CRC RESEARCH #14

1. Neulasta Reduces Risk of Neutropenia in CRC Patients.

Neulasta (pegfilgrastim) reduces the risk of severe low white blood cell count in crc patients who are receiving chemo every two weeks. Researchers conducted a Phase II clinical trial and reported their rather prominent findings in respect of neulasta at the 9th World Congress on GI Cancer in Barcelona, Spain (June 28, 2007 – Abstract #PD0025) The drug is recommended by Cancer Care Ontario whereby a single injection is needed per cycle of chemo. *Hecht J et al.*

2. Vectibix is Effective as Single Agent for CRC

According to an online publication in the journal *Cancer*, Vectibix (panitumumab) has anticancer activity when used as a single agent among patients who have received prior therapy for crc. Researchers from U of California at Los Angeles conducted a clinical trial to evaluate use of vectibix as a single agent in the treatment of crc among patients who had received prior therapy that included 5FU plus irinotecan or oxaliplatin or both. The results were positive concluding that vectibix used as a single agent provides anticancer activity among patients with crc who have received prior standard chemo regimens. *Hecht J et al, Cancer. Aug. 1, 2007.*

3. Smokers May Benefit Less From Irinotecan Than Non Smokers in CRC

Smoking may reduce the body's ability to effectively metabolize the chemotherapy agent camptosar (irinotecan) in the treatment of crc. Smoking may reduce the exposure of the drug's cancer killing effects to cancer cells. Different ingredients in cigarette smoke may affect the metabolism (breakdown and absorption) of certain drugs and thus keep them from working to their full potential. *Van der Bol J, et al. J of Clinical Oncology. 2007; 25: 2719-2726*.

4. Panitumumab vs. Cetuximab – Infusion Reactions

Data from the University of Wisconsin provides new data on research wherein a patient was successfully treated with panitumumab after the patient had a severe infusion reaction to cetuximab. Even with premedication, erbitux can result in an infusion reaction in select patients. In a portion of these patients, the reaction is severe, and further therapy with erbitux is contraindicated, thus preventing these patients from receiving potentially beneficial anti-EGFR therapy. Panitumumab is given without premedication and, has rarely been associated with infusion reactions. *Heun et al, Clinical Colorectal Cancer. 2007; 6(7): 529-531.*

5. Link Between Drinking And Colon Cancer

Researchers in Britain say the more a person drinks alcohol, the greater the risk of developing colon cancer. One large glass of wine/pint beer ↑ risk by10%. Two large glasses wine/two pints beer ↑ risk by 25%. The more alcohol you drink, the greater your risk of bowel cancer. *International J of Cancer. Online publication. 2007*

6. Smoking Associated With Increased Risk of CRC

Researchers from Hawaii recently concluded from a clinical study that smoking increases the risk of crc with a greater number of cigarettes smoked during a lifetime adding to this risk. In addition filtered cigarettes are associated with an increased risk of rectal cancer whereas non-filtered cigarettes are associated with an increased risk of both colon and rectal cancer. *Luchtenborg M, et al. Cancer Epidemiology, Biomarkers and Prevention. 2007; 126: 1341-1347.*

7. Higher Vitamin D Levels Linked With Reduced Risk of Colon Cancer

People with higher plasma levels of vitamin D may have a reduced risk of developing colon cancer. *Wu K et al. J of the National Cancer Institute. 2007; 99; 1120-9.*

8. Sequential Chemo as Effective as Concurrent Chemo in Advanced CRC.

Sequential administration of chemo appears just as effective as concurrent administration among patients with advanced crc. The **CAIRO** study (capecitabine, irinotecan and oxaliplatin in advanced crc) compared sequential to combination chemo. The trial included 820 patients from the Netherlands who were treated with one of the following regimens:

a. **Sequential**: Xeloda followed with Camptosar, followed with Xeloda plus oxaliplatin.
b. **Combination:** Xeloda + Camptosar, followed by Xeloda + oxaliplatin.

Conclusion was that sequential chemo appears just as effective as combination chemo for treatment of advanced crc. *Koopman M, et al. The Lancet. 2007; 370: 135-142.*

9. ASCO Conference – Part II

A. Emerging Data with Targeted Therapies

Multimodality therapy regimens consist of

- Systemic (cytotoxic & biologics -> medical oncology)
- Surgical
- Interventional Radiology
- Radiation Therapy

- Every mcrc patient should be approached with a team of multimodality therapy regimens.
- For surgical candidates, neoadjuvant and adjuvant therapy is favored.
- Capecitabine may be slightly better in the metastatic setting when compared to 5FU.

Resectability of Disease Depends on:

- # of lesions
- location of lesions (ie vascular involvement)
- distribution of lesions (occupation of surface area)

- Before up to 1/3 of mcrc patients were candidates for resectioning. Currently, 2/3 of patients are now candidates for resectioning, and therefore curable.

- Trick is to shrink tumours as much as possible before resectioning takes place.
- Mcrc is now a curable disease, particularly if mets are isolated to liver.
- But if mets are also in lungs and quite small, the potential for a cure is still present. (Dr. Neal Meropol, M.D., Philadelphia, P.A).
- If surgery is an option, neoadjuvant and adjuvant therapy is best approach for disease free survival.

Negative Effect of Neoadjuvant Systemic therapies on Surgery:

- Hepatotoxocity of chemo agents
- Avastin's effect on wound healing after surgery
- Excellent response in liver may result in difficulty locating and resecting all original sites of disease after chemo ("hiding effect")

Recommendations:

- Resectable: Administer neoadjuvant for ~ 2 months (3-4 cycles). Discontinue avastin 6-8 weeks before surgery (follow with adjuvant.).
- Unresectable: Deliver systemic therapy until hepatic lesions become resectable; discontinue avastin 6-8 weeks before surgery (follow with adjuvant).

B. Individualizing Treatment For Patients with Non-Resectable Metastatic Disease

- A biologic such as avastin is not being recommended as a maintenance therapy. Rather, 5FU or 5FU + avastin can be recommended as a maintenance therapy.
- For those patients who cannot receive avastin, erbitux is being recommended as a first line therapy with folfiri.

- Folfox = folfiri + avastin
- As for **combo** vs. **sequential** such as **folfoxiri:** there was a study that produced sky high response rates but had high toxicity; and currently there is no data available with biologics. There is also no "plan B" available to the patient if end up combining the chemo's at once and a recurrence takes place.
- **CAIRO study =** Xeloda + Irinotecan + Oxaliplatin: Patients performed comparably whether they were on the sequential regimen or the combo regimen. However, generally speaking, in crc, sequential trials have shown better outcomes. **The only caveats are:**
    a. Combo regimens ensure better exposure to all active agents, which may be associated with better outcomes
    b. Combo regimens are associated with better objective response rates (ie tumor shrinkage) which may be important in certain settings, such as with liver mets.

10. Mag/Cal Infusions With Folfox/Avastin

Sanofi-Aventis USA issued an alert in respect of concurrent use of cal/mag infusions preventing neuropathy when having folfox administered in conjunction with avastin. An unplanned interim analysis of data from a Phase IV study showed decreased efficacy of the regimen and they are not sure if the decreased efficacy is due to the cal/mag infusion. They are currently analyzing the data and will release their findings as quickly as possible. **Cal/mag** infusions were approved for use with **folfox administrations** sans the biologics (ie avastin). The new element to this equation is the introduction of **avastin.** It may very well be the efficacy of avastin that is compromised not **oxaliplatin** seeing that prior studies have confirmed no efficacy compromised by cal/mag infusions. It may be something entirely different causing the decreased efficacy. Scientists are not sure and are not commenting but would like to err on the side of caution.