COLORECTAL CANCER ASSOCIATION OF CANADA

COLORECTAL CANCER RESEARCH
Week Ending December 12, 2008

The following colorectal cancer research update extends from November 29 – December 12, 2008 inclusive and is intended for informational purposes only.

DRUGS

1. **Folfox and Flox Regimens for the Adjuvant Treatment of Resected Stage II and III Colon Cancer** (Dec. 3/08)

   Past trials such as the MOSAIC trial showed that the use of oxaliplatin after surgical removal of the primary together with an infusional regimen of 5FU and Leucovorin (folfox) in the treatment of stage II/III colon cancer improved disease free survival. Another trial, NSABP's C-07, evaluated the addition of oxaliplatin to a weekly Roswell Park regimen of bolus 5FU and Leucovorin (flox) and found a similar improvement in disease free survival. The conclusion was that the benefit of oxaliplatin appears to be independent of the type of 5FU/Leucovorin regimen used, ie either infusional (folfox) or bolus (flox). This research reviewed the efficacy and toxicities of these two regimens (infusional vs. bolus 5FU/LV) and serves as a guide for clinical practice.

   Sharif, Saima, et al., Folfox and Flox Regimens for the Adjuvant Treatment of Resected Stage II and III Colon Cancer. Cancer Investigation, Volume 26, Issue 9, November 2008, pp 956-963

2. **Ontario Takes a Bold Step towards Personalized Medicine by Approving Panitumumab (Vectibix) for Funding** (Dec. 3/08)

   Vectibix (panitumumab), the first and only fully human monoclonal antibody for patients with advanced colorectal cancer, is now funded by the Ontario government, the first province to do so. It is an important treatment option for crc patients following standard chemotherapy regimens. As monotherapy, vectibix has been shown to significantly reduce the chance that certain patients' metastatic colorectal cancer would continue to grow. As a fully human monoclonal antibody, vectibix offers an effective targeted therapy with a low risk of the body reacting adversely to the infusion. Vectibix, at a dose of 6mg/kg, is administered via infusion once every two weeks. Vectibix works by recognizing a protein in the body known as epidermal growth factor receptor (EGFr), which is over expressed on the surface of some cancer cells. When growth factors (other body proteins) attach to the EGFr, the cell is stimulated to grow and divide. Vectibix binds to the EGFr and prevents the highly active cancer cell from receiving the messages it needs for growth and division. In patients whose tumours have a mutation in a gene called KRAS, cancer cells continuously receive messages to grow and divide despite anti-EGFr treatment. These patients do not respond to anti-EGFr therapy. It is important to detect the mutated gene so the right treatment can be prescribed. KRAS analysis provides guidance in therapeutic treatment decisions for patients with metastatic colorectal cancer. KRAS testing can be performed at several pathology labs across Canada. Mt. Sinai Services has been designated by MOHLTC to conduct KRAS testing for patients who may be eligible to receive vectibix. Amgen Canada is currently funding KRAS testing for patients who may be eligible to receive vectibix at Mt Sinai Services and St. Michael's Hospital in Toronto, Ontario. Mutant KRAS is detected in approximately 40% of crc tumours which means that 60% of patients could potentially benefit from vectibix.

   www.newswire.ca/en/releases/archive/December2008/03/c6213.html

3. **The Efficacy of Adjuvant Chemotherapy with 5FU in CRC Depends on the Mismatch Repair Status** (Dec. 4/08)

   The aim of this study was to evaluate if mismatch repair defective colorectal cancer had a different response to adjuvant 5FU chemotherapy in a cohort of patients prospectively followed during 5 years. The cohort included 754 surgically treated patients with crc. Mismatch repair status - which could consist of mismatch repair competent tumours (which is favorable) or mismatch repair defective tumours (not favorable) - was diagnosed and found in 76 patients. No differences were found in overall survival or disease free survival regarding mismatch repair status. Adjuvant chemo improves survival in patients in the stage II or III, but this improvement is only evident in patients with mismatch repair competent tumours. Survival of patients with mismatch repair defective tumours does not improve with adjuvant chemo. Investigators concluded that in a cohort of crc patients, those with mismatch repair deficient tumours seem not

to benefit from 5FU based chemo whereas those with mismatch repair competent tumours appeared to respond well.

Jover,Rodrigo, et al., The Efficacy of Adjuvant Chemotherapy with 5Fu in Colorectal cancer Depends on the Mismatch Repair Status. European J of Cancer. Online Edition. Doi:10:1016. 1008.07.016

4. FDA Releases Questions and Answers about ESA Medication Guides (Dec. 5/08)

Erythropoiesis-stimulating agents (ESAs) trigger the bone marrow to produce more red blood cells when anemia is due to low red cell counts. For cancer patients, ESAs are only used during chemo to reduce the need for blood transfusions. They are not appropriate for anemic cancer patients who are not having chemo, nor are they approved for chemo patients whose treatment goal is cancer cure. The FDA now provides answers to questions about using ESAs and their FDA approved medication guides. Examples of ESAs are aranesp, epogen, and procrit. The guides are designed to help patients make informed decisions about the risks and benefits of using ESAs and to give them a starting point for discussions with their physicians. The FDA tells cancer patients who are considering ESA treatment that:

- The tumor may grow faster and the patient may die sooner when ESA treatment is used
- The healthcare provider should prescribe the lowest dose of the ESA that is needed to avoid red blood cell transfusions
- ESAs work by stimulating the bone marrow to make more red blood cells. ESAs have not been shown to improve the symptoms of anemia, quality of life, fatigue, or well being for patients with cancer. For that reason, ESAs should be used only to reduce the chance that a patient with low red blood counts will get a blood transfusion
- Treatment with an ESA should be stopped when chemo treatment is finished

www.colorectalcancercoalition.com

5. Comparing 5FU or Capecitabine Combined with Oxaliplatin (Dec. 9/08)

5FU or Xeloda are two chemos that can be combined with oxaliplatin to treat crc that has metastasized. This study analyzed six different randomized clinical trials that compared the two approaches. Researchers wished to determine which of the two regimens was most efficacious. While they found that there were different side effects associated with each regimen, the time until cancer got worse (progression free survival) and overall survival time were the same for both regimens. The percentage of patients who received infusional 5FU and had their tumors shrink (response rate) was greater than those who had shrinkage with capecitabine. However, this did not translate into better progression free survival or longer survival time. While there was a 15% better response rate with infusional 5FU, there was no difference in either progression free survival or overall survival time. Patients who received xeloda had more blood clots, serious diarrhea, and changes in the skin on their hands and feet (hand-foot syndrome). 5FU treatment caused more low white cells counts (Neutropenia). In discussing side effects, the researchers noted that lower doses of xeloda might have reduced its side effects and that lower doses are being used in some new studies of the drug. Lead researcher comments: The combination of capecitabine and oxaliplatin resulted in lower response rate, but this did not affect progression free survival and overall survival, which were similar in both treatment arms. The toxicity analysis showed the characteristic toxicity of each of the different FU schedules, with thrombocytopenia and hand and foot syndrome consistently more prominent in the capecitabine regimens. The use of capecitabine and oxaliplatin is a valid alternative for patients with metastatic colorectal cancer and can be regarded as an appropriate backbone for the addition of novel targeted agents in clinical practice and future clinical trials.

Arkenau, Hendrik-Tobias, et al., Efficacy of Oxaliplatin Plus Capecitabine or Infusional Fluorouracil/Leucovorin in Patients with Metastatic Colorectal Cancer: A Pooled Analysis of Randomized Trials. J of Clinical Oncology. Published Online Ahead of Print, November 17, 2008.

6. FDA Warns Against Bowel Cleansing Drugs For Colonoscopy (Dec. 12/08)

Bowel cleansing products that contain sodium phosphate have received a stern warning from the FDA about the potential of the products to cause acute kidney damage. Two products available by prescription, Visicol and OsmoPrep have received “black box” warnings from the FDA. The over the counter bowel cleanser, Fleet Phospho-soda, is also not recommended for consumer use because of the same potential for kidney injury as seen in the prescription bowel cleansers. The FDA reveals they have received 20 reports of sudden kidney injury within the

past two years, associated with the use of OsmoPrep and Visicol. Both products were approved by the FDA in 2006. Since that time, nineteen cases of kidney failure have been confirmed by biopsy, occurring within hours or weeks after the prescriptions were used for bowel cleansing. FDA officials claim that not everyone is at risk. The majority of patients don't run into problems. Those at risk include anyone over age 55, people with colon problems causing a delay in bowel evacuation and those dehydrated.

www.emaxhealth.com/1020/34/27510

OTHER

7. Commercial Test for BRAF Gene Available (Dec. 2/08)

Clarient Inc. announced the launch of a commercially available test for the BRAF mutation in crc. The test detects mutations in crc tumour tissue. In a recent study, patients with mutated BRAF did not respond to treatment with 2 drugs that block epidermal growth factor receptors (EGFR) – Erbitux (cetuximab) and Vectibix (panitumumab). Patients in the study all had normal wild-type Kras, another mutation that blocks response to Erbitux and Vectibix. Proteins controlled by the BRAF gene lie in a pathway of signals between the cell surface and its nucleus and control cell division. When BRAF is mutated, uncontrolled cell growth can lead to cancer. Because a mutated gene is already in active downstream of the receptor, trying to block the pathway by blocking an EGF receptor on the cell surface doesn't work to control the cancer. About 12% of patients with normal, wild type Kras had mutated BRAF in the study adding to the number of patients who did not respond to Erbitux or Vectibix. Like Kras, BRAF is a predictive biomarker that can help patients and doctors choose the best treatment for advanced colorectal cancer.

www.C3:Research&TreatmentNews.com

Other

8. Gallstones a Risk Factor For Colon Tumors (Dec.4/08)

People with gall stones appear to be at increased risk for colon tumors called adenomas, which frequently develop into cancer over time. Many studies have reported a moderately increased risk of crc in patients who have undergone gall ladder removal. In contrast, few reports have been published regarding colorectal adenoma. Moreover, very few studies have investigated the association between gallstones that have not been removed and colorectal adenoma, but data indicate that the two are not related. The researchers in this study, therefore, examined the association between gallstones and colorectal adenoma in subjects who underwent ultrasound, to look for gallstones, and colonoscopy, as well as colorectal adenomas. The rate of colorectal adenoma was 29.6% in gallstone patients, significantly higher than the 17.7% rate in subjects with normal gallbladders. Only 15.9% of patients who had their gallbladders removed developed colorectal adenomas, which was not significantly different from patients without gallstones. On final analysis, gallstones increased the risk of colorectal adenomas by 57%.

Jamaji, Yutaka, et al., Gallstones a risk factor for colorectal adenoma. Am J Gastroenterol. 2008: 103: 2847-2852

9. Iron Status and Colorectal Cancer in Symptomatic Elderly Patients (Dec. 8/ 08)

The prevalence of colorectal cancer is high in anemic and non-anemic elderly symptomatic patients, therefore the decision to order a colonoscopy in older patients is recommended irrespective of the iron status. This study sought to determine the relationship between the prevalence of crc and iron status in elderly anemic and non anemic patients. 359 elderly patients aged 70 years and more were retrospectively investigated by undergoing a total colonoscopy and evaluating iron levels. Less than half of the patients with crc had iron deficiency anemia. The prevalence of colorectal carcinoma was similar among anemic and non-anemic patients. However, those with a proximal (right sided)colorectal carcinoma had a lower hemoglobin and ferritin level and higher prevalence of iron deficiency anemia compared with patients with a distal (left-sided) colorectal carcinoma.

Joosten, Etienne, et al., Iron Status and Colorectal Cancer in Symptomatic Elderly Patients. The American J of Medicine. Vol 121, Issue 12, pp 1072-1077

10. Protein Rates May Show Death risk in Colorectal Cancer Patients (Dec. 12/08)

A pair of proteins may help explain why people with surgically removed colorectal cancer who are overweight, physically inactive and follow a Western-pattern diet may have an increased risk of dying of the disease or other causes, according to a report from the Dana-Farber Cancer Institute and published online by the Journal of Clinical Oncology. Researchers found that in people who have undergone surgery for colorectal cancer, the levels of two insulin-related proteins in their blood before diagnosis predicted their chances of dying from the cancer or other conditions. Patients with high prediagnosis levels of insulin-like growth factor binding protein-1 **(IGFBP-1)** were more than half as likely to die; while those with high levels of **C-peptide** were nearly twice as likely to die. The study was the first to consider whether proteins whose blood levels are influenced by lifestyle factors can be a gauge of a patient's chances of surviving stage I-III colorectal cancer. It was designed to explore why people with certain characteristics – obesity, physical inactivity and an unhealthy diet – have an increased risk of colon cancer, cancer recurrence and death. These lifestyle factors can lead to high levels of circulating insulin, a hormone that may bind directly to colon cancer cells and spur their growth. High insulin levels also lead to numerous alterations in other blood proteins that may influence cancer cell growth.

Wolpin, Brian, et al., Insulin, the Insulin-Like growth Factor Axis, and Mortality in Patients with Nonmetastatic Colorectal cancer. J of Clinical Oncology. On-line Edition:JCO.2008.17.9945v1

NUTRITION

11. Dietary Calcium, vitamin D and the Risk of Colorectal Cancer (Dec. 12/08)

Calcium and vitamin D have a potential protective effect against colorectal cancer. The association of dietary intake of calcium and vitamin D with the risk of colorectal cancer in a large cohort study of middle aged Japanese men and women was investigated. A total of 74,639 subjects where followed from 1995 to 1999 to the end of 2004, during which time 761 cases of colorectal cancer were newly identified. Dietary intake of nutrients was calculated. The results showed a potential decrease in the risk of colorectal cancer with higher dietary intake of calcium among middle aged Japanese men, who have a relatively low dietary intake of calcium. Although vitamin D and colorectal cancer risk were not associated, potential effect modification between calcium and vitamin D or the risk of colorectal cancer **was** indicated.

Sasuzuki, Shizuka, et al., Dietary calcium, vitamin D, and the risk of colorectal cancer. The American J of Clinical Nutrition. Online Edition: doi:10.3945/ajcn.200826195

12. Ginger Capsules Do Not Boost Nausea Medicines During Chemotherapy (Dec. 9/08)

Although ginger is often recommended as a simple remedy for chemotherapy nausea, ginger capsules do not appear to work any better than a sugar pill to improve the effects of standard nausea drugs. In a randomized study, 162 patients received either ginger capsules or a placebo for chemo induced nausea and vomiting. Neither the patients nor their doctors know which they were getting. All patients were already receiving a 5-HT_3 inhibitor such as Zofran or Kytril for the symptoms. Some were also being treated with Emend (aprepitant). All patients in the trial had already had at least one episode of nausea or vomiting during chemo. They were given either 1 gram or 2 grams of ginger within a capsule or an identical looking placebo in addition to their regular anti-nausea medicine for three days after chemo. Researchers found no difference in either acute nausea and vomiting on the day of chemo or delayed nausea over the next few days. Combining ginger with Emend actually increased acute nausea and vomiting. There were no significant differences in side effects between the 2 groups, although the patients who received ginger capsules had less fatigue.

Zick, Suzanna, et al., Phase II trial of encapsulated ginger as a treatment for chemotherapy-induced nausea and vomiting. Supportive Care in Cancer. Online First. November 13, 2008