WELLNESS RESTORATION PROGRAM

ON THE COPPER RESTRICTION TECHNIQUE

Copper chelation is not without risks since many of the body's vital functions also need copper. The trick is to restrict enough copper so that the cancer process that not benefit from it while making it available for the body's vital functions. Holistically, they may be accomplished via diet, in which case Yvonne can look at the copper charts and decide which foods she wants to avoid. For example, kale risk in copper, but not broccoli. So a little more broccoli than kale may be beneficial. In terms of integrative oncology, copper chelation can make sense , especially if the dietary copper restriction was working well enough. If that is chosen, the blood needs to be carefully monitored to make sure there's still a bit of copper left for the other body's functions. But all in all, it appears that copper deprivation hurts the cancer more than the healthy cells. But the ultimate choice is Yvonne's.

EXHIBIT A

Clin Cancer Res. 2000 Jan;6(1):1-10.

Treatment of metastatic cancer with tetrathiomolybdate, an anticopper, antiangiogenic agent: Phase I study.

Brewer GJ1, Dick RD, Grover DK, LeClaire V, Tseng M, Wicha M, Pienta K, Redman BG, Jahan T, Sondak VK, Strawderman M, LeCarpentier G, Merajver SD.

Preclinical and in vitro studies have determined that copper is an important cofactor for angiogenesis. Tetrathiomolybdate (TM) was developed as an effective anticopper therapy for the initial treatment of Wilson's disease, an autosomal recessive disorder that leads to abnormal copper accumulation. Given the potency and uniqueness of the anticopper action of TM and its lack of toxicity, we hypothesized that TM would be a suitable agent to achieve and **maintain mild copper deficiency to impair neovascularization in metastatic solid tumors.** Following preclinical work that showed efficacy for this anticopper approach in mouse tumor models, we carried out a **Phase I clinical trial in 18 patients with metastatic cancer who were enrolled at three dose levels of oral TM (90, 105, and 120 mg/day) administered in six divided doses with and in-between meals.** Serum ceruloplasmin (Cp) was used as a surrogate marker for total body copper. Because anemia is the first clinical sign of

copper deficiency, the goal of the study was to reduce Cp to 20% of baseline value without reducing hematocrit below 80% of baseline. Cp is a reliable and sensitive measure of copper status, and TM was nontoxic when Cp was reduced to 15-20% of baseline. **The level III dose of TM (120 mg/ day)** was effective in reaching the target Cp without added toxicity. **TM-induced mild copper deficiency achieved stable disease in five of six patients who were copper deficient at the target range for at least 90 days.**

COMMENTS

This means that 5 out of 6 patients prospered with this TM technique during three months when their metastatic cancer did not grow, was "stable". Even if this is a limited and short study, it's all the more encouraging that at the indicated dose, there was no toxicity or excessive copper deprivation for other vital functions.

EXHIBIT B

We also have a more recent study on triple negative breast cancer from a clinical trial at Weill Cornell Medical College, with even better results.

"CLEVELAND, Ohio -- A nontoxic drug that removes copper from the body has shown remarkable early success in preventing relapse in women with one of the most difficult-to-treat forms of cancer -- metastatic triple negative breast cancer. If proven effective in a larger trial, the treatment could offer a ray of hope to a patient group that currently faces a grim prognosis and only one available therapy.

Median survival for metastatic triple-negative patients is a year or less, according to current research. Triple-negative breast cancer patients have a poorer prognosis than others with breast cancer even when the disease is diagnosed in early stages.

Yet 81 percent of the women with metastatic triple-negative breast cancer who took the copper-reducing drug tetrathiomolybdate, or TM, daily in a small study a at Weill Cornell Medical College, **were relapse-free after 10 months.** One of the women,

diagnosed with the most advanced stage of the disease when she entered the trial in 2007, remains cancer-free six years later. The results were published online in the journal Annals of Oncology.

"This is a very exciting and promising result," said study author Dr Linda Vahdat, director of the Breast Cancer Research Program at Weill Cornell. Vahdat said that **three other women with triple-negative cancer in the trial also had long-term success with the treatment.**

As exciting as the finding is, it's extremely preliminary. The trial involved only 40 patients with high-risk breast cancer, defined as those with Stage 3 or Stage 4 NED (no evidence of disease), or triple-negative patients with Stage 2 disease. **Eleven of the 40 study patients had triple-negative breast cancer.**

Stage 3 breast cancer patients, those whose disease has spread to many lymph nodes, have a 50 percent to 70 percent risk of relapse over five years. Patients with Stage 4 NED breast cancer, those who have been treated for cancer that has spread to one or more other body parts and currently show no sign of active disease, always face a recurrence. The study was published online Feb. 13 in the journal Annals of Oncology.

Dr Josehp Barr director of breast cancer research and the Breast Cancer Survivor Program at University Hospitals Case Medical Center, said the concept is sound but it's much too soon to make any conclusions about TM's potential for triple-negative patients.

"Looking at a small cohort like that is a bit of a problem," he said. "I'd be thrilled if giving something as straightforward as copper chelation [reduction] improved survival, but it's going to take a much larger study to determine that."

That study is in the works, Vahdat said. There are currently 60 patients enrolled in the TM trial, and with increased funding it will be expanded to include 75 in the near future. Researchers at **Cornell are looking primarily for women with triple-negative breast cancer now, because they have seen the largest benefit from the therapy.**

About 10 percent to 20 percent of breast cancers are triple negative, according to the Triple Negative Breast Cancer Foundation. They represent a disproportionate share -- about 30 percent -- of metastatic breast cancers, however, said Vahdat. The cancer's name refers to a lack of three protein receptors that line the inside or outside of cells, called estrogen receptor, or ER; progesterone receptor, or PR; and human epidermal growth factor 2, or HER2.

In ER, PR or HER2-positive breast cancers, treatments prevent or slow the growth of the cancer. Tamoxifen, for example, targets the estrogen receptor, while

trastuzumab (Herceptin) targets the HER2 receptor. Chemotherapy is currently the only available treatment for triple-negative breast cancer patients.

"[Triple-negative] tends to grow very differently than 'regular' breast cancer, and we don't have the same tools to treat it," Vahdat said. "There are far fewer options, and there's no triple-negative directed therapy, so far."

The Cornell study included non-triple-negative patients as well, as long as they had stable disease and were at high risk of recurrence.

An evolving understanding of how tumor cells spread and set up shop in other organs led to the study of TM to prevent relapse in high-risk patients.

In order for a breast tumor to spread, it needs help. Tumor cells can migrate freely in the blood, but they need a specialized group of bone-marrow-derived cells called **endothelial progenitor cells, or EPCs, to grow the blood vessels that feed a new tumor.**

"If a breast cancer cell decides to go to the liver or lung or bone, these EPC cells help with establishment of those tumors," said Baar.

Copper is a trace element we all need in small amounts for the formation of red blood cells and bone, as well as the absorption of iron. **It's also critical to mobilizing EPCs -- when there isn't enough copper available, the level of EPCs in the blood drops significantly.**

TM is a copper chelation compound used to treat patients with Wilson's disease, a rare genetic metabolism disorder that leads to excess copper in the blood. TM binds the excess copper and is then excreted as waste.

In the Cornell study, about 75 percent of the patients achieved the copper-depletion target using TM after one month of therapy, and in these patients there was a significant reduction in EPCs.

"What was really amazing was that when their EPCs went down and stayed down, it appeared their tumors didn't come back," Vahdat said. "We knew from previous work that we'd done that EPCs need to surge before a metastatic relapse. So if you're able to prevent that surge, you could probably prevent a metastasis."

TM and other copper-depletion methods aren't new to the cancer research field. Numerous lab and animal studies have confirmed the connection between copper and tumor blood vessel growth, or angiogenesis. TM has been studied in renal cell cancer, prostate cancer and mesothelioma, a rare cancer usually caused by exposure to asbestos.

That research has confirmed that TM isn't any good at slowing active disease, though. **Once a tumor is established, lowering EPC levels won't affect it. Where it appears to work is in suppressing tumor spread or new tumor growth.**

"The niche for this drug is to maintain tumor dormancy and to prevent metastasis," Vahdat said. "I could certainly see it being used as a prevention agent in the future. Whether that's for someone [at high risk] who doesn't have cancer to then developing cancer, or someone who's had cancer but doesn't have it now, it just seems to take those cells out of play."

It's no surprise that Vahdat has already had a lot of interest in her team's research, as preliminary as it is. Many of her study participants are from out of state, and one comes from as far away as San Francisco once a month for testing.

The treatment itself is a pill taken several times a day -- one of its biggest drawbacks. The only major side effects were from low white or red blood cell counts when copper levels were driven too low. One patient required hospitalization, but Vahdat said most of the cases of low blood counts were mild and reversible after a short respite from the study medication.

The next step in figuring out if TM will live up to its potential for triple-negative breast cancer patients is a much bigger, randomized controlled trial. It'll take a comparison of the new therapy against traditional treatments to see if it has a real impact. That can't come soon enough for those with metastatic triple-negative breast cancer.

"There's a lot of interest in this from patients," Vahdat said. "We'll see. We're all scientists and we want to make sure that what we say we're doing is true."

http://www.cleveland.com/healthfit/index.ssf/2013/03/copper_depletion_shows_early_s.html

COMMENTS

This trial showed that 4 of 40 women survived long terms and 81 percent had stable disease for 10 months with no new growth. So this technique is not a “panacea”, a “cure”. But it can be an added technique to many others. Furthermore, this trial has some flaws, like there were mixed diagnoses, only 11 trimple negatives, there may have been other variables and the study was small and its mechanism of action does not remove the cancer, it

just acts on endothelial progenitor cells the EPCs' (which need copper) do downregulate (inhibit) them so that new growths can't occur. But the strong point is that it does corroborate that dietary restriction can help and in holistic oncology, we have many forms of dietary restrictions, including from animal products, sugar, glutamine and many other molecules that hurt cancer more than healthy cells.

Meanwhile, if Yvonne could switch her HER 2 to negative, she would be back to triple negative and then Cornell university could include her for free in this trial and the results could be interesting because of all patients, it were the TN ones who did best. But even with a HER2 positive, she still may achieve great results using this and other modalities.

Chlorella can also be indicated. A unicellular green algae, this superfood has the ability to bind cadmium (in animal models) and zinc, copper, and lead (*in vitro*), has been used to detoxify wastewater of metal contaminants (Almaguer Cantu 2008; Shim 2008; Uchikawa 2010). In preclinical studies, chlorella lowered the bioavailability and accelerated the excretion of methylmercury (Uchikawa 2010) as well as cadmium (Shim 2009) and reduced lead-induced bone marrow toxicity (Queiroz 2011), all of which affect immune function and the body's delicate messaging pathways.