COLORECTAL CANCER ASSOCIATION OF CANADA

COLORECTAL CANCER RESEARCH
Week Ending November 28, 2008

The following colorectal cancer research update extends from November 15 – November 28, 2008 inclusive and is intended for informational purposes only.

ENCOURAGING

Cancer Incidence, Death Rates Decline (Nov. 25/08)

A new report from the U.S.'s leading cancer organizations shows that, for the first time since the report was first issued in 1998, both incidence and death rates for all cancers combined are decreasing for both men and women, driven largely by declines in some of the most common types of cancer. The findings come from the "Annual Report to the Nation on the Status of Cancer, 1975-2005". Although cancer death rates have been dropping since the publication of the first Annual Report to the Nation 10 years ago, the latest edition marks the first time the report has documented a simultaneous decline in cancer incidence, the rate at which new cancers are diagnosed, for both men and women. The decline in both incidence and death rates for all cancers combined is due in large part to declines in the three most common cancers among men (lung, colorectal, and prostate) and the two most common cancers among women (breast and colorectal) combined with a leveling off of lung cancer death rates among women.

www.emaxhealth.com/2/51/26957/cancer-incidence-death-rates-decline.html

DRUGS

1. **Preoperative Avastin Does Not Significantly Increase Postoperative Complications in Patients Undergoing Liver Resections From CRC** (Nov. 17/08)

   A study to evaluate whether neoadjuvant avastin is associated with an increase in postoperative compilations in patients undergoing surgery for crc liver mets was performed at MD Anderson Cancer Center. Two subgroups of patients received neoadjuvant chemotherapy plus avastin or chemotherapy alone. Postoperative complications developed in 49% of patients from chemotherapy plus avastin and 43% in the chemotherapy alone group. The median time from avastin discontinuation to surgery was 58 days. The lead investigator notes no associations between avastin use, its discontinuation and postoperative complications. Instead, lower serum albumin and affiliated surgical procedures were associated with an increased risk of developing any complication. The lead investigator concludes: Combination of avastin with neoadjuvant chemotherapy in patients who have colorectal cancer liver mets does not increase surgical complications.

   Feig, Barry, et al., Preoperative Bevacizumab Does Not Significantly Increase Postoperative Complication Rates in Patients Undergoing Hepatic Surgery for Colorectal Cancer Liver Metastases. J of Clinical Oncology, Vol 26, No 32 (Nov. 10), 2008: pp.5254-5260.

2. **Colorectal Cancer Patients with Liver Mets and Severe Hyperbilirubinemia: A Consecutive Series that Explores the Benefits and Risks of Chemotherapy** (Nov. 24/08)

   A study was undertaken to determine if crc patients who had liver mets and severely elevated levels of bilirubin would benefit from chemotherapy. 3,019 patients were reviewed and 20 met the study's selection criteria wherein there had been a new diagnosis of crc and no prior therapy had been administered and bilirubin levels were severely elevated, as well as having liver mets. Six patients received chemotherapy with an oxaliplatin containing regimen, and 4 subsequently sustained a drop in their bilirubin. In one instance, the drop was considerable. These 6 patients lived a median of 71 days, but one treatment related death occurred. In contrast, patients who received only supportive care lived a median of 28 days. The lead investigator concluded that chemotherapy appears to provide modest benefit to newly diagnosed colorectal cancer patients with severe hyperbilirubinemia.

   Walia, Tamana, et al., Colorectal Cancer Patients With Liver Metastases and Severe Hyperbilirubinemia: A Consecutive Series That Explores the Benefits and Risks of Chemotherapy. Therapeutics and Clinical Risk Management. On-Line Early Edition: November 2008. 3882 OLE-TCRM OA 2008 – 4(6)-Walia.pdf

3. **Erbitux plus Irinotecan in Heavily Pretreated Metastatic Colorectal Cancer Progressing on Irinotecan: MABEL Study** (Nov. 21/08)

In a study to confirm the efficacy and safety of erbitux plus irinotecan in patients with epidermal growth factor-expression metastatic colorectal cancer who had recently failed an irinotecan containing regimen, it was shown that tolerability, progression free survival rate, and overall survival rate were in line with previous results. At 1%, rate of adverse events in patients who received prophylactic premedication with both antihistamine and corticosteroid was lower than previously reported. The MABEL study clearly confirms the efficacy and safety of erbitux plus irinotecan in treatment of mcrc.

Wilke, H, et al., Cetuximab plus Irinotecan in Heavily Pretreated Metastatic Colorectal Cancer Progressing On Irinotecan: MABEL Study. J of Clinical Oncology. Vol. 26, No. 32 2008

4. Avastin Beyond First Progression is Associated with Prolonged Overall Survival in Metastatic Colorectal cancer: Results from A Large Observational Cohort Study (BRITE Study) (Nov. 21/08)

In a trial to examine the association between various pre- and post-treatment factors (including the use of avastin beyond first progression) and survival, it was concluded that continued vascular use of avastin beyond initial disease progression could play an important role improving overall success of therapy for patients with metastatic colorectal cancer. 1445 of 1953 previously untreated patients with mcrc who were enrolled in BRITE and who experienced disease progression were classified into 3 groups:

- No post disease progression treatment (253 patients) -> overall survival was 12.6 months
- Post disease progression treatment without avastin (531 patients) -> OS was 19.9 months
- Post disease progression treatment with avastin (642 patients) -> OS was 31.8 months

The lead investigator concluded that the avastin treated group was strongly and independently associated with improved survival.

Grothey, A., et al., Bevacizumab Beyond First Progression is Associated with Prolonged Overall Survival in Metastatic Colorectal Cancer: Results From a Large Observational Cohort Study (BRITE). J of Clinical Oncology. Vol 26, No 32. 2008

5. Dendreon Presents Integrated Analysis of Clinical Data From Neuvenge Trials At Chemo Foundation Symposium (Nov. 15/08)

Dendreon Corp announced its results of two phase 1 studies which were designed to evaluate the safety and immunologic activity of Neuvenge in patients with metastatic HER2/neu-expressing cancer who had evidence of progressive disease following standard therapies. Patients underwent three infusions of Neuvenge over an approximately one month period. Patients who achieved a partial response, or had stable disease lasting through week 48, were eligible for re-treatment with a booster, using the same protocol and dose as the initial treatment. Trial patients included those with advanced breast, ovarian and colon cancer. The therapy was well tolerated and demonstrated evidence of clinical activity, with several patients experiencing prolonged periods of disease stabilization following treatment. Neuvenge is an investigational product in a new class of active cellular immunotherapies (ACIs) that are uniquely designed to stimulate a patient's own immune system. ACIs hold promise because they may provide patients with a meaningful clinical benefit with low toxicities. Neuvenge is designed to stimulate cellular immune responses against HER2/neu. HER2/neu is over-expressed in a variety of solid tumors, including breast, colorectal, bladder and ovarian cancer. In clinical studies, patients typically received three infusions over a one month period as a complete course of therapy.

www.cancercompass.com/cancer-news/1,14965,00.htm?c=1004:5:1:2

6. Five Year Data and Prognostic Factor Analysis of Oxaliplatin and Irinotecan Combinations for Advanced Colorectal Cancer (Nov. 17/08)

The 9.8% 5-year overall survival in patients with metastatic colorectal cancer who were treated with first line infusional 5FU, leucovorin, and oxaliplatin (folfox) sets a new benchmark according to an update from the Intergroup trial N9741 study. A total of 1,691 patients were randomly assigned to one of seven fluorouracil-, oxaliplatin-, and irinotecan-containing regimens. Overall survival and time to treatment progression were calculated. The observed 5-year survival with infusional 5FU, leucovorin and oxaliplatin (folfox) of 9.8% was better than with irinotecan plus bolus 5FU and leucovorin (IFL; 3.7%) or with bolus irinotecan/oxaliplatin (IROX; 5.1%). Overall survival and time to treatment progression were significantly longer for folfox (20.2 months and 8.9 months respectively) than for IFL (14.6 months and 6.1 months) or for IROX (17.3 months and 6.7 months). Folfox therapy was superior in all risk groups and was the most powerful

prognostic factor for overall survival, time to treatment progression and response rate, and toxicity.

Sanoff, HK, et al., five Year Data and Prognostic Factor Analysis of Oxaliplatin and Irinotecan Combinations for Advanced Colorectal Cancer: N9741. J of Clinical Oncology. JCO Early Release, Published Online, Nov 10, 2008. 10.1200/JCO.2008.17.7147

NUTRITION

7. Calcium May Only Protect Against Colorectal Cancer in Presence of Magnesium (Nov. 16/08)

High magnesium intake has been associated with low risk of colorectal cancer. Americans have similar average magnesium intake as East Asian population. If that were all that were involved, observers might expect both groups to have similar risk for colorectal cancer. However, the US has seen a much higher colorectal cancer incidence rate than East Asian populations. Furthermore, when East Asians immigrated to the US, their incidence rates for crc increased. This led researchers at Vanderbilt University to suspect there was something else at work. Calcium supplementation has been shown to inhibit colorectal carcinogenesis although high calcium may simultaneously be preventing the body from absorbing magnesium. United States patients have a higher calcium intake and higher colorectal cancer incidence. If calcium levels were involved alone, you'd expect the opposite direction. There may be something about these two factors combined – the ratio of one to the other – that might be at play. Lead researcher Dr. Dai and colleagues examined this hypothesis in a large clinical trial and found indeed that supplementation of calcium only reduced the risk of adenoma recurrence if the ratio of calcium to magnesium was low and remained low during treatment. The risk of colorectal cancer adenoma recurrence was reduced by 32% among those with baseline calcium to magnesium ratio below the median in comparison to no reduction for those above the median. The implications for prevention of adenoma recurrence or reduced risk of primary colorectal cancer is that designing a personalized diet/supplementation regimen that takes the ratio of both nutrients into account may be better than supplementing with one or the other alone.

www.medicalnewstoday.com

8. Role of Vitamin D in Cancer Therapy Clarified By Study (Nov. 18/08)

A colon cancer cell isn't a lost cause. Vitamin D can tame the rogue cell by adjusting everything from its gene expression to its cytoskeleton according to the November 17 issue of the J of Cell Biology wherein researchers show that one pathway governs the vitamin's diverse effects. The results help clarify the actions of a molecule that is undergoing clinical trials as a cancer therapy. Vitamin D hinders colon cancer cells in two ways:

1. It switches on genes such as the one that encodes E-cadherin, a component of the adherens junctions that anchor cells in epithelial layers.
2. The vitamin also induces effects on the cytoskeleton that are required for gene regulation and short circuiting the Wnt/b-catenin pathway, which is overactive in most colon tumors.

The net result is to curb division and prod colon cancer cells to differentiate into epithelial cells that settle down instead of spreading.

To delve into the mechanism, the team dosed colon cancer cells with calcitriol, the metabolically active version of vitamin D. Calcitriol triggered a surge of calcium into the cells and the subsequent switching on of RhoA-RhoGTPases, which have been implicated in the cytoskeletal changes induced by vitamin D. The activated RhoA in turn switched on one of its targets, the rho-associated coiled kinase (ROCK), which then roused two other kinases. Each step in this nongenomic pathway was necessary to spur the genomic responses, the researchers showed. The team also identified the contribution of the vitamin D receptor (VDR). The receptor was crucial at the beginning of the pathway, where it permitted the calcium influx and at the end where it activated and repressed genes. The study is the first to show that vitamin D's genomic and nongenomic effects integrate to regulate cell physiology.

Ordonez-Moran, P, et al., Role of Vitamin D in Cancer Therapy. J Cell Biology. Doi:10.1083/hcb,200803020

9. How Red Meat Causes Cancer (Nov. 23/ 08)

Red Meat has previously been implicated as cancer producing. Researchers have now unraveled exactly how consuming red meat and milk contributes to tumor growth. According to the results of a study, published in Proceedings of the National Academy of Sciences (PNAS), when we eat red meat, we are introducing Neu5Gc (N-glycoly/neuraminic acid) into our bodies –

a type of sugar molecule. We don't naturally produce Neu5Gc. The body tries to fight the foreign substance by producing antibodies. The response causes inflammation, in turn promoting the growth of cancerous tumors. The study showed that tumor tissues contained much more Neu5Gc than is usually found in normal human tissues. Investigators therefore surmised that Neu5Gc must somehow benefit tumors…chronic inflammation results from interaction of Neu5Gc accumulating in our bodies from eating red meat with the antibodies that circulate as an immune response to this non human molecule – and this may contribute to cancer risk. Researchers noticed that employing NSAIDS (non steroidal anti-inflammatory drugs) actually reduced the process, blocking the cancer promoting effect of Neu5Gc. The study authors surmised that Neu5Gc, from red meat, benefits cancerous tumors. The accumulation of unnatural substances in the body is increasingly shown to promote disease. Anti-inflammatory drugs, stress reduction, and exercise ameliorate the effects.

www.emaxhealth.com/1020/51/26843/how-red-meat-causes-cancer.html

10. Grape Seed Extract Induces Cell Cycle Arrest and Cell Death in Human Colon Cancer Cells (Nov. 22/08)

One approach to control colorectal cancer is its preventive intervention by dietary agents or those consumed as supplements. However, because most of these products are often consumed by patients as a complementary and alternative medicine practice, a scientific base such as efficacy, mechanism, and standardized preparation needs to be developed. Grape Seed Extract (GSE) is one such supplement widely consumed by humans for its several health benefits. Recently, GSE was reported to inhibit crc cell HT29 growth in culture and nude mice xenograft. This particular study sought to assess whether GSE from 2 different manufacturers produced comparable biological effects in a panel of human crc cells lines. The results showed that irrespective of source, GSE strongly inhibited Lo/Vo, HT29, and SW/480 cell growth with a G1 arrest in Lo/Vo and HT29 cells but an S and/or G2/M arrest in SW/480 cell cycle progression. GSE also induced Cip/p21 levels in all 3 cell lines. Furthermore, cell death was observed in all 3 cell lines by GSE. Taken together, the findings suggest that GSE could be an effective complementary alternative medical agent against crc possibly due to its strong growth inhibitory and cell death inducing effects.

Kaur, M, et al., Grape Seed Extract Induces Cell Cycle Arrest and Apoptosis in Human Colon Carcinoma Cells. Nutrition and Cancer. 2008; 60; Supplement 1: pp 2-11.