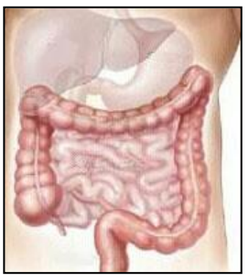
COLORECTAL CANCER RESEARCH UPDATES

Month Ending March 16th, 2012



The following colorectal cancer research update extends from February 18th, 2012 – March 16th, 2012 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Colorectal Cancer Resistant to Cetuximab May Be Treated with Panitumumab (Feb. 21/12)

The results of this study show that patients who have colon cancer that is no longer responding to therapy may benefit from switching to a similar drug in the same class. Of the two colon cancer drugs (erbitux or vectibix), Erbitux (cetuximab) is more commonly used. However, resistance to the drug is also common. Researchers have shown that for these patients with a resistant cancer, switching to Vectibix (panitumumab) is a valid option. A team from Spain's Hospital del Mar has demonstrated that while both Erbitux and Vectibix target the same molecule in colon cancer, resistance to one drug does not mean the end of treatment. Both of these drugs target the growth signal molecule EGFR, which is commonly found on cancer cells. The results justify developing tests to detect this mutation in patients that are being treated with cetuximab for colorectal cancer. Later studies shall also have to validate whether this mutation contributes to acquiring a resistance to cetuximab in tumors for which it is also used, such as head and throat cancer. The study was quite small and more testing is required to validate the results.

Montagut, Clara, et al., Identification of a mutation in the extracellular domain of the epidermal growth factor receptor conferring cetuximab resistance in colorectal cancer. Nature Medicine. 18: 221-223.

2. **Celecoxib May Prevent Xeloda-related Hand & Foot Syndrome** (Feb. 24/12)

Hand-foot syndrome (HFS) is the most common adverse side effect induced by capecitabine (better known as xeloda). Some clinicians think that HFS is a type of inflammation limited to the hands and feet and can be prevented with a COX-2 inhibitor (such as celecoxib). From August 2008 to December 2010, stage II and III colorectal cancer patients receiving capecitabine-based chemotherapy enrolled in the trial voluntarily. All patients were divided randomly into two groups treated with or without celecoxib. All adverse events were recorded. Grade 1 and grade 2 HFS were more common in the capecitabine group than in the capecitabine/celecoxib group (74.6% versus 57.4%, and 29.6% versus 14.7%). The use of celecoxib affected the incidence of grade 1 and 2 HFS. The results analysis indicated that the use of celecoxib was the only factor that affected the incidence of ≥ grade 1 HFS and ≥ grade 2 HFS. The investigators concluded that celecoxib can be used effectively and safely to prevent capecitabine-related HFS.

Zhang, RX, et al., Celecoxib can prevent capecitabine-related hand-foot syndrome in stage ii and iii colorectal cancer patients: result of a single-center, prospective randomized phase iii trial. Annals of Onc. Doi: 10.1093/annonc/mdr400

3. Cetuximab (Erbitux) Sensitivity Associated with Oxaliplatin Resistance in Colorectal Cancer (Mar. 10/12)

Clinical studies have suggested that the epidermal growth factor receptor (EGFR)-inhibiting antibody therapy called cetuximab (better known as erbitux) may have a better effect in the third-line treatment of metastatic colorectal cancer, after failure of standard chemotherapy including oxaliplatin, compared to using it up-front in the first line. The reason behind this suggestion is unclear. The effect of cetuximab on cancer cell growth was investigated in five colon cancer cell lines with increasing level of acquired oxaliplatin resistance. A marked increase in sensitivity to cetuximab was observed in the oxaliplatin-resistant cell lines. The connection between oxaliplatin resistance and cetuximab sensitivity has not been previously reported in the literature. The investigators concluded that such a connection could be of clinical importance and constitutes a substantial argument for saving cetuximab until later treatment lines, when the tumours have become chemotherapy resistant.

Ekblad, Lars, et al., Cetuximab sensitivity associated with oxaliplatin resistance in colorectal cnacer. Anticancer Research. March 2012. Vol. 32, No. 3: pp.783-786

4. Resectability and Outcome with Anti-EGFR Agents (Erbitux & Vectibix) with Kras Wild Type Colorectal Liver Mets (Mar.11/12)

Cetuximab (C), also known as erbitux, and panitumumab (P), also known as vectibix, increase response rate and survival in KRAS wild-type metastatic colorectal cancer (mCRC). Researchers performed a review of randomized controlled trials (RCTs) to assess their effect on overall response rate (ORR), the rate of radical liver resection (R0) and survival in patients with liver-limited initially unresectable mCRC. Researchers searched for RCTs comparing first-line chemotherapy plus or minus C or P and reporting data in patients with KRAS wild-type, unresectable liver-limited mCRC. Four RCTs involving 484 KRAS wild-type patients were included. Compared to chemotherapy alone, the addition of C or P significantly increased the ORR, the R0 resection rate from 11% to 18% and PFS, but not OS. The addition of C and P increased the R0 resection rate by 60% and reduced the risk of progression by 32% in patients with mCRC and unresectable liver-limited disease. The researchers concluded that this combination represents one of the preferred choices as conversion therapy in KRAS wild-type patients with unresectable liver metastases.

Petrelli, F. et al., Resectability and outcome with anti-egfr agents in pateitns with kras wild type colorectal liver-limited metastases: a meta-analysis. Inter J of Colorectal Disease. DOI: 10.1007/s00384-012-1438-2

5. Quebec-based Phase II Clinical Trial Involving Pentamidine for mCRC Patients Undergoing Second Line Therapy (Feb. 17/12)

The purpose of this study is to investigate the safety and efficacy of the use of OCZ103-OS or Pentamidine in combination with standard of care (folfiri or folfox) for metastatic colorectal cancer patients with disease progression following a first line treatment. The objectives of the study are:

- To assess the efficacy of OCZ103-OS in prolonging overall survival duration in metastatic colorectal cancer patients treated concurrently with mFOLFOX6 or FOLFIRI.
- To assess the efficacy of OCZ103-OS in prolonging progression free survival duration in metastatic colorectal cancer patients treated concurrently with mFOLFOX6 or FOLFIRI.

For more information, please visit http://www.colorectal-cancer.ca/en/research-treatments/listing-trials/ or visit the Oncozyme website at:
http://www.oncozymepharma.com/index.php?option=com_content&view=article&id=5&lang=en

http://www.oncozymepharma.com/index.php?option=com_content&view=article&id=5&lang=en

SURGICAL THERAPIES

6. Treating Peritoneal Carcinomatosis with Complete Cytoreductive Surgery & HIPEC (Hyperthermic Intraperitoneal Perioperative Chemotherapy That Includes Oxaliplatin (Mar.13/12)

Up to 25% of patients with metastatic colorectal cancer (CRC) present with peritoneal carcinomatosis (PC) as the only site of metastases. Peritoneal carcinomatosis is the term that refers to cancer that has spread to the peritoneal sack that encompasses the organs in the abdomen. Peritoneal carcinomatosis can be caused by several types of cancer, including gastro-intestinal cancers, like colorectal cancer. The treatment that includes complete cytoreductive surgery (CCRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) aims for locoregional disease control and long-term survival. Oxaliplatin is effective for treating advanced CRC. This study assessed the safety and efficacy of CCRS with HIPEC with oxaliplatin for patients with PC of CRC. A Belgian prospective multicenter registry was performed to monitor perioperative morbidity and assess mortality, disease-free survival (DFS), and overall survival (OS). Forty-eight consecutive patients underwent CCRS (R0/1) with HIPEC (male/female ratio 17/31, median age 60 years, range 24-76 years). Median operation time was 460 (range 125-840) min. Thirty-day mortality was 0%. Complication rate (any grade) was 52.1. Median hospital stay was 20 (range 5-65) days. At median follow-up of 22.7 (range 3.2-55.7) months, OS was 97.9% at 1 year and 88.7% at 2 years. DFS at 1 year was 65.8% and 45.5% at 2 years. Median time until recurrence was 19.8 months. Investigators concluded that CCRS followed by HIPEC with oxaliplatin for PC from CRC can be implemented with acceptable morbidity. Long-term DFS and OS can be achieved in selected patients.

Hompes, Daphne, et al., The treatment of peritoneal carcinomatosis of colorectal cancer with complete cytoreductive surgery and hyperthermic intraperitoneal perioperative chemotherapy (HIPEC) with oxaliplatin: a Belgian multicentre prospective phase II clinical study. Annals of Surg Onc. DOI: 10.1245/s10434-012-2264-z

RADIOTHERAPY / INTERVENTIONAL RADIOLOGY

7. CT Scans Aid Colon Cancer Treatment (Feb. 24/12)

CT colonography (CTC) has been shown to be comparable to standard colonoscopy in accurately detecting cancer in older patients. According to a research paper published online in Radiology, CTC can be just as effective as standard methods when used to check for cancer and precancerous polyps in people aged 65 and over. The results are consistent with findings from the ACRIN National CT colonography trial, published in 2008 by the New England Journal of Medicine, which showed that CTC can be used for adults aged 50 and above as a primary option for colorectal cancer screening. The lead study author described CTC as a perfectly viable tool for colorectal cancer screening for people in the traditional Medicare demographic. "Wider availability made possible by Medicare coverage of CT colonography would attract more seniors to be screened for colorectal cancer - which is so successfully treated when detected early".

Johnson, Daniel, et al., The national ct colonography trial: assessment of accuracy in participants 65 years of age and older. Radiology. DOI: 10.1148/radiol.12102177

SCREENING

8. Removal of Polyps During Colonoscopy Reduces Colon Cancer Deaths (Feb. 23/12)

New research finds that colonoscopy is very effective at reducing colon cancer mortality when it includes removal of adenomas (benign but potentially pre-malignant polyps). This study tracked 2,602 people who between 1980 and 1990 had adenomas removed during colonoscopy. The researchers compared the number of colon-cancer deaths among the study population with the projected number of such deaths among the general population. (The authors note that they couldn't establish a true control group against which to make comparisons because it would be unethical and potentially harmful to patients to not remove detected adenomas.) During the first 10 years of follow-up, 12 deaths from colorectal cancer occurred among the study group. But among the general population, the researchers determined, 25.4 people would have been expected to die of colon cancer during that time. That amounts to an estimated 53% reduction in colon cancer mortality associated with removal of adenomas during colonoscopy. The findings add to the argument in favor of widespread screening via colonoscopy. But the authors point out that their research has some limitations, including the fact that people in the study received thorough colonoscopies and polypectomies (removal of polyps) from highly trained physicians. It is unlikely, they note, that everyone in the general population would have access to such top-quality care.

Zauber, Ann et al., Colonoscopic Polypectomy and long term prevention of colorectal cancer deaths. New England J of Med.
http://www.nejm.org/doi/full/10.1056/NEJMoa1100370?query=featured_home

9. New Guidance For Colorectal Cancer Screening (Mar. 9/12)

The American College of Physicians (ACP) has published a new guidance statement in regards to conducting colorectal cancer screenings. ACP has created the guidance to give clear, concise information to both doctors and patients, so they can better understand both the risks and benefits of colorectal cancer screening. This is a particularly salient point at the moment, with research showing that there is both too much cancer screening taking place, putting patients at risk and creating unnecessary costs, as well as over treatment and unnecessary treatments being implemented for some types of cancer. The ACP recommends that doctors screen their patients for colorectal cancer from the age of 50, or where patients are seen as higher risk, due to previous illness or family history. They start around 40, or ten years earlier than a family member who was diagnosed with colorectal cancer. Other risk factors also need to be taken into account. These include race (African Americans have the highest risk and mortality rate from the disease), as well as other medical issues such as polyps, inflammatory bowel disease, or previous colorectal cancer. Options for screening for colorectal cancer include: stool based and endoscopic/radiologic tests. The screening interval for average risk adults over the age of 50 is 10 years for colonoscopy; five years for flexible sigmoidoscopy, virtual colonoscopy, and double contrast barium enema; and annually for fecal occult blood test. Colonoscopy is thought of as the gold standard to which other screening tests are compared. However, the invasive nature of the test carries risks including: possible bleeding, perforation of the intestine, and adverse reactions, as a result of preparations required and, because of this, the ACP guidance doesn't recommend screening those over 75 or those with a life expectancy of less than ten years.

http://www.medicalnewstoday.com/articles/242561.php

NUTRITION & HEALTHY LIFESTYLE

10. Link Between Fatty Diet & Colon Cancer (Mar.1612)

There have always been questions about why things like diet and obesity are independent risk factors for colon cancer. This study suggests how and why high-fat diets are linked to colon cancer. Researchers examined healthy colon tissue from colon cancer patients and found that epigenetic marks on genes involved in breaking down carbohydrates, fats and amino acids -- which are all common in a fatty Western diet -- seem to have been retrained. Epigenetic marks are chemical modifications that act as on/off switches for many genes. These foods are changing the methylation patterns on a person's insulin genes so that they express differently, pumping out more insulin than the body requires. In people that have colon cancer, their glucose metabolic pathways and insulin-signaling pathways are running at completely different levels than people who don't have colon cancer. Cancer cells "love" insulin and studies have shown that tumors feed off insulin. Most cases of colon cancer occur in people 50 and older, and it is unclear when these genetic changes begin. If such changes can be detected in other healthy tissues in the body, it might be possible to use blood or saliva tests to determine a person's colon cancer risk or diagnose the disease,

Sapienza, Carman, et al., Epigenetic differences in normal colon mucosa of cancer patients suggest altered dietary metabolic pathways. Cancer Prev Res March 2012. 5: 374-384