (Encorafenib+cetuximab+binimetinib) and 9.3 months for the doublet, compared to 5.9 months for the control. By several international quality-of-life measures, both the doublet and triplet regimens significantly extended the time to deterioration of quality of life. On the Patient Global Impression of Change scale, more than 20% of patients in the doublet and triplet arms said they were “very much improved” compared to 10% of those in the control arm.

Reintroduction of FOLFOXIRI plus bevacizumab in patients with metastatic colorectal cancer
March 31 2020

Results from the phase III TRIBE2 trial found that reintroduction of FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) plus bevacizumab after progression on first-line treatment was associated with improved progression-free survival, compared to modified FOLFOX6 (fluorouracil, leucovorin, and oxaliplatin) and FOLFIRI (fluorouracil, leucovorin, and irinotecan) doublet treatment in combination with bevacizumab among patients with previously untreated metastatic colorectal cancer (mCRC). First-line FOLFOXIRI plus bevacizumab followed by the reintroduction of the same regimen after disease progression appears to be a promising therapeutic strategy compared to sequential administration of chemotherapy doublets in combination with bevacizumab among patients with mCRC.

COVID-19 AND COLORECTAL CANCER

Cancer care “transformed in space of a month” due to pandemic
16 April 2020

Due to the COVID-19 pandemic, approaches to oncology care and accepted norms of cancer care delivery have been transformed. One of the greatest changes has been the rapid move toward telehealth solutions. While certain situations in oncology demand the presence of the patient and the doctor, other situations such as follow-up visits or getting results from exams and tests could now become a telehealth reality.

Another important impact of the pandemic is the tipping of the risk-benefit ratio away from treatments that have a marginal effect on quality or quantity of life, forcing an “elimination of low-value treatments that were identified by the Choosing Wisely campaign”, an initiative that promotes patient-physician conversations about unnecessary medical tests and procedures. For example, many metastatic solid
tumours do not respond to chemotherapy in the third line setting, where survival has been shown to improve by barely a few weeks. In these cases, oncologists are advising support care instead. Despite changes such as these, cancer treatments that do have the potential to cure and cannot be safely delayed are continuing, as certain cancers are likely more lethal than COVID-19.

Cancer patients who do not fit into the above-mentioned categories remain the greatest treatment challenge during the pandemic, where a delay in treatment would have a moderate clinically important adverse influence on quality of life and survival. In such cases, oncologists are attempting to prescribe regimens that carry lower risks of requiring hospitalizations due to toxicity or complications.

Colorectal cancer: proposed treatment guidelines for the COVID-19 era

3 April 2020

Doctors David and Rachel Kerr, specialists in gastrointestinal cancers at the University of Oxford, designed provisional guidelines for the use of chemotherapy in colorectal cancer patients during these times of the COVID-19 pandemic. Their aim in creating these guidelines was to reduce the comorbidity of chemotherapy and decrease the risk of patients dying from COVID-19 compared to the potential benefits of receiving chemotherapy. Furthermore, the guidelines were created in such a way to decrease the total number of patients receiving chemotherapy, especially in the adjuvant setting, and reduce the overall immune impact of chemotherapy on these patients. To view the complete table of guidelines for colorectal cancer treatment, access the full article below.

Patients with COVID-19 may experience GI symptoms, possible fecal-oral transmission

6 March 2020

Results from two studies published in Gastroenterology examined the gastrointestinal symptoms and possible fecal-oral transmission in patients with COVID-19. Two laboratories from China reported that live COVID-19 virus was successfully isolated from patients’ stool. Using laboratory assays, researchers found that the ACE2 protein, a cell receptor for the COVID-19 virus, is abundantly expressed in specific cells of gastric, duodenal and rectal mucosa, indicating a potential means of entry of the COVID-19 virus into host intestinal cells. Before respiratory symptoms, some patients with COVID-19 also present with diarrhea, nausea, vomiting and abdominal discomfort. When researchers examined the stools of patients who tested positive for COVID-19, over 50% tested positive for COVID-19 RNA in the stool sample, with 44% of patients presenting as COVID-19-positive in stool even after they demonstrated negative in respiratory samples. These findings are reminders that the digestive system may serve as an alternative route of infection and dissemination of the virus, especially when people are in contact with asymptomatic carriers or individuals with mild gastrointestinal symptoms who may have been neglected at early stages of the outbreak.
Guidelines on delaying cancer surgery during COVID-19

26 March 2020

As hospitals are forced to dedicate their resources to treat COVID-19 patients, cancer surgeries may need to be delayed. The American College of Surgeons (ACS) notes that most surgeons have suspended all elective surgeries in the midst of the pandemic, making room for the care of critically ill patients during this time. The ACS has developed new clinical guidelines for the triage of elective surgeries and includes recommendations that are specific to certain cancer types including colorectal, and are organized into three phases of pandemic that reflect the local COVID-19 situation (semi-urgent, urgent, all hospital resources are routed to COVID-19 patients). The full guidelines are available in the link below.

READ THE FULL ARTICLE

How is oncology adapting to COVID-19?

20 March 2020

Perspectives from American and British oncologists on how their oncology practice is changing during the pandemic.

Re: shifting non-urgent follow-up visits to telemedicine

Kathy Miller, MD, Associate Director of Indiana University Simon Cancer Center: We are reviewing our clinic schedules and identifying "routine" follow-up patients who can be rescheduled. When patients are contacted to reschedule, they are asked if they have any urgent, immediate concerns that need to be addressed before the new appointment. If yes, they are offered a virtual visit.

Don Dizon, MD, Director of Women's Cancers, Lifespan Cancer Institute; Director of Medical Oncology, Rhode Island Hospital: We have started to do this in preparation for a surge of people with COVID-19. Patients who are in long-term follow-up (no evidence of disease at 3 years or longer, being seen annually) or those in routine surveillance after curative treatment (that is, seen every 3 months) as well as those being seen for supportive care–type visits, like sexual health or survivorship, are all being contacted and visits are being moved to telehealth.

Re: delaying or cancelling cancer surgeries

Ravi B. Parikh, MD, MPP, Medical oncologist at the University of Pennsylvania and the Philadelphia VA Medical Center: The University of Pennsylvania has taken this seriously. We've canceled all elective surgeries, have ramped up our telemedicine (video and phone) capabilities significantly, are limiting our appointments mostly to on-treatment visits, and have been asked to reconsider regular scans and reviews.

Dizon: We have not done this. There are apparently differences in interpretation in what institutions might mean as "elective surgeries." At our institution, surgery for invasive malignancies is not elective. However, this may (or will) change if resources become an issue.
Lidia Schapira, MD, Associate Professor of Medicine and Director of Cancer Survivorship at the Stanford Comprehensive Cancer Institute: Delaying elective surgery is something that hospitals here have already implemented, and I imagine that this trend will spread. But it may be difficult to decide in situations that are not exactly "life-saving" but where an earlier intervention could preserve function or improve quality of life.

Mark A. Lewis, MD, Director of Gastrointestinal Oncology at Intermountain Healthcare in Utah: Cancer surgeries have not been deemed elective or delayed.

Re: delaying or altering the delivery of potentially immune-compromising treatments

David Kerr, MD, Professor of Cancer Medicine at the University of Oxford in England: We are considering delaying initiation of our adjuvant colorectal cancer treatments, as we have data from our own QUASAR trials suggesting that patients who commence chemotherapy between 2 and 6 weeks do equally as well as those who begin 6-12 weeks after surgery.

Lewis: The most difficult calculus is around adjuvant therapy. For metastatic patients, I am trying to use the least immunosuppressive regimen possible that will still control their disease. As you can imagine, it's an assessment of competing risks.

Colorectal cancer care in the age of coronavirus: strategies to reduce risk and maintain benefit

16 April 2020

While essentially all approaches to medical care have been forced to undergo drastic changes in the era of COVID-19, cancer treatment remains a particular challenge as non-elective care that must be maintained throughout the pandemic. Cancer care providers are on a mission to achieve balance between offering the best treatment possible to cancer patients while minimizing risks of infection by COVID-19.

Ongoing research throughout the pandemic is generating data to help to determine the best courses of action. In partnership with the Colorectal Cancer Alliance and the Otto J Ruesch Centre for the cure of gastrointestinal cancers, a practical set of guidelines and recommendations for the management of colorectal cancer during the COVID-19 pandemic was developed.

Key recommendations:

1. Avoid clinical and hospital exposure

As much as possible, it is recommended to avoid visits to clinics or hospitals given the increasing number of COVID-19-positive individuals in and around these spaces. Rapidly evolving solutions to replace many face-to-face encounters with remote “telemedicine” visits are being embraced positively by both staff and patients. It is recognized, however, the critical lack of the important aspects of human touch and heightened diagnostic abilities that come from directed physical examinations, making telemedicine specifically useful for more long-term follow-up appointments.
For patients who are on intravenous therapies, their presence among skilled nurses and clinicians to administer agents such as oxaliplatin, irinotecan, bevacizumab, anti-EGFR agents and others is critical. As such, it is essential that the importance of these drugs in a patient’s regimen are considered and compared to the risk of infection.

2. **Maintain optimal clinical outcomes, especially in the curative setting**

While the current guidelines are aimed toward optimizing clinical outcomes based on clinical trial data and standards of practice, significant modifications can still be made that are unlikely to have major negative impact on patient outcomes.

3. **Reduce myelosupression**

In colorectal cancer treatment, regimens such as FOLFOXIRI that generate regular myelosupression are being increasingly administered. Myelosupression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells and platelets – the cells that are the workforce of a healthy immune system. While there is not enough data about whether being myelosuppressed when exposed to COVID-19 will make one more likely to become infected, it makes sense to avoid inducing very low immune cell counts in patients during this time. That means avoiding other cancer treatments such as Trifluridine-tipiracil (Lonsurf) and other regimens associated with high rates of grade 3-4 neutropenia and anemia (white blood cell and red blood cell deficiencies).

4. **Avoid grade 3-4 toxicity that would require emergency room visits or hospitalizations**

Many colorectal cancer treatments cause nausea, vomiting, diarrhea and other conditions that result in ER evaluations and admissions. Careful monitoring of kidney and liver function throughout treatment can help to predict a patient’s risk of ending up in the ER. Furthermore, by lowering doses of treatments, the frequency of grade 3-4 toxicities can be mitigated. More is not necessarily better for survival, especially in a colorectal cancer setting. It is recommended that doses be reduced by as much as 25%, particularly in the first few cycles of a patient’s treatment to reduce the risk of grade 3-4 toxicities.

**Modifications to standards of care in colorectal cancer treatment**

1. **Drop the bolus 5-fluorouracil (5-FU)**

The 5-FU of a FOLFOX or FOLFIRI regimen has little consistent evidence to support any significant benefit. Strong evidence demonstrates that 5-FU adds significant toxicity to the regimen causing myelosupression, diarrhea and inflammation of the mucosas (mucositis). Furthermore, if the 5-FU bolus is dropped, there is discussion about whether leucovorin should persist in the regimen – its removal would further reduce the time necessary in the infusion clinic and possibly minimize toxicity even further.

2. **Change intravenous 5-FU to oral capecitabine**

Capecitabine has proven to be equal or superior to 5-FU in almost every clinical setting including adjuvant therapy, metastatic treatment or chemoradiation. Standard dosing of this drug alone or in combination with intravenous chemotherapy is linked to more diarrhea and mucositis, thus modifications to standard dosing such as a 7-day-on, 7-day-off regimen are recommended.
3. **Skip cycles of treatment**

Given that the COVID-19 adaptations are predicted to last for months, another modification to CRC treatment suggests longer-term changes such as skipping cycles of certain treatments. Specific therapies, such as bevacizumab as maintenance therapy, due to their long half-lives (how long the drug concentration persists in the body) could be skipped for a month or more without major impact on treatment efficacy.

4. **Dropping intravenous portions of a regimen and maintaining with oral medications**

Patients who are beginning adjuvant chemotherapy for high-risk disease should still be offered doublet chemotherapy, though starting with single agent oral therapy and adding oxaliplatin later on could be justified. Data confirms that delaying adjuvant chemotherapy leads to inferior survival outcomes, reinforcing the importance of its timely application despite the pandemic.

In the metastatic setting, standard maintenance therapy includes capecitabine with or without bevacizumab. It is recommended that single-agent capecitabine be considered.

5. **Management of oral medications using telemedicine visits**

It is recommended that patients on most oral regimens be accompanied without in-person clinic visits, restricting their laboratory visits to routine testing that is part of most regimens.

6. **Short-course radiation when possible**

When appropriate, it is recommended that short-course radiation be used for neoadjuvant treatment of rectal cancer. Newer technologies that involve stereotactic radiosurgery have allowed for shorter treatment regimens that are recommended for palliative radiation whenever possible.

7. **Consider ctDNA for adjuvant decision making**

Circulating tumour DNA (ctDNA) technologies can be used to assist in adjuvant therapy decision making by detecting minimally residual disease.

8. **Delay surgeries when appropriate (may be upwards of 2-3 months)**

Decisions to postpone surgeries must involve multidisciplinary opinion, but could be justified based on hospital and ICU resources and patient risk. A watch-and-wait approach may be necessary to avoid surgery and the resultant hospitalization during the pandemic. Patients with scheduled surgeries could be maintained on oral chemotherapy or a “treatment holiday” until the time is safe again to undergo surgery. Such delays in surgery are not likely to cause major negative impact on a given patient apart from the anxiety of waiting. Extra time should be spent to explain the rationale for the recommendation and the development of a revised plan that is commonly agreed upon.
Prophylactic endoscopic clipping does not prevent delayed postpolypectomy bleeding

30 March 2020

New study findings demonstrate that prophylactic endoscopic clipping does not help to prevent delayed postpolypectomy bleeding (DPPB) and should not be used routinely among patients. Following endoscopic polypectomy, bleeding is the most common complication that patients face. While immediate postpolypectomy bleeding is generally inconsequential, DPPB can be greater cause for concern and clinically significant.

Endoscopic clipping is an established treatment for immediate postpolypectomy bleeding whereby the surrounding mucosal tissues are joined after the removal of a polyp to reduce the patient’s risk of
bleeding. There is conflicting evidence, however, to support this procedure as a preventive measure for DPPB. In the study, it was found that no significant protective effect of clipping was seen in any patient subgroup. The researchers note that additional effectiveness and cost-effectiveness studies are necessary in patients with lesions 20mm or larger, in whom prophylactic clipping may be advantageous.