American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
November 15th, 2017

Second Wednesday of Every Month
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

Clinical Pearl: The Role of Copper in Angiogenesis and Metastasis

Angiogenesis:

- Normal physiological process through which new blood vessels form from pre-existing vessels
  Present in normal growth and development of our tissue and wound healing
  Fundamental step in the transition of tumors from a benign state to a malignant state
  Promotes tumor growth and metastasis (inhibit to control disease progression)
- Capillaries that form are not health vessels (disorganized)
- Contain specialized cells that swim away and establish elsewhere, escaping immune defenses; also contain enzymes that penetrate other tissues
- Occur more in vascular areas (brain, lungs, liver) and also travel through lymphatic system

Copper and Angiogenesis [Finney, 2009]

- Angiogenesis displays an exquisite sensitivity to bioavailable copper.
- Depletion of copper has been shown to inhibit angiogenesis in a wide variety of cancers.
- Copper is one of the key components of enzymes that control the tumor microenvironment, as well as appearing to have a role in how cancer cells migrate

Copper Lowering Therapy with Tetrathiomolybdate (TM - copper chelator) [Brewer, 2014]

- Study demonstrated major efficacy of TM, against advanced human cancers, previously virtually incurable
- TM therapy appears to be CURATIVE (put brakes on progression)
- TM also has major anti-inflammatory properties by inhibiting copper dependent cytokines involved in inflammation
- Cancers, as they advance, attract inflammatory cells that provide a plethora of additional pro-angiogenic agents

Copper Depletion and Breast Cancer [Jain, 2013]

- Patients who were at high risk of recurrence and received TM copper depletion therapy experienced an overall increase in survival time as well as a decreased risk of relapse

Oral Copper Depletion

- Nutraceuticals
- Oral Tetrathiomolybdate
- Control Copper Intake

Normal Laboratory Values - Goals for Inhibition of Angiogenesis

Serum Copper 72-166 ug/dl (Goal: 72-95)
Ceruloplasmin 16-39 mg/dl (Goal: 10-22)
Serum Zinc 56-134 ug/dl

Zn: Cu Ratio at least > 1:1 Better 2:1-3:1

Copper Depletion: Tetrathiomolybdate

- TM Dose: 20-40 mg po with each meal **plus** 60 mg po at bedtime on empty stomach
- Monitor Serum Cp, Cu, Zn and CBC q 2-4 weeks

- Target Goals:
    - Cp and Cu lowest quartile of normal (do not chelate to below 10mg/dl)
- Zn:Cu Ratio 3:1 - 2:1
- Requires Oral Zn Supplementation (60-120mg/day) as Zinc citrate or picolinate
- Contraindications: RBC anemia

Copper Depletion: Nutraceuticals (Sulfhydryl containing compounds)
EMPTY STOMACH
- N-AcetylCysteine 500-1000mg qid
- Alpha Lipoic Acid 100mg (3-4 times per day) qid

WITH FOOD
- Zinc citrate or picolinate 30-120/mg/d

Control Copper Intake: Avoid liver, organ meats, oysters, nuts and seeds, copper cookware, copper containing supplements

Questions & Answers

Judy Pruzinsky: **What are your thoughts on consuming sugar alcohols such as xylitol?**

Sugar alcohols do not raise insulin but they do disrupt the intestinal microbiome in many patients leading to the potential for diarrhea, gas and bloating.

Sugar alcohols arrive in the LI intact and draw water into the gut and then start to break down and act like a fermentable soluble fiber and become fuel for certain existing populations of methane producing bacteria. Thus depending upon the populations of microbes in an individual, xylitol may or may not increase those methane producing populations.

They are CHO. They do have calories and some Type 1 Diabetes patients see insulin rise with sugar alcohols.

Erythritol is not fermentable and does not cause gas and bloating. Erythritol is one of the ingredients in TRUVIA, a stevia based sweetener.

Disruption of the intestinal epithelium and dysbiosis can result from fermentation of sugar alcohols. Dysbiosis can then lead to glucose intolerance and a higher risk for, or worsening of, diabetes (a large population of people who use artificial sweeteners) and autoimmune inflammation due to dysbiosis.

Conclusion: Avoid Sugar Alcohols!!!

TEXT BELOW: Yale New Haven Hospital Newsletter https://www.ynhh.org/services/nutrition/sugar-alcohol.aspx

Sugar alcohols, also known as polyols, are ingredients used as sweeteners and bulking agents. They occur naturally in foods and come from plant products such as fruits and berries. As a sugar substitute, they provide fewer calories (about a half to one-third less calories) than regular sugar. This is because they are converted to glucose more slowly, require little or no insulin to be metabolized and don't cause sudden increases in blood sugar. This makes them popular among individuals with diabetes; however, their use is becoming more common by just about everyone. You may be consuming them and not even know it.

Common sugar alcohols are mannitol, sorbitol, xylitol, lactitol, isomalt, maltitol and hydrogenated starch hydrolysates (HSH) and are found in many processed foods. Food products labeled "sugar-free," including hard candies, cookies, chewing gums, soft drinks and throat lozenges often consist of sugar alcohols. They are frequently used in toothpaste and mouthwash.

FORMS OF SUGAR ALCOHOLS
Mannitol occurs naturally in pineapples, olives, asparagus, sweet potatoes and carrots. It is extracted from seaweed for use in food manufacturing. Mannitol has 50-70 percent of the relative sweetness of sugar, which means more must be used to equal the sweetness of sugar. Mannitol lingers in the intestines for a long time and therefore often causes bloating and diarrhea.

Sorbitol is found naturally in fruits and vegetables. It is manufactured from corn syrup. Sorbitol has only 50 percent of the relative sweetness of sugar which means twice as much must be used to deliver a similar amount of sweetness to a product. It has less of a tendency to cause diarrhea compared to mannitol. It is often an ingredient in sugar-free gums and candies.

Xylitol is also called "wood sugar" and occurs naturally in straw, corncobs, fruit, vegetables, cereals, mushrooms and some cereals. Xylitol has the same relative sweetness as sugar. It is found in chewing gums.

Lactitol has about 30-40 percent of sugar's sweetening power, but its taste and solubility profile resembles sugar so it is often found in sugar-free ice cream, chocolate, hard and soft candies, baked goods, sugar-reduced preserves and chewing gums.

Isomalt is 45 - 65 percent as sweet as sugar and does not tend to lose its sweetness or break down during the heating process. Isomalt absorbs little water, so it is often used in hard candies, toffee, cough drops and lollipops.

Maltitol is 75 percent as sweet as sugar. It is used in sugar-free hard candies, chewing gum, chocolate-flavored desserts, baked goods and ice cream because it gives a creamy texture to foods.

Hydrogenated starch hydrolysates (HSH) are produced by the partial hydrolysis of corn. HSH are nutritive sweeteners that provide 40 - 90 percent of the sweetness of sugar. HSH do not crystallize and are used extensively in confections, baked goods and mouthwashes.

Kamron Keep: **Is there anyone who shouldn't take Huang Qin Tang or any side effects we should watch for? Did you say this is a supplement someone could stay on for long periods of time?**

HQT is a very balanced formulation and can be used long term if needed for ex chronic diarrhea during and post chemo or chronic IBS as part of a comprehensive tx. Contraindications: some patients cannot tolerate the berberine in the Huang Qin. The beauty of this ancient formula is that it is very balanced. As with any therapeutic agent…..individual dosing and assessment are required.

Carla Halford: **What lymphoma is as it doesn't have tumour growth. So far we have talked about tumors and how to deal with them. I understand the cancer is in the WBC but not much further than that. In neutrophils, eosinophils, lymphocytes, monocytes or basophils. I guess lymphocytes...?**

The hematologic cancers are not solid tumors, they arise in the bone marrow and include Multiple Myeloma (invades bone), Leukemias (leukocytes) and Lymphomas (lymphocytes-invade the lymph nodes). This class of malignant syndromes has some unique traits. They are invasive, proliferative, inflammatory and often pro-coagulation. A proliferation of one type of cell will crowd out other cells and therefore there may be sequela such as RBC anemia or Thrombocytopenia, for example. With leukemias and lymphomas there can be a viral component (HSV, EBV, HVB HVC). The hematologic cancers will be a topic of a future clinical pearl and an advanced module.

- Often diagnosed by blood smear analysis
- Watch CBC+Diff, LDH, Uric Acid (uricemia), LFT (biliary obstruction), Creatinine (renal obstruction) as reflections of inflammation and tumor load

Cynthia Watson: **Post-Call Follow-up Questions**

When you treat lymphoma to any type of anti-viral treatment since it might be related to EBV?

- Burkitt's lymphoma is know to be related to EBV
- Viral DNA has also been found in leukemia and lymphoma cells
- There are anti-tumor botanicals such as andrographis that are also strong anti-virals, so I always think about including those in a formula

With Leukemia, since these aren't solid tumors, is chelating copper important?

Only solid tumors are impacted by copper chelation

Do people with allergy to sulfa drugs have issues with the tetrathiomolybdate?
The only adverse effects of TM therapy in my experience:

- GI distress - gas, constipation (both mild)
- RBC anemia

When you use the herbal mixtures how to do mix them – do you use a powder and mix them or do you use tinctures?
I prefer tinctures as the shelf life is at least 5 years and it reduces the number of capsules in a complex tx plan. Many clinicians do mix powders, however I feel that they degrade quickly and have a very short shelf life. Powdered herbs that are supplied in sealed packets have a longer shelf life, but it is difficult to mix formulas this way. I do use single Phytochemicals such as Resveratrol and Ursolic Acid and Honokiol, but with herbal extracts I prefer liquids.

Case Study

39F with Chronic Lymphocytic Leukemia (CLL) - Submitted by Sarah Shehab

Background: Dx 03/2015, No conventional treatment

Recommendations:

Chronic Lymphocytic Leukemia (CLL)

- Highly inflammatory
- Characterized by failure of apoptosis (BCL2), VEGF, Pi3K>AKT>MTOR
- Use of botanicals and nutraceuticals that raise WBC and lymphocytes is contraindicated (Vitamin C, Echinacea, Astragalus, Medicinal Mushrooms (except Ganoderma), IP-6 for example)
- VIT E shown to interfere with action of EGCG on CLL

Sample Protocol
EGCG 2 g bid
Curcumin 2 g bid
Omega 3 fatty acids 2 g bid
Zinc 30 mg bid
Vitamin D optimize blood levels to 65-80 start 5000iu
Vitamin A 10,000 iu/day monitor serum
Resveratrol 1 g bid
Feverfew 1 g bid
Honokiol 1-2 g /day
Ganoderma 3 g/day
(Consider NATURA Botanical Treasures_ contains Green Tea, Resveratrol Curcumin)

Sample Chinese Herbal Formula
240 ml (8 oz) 1 tsp 2-3x/day
40 Scutellaria baicalensis Huang Qin
30 Heydotis diffusa (Oldenlandia) Bai hua she she cao
30 Curcuma Longa Yu Jin
30 Camelia sinensis Cha Ye
30 Salvia milthiorrihiza Dan Shen
20 Magnolia off cortex Hou Po
20 Tanacetum parthenium Feverfew
20 Rabdosia pubescens Dong Ling Cao
10 Paeonia lactiflora Whitel Peony Bai Shaoyao
10 Glycyrrhiza glabra (raw) Gan Cao

Promote apoptosis - Inhibit Bcl2
Scutellaria baicalensis (baicalin, baicalein, wogonin)
Curcumin
Oridonin
Quercetin
Resveratrol
Sulforaphanes
Rabdosia (oridonin)

Support Inflammation Control and NFkB
Boswellia
Curcumin
O3FA
Parthenolide (many studies with AML) Feverfew 1 g bid

Steroid like inflammation control
Glycyrrhiza glabra (licorice root) extract 1-2 teaspoons qid
NATURA Inflamaway

Antiviral
Zinc
Vitamin D
Vitamin A

VEGF inhibition
EGCG
Curcumin

Promote DIfferentiation
Vitamin D
Vitamin A

Prevent Thrombosis (caution—some patients >>hemorrhage not thrombosis)
Curcumin
Omega 3 Fatty Acids

Inhibit PI3K>AKT>mTOR pathway (Rapamycin)
Pure Honokiol 1 g tid
Resveratrol
Curcumin
Quercetin

Thymoquinone induces apoptosis
Nigella Sativa (Black Cumin Seed) Oil

Nrf2 Activation
White Peony Paeonia lactiflora
EGCG
Resveratrol
Sulforaphanes
Curcumin
Milk Thistle
Pomegranate

Olive Leaf
Gingko biloba

Marjanovic, G. (2017). The use of inexpensive broad spectrum lower toxicity therapeutics in chronic lymphocytic leukemia. Journal of BU ON.: official journal of the Balkan Union of Oncology, 22(2), 288. (PMID: 28534346)

Abstract
The use of new and highly efficient targeted therapies for chronic lymphocytic leukemia (CLL) is costly and out of reach for many health care systems. On the other hand, in recent years, few inexpensive, broad-spectrum low-toxicity therapeutics have proven to be effective both in the preclinical and clinical settings. **In early-stage CLL, the use of 2000 mg of epigallocatechin-3-gallate (EGCG) from the green tea extract twice a day was able to reduce the absolute leukocyte count. Supplementation of >2000 IU/day of Vitamin D in early low-risk CLL patients is able to delay disease progression and postpone the moment of initiation** of the first treatment. The doses of both vitamin D and EGCG were shown to be safe in older patients. **Vitamin D, EGCG and Curcumin, either as monotherapy or in combination, have additive and synergistic effects with conventional chemotherapy.** Further observations have identified the **improvement of response to rituximab-fludarabine-cyclophosphamide (R-FC) therapy with concomitant administration of statin and aspirin combination in relapsed/refractory CLL.** Finally, **high dose dexamethasone with 40mg/m2/day for 4 days, every 28 days, either alone or with monoclonal antibody, might be used as a salvage therapy or for debulking before transplantation in refractory/resistant cases**. Dexamethasone therapy is followed by transient response and high rate of infections, but fluid retention and other toxicities are lower compared to high dose methylprednisolone schedules. The low cost therapeutics discussed in this review could not be a substitute for the more effective targeted therapies, but their use in everyday practice might postpone the need for early implementation of new and costly medications.

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Fleischer, T., Chang, T. T., Chiang, J. H., Hsieh, C. Y., Sun, M. F., & Yen, H. R. (2016). Integration of Chinese herbal medicine therapy improves survival of patients with chronic lymphocytic leukemia: a nationwide population-based cohort study. Medicine, 95(21). (PMCID: PMC4902377)

.. **herbs or compounds from within the CHM pharmacopeia, that may be beneficial for CLL patients, for example, Indirubin (Isatis tinctorium=Indigo), Curcumin, *Hedyotis diffusa (ursolic acid),* and *Ganoderma lucidum* (ganoderic acid) *Salvia miltiorrhiza (tanshinones and salvionolic acids),…***

Case Study
Patient 67 M "JT" - Follicular (Non-Hodgkins B Cell) Lymphoma Stage 3 - Submitted by Judy Pruzinsky
Background: CT + Rituxan completed, recent scans NED
Question: Lymphoma is recurring dx - how to delay? How to support immunity? **Question:** Told that post tx would have decrease in fatigue, brain fog and inc in WBC within 30 d (recent 6.2) 2.5+ = adequate immunity to mount a response to infection

Neutropenic diet guidelines are for stem cell transplant patients and pts with WBC below 2.5

Recommendations:
Caution Resveratrol

Acupuncture

Botanicals-Nutriceuticals
Green Tea EGCG can induce apoptosis
Curcumin RANKL (osteoporosis) inhibits NFkB (inflammation), inhibits tumor metastasis, invasion, and angiogenesis, promotes apoptosis
VIT D optimize — maintain bone integrity, modulate immunity and cell adhesion, antiviral
Ganoderma anti inflammatory and immune modulating
Scutellaria baicalensis: Berberine and Baicalein NFkb, TNFa, Bcl-2
Honokiol promote PTEN expression -suppression of oncogenes and PI3K-AKT-mTOR pathway
Vitamin A 5000-10,000 iu 3x/week (monitor blood levels) antiviral
Zinc 30-120mg (antiviral)
Andrographis (antiviral, anti-proliferation, anti-inflammatory) 2-3g/day
Salvia milthirorrhiza modulate coagulation, anti-proliferative
Oldenlandia (Heydotis) Ursolic acid, promotes apoptosis, inhibits proliferation, initiation, progression
Proteolytic enzymes: inflammation, coagulation, Bcl-2

Inhibit Blc-2 EPA, DIM, Sulphoraphane, Rabdosia (Oridonin), Ganoderma, Chaga, Quercetin, Gingko, Thymoquinone (Nigella seed oil), Ashwaganda (withanolide), Panax Ginseng

FATIGUE assoc with abnl CBC and with increased inflammation - Ashwaganda, Panax Ginseng, Ganoderma

LAB
CBC+Diff, ANC, NLR, LDH, Uric Acid (uricemia), LFT (biliary obstruction), Creatinine (renal obstruction) as reflection of inflammation and tumor load and prognosis
Inflammation markers CRP, IL1B, IL6, IL2, TNFa, INF, (IL-5 assoc with B cell lymphomas)

Monitor ANC
One measure of risk is the absolute neutrophil count (ANC). The ANC is calculated by multiplying the total white blood count by the percent of neutrophils (also called segmented neutrophils, segs, polymorphoneucleated cells or PMNs, polys)
Total white blood count x % neutrophils* = ANC

* Neutrophils may be reported as segs & bands (a band is slightly less mature form of a seg). In this case add the % of segs to the % of bands then multiply by the total number of white blood cells.
(% segs + % bands) x Total white blood count = ANC

Patients with Low WBC/Low ANC do NOT present with typical S&S of infection. Such as:
- Redness
- Swelling
- Pus formation (at the site of an injury or incision)
- Cough
- Sputum
- Nasal drainage (from a sinus or respiratory infection)

Be on the alert for:
- A temperature greater than or equal to 100°F. Chills (rigors) or shakes
- Sudden onset of a new unexplained pain.
- Sore throat
- Sores in mouth
- A white coating in mouth-tongue, especially

- Signs of a bladder infection

Risk of Infection based on Absolute Neutrophil Count (ANC)
- ANC greater than 1500 - No increased risk of infection
- ANC 1000-1500 - Slight increase in risk of infection
- ANC 500-1000 - Moderate increase in risk of infection
- ANC 100-500 - High risk of infection
- ANC less than 100 - Extremely high risk of infection

Post-Call Follow-up Q&A:

Are most hematologic cancers virally induced?
An ONCOGENIC virus is a virus that can induce tumorigenesis and cause cancer
An ONCOLYTIC virus can lyse tumor cells and kill them and can be used therapeutically (theoretically)

What differences and similarities are there between treatment protocols for lymphocytic leukemia and follicular non-Hodgkin's lymphoma?
In "Integrative Oncology" in the context of this course, we are not TREATING cancer. We are transforming the tumor microenvironment to change signalling and exert epigenetic effects on the behavior of tumor cells. In this context, the approach to altering the tumor microenvironment is quite similar. In conventional oncology today there are excellent targeted treatments (such as Rituxamab that bind to a CD20 receptor) that TREAT the cancer cells.

I didn't catch what you were saying about interferon nor interleukin 5 re: B cell lymphoma. I know of the connection to allergic rhinitis and asthma. Is there something specific to JT's case as he has such an extensive aggressive history of asthma?
Cancer is complex and each tumor cell line is unique and exists within the physiology of each unique patient.
There are different patterns of pro-inflammatory cytokines expressed by different cancers and in different individuals.
We also know that individuals who have SNPs and histories of producing more inflammation (good studies on IL1B, IL6, TNFa) will have more inflammation as cancer patients as well. IL-5 stimulates B cell growth and is linked to eosinophil activation in both normal and malignant cell lines.

Resources

Brewer, G. J., Dick, R. D., Grover, D. K., LeClaire, V., Tseng, M., Wicha, M., ... & Strawderman, M. (2000). Treatment of metastatic cancer with tetrathiomolybdate, an anticopper, antiangiogenic agent: Phase I study. Clinical Cancer Research, 6(1), 1-10.

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Copper Chelation and Inhibition of Angiogenesis

Angiogenesis: A Copper Dependent Process

Therapeutic Copper Depletion: Anti-Angiogenic & Anti-Metastatic

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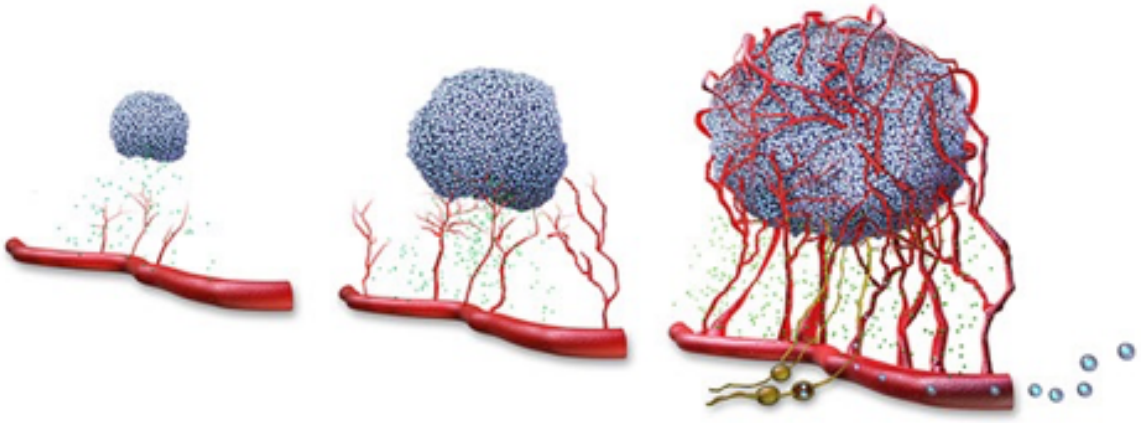
FOUNDER, DR. NALINI CHILKOV

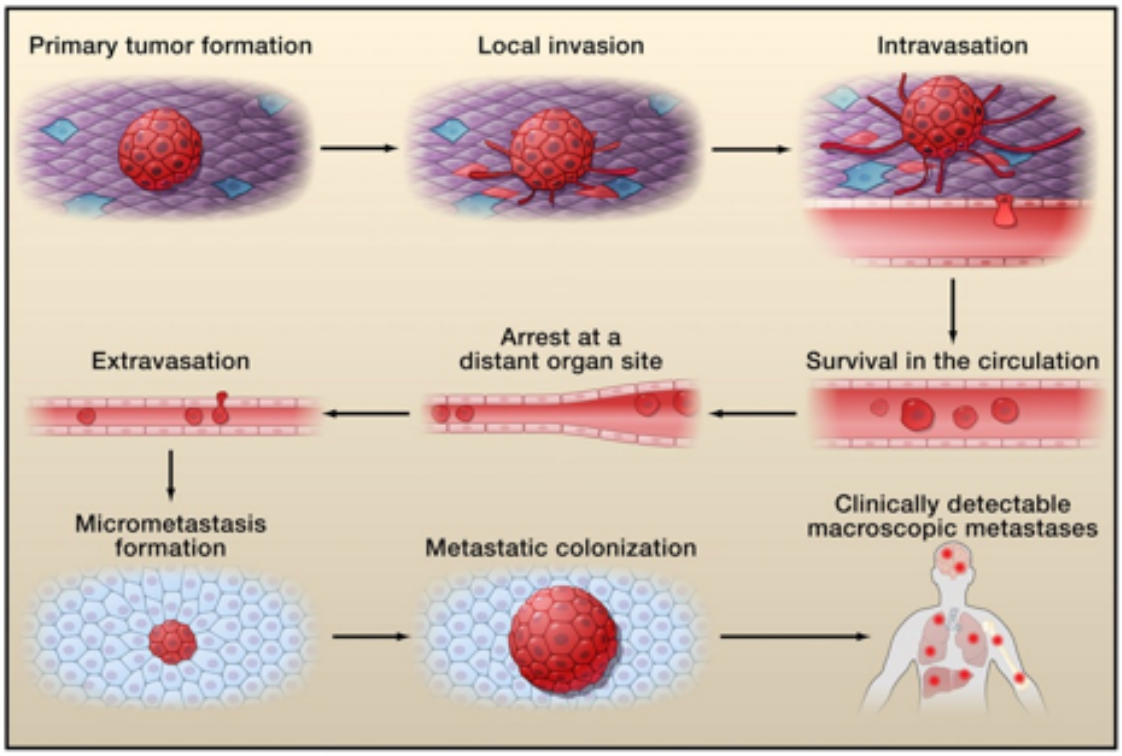
ANGIOGENESIS

- Normal physiological process through which new blood vessels form from pre-existing vessels
- Present in normal growth and development and wound healing
- Fundamental step in the transition of tumors from a benign state to a malignant state
- Promotes tumor growth and metastasis

ANGIOGENESIS

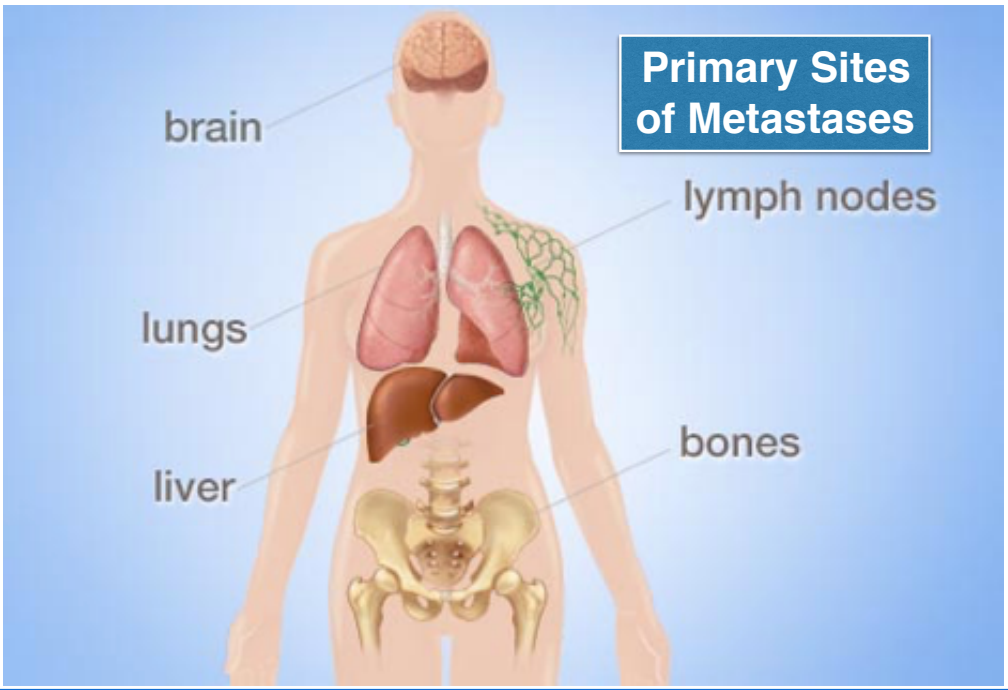


https://www.behance.net/gallery/11816509/Tumor-Angiogenesis-Infographic-Colorectal-Cancer



REVIEW Front. Oncol., 03 July 2012 **Cornering metastases: therapeutic targeting of circulating tumor cells and stem cells**

METASTASIS the development of secondary malignant growths at a distance from a primary site of the cancer



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Clin Exp Pharmacol Physiol. 2009 Jan;36(1):88-94.
Copper and angiogenesis: unravelling a relationship key to cancer progression.
Finney L1, Vogt S, Fukai T, Glesne D.

Angiogenesis displays an exquisite sensitivity to bioavailable copper

Depletion of copper has been shown to inhibit angiogenesis in a wide variety of cancers

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Inhibition of Angiogenesis & Metastasis

- **Copper is one of the key components of enzymes that control the tumor microenvironment**, as well as appearing to have a role in how cancer cells migrate.
- **Copper depletion inhibits angiogenesis (formation of new blood supply to tumor) and metastasis (cancer cell migration)**

Clin Exp Pharmacol Physiol. 2009 Jan;36(1):88-94.

J Trace Elem Med Biol. 2014 Oct;28(4):372-8. 2014 Aug 10. Brewer GJ1.

The promise of copper lowering therapy with tetrathiomolybdate in the cure of cancer and in the treatment of inflammatory disease.

The study showed **major efficacy of TM, against advanced human cancers, heretofore virtually incurable,** particularly if the cancer has been reduced to no evidence of disease (NED) status….

Where the remaining disease is micrometastatic, TM therapy appears to be **CURATIVE**

J Trace Elem Med Biol. 2014 Oct;28(4):372-8. 2014 Aug 10. Brewer GJ1.

The promise of copper lowering therapy with tetrathiomolybdate in the cure of cancer and in the treatment of inflammatory disease.

TM also has **major anti-inflammatory properties** by inhibiting copper dependent cytokines involved in inflammation.

This anti-inflammatory effect may be involved in TM's anticancer effect because cancers**, as they advance, attract inflammatory cells that provide a plethora of additional pro-angiogenic agents**

Tetrathiomolybdate-associated copper depletion decreases circulating endothelial progenitor cells in women with breast cancer at high risk of relapse

Ann Oncol (2013) 24(6): 1491-1498. Jain,S, Vahdat, LT et al

Patients who were at high risk of cancer recurrence and received copper depletion therapy - in the form of the drug tetrathiomolybdate (TM) - experienced **an overall increase in survival time as well as a decreased risk of relapse.**

Clin Cancer Res. **2016** Oct 21. 1326.2016. Chan N, Vahdhat, L et al

Influencing the Tumor Microenvironment: Phase 2 Study of Copper Depletion with tetrathiomolybdate in high risk breast cancer and preclinical models of lung metastases

75 pts enrolled; 51 pts completed 2 years (1396 cycles). Stage 2 triple negative BC (TNBC), Stage 3 and stage 4 without any evidence of disease, (NED) BC pts, received oral TM to **maintain ceruloplasmin (Cp) between 8-17mg/dL for 2 years or until relapse.**

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Clin Cancer Res. **2016** Oct 21. 1326.2016. Chan N, Vahdhat, L et al

Influencing the Tumor Microenvironment: Phase 2 Study of Copper Depletion with tetrathiomolybdate in high risk breast cancer and preclinical models of lung metastases

2 year **EFS for stage 2-3 and stage 4 NED was 91% and 67%, respectively. For TNBC pts EFS 90% (adjuvant pts) and 50% (stage 4 NED pts) at a median follow-up of 6.3 years.** In preclinical models, TM decreased metastases to lungs (p=0.04), LOX activity (p= 0.03) and collagen crosslinking (p=0.012).

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Selected References

J Trace Elem Med Biol. 2014 Oct;28(4):372-8 **The promise of copper lowering therapy with tetrathiomolybdate in the cure of cancer and in the treatment of inflammatory disease.** Brewer GJ

Clin Cancer Res. 2000 Jan;6(1):1-10. **Treatment of metastatic cancer with tetrathiomolybdate, an anticopper, antiangiogenic agent: Phase I study.**Brewer GJ, Merajver SD et al

Integr Cancer Ther. 2002 Dec;1(4):327-37. **Cancer therapy with tetrathiomolybdate: antiangiogenesis by lowering body copper--a review**. Brewer GJ, Merajver SD.

The Role of Copper in the Angiogenesis Process, Dwight L. McKee, M.D. (unpub)

ORAL COPPER DEPLETION

- Nutraceuticals
- Oral Tetrathiomolybdate
- Control Copper Intake

Normal Laboratory Values

Goals for Inhibition of Angiogenesis

		Goal
Serum Copper	72-166 ug/dl	(72-95)
Ceruloplasmin	16-39 mg/dl	(10-22)
Serum Zinc	56-134 ug/dl	

Zn: Cu Ratio at least ≥ 1:1 Better 2:1-3:1

Copper Depletion I Tetrathiomolybdate

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60 mg po at bedtime on empty stomach

Monitor Serum Cp, Cu, Zn and CBC q 2-4 weeks

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Cp and Cu lowest quartile of normal
(do not chelate to below 10mg/dl)

Zn:Cu Ratio 3:1 - 2:1
Requires Oral Zn Supplementation (60-120mg/day) as
Zinc citrate or picolinate

Copper Depletion: Nutraceuticals Sulfhydryl containing compounds

EMPTY STOMACH

- **N-AcetylCysteine** 500-1000mg qid
- **Alpha Lipoic Acid** 100mg qid

WITH FOOD

- **Zinc citrate or picolinate** 30-120/mg/d
- **Control Copper Intake**: Avoid liver, organ meats, oysters, copper cookware, copper containing supplements

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CASE STUDY SUBMISSION

Important: In observance of HIPAA and the sacred trust between care giver and patient, absolutely no patient names or identifying information is to be disclosed. Patient privacy is to be preserved. If you attach any medical records, pathology, surgical or laboratory reports, all names are to be removed.

Date	9/25/17
Clinician Name & Credentials	Sarah Shahab, MD
Email	sshahab2012@gmail.com

Describe Your Patient (Please SUMMARIZE and use economy of words. You will have 15 minutes to present)

Age, Gender & Ethnicity	39 year old , female
Body Type	
Values *What is most important to this patient? (Quality of Life, Decision Making, Side Effects?)*	Quality of life, being able to be there for her teenagers
Stress Resilience	very strong
Other	
Primary Diagnosis & Date *(ex. Breast Cancer L, T3 N1 M0, BRCA1 positive, grade 3, Ki67 > 45%)*	CLL diagnosed in 3/15 incidental finding while getting blood work for a throat infection.
Secondary Diagnosis *(ex. Diabetes Type 2, Obesity)*	fatigue

Patient Status

☐ New Diagnosis ☐ Recurrence ☐ In Treatment ☐ In Recovery ☐ In Remission ☐ At Risk

Concomitant and/or Complicating Factors *(ex: poorly controlled diabetes, insomnia, poor support system)*	none
Adverse Effects of Cancer or Cancer Treatments *(ex. anxiety-depression, diarrhea, peripheral neuropathy)*	no cancer treatment so far
Relevant Laboratory, Pathology & Medical Reports *(attach a PDF with patient identifying information removed or summarize)*	please see attached - labs since 3/15 WBC at diagnosis 138, negative CD38 and ZAP70, positive 13q deletion. Now, WBC 200

Brief Summary of Recent History

Incidental diagnosis following throat infection. Wait and watch so far. when diagnosed WBC was 138,000, WBC count now 200,000! She is feeling increasingly 'weak'.

Hg stays between 11 -13 mg%. At its highest WBC count was 267,000 in December 2016. I met her via skype in January and she implemented some of the things I asked her to. Her numbers did improve after that, but she stopped following recommendations.

Brief Summary of Additional Relevant Health, Medical, Psycho-Social and/or Family History

very good family support

Other Relevant Information

Such as Chinese or Ayurvedic diagnosis, Naturopathic/Homeopathic Information, etc. *(ex. Liver Qi Stagnation, Dysbiosis)*

no

Brief Summary of Relevant Past Oncology or Medical Treatments

(ex. surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)

none

Summary of Recent and Current Treatments

Medical Oncology Care *(surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)*

none

Integrative Oncology Care *(nutraceutical, botanical, phytochemical, acupuncture, energy medicine, other)*

In January, I met her via Skype she lives overseas. Talked to her about a clean, low carb plant based diet, meditation and other stress management techniques. put her on VitD, Magnesium, Fish oil, MVIs. She took some things for some time , numbers improved!

Your 2 Core Questions (stated clearly and succinctly)

1. What can we do while we 'wait'?

2. Any specific supplements?

Attached Medical Records for Reference (with patient identifying information removed)

American Institute of Integrative Oncology
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Date	9/30/17
Clinician Name & Credentials	Judy Pruzinsky, L.Ac.
Email	judy@judypruzinsky.com

Describe Your Patient (Please SUMMARIZE and use economy of words. You will have 15 minutes to present)

Age, Gender & Ethnicity	67 yo, Male, Caucasian
Body Type	short medium build
Values *What is most important to this patient? (Quality of Life, Decision Making, Side Effects?)*	Misses freedom of movement Looking forward to rejoining socity
Stress Resilience	
Other	
Primary Diagnosis & Date *(ex. Breast Cancer L, T3 N1 M0, BRCA1 positive, grade 3, Ki67 > 45%)*	6/21/2017 Low-grade or follicular non-Hodgkin's lymphoma, stage 3. Primary group of nodes affected: from groin to sternum left side same as the TKR (Total Knee Replacement) and a node in arm pit Biopsy done by ultra-sound on largest 6 cm. node, in groin
Secondary Diagnosis *(ex. Diabetes Type 2, Obesity)*	High cholesterol, LDLs, and Total cholesterol/HDL

Patient Status

☐ New Diagnosis ☐ Recurrence ☑ In Treatment ☐ In Recovery ☐ In Remission ☐ At Risk

Concomitant and/or Complicating Factors *(ex: poorly controlled diabetes, insomnia, poor support system)*	
Adverse Effects of Cancer or Cancer Treatments *(ex. anxiety-depression, diarrhea, peripheral neuropathy)*	see attached in email Lymphoma symptoms
Relevant Laboratory, Pathology & Medical Reports *(attach a PDF with patient identifying information removed or summarize)*	2nd PET CT scan 8/17 1. Favorable interval response to therapy, with significant decrease in extent and FDG avidity of hypermetabolic adenopathy above and below the diaphragm compared with the prior study. Lugano response category for NHL interim scan: Responding disease, 5-PS score = 3 2. No evidence of new or progressive FDG avid lesions. 3. Incidental CT and PET findings as detailed in report, including aortic atherosclerosis.

Brief Summary of Recent History

DIVERTICULOSIS OF COLON 5/3/2004
HYPERLIPIDEMIA 2/2/2009 Cardiovascular risk score 2016 - 15.1% advised meds
ASTHMA, MILD PERSISTENT 2009 - see below for details showing severity

RETROPERITONEAL MASS 6/2017
HYPERCALCEMIA 6/2017
FOLLICULAR LYMPHOMA GRADE 2, MULTIPLE LN SITES 6/2017
AORTOILIAC ATHEROSCLEROSIS 7/2017 noted on CT

Brief Summary of Additional Relevant Health, Medical, Psycho-Social and/or Family History

1986 Major reaction to MOLD from remodeling home and local fora
- Asthma acted up really bad, requiring continuing medication to control - 3 years of allergy shots which proved to be successful
2011-2017 Severe upper respiratory infection - No medication taken Stress induced;
- Bedreddin for 6 weeks - Several Blackouts from Vegus Nerve (coughing) , once requiring stitches

Other Relevant Information

Such as Chinese or Ayurvedic diagnosis, Naturopathic/Homeopathic Information, etc. *(ex. Liver Qi Stagnation, Dysbiosis)*

Exercise: Exercise - used to do gym / crossfit training (about 2-3 times per week) Now walking or golf (2/week)

Brief Summary of Relevant Past Oncology or Medical Treatments

(ex. surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)

Chemotherapy Regime - BR - Bendamustine and Rituxan (Rituximab)Therapy 4-week cycle for 6 cycles (24 weeks)
Day 1 Rituxan and Bendamustine and Day 2 just Bendamustine

Summary of Recent and Current Treatments

Medical Oncology Care *(surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)*

see attached in email Med list

Integrative Oncology Care *(nutraceutical, botanical, phytochemical, acupuncture, energy medicine, other)*

Reiki - wife does

Your 2 Core Questions (stated clearly and succinctly)

1. Since lymphoma is a recurring event, how to delay (or possible to stop) recurrence.
   Can•t take Rituxin, as we build immunity,
2. Has been told WBC should get better within 30 days and fatigue and brain fog should abade in 90 days. Your experience?

Attached Medical Records for Reference (with patient identifying information removed)

I attached in email the blood tests that were preformed.
The results that were out of range were high Calcium, low Lymphocytes, and lipids mentioned elsewhere.
There•re low/high normals which I can send to you electronically if helpful.