

COLORECTAL CANCER ASSOCIATION OF CANADA

COLORECTAL CANCER RESEARCH

Week Ending January 9, 2008

The following colorectal cancer research update extends from December 27 – January 9, 2008 inclusive and is intended for informational purposes only.

DRUGS

1. Adding Panitumumab (Vectibix) to Chemotherapy and Avastin Results in Poorer Outcomes (PACCE Results) (Jan. 5/09)

Patients being treated for the first time with chemotherapy (either folfiri or folfox) and avastin do worse if vectibix (panitumumab) is added to their chemo. Median time until the cancer progresses is shorter, and they have more serious side effects. KRAS status made no difference, for both patients with wild-type and mutated Kras in their tumors had worse outcomes when vectibix was part of their treatment. Researchers recommend that vectibix not be added to chemo with avastin to treat colorectal cancer that had spread. The PACCE trial (Panitumumab Advanced Colorectal Cancer Evaluation) was stopped early when researchers reviewing data from the clinical trial found that both progression free survival and overall survival were better in the standard chemo arm that did not include vectibix. Over 1,000 patients were originally enrolled in the trial, 823 on an oxaliplatin regimen and 230 receiving irinotecan. All patients received avastin, and half were randomly assigned to get vectibix as well. The primary goal of the trial was to find out if adding vectibix to chemo and avastin increased time before cancer got worse (progression free survival). Researchers concluded that combining chemotherapy and avastin with vectibix led to poorer outcomes for patients having their first treatment for stage IV or recurrent colon or rectal cancer. Patients who received vectibix in addition to chemo with avastin had their cancer get worse more quickly and also had shorter survival time (overall survival). Earlier analysis of side effects found that including vectibix increased serious diarrhea, dehydration, infection and blood clots in the lungs. Overall, adding vectibix to standard chemotherapy with folfox or folfiri plus avastin resulted in **more toxicity and less effectiveness**.

Hecht, J Randolph, et al., A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J of Clinical Oncology. Early Release, Published online Ahead of Print December 29, 2008. 10.1200/JCO.2008.19.8135

2. Erbitux Enhances Efficacy in mCRC Patients with Kras Wild-Type Tumors in First Line Setting Receiving Folfox (Jan. 5/09)

The OPUS study was a randomized, multi-center, phase II trial comparing the efficacy and safety of erbitux combined with folfox vs. folfox alone in the first line treatment of epidermal growth factor receptor (EGFR)-expressing mCRC. The primary objective was response rate. It demonstrated that the addition of erbitux to folfox-4 in previously untreated metastatic colorectal cancer patients with Kras wild-type tumors resulted in significantly higher efficacy than chemotherapy alone (folfox 4). It demonstrated a remarkably high response rate of 61%, clearly exceeding that seen in patients treated with chemotherapy alone. 46% of patients receiving erbitux in combination with folfox experienced a response, compared to 36% of patients treated with chemo alone. In a retrospective efficacy analysis it was shown that 61% of patients with Kras wild type tumors responded when treated with erbitux plus chemo, compared to 37% of patients in the chemo alone group (folfox 4). In addition, the risk of disease progression in the erbitux plus chemo arm decreased by 43% and the complete resection rate more than doubled compared with those in the chemo alone group. Safety and tolerability were also studied in the OPUS trial, and the erbitux plus folfox combination was found to be generally well tolerated with no evidence to suggest that erbitux increased the frequency or severity of the known toxicities of oxaliplatin-based chemo. Moreover, the incidence and severity of skin reaction, infusion-related reactions and mucositis (inflammation in the membranes lining the mouth and upper digestive tract) were consistent with the known safety profile of erbitux.

Bokemeyer, Carsten, et al., Fluorouracil, Leucovorin and Oxaliplatin with and without cetuximab in the first-line Treatment of metastatic colorectal cancer. J of Clinical Oncology. JCO Early Release. Published Online Ahead of Print December 29, 2008. 10.1200/JCO.2008.20.8397

RADIATION

3. Xeloda plus Oxaliplatin in Combination with Radiotherapy for Unresectable Colorectal Cancer: The CORGI-L Study (Jan. 5/09)

In a trial to assess radiotherapy combined with xeloda and oxaliplatin in patients with primary, unresectable colorectal cancer, it appears that Xeloda plus radiotherapy was feasible and showed promising efficacy when treating patients with primary unresectable colorectal cancer, establishing high local control rate. 49 patients entered the CORGI-L study. 2 cycles of xeloda (xeloda plus oxaliplatin) were followed by radiotherapy, combined with xeloda twice daily every radiotherapy day and oxaliplatin once weekly. 47 patients were evaluable. 29 achieved complete or partial response. 38 patients went through surgery. 78% were alive and estimated local progression rate was 11% at 2 years. Swedish researchers are optimistic about their findings.

Gunnlaugsson, Adalsteinn, et al., Multicentre phase II trial of capecitabine and oxaliplatin in combination with radiotherapy for unresectable colorectal cancer: The CORGI-L study. European J of Cancer. Doi:10.1016

SURGERY

4. CEA and Metastectomy (Dec. 30/08)

According to results of a prospective clinical study performed in France, patients with the lowest carcinoembryonic antigen (CEA) levels after liver resection for colorectal metastases have the highest survival rates. CEA blood level is the most commonly used tumor marker to monitor patients after resection of primary colorectal cancer and colorectal liver mets, the authors explain, but few studies have investigated its prognostic value among patients undergoing resection of colorectal liver mets. Researchers evaluated the value of CEA measurements obtained a week before and 6 weeks after surgery to predict cure after resection of colorectal liver mets in 213 patients. Five-year overall and disease-free survival rates were highest (50.2% and 21.9%) among patients with normal preoperative and postoperative CEA levels, the authors report. They were lower (38.5% and 18.3%) for patients with elevated preoperative and normal postoperative CEA levels, and lowest (0.0% and 0.0%) for patients with elevated preoperative and postoperative CEA levels. Normalization of CEA levels 6 weeks after colorectal liver mets resection may indicate improved long-term outcomes in these patients, according to the researchers. And CEA levels as early as 6 weeks after surgery may be helpful in assigning patients to adjuvant (post-surgical) chemo after resection of colorectal liver mets.

Jaeck, Daniel, et al., Perioperative Carcinoembryonic Antigen Measurements to Predict Curability After Liver Resection For Colorectal Metastases. Archives of Surgery. 2008; 143 (12):1150-1158

OTHER

5. High Levels of Gene MACC1 Predicts Colorectal Cancer Spread (Dec. 27/08)

German scientists have identified a gene that has higher levels in colon cancer patients whose tumours are destined to spread. By initiating a signaling pathway in the cancer cell, MACC1 (Metastasis-Associated in Colon Cancer 1) promotes faster cell growth and cancer spread to distant sites in the body. About a third of patients whose cancer is found in early stages will eventually have it spread to other organs. Measuring MACC1 may help doctors identify those patients, treat them more aggressively, and follow them more closely. Researchers compared tissue from healthy persons with tissue from 103 patients with colon cancer between 20 to 88 years of age. 60 cancer patients had no mets at the time they underwent surgery. Of these 60 patients, 37 had no mets 5 years after surgery and treatment. These patients were shown to have had low levels of MAC1 when first diagnosed with colon cancer. In contrast, 23 patients had developed mets in the course of 5 years after surgery. Researchers detected high levels of MACC1 in their colon cancer tissue. Thus, patients with high MACC1 levels have a much higher risk for developing mets than patients with a MACC1 gene that is not very active. The researchers are convinced that MACC1 will enable physicians to decide if a patient needs a more intense therapy or if a less aggressive treatment is sufficient. The expression analysis of MACC1 in the original tumor tissue will probably contribute to individualize and optimize colon cancer therapy.

Stein, Ulrike, et al., MACC1, a newly identified key regulator of HGF-MET signaling, predicts colon cancer metastasis. Nature Medicine. Advance Access December 27, 2008.

6. **New Tool Developed to Predict Colorectal Cancer Risk** (Dec. 29/08)

A new online tool for calculating colorectal cancer risk in men and women age 50 or older was launched, based on a new risk-assessment model developed by researchers at the National Cancer Institute (NCI), part of the National Institutes of Health. This new tool may assist health care providers and their patients in making informed choices about when and how to screen for colorectal cancer and can be used in designing colorectal cancer screening and prevention trials. An article describing the new risk assessment model and a second article describing its validation appeared online December 29, 2008 in the *J of Clinical Oncology*. The risk assessment tool is available on the NCI web site at www.cancer.gov/colorectalcancerrisk, and people using this tool should work with their health care providers to interpret the results. Using easily obtainable information, the tool provides an estimate of an individual's risk of developing colorectal cancer over certain time periods (within 5 years, 10 years, and over the course of a lifetime). This risk assessment model is the first to provide an absolute risk estimate for colorectal cancer (ie the probability of developing colorectal cancer over a given period of time) for the general, non-Hispanic white population age 50 or older in the US.

Freedman, AN, et al., A Colorectal Cancer Risk Prediction Tool For White Men and Women Without Known Susceptibility. J Clinical Oncology. Early Online Edition. December 29, 2008.

7. **Inflammation Contributes to Colon Cancer** (Jan. 3/09)

Researchers at the University of Washington found that mice that lack the immune inhibitory molecule Smad3 are acutely sensitive to both bacterially-induced inflammation and cancer. Bacteria contribute to the development of certain cancers, in some measure by stimulating chronic inflammation. Absence of a molecule that inhibits inflammation, Smad3, may therefore increase susceptibility to colon cancer. Researchers examined mice deficient in Smad3 that lack adaptive immune responses. They found that these mice are acutely sensitive to bacterially-induced inflammation and cancer due to both deficient T regulatory cell function and increased expression of proinflammatory cytokines. Through increased expression of certain proteins, epithelial cells in the tissues of the colon underwent both enhanced proliferation and survival. The lead researcher commented as follows: that the inflammatory response to microorganisms is a key event in these results revealing important tumor suppressive functions for Smad3 in T effector cells, T regulatory cells and intestinal epithelial cells, all of which may normally limit the development of colon cancer in response to bacterial inflammation.

Maggio-Price, L. et al., Bacterial infection of Smad3/Rag2 double-null mice with TGF beta dysregulation as a model for studying inflammation-associated colon cancer. American J of Pathology. 2009, 174: 317-329.

8. **Hormone Therapy Associated with Reduced Colorectal Cancer Risk** (Jan. 8/09)

According to this study, the combination of estrogen plus progestin may decrease the risk of colorectal cancer in women. Compared to women who had never taken these hormones, the use of estrogen plus progestin was associated with a reduced risk of colorectal cancer. The largest risk reduction, approximately 45%, was seen among women who had completed use of estrogen plus progestin 5 or more years previously. Johnson and colleagues extracted data from 56,733 postmenopausal women who participated in the Breast cancer detection Demonstration project follow-up study. Hormone therapy use and other risk factors were ascertained through telephone interviews and mailed questionnaires between 1979 and 1998. During an average 15 years of follow-up, researchers identified 960 new cases of colorectal cancer in this population. Any use of estrogen therapy was associated with a 17% reduced risk in colorectal cancer. Among those who used estrogen, the largest reductions were seen among those who were current users (25% reduced risk) and users of 10 or more years duration (26% reduced risk). Researchers also found a 22% reduced risk among those who had ever used estrogen plus progestin in combination. They further found a 36% reduction in risk among those who had used progestin sequentially or less than 15 days per month. Past users of estrogen plus progestin, who had stopped at least 5 years ago, had a 45% risk reduction.

Johnson, Jill R, et al., Cancer Epidemiology, Biomarkers & Prevention 2009; 18:196-203

NUTRITION

9. Maslinic Acid, Isolated From Olive Pomace, Provides A Natural Defence Against Colon Cancer (Dec. 27/ 08)

Researchers from the University of Granada and the University of Barcelona have shown that treatment with maslinic acid, a triterpenoid compound isolated from olive-skin pomace, results in a significant inhibition of cell proliferation and causes apoptotic death (programmed cell death) in colon cancer. Maslinic acid is a novel natural compound and it is able to induce cell death in human colon cancer cells. Scientists suggest this could be a useful new therapeutic strategy for the treatment of colon carcinoma. This study is the first to investigate the precise molecular mechanisms of the anti-tumoral and pro-apoptotic effects of maslinic acid against colon cancer. Chemopreventive (cancer prevention) agents of a natural origin, often a part of our daily diet, may provide a cheap, effective way of controlling such diseases as cancer of the colon. A wide range of studies in recent years has shown that compounds such as maslinic acid hinder carcinogenesis (the process of creating malignant tumours) by intervening in pathways such as carcinogen activation, DNA repair, cell cycle arrest, cell differentiation and the induction of cell death in cancer cells. Triterpenoids are compounds present in a wide range of plants used in traditional medicine and known to have antitumoral properties. Low concentrations of maslinic acid are to be found in plants with medicinal properties, but its concentration in the waxy skin of olives may be as high as 90%. The results of the study could contribute to the development of maslinic acid for use as cancer chemotherapeutic (cancer fighting) or chemopreventive agents.

Reyes-Zunta, Fernando, et al., Maslinic acid, a natural triterpene from Olea europaea L., induces apoptosis in HT29 human colon cancer cells via the mitochondrial apoptotic pathway. Cancer. Volume 273, Issue 1; pp.44-54. Jan. 2009.

10. Genes and Alcohol: A Cancer Cocktail (Dec. 31/08)

A study performed at the University of Helsinki found that regular drinking could put you at greater risk of developing colorectal cancer. Researchers report that regular consumption of alcohol – more than 30 grams per day – can cause an interaction that increases colorectal tumors in people with a mutation of the ADH1C gene. This genetic mutation is found in Caucasians. When these patients drink, they produce more acetaldehyde – an enzyme that creates a higher risk for colorectal cancer. Lead researcher comments that regular alcohol consumption of about 50 grams, or approximately four drinks per day, results in a 1.4-fold risk for colorectal cancer compared to non-drinkers. Researchers found patients with ADH1C mutations metabolize alcohol to acetaldehyde more rapidly. Acetaldehyde goes on to cause cellular DNA damage throughout the body, including the colon and rectum, the upper digestive tract and the breast. Study authors concluded that the high rates of alcohol consumption are contributing to making colorectal cancer one of the most highly diagnosed cancers worldwide.

www.news-medical.net/?id=44460