

Collaborating Effectively with Conventional Cancer Therapies

Dwight McKee MD
Board Certified in
Oncology, Hematology,
Internal Medicine, Nutrition
and Integrative Medicine.

Enhance Oncologic Care

- **Goals:**
 - **To reduce side effects**
 - **To enhance efficacy of chemotherapy, radiation or hormonal therapy**
 - **To target mechanisms of multi-drug resistance and radiation resistance**
 - **To alter the ‘terrain’ of the patient to be non-supportive of tumor cells**

Developing an Integrative Protocol and Monitoring Patients

- Consider multiple processes utilized by neoplastic cells to support their
 - Proliferation
 - Progression
 - Resistance to treatment

Processes exploited by neoplasms

1. Aberrant signal transduction
2. Altered gene expression/stability
3. Up-regulated inflammatory response
4. Evasion of apoptosis
5. Immune evasion and suppression

Processes exploited by neoplasms

6. De-differentiation
7. Hormonal dependency (some)
8. Invasion and metastasis
9. Radio/chemo resistance
10. Loss of stromal integrity
11. Neo-angiogenesis

A Comprehensive Protocol

- Selects agents that target each of these processes
- Aims for a synergistic combination

A Comprehensive Protocol

- General Wellbeing
- Promote Gene Stability
- Modify Gene Expression
- Control Inflammation
- Provide Immune Support
- Induce Cytostasis
- Induce Re-Differentiation
- Induce Apoptosis
- Modulate Hormones (if relevant)
- Inhibit Invasion and Metastasis
- Support Anti-Angiogenesis

The Foundation: General Wellbeing

- Goal:
 - address self-nourishment and self-care
 - breathing, water intake
 - diet nutrition habits, laughter, emotional outlets
 - relaxation, sleep, play/creativity
 - exercise/movement, social support and spiritual pursuit
 - address areas of poor organ function

General Wellbeing

Potential Agents:

- Diet Goals: wholesome diverse, organic, mostly plant-based diet, low-glycemic
 - Increase phytonutrients: 8-10+ servings/day seasonal organic vegetables and fruits, legumes, nuts & seeds
 - Reduce blood sugar: Low glycemic, high fiber, no refined carbs
 - Decrease omega-6 intake; increase omega-3 and omega-9 (olive oil)
 - Restrict high copper foods

General Wellbeing Potential Agents:

- Multiple vitamin/mineral
 - iron free
 - copper free
 - Boron free if ER+
- Digestive Aid
 - adequate chewing
 - bitters
 - digestive enzymes

General Wellbeing Potential Agents:

- Support glucose metabolism
 - low-glycemic high-fiber diet
 - chromium, vanadium, biotin, lipoic acid, gymnema, bitter melon, cinnamon, holy basil, goat's rue seed extract, fenugreek seed extract, B-complex vitamins, luteolin
- Probiotic flora
- Soluble-fiber supplement

General Wellbeing Potential Agents:

- Thyroid modulation (if TSH < 3.5):
 - crucifers,
 - soy,
 - lemon balm,
 - bugleweed
- Mitochondrial support
 - L-carnitine, Acetyl-L-carnitine
 - COQ10, Lipoic acid, NADH

General Wellbeing Potential Agents:

- Adaptogen herbal combinations
 - Main actions of primary adaptogens
 - Anti-fatigue effect
 - Aids in the stress response
 - Improves oxygen uptake
 - Supports optimum endocrine function
 - Improves learning, memory, and mood
 - Improves eyesight and hearing

Adaptogen Herbal Combinations

- Main actions of primary adaptogens (cont)
 - Regulates blood sugar levels
 - Organ protective
 - Anti-viral: Increases the body's ability to resist infection, prevents colds and the flu, shortens recovery time
 - Immuno-protective
 - Anti-toxic (environmental, chemo, radiation)
 - Free radical scavenging, redox-cycling, anti-lipid peroxidative

Adaptogenic Plants

Promote Gene Stability

- GOAL: Control chronic excessive oxidative stress
 - may promote genetic instability
 - fosters more aggressive tumor behavior
- TESTING:
 - assessments of redox balance
 - ratio oxidized/reduced glutathione is a good marker
 - urinary isoprostanes –end products of lipid peroxidation
 - functional Liver Detoxification
 - Phase I and II pathway assessment
 - methylation status
 - Homocysteine, methyl malonic acid, organic acids
 - urinary hormone metabolites

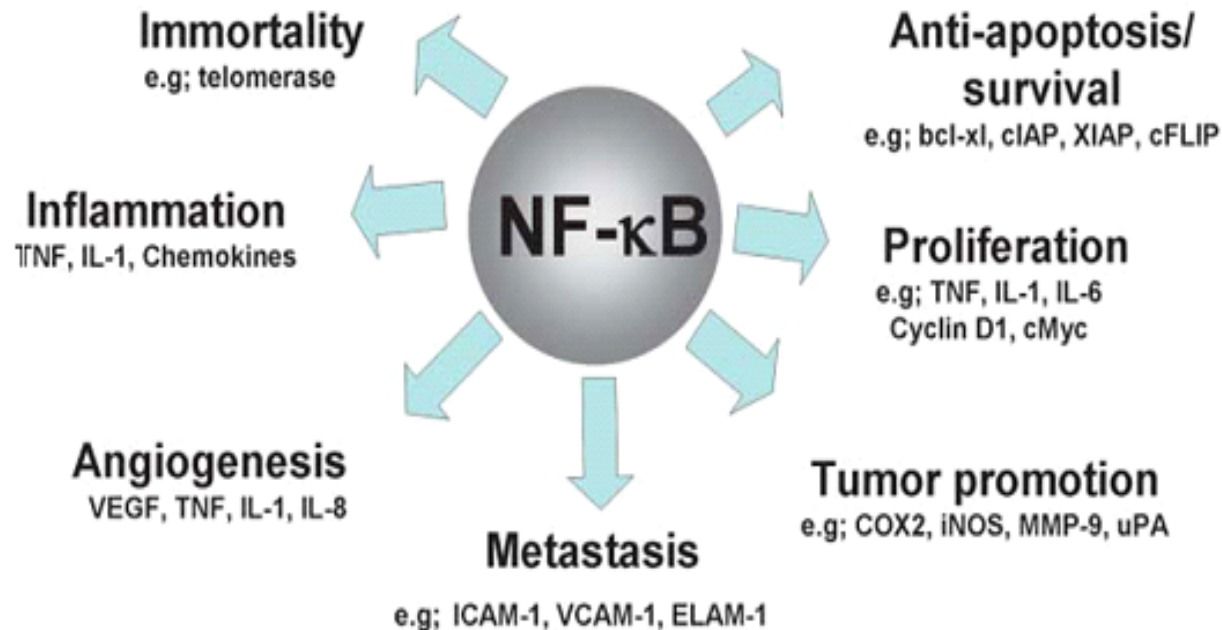
Promote Gene Stability

- DIET:
 - Fruits, vegetables, spices
 - Diet goal target $\geq 5,000-7,500$ ORAC units/day
- POTENTIAL AGENTS:
 - Antioxidant nutrients
 - carotenoids, tocopherols/tocotrienols
 - Anti-inflammatory agents
 - Methylating agents

Modifying Gene Expression

- TESTING: Antibody staining of tumor sample for various gene products (proteins)
- POTENTIAL TARGETS:
 - Nuclear Factor-kB (NF-kB) Her-2/neu (Erb-B-2)
 - PDGF
 - Survivin
 - Cyclin D1
- VEGF
- EGFR (her-1)
- P53
- Multi-drug resistance gene (MDR)

What NF- κ B Activates



Modifying Gene Expression

Potential Agents

- Nuclear Factor-kB (NF-kB) inhibitors
 - culinary spices:
 - curcumin, basil, cinnamon, cardamom, clove, ginger, garlic, nutmeg, coriander, cumin, mint, parsley, rosemary
 - green tea (EGCG)
 - luteolin (artichoke leaf extract)
 - parthenolide (feverfew)
 - quercetin
 - resveratrol

Modifying Gene Expression Potential Agents

- VEGF
 - boswellia
 - curcumin
 - fish oil EPA
 - selenium
 - grape seed extract
 - green tea
 - resveratrol
 - Baikal skullcap (*Scutellaria baicalensis*)

Modifying Gene Expression

Potential Agents

- EGFR (her-1, Erb-B-1)
 - green tea
 - grape seed extract
 - licorice
 - pycnogenol
 - quercetin
 - soy (genistein)
 - vitamin D

Modifying Gene Expression Potential Agents

- P53
 - soy (genistein)
 - folic acid
 - selenium
 - quercetin
 - vitamin E (succinate)
 - cruciferous-family vegetables

Modifying Gene Expression Potential Agents

- Her-2/neu (c-erb)
 - fish oil DHA
 - oleic acid (olive oil)
 - flaxseed
 - soy genistein
 - quercetin
 - emodin (in aloe vera and *Polygonum cuspidatum*)

Control Inflammation

- TESTING:
 - High-sensitivity or cardio-C-Reactive Protein < 1.0
- GOAL:
 - Block inflammatory compounds that can promote tumor growth, proliferation, metastasis and angiogenesis and also suppress the immune response.
 - COX-2
 - LOX-5
 - 5-HETE,
 - 12-HETE
 - 15-HETE

Control Inflammation

Potential Agents

- bromelain
- quercetin
- boswellia
- curcumin
- resveratrol
- hops (*Humulus lupulus*)
- green lipped mussel extract
- sea cucumber
- stinging nettle root
- holy basil (*Ocimum sanctum*)
- fish oil omega-3
- ginger
- pancreatic enzymes
- combination anti-inflammatory formulations

Provide Immune Support

- TESTING:
 - NK Cell Cytotoxic Function (4-hr Cr-release assay) > 25 LU
 - WBC > 4.0; Lymph % >20%
 - T-cell subsets (CD4:CD8 ratio)

Provide Immune Support

Potential Agents

- Vitamin C
- Bromelain
- Selenium
- PSK or PSP from *Coriolus versicolor*
- Arginine
- Thymic peptides or Rx: Zadaxin
- Maitake-D fraction
- Arabinogalactans
- Garlic
- Agaricus blazei
- Astragalus
- Reishi (*Ganoderma*)
- Lactoferrin
- Cordyceps sinensis
- Transfer Factor, colostrum
- Whey protein
- Acidophilus / Bifidus probiotics
- Mistletoe (*Viscum album*)
- AHCC
- Panax ginseng
- Chlorella
- Aloe vera
- Zinc
- Schisandra
- Vitamin A

Induce Cytostasis (Cell Cycle Arrest)

- GOAL:
 - upon completion of chemotherapy and/or radiotherapy, induce residual cells to cell cycle arrest
 - may not be an appropriate goal *during* cytotoxic treatment if the therapy is cell cycle dependent
- TESTING:
 - not directly available.
 - prioritize if ki-67/MIB-1 elevated.
 - may be monitored with functional MR-SPECT or PET scans.

Induce Cytostasis

Potential Agents

- melatonin
- garlic
- quercetin
- bacopa
- green tea
- perillyl alcohol
- D-limonene
- blood sugar
- regulation
- redox balance

Induce Re-Differentiation (Maturation to Healthy Cell Types)

- TESTING:
 - 25-OH-vitamin D3 (>60 but <80 ng/ml)
 - serum retinol 1.2-2.4mg/L
 - consider surgical path report
 - description of tumor as well vs. poorly differentiated

Induce Re-Differentiation (Maturation to Healthy Cell Types)

- Vitamin D3
- Vitamin A (retinoic acid)
- Butyrate (fiber + bifidus probiotic)
- Boswellia (boswellic acids)
- Berberine
- Monoterpenes (Perillyl alcohol, limonene)
- Caffeic esters (propolis)
- Resveratrol
- Flavonoids (quercetin, apigenin, luteolin)
- Phenylbutyrate phenylacetate
phenylacetyl glutamine

Induce Apoptosis Programmed Cell Death

- TESTING:
 - may be partially inferred by functional status of p53
 - BCL-2
 - survivin

Induce Apoptosis Potential Agents

- Green tea EGCG
- Quercetin
- Vitamin A
- (retinoic acid)
- Selenium
- Boswellia
- (boswellic acids)
- Vitamin D3
- Curcumin
- Genistein
- Vitamin E succinate
- Schisandra
- Berberine
- Artemether / artemisinin / artesunate
- Vitamin C
- Monoterpenes (Perillyl alcohol, limonene)
- Fish oil EPA
- Resveratrol

Modulate Hormones

- Relevant in breast, prostate (some ovarian, endometrial) cancers
- Note: Elevated estrogen favors angiogenesis
- TESTING:
 - 2:16-hydroxyestrogen ratio
 - methylation capacity
 - estrogen-progesterone ratio
 - ratio of estradiol+estrone (unfavorable) vs. estriol (favorable)

Modulate Hormones

- DIET & LIFESTYLE:
 - avoidance of xenoestrogens
 - eg. Bisphenol A
 - adequate soluble fibers
 - adequate GI flora (cultured foods)
 - avoidance of alcohol, caffeine (except green/white tea)

Modulate Hormones

Potential Agents

- Indoles (DIM)
- Calcium d-glucarate
- Curcumin
- Melatonin (controversial)
- Flaxseed meal
- Soy isoflavones

Modulate Hormones Potential Agents

– Aromatase inhibitors:

- button mushrooms
- resveratrol
- biochanin A
- luteolin
- ursolic acid (sage, rosemary & thyme)
- flaxseed
- chrysin

Inhibit Invasion and Metastasis

- GOAL:
 - Select inhibitors of matrix metalloproteins (MMPs)
 - Maximize NK Cell function
 - Reduce inflammation and hypercoagulation

Inhibit Invasion and Metastasis

- TESTING:

- NK Cell Cytotoxic Function (4-hr Cr-release assay) >25 LU
(*rr* 20-48 LU)
- CRP <0.8; Platelets (*rr* 150-300 kmm³)
- Fibrinogen 150-350mcg/dL (*rr* 190-425 mg/dL)
- D-dimer <300ng/mL, some sources suggest <150 ng/ml
(*rr* <300ng/ml)

Inhibit Invasion and Metastasis Potential Agents

- Arabinogalactans
- Avemar
- Coriolus versicolor (PSK/PSP)
- Green Tea EGCG
- Flaxseed meal
- Panax ginseng
- Bromelain
- Nattokinase
- Lumbrokinase
- Butyrate-fiber and bifidus probiotic
- Garlic
- Vitamin C Soy esp. genistein
- Bioflavonoids
- Vitamin A
- Anthocyanins
- Alkylglycerols (in brain tumors)
- Proanthocyanidins (GSE, PCO)
- Fish oil EPA
- Melatonin (high dose)

Support Anti-Angiogenesis

- TESTING:
 - serum copper ≤ 90 (*rr* 70-145mg/dl)
 - ceruloplasmin ≤ 22 (*rr* 18-36 μ g/L)
 - free copper {serum Cu minus 3x ceruloplasmin} ≤ 15).
- Consider surgical report statement of
 - vascularity or microvessel density (if any) and
 - immunohistochemistry
 - VEGF
 - EGFR
- Also relevant: elevated inflammation and insulin are angiogenesis promoters
 - fasting glucose / HbA1c
 - hs-CRP

Support Anti-Angiogenesis

- DIET:
 - avoid high copper foods (and supplements)
 - organ meats
 - Shellfish
 - prepared chocolates
 - water-soluble chlorella
 - rooibos tea
 - filter water if copper plumbing and water is acidic pH.

Support Anti-Angiogenesis Potential Agents

- POTENTIAL COPPER LOWERING AGENTS:
 - Rx: Tetrathiomolybdate (TM)
 - 20 mg TID with meals + 60 mg at hs
 - GOAL: 8-12 mg/dl Cu⁺⁺
 - Molybdenum
 - Zinc
 - Chlorella
 - Sulfur compounds (NAC, taurine)
 - Lipoic acid
 - Vitamin C

Support Anti-Angiogenesis Potential Agents

- Apigenin (mint and propolis)
- Selenium
- Soy isoflavones, esp. genistein
- Vitamin D3
- Green Tea EGCG
- Curcumin
- Garlic
- Resveratrol
- Vitamin A
- Cordyceps sinensis
- Shark liver oil (squalene)
- Berry flavonoids
- Fresh/frozen shark cartilage
- Glycine
- Bindweed (*Convolvulus arvensis*)

Enhance Oncologic Care

- Goals:
 - To reduce side effects
 - To enhance efficacy of chemotherapy, radiation or hormonal therapy
 - To target mechanisms of multi-drug resistance and radiation resistance
 - To alter the ‘terrain’ of the patient to be non-supportive of tumor cells