COLORECTAL CANCER ASSOCIATION OF CANADA

COLORECTAL CANCER RESEARCH
Week Ending February 6, 2009

The following colorectal cancer research update extends from January 24 –February 6, 2009 inclusive and is intended for informational purposes only.

DRUGS

1. Folfiri-3 is A Promising Second Line Chemotherapy For Colorectal Cancer (Jan. 25/09)

Second-line irinotecan-based chemotherapy is commonly used in metastatic colorectal cancers after first-line oxaliplatin-based chemotherapy. This study compared the efficacy of Folfiri-3, Folfiri-1 and other irinotecan based regimens in oxaliplatin-pretreated metastatic colorectal cancer patients in the GERCOR OPTIMOX1 study. Metastatic colorectal cancer patients included in the OTIMOX1 phase III study received first line oxaliplatin-based chemotherapy (folfox). Patients then went on to receive irinotecan-based second line chemotherapy. Investigators then wished to measure such things as second line progression free survival and tumor response according to the type of irinotecan based regimen that was used (ie folfiri-3, folfiri-1 or other regimens). According to the results, folfiri-3 appeared to have the longest second-line progression free survival and best response. Investigators concluded that for colorectal cancer patients who had been pretreated with oxaliplatin, progression free survival in second line therapy appeared to be improved by folfiri-3 regimen.

Bidard FC, et al., Efficacy of Folfiri-3 or other irinotecan-based regimens in oxaliplatin-pretreated metastatic colorectal cancer in the GERCOR OPTIMOX1 study. Annals Oncology. 2009. Online Edition. Ahead of Print.

2. Oncolytics Biotech Inc. Announces Start of Patient Enrolment in Translational Clinical Trial Investigating Reolysin in patients with Metastatic Colorectal Cancer (Jan. 27/09)

Oncolytics Biotech Inc. is a Calgary-based biotechnology company focused on the development of oncolytic viruses (viruses that kill cancer cells) as potential cancer therapy. Oncolytics Biotech has announced that patient enrolment has begun in a UK clinical trial investigating intravenous administration of Reolysin in patients with metastatic colorectal cancer prior to surgical resection of liver metastases. The trial (REO 013) is an open-label, non-randomized, single centre study of Reolysin given intravenously to patients for five consecutive days in advance of their scheduled operations to remove colorectal cancer mets to the liver. Patients will comprise two groups receiving Reolysin, either at an early (21-10 days) or late time point (less than 10 days) before surgical resection. After surgery, the tumour and surrounding liver tissue will be assessed for viral status and anti-tumour effects. Eligible patients are those with proven crc, planned for potentially curative surgical resection of liver mets. Up to 20 patients will receive one cycle of treatment in this trial, with approximately 10 in each of the early and late virus groups.

www.cancercompass.com/cancer-news/1,15261,00.htm?c=1004:5:1:2

3. Action of BITE Antibody MT110 Described (Jan. 28/09)

Micromet Inc., a biopharmaceutical company, announced new data describing the mode of action of BITE antibody MT110. MT110 is a T cell-engaging antibody that targets a protein (EpCAM) which is expressed with high frequency on most human adenocarcinoma, including colorectal cancer. The data demonstrate that when T cells are connected to cancer cells by MT110, they deliver two kinds of toxic proteins into cancer cells. One toxic protein called perforin, forms holes in the cancer cell's outer membrane. The second kind of protein called granzymes is a family of proteolytic enzymes that triggers the self destruction of the cancer cell, a process called programmed cell death or apoptosis. Between the two toxic proteins, there is enhanced killing of cancer cells. This is obviously the desired effect. MT110 is currently in a phase I clinical trial for the treatment of patients with colorectal cancer.

Haas C et al., Mode of cytotoxic action of T cell-engaging BITE antibody MT110. Immunobiology. Published online ahead of print. PubMed ID 19157637

4. Pro-Pharmaceuticals ' DAVANAT will be entering a Phase III trial (Jan. 29/09)

Pro-Pharmaceuticals Inc. has received permission to conduct a phase III trial in respect of its agent DAVANAT to demonstrate superiority to the best standard of care for late stage colorectal cancer patients. The results of the Company's completed Phase I trial for late stage cancer patients indicate that DAVANAT may improve the pharmacokinetic profile of 5FU in patients by keeping the chemotherapy 5FU in the bloodstream longer with no increase in toxicity. In a phase II trial for end-stage colorectal cancer patients, DAVANAT extended median survival to 6.7 months with significantly reduced side effects, as compared with 4.6 months for the best standard of care. DAVANAT is a carbohydrate compound that is administered with chemotherapies and biologics to treat cancer. DAVANAT's mechanism of action is based on binding to lectins (sugar binding proteins). DAVANAT targets specific lectin receptors (Galectin) on cancer cells. Current research indicates that Galectins affect cell development and play important roles in cancer, including tumor cell survival, angiogenesis and tumor metastasis.

http://www.genengnews.com/news/bnitem.aspx?name=48757614&chid=0&taxid=7

5. Biothera Expands Metastatic Colorectal Cancer Trial (Feb. 1/09)

Biothera has expanded the second arm of its clinical trial evaluating whether the combination of Imprime PGG and Erbitux can achieve positive outcomes for metastatic colorectal cancer patients without the use of chemotherapy. Imprime PGG is a targeted immunotherapeutic drug candidate from Biothera that works synergistically with monoclonal antibodies such as Erbitux through specific innate immune cell activation. It activates a large population of the body's immune cells (neutrophils) to kill cancer cells. Unlike other drugs that trigger a broad innate immune response, Imprime PGG selectively activates immune cells without inducing side effects and therefore has the potential to improve patient response rates for existing monoclonal antibody therapies in approved indications, as well as create new indications for these drugs as well as enhance the efficacy of development-stage monoclonal antibody drugs.

www.medicalnewstoay.com/articles/137360.php

6. Treating Rectal Cancer Post-Surgical with Avastin + Folfox (Clinical Trial E5204) (Feb. 2/09)

Can adding avastin to folfox therapy after rectal surgery reduce recurrence and improve survival for patients with rectal cancer? A clinical trial to answer this question is underway and is looking for participants. The E5204 study randomly assigns patients who have already completed a course of chemoradiotherapy and had their rectal cancer removed surgically to folfox or folfox plus avastin. The primary objective is to improve survival after treatment for rectal cancer. Stage II or III rectal cancer patients are eligible if they completed chemoradiotherapy before surgery; and have had surgery to remove the rectal tumor between 4 and 8 weeks previously. Also, there must not be any indication of distant metastases. Clinical trials are going on in major centres in New Brunswick, Ontario, Quebec and Saskatchewan. For a list of centres, please visit http://clinicaltrials.gov/ct2/show/NCT00303628

www.C3ColorectalCancerCoalition.com/Research&TreatmentNews

7. Combining Targeted Therapies Shortens Survival in Colon Cancer (Feb. 5/09)

Attempting to boost the efficacy of standard chemotherapy plus avastin against metastatic colon cancer by adding erbitux was a complete failure according to the researchers who reported their findings in the latest issue of the New England Journal of Medicine. Far from improving outcomes, the combination of monoclonal antibodies and chemotherapy cut median progression free survival by more than a month in a randomized trial. Median progression free survival was 10.7 months among 378 patients assigned to a regimen of oxaliplatin, xeloda and avastin. In 377 patients who took the same drugs plus erbitux, median progression free survival was 9.4 months. Across all patients, median overall survival was 19.4 months in the patients given erbitux compared with 20.3 months in the control arm. Moreover, the erbitux-avastin-chemo combination led to more grade 3 and 4 adverse effects – primarily skin problems previously

associated with erbitux. According to the investigators, the results argue against the combined use of avastin and erbitux with chemotherapy in cases of metastatic colorectal cancer, even in patients with wild type Kras. As for why, the researchers speculated that the two antibodies had some kind of interaction, perhaps involving hypertension, a known side effect of avastin. But they admitted that specific evidence for such an interaction was lacking.

Tol J et al., Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. New England Journal of Medicine. 2009; 360: 563-572

SURGICAL

8. Survival of Medicare Patients After Surgery for Liver Mets (Feb. 3/09)

While some surgical studies are now reporting 5-year survival after surgery to remove colorectal cancer tumors that have spread to the liver of 40-60%, a review of more general national experience for patients enrolled in Medicare in the US found lower survival rates. Among Medicare-enrolled colorectal cancer patients 65 and over who had liver resection, only 26% (1 in 4) were alive 5 years later. Those eighty and over were almost twice as likely to die within three months after surgery. And removing both the primary tumour in the colon or rectum and the liver tumours also raised the risk of death in those three months. Simultaneous resection of both colon and liver tumours increased three-month mortality two and a half times. Survival at 5 years was 25.5%. Those at higher risk of not surviving were patients aged 80 and older and who had both colorectal and liver tumours removed at the same time.

Robertson Douglas, et al., Survival after hepatic resection of colorectal cancer metastases. Cancer, Volume 115, Issue 4, February 15, 2009; pp752-759.

9. Combining Laparoscopic-Endoscopic Resections of Colorectal Polyps (Jan. 28/09)

Large, colorectal polyps or those that are difficult to access may not be amenable to conventional excision through colonoscopy and may require surgical resection. This study was designed to evaluate the resection of such polyps by the use of ***combined laparoscopic-endoscopic resections (CLER).*** Patients received CLER from January 1997 and December 2006 – a total of 146 patients. Postoperative complications occurred in only 5 patients which necessitated surgical intervention in four of them. Researchers concluded that combined laparoscopic-endoscopic resection is an efficient, safe, and minimally invasive alternative to open resection for selected patients with difficult polyps, but should be restricted to benign disease.

Wilhelm Dirk, et al., Combined laparoscopic-endoscopic resections of colorectal polyps: 10 year experience and follow up. Journal of Surgical Endoscopy. Published online: Ahead of print. DOI 10.1007

RADIATION / INTERVENTIONAL RADIOLOGY

10. Preoperative Short Course Radiotherapy vs. Combined Radiochemotherapy in Locally Advanced Rectal cancer (Feb. 6/09)

The additional use of radiotherapy has changed the treatment of locally advanced rectal cancer dramatically. But a major achievement has been the development of total mesorectal excision (TME) as a surgical standard and the recognition that the surgeon plays a significant role as a prognostic factor. The benefit of administering hypofractionated radiotherapy before surgery (SCRT: five fractions each of 5Gy) has been demonstrated in conjunction with TME by the Dutch Colorectal Cancer Group. The concept of combined radiochemotherapy after surgery (conventional radiation of about 50 Gy with chemotherapy) has not been compared over surgery alone with TME. However, the German Rectal Cancer Study Group recently demonstrated that radiochemotherapy administered before surgery was better than radiochemotherapy after surgery in terms of local control. This study sought to compare preoperative radiochemotherapy to preoperative hypofractionated radiotherapy and as it is ongoing hypothesized that preoperative radiochemotherapy is superior to preoperative hypofractionated radiotherapy. Results will be forthcoming.

Siegel Robert, et al., Preoperative short course radiotherapy vs Combined radiochemotherapy in locally advanced rectal cancer: a multi-centre prospectively randomized study of the Berlin Cancer Society. BMC Cancer: 2009; 9: 50; doi: 10.1186/1471-2407-9-50

11. Microwave Ablation to Treat Liver Mets (Feb. 6/09)

The FDA has cleared a new microwave ablation system to treat liver tumors that cannot be surgically removed. The device uses microwaves to create intense heat within the tumor to destroy it. Now being used at the University of California at San Diego Medical Center, a thin antenna that emits microwaves can be inserted through the skin, laproscopically, or during an open surgery.

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SCREENING

12. Comparing Immunochemical Fecal Occult Blood Tests for Colorectal Adenoma Detection (Feb. 5/09)

This study sought to compare 6 immunochemical FOBTs for identifying colorectal adenomas among adults who attended screening colonoscopy examinations. The study took place from January 2006 to December 2007 in Germany with 1319 participants at average risk for colorectal cancer. 6 different qualitative immunochemical FOBTs were done with stool samples collected before bowel preparation for colonoscopy. Technicians who read the tests were blinded to colonoscopy results, and colonoscopists were blinded to FOBT results. For the 2 best performing tests, sensitivity for detection of advanced adenomas was 25% and 27% and specificity was 97% and 93% and investigators concluded that qualitative immunochemical FOBTs could be an option for future colorectal cancer screening because they showed better performance characteristics for precursor lesions than guaiac-based FOBTs and are practical for mass screening.

Hundt, Sabrina, et al., Comparative Evaluation of Immunochemical fecal occult blood tests for colorectal adenoma detection. Annals of Internal Medicine.2009 Volume 150; Issue 3: pp162-169.

OTHER

13. African Americans Are Usually Diagnosed Later and with Worse Colorectal Cancer Survival (Feb. 2/09)

African Americans in both a large national database of colorectal cancer patients and in records of a Philadelphia hospital were more likely to be diagnosed at an advanced stage and have poorer survival at every stage of crc than white patients. African American patients diagnosed with colorectal cancer face higher overall risk and mortality as compared to Caucasian patients. The disparity among African Americans and Caucasians has been attributed to multiple factors, including later stage at diagnosis, a higher proportion of poor histopathological features, inadequate and unequal treatment and socioeconomic factors. The objective of this study was to compare survival in African American and Caucasian colorectal cancer patients. African American patients presented with a more advanced stage and had worse five year survival both overall and stage by stage, than Caucasian patients. Nodal involvement was also greater for African American patients. African American patients with colorectal cancer were more likely to present with later stage, more proximal (left sided) tumours and had higher nodal involvement in early stage disease (I/II) when compared to Caucasian patients, such wee the conclusions of the lead investigator.

2009 GI Symposium, Mitchell EP, et al., Differences in Colorectal disease in African-American and Caucasian patients: A comparison of an urban, university hospital with the National Cancer Institute SEER database.. Abstract 306

14. Targeted Psychosocial Counseling can Ease Cancer Fatigue (Jan. 28/09)

Counseling that focuses specifically on fatigue can reduce its symptoms and help cancer patients cope with it during cancer treatment. The Cochrane Collaboration reviewed randomized clinical trials of psychological interventions aimed at managing cancer fatigue. Studies included both interventions that included fatigue among other symptoms and those that were aimed directly at fatigue alone. In the 22 studies that included fatigue but didn't focus on it, there was little impact. However, four of five studies which were designed to treat fatigue specifically were effective in reducing it and maintaining that reduction. Three counseling sessions of about an

hour helped patients by educating patients about fatigue, teaching self-care and coping techniques, and helping patients learn to balance periods of activity and rest. The Cochrane Collaboration summarized as follows:
There is limited evidence that psychosocial interventions are effective in reducing fatigue during active treatment in cancer patients. Most promising are psychosocial interventions specifically designed to treat fatigue. In general, during these interventions patients were educated about fatigue, were taught in self-care or ongoing techniques, and learned to manage their activity. Interventions that did not focus on fatigue were rarely effective in reducing fatigue.

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15. Estrogen Plus Progestin Use Showed Greatest Reduction in Cancer Risk (Jan. 28/09)

Sequential estrogen plus progestin use was associated with the largest overall risk reduction for colorectal cancer compared with other hormone therapy formulations and regimens. Researchers examined cancer risk associated with duration and recency of Hormone Therapy (HT) formulations and regimens in postmenopausal women from the Breast Cancer Detection Demonstration project follow up study. They conducted telephone interviews and mailed questionnaires to gather HT use and other risk factor information. 960 women were identified as new cases of colorectal cancer. The largest reduced risk among estrogen users was for current users and users of greater than ten years duration. There was a greater reduction in risk for users of estrogen plus progestin therapy and sequential regimen users had the greatest reduction according to the researchers. The largest risk reduction was observed for past users of greater than five years.

Johnson, Jill, et al., Menopausal Hormone Therapy and Risk of Colorectal Cancer. Cancer Epidemiology, Biomarkers and Prevention. 2009; 18: 196-203

NUTRITION

16. Effect of Body Mass Index on Short Term Outcomes after Colectomy for Cancer (Jan. 15/09)

Obesity has been known to be associated with an increased risk of postoperative complications after colectomy for cancer, but it is unclear which specific complications occur more frequently in obese patients. The objective of this study was to assess the association of body mass index (BMI) on short term outcomes after colectomy for cancer. Investigators found that the morbidly obese have worse outcomes after colon cancer surgery. After colectomies, complications occur in more than 30% of patients with a body mass index over 34 compared to 29.5% of normal weight patients. More frequent complications include kidney failure, surgical site infections, wounds reopening, and pulmonary embolism. Occurring in 20.7% of patients, site infections were more than twice as common in the morbidly obese.

Merkow, Ryan, et al., Effect of Body Mass Index on Short Term Outcomes After Colectomy for Cancer. Journal of the American College of Surgeons. 2009. V. 208; Issue 1: pp 53-61.

17. Consuming Fish Has a Protective Effect on Colorectal Cancer Risk (Feb. 2/09)

One of the largest epidemiological studies on dietary habits and colorectal cancer incidence in Eastern Europe determined that increased fish consumption has a preventive effect on colorectal cancer and modulates the effect of meat consumption. Excessive red and processed meat intakes have been positively associated with colorectal cancer. This hospital based case-control study was performed in 548 colorectal cancer patients between November 2000 and May 2008. The control group consisted of 745 patients of the same hospital with no history of cancer admitted for treatment of non-cancer related conditions. During the 5 year study period, a food frequency questionnaire was used to gather necessary data. The risk of colorectal cancer increased with intake of stewed or cooked meat, and there was a significant reduction in colorectal cancer already at the moderate fish intake of one or two servings per week, but there was an even lower risk of colorectal cancer at higher fish consumption. All multivariate statistical models employed in the analysis considered potential confounders, such as demographic characteristics of subjects, body mass index, smoking status, leisure time, physical activity, energy consumption and intake of meat products.

Jedrychowski, W, et al., A Protective Effect of Fish Consumption on Colorectal cancer Risk. Annals of Nutritional Metabolism. 2009, January 26; 53(3-4): 295-302

18. **Soy Intake Linked to Lower Risk for Colorectal Cancer in Postmenopausal Women** (Jan. 29/09)

Consumption of soy foods has been found to be associated with a lower risk for colorectal cancer in postmenopausal women. Soy and some of its constituents such as isoflavones, have been shown to have cancer-inhibitory activities in experimental studies. The goal of this study was to evaluate whether intake of soy food is associated with a risk for colorectal cancer. The study cohort consisted of 68,412 women aged 40 to 70 years and without cancer or diabetes at enrollment. In-person interviews using a validated food-frequency questionnaire evaluated usually soy food intake at baseline (1997-2000) and during the first follow-up (2000-2002). There were 321 incident cases of colorectal cancer identified during a mean follow-up of 6.4 years. Total soy food intake was inversely associated with colorectal cancer risk, after adjusting for potentially confounding variables. For each 5g/day increment in dietary intake of soy as measured by dry weight to approximately 1 oz there was an 8% reduction in risk. This study suggests that consumption of soy foods may reduce the risk of colorectal cancer in postmenopausal women. Given the fact that colorectal cancer is one of the most common cancers worldwide and that soy can be readily incorporated into most diets, the findings have important public health implications in the prevention of this common malignancy.

Yang, Gong et al., Prospective cohort study of soy food intake and colorectal cancer risk in women. American Journal Clinical Nutrition. 89: 577-583, 2009.

19. Inflammation in Colon may be Suppressed by Nutrient Quercetin (Feb. 409)

Repeated inflammation has been determined to lead to colon cancer. This study has shown the anti-inflammatory and therapeutic effects of a tiny molecule, called quercetin, can have on the colon. It is found in most plant-based foods and can be obtained easily be eating vegetables and fruits (onions, peppers, tomatoes etc.). Previous studies showed quercetin was effective in reducing the rate of colon cancer in laboratory tests, but this latest research shows how the compound works. It examined the response of quercetin-supplement diets in lab rats – some in the early stages of colon cancer formation and others without cancer. Early lesions in the colon are thought to be a marker or predictor of tumor formation. Quercetin is known to reduce the number of these lesions. One of the major determinations of he study was that inflammation is one of the biggest contributors of the development of colon cancer. Two enzymes were targeted – known to researchers as Cox-1 and Cox-2. The first one is a routine protein that the body expresses all the time. But the second Cox has implication in a lot of diseases. High levels of Cox 2 is indicative of a bad thing, such as in colon cancer. Not only is Cox 2 present in colon cancer, but recent research showed that before Cox 2 levels rose in colon cancer, the Cox 1 levels first became elevated. Cox 1 therefore, has some sort of control over whether Cox 2 gets expressed. Both the control group and the cancer injected group in the study that were consuming quercetin in their diets, had lower levels of both Cox 1 and Cox 2. This suggests that there may be opportunity for quercetin to suppress tumor development. Investigators are therefore recommending to ingest fruits and vegetables containing quercetin, and to especially ingest the whole food such as the peel of the apple where the quercetin is contained, so that you can obtain the most from these beneficial compounds.

Turner, Nancy, et al., Quercetin may suppress rat aberrant crypt foci formation by suppressing inflammatory mediators that influence proliferation and apoptosis. Journal of Nutrition. 2009 Vol 139; No 1: pp101-105

20. Ginseng Preventing Colorectal Cancer (Feb. 5/09)

Researchers have discovered that ginseng, particularly when heated, may be very effective against colorectal cancer. Ginseng has been a staple of Asian herbal medicine, and studies have indicated that it might help not only prevent cancer, but also relieve some of the side effects (such as nausea and vomiting) of cancer therapies. Ginseng comes in Asian and American varieties, both of which contain active compounds called saponins, which are responsible for the herb's anti-cancer properties. Although Asian ginseng has a long history of use, and research, American ginseng has not been as well studied. As Researchers treated human colorectal cancer cells with extracts of American ginseng berry and root that had been steam heated. The steamed extracts increased the saponin activity, and halted the cancer cells' growth by as much as 99%. Steaming the Chinese herb notoginseng similarly increased its anti-cancer effect. Although treatment with ginseng doesn't work as well as chemo, it might be an

effective adjuvant cancer treatment. Researchers say it could be used together with chemo to increase its efficacy and also to reduce the chemo side effects. The challenge is to determine the optimal dose, and figure out how to deliver ginseng in the most effective way to target the cancer cells without causing significant side effects. Currently researchers are only in the animal testing phase.

Yuan, Chun-Su, et al., Potential role of ginseng in the treatment of colorectal cancer. The American Journal of Chinese Medicine. 2008; 36:1019-1028