CRC RESEARCH #18

Sunday, January 20, 2008

1. Major Clinical Cancer Advances in 2007

ASCO lists the following as notable advances in colorectal cancer:

- Erbitux improves outcomes in colon cancer when added onto the folfiri regimen (fluorouracil, irinotecan and leucovorin)
- High fat diets linked to recurrence of colon cancer
- Aspirin use promising for prevention of colorectal cancer

Journal Clinical Oncology, Clinical Cancer Advances 2007 Published online Dec. 17, 2007

2. Minocycline reduced acne-like rash symptoms from erbitux treatment

Dermatologists at Memorial Sloan Kettering Cancer Center in New York randomly assigned 48 patients to receive either daily oral minocycline or a placebo as soon as they began treatment with Erbitux. Antibiotic minocycline reduced facial rash and itching when given to patients with colorectal cancer from the beginning of their treatment with Erbitux. However, there were few differences between the treated and placebo groups after 8 weeks. The conclusion by the team was that prophylaxis with oral minocycline may be useful in decreasing the severity of the acne-form rash during the first month of erbitux treatment. ***Scope et al., J of Clinical Oncology, Vol 25, Number 34, December 1, 2007.***

3. Romiplostim Improves Low Platelet Levels

According to results recently presented at the 2007 annual meting of the American Society of hematology, the investigative agent romiplostim (AMG531) continues to significantly improve platelet levels in patients with cancer. Romiplostim is an agent that stimulates the production of platelets and researchers in the US and Europe continue to evaluate its effectiveness in reducing thrombocytopenia in patients with cancer as well as its long term safety. The results of several clinical trials indicate that romiplostim significantly improves platelet levels among patients with low platelet counts, and is well tolerated, (even when used long term).
Cancer Consultants, www.cancerconsultants.com , Daily Cancer News, Romiplostim Improves Low Platelet Levels

4. Capecitabine (Xeloda) Plus Oxaliplatin and Irinotecan Regimen Every Other Week: A Phase I/II Study in First-Line Treatment of Metastatic CRC

A phase I/II study was performed to determine the safety and activity of xeloda plus oxaliplatin and irinotecan regimen using xeloda concurrently with oxaliplatin and irinotecan in previously untreated patients with mcrc. Patients received irinotecan on day 1, oxaliplatin on day 2 and xeloda on days 2-6 of a biweekly schedule. The results of the trials indicated that toxicity was manageable, the most common of which was diarrhea (24%) and nausea (16%). Biweekly COI is feasible and active. Tolerability and ease of administration make the regimen well suited for downsizing hepatic crc mets before curative surgery. ***Annals Oncology. 2007; 18(11):1810-1816***

5. Can Oxaliplatin Induced Neuropathy Be Decreased without Affecting Treatment Efficacy?

European researchers had an opportunity to present their findings from their OPTIMOX 2 Trial which compared ways to decrease neuropathy due to treatment with folfox using an induction-maintenance strategy.

- Induction treatment: Intense initial treatment to shrink tumours
- Maintenance period: time off from oxaliplatin treatment to allow the body to recover from neuropathy.

Final results from OPTIMOX 2 were presented at ASCO in June 2007 and results from the two trials were compared. The trial arms and conclusions have been charted below:

TRIAL NAME	TRIAL ARM	CONCLUSION
OPTIMOX 1	1. Continuous Folfox 2. Induction treatment with folfox followed by maintenance with infusional 5FU/Leucov	**Continuing folfox until treatment failure is no more effective and has more toxicities than induction treatment with folfox and maintenance treatment with 5FU/Leucov**
OPTIMOX 2	1. Induction treatment with folfox followed by maintenance with infusional 5FU/Leucov 2. Chemotherapy-free interval (CFI)	**Maintenance treatment with 5FU/Leucov increases patient survival when compared to a CFI**

***Optimox 2: Maindrault-Goebel F, et al. ASCO 2007. Abstract 4013. Optimox 1. DeGramont A, et al. ASCO 2004. Abstract 3525*.**

6. Symptoms Minimal 4 Years After Successful CRC Treatment

An article published in the Journal of Cancer reports that the number of long term crc survivors are increasing yet relatively few studies have addressed survivors' reported symptoms beyond the initial year after diagnosis. The most commonly reported symptom was fatigue followed by negative feelings about body appearance, diarrhea, constipation, physical discomfort and limitation in activity. And the majority of crc survivors can reasonably expect a probability of physical symptoms that do not differ substantially from the general population.
Cancer 2007; 110: 2075-2082

7. First Patient Dosed with KX2-391 in Phase I Clinical Trial

The drug KX2-391 which belongs to an emerging new family of targeted treatments called protein kinase inhibitors, has begun clinical trials at Roswell Park Cancer Institute in Buffalo and has also commenced at M.D. Anderson in Houston, Texas. The drug has worked against every cancer and in every animal model to date as it targets an important cell signaler called Src kinase, a protein linked to the rapid growth and spread of cancer cells. A potential advantage of this kinase inhibitor is that it disrupts Src at a site different from where other currently studied compounds are targeted, reducing the chance that patients will develop resistance to the new drug. It was developed for crc but has had positive results in a broad range of tumour types. Roswell is accepting Canadian candidates for the trial. **The trial is designed for crc patients who have failed all conventional therapies.** Please see me for further information on the trail.
www.medicalnewstoday.com/articles/89974.php

8. Nektar's Phase 2 Clinical Development of NKTR-102 for CRC

NKTR-102 is Nektar's lead oncolytic candidate using the company's innovative small molecule PEGylation technology platform. The phase 2 program is designed to evaluate the safety and efficacy of NKTR-102 (PEG-irinotecan) for the treatment of patients with solid tumours. The colorectal study is comprised of 2 sequential stages. The phase 2a is an open label, dose-finding trial in multiple solid tumour types that are refractory to standard curative or palliative therapies. The phase 2b is an open label randomized, double arm study in patients with second line metastatic colorectal cancer and study participants will be randomized in one of two arms of the trial to receive either NKTR-102 and erbitux or standard irinotecan and erbitux. **Preclinical studies show that treatment with NKTR-102 results in significant suppression of tumour growth in an irinotecan-resistant mouse colorectal tumour model. Administration of NKTR-102 in an animal model results in a significantly improved time-concentration profile for the active metabolite of irinotecan as compared to treatment with standard irinotecan**.
Therapeutics Daily News www.therapeuticsdaily.com/news/ Nektar Commences Phase 2 Clinical Development Program for NKTR-102 in CRC

9. Second Surgery to Remove Colorectal Liver Mets provides Good Outcomes

According to results recently published in the Archives of Surgery, a second surgery to remove colorectal cancer that has spread to the liver can significantly improve survival. Surgeons at the University Hospital of Bordeaux in France reviewed records of patients who had a second operation to remove tumours in their liver that had spread from a colon or rectal cancer. The researchers concluded: "A second liver resection because of recurrent liver mets from colorectal cancer is safe and provides a survival benefit similar to that with single hepatectomy. Our analysis suggests that the benefit of treatment is limited in patients who undergo a second hepatectomy within 1 year of the first operation and in those with extrahepatic disease."
Cunha A, Laurent C et al., A second liver resection due to recurrent colorectal liver metastases. Archives of Surgery. 2007; 142: 1144-1149.

10. Treatment Outcomes of Liver & Lung Mets from CRC

The resection of pulmonary and liver mets is an aggressive treatment option for patients with stage IV colorectal cancer and has been shown to yield acceptable long term survival by surgeons in South Korea and their study was published in the Journal of Gastroenterology and Hepatology. Patients who underwent resection of both hepatic and pulmonary mets secondary to colorectal cancer had a 5-year overall survival rate of 60.8% from initial operation and there was no perioperative mortality. ***Lee, Won-Suk, et al., J of Gastroenterology and Hepatology, (online publication) doi:10.1111/j.1440-1746.2007.05178***

11. Given Before Surgery for Liver Mets, Avastin Reduces tumours and Protects The Liver

A research team at MD Anderson Cancer Center in Texas studied liver tumours from crc patients removed during surgery and also changes in non-cancerous liver tissue. They compared liver pathology from patients who received folfox alone to those who were treated with Avastin along with folfox. When avastin was added to folfox chemo,

- there was significantly less tumour viability – 32% compared to 45%
- and avastin protected the liver from chemo damage. Changes in small blood vessels in the liver known as hepatic sinusoidal dilation occurred less often and was less severe (27% vs. 53%)

The research team concluded: "In patients treated with folfox chemo, avastin improves the pathologic response, as demonstrated by a reduction of the degree of tumor viability, and reduced the incidence and severity of hepatic injury. This retrospective study provides additional evidence supporting the use of avastin in combination with folfox for crc liver mets." ***Riberio et al, Cancer, Volume 110, Issue 12, December 2007***

12. Irinotecan Plus Hepatic Arterial Infusion for Colon Cancer

Doctors at Sloan Kettering Cancer Centre in New York combined IV chemotherapy with chemo infused directly into an artery leading to the liver to treat advanced colorectal cancer. All patients had already been heavily treated with chemotherapy, and their liver tumours could not be surgically removed. All had previously received oxaliplatin. Patients received IV Irinotecan along with hepatic arterial infusion of floxuridine and dexamethasone which achieved a response rate of 44% and a median overall survival of 20 months. 16% of the patients proceeded to surgical resection or ablation. ***Gallagher et al, Annals of Oncology, Volume 18, #12, December 2007.***

13. CT Scans Increase Radiation Exposure

According to an article recently published in the New England Journal of Medicine, radiation exposure to computed tomography (CT) scans may increase the risk of developing cancer. However, the risk remains small and is associated in particular with increased frequency of CT scans. CT scans are associated with higher doses of radiation than conventional X-rays and this carries a risk of turning cells affected by the radiation cancerous. The researchers extrapolated that 1.5-2% of cancers in the US could be attributed to CT scans but that CT scans represent an important part of modern medicine and may provide optimal benefit for many patients despite the risk. ***Brenner D, et al. Computed Tomography – an increasing source of radiation exposure. New England Journal of Medicine. 2007; 357: 2277-2284.***

14. Direct Link Between Obesity & CRC

A report published in the journal Cancer Epidemiology shows that obese individuals (BMI > 30) have a 20% greater risk of developing crc compared with those of normal weight (BMI < 25). Researchers have identified **3 major ways** that excess body fat seems to increase cancer risk.

- Proteins called cytokines are secreted by body fat and promote inflammation through the body; this increased inflammation can promote cell damage and potentially initiate cancer.
- Excess body fat triggers insulin resistance, which in turn raises levels of cancer-promoting insulin and insulin-related growth factor.
- Increased production of estrogen by fat tissue increases circulating levels of the hormone and may promote hormone-related cancers.

Waistline fat includes not only fat directly under the skin, but also the visceral fat that is nestled around vital organs, ie liver. It is this type of fat that is most strongly implicated in the aforementioned metabolic disturbances. www.News-Medical.net /news

15. Mild Deficiencies of B Vitamins Raise Colorectal Cancer risk

Mild deficiency of dietary folate and other B vitamins alters multiple components of the Wnt pathway, raising risk of crc, according to a new animal study published in the December 2007 issue of the Journal of Nutrition. Early preclinical and clinical studies suggest that depletion of folate alone or in combination with the other B-vitamins increases the risk of colorectal cancer. The study was performed in collaboration with researchers from the U of Southern California, Harvard Medical School, and New England Medical Center.

Liu, Z et al., Mild Depletion of dietary folate combined with other B-vitamins alters multiple components of the Wnt pathway in the mouse colon. J of Nutrition. V 137; 2701-2708

16. Green Tea May Protect Against Colon Cancer

According to research reported at the Sixth International Conference on Frontiers in Cancer Prevention, sponsored by the American Association for Cancer Research, a standardized green tea polyphenol preparation limited the growth of colorectal tumours in rats treated with a substance that causes the cancer. The findings showed that rats that were fed a diet containing polyphenon E were less than half as likely to develop colon cancer, which were consistent with previously published results, which showed that green tea consumption was associated with lower colon cancer rates in China. Polyphenon also decreased the total number of tumours per rat and decreased tumour size, compared with control rats that were not given polyphenon E. The results were as follows: In the control group, 67% of the rats developed tumours while in the treated group only 27% of rats had tumours. Most importantly, tea polyphenols decreased the number of existing malignant tumours per rat by 80% compared to the control group.

Sixth International Conference on frontiers in Cancer Prevention, www.Reuters.com/News

17. See NCCN Practice Guidelines for mcrc H/O.