# Clinical Pearls

**This column is featured in every issue of the Cancer Strategies Journal, edited by Dwight McKee, MD. Do you have a Clinical Pearl that you would like to share with our readers? Please forward them to editorial@cancerstrategiesjournal.com.**

**In this issue we feature off-label pharmaceutical use for cancer.**

### Rapamycin

Grapefruit doubles the bioavailability of rapamycin (via inhibition of small intestinal 3A4) - can use half dosage - less drug, less cost, and less toxicity without losing effectiveness (100th Annual Meeting in Denver in a session on "Late-Breaking Research: Clinical Research 1: Phase I-III Clinical Trials," Poster Section 27 on April 20, 2009)—**courtesy of Donald Yance, CN, MH(AHG)**

Rapamycin with herceptin, significantly increased anti-tumor efficacy compared to either drug alone in Her II neu over expressing breast cancer cells. (Int J Cancer. 2007 Jul 1;121(1):157-64. —**courtesy of Donald Yance, CN, MH(AHG)**

Rapamycin Inhibition Promotes Response to EGFR Inhibitors in PTEN-Deficient and PTEN-Intact Glioblastoma Cells. (doi: 10.1158/0008-5472.CAN-04-4392, Cancer Res August 15, 2006 66; 7864.)—**courtesy of Donald Yance, CN, MH(AHG)**

Twenty-eight heavily pretreated patients with recurrent malignant GBM were administered EGFR inhibitors in combination with Rapamycin. Nineteen percent of patients experienced a partial response and 50% had stable disease. Six-month progression-free survival for glioblastoma patients was 25%. (*J Neurology* 2006; 67:156-158). —**courtesy of Donald Yance, CN, MH(AHG)**

### Clarithromycin and Non-Small-Cell Lung Cancer

Clarithromycin (Biaxin) antibiotic treatment (200 mg bid) significantly increased the median survival time for non-small-cell lung cancer patients, the median survival for the Biaxin group was 535 days and that for the non-Biaxin group was 277 days. (Mikasa K, Sawaki M, Kita E, Hamada K, Teramoto S, Sakamoto M, Maeda K, Konishi M, Narita N. Department of Medicine II, Nara Medical University, Kashihara, Japan)—**courtesy of Barry Boyd MD**

### Beta-Blockers Reduce Breast Cancer Mortality

Beta-Blockers Reduce Breast Cancer Mortality, are associated with Improved Relapse-Free Survival in Patients With Triple-Negative Breast Cancer, Reduce Hepatocellular Carcinoma Incidence in Patients with HCV-Associated Cirrhosis, and improve survival in non-small cell lung cancer. Adrenergic activation increases tumor invasiveness, and increases metastases. Evidence to date suggests propranolol (Inderal), the original and less selective beta blocker, is most active in blocking effects of stress hormones on cancer, typical dose 40 mg qid. This research also provides insight into the importance of stress and cancer, importance of relaxation training and other stress management practices —**courtesy of Barry Boyd MD**

### Off-Label Use of Metformin

Metformin can be safely given as an off-label adjunctive treatment in cancer patients, especially breast, ovarian, colorectal, prostate, pancreas and perhaps in glioma patients who have Type 2 diabetes, metabolic syndrome, elevated circulating insulin levels, or are obese, or even simply those who cannot or do not adhere to a low carb low fat diet.—**courtesy of Ray Chang MD**

Metformin with neoadjuvant chemotherapy in breast cancer MD Anderson: 68 diabetics with stage II and III breast cancer not taking metformin and 87 that were diabetic and on metformin. The researchers found that the pathologic complete response (pCR) rates in the breast cancer patients taking metformin was 24 percent, vs 8% in those not on metformin. —**courtesy of Raymond Chang MD**

### Cimetidine

Randomized controlled study showed 800 mg of cimetidine BID for only 5 days preoperatively appeared to have had a positive effect on colorectal cancer patient's survival (Kelly MD et al. Cancer 85:8, pp.1658-1663, 1995). —**courtesy Raymond Chang MD**

Given its low toxicity and low cost, cimetidine can be administered to patients with colorectal cancer and possibly other adenocarcinomas that express the Sialyl Lewis antigens to minimize metastases and recurrence and enhance survival. Typical dose 400-800 mg bid. Interacts with many other medications, need to study its pharmaco-interactions. —**courtesy Raymond Chang MD**

### Dipyridamole

Given the safety and low cost of dipyridamole (Persantine, 4 mg/kg/day) consider it as part of a cocktailed approach to cancers, especially melanoma and pancreas cancer. For such cancers, it is reasonable to consider dipyridamole as a secondary preventative to minimize metastases and optimize survival as well. Also, given the negative prognostic implications of elevated platelets during cancer Tx, consider it in this setting as well (inhibits uptake of adenosine by platelets and endothelials cells). —**courtesy of Raymond Chang MD**

### Do Red Yeast Rice and Lovastatin Inhibit Prostate Tumor Growth?

A pre-clinical study was designed to determine whether red yeast rice (RYR) and lovastatin (LV) inhibit prostate tumor growth in SCID mice. Red yeast rice significantly reduced tumor volumes of androgen-dependent and androgen-independent prostate xenograft tumors compared with animals receiving vehicle alone ($P < 0.05$). Inhibition by RYR was greater than that observed with LV at the dose found in RYR, showing that other compounds in RYR contributed to the antiproliferative effect. There was a significant correlation of tumor volume to serum cholesterol ($P < 0.001$). RYR decreased gene expression of androgen synthesizing enzymes (HSD3B2, AKR1C3, and SRD5A1) in both type of tumors ($P < 0.05$).

Clinical studies of RYR for prostate cancer prevention in the increasing population of men undergoing active surveillance should be considered. *Cancer Prev Res*. 2011: 4(4); 608–15. AACR. –**courtesy of Dwight McKee MD**

### Statins and Colon Cancer

Epidemiological studies show that individuals taking statins have a reduced risk of colon cancer. In the present study, LV decreased cellular proliferation (P<.001) and induced apoptosis (P<.05) in HCT-116 and HT-29 human colon cancer cells. RYR inhibited both tumor cell growth (P<.001) and enhanced apoptosis (P<.05) in HCT-116 cells. Inhibition of proliferation was reversed by mevalonate (MV) in LV-treated cells, since LV is an HMGCoA reductase inhibitor. However, RYR with MV did not reverse the observed inhibition of growth. Monocolin K(MK, identical to lovastatin)-free RYR did not reverse the observed LV-mediated inhibition of cancer cell growth. These observations suggest that other components in RYR, including other monacolins, pigments or the combined matrix effects of multiple constituents, may affect intracellular signaling pathways differently from purified crystallized LV in colon cancer cells. RYR was purified into two fractions: pigment-rich fraction of Chinese red yeast rice (PF-RYR) and monacolin-rich fraction of Chinese red yeast rice (MF-RYR). The effect of MF-RYR was similar to that of LV, while the effect of PF-RYR was similar to the effect of the whole RYR extract on the proliferation, apoptosis and mRNA level of HMGCR and sterol response element binding protein-2.

These results suggest that the matrix effects of RYR beyond MK alone (statin component) may be active in inhibiting colon cancer growth. RYR with or without MK may be a botanical approach to colon cancer chemoprevention worthy of further investigation. —**courtesy of Dwight McKee MD**

### Amino-Bisphosphonates as Anti-Cancer Agents

Amino-bisphosphonates include Aredia (pamidronate disodium) Zometa (zoledronic acid) Fosamax (alendronate) Actonel (risedronate) and Boniva (ibandronate). It was originally thought that amino-bisphosphonates are useful in bone metastases because of the ability of these agents to inhibit bone resorption; newer understanding leads us to knowledge that these drugs are really direct anti-cancer agents as well.

Combining aminobisphosphonate (such as Zometa 4 mg IV over 15 minutes monthly, or 1 mg over 5 minutes weekly), with low dose interleukin-2 (Proleukin) (1 million units 5 days/wk), also stimulates gamma delta T-cells, which are capable of tumoricidal activity. Non-randomized clinical trials in a wide variety of tumor types from Europe have shown promising activity for this combination in a variety of cancer types. Research finding that the therapy can efficiently kill cancer stem cells is also exciting. Very likely most effective with very low disease burdens. —**courtesy of Raymond Chang MD**

### Artemisinin Compounds Reasonable to Try Against Cancer

Despite some concern for neurotoxicity based on animal studies, artemisinin and related compounds are some of the least toxic medications on the market for any condition, without clinically relevant toxicity after extensive oral and parenteral use in various populations for the past two decades, except for sporadic and transient cardiac dysrhythmias. These compounds are also relatively inexpensive, being dispensed mainly in the third world in poor populations where malaria is endemic. With the demonstrated bioactivity in the laboratory and the promising anecdotal cases, these seem to be reasonable compounds to try against cancers, either in combination or when other treatments fail. —**courtesy Raymond Chang MD**

### HIV Protease Inhibitor Drugs

Dr. Phillip Dennis and colleagues took existing HIV protease inhibitor drugs and tested 6 of them against cancer cell lines derived from 9 different human tumor types and found that three of the drugs (ritonavir, nelfinavir and saquinavir) reduced the growth of 60 of those cell lines. In the laboratory, nelfinavir or Viracept®, a first generation speific protease inhibitor designed for HIV appeared most potent (Autophagy 4(1):107-9, 2008). Nelfinavir seems to exercise a broad-spectrum cancer killing effect through multiple pathways: apoptosis, necrosis and autophagy (See Clin Cancer Res. 2007; 13(17): 5183-94), and is also noted to have antiangiogenic and immunomodulatory ability.

Nelfinavir has also been shown to have radiosensitizing properties (Cancer Res. 2005 Sep 15;65(18):8256-65.) via Akt activation making it a logical addition to radiation therapy and trials using it in this fashion are underway against brain, rectal and pancreas cancers. One of the ways it works with chemo and radiation may be via disruption of the process by which hypoxia occurs by restoring proper blood flows to tumors ad making them more vulnerable to other therapies according to research by McKenna of Oxford. McKenna's group also demonstrated as early as 2005 that Nelfinavir radiosensitized cancer cells and a small trial he conducted with nelfinavir + chemoradiation showed that 6 out of 10 patients with advanced pancreas cancer had their cancer regress enough to be surgically removed whereas normally it would be only 1 in 10 (J Clin Oncol. 2008 Jun 1;26(16):2699-706)

The anti-HIV protease inhibitors have been around since the mid 1990s-- their dosage, safety and toxicity in humans are well known. Currently, multiple phase 1/2 studies are under way to evaluate the potential of nelfinavir in renal cell, rectal, lung, adenocystic, liposarcoma, brain and pancreas cancers, alone, and in combination with chemotherapy and radiotherapy and other targeted agents such as bortezomib or Velcade® and temsirolimus or Torisel®.

The usual starting dose for nelfinavir is 1250 mg twice a day (costs about $25/day in the US) but ongoing phase 1/2 trials are testing higher doses. Common side-effects include diarrhea, blood lipid abnormalities (good reason to add a statin as another off-label anti-cancer treatment), but caution must be exercised when adding or selecting a statin due to potential drug-drug interaction via the CYP pathway where the lactone pro-drugs simvastatin and lovastatin should not be used (atorvastatin at 2/3 dose a good choice). Other side effects include redistribution of body fat (64% at 13 months of usage), as well as glucose intolerance (with a diabetes risk of 3% with long-term use-consider metformin) but its side-effects do not overlap with mainstream anti-cancer agents' and it is usually tolerable for long term treatment.—**courtesy of Raymond Chang MD**

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