Tocotrienols

A surprise outcome in the management of lymphomas

Joseph Keenan MD, former Professor, University of Minnesota Department of Family Medicine
Overview

- Case report
- Tocotrienols and health/cancer benefits
- Epigenetics and cancer
- Non-Hodgkins follicular lymphoma (fNHL)-Pilot studies
Case study

- J.K. is a 72 yo male, academic/emergency medicine physician, thoroughbred race horse breeder/owner, nice guy, intelligent, good looking, I know him well!
- July 2013 discovered 3x4 cm mass in left supra-clavicular space.
- Prior health good, no systemic symptoms.
- Biopsy = Non-Hodgkins follicular lymphoma (fNHL), grade 1-2/3, stage II/IV, FLIPI (prognostic index score =1/5; age>60, stage III-IV, LDH> nl, Hgb < 12, >4 nodal sites)
- CT scans (chest, abd/pelvis,neck)= primary tumor in mediastinum
CT chest- 7/8/2013

“CT shows diffuse lymphadenopathy in mediastinum with large approximate 3-cm lymph node mass in AP window. Lymph nodes in bilateral tracheal space extending into the subcarinal region.”
Case Study (cont’d.)

- “watch and wait” monitor signs and symptoms.
- Initiate chemotherapy when clinical symptoms or lab findings suggest significant progression.
- Over the following year there was increasing fatigue/shortness of breath with activity.
- New CT-scan 6-23-2014
CT Chest 6/23/2014

"There is increased mediastial adenopathy in the aorta-pulmonic space"
Case study cont’d

- Tentative plans to start chemo in Oct 2014.
- Coincidently started tocotrienols 200mg/day in July 2014 for “brain health”.
- Oct 2014 feeling pretty good and decided to defer chemo till spring.
- Repeated CT scans of neck, chest, abdomen/pelvis in June 2015 as baseline for starting chemo.
CT Chest -6/8/2015

“Chest shows decreased size in the anterior mediastinal and middle mediastinal lymph nodes, largest currently in the middle mediastinum at 1.5-cm. Previous CT June 23, 2014 node was 3-cm with an anterior mediastinal lymph node at 2-cm which is now not visualized. Multiple smaller subcentimeter mediastinal lymph nodes all appear decreased in size from previous.”
Case study (cont’d)

- Surprise findings in face of my derilict lifestyle *vis a vis* epigenetic factors
- Resume “watch and wait” approach
- Focus on epigenetic factors
Known benefits of toco’s

- Brain health (↓ WMLs, stroke mitigation)
- Cardiovascular Health
- Anti-inflammatory
- Cancer suppression
- Anti-aging
- Skin health
Toco’s and cancer

- Toco’s show inhibition of growth of breast Ca cells in tissue culture.
- Toco’s show inhibition of prostate Ca cells in tissue culture.
- Toco’s prolong life span in Ca model in mice.
- Clinical trials are underway.
Cancer and Epigenetics

“epigenetic change is a process of altered gene activity resulting from gene expression rather than from a change to the genetic code itself.”
Epigenetic Mechanisms

EPIGENETIC MECHANISMS are affected by these factors and processes:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

CHROMOSOME

METHYL GROUP

CHROMATIN

DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

DNA accessible, gene active
DNA inaccessible, gene inactive

Histone TAIL

Histones are proteins around which DNA can wind for compaction and gene regulation.

HEALTH ENDPOINTS
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

EPIGENETIC FACTOR

Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.
A

Chromosome

Chromatin → Nucleosome

Histone modifications

DNA methylation

B

Gene “switched on”
- Active (open) chromatin
- Unmethylated cytosines (white circles)
- Acetylated histones

Gene “switched off”
- Silent (condensed) chromatin
- Methylated cytosines (red circles)
- Deacetylated histones

Transcription possible

Transcription impeded
Epigenetic factors in fNHL

Aspartame, Glutamine/Glutamates, High Carbohydrate Diet, Stress, Environmental Toxins
Selenium, Bitter Melon, Sleep, Cinnamon, Milk Thistle, Ellagic acid, Omega 3’s, Sulforaphane, Exercise, Probiotics Tocotrienols, Quercetin, Vitamin D, Glucose Deprivation, Resveratrol, Vitamin K
Epigentics – gene loci

- p53, Myc, PI3K, AMPK, mTOR signaling and BCL-2 are all identified tumor suppression gene loci.
- All persons with fNHL have a mutation at BCL-2, a site that controls cellular apoptosis, but so do many persons without fNHL.
- DNA repair genes have also been identified.
- Epigenetic factors are thought to influence gene expression at such loci.
- Tocotrienols are have been shown to effect gene locus P53.
Robert Miller- fNHL Poster Child
Epidemiology of fNHL

- NHL is the 5th most common CA, and fNHL makes up 30% of NHL
- Minnesota has the 2nd highest incidence of fNHL per capita in USA
- More prevalent in northern latitudes USA, Canada, Northern Europe, possibly related to Vit D3 deficiency.
Proposed pilot studies

- Pilot study -1: Tocotrienols supplement in previously untreated subjects as part of “watch and wait” management.
- Pilot study- 2: Tocotrienols supplement as adjuvant in active treatment subjects.
Proposed pilot study-1

- Consultation with researcher at U of MN with expertise in oncology/ nutrition epigenetics.
- Recruit 40 subjects with recent imaging of fNHL and are in “watch and wait” treatment.
- Start 200mg/day tocotrienol supplement. (100mg/d)
- Bi-monthly questionnaire regarding use/change of epigenetic factors (diet, exercise, sleep. Etc)
- Dose monitoring (pill count).
- 3 day food record every 3 months.
- Tumor monitoring reports, labs (LDH, WBC) FLIPI score with interval summary every 6 month.
- Study endpoints: 1) length of time from initiation of tocos to start of treatment (chemo); 2) change in tumor size, mass, location on subsequent imaging.
Pilot study -2

- Recruit 40 subjects with fNHL (with recent imaging) who are about to initiate active treatment.
- Increasing experience with trial of limited chemo (Rituxan, antibody to CD20 lymphocyte) in early treatment rather than “watch and wait”.
- Start tocotrienols 200mg/d (100mg/d) as adjuvant to active treatment.
- Same monitoring and reporting as Pilot study -1