Colorectal Cancer Association of Canada

COLORECTAL CANCER RESEARCH
Week Ending September 5, 2008

The following colorectal cancer research update extends from August 23 – September 5, 2008 inclusive and is intended for informational purposes only.

DRUGS

1. **Early Skin Treatment Reduces Skin Reactions in Colorectal Cancer Patients Treated with Vectibix** (Aug 23/08)

   Researchers from several institutions in the US recently conducted a trial, referred to as the STEPP trial, which compared two different approaches aimed at minimizing skin reactions associated with treatment with Vectibix. This trial included nearly 100 patients with advanced, recurrent colorectal cancer who were treated with Vectibix plus a Camptosar (irinotecan)-based chemo regimen. Patients were divided into 2 groups, one group received preemptive skin treatment, which started the day before beginning therapy and continued through the sixth week of therapy, while the other group received reactive treatment, which was administered anytime during the six weeks of therapy if the healthcare provider felt that side effects of the skin necessitated therapy. Skin treatment included skin moisturizer, sunscreen, topical steroid and the antibiotic doxycycline. Upon the seventh week of treatment, patients had the option to continue skin treatment. Only 29% of patients experienced serious skin reactions in the preemptive group compared with 62% in the reactive treatment group and the efficacy of vectibix/chemo was not affected by the preemptive skin therapy. Researchers concluded that preemptive therapy for skin reactions appears to significantly reduce the rate of skin reactions associated with treatment with vectibix among crc patients without affecting efficacy.

   Mitchell E, et al., Updated Results of STEPP, a Phase 2, Open Label Study of Pre-Emptive Versus Reactive Skin Toxicity Treatment in Metastatic Colorectal Cancer Patients Receiving Panitumumab + Folfiri or Irinotecan-Only Chemotherapy as Second-Line Treatment. 10th World Congress on Gastrointestinal Cancer. June 2008 Barcelona, Spain.

2. **Aveo Pharmaceuticals Initiates Phase 1b Combination Trial of AV-951 with Folfox6 in Patients with Advanced Colorectal Cancer** (Aug 25/08)

   Aveo Pharmaceuticals, a Massachusetts based company, has initiated another Phase 1b clinical study for its lead product candidate, the novel triple VEGF receptor inhibitor AV-951. It will be conducted at leading cancer institutions in Europe and will evaluate AV-951 in combination with the folfox6 chemotherapy regimen in patients with advanced crc and other g.i. cancers. This phase 1b combination therapy trial is designed to determine the safety, tolerability, and maximum tolerated dose of AV-951 when given in combination with folfox6 in approximately 30 patients with advanced crc. Patients will receive once daily doses of AV-951 for 3 weeks followed by a one-week break, and folfox6 chemo at standard doses once every 2 weeks. AV-951 is a novel, highly potent and specific inhibitor of VEGF receptors 1, 2 and 3 and functions by cutting off the blood supply to tumours thereby depriving them of oxygen and nutrients. For more information about the trials of AV-951, please visit the NIH clinical trials web site at www.clinicaltrials.gov

   www.centredaily.com/business/technology/

3. **Colon Cancer Drug Gets U.S. Approval** (Aug 26/08)

   DiagnoCure Inc. has received regulatory approval for its sales team to begin actively promoting its Previstage GCC colorectal cancer staging test, which the company says is 100,000 times more sensitive than the current method. GCC (guanylyl cyclase C) is a protein found in intestinal lining and is used for precise detection of lymph node metastatic disease from crc. The presence of GCC mRNA can be detected at a rate of a single cancer cell out of 10,000,000 normal cells, versus one in 200 normal cells with traditional methods, which makes it the most precise staging tool available.

   www.thestar.com/Business-ColoncancerdruggetsUSAproval

4. Two Different First-Line Irinotecan Treatments Have Similar Results (Aug 26/08)

Spanish researchers have found that patients treated every week with Camptosar (Irinotecan, CPT-11) plus a high dose of continuous infusion 5FU without leucovorin had similar outcomes to those treated with the more common biweekly Folfiri treatment that includes leucovorin. Folfiri is camptosar, 5FU and leucovorin. They called the new treatment Fuiri. In a randomized trial, patients received either folfiri every two weeks or fuiri weekly. None had been treated for advanced crc before. In the study of 346 patients a comparison of folfiri vs fuiri found that tumor shrinkage was 57% for folfiri and 51% for fuiri and that overall survival wasn't significantly different: 21.6 months vs. 19.2 months. Progression free survival (time until cancer worsened) was 8.3 months for folfiri and 8.4 months for fuiri.

Aranda et al., Annals of Oncology, Advance Access published online August 26, 2008.

5. FDA Approves Oral Aloxi to Prevent Chemo-Induced Nausea and Vomiting (Aug 25/08)

The FDA has approved an oral formulation of Aloxi (palonesetron) to prevent nausea and vomiting from chemo. A single 5mg capsule reduces the risk of nausea during the first 24 hours after chemo and for up to 5 days afterwards. The medicine is taken about an hour before chemo starts. The most common side effects were headache, experienced by about 4% of patients and constipation in less than 1%. Intravenous Aloxi has been available since 2003 to manage both acute nausea and vomiting in the hours after chemo and delayed nausea during following days.

C3: Colorectal Cancer Coalition – Research & Treatment News www.colorectalcancercoalition

SURGICAL

6. Stents Can Manage Colon Obstruction Effectively (Aug 29/08)

Self-expanding metal stents can help patients with an obstruction from advanced colon cancer avoid surgery. When a large tumor blocks the left side of the colon, surgeons can remove the tumor or put in a stent to move bowel contents around the obstruction. According to a recent study, patients live as long with either technique but spend less time in the hospital and have fewer complications with stents. Australian surgeons reviewed 55 consecutive cases who underwent colonic stenting or palliative surgery for incurable, obstructing adenocarcinoma of the left colon. 29 patients underwent colonic stenting, and 26 had surgery during the study period. Survival was similar in the two groups (14 months in the stent group vs 11 months in the surgery group), but hospital stay was shorter in the stent group (4 vs 13.5) and fewer patients in the stent group had complications (2 vs 14). The lead investigator concluded: Colonic stenting provides effective and durable palliation for patients with incurable, obstructing adenocarcinomas of the left colon. It can be performed with less morbidity than palliative surgery, and offers similar long-term survival.

Faragher I, et al., Long term results of palliative stenting or surgery for incurable obstructing colon cancer. Colorectal Disease, Volume 10, Number 7, September 2008, p 668-672

RADIATION

7. PET Leads to Treatment Changes in Majority of Colorectal Cancers (Aug 26/08)

The largest multi-institutional study to date examining the effect of PET on the management of recurrent colorectal cancer has found that its findings led to change in the treatment plans for more than half of the patients. The study, which appeared in the September issue of the Journal of Nuclear Medicine, was conducted at 4 sites throughout Australia and followed 191 patients divided into 2 groups.

- **Group A:** consisted of symptomatic patients who had residual structural lesions suspicious for recurrent tumor after initial therapy.
- **Group B:** had pulmonary or hepatic mets that were potentially operable.

Results of the PET were compared with findings from conventional imaging such as CT and participants were followed for 12 months.

Based on the extent and progression of disease revealed by the scans, treating physicians changed the planned management in more than 65% of patients in group A and nearly 50% in

group B. The researchers also found additional disease sites in 48% of patients in group A and 44% of group B, providing valuable prognostic information about patients that allowed their stratification into curative or palliative groups. PET was able to identify those patients who had potential for long-term, progression-free survival and even a potential cure, said lead investigator Scott. And it identified those patients with aggressive disease, enabling them to avoid unnecessary treatment such as surgery.

Scott, et al., PET Changes Management & Improves Prognostic Stratification in Patients With Recurrent Colorectal: Results of a MultiCenter Prospective Study. Journal of Nuclear Medicine, 2008, DOI: 10.2967

8. Radioembolotherapy Using Yttrium 90 For CRC Mets To the Liver (Sept 3/08)

One of the newer applications of interventional radiology is a form of brachytherapy for unresectable liver mets that uses glass or resin microspheres to carry yttrium 90 (90Y), which is a high-energy, beta particle-emitting isotope. The microspheres, about the diameter of a human hair, are administered via a catheter by intra-arterial hepatic injection guided by fluoroscopy. Once injected, the particles embed themselves in the capillary network of the tumor in the liver. The radiation is effective on adjacent tissue but does not travel beyond the tumor, and therefore there are minimal effects outside the tumor itself to the liver. Once placed, 90Y emits therapeutic doses of radiation for the next few days helping to shrink liver tumors/mets. This procedure takes advantage of the fact that liver mets are highly vascular and receive their blood supply via the hepatic artery, whereas the healthy liver tissue receives its blood supply primarily through the portal vein. Since the blood supplies are independent, the injection can target tumor tissue and spare normal liver tissue.

A detailed mapping of the vessels leading to the tumor is done prior to the procedure to detect anatomic variations and deviant vessels. An important part of this is to identify potential ways for the radioactive microspheres to disperse to locations other than the intended target, such as the g.i. tract. Variations in anatomy are not unusual. For example, the gastric arteries may branch from the left hepatic artery in some patients and from the common, proper, or right hepatic arteries in other patients. A detailed study of vessels branching from the hepatic artery to supply various other organs is therefore important before delivering radioactive microspheres into the hepatic vasculature. And when potential outflow vessels are found, they are blocked by small coils. Usually this procedure is performed in two parts – given to half the liver at one time and then four weeks later given to the other half of the liver. But with improvements in technique and supportive care, patients now generally receive only one treatment at centers such as **M.D. Anderson**. And this procedure was typically offered in the past only when other treatments had failed or were not feasible, but Dr. Murthy from M.D. Anderson believes it has greater potential and should be administered with systemic treatments so as to augment their benefits. Dr. Murthy and colleagues have designed a trial for crc patients. It consists of a randomized, phase II clinical trial in which 90Y microspheres will be combined with erbitux and irinotecan to treat liver mets in colon cancer patients, which will offer patients the best of 3 worlds: medical oncology nuclear medicine and interventional radiology.

http://www2.mdanderson.org/depts/oncolog/articles/

OTHER

9. Scientists Discover Major Genetic Cause of Colorectal Cancer (Aug 26/08)

About one third of crcs are inherited, but the genetic cause of most of these cancers is unknown. The genes linked to colorectal cancer account for less than 5% of all cases. Scientists at Northwestern University's Feinberg School of Medicine and colleagues have discovered a genetic trait that is present in 10 - 20% of patients with colorectal cancer. The findings strongly suggest that the trait is a major contributor to colorectal cancer risk and likely the most common cause of colorectal cancer to date. If a person inherits this trait – which is dominant and clusters in families – the study found the lifetime risk of developing colorectal cancer is 50%, compared to 6% for the general population. This gene mutation probably accounts for more colorectal cancers than all other gene mutations discovered thus far, according to the lead investigator Boris Pasche. The trait was named **TGFBR1 ASE** and it results in decreased production of a key receptor for TGF-beta, the most potent inhibitor of cell growth. With less of this vital protective substance to inhibit cell growth, colon cancer can more easily develop. The hope is that a clinical test will soon be developed that could be offered to families with a history of colorectal cancer and other individuals to determine whether they carry this mutation.

Pasche, B et al., Germline Allele-specific Expression of TGFBR1 Confers an Increased Risk of Colorectal Cancer. Science. DOI: 10.1126. Published online. August 26, 2008

10. A-Type Lamins Associated With Aggressive Colorectal Cancer (Aug 28/08)

Proteins called A-type lamins appear to indicate the presence of aggressive disease in patients with colorectal cancer. A-type lamins may also play a role in determining treatment options among these patients. These results were recently published in the journal PLoS ONE. Researchers from Europe recently conducted a clinical study to evaluate data from tissue collected from patients with crc. Specifically, researchers evaluated the presence of A-type lamins in tissue and associated outcomes among patients.

- Patients who have A-type lamin expressing cancers have a significantly worse outcome compared with patients whose cancer does not express A-type lamin
- A-type lamin was implicated in promoting the movement of cancer cells in the body, as well as their ability to invade areas such as organs.

The researchers concluded: "Expression of A-type lamins increases the risk of death from crc." If confirmed, A-type lamins may play a role in understanding the prognosis of a patient with crc and in determining subsequent treatment options.

Willis N, et al., Lamin A/C is a risk biomarker in colorectal cancer. PloS One. Available at: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0002988.Accessed August2008

11. New Self-Administered Test allows For Private, At-Home Colon Cancer Screening (Aug 28/08)

Colon Health Check has been introduced in the US as a diagnostic tool. It is a self-administered diagnostic test that allows for quick, private and highly accurate screening for colon cancer at home. Colon Health Check detects the presence of blood in stool – a major symptom of colorectal cancer and other g.i. disorders- and provides a negative or positive result to the test user within 5 minutes. Colon Health Check, an immunochemical-based fecal-occult blood test (FOBT) has been subjected to rigorous testing and has been cleared by the FDA. If used properly, this test is virtually as accurate and comparable to the type of tests administered in a physician's office or medical lab. The Colon Health Check Kit is available to US citizens for $34.95 at www.colonhealthcheck.com or by calling 1 800 216 8100.

www.cancercompass.com/cancer-news/1,14656,00.htm

NUTRITION

12. The Antioxidant Lycopene is Effective against Colon Cancer (Aug 24/08)

Emerging research has offered up another weapon in the battle against colorectal cancer, another tool which can be used to assist in the prevention of this and other types of cancer: the antioxidant lycopene. There are steps to take to prevent colorectal cancer. **Exercise**, which helps to ease the passage of waste material through the colon; **eating vegetables**, **fruits** and **whole grains** dense in **fiber** and avoiding starchy foods; consuming healthy levels of **natural fats** and animal products; these are all good and necessary steps to take in cancer prevention. Adding lycopene-rich foods is another potent option to assist in impeding cancer growth, however, and an option that needs to be more exercised. This highly publicized nutrient is more famous for its actions against prostate cancer; however, its effects have been documented in other cancers, including colon cancer. In a recent study conducted by the China Medical University Department of Nutrition, the cancer-combating antioxidant lycopene has been shown to inhibit the proliferation of crc cells. It accomplishes this by suppressing an important signaling pathway that enables cancer cells to grow and survive. Curtailing the actions of this particular pathway has been suggested as a potential way to begin treating and preventing other cancers as well, and the actions of this antioxidant have opened a new area of cancer research that could facilitate cancer prevention in the future. Lycopene is a red pigment found in tomatoes and other such red colored produce such as **watermelon, guava and pink grape fruit**. It is a precursor to vitamin A in the body and has far reaching capabilities in cancer prevention and preventing degenerative disease such as heart disease.

www.naturalnews.com/z023959.html

13. Vitamin E is Anti-Cancer (Aug 28/08)

Vitamin E is an important antioxidant micronutrient. Research shows that vitamin E not only improves skin health, boosts the immune system, protects against heart disease, aging and

Alzheimer's, but also has a role in protection against some types of cancer. Unlike some vitamins, which consist of a single compound, vitamin E consists of 8 different compounds, four tocopherols and four tocotrienols. Our food contains all eight compounds. Tocopherols are most commonly found in nuts and vegetable oils, whereas tocotrienols are primarily derived from palm oil, oat, rye, wheat germ, barley and rice bran. Even though the vitamin E family consists of 8 members, most research has traditionally focused on alpha-tocopherol. Alpha-tocopherol is the most abundant form of vitamin E in the plasma and tissue of humans as well as in vitamin supplements, while the seven other types of vitamin E were greatly ignored for many years. Recent research over the last few years has led to the conclusion that the 8 vitamin E compounds have different anti-carcinogenic potencies which need to be considered.

The cancer preventive properties of vitamin E were first suspected when studies showed that people in the Mediterranean area who consumed diets rich in vitamin E have a lower risk of colon cancer than people in Northern Europe and the US (Eur J Clin Nutr. 1989; 43: 49-55, Cancer Causes Control 1995; 6:525-31). More recently, the Melbourne Colorectal Cancer Study showed that dietary vitamins E and C were protective for both colon and rectal cancer, and that for both vitamins there was a dose-response effect of increasing protection. (Nutr Cancer. 2006; 56:11-21)

You should however, be aware, that all vitamin E supplements are not created equal. Many contain **synthetic** vitamin E, and many do not contain all of the various types of **natural** vitamin E that the body requires. It is important to make certain that the supplement contains both natural tocopherols and tocotrienols in their natural forms if you want to get the most out of what the vitamin has to offer. Only products that contain the complete vitamin E family – tocopherols plus tocotrienols – provide the full spectrum of benefits of vitamin E.

www.stopagingnow,com/news/news_flashes/4340

14. Weight Loss May Cut Risk of Colorectal Growths (Aug 29/08)

Obesity is associated with an increased risk of colorectal adenomas – growths or polyps that can become cancerous. But a study found that weight loss might reduce the risk. Researchers investigated the relationship between obesity and the prevalence of colorectal polyps and studied the effect of weight loss on the development of these abnormal growths after one year. Almost 8,000 average risk subjects had an initial colonoscopy and about 2500 of them had a second examination a year later. The prevalence of colorectal polyps at the initial colonoscopy increased proportionally with increasing body weight, the team found. Increasing body mass index or BMI was also associated with increasing numbers of colorectal polyps, but not with size or stage of the polyps. Losing weight appeared to have a beneficial impact on colorectal growths. While the incidence of polyps 1 year after the initial exam increased proportionally with increasing BMI, the researchers found that the incidence was lower in people who lost weight (9.3%) than in those that gained weight (16.2%) or maintained their weight (17.1%).

www.reuters.com/article/healthnews/

15. Trans Fats Tied To Colorectal Polyps (Sept 2/08)

People who ate the most trans fats were almost twice as likely to have colorectal adenomas found when they had a colonoscopy. Researchers interviewed more than 600 people after colonoscopies performed in University of North Carolina Hospitals between 2001 and 2002 asking them about lifestyle and diet. They divided the whole group into 4 smaller groups based on consumption of foods high in trans-fatty acids. The group with the highest intake of trans fats were 86% more likely to have adenomas, the colon polyps that can develop into cancer. When vegetable oils are processed or hydrogenated to increase the shelf life of baked goods, trans fats are produced. They are commonly found in baked goods, crackers, cookies and snack foods. Solid shortenings and some margarines also contain trans fats as do foods fried in them. Trans fats raise levels of low-density lipoprotein (LDL) or "bad cholesterol" in the blood which is associated with heart disease. However, they may work differently in the intestinal tract to increase polyps. The lead investigator concluded: these results suggest that consumption of high amounts of trans-fatty acid may increase the risk of colorectal neoplasia, and they provide additional support to recommendations to limit trans-fatty acid consumption.

Vinikoor, L, et al., Consumption of trans-Fatty Acids and Its Association with Colorectal Adenomas. American Journal of Epidemiology, Volume 6, Number 3, August 1, 2008, pp. 289-297

16. Alcohol Increases Colorectal Cancer Risk (Sept 2/08)

Drinking increases risk for crc, but the types of alcoholic drinks don't appear to make a difference. Instead, danger seems to come from the alcohol itself rather than other ingredients. In the Netherlands Cohort Study on diet and cancer, alcohol consumption and specific alcoholic drinks were studied for more than 2300 people who had colon or rectal cancer. Compared to people who did not drink at all, there was a 30% increase in colorectal cancer among people who had 3 or more alcoholic drinks a day. Both men and women were affected by alcoholic consumption in the study. Alcohol increased cancer risk more in the rectum, and colon near the rectum, than higher in the colon. The lead investigator concluded: Our data showed a positive association between alcohol consumption and risk of crc, which seemed to be mainly explained by the alcoholic content of alcoholic beverages, rather than other constituents. Also, cancer risk may vary according to anatomical subsite.

Bongaerts B et al., Alcohol Consumption, Type of Alcoholic Beverage and Risk of Colorectal Cancer At Specific Subsites. International Journal of Cancer, published online August 27, 2008