COLORECTAL CANCER ASSOCIATION OF CANADA

COLORECTAL CANCER RESEARCH
Week Ending December 26, 2008

The following colorectal cancer research update extends from December 13 – December 26, 2008 inclusive and is intended for informational purposes only.

DRUGS

1. **Addition of avastin to 5FU-based First line Treatment of Metastatic Colorectal Cancer: Pooled Analysis of Cohorts of Older Patients from Two Randomized Clinical Trials** (Dec. 15/08)

   This study examined the clinical benefits of adding avastin to 5FU-based chemotherapy in first line metastatic colorectal cancer treatment. A pooled efficacy data for 439 patients was retrospectively analyzed on an intent to treat basis for overall survival, progression free survival and objective response. Patients who received avastin plus chemo had an overall survival of 19.3 months vs. 14.3 months for those who received placebo plus chemo. Patients treated with avastin plus chemo had a median progression free survival of 9.2 months vs. 6.2 months for placebo plus chemo patients. Response rate was 34.4% with avastin plus chemo vs. 29% with placebo plus chemo. Researchers found that patients over the age of 65 years who were included in the studies from two similar trials in metastatic colorectal cancer indicates that adding avastin to 5FU based chemo improved overall and progression free survival, similar to the benefits in younger patients.

   Kabbinavar FF et al., Addition of Bevacizumab to Fluorouracil-Based First-line treatment of metastatic Colorectal Cancer: Pooled analysis of cohorts of older patients from two randomized clinical trials. J of Clinical Oncology. Early Release, published online ahead of print December 15, 2008. 10.1200/JCO.2008.17.7931

SURGERY

2. **Colonoscopies Not Perfect in Stopping Colorectal cancer Deaths** (Dec. 15/08)

   A new study suggests that while a colonoscopy is a very effective procedure for combating colorectal cancer, it may not be quite as good as previously thought. The procedure does a good job of detecting early signs of disease on the left side of the colon, or large intestine, but is not as effective at spotting potential problems of the right side of the organ. This means a colonoscopy's success at preventing colorectal cancer deaths seems to lie with its ability to uncover so-called "left-sided" problems. The procedure does not appear to be as effective in picking up growths on the right side of the colon as it is in detecting them on the left side. To gauge the effectiveness of colonoscopies at reducing colorectal cancer death, the researchers analyzed Ontario provincial health records for more than 10,000 colorectal cancer patients between the ages of 52 and 90. All the patients had been diagnosed with colorectal cancer between 1996 and 2001, and all had eventually died from the disease by 2003. The researchers found that having a complete colonoscopy was strongly linked to a lower death rate related specifically to colon cancer on the left side of the organ. But, the screening process showed virtually no death-prevention benefit with right-sided colon cancer. Researchers claim there are probably several factors that contribute to the left side/right side discrepancy

   - Poor bowel cleansing before colonoscopy
   - Not completely evaluating the entire right colon
   - Different biology for right sided lesions including more flat or sessile polyps
   - Different molecular basis for the cause and development of right sided cancer

   Researchers continue to emphasize that despite the apparent limitations highlighted in the new study, colonoscopies are still the gold standard for detection of colorectal cancer. And whether screening for it results in a 60% reduction in death or 90% reduction, there is just no other cancer that can be seen this well, and colonoscopy certainly reduces mortality.

   Baxter, N, et al., Association of Colonoscopy and death from colorectal cancer: a population based, case-control study. Annals of Internal Medicine, Early Release article. December 16, 2008.

3. Surgery with HIPEC Increases Long Term Survival for Peritoneal Carcinomatosis (Dec. 23/08)

Over half the patients whose colorectal cancer had spread to their abdominal cavity were alive 5 years after treatment in a French center with surgery and heated chemo. This was substantially better than those who only received modern chemo without surgery. Peritoneal carcinomatosis is diagnosed when cancer spreads into the abdominal cavity and tumors develop on the surface of abdominal organs. In the past peritoneal carcinomatosis has been a difficult condition to treat with very poor results from chemo. However, surgery to remove all signs of tumor followed by washing the open abdomen after surgery with heated chemo is achieving some remarkable results. 5 years after cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC) in a French cancer center, 51% of patients were alive. Research surgeons compared these results to a comparable group of patients treated with modern systemic chemo where cytoreductive techniques were not available. After systemic chemo with modern drugs, 13% of patients were alive 5 years later. Median survival time was 24 months, compared to 63 months for patients treated with cytoreductive surgery and HIPEC. All patients in the study had tumors that were isolated in their abdomen, and their cancer had not spread beyond the abdomen.

Elias et al., Surgery with HIPEC Increases Long Term Survival for Peritoneal Carcinomatosis. J of Clinical Oncology, published ahead of print, December 22, 2008.
www.C3:ColorectalCancerCoalittion.com

4. Repeated Transarterial Chemoembolization in the Treatment of Liver Metastases of Colorectal Cancer (Dec. 23/08)

In a trial to evaluate local tumor control and survival data after transarterial chemoembolization with different drug combinations in the palliative treatment of liver metastases in patients with colorectal cancer (crc), it was shown that chemoembolization is a minimally invasive therapy option for palliative treatment of liver metastases in patients with crc, with similar results among 3 chemoembolization protocols. 463 patients with unresectable liver mets of crc that did not respond to systemic chemotherapy were repeatedly treated with chemoembolization in 4 week intervals. 2441 chemoembolization procedures were performed. Local chemotherapy protocol consisted of mitomycin C alone in 243, mitomycin C with gemcitabine in 153, or mitomycin C with irinotecan in 67. Embolization was performed with lipiodol and starch microspheres for vessel occlusion (blockage). MRIs were performed to evaluate tumor response. 1 year survival rate after chemoembolization was 62% and 2 year survival rate was 28%. There was no statistically significant difference between the 3 treatment protocols.

Vogl, TJ et al., Repeated Transarterial Chemoembolization in the Treatment of Liver Metastases of Colorectal Cancer: Prospective Study. Radiology. 2009: 250:281-289

5. Long Term Results of 2-Stage Hepatectomy for Irresectable Colorectal Cancer Liver Mets (Dec. 23/08)

This study assessed feasibility, risks, and long term outcome of 2-stage hepatectomy as a means to improve resectability of colorectal liver mets. It concludes that 2-stage hepatectomy provides a 5 year survival of 42% and a hope of long term survival for selected patients with extensive bilobar colorectal cancer mets, irresectable by any other means. Among 262 patients with initially irresectable colorectal cancer mets to the liver, 59 patients were planned for 2 stage hepatectomy. Patients were eligible when single resection could not achieve complete treatment, even in combination with chemo, portal embolization, or radiofrequency ablation, but tumors could be totally removed by 2 sequential resections. A 2 stage hepatectomy was feasible in 41 of 59 patients. 18 failed to complete the second resection. Chemo was delivered before, in between and after the 2 hepatectomies for the 41 remaining patients. The mean delay between the 2 liver resections was 4.2 months. After the median followup of 24.4 months, overall 3- and 5 year survivals for patients that completed both hepatectomies were 60% and 42%, respectively and disease free survivals were 26% and 13% at 3 and 5 years.

Wicherts Dennis, et al., Long-Term Results of Two stage Hepatectomy for Irresectable Colorectal Cancer Liver Metastases. Annals of Surgery. 248(6):994-1005 December 2008.

6. Ratio of Metastatic to Examined Lymph Nodes is a Powerful Independent Prognostic Factor in Rectal Cancer (Dec. 23/08)

The aim of this study was to evaluate the prognostic value of the ratio of metastatic to examined lymph nodes (LNR) in patients with rectal cancer. Lymph node ratio has been shown to have prognostic value in patients with colon cancer. The impact of lymph node ratio on disease free and overall survival in patients with rectal cancer is unknown. From 1998 to 2004, 307 patients underwent rectal resection for adenocarcinoma. The relationships between overall and disease free survival at 3 years and 15 variables, including the presence or absence of metastatic lymph nodes, the total number of lymph nodes examined, and LNR were analyzed. Patients were then assigned to 4 groups based on lymph node ratio: LNR = 0, LNR = 0.01 to 0.07, LNR > 0.07 to 0.2, LNR >0.2. The mean number of lymph nodes examined was 22+/- 12. LNR was a significant prognostic factor for both disease free and overall survival whereas the presence or absence of metastatic lymph nodes was not. According to LNR values, disease free and overall survival decreased significantly with increase LNR. Researchers concluded that LNR is the most significant prognostic factor for both overall and disease free survival in patients with rectal cancer, even in patients with fewer than 12 lymph nodes examined.

Frederique, Peschaud, et al., The Ratio of Metastatic to Examined Lymph Nodes is a Powerful Independent Prognostic Factor in Rectal Cancer. Annals of Surgery. 248(6):1067-1073 December 2008

7. Survival After Laparoscopic Surgery vs. Open Surgery for Colon Cancer (Dec. 23/08)

This study compared laparoscopic surgery for colon cancer vs. open resection (colectomy). It compared 3 year disease free survival and overall survival after laparoscopic and open resection of solitary colon cancer. 542 patients were randomized to open colectomy and 534 to laparoscopic surgery. The median follow-up was 53 months. The 3 year disease free survival in the laparoscopic group was 74.2% vs. 76.2% in the open surgery group. The difference between the 2 groups was 2%. The 3 year overall survival in the laparoscopic group was 81.8% vs. 84.2% for the open surgery group. The difference between the 2 groups was 2.4%. Researchers concluded that their findings could not rule out a difference in disease free survival at 3 years in favor of open colectomy; however, this difference between groups was small and clinically acceptable, supporting use of laparoscopic surgery in colon cancer.

Bonjer, Hendrik, et al., Survival After Laparoscopic Surgery versus Open Surgery For Colon Cancer: Long-Term Outcome of a Randomized Clinical Trial. The Lancet Oncology. Online First. Doi:10.1016/S1470-2045(08)70310-3. December 23, 2008

OTHER

8. Inflamed Gallbladder More Common After Colorectal Cancer (Dec.24/08)

Cancer increases the risk of gallbladder attacks (cholecystitis), particularly in the first six months after diagnosis. In a study of over 50,000 cancer patients in Denmark, the risk of a gallbladder infection was twice that of the general population in those first six months. Risk for people with colorectal cancer was nearly five times that of people who didn't have cancer. After six months, risk went down, but there was still about a 25% greater chance that someone with cancer would have pain from an inflamed or infected gallbladder. Danish researchers compared over 50,000 people with cancer to another large group over half a million who didn't have cancer in their medical databases. They found 280 cases of cholecystitis. The greatest risk was for cancer patients between 51 and 70. People with pancreatic cancer had the most risk, increases almost 10 fold. The second largest increase was among people with colorectal cancer who had five times the risk of the general population.

Thomsen et al., Risk of Cholecystitis in Patients with Cancer. Cancer. Volume 113, Number 12, December 15, 2008.

www.C3Research&TreatmentNews.com

9. Pain Pills May Cut Risk of Bowel Cancer (Dec. 26/ 08)

This study suggests that use of a non-steroidal anti-inflammatory drug (NSAID) for over 5 years may lessen a person's risk of developing cancer of the lower portion of the large bowel. This risk reduction appears more robust among whites than among African Americans. The investigators evaluated use of NSAIDs (ie aspirin, ibuprofen, and selective COX-2 inhibitors, taken to ease pain and inflammation) among 1,057 white and African American men and women with cancer of the lower bowel and rectum and 1019 individuals who were cancer free. Compared with those never using NSAIDs, NSAID use was associated with about 40% reduced risk for cancer in the lower portion of the large bowel overall. The investigators found a strongly protective association between NSAIDs and large bowel cancer in whites.

Kim, Sangmi, et al., Use of Nonsteroidal Anti-inflammatory Drugs and Distal Large Bowel Cancer In Whites and African Americans. American Journal of Epidemiology. 168(11): 1292-1300. December 1, 2008

NUTRITION

10. Smoking Associated With Increased Risk For Colorectal Cancer And Death (Dec. 24/08)

An Analysis of previous studies indicates that smoking is significantly associated with an increased risk for colorectal cancer and death, according to this study emanating from the European Institute of Oncology in Milan, Italy. Researchers conducted a meta-analysis to review and summarize published data examining the link between smoking and CRC incidence and death. The researchers identified 106 observational studies, and the meta-analysis was based on a total of nearly 40,000 new cases of colorectal cancer. For the analysis on incidence, smoking was associated with an 18% increased risk of colorectal cancer. The researchers also found a statistically significant dose-relationship with an increasing number of pack-years (number of packs of cigarettes smoked/day, multiplied by years of consumption) and cigarettes per day. However, the association was statistically significant only after 30 years of smoking. Seventeen studies were included in the analysis of mortality, which indicated that smokers have a 25% increased risk of dying from colorectal cancer than people who have never smoked. There also was an increase in risk of colorectal cancer death with increasing number of cigarettes per day smoked and for longer duration of smoking. For both incidence and death, the association was stronger for cancer of the rectum than of the colon.

www.cancercompass.com/cancer-news/1,15147,00.htm

11. Mistletoe May Kill Off Cancer Cells (Dec. 16/08)

Australian scientists are probing into the powerful cancer killing effects of mistletoe. Work is underway at the University of Canberra to improve understanding of the parasitic plant, which is used extensively in cancer treatment programs in Germany, for in Germany they have recognized the mistletoe's ability to stimulate the body's immune system while killing off cancer cells; and it does so without harming healthy cells nearby. Researchers are noticing that it kills the tumour cells without killing any of the healthy cells at the same time. Though they have yet to determine how it is being so selective for they have to determine several of the components which fully characterize this plant. Lab tests conducted outside of the human body have shown that a mistletoe extract could kill 80% of a cancer tumour. The extract was known to activate a sub-class of white blood cells, the eosinophils, which had already been shown to be effective in the treatment of cancer. Mistletoe also acted as a coagulant when introduced to the cancer cells, which increases adhesion and helps the mistletoe product basically start to break apart the tumour cells. Mistletoe also contains a toxin which is effective at killing tumour cells. While researchers admit the mistletoe is not a cure, they do admit it might provide another treatment option and improve quality of life during treatment with mainstream chemotherapies.

www.cancercompass.com/cancer-news/1,15117,00.htm