American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
July 12th, 2017

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

Clinical Pearl: Vitamin B12 & Cancer

Reference Article: **Elevated Plasma Vitamin B12 Levels as a Marker for Cancer**
Reference Article: **Plasma Folate and Vitamin B12 Levels in Patients with Hepatocellular Carcinoma**

See slides below for the clinical pearl overview.

Case Study

Patient "DW" - St III metastatic OVCA at age 52

Background:
DOB 5/30/57
DX 2009 St III metastatic OVCA at age 52
Diffuse multiple lesions throughout pelvis adhering to spleen and intestines
2017 NED

Mixed high grade serous epithelial carcinoma (serous 25%, undifferentiated/anaplastic 75%)
Histologic grade G4
Primary site not determined
Tumor size R ovary 6cm L ovary 10.5cm
Ovarian surface involvement present
Organs/Tissues microscopically involved: R&L ovaries, Fallopian tubes, Omentum, Peritoneum, Bladder serosa perivesical soft tissue, R Gerota's fascia, Spleen
Lymph-vascular invasion present

Staging
Primary tumor "cannot be assessed"
# of lymph nodes identified/involved 0 0

Hx: Left Hip pain 11/08 accompanied by non-stress urinary incontinence
No c/o bloating, spotting, change in bm
U/S revealed bilateral pelvic masses
Exploratory laparoscopy revealed multiple pelvic tumor implants throughout
Normal uterus and endometrium, normal rectosigmoid

Family Hx: Onco + melanoma (P aunt), renal CA (P uncle), breast CA (age 78 M uncle)
Pt. Hx: hyperlipidemia (statin), Para 2 (1 Csx), Hx nl Pap smears, normal menses through June 2009

8/20/09 Initial Dx	08/2011 Recurrence	4/2013	11/2013 NED	2015 NED
Ceruloplasmin 41	35		20	
Copper 110	125		80	
Zinc 86	92		74	
D Dimer 2.385	1.49		0.9	
Fibrinogen 495	420		319	
Homocysteine	12.0	9.6	8.0 (+MTHFR C677T DNA mutation)	
Hs CRP 0.76	3.9		0.5	
CA-125 371	16.8	8.0	7.0	

2009 Onco Tx
Surgery
Total Hysterectomy
Splenectomy
Omentumectomy

2009 Surgical-Pathology
Bilateral complex adnexal masses
Metastatic lesions adjacent Liver and Spleen
Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, splenectomy
Cytoreduction of tumor implants in R. Gerota's fascia, L. pelvic peritoneum and bladder serosa
Placement of intraperitoneal port-a-cath

Tolerated surgery well
Post op d/c : 7/27/09 Hct 8.0 (Hemagenics p/o until iron stores in nl range and Hct nl)

- Followed by IV and IP Chemotherapy - 6 cycles
- Lorazepam 1mg
- Dexamethasone 4mg taken the night before and morning of chemo (Taxol IV)
- Prochlorperazine (generic Compezine) 10mg
- Emend 80mg
- Ondansetron ODT (generic Zofran) 8mg
- Ibuprofen 600 mg as needed for pain

START
Monday, 8/31/09 Taxol IV
Tuesday, 9/1 Cisplatin IP
Tuesday, 9/8 Taxol IP

END
Monday, 12/14/09
Tuesday, 12/15/09
Monday, 12/21/09

CA-125
2009 371
2010 6.0 post treatment
2011 16.8 rising steadily each month x 8 months and doubled from 7.8 09/2010;16.8 07/2011
Oncologist recommends another course of chemotherapy
Patient declined chemotherapy, opts for nutraceutical-botanical-dietary plan

8/15/2011 Radiology Report CA 125 16.8 D dimer 1.54 hs CRP 3.9
Intense metabolically active enlarged lymph node L retroperitoneum plus several areas of transverse and descending colon; "possibility of metastatic serosal implants"

Recommendations:

6 months

- Modified Citrus Pectin 5 g tid
- Curcumin 800mg tid
- EPA DHA 1000 mg tid
- Zinc glycinate chelate 30mg + 250mcg Molybdenum Glycinate tid

Botanicals-Phytochemicals

- Honokiol capsules 500mg tid
- Resveratrol 1000mg tid

Custom Compounded Formula #1 x 6 months
1 tsp tid

- 70 To Jing-Crack Blood Formula
- 70 Persica and Carthamus Formula
- 20 Curcuma Yu Jin
- 20 Rabdosia
- 40 Scutellaria baicalensis Huang Qin
- 20 Silybum marianum Milk Thistle

Custom Compounded Formula #2 x 2 months
28 days
60 drops tid 5 days on 2 days off
Repeat a 10 day course every 4 months for 2 years

- 40 Taxus brevifolia Pacific Yew leaf and bark
- 40 Camptotheca acuminata seed
- 30 Viscum album Mistletoe aerial
- 30 Asimina triloba Paw Paw seed/bark
- 40 Phytolacca Americana root Poke
- 20 Podophyllum peltatum root May Apple
- 15 Citrus aurantia sinensis Chen Pi Tangerine peel
- 15 Zingiber off. Rhizome Ginger rhizome
- 5 Glycyrrhiza glabra Gan Cao Licorice Root

Response to protocol - CA 125
Inception 16.8
30 days 9.0
60 days 8.5
90 days 7.5
180 days 7.0 Stable 2011-2015

Questions & Answers

1. Judy Pruzinsky: You talked of measuring estrogen metabolites; which test do you like?

Factors to Consider when Assessing Estrogen and Estrogen Metabolism:

- Serum Estradiol, Estrone Sulphate - also look at DHEA-Sulphate, Total and Free Testosterone, Pregnenolone (consider inter-conversion of steroid hormones)
- Urinary 2, 4, 16 Hydroxyestrogens (note more recent research gives less significance to correlations of 2/16 ratio to risk, but you can still get a sense of estrogen metabolism)
- OH >> **production of carcinogenic quinones >> DNA damage**
- Two of the main estrogen metabolites are hydroxylated (metabolized) by genes called CYP1A1 and CYP1B1
- The 2-OH estrogen metabolites are protective while the 16-OH metabolites are estrogenic and increase risk

HydroxyEstrone (4-OHE1) >> production of carcinogenic quinones
More of this estrogen metabolite indicates a more estrogenic, potentially more carcinogenic physiology. This can promote cancer and tissue proliferation. This may result in direct damage to DNA the initiating step in cancer

development.

- **Also useful to look at genomic factors**; see Genova Diagnostics Estrogenomics Panel and also consider genomic factors influencing **methylation** (Methyl Donors-methyl folate, methyl B12, SAMe) and **sulfation (**N-Acetyl cysteine), Glutathione (Liposomal)
- Also consider **Methoxyestrogen Metabolites**--(methylation capacity and factors). Look at SNPs for MTHFR and COMT (full detailed curriculum of Methylation-- Ben Lynch).
- Consider use of **DIM (Di Indole Methane**). Good when there is estrogen dominance **DFH DIM Evail i**s a good product, also **DFH FemGuard Balance+** and also **Natura Cell Guardian (both with sulphoraphanes and methyl donors)**
- **DFH Broccoprotect or Thorne Crucera (broccoraphanin)**
- Also consider **Estrobolome** (see notes and slides from prior Clinical Pearl on this subject)

*"**Use DIM or I-3-C to increase 2-hydroxylation,** 4-OH-E1 either stays about the same or goes up slightly. People often mistakenly think DIM will drive down 4-OH. **It usually does drive down 16-hydroxyestrogens and also E1 and E2 (which is a good way to decrease E1, E2 when there is estrogen dominance).***

In terms of how this is protective IF the 4-OH is not going down,
both 2-OH and 4-OH can create a reactive quinone (if not methylated…that's why methylation is important) a**nd then **both can attach to and theoretically damage DNA**. In this sense they are competing to attach to DNA and so it is better to have more 2-OH to dominate the 4-OH in this step because 4-OH-DNA (attaches to either guanine or adenine) adducts are stable pairings causing a **break in the DNA and requiring repairing (this is where the carcinogenic potential comes from).** The 2-OH-DNA adducts are not as stable, so they don't require repairing as much…this is my understanding of this. Also 2-methoy-estrogens are protective (not sure how) and making more of those is good. **Methylation protects against 4-OH estrogens.** If patients are not good at methylation (and even if they are) **glutathione also can make a last second save by taking the quinone and conjugating it for excretion before DNA damage…"

Mark Newman, President
Precision Analytical, Inc.
mnewman@PrecisionHormones.com
www.PrecisionHormones.com

2. Judy Pruzinsky: For a patient who wants to **add as much as possible to her shake,** since she hates taking so many pills, what would you suggest and NOT suggest she add: Stabilized R Lipoic, Broccoprotect, Resveratrol, NA Cysteine, Ultimate Antiox, Mushrooms, B complex, D3, Triphala, Kidney Correct, Immunitone, Q Avail, Curcumen

Most supplements can be added to shake…avoid bitter substances, do not add probiotics unless you are going to drink right away (ferments), **do not add enzymes** (makes it taste bitter), **do not add Modified Citrus Pectin** (binds nutrients as it is a chelating agent)

3. Judy Pruzinsky: How long is a reasonable amount of time for a patient to believe she is "safely" clear of recurrence, if originally treated for triple negative breast DCIS?

- 1:2 Men and 1:3 Women at risk for cancer occurrence
- DCIS very low risk overall, Adenocarcinomas of the breast higher risk.
- Overall...any person with hyperplasia, malignant cells, high risk exposures, strong family hx should always be mindful of maintaining a physiology that is not supportive of carcinogenesis, tumorogenesis, proliferation or metastatic potential. Patients who are **NED (No Evidence of Disease=Remission)** and have been treated with chemo or RT or hormonal blockade may have treatment resistant cells, cancer stem cells.
- **Managing and monitoring the tumor micro-enviornment is an ongoing lifelong (lifestyle) dynamic process. There is always risk of recurrence.**
- Vigilance is relative to risk of recurrence: aggressiveness and stage of dx as well as type of tx.
- First 2 years after dx and tx is most crucial for all pts.
- 5 year mark is theoretical; recurrence can appear as long as 10 years after dx.

4. Judy Pruzinsky: 65 year old with stage 3 **Non-Hodgkins Lymphoma,** already started chemo. Are there any studies, articles that would be good background?

VERY INFLAMMATORY SYNDROMES High rate of recurrence

Pathways to consider

- BCL2 andrographis, coriolous, **parthenolide from tanacetum/feverfew,** ginger green tea
- NFkb **curcumin O3FA Resveratrol Quercetin**
- TNFa curcumin schizandrins ursolic acid (sage, crataegus, **oldenlandia-hedyotis diffusa**)
- PI3K (phostatidyl inositol 3 kinase) -AKT-mTOR **honokiol, O3FA, sulforaphane, EGCG**

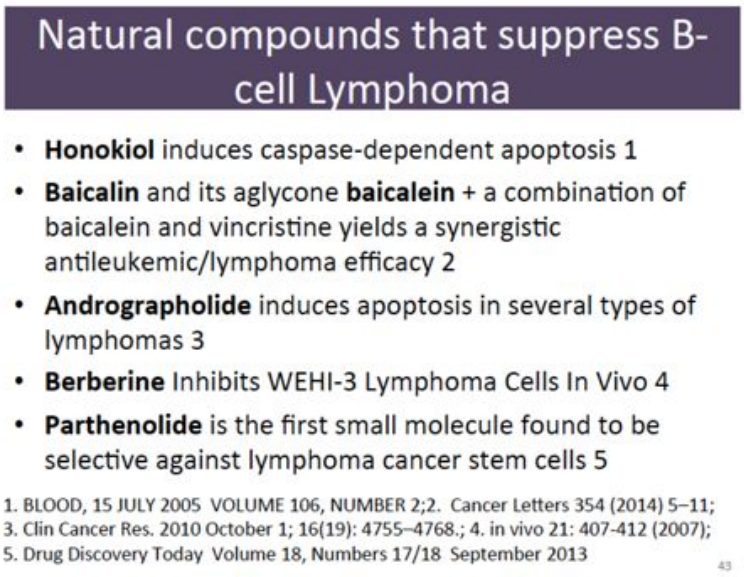
Definitely include Curcumin, EGCG, Baicalein (Scutellaria baicalensis), Resveratrol, O3FA

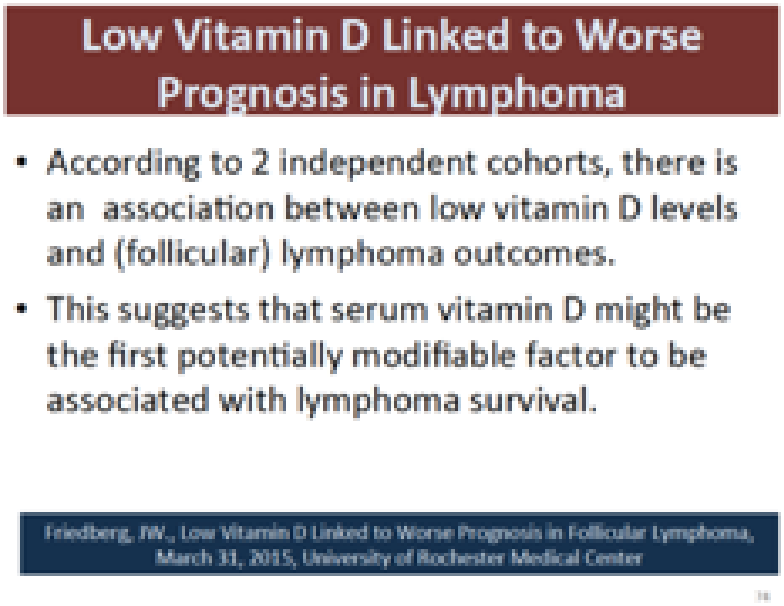
Studies in mice show **Beta-Glucans synergize with Rituxan and support immune response and tumor growth inhibition** (Ganoderma, Chaga, Trametes (Corilous), Cordyceps, Beta 1 3 D Glucan products)

Bio-Markers of CLL (Chronic Lymphocytic Leukemia) and B Cell Lymphoma
Beta-2-microglobulin (B2M): Normal levels are usually below 2.5-2.8 micrograms per milliliter (ug/mL). B2M is useful in helping to determine prognosis (long-term outlook for survival) in some of these cancers. **Patients with higher levels of B2M usually have a poorer prognosis**. Also useful in multiple myeloma.

- Lactate Dehydrogenase **(LDH):** Normal range is between 80-285
- hs-C-reactive Protein **(CRP)**: Normal range is <.8 (also can test ESR)
- **Copper, zinc and ceruloplasmin**
- **25-OH Vitamin D** (usually low) goal 55-80
- **High risk of osteoporosis and fracture** (and pain)

From Donald Yance:





5. Sarah Shahabuddin: Estrogen or progesterone supplementation problematic for multiple myeloma?
No, estrogen and progesterone are not linked to hemologic cancers

6. Judy Pruzinsky: Favorite lab for heavy metal testing? Quicksilver Scientific: https://www.quicksilverscientific.com/ (Owner and specialist: Christopher)

Resources

Arendt, J. F. B., Pedersen, L., Nexo, E., & Sørensen, H. T. (2013). Elevated plasma vitamin B12 levels as a marker for cancer: a population-based cohort study. Journal of the National Cancer Institute, 105(23), 1799-1805.

Cui, L. H., Quan, Z. Y., Piao, J. M., Zhang, T. T., Jiang, M. H., Shin, M. H., & Choi, J. S. (2016). Plasma Folate and Vitamin B12 Levels in Patients with Hepatocellular Carcinoma. International journal of molecular sciences, 17(7), 1032.

Elevated Vitamin B12 and the Tumor Microenvironment

CREATE AN ENVIRONMENT WHERE CANCER CANNOT THRIVE

American Institute of Integrative Oncology
RESEARCH & EDUCATION

FOUNDER, DR. NALINI CHILKOV

Normal Range

Serum VITAMIN B12 COBALAMIN

200 to 1100 picograms per milliliter (pg/mL)

> 2000 pg/ml High

Vitamin B12 (Cobalamin) Metabolism

- Food-bound vitamin B12 is released in the stomach's acid environment and is bound to R protein (haptocorrin).
- Pancreatic enzymes cleave this B12 complex (B12-R protein) in the small intestine.
- After cleavage, intrinsic factor, secreted by parietal cells in the gastric mucosa, binds with vitamin B12.
- Intrinsic factor is required for absorption of vitamin B12, which takes place in the terminal ileum.

Vitamin B12 (Cobalamin) Metabolism

- Vitamin B12 in plasma is bound to transcobalamins I & II.
- Transcobalamin II is responsible for delivering vitamin B12 to tissues.
- **The liver stores large amounts of vitamin B12.**
- Enterohepatic reabsorption helps retain vitamin B12.
- Liver vitamin B12 stores can normally sustain physiologic needs for 3 to 5 yr if B12 intake stops (eg, in people who become vegans) and for months to 1 yr if enterohepatic reabsorption capacity is absent.

Biochimie. 2013 May;95(5):1033-40. doi: 10.1016/j.biochi.2013.01.020. Epub 2013 Feb 14.

Molecular and cellular effects of vitamin B12 in brain, myocardium and liver through its role as co-factor of methionine synthase.

Guéant JL1, Caillerez-Fofou M, Battaglia-Hsu S, Alberto JM, Freund JN, Dulluc I, Adjalla C, Maury F, Merle C, Nicolas JP, Namour F, Daval JL.

Vitamin B12 influences
- **cell proliferation**
- **differentiation**
- **apoptosis**

Vitamin B12 (cobalamin, cbl) is a **cofactor** of methionine synthase (MTR) in the **synthesis of methionine**

Methionine is the precursor of the universal methyl donor S-Adenosylmethionine (SAM)
which is involved in
epigenomic regulatory mechanisms (gene expression)

J Natl Cancer Inst. 2013 Dec 4;105(23):1799-805.

Elevated plasma vitamin B12 levels as a marker for cancer: a population-based cohort study.

Arendt JF1, Pedersen L, Nexo E, Sørensen HT.

- 333 667 persons without prevalent cancer and not receiving Cbl treatment.
- Six percent had Cbl levels greater than the upper reference limit ≥601 pmol/L
- **Cancer risk increased with higher Cbl levels and was highest during the first year of follow-up** (Cbl 601-800 pmol/L: SIR = 3.44, 95% CI = 3.14 to 3.76; **Cbl >800 pmol/L:** SIR = 6.27, 95% CI = 5.70 to 6.88; both P < .001).
- **The risks were particularly elevated for hematological and smoking- and alcohol-related cancers for persons with high Cbl levels.**

Cancer Epidemiol. 2016 Feb;40:158-65.
Elevated plasma vitamin B12 levels and cancer prognosis: A population-based cohort study.
Arendt JF et al

Survival probabilities were lower among patients with elevated Cbl levels
than among patients with normal levels and among members of the comparison cohort

1998–2014. 25,017 patients with a cancer diagnosis and Cbl levels of 200– 600 pmol/L (reference/normal range), 601–800 pmol/L and >800 pmol/L measured up to one year prior to diagnosis, and a comparison cohort of **61,988 cancer patients** without a plasma Cbl measurement.

1-year survival,% : Cbl: 200– 600 pmol/L: 69.3%; 601–800 pmol/L: 49.6%; >800 pmol/L: 35.8%;

Cancer Epidemiol. 2016 Feb;40:158-65.
Elevated plasma vitamin B12 levels and cancer prognosis: A population-based cohort study.
Arendt JF et al

Thirty-day mortality was elevated for patients with Cbl levels of 601–800 pmol/L or >800 pmol/L, compared to patients with levels of 200–600 pmol/L

MRR (95% confidence interval):
601–800 pmol/L vs. 200–600 pmol/L:
1.9 (1.6–2.2); >800 pmol/L vs. 200–600 pmol/L: 2.7 (2.4–3.1)].

This association remained robust for 31–90-day and 91–365-day mortality, showing similar dose-response patterns.

PLoS One. 2012; 7(9): e45979.
Published online 2012 Sep 21. doi: 10.1371/journal.pone.0045979
PMCID: PMC3448722

Cobalamin Related Parameters and Disease Patterns in Patients with Increased Serum Cobalamin Levels

Johan F. B. Arendt* and Ebba Nexo

Elevated serum Cbl levels are most consistently found in some types of **myeloproliferative disorders**, such as
- chronic myeloid leukemia,
- polycythemia vera, and
- hypereosinophilic syndrome

This is due to **increased concentrations of haptocorrin (HC), one of the two circulating Cbl binding proteins**

PLoS One. 2012; 7(9): e45979.
Published online 2012 Sep 21. doi: 10.1371/journal.pone.0045979
PMCID: PMC344872

Cobalamin Related Parameters and Disease Patterns in Patients with Increased Serum Cobalamin Levels

Johan F. B. Arendt* and Ebba Nexo

Several studies have been conducted to link a number of other **diseases** or group of diseases to **high Cbl levels and/or high levels of Cbl binding proteins.**

These include different **malignancies** and
- **hepatic and renal** cancers
- **myeloproliferative disorders**
- infectious diseases
- autoimmune diseases

Int J Mol Sci. 2016 Jun 30;17(7)

Plasma Folate and Vitamin B12 Levels in Patients with Hepatocellular Carcinoma.

Cui LH1, Quan ZY2, Piao JM3, Zhang TT4,5, Jiang MH6, Shin MH7, Choi JS

-**Folate and vitamin B12 involved in the one-carbon metabolism may play a key role in carcinogenesis and progression of hepatocellular carcinoma (HCC) through influencing DNA integrity.**

-Compared to the subjects in the lowest quartile of plasma vitamin B12, only the **subjects in the highest quartile of vitamin B12 exhibited a significant positive relationship with HCC**, the adjusted OR was 2.01 (95% CI, 1.02-3.98).

-HCC patients with **Stage III and IV or bigger tumor size had *lower folate and higher vitamin B12 levels.***