COLORECTAL CANCER ASSOCIATION OF CANADA

COLORECTAL CANCER RESEARCH
Week Ending November 14, 2008

The following colorectal cancer research update extends from November 1 – November 14, 2008 inclusive and is intended for informational purposes only.

DRUGS

1. **A Phase I Study of Combination Therapy with S-1 and Irinotecan (CPT-11) in Patients with Advanced Colorectal Cancer** (Nov. 1/08)

   5FU is the key drug to treat advanced colorectal cancer. It is used with other drugs, such as leucovorin and irinotecan, to increase effectiveness of anticancer drugs. Recent studies have shown that excessive toxicity results when bolus 5FU, leucovorin and irinotecan are combined. S-1 is an oral fluoropyrimidine preparation and it might be used as an anticancer drug instead of 5FU. It is a novel oral fluoro-uracil antitumor drug that contains a combination of 3 pharmacological agents: **tegafur** (FT), a 5-fluorouracil (5FU) prodrug, **5-chloro-2,4-dihydroxypyridine** (CDHP) and **potassium oxonate** (Oxo) which reduces the gastrointestinal toxicity of 5FU. The convenient oral route, antitumour activity, and improved toxicity profile in comparison with intravenous 5FU makes S-1 an attractive option for combining with intravenous CPT-11 in the treatment of advanced colorectal cancer. This study evaluated the tolerability and clinical efficacy of combining S-1 orally and CPT-11 in patients with advanced or metastatic colorectal cancer. A total of 21 patients were entered in this study. The maximum tolerated dose of CPT-11 was considered to be 150 mg/m2, because 2 of 3 patients developed dose-limiting toxicities such as leucopenia, diarrhea and anorexia. The recommended dose of CPT-11 was set at 120 mg/m2. S-1 was administered orally at 80 mg/m2 per day for 14 consecutive days followed by a 2 week rest. CPT-11 was given intravenously on days 1 and 15 of each course. Courses were repeated every 4 weeks. Tumour response rate was 42.8% and progression free survival time was 10 months. Researchers concluded that a combination of S-1 and CPT-11 showed a good safety profile and can be recommended for further phase II studies in patients with colorectal cancer.

   Shiozawa, M, et al., Combination of S-1 and Irinotecan (CPT-11) Has a Good Safety Profile and is Recommended for Further Phase II Studies in Colorectal Cancer. Journal of Cancer Research & Clinical Oncology. Online Edition. 1432--1335

2. **Micromet Presents Data on Human Antibody Adecatumumab Against Kras-Mutated Colon Cancer Cells** (Nov. 4/08)

   Micromet Inc., a biopharmaceutical company developing novel, proprietary antibodies for the treatment of cancer, presented data from a preclinical study showing cytotoxic activity of anti-EpCAM antibody adecatumumab (MT201) against KRAS-mutated human colon cancer cells on November 1, 2008 at the 23rd Annual meeting of the International Society for Biological Therapy of Cancer, that took place October 31-November 2, 2008 in San Diego, California. The new preclinical data indicated that human colon cancer cells are efficiently eliminated in tested cell lines by adecatumumab, mediated by antibody-dependent cellular cytotoxicity (ADCC), irrespective of their KRAS mutation status. Recent studies suggest that anti-EGFR antibodies cetuximab (erbitux) and panitumumab (vectibix) are beneficial for patients with Kras wild type tumors, however, show limited or no efficacy in the treatment of colon cancer patients with a mutated Kras gene in their cancer cells. These findings recently led to the approval of cetuximab for first line therapy in patients with Kras wild type tumors. As a consequence, there is a high need for the development of treatment strategies covering those patients who are not able to benefit from this important new treatment option as their tumors carry the Kras mutated gene. This mutation is found in approximately 35-40% of patients with this disease. Given that more than 95% of colon cancer patients strongly express EpCAM on their tumors, and that 35-40% of patients who have a Kras mutant tumor may not benefit from treatment with anti-EFGR antibodies, adecatumumab could be investigated as a potential alternative for the treatment of Kras mutant colon cancer tumors. Micromet plans to initiate a phase II study investigating the activity of adecatumumab in colon cancer patients with completely resected liver mets.

   www.therapeuticsdaily.com/news/

3. **A Phase II Study of Gefitinib, 5FU, Leucovorin, and Oxaliplatin in Previously Untreated Patients with Metastatic CRC** (Nov. 12/08)

   Researchers at Stanford University investigated gefitinib, 5FU, leucovorin and oxaliplatin (IFOX) regimen as first line therapy in patients with metastatic colorectal cancer. Eligible patients had stage IV colorectal adenocarcinoma, and had not received prior chemo. Each cycle consisted of

14 days. Cycle 1 consisted of oxaliplatin, leucovorin and 5FU (folfox 4). All subsequent cycles consisted of folfox 4 with gefitinib at 55 mg orally daily throughout the 14 day cycle. 43 of the 45 patients were assessable for response. 31 of the 43 had either a complete or partial response. Researchers concluded that IFOX is an active first line regimen in patients with metastatic colorectal adenocarcinoma, showing higher response rates but also increased toxicities compared with folfox4 alone in a similar patient population.

Fisher, George, et al., A phase II study of Gefitinib, 5 Fluorouracil, Leucovorin and Oxaliplatin in Previously Untreated Patients with Metastatic Colorectal cancer. Clinical Cancer Research. 14: 7074-7079, November 2008

SURGERY

4. Risk of Developing Proximal (Right Sided) Vs. Distal (Left Sided) Colorectal Cancer After a Negative Colonoscopy: A Population-Based Study (Nov. 1/08)

A study published in Clinical Gastroenterology and Hepatology confirms that patients who undergo a complete negative colonoscopy have a reduced incidence of colorectal cancer. However, in the proximal colon (right sided), the incidence reduction of colorectal cancer following complete negative colonoscopy differs in magnitude and timing. The reduction of colorectal cancer is observed in about half of the 14 follow-up years and for the most part occurs after just seven years of follow up. The study raised the question about the effectiveness of colonoscopy in usual clinical practice. **The findings suggest that the effectiveness of colonoscopy is reduced for cancers arising in the proximal colon.** Whether this is due to colonoscopy quality, or whether it is due to tumour biology is the key issue that needs to be addressed. The relative rate of colorectal cancer overall and the relative rate of distal (left sided) colorectal cancer in the study group remained significantly lower than the control population. The relative rate of proximal (right sided) colorectal cancer was significantly lower than the control population in half of the follow up years, mainly after seven years of follow up. Researchers identified 110,402 Ontario residents aged 50-80 years old who had a negative complete colonoscopy between Jan.1/92 and Dec.31/97. Cohort members had no prior history of crc, inflammatory bowel disease or recent colonic resection. Each individual was followed through Dec.31/05 and the relative rate of overall colorectal cancer, distal colorectal cancer and proximal colorectal cancer was compared with the remaining Ontario population. Over a 14 year follow up period, negative complete colonoscopy was associated with a subsequent reduced incidence of crc overall, and of incident crc in the distal colon. However, the reduction in incidence of proximal crc differed in magnitude and timing, and occurred in half of the follow up years, mainly after 7 years of follow up. These results highlight an important limitation of colonoscopy in usual clinical practice.

Rabeneck, Linda, et al., Risk of Developing Proximal Vs. Distal Colorectal Cancer After a Negative Colonoscopy: A Population Based Study. J of Clinical Gastroenterology and Hepatology. Vol 6, Issue 10, 1117-1121

5. Unresectable Colorectal Cancer Can be Cured with Multimodality Therapy (Nov. 3/08)

Colon and rectal cancer that is attached to critical body structures like the wall of the pelvis or important large veins has traditionally been considered not surgically treatable. Patients have been offered palliative treatments designed to extend life or reduce symptoms, but the goal wasn't cure. However, Mayo Clinic surgeons are now working together with teams of surgeons, radiologists, and oncologists to treat normally unresectable colon and rectal cancer with a combination of therapies. Surgery, both external radiation and radiotherapy done during surgery, and chemotherapy have gone beyond palliative care for this group of patients. Almost half of the patients treated with the multimodality approach were alive and cancer free five years after treatment began. Their results are published in the Annals of Surgery. 146 patients were treated whose colon or rectal cancer was considered unresectable because it was attached to a critical body structure with combination of surgery, external beam radiotherapy, intraoperative radiation, and chemo. Five years later, 76 patients were alive (52%) and 66 were alive with no sign of cancer (43%). The best results were achieved in patients under age 58 where there were no cancer cells in the surgical margins, and patients who received chemo after surgery.

Mathis, Kellie, et al., Unresectable Colorectal cancer Can Be Cured with Multimodality Therapy. Annals of Surgery. 248(4): 592-598.

6. Finding Polyps Missed During Colonoscopies for Lynch Syndrome (Nov. 6/08)

Lynch syndrome (also known as hereditary nonpolyposis colon cancer) greatly increases the risk for colon and rectal cancer. People with the gene have about an 8 in 10 chance of getting colon cancer during their lives. Because Lynch cancers develop quickly and grow rapidly, it's important to monitor people who carry the genes closely with colonoscopy every year or two. When doctors in four research centers immediately followed up Lynch syndrome patients after a regular colonoscopy with more intense colonoscopy scrutiny, they discovered they had missed more polyps than they found. During the first exam, their miss rate for adenomas, polyps with the greatest risk of developing into cancer, was 55%. In the study, patients with Lynch syndrome had a conventional colonoscopy and then were randomly assigned for an immediate follow-up test. One half had colonoscopies enhanced with a blue dye that makes polyps easier to see (chromoendoscopy). In the other group, doctors spent a longer time, more than 20 minutes, searching for polyps (intensive inspection).

- 54 patients had an initial colonoscopy where 10 adenomas and 7 hyperplastic polyps (benign polyps). During the second exam, there were 12 more adenomas and 11 hyperplastic polyps
- 28 patients had their colons sprayed with a blue dye during their follow up exam. 15 more polyps (5 adenomas and 11 hyperplastic) were found
- 26 patients had intensive inspections that lasted longer than regular colonoscopies. Doctors found 7 adenomas and 1 hyperplastic polyp

The lead researcher concluded that small adenomas are frequently missed in patients with Lynch syndrome. Although chromoendoscopy did not detect more missed adenomas than intensive inspection in this pilot study, larger trials are needed to determine optimal surveillance techniques in this high risk population.

Stoffel, Elena, et al., Missed Adenomas during colonoscopic surveillance in individuals with Lynch Syndrome (Hereditary Nonpolyposis Colorectal cancer). Cancer Prevention Research, Vol 1, Number 6, November 1, 2008.

www.C3Research&TreatmentNews.com

7. Surgery or RFA for Liver Mets? (Nov. 11/08)

Both surgery and radiofrequency ablation (RFA) are sued to destroy liver tumors that have spread from colorectal cancer, but which approach is better? Hepatic mets of colorectal cancer is quite common occurring at some time in 23% of all of the 190,000 crc patients diagnosed each year. While systemic chemo can slow growth and even cause regression of hepatic mets, long term survival without local therapy is unlikely. Surgical resection of hepatic mets continues to remain the optimal first line treatment for hepatic crc mets. Other therapies that have been used are ethanol injection and cryotherapy which have been replaced by radiofrequency ablation (RFA) and microwave ablation. The role of RFA of hepatic colorectal mets continued to evolve as the technology evolves and experience with RFA matures. There are many conflicting published series comparing efficacy of RFA and resection with some authors advocating a prospective trial comparing RFA and resection while others maintain that RFA is inferior to resection and patients should not be put at risk to compare the 2 therapies. The goal of this study was to evaluate the comparative therapeutic efficacy of RFA and surgical resection for hepatic colorectal mets. Surgeons at the University Of Louisville School Of Medicine reviewed all the cases where patients received either surgery only or RFA only in their hospital over the past 12 years. They had over 1,100 cases involving liver tumors during that time, and 192 involved either a single liver surgery or only RFA. They found the time before cancer came back was considerably shorter for RFA. In addition, cancer returned at the RFA or surgical site more often for RFA, and also recurred more often elsewhere in the liver. Comparing the 2 approaches:

- Time to recurrence anywhere in the body was 12.2 months for RFA and 31.1 months for surgery
- 17% for RFA patients had cancer return at the treatment site compared to 2% of surgical patients
- 33% of RFA patients had cancer return somewhere else in their liver compared to 14% of those who had surgery

Lead investigator made the following comment: Surgical resection is associated with a lower chance of recurrence and a longer disease-free interval than RFA and should remain the treatment of choice in resectable hepatic colorectal mets.

Reuter, Nathaniel, Radiofrequency Ablation vs. Resection for Hepatic Colorectal Metastasis: Therapeutically Equivalent? J of Gastrointestinal Surgery, Online First, October 30, 2008

NUTRITION

8. Green Tea Extracts May Decrease Colorectal Adenomas (Nov. 1/08)

Researchers from Japan have reported that green tea extracts may decrease the incidence of recurrent colorectal adenomas. Experimental studies have shown that tea and tea polyphenols and flavonoids have anti-carcinogenic properties. Some studies have shown that green tea consumption is associated with a lower risk of colorectal cancer. The current study evaluated green tea extracts vs. placebo in 136 patients who had colorectal polyps removed and were negative for polyps one year later. Following the second colonoscopy, when no polyps were detected, patients were randomly allocated to receive 1.5 g of green tea extracts per day for 12 months or nothing. At colonoscopy one year later, the incidence of polyps was 31% in the control group and 15% in the green tea extract group. These authors also reported that the size of recurrent polyps was smaller in the green tea group than in the control group. This appears to be a clean study with the major advantage of using a quantified dose of green tea extract in he treated group. This may be the first demonstration of a positive effect for green tea.

Shimizu M, et al., Green Tea extracts for the prevention of metachronous colorectal adenomas: A pilot study. Cancer Epidemiology Biomarkers and Prevention. 2008;17:3020-3025

9. New Study Reveals Link between Obesity and Colon Cancer Risk (Nov. 1/ 08)

A new study reveals the first-ever genetic link between obesity and colon cancer risk, a finding that could lead to greater accuracy in testing for the disease. The discovery which emanates from the University of Alabama at Birmingham, may also improve efforts to ward off colon cancer with obesity-fighting activities like exercise, weight loss and healthy eating. The research focuses on a gene called ADIPOQ that results in the formation of a fat hormone called adiponectin. It shows those who inherit a common genetic variant of ADIPOQ carry up to 30% reduced risk of colon cancer compared to others. Those identified without the gene variant or those who have unhealthy blood levels of adiponectin may benefit from early colorectal testing. Additional studies are needed to confirm whether those without the variant benefit from cancer prevention lifestyle changes such as diet and exercise.

www.topcancernews.com/news/1839/1/

10. Colorectal Cancer and Meat Eating (Nov. 7/08)

A recent study from the Ontario Family Colorectal cancer Registry, established by the U.S. National Cancer Institute, compared the diets of people who had been diagnosed with colorectal cancer to the diets of people who did not have cancer. It turned out that those who ate the most red meat had a 67% higher risk of colorectal cancer, regardless of any genetic factors they may have had. However, some people with specific genes had a much higher risk from meat-eating – up to 4 times the cancer risk – compared to people who avoid meat.

Cotterchio, M, et al., Red meat intake, doneness, polymorphisms in genes that encode carcinogen-metabolizing enzymes, and colorectal cancer risk. Cancer Epidemiology Biomarkers and Prevention. 2008; 17:3098-3107

11. Vitamin D Prevents Colorectal Adenomas (Nov. 7/08)

Researchers from several U.S. medical institutions have reported that higher circulating vitamin D levels and high vitamin D intake are associated with a decreased incidence of colorectal adenomas and recurrent adenomas. Several case-control studies have suggested that calcium and vitamin D supplementation can decrease the incidence of colorectal cancer, especially in high-risk individuals. However, no randomized trial has confirmed these observations. Researchers involved in the current study performed meta-analyses of 17 epidemiological studies involving vitamin D serum or plasma levels or vitamin D intake. They found that persons with the highest serum or plasma vitamin D levels had a 30% reduction in the risk of developing colorectal adenomas compared with persons with the lowest levels. Persons with highest intake of vitamin D had a 10% reduction in the risk of developing colorectal adenomas compared with those with the lowest intake. The same association was present for patients with recurrent adenomas. These data support the concept that a high intake of vitamin D can decrease the risk of colorectal adenomas. Other studies have suggested that 1-2000 units of vitamin D per day is required for a preventive effect.