American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
June 14th, 2017

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

Clinical Pearl: Hypercoagulation and Risk of Thromboembolism in Cancer Patients

See slides below as a companion to the audio recording.

Case Study: Post-Treatment Neuropathy (Breast Cancer)

Patient "LS" - Submitted by Judy Pruzinsky

Background: 59 yo Caucasian Female BRCA1 POSITIVE , GRADE 3 PT3, N1, M0, Ki67>45%
CHIEF COMPLAINT: Persistent Post Tx Neuropathy
04/16 dx TNBC 2 tumors 1 + Node and a third ER+PR+ Tumor,
05-09/16 TAXOL AND AC? Adiramycin and Cytoxan or Carboplatin or Cyclophosphamide? Suffered many adverse effects, neuropathy persists. Now on AI Letrozole with adverse effect of neuropathy which is better when AI is d/c. ONCO -> to a new AI
10/16 Lumpectomy 7-8 positive nodes (??)
11/16 RT
6 month Mammo negative
Pt is anxious, hx of depression, poor resilience, abusive and stressful family environment, hx of constipation (better warming herbs)
TCM: Kid Qi and Yang Deficiency Some Damp Heat
Current meds Gabapentin, Hydrochlorothiazide for HT

Questions:
How important to stay on AI? Would neuropathy improve if she d/c?
In addition to diet and supplements, how long after tx is completed and patient is in remission do we continue an integrative oncology protocol, if they are NED...How is treatment plan changed… How long is tx continued?

Recommendations:

1. BRCA1 positive and under ongoing duress, therefore immune compromised. Should try to stay on AI x 2 years and manage side effects. Botanical AI: resveratrol, chrysin, Rdx Uritica urens. Consider Adaptogenic Herbs for ongoing stress (Rhodioloa, Ashwaganda, Eleutherococcus, Schizandra, Panax ginseng, Panax quinquifolium, Cordyceps, Glycyrrhiza).
2. Neuropathy: Reduce oxidative stress (Vitamin E, Greens and Reds powders, N Acetyl Cysteine 900g tid, Stabilized R Lipoic Acid 100mg tid), provide support for neuronal repair: O3 FA 2-4 g, Acetyl L Carnitine 1g bid, (L Glutamine 5-15 grams/day), Acupuncture 1-2x week x 8-12 weeks
3. How long is OutSmart Cancer protocol continued once a pt is NED? The tumor microenvironment must be managed and monitored long-term in any patient who has has any stage of cancer. Every patient has microscopic local or metastatic cells after treatment.
4. BRCA 1 patients need more antioxidant protection, should also include Niacinamide 2000mg/day - a natural PARP inhibitor. Also consider Resveratrol, Nicotinamide ribonucleoside (Niacel, Niagen 500mg /day)
5. Consider Melatonin - Super antioxidant for neural tissue and many studies recommending 10-20 mg/hs for breast cancer patients.
6. Natural Aromatase Inhibitors: Urtica Dioica (Stinging Nettle) Root, Chrysin, Resveratrol, Genistein

Questions & Answers

Judy Pruzinsky: One of my favorite formulas is **Inflammatone**. I love its botanical components, but also the level of proteolytic enzymes. I Rx it for many different forms of inflammation, usually suggesting 4-5 at night (empty stomach). Is it appropriate to take long term as maintenance against inflammation, infection, almost like a systemic "PacMan;" or is it better to take a break from it, and/or only take when inflammation is a known condition?

Per two capsules contains:
n-zymes (proprietary blend) 222 mg
Protease 6.0 (concentrate) 50,000 HUT
Protease 4.5 40,000 HUT
Trypsin 1:150 25mg
Serrazimes 10,000 U
Chymotrypsin 2 USP Units

Turmeric (Curcuma longa) root 200 mg
(standardized to contain 8% (16mg) curcumin)
Boswellia (Boswellia serrata) (resin) 200 mg
(standardized to contain 60% (120 mg) boswellic acid)
Ginger (Zingiber officinale) (root) 200 mg
(standardized to contain 5% (10mg) gingerols)

Quercitin 75 mg
Rutin 75 mg
Rosemary (Rosmarinus officinalis) (aerial) 50 mg
Resveratrol (Polygonum cuspidatum) 3 mg
(root) (standardized to contain 20% (0.6 mg) resveratrol)

> Depends on inflammation levels of the patient - tracking QRP
> Typical dose of two 4x/day, up to four 4x/day (very short half life in the blood)
> Active infection/cancer - higher dose, often for months, then reduce to the maintenance dose of two 2x/day

Link: http://catalog.designsforhealth.com/Inflammatone-240

Lowering Beta Glucuronidase
Traditional Chinese Herbal Formula Modern Research
Xiang Sha Liu Ju Zi Tang Modified FRAGRANT Six Gentleman Formula
Increases appetite
Cancer Cachexia
GERD
SpYang Deficiency, Spleen damp syndromes

Also decreases b glucuronidase

Xiang Sha Liu Jun Zi Tang
**Dang Shen Codonopsis or Ren Shen Panax gingseng* Tonifies Spleen QI
**Fu Ling Poria* Tonifies Spleen, Drains Damp
**Bai Zhu Atractylodes (Alba)* Tonifies QI and Spleen, Dries Dampness
**Zhi Gan Cao Licorice (Baked)* Tonifies QI, Harmonizes Formula
+
Ban Xia Pinellia Dissolves Cold Phlegm
Chen Pi (Ju Pi) Citrus Peel Regulates QI, Tonifies Spleen
+
Mu Xiang (Chuang)(Cultivated) Vladimiria aka Saussuerea (Cultivated) Regulates QI, Benefits Bowels Saussurea. Rdx Aucklandia
Sha Ren Amomum Regulates QI, Dries Damp

(* Ingredients for Si Jun Zi Tang Four Gentlemen Formula)

What Are Normal Levels of Beta Glucuronidase in the Stool?

Beta-glucuronidase activity must be sufficient to permit deconjugation and absorption of desirable molecules, while remaining low enough to prevent widespread deconjugation and subsequent reabsorption of toxins and other undesirable molecules.

See Genova Diagnostics CSDA Support Guide
https://www.gdx.net/core/support-guides/CDSA-CDSA2-combo-Support-Guide.pdf

Beta-glucuronidase
The Biomarker Beta-glucuronidase is an enzyme that breaks down complex carbohydrates.

Additionally, it acts to deconjugate glucuronide molecules from a variety of toxins, carcinogens, hormones, and drugs, which are naturally glucuronidated in the liver to facilitate biliary excretion. Deconjugation of these molecules in the gut permits their reabsorption via enterohepatic recirculation, producing higher than desired blood levels of potentially harmful compounds.

Additionally, many beneficial nutrients are ingested as the glucuronide conjugate of the active molecule, which must be deconjugated in order for the beneficial molecule (the “aglycone”) to be absorbed. Such nutrients include lignans, flavonoids, ceramides, and glycyrrhetinic acid.

Thus, a proper balance of glucuronidase in the gut lumen is essential.

Beta-glucuronidase is inducible in colonocytes, but it is also produced by anaerobic gut bacteria (particularly E. coli, but also Peptostreptococcus, Bacteroides, and Clostridium).

Biomarker Key Points *• Limited research suggests an association between elevated fecal beta-glucuronidase and colon cancer risk 75,148,149 • Low fecal beta-glucuronidase may also represent a problem, because the enzyme is needed to release the active aglycone forms of many dietary phytonutrients Patient Populations of Interest Evaluating beta-glucuronidase may be of interest to clinicians interested in evaluating substances that require deconjugation of glucuronide molecules, such as hormones, vitamin D, toxins, and phytonutrients.*

Outcomes and General Therapeutic Considerations *Further evaluation of patients with elevated fecal beta-glucuronidase includes consideration of exposure to and intake of toxins, hormones, and drugs. Supporting the Patient with abnormal fecal beta-glucuronidase: For patients with elevated fecal beta-glucuronidase: • The following supplements may be helpful: › Calcium-D-glucarate › Milk thistle › Probiotics (Lactobacilli and Bifidobacteria) • The following dietary management may be helpful: › Increased consumption of vegetables and insoluble fiber Beta-glucuronidase may be lower following antibiotic administration, which may reduce beta-glucuronidase activity due to reduction of gut bacteria.1*

What is the clinical significance of elevated beta-glucuronidase?
By uncoupling glucuronides, beta-glucuronidase can deconjugate potential toxins, increasing the formation of carcinogens in the bowel and promoting the enterohepatic recirculation of toxins, hormones, and various drugs in the body.

How strongly is beta-glucuronidase linked to colon cancer?
Research correlates elevated levels of beta-glucuronidase with increased colon cancer risk.
In fact, excessive beta-glucuronidase activity may be a primary factor in the etiology of colon cancer.

Does excessive beta-glucuronidase increase the risk of other cancers?
Human studies that directly link fecal beta-glucuronidase and breast cancer are lacking. Animal studies, however, have shown reductions in breast cancer risk via administration of calcium D-glucarate, a compound known to inhibit the enzyme.4 Animal or invitro studies suggest a similar relationship for liver, lung, and skin cancers.

Are there any problems associated with LOW beta-glucuronidase levels?
A certain amount of beta-glucuronidase activity appears to be important for normal enterohepatic recirculation of endogenous compounds such as vitamin D, thyroid hormone, and estrogen. Broad-spectrum antibiotics suppress intestinal microflora, which reduces beta-glucuronidase activity and intestinal reabsorption of estrogen. This may cause

reduced efficacy of oral contraceptives in a subset of women administered antibiotics. The bioavailability of genestein and daidzein (cancer-preventive agents) depends upon initial hydrolysis by intestinal beta-glucuronidase and sulfatase enzymes. Low levels of beta-glucuronidase may reduce the efficacy of these compounds.

Resources

Support Care Cancer. 2006 May;14(5):484-7. Epub 2006 Feb 1.
N-acetylcysteine has neuroprotective effects against oxaliplatin-based adjuvant chemotherapy in colon cancer patients: preliminary data.
Lin PC, Lee MY, Wang WS, Yen CC, Chao TC, Hsiao LT, Yang MH, Chen PM, Lin KP, Chiou TJ.

Oncologist. 2007 Mar;12(3):312-9.
Oral glutamine is effective for preventing oxaliplatin-induced neuropathy in colorectal cancer patients.
Wang WS, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Chiou TJ, Liu JH, Yen CC, Chen PM.

Glutathione reduces the toxicity and improves quality of life of women diagnosed with ovarian cancer treated with cisplatin: results of a double-blind, randomised trial.
Smyth JF, Bowman A, Perren T, Wilkinson P, Prescott RJ, Quinn KJ, et al. Ann Oncol.1997;8(6):569–573

Bianchi G, Vitali G, Caraceni A, Ravaglia S, Capri G, Cundari S, et al.
Symptomatic and neurophysiological responses of paclitaxel- or cisplatin-induced neuropathy to oral acetyl-L-carnitine. Eur J Cancer. 2005;41(12):1746–1750

Mestri A, De Pasquale Ceratti A, Cundari S, Zanna C, Cortesi E, Crino L.
A pilot study on the effect of acetyl-L-carnitine in paclitaxel- and cisplatin-induced peripheral neuropathy.
Tumori. 2005;91(2):135–138

Hershman DL, Unger JM, Crew KD, Moinpour C, Minasian LM, Hansen L, et al.
Randomized placebo-controlled trial of acetyl-L-carnitine for prevention of taxane-induced neuropathy during adjuvant breast cancer therapy. J Clin Oncol. 2012;Suppl.:abstr 9018:

Vitamin E: 400-800 IU daily to prevent Cisplatin-induced neuropathy (Neurology. 2010 Mar 2;74(9):762-6)

“70% lower risk of PN incidence”
DOSE: 640 mg (54% DHA, 10% EPA) 3x/day (1920 mg qd) during chemotherapy with paclitaxel and **one month after the end of therapy**

Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: A randomized double-blind placebo controlled trial
Zohreh Ghoreishi, Ali Esfahani, Abolghasem Djazayeri, Mahmoud Djalali, Banafsheh Golestan, Hormoz Ayromlou, Shahriar Hashemzade, Mohammad Asghari Jafarabadi, Vahid Montazeri, Seyed Ali Keshavarz and Masoud Darabi
BMC Cancer 15 Aug 2012 Volume 12 p 355

Acupuncture Chemotherapy Induced Peripheral Neuropathy, Acupunct Med. 2011 Sep;29(3):230-3

Clinical Pearl: Hypercoagulation and Risk of Thromboembolism in Cancer Patients

Hypercoagulation and Risk of Thromboembolism in Cancer Patients

Dr. Nalini Chilkov

A. A. Khorana, C. W. Francis, E. Culakova, N. M. Kuderer, and G. H. Lyman,
"Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy,"

Journal of Thrombosis and Haemostasis, vol. 5, no. 3, pp. 632–634, 2007.

CANCER AND THROMBOSIS: OVERVIEW

Cancer Cells Contribute to a Hypercoagulable State
Express Tissue Factor that release TF bearing microparticles
Express pro-coagulant cytokines and fibrinolytic substances

Cancer Thrombosis: **Endothelial Injury**
- By direct extension of cancer cells into blood vessels
- Via pro-thrombotic cytokines
- Via platelet-endothelial adhesion
- Via direct endothelial injury

Cancer Thrombosis: **Stasis**
- Due to vascular compression of tumor mass
- Due to reduced mobility

Cancer Thrombosis: **Cancer Treatments**
Catheter associated thrombosis
Surgery Chemotherapy
RadioTherapy Hormonal Therapy

Trousseau's Syndrome Sign of Malignancy 1865

Association between Hypercoaguability Thromboembolism and Malignancy

TRADITIONAL CHINESE MEDICINE

CANCER IS A CONDITION OF "BLOOD STASIS"

Positive BioMarkers of Activated Coagulation are Correlated with

- Elevated Tumor Markers
- Larger Tumor Mass
- Increased Tumor Burden
- Advanced Stage of Disease
- Vascular and Stromal Invasion
- Lymph Node Metastasis
- More Aggressive Disease
- Increased Systemic Inflammation
- Disease Progression
- Disease Free Survival
- Overall Survival
- Response to Chemotherapy

Cancer patients overall have a **7 fold higher risk** of venous thrombosis

Patients with **hematologic malignancies** have a **28 fold higher risk** of Venous thrombosis

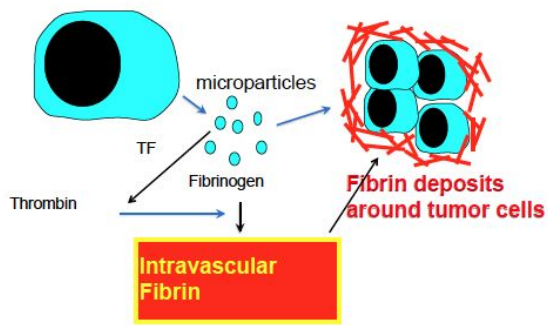
Patients with **distant metastases** have a **20 fold higher risk** of venous thrombosis

Postgrad Med J 2006;82:642-648 doi:10.1136/pgmj.2006.046987 Venous thromboembolic disease and & and cancer A Fennerty

VTE is the second most common cause of death in patients with cancer, but can also be the initial presenting complaint in patients with an occult malignancy.

Nat Rev Clin Oncol. 2012 Jul 10;9(8):437-49. doi: 10.1038/nrclinonc.2012.106. **Thrombosis and cancer.** Young A et al

Curr Oncol. 2015 Feb; 22(1): 49–59. PMCID: PMC4324343
Clinical challenges in patients with cancer-associated thrombosis: Canadian expert consensus recommendations M. Carrier, et al



Adapted from Dvorak et al, 1981

Venous Thromboembolism Risk Factors

- Age Gender Ethnicity
- Sedentary Immobility
- Smoking
- Inflammation
- Obesity BMI
- Hyperlipidemia
- Insulin Resistance
- Hypertension
- Hx of VTE or PE
- TX+RX >Pro-thrombotic effects

Identify High Risk Patients

Venous Thromboembolism
Risk Factors in Cancer Patients

Tumor Type pancreatic, gastric, colon, brain, kidney, ovarian, prostate, hematologic and lung

Advanced Clinical Stage-Metastatic Cancers

Use of anti-angiogenic drugs (Bevacizumab-Avastin)

History of VTE-PE

Use of Erythropoietic Growth Factors (Erythropoetin)

Insertion of **Central Venous Catheters (Port)**

Surgical Procedures **Radiotherapy**

Chemotherapy Drugs (Thalidomide, Lenalidomide)

Hormonal Therapies (Tamoxifen, Lupron)

Biomarkers | Pro-Thrombotic Micro-Environment

- **Leukocytes** ≥ 11.0 m/uL inflammation- amplify thrombin generation and platelet adhesion
- **Platelets** ≥ 350K mm/L inflammation, IL6
- **Hemoglobin** ≤ 10.0 g/dl inflammation IL1, IL6,TNFa accelerated platelet aggregation
- **Fibrinogen activity** ≥ 275 mg/dL inflammation
- **D-Dimer**(no consensus) ≥ 250 ng/ml, > 0.30-0.50 DDU
- ongoing fibrinolysis, tumor progression, angiogenesis, metastasis
- **BMI** ≥35 kg/m^2
- **(hs-C Reactive Protein** ≥ 2.0 inflammation IL6, IL8, TNFa, NFkB not considered an "independent" risk factor")
- Specialty Labs:
  - Tissue Factor P-Selectin

Cancer-Associated Thrombosis: An Overview Clinical Medicine Insights: Oncology 2014:8

Breast. 2015 Oct;24(5):667-72. doi: 10.1016/j.breast.2015.08.003. Epub 2015 Sep 4.
An elevated preoperative plasma fibrinogen level is associated with poor disease-specific and overall survival in breast cancer patients.
Krenn-Pilko S[1], Langsenlehner U[2], Stojakovic T[3], Pichler M[4], Gerger A[4], Kapp KS[1], Langsenlehner T[5].

Cancer Biomark. 2015;15(4):405-11. doi: 10.3233/CBM-150477.
D-dimer and international normalized ratio (INR) are correlated with tumor markers and disease stage in colorectal cancer patients.
Kilic L[1], Yildiz I[2], Sen FK[2], Erdem MG[3], Serilmez M[4], Keskin S[2], Ciftci R[2], Karabulut S[2], Ordu C[5], Duranyildiz D[4], Tas F[2].

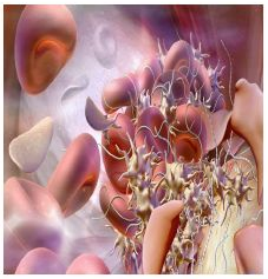
Ann Surg Oncol. 2013 Sep;20(9):2908-13. doi: 10.1245/s10434-013-2968-8. Epub 2013 Apr 25. **Preoperative plasma hyperfibrinogenemia is predictive of poor prognosis in patients with nonmetastatic colon cancer.**Son HJ[1], Park JW, Chang HJ, Kim DY, Kim BC, Kim SY, Park SC, Choi HS, Oh JH.

Man YN, Wang YN, Hao J, et al. **Pretreatment plasma D-dimer, fibrinogen, and platelet levels significantly impact prognosis in patients with epithelial ovarian cancer independently of venous thromboembolism**. *Int J Gynecol Cancer*. 2015;25(1):24-32.

Kilic L, Yildiz I, Sen FK, et al**. D-dimer and international normalized ratio (INR) are correlated with tumor markers and disease stage in colorectal cancer patients**. *Cancer Biomark*. 2015;15(4):405-411.

HYPERCOAGULATION

SELECTED INTERVENTIONS



Coagulation Promotes Tumor Progression and Metastasis

Curcumin 1-6 g/day

Curcumin, a polyphenol possesses antiinflammatory, antiproliferative, antiangiogenic and **anticoagulant activities.** Curcumin and bisdemethoxycurcumin (BDMC) **showed anticoagulant effect in vivo**. Data showed that curcumin and bis-demethoxy-curcumin BDMC **prolonged PTT and PT significantly and inhibited thrombin** and activated Factor X (Fxa) activities.

BMB Rep. 2012 Apr;45(4):221-6. **Anticoagulant activities of curcumin and its derivative.** Kim DC1, Ku SK, Bae JS.

Resveratrol and Thrombosis 1-5g/day

Reduces platelet activation and aggregation

Reduces synthesis of prothrombotic eicosanoid mediators

Decreases gene expression of Tissue Factor

Inhibits the generation of reactive oxygen species

Reduces fibrinogen levels

Increases fibrinolysis

Decreases Plasma Homocysteine

Antiplatelet properties of natural products
Vascular Pharmacology 59 (2013) 67–75Gemma Vilahur, Lina Badimon

OMEGA-3 Fatty Acids and Thrombosis 2-6g/day

Semin Thromb Hemost. 2013 Feb;39(1):25-32. **Effects of omega-3 polyunsaturated fatty acids on platelet function in healthy subjects and subjects with cardiovascular disease.** McEwen et al

Atherosclerosis. 2013 Feb;226(2):328-34. doi: 10.1016/ j.atherosclerosis.2012.10.056. **Influence of omega-3 poly unsaturated fatty acid-supplementation on platelet aggregation in humans: a meta-analysis of randomized controlled trials.**Gao LG et al

Salvia miltiorhizza | Dan Shen and Thrombosis

Primary Active Consituents **1-3 g/day**

Salvianolic acid Acetyl Salvianolic Acid

Tanshinone IIa Cryptotanshinone

- Inhibits Platelet Aggregation & Activation
- Inhibits Thrombus Formation
- Reduces leukocyte-endothelial adherence
- Inhibits ThromoboxaneB2, COX1 COX2 NOX1 NOX2 NOX4
- Inhibits MMP –matrix metalloproteases
- Inhibits P13K kinase pathway

Salvia miltiorhizza | Dan Shen and Thrombosis

J Thromb Haemost. 2010 Jun;8(6):1383-93. doi: 10.1111/j.1538-7836.2010.03859.x. Epub 2010 Mar 19. **Salvianolic acid A inhibits platelet activation and arterial thrombosis via inhibition of phosphoinositide 3-kinase.** Huang et al

Thromb Res. 2010 Jul;126(1):e17-22. **Antiplatelet and antithrombotic activities of salvianolic acid** A. Fan HY et al

Summary : Monitor All Patients for Signs of Thrombosis & Active Coagulation

Screen Patients >45 yo and with risk factors for early identification of signs of potential malignancy

Monitor Patients In Treatment for risk of VTE & PE

Monitor Patients Living with Cancer as a Chronic Illness for signs of progression

Monitor Patients in Remission (NED) for signs of Recurrence