June 2022

LIVING WITH CANCER

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RESEARCH & PRACTICE UPDATES

Colorectal Cancer Canada curates monthly Research & Practice Updates to inform patients and their loved ones of new innovations in colorectal cancer care. The following updates extend from June 1st 2022 to June 31th, 2022 inclusive and are intended for informational purposes only

JUNE 2022 PREVIEW

ASCO 2022 updates: Immunotherapy treatment results in an "unprecedented" clinical complete response in 100% of first 14 patients with rectal cancer

June 2022

In a study of patients with locally advanced mismatch repair-deficient (dMMR) rectal cancer, 6 months of treatment with the immunotherapy agent dostarlimab-gxly alone led to a clinical complete response (the absence of all detectable cancer) in 100% of the study's first 14 patients. Currently, the standard treatment for locally advanced rectal cancer involves treatment with chemotherapy and radiation followed by surgery to remove the rectum. With the experimental treatment, none of the patients have had to undergo treatment with chemotherapy, radiation, or surgery, and there were no grade 3 or 4 adverse events experienced by the patients. By eliminating the need for standard therapies, patients are spared the significant risk of morbidities such as urinary, sexual, and defecatory dysfunction that are associated with these treatments.

Though the patients have been followed for an average of only 6.8 months, four patients have been followed for nearly 2 years, and only four have received less than 6 months of the required treatment. In dMMR rectal cancer, the use of PD-1 inhibitors like dostarlimab-gxly may be a potential treatment to replace some or even all the standard of care treatments currently in place to treat rectal cancer – chemotherapy, chemotherapy plus radiation, or chemotherapy, radiation and surgery. The researchers caution, however, that the study population is small and therefore these findings must be replicated in larger populations with longer follow-up before any definitive changes to the standard of care treatment can be made.

READ THE ARTICLE

ASCO 2022 updates: Use of ctDNA to identify need for adjuvant therapy in stage II colon cancer

June 2022

Results from the phase II DYNAMIC trial demonstrated that adjuvant (post-operative) chemotherapy could be omitted for patients with stage II colon cancer who did not show detectable levels of circulating tumour DNA (ctDNA) in the blood without compromising recurrence-free survival. For patients with ctDNA present in the blood after surgery, the rate of cancer recurrence was low among those that did receive adjuvant chemotherapy, suggesting a survival benefit from the additional treatment with chemotherapy.
ctDNA is a tool that can detect minimal residual disease, or very small amounts of remaining cancer cells after surgery. This can be used to better predict a patient's risk for disease recurrence and selection of specific patients who are most likely to benefit from additional adjuvant therapy.

The DYNAMIC study findings are encouraging because they show that with adjuvant therapy, ctDNA-positive patients can receive significant benefit from the additional chemotherapy. Next steps including a randomized trial assigning ctDNA-positive and ctDNA-negative patients to adjuvant treatment vs. no treatment, to provide more conclusive evidence of the impact or lack of impact in the two patient subsets.

READ THE FULL ARTICLE

ASCO 2022 updates: Panitumumab plus mFOLFOX6 improves overall survival in left-sided RAS wild-type mCRC

June 2022

Findings from the PARADIGM phase III study showed that the use of the targeted therapy panitumumab plus the chemotherapy regimen mFOLFOX6 (5-FU, folinic acid, oxaliplatin) significantly improved overall survival of patients with metastatic colorectal cancer (mCRC) tumours identified as RAS wild-type that originated on the left-side of the colon. Patients were randomly assigned to receive panitumumab plus mFOLFOX6, or bevacizumab plus mFOLFOX6. Patients who received panitumumab had an overall survival of 37.9 months vs 34.4 months for those who received bevacizumab and experienced a 18% lower risk of death.

These findings highlight the important of early molecular profiling of tumours to select the optimal treatment option for patients at the right time. If a tumour is RAS wild-type and originates on the left-side of the colon, the study findings suggest that initial treatment with panitumumab plus mFOLFOX6 is superior to first-line treatment with bevacizumab plus mFOLFOX6.

READ THE FULL ARTICLE

Regional Therapy for Colorectal Cancer Liver Metastases: Which modality and when?

June 2022

Patients who have colorectal cancer that has spread to the liver (liver metastases) and cannot be removed by with surgery may receive regional therapies to deliver targeted treatment to the liver to diminish the size and number of tumours. The liver is a unique organ in that it receives two separate blood supplies: the blood supply via the **hepatic artery** which serves as the primary supply for liver tumours, and the blood supply through the **portal vein** which supplies most of the normal liver cells. Since the hepatic artery is the dominant supplier of blood to liver tumours, selective delivery of cancer therapies to the tumours can be achieved while mostly sparing normal liver tissue as well as surrounding tissues outside the liver, helping to limit the systemic side effects of

such therapies. There is, however, a lack of evidence from **randomized controlled trials** to effectively identify the optimal treatment approach to integrate regional therapies in the management of colorectal cancer liver metastases.

Randomized controlled trial (RCT): *RCTs are a type of clinical trial that are used in cancer research that randomly assign participants into the experimental group (those receiving the novel treatment) or a control group (those receiving the standard of care treatment). RCTs are considered the gold standard in cancer trials.*

Types of regional therapies for colorectal cancer liver metastases

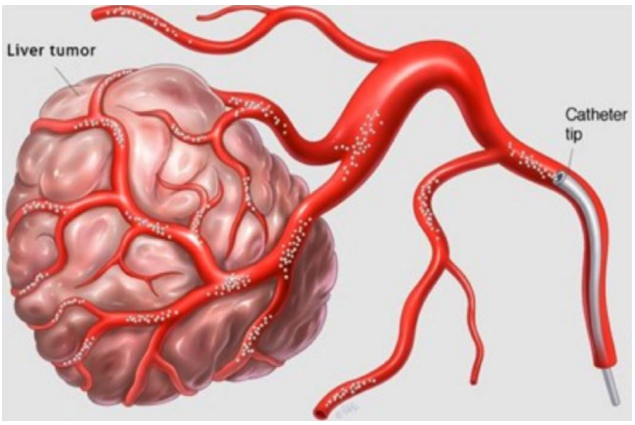
1. **Hepatic arterial infusion pump (HAIP) chemotherapy** is a small, disc-shaped device that is surgically implanted just below the skin of a patient with colorectal cancer that has spread to the liver. It is connected via a catheter to the hepatic artery of the liver, allowing 95% of the chemotherapy that passes through the pump to stay localized to the liver[1]. HAIP chemotherapy can be safely given together with systemic chemotherapy and is associated with a high objective response rate (proportion of patients with a complete response or partial response to treatment) as well as a high rate of conversion to resectable tumours (tumours that can be removed successfully by surgery).

The hepatic arterial infusion pump

Image source: https://sunnybrook.ca/content/?page=colorectal-colon-bowel-haip-chemotherapy

2. **Transarterial chemoembolization** uses microscopic beads ("microspheres") that are coated with the chemotherapy drug irinotecan to deliver localized chemotherapy through the hepatic artery. It is associated with high response rates in the liver and has a well-established safety profile among patients with colorectal cancer liver metastases.

[1] https://sunnybrook.ca/content/?page=colorectal-colon-bowel-haip-chemotherapy



Microsphere embolization through the hepatic artery to a liver tumour

Image source: https://twitter.com/eliebalesh/status/925208219173220352/photo/3

3. **Transarterial radioembolization** involves the use of microscopic beads ("microspheres") that are impregnated with the radioactive yttrium-90 (y90) which are selectively delivered through the hepatic vasculature to the target tumours. Though this regional therapy achieves high rates of response within the liver, it is not associated with improvements in overall survival or quality of life when it is used as a first-line (initial) treatment or second-line treatment for patients with colorectal cancer liver metastases.

   In summary, the ideal treatment approach for patients with colorectal cancer liver metastases is one that aligns with the patients' values, preferences and overall philosophy of care. After progression on chemotherapy, the three above-mentioned regional therapies are valuable treatment options to consider among patients who have colorectal cancer metastases in the liver. Further research is needed to best define the role of regional therapies in this subset of patients.

READ THE FULL ARTICLE

The association between Tumour Mutational Burden and Immunotherapy Response
June 2022

Immunotherapy has shown remarkable clinical benefits across many different cancer types, though its use is currently limited to a subset of patients who exhibit microsatellite instability high (MSI-H) / mismatch repair deficient (dMMR) tumours, raising the need for further research on other biomarkers that may be indicative of response to immunotherapies.

Tumour mutational burden (TMB) is an emerging biomarker that indicates the total number of mutations (changes) found in the DNA of cancer cells. The Food and Drug Administration (FDA) recently approved a high TMB (TMB-high), defined by greater than or equal to 10 mutations/Mb

(Mb is the basic unit of measure of DNA) for the treatment of solid tumours with pembrolizumab – an immunotherapy agent that helps to stimulate and reactivate the activity of the immune system against tumour cells.

Certain studies, however, have indicated that the TMB-high biomarker is only able to identify which patients will effectively respond to immunotherapy in a subset of cancer types, with certain immune-related factors of the tumour microenvironment being implicated in modulating the ability of TMB to predict response to immunotherapy.

Tumour microenvironment: *the normal cells, molecules, and blood vessels that surround and feed a tumour cell. A tumour can change its microenvironment, and the microenvironment can affect how a tumour grows and spreads.*

With a deeper understanding of how TMB might be combined with other variables such as the presence of certain immune-related factors in the tumour microenvironment, in the future it may be possible to arrive at a more predictive biomarker that can more consistently and accurately predict response to immunotherapy across cancer types.

READ THE FULL ARTICLE