"We're here because we're thrivers, not survivors."

Scott Berliner,
Myelofibrosis thriver

Overcoming the Side Effects of Cancer Treatments

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Cancer Thriver

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- **The key strategy for preparing yourself for conventional cancer therapies such as chemotherapy and radiation is to be as strong and as healthy as possible *before your treatment.***

What I did prior to my bone marrow transplant

- I went on a paleo diet eliminating all sugar and grains.
  - I gained 12 pounds since being warned of losing 20% of body weight.
- I increased my cardiovascular activity to strengthen my heart and my muscles.
- A specific regimen of supplements based on my chemo
- Extra minerals especially magnesium
- Glutathione IV three times a week
- Reiki twice a month
- Yoga three times a week
- Chinese herbs twice a day
- Homeopathic constitutionals

- If possible, allowing 2-4 weeks before treatment to modify diet and take supplements can substantially improve how you feel during conventional treatments.

- Dietary: discussion of a hypoallergenic & anti-inflammatory diet

- Supplements: the use and controversy of "loading up" on antioxidants

- Enhancing organ functions & eliminations: primarily the liver, kidneys, colon, and skin. If these organs are not functioning properly before treatment, they will have more difficulty with the increased toxicity, thereby increasing side effects.

- Many of the side effects due to chemotherapy and radiation are due to the body not being able to rid the breakdown toxins fast enough. The use of herbs, homeopathic drainage remedies, and hydrotherapy methods to aid in this process can have a substantial benefit.

- Mental & Emotional support: understanding where the person is at emotionally and supporting this with natural strategies is critical to reducing side-effects and enhancing outcomes.
  - L-Theanine and GABA

The primary goals for incorporating diet, nutritional supplements, herbal and homeopathic medicines during conventional treatment programs are to:

- Reduce the toxicity of conventional treatment strategies while enhancing their effectiveness, thus dramatically lowering common side effects…..
- Eliminate or substantially reduce malnutrition and tissue wasting: the science behind the use of omega-3 oils (fish oil) and alkylglycerols.
- Bolster the immune system: consideration of antioxidants, herbs, mushroom products, essential oils, and the use of castor oil packs and other hydrotherapy measures to prevent infection and keep blood counts from getting too low
- Increase the chances of remission and cure while lowering the risk of recurrence.

What are the side effects of cancer treatments?

- The side effects you experience will depend on the type, location, and extent of your cancer and the treatment you received.

- Side effects are very individual and may not be the same for two people with similar diagnoses receiving the same treatment.

  - They may be:
    - short term side effects
    - long term side effects
    - late term side effects

COMPARISON CHART

Hormonal Therapy Side Effects

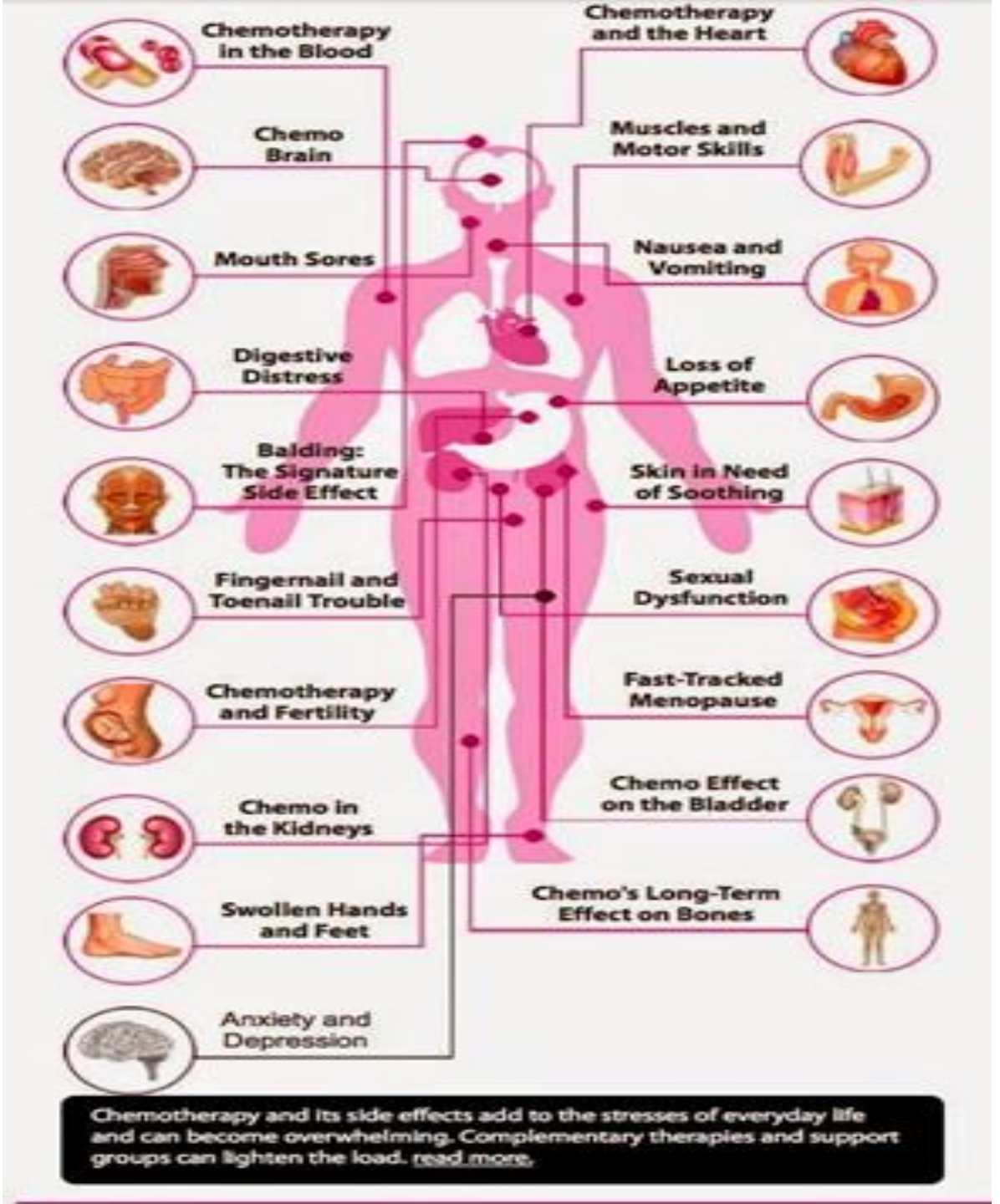
	Aromatase Inhibitors			SERMs			ERDs
	Arimidex	Aromasin	Femara	Tamoxifen	Evista	Fareston	Faslodex
bone/joint pain	●	●	●		●	●	
osteoporosis	●	●	●				
bone thinning	●	●	●				
nausea	●		●	●		●	●
vomiting	●		●				●
hot flashes	●	●	●	●	●	●	●
weakness	●	●					
fatigue	●	●	●	●			
headache		●		●			●
insomnia		●			●		
increased sweating					●	●	
dizziness			●			●	
drowsiness			●				
higher cholesterol			●				
weight gain			●				
blood clots				●	●		
stroke				●	●		
endometrial cancer				●		●	
increased bone/tumor pain				●		●	
mood swings				●		●	
depression				●			
hair thinning				●			
constipation				●			●
dry skin				●	●	●	
loss of libido				●			
leg cramps					●		
swelling					●	●	
flu-like symptoms					●		
hypercalcemia						●	
rash						●	
vaginal discharge/bleeding						●	
vision problems						●	
dry eyes						●	
diarrhea							●
sore throat							●
back pain							●
stomach/abdominal pain							●
injection site pain							●

BREASTCANCER.ORG

Getting the best breast cancer treatment can feel like a balancing act: you want to do as much as you can to get rid of the cancer and reduce the risk of it coming back. But you'd like to avoid uncomfortable side effects that might lower your quality of life.

When choosing a hormonal therapy medicine, you and your doctor will weigh the benefits and possible side effects of each one. Together, you will decide on a hormonal therapy treatment plan that's right for you and your unique situation.

This table gives you a summary of some of the most common possible side effects of the different hormonal therapy medicines so you can do a general side-by-side comparison.


Chemotherapy in the Blood
Chemo Brain
Mouth Sores
Digestive Distress
Balding: The Signature Side Effect
Fingernail and Toenail Trouble
Chemotherapy and Fertility
Chemo in the Kidneys
Swollen Hands and Feet
Anxiety and Depression
Chemotherapy and the Heart
Muscles and Motor Skills
Nausea and Vomiting
Loss of Appetite
Skin in Need of Soothing
Sexual Dysfunction
Fast-Tracked Menopause
Chemo Effect on the Bladder
Chemo's Long-Term Effect on Bones
Chemotherapy and its side effects add to the stresses of everyday life and can become overwhelming. Complementary therapies and support groups can lighten the load. read more.

Side Effects

- Short-term side effects begin during treatment and stop when treatment is discontinued.
- Long-term side effects begin during treatment and continue after all treatment is stopped.
- Late side effects are symptoms that may appear weeks, months or years after treatment ends.

- Many cancer survivors face some of the following side effects:
  - Physical side effects
  - Social and emotional side effects
  - Legal and financial impacts

We will address the physical side effects of treatments in this workshop

CHEMOTHERAPY – HOW TO MAKE IT MORE EFFECTIVE AT KILLING CANCER CELLS WITH FEWER SIDE EFFECTS

- **FASTING** (for at least 72 hours prior to chemotherapy) can improve effectiveness and reduce the side-effects of chemotherapy

- It has become clear that cancers need glucose to encourage their growth, and without this nutrient many cancers wither.

- Fasting reduces plasma glucose, IGF-1 and insulin levels and produces a state of ketosis which clearly has health benefits, one of those being to deprive cancer cells of glucose.

Fasting con't

- Studies show that:
  - Fasting makes cancer cells more sensitive to chemotherapy.
  - Fasting stopped cancer cells from producing protection proteins from their mutated genes, while healthy cells made more protective proteins.
  - Healthy cells stop dividing and are less attacked by the chemotherapy, resulting in lowered side-effects.
  - Cutting protein consumption has further anti-inflammatory and cancer-driving mechanisms.
    - Maybe this is responsible for the success of the macrobiotic diet

MANAGING FATIGUE FROM CHEMOTHERAPY AND RADIATION

- The main difference between cancer-related fatigue and just being tired is that you DO NOT feel better after getting more rest.

- The best remedy for fatigue is exercise. This has been shown in research studies. Do a minimum of three hours of exercise a week, and if you can, five to six hours a week. Almost any type of exercise will help.

- Yoga can be particularly useful because it also tackles issues like ability to concentrate and stretching tight muscles, tendons, and ligaments.

Fatigue con't

- Cancer-associated fatigue and the chronic adverse effects of cancer therapy may also be reduced by lipid replacement therapy using membrane lipids along with antioxidants and enzymatic cofactors, such as coenzyme Q(10), given as food supplements.

- Lecithin granules is a good source of phospholipids

- Clinical trials using cancer and non-cancer patients with chronic fatigue have shown the benefits of lipid replacement therapy in reducing fatigue and restoring mitochondrial electron transport function.

These chemotherapies have been associated with hand-foot syndrome:

- Capecitabine
- Cytarabine
- Doxil
- Doxorubicin
- Fluoruoracil
- Sorafenib
- Sunitinib
- Pazopanib
- Vemurafenib

Hand-foot syndrome (Palmar-Plantar Erythrodysesthesia or PPE)

- This is the result of chemotherapy or biologic drugs leaking into the capillaries of your outer extremities, like the palms of your hands or the soles of your feet. It can cause irritating symptoms like redness, pain and tenderness. Dryness and cracking may occur in areas, in addition to a numbing or tingling sensation.
- Prevention: Avoid anything that causes heat or friction near these areas for at least a week after exposure to cancer-treatment drugs. Stop activities like prolonged baths or exposure to warm water, vigorous exercise or unnecessary walking, everyday chores (like washing dishes, cooking, gardening), and anything that rubs the surface of the skin (like using Band-Aids).

Hand foot syndrome cont'd

- Vitamin B6 may help reduce the intensity of hand-foot syndrome in patients.
  - P5P or pyridoxal-5-phosphate is the coenzymatic form of B6 and is much better absorbed.
- If hand-foot syndrome has already developed, try to expose your hands and feet to cool running water or put them in an ice bath for 15 to 20 minutes per day.
- Soaking the affected areas in lukewarm water and Epsom salts also helps alleviate pain. Applying a thick, toxin-free gel that has been cooled in the refrigerator may also bring relief.

How to Use Henna to Treat Hand-Foot Syndrome/PPE

•1/4 cup water •1/8 cup henna powder •A squirt of lemon juice* (optional)

- Bring the water to a boil, then turn off the heat.
- Add the henna slowly and stir until it is like cream of tomato soup. You will probably use about 1/8th of a cup.
- *Add a squirt of lemon juice. Let it cool. (If you already have cracks, skip the lemon juice. It will sting.)

APPLY IT: Cover a work area with plastic bags or an old towel (henna stains). Paint a thin layer on your bare feet and hands. I use a foam paint brush to apply it.
LET IT DRY: It takes up to 15 minutes to dry. You can rinse it off or put socks on and leave it for your next shower

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY (CIPN)

- The use of vitamin E to treat peripheral neuropathy caused by chemotherapy:

  This was tested and found effective in a 2010 study in "Neurology." The chemotherapy agent cisplatin, which has a high incidence of severe peripheral neuropathy at certain dose levels, was used. Patients were given oral vitamin E, in the alpha-tocopherol form, before starting chemotherapy and for three months after.

- RESULTS: The incidence and severity of neuropathy was found to be significantly lower in the vitamin E group than in the control group that received a placebo

Platinum compounds

- Cisplatin – The first to be developed
- Oxaliplatin
- Satraplatin
- Picoplatin
- Nedaplatin
- Triplatin
- Lipoplatin – A liposomal version of cisplatin

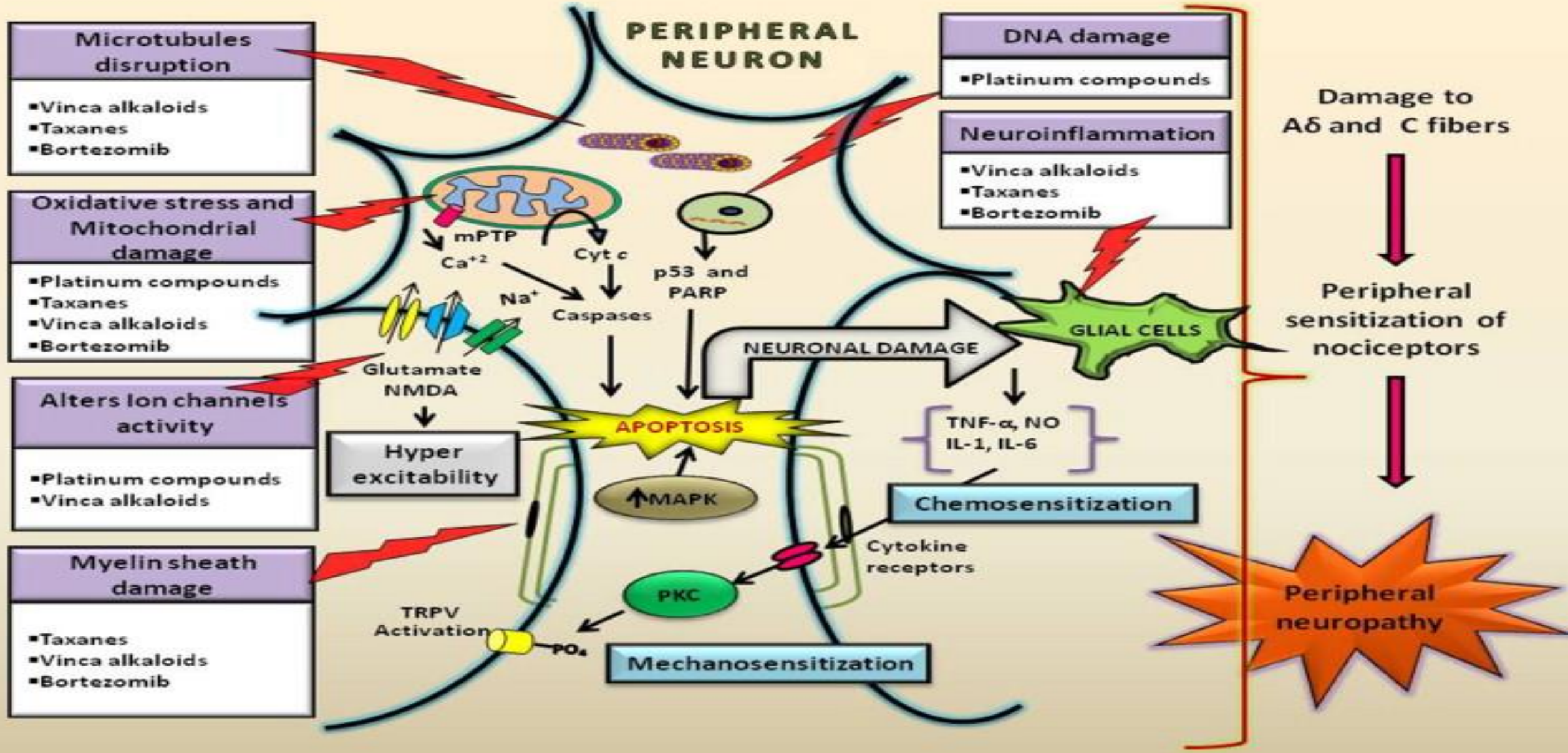
- The main dose-limiting side effect of platinum compounds is neurotoxicity, which causes neuropathy including polyneuropathy

Vinca compounds – Antimitotic Antimicrotubule alkaloids from Periwinkle

- Vincristine
- Vinblastine
- Vindesine
- Vinorelbine

- These are a class of cytotoxic drugs that work by preventing cancer cells from dividing and forming microtubules that are necessary for cellular division.
- Second most widely prescribed class of chemotherapy drugs with CIPN being one of the main side effects.

CIPN CONT'D


Microtubules disruption
▪Vinca alkaloids
▪Taxanes
▪Bortezomib
Oxidative stress and Mitochondrial damage
▪Platinum compounds
▪Taxanes
▪Vinca alkaloids
▪Bortezomib
Alters Ion channels activity
▪Platinum compounds
▪Vinca alkaloids
Myelin sheath damage
▪Taxanes
▪Vinca alkaloids
▪Bortezomib
PERIPHERAL NEURON
mPTP
Ca+2
Cyt c
Na+
Caspases
p53 and PARP
Glutamate NMDA
Hyper excitability
APOPTOSIS
MAPK
NEURONAL DAMAGE
GLIAL CELLS
TNF-α, NO
IL-1, IL-6
Chemosensitization
Cytokine receptors
PKC
TRPV Activation
PO4
Mechanosensitization
DNA damage
▪Platinum compounds
Neuroinflammation
▪Vinca alkaloids
▪Taxanes
▪Bortezomib
Damage to Aδ and C fibers
Peripheral sensitization of nociceptors
Peripheral neuropathy

Anti-oxidants being studied (these are mostly prevention)

- Role of nutraceutical antioxidants in the treatment of chemotherapy induced peripheral neuropathy (CIPN):

  Additional supplements which support normal liver function include Milk Thistle, N-Acetylcysteine and Alpha Lipoic Acid and s-acetylglutathione. Alpha Lipoic Acid is also very useful to support the repair of nerves damaged by chemotherapy.

  Nutraceutical antioxidants exhibited significant **neuroprotection** towards chemotherapy induced neurotoxicity by decreasing cellular oxidative stress through their free radical scavenging property.

Anti-oxidants being studied

- Glutathione, melatonin, n-acetyl cysteine, ω-3 fatty acids, α-lipoic acid etc)
- Indirectly helping by increasing whole blood concentrations of antioxidant enzymes (glutamine, n-acetyl cysteine)
- Normalizing mitochondrial functions (n-acetyl carnitine, α-lipoic acid by attenuating the production of proinflammatory mediators (ω-3 fatty acids) etc.
- These nutraceutical antioxidants normalize the cellular functions, rescue mitochondrial impairment, inhibit nerve inflammation, apoptosis and therefore diminish the sensory nerve degeneration.

Mouth Sores

- The mouth and digestive tract tend to slough off and become raw and tender due to normally rapidly dividing cells.

- Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. Studies show that the duration of mouth pain was 4.5 days less in chemotherapy courses in which glutamine supplementation was compared with placebo (Wilcoxon's signed rank test, P=0.0005).

- The severity of oral pain also was reduced significantly when glutamine was provided with chemotherapy.

Glutamine: Broad Protection Against Chemotherapy Side Effects

- Stomatitis reduced by 4g (1 teaspoonful) two times a day or 2g (1/2 teaspoonful) 4 times a day of glutamine powder, swish & swallow

- Esophageal cancer: 10g tid ameliorated lymphopenia, enhanced lymphocyte mitogen stimulation and diminished increase in intestinal permeability due to radiochemotherapy.

- Glutamine increases glutathione in normal cells and reduces glutathione in cancer cells.

Nausea and Vomiting

- During chemotherapy the liver becomes overburdened with the job of detox. **The use of herbal and nutraceutical supplements which support normal liver function are discouraged when chemotherapy is being administered but may be taken in between chemotherapy cycles.**

Nausea and vomiting cont'd

- Ginger root tea is a traditional remedy for enhancing normal digestive function and normal inflammatory function and may be taken daily.
- Make sure you are hydrated properly.
- Try not drinking with meals
- Avoid spicy foods
- Avoid hard to digest foods
- Avoid raw foods

Acupressure

- This technique has helped some with nausea.
- Acupressure puts pressure on one part of the body to bring about change elsewhere in the body.
- It’s similar to the ancient Chinese method of acupuncture.
- To try to quell nausea this way, use your middle and index fingers to press down on the groove between the two large tendons on the inside of her wrist that start at the palm of her hand

CoQ10 – A coenzyme for the mitochondria

- Another area in which antioxidants may play a critical role is in preventing the toxicity of anthracyclines, in particular doxorubicin (Adriamycin). This class of drugs has a major health-impairing as well as dose-limiting effect: it can lead to irreversible damage to the heart muscle. This phenomenon was described more than 3 decades ago.

- Anthracycline-induced cardiotoxicity is easily preventable. Both preclinical and clinical studies suggest that the antioxidant CoQ10 administered before, during, and after anthracycline chemotherapy can largely prevent the heart damage for which that drug is notorious (K. Conklin, personal communication, September 27, 2005).

Vitamin C – From the same Ralph Moss article

- Oral vitamin C does not reach the same high plasma concentrations as IV.

- IV vitamin C in higher doses

  - "Only intravenous administration of vitamin C produces high plasma and urine concentrations that might have anti-tumor activity. Because efficacy of vitamin C treatment cannot be judged from clinical trials that use only oral dosing, the role of vitamin C in cancer treatment should be reevaluated."

List of clinical studies conducted using nutraceuticals and dietary antioxidants in patients suffering from chemotherapy induced peripheral neuropathy

Model used	Treatment schedule	Parameters evaluated	Results observed
Paclitaxel/ cisplatin induced neuropathy in patients	N-acetyl carnitine oral (1 g t.i.d for 8 consecutive weeks)	Neurological examination, total neuropathic score (TNS) and quantitative sensory testing were measured.	Improvement in TNS, sensory symptoms and neurophysiology were observed in N-acetyl carnitine treated patients.
Cisplatin/ docetaxel induced neuropathy in patients	α-lipoic acid 600 mg i.v. once a week for 3–5 weeks followed by 1800 mg td p.o upto 6 months	Neurological examinations and WHO toxicity score assessment were evaluated	Improvement in neurological symptoms after treatment with α-lipoic acid.
Cisplatin induced neurotoxicity in women.	Glutathione (3 mg/m^2) i.v every 3 weeks for six courses.	A questionnaire on the subjective symptoms of peripheral neuropathy and quality of life was assessed.	Decreased incidence of CINP in glutathione treated arm.
Oxaliplatin induced neuropathy in patients	GSH (1500 mg/m^2 over a 15-min infusion period before oxaliplatin)	Electrophysiological parameters and assessment of neurological symptoms	Increased sural sensory nerve conduction velocity observed in GSH treated patients
Paclitaxel/ docetaxel induced neuropathy in patients	Melatonin 21 mg daily at bedtime	Neurological examinations, toxicity assessment as per NCI-CTC 3.0 scale and FACT-Taxane quality of life questionnaire were evaluated.	FACT-Taxane quality of life end of study score was 137. Reduced incidence of neuropathy was observed in melatonin treated patients.
Oxaliplatin induced neuropathy in patients	Oral N-acetyl cysteine (1200 mg) (arm A) or placebo (arm B).	Electrophysiological parameters and assessment of neurological symptoms.	Improved NCV (nerve conduction velocity), CMAP (compound muscle action potential) and decreased SAP (sensory amplitude potential) were observed after N-acetyl cysteine treatment.
Paclitaxel induced peripheral neuropathy in patients	ω-3 fatty acids 640 mg t.i.d orally/placebo	Electrophysiological parameters and assessment of neurological symptoms.	Reduced total sensory neuropathy score, improved NCV after treatment with ω-3 fatty acids.
Oxaliplatin induced neuropathy in patients	Glutamine (15 g twice a day orally for seven consecutive days every 2 weeks starting on the day of oxaliplatin infusion)	Electrophysiological parameters and neurological symptoms were assessed	Lower percentage of grade 1–2 peripheral neuropathy after 2 cycles and lower incidence of grade 3, 4 neuropathy after 4–6 cycles of glutamine administration was observed.
Taxanes, platinum compounds and combination drug induced neuropathy in patients.	Twice daily dosing of vitamin E (400 mg)/ placebo.	The outcome was evaluated using the common terminology criteria for adverse events (CTCAE v 3.0) and A questionnaire on the subjective symptoms of peripheral neuropathy.	Significant difference in the incidence of sensory neuropathy between the two arms was not observed.
			Vitamin E did not appear to reduce the incidence of sensory neuropathy.
Cisplatin induced neurotoxicity in patients	vitamin E (300/day mg/placebo)	The outcome was evaluated by measuring total neuropathic score (TNS) and quantitative sensory testing	Vitamin E reduced the incidence of sensory neuropathy

Vitamin E

- The platinum-based drug cisplatin causes peripheral neuropathy in 15% to 20% of patients. Certain nutrients may offer a protective effect. An RCT was conducted to measure the neuroprotective effect of vitamin E in patients who were being treated with platinum-based chemotherapy (cisplatin)
- The incidence and severity of peripheral nerve damage was significantly lower in the vitamin E treated group (30.7%) than in the cisplatin group (85.7%). The authors concluded that "supplementation of patients receiving cisplatin chemotherapy with vitamin E decreases the incidence and severity of peripheral neurotoxicity."
- Furthermore, in the clinical work, as well as in preclinical studies, no interference was seen between vitamin E and cisplatin.

Cisplatin

- Depletes Mg, K, Se, VIT E
- Inhibits Mg transport proteins promoting renal Mg wasting.
- Depletes muscle magnesium and potassium before serum.
- 75% incidence of hypomagnesemia, 50% lasts more than 3 years
  - Sensory neuropathy correlates with serum magnesium.
- Depletes circulating vitamin E and other antioxidants that can promote neurotoxicity.
- Selenium in serum decreases progressively with each treatment

Cisplatin- protective supplements (Dr. Galland)

- Bismuth 150 mg/kg/day X 10 days
- Ginkgo biloba 100 mg/kg single dose
- Glutathione 5 gm i.v. prior to infusion
- MgSO4 3 gm i.v./ Mg 160 mg tid
- N-acetyl cysteine 8 gm/day
- Selenium 4000 mcg/day X 8 days
- Vitamin C 50-200 mg/kg i.v. single dose
- Vitamin E 300 IU/day till 3 months post

Cisplatin and the Problem of Ototoxicity

- One major problem with certain anticancer drugs is their potential to cause nerve damage even in the ear.
- The platinum-containing drugs, such as cisplatin, are particularly liable to produce peripheral neuropathy, one form of which, ototoxicity, or damage to the auditory nerve, can result in auditory changes that range in severity from annoying tinnitus to profound, irreversible hearing loss.
- While recognizing the theoretical concern of the use of thiol antioxidants, the preponderance of clinical data does support the concurrent use of glutathione with platinum-containing drugs.

Magnesium and cisplatin

- Diminishes toxicity.
- Combined oral and i.v. Mg reduced nephrotoxicity in patients with testicular cancer.
- Prophylactic Mg is more effective than attempted correction of a deficit.
- Mg does not interfere with efficacy

Melatonin

- In 2003, Lissoni and colleagues looked at 5-year survival rates from metastatic NSCLC. One hundred patients received the standard drugs cisplatin and etoposide, with or without the concomitant administration of melatonin (20 mg/d orally in the evening).
- According to the authors, “Both the overall tumor regression rate and the 5-year survival results were significantly higher in patients concomitantly treated with melatonin.”
- In particular, no patient treated with chemotherapy alone was alive after 2 years, whereas a 5-year survival was achieved in 3 of 49 (6%) patients treated with chemotherapy and melatonin.

Melatonin

- Melatonin (20 mg at bedtime) improved survival and reduced side effects of patients with non-small cell lung cancer being treated with cisplatin and etoposide, with doubling of one-year survival and reduction of myelosuppression, neuropathy and cachexia.

- Appeared to enhance effectiveness of low-dose irinotecan in patients with colorectal cancer.

Melatonin and tamoxifen

- Melatonin, 20 mg/day at bedtime with tamoxifen 20 mg/day at noon, improved clinical status in 28% of patients with metastatic breast cancer unresponsive to tamoxifen alone.

- Melatonin augments sensitivity of breast cancer cells to tamoxifen in tissue culture

- Melatonin interferes with activation of the estrogen receptor by estradiol and also inhibits aromatase

GLA (Evening Primrose or Borage oil) plus Tamoxifen

- GLA (2800 mg/d) speeded the response to tamoxifen (20 mg/d) as primary treatment for postmenopausal breast ca.

- GLA down-regulates estrogen receptor expression in human breast cancer xenografts in mice and in tissue culture.

Glutathione

- In one study, 151 patients received cisplatin for ovarian cancer.
- 58% of patients who also received glutathione were able to complete the full 6 courses of cisplatin compared to just 39% in the control group.
- The patients' quality of life was also improved.
  - The authors wrote, "There was a statistically significant improvement in depression, emesis, peripheral neurotoxicity, hair loss, shortness of breath and difficulty concentrating."
- Despite their fears glutathione did not result in either a reduced number of responses or diminished survival. There were better outcomes in the glutathione-added group (73% vs 62%, not statistically significant). The authors concluded that adding glutathione to cisplatin allowed more cycles of treatment to be administered "because less toxicity is observed and the patient's quality of life is improved.

From Ralph Moss PhD. on Anti-oxidants in Chemo & Radiation (Cancer Journal for Clinicians 2005)

Concerns About Antioxidant-Chemotherapy Interactions

The *CA* article offers 3 specific types of evidence to establish the alleged danger of the concurrent usage of antioxidants and cytotoxic treatments:

- Theoretical concerns, based primarily on in vitro studies
- A selective group of clinical trials demonstrating the interaction of antioxidants with radiotherapy or chemotherapy, and
- Studies critical antioxidant use in general but not specifically addressing the issue of concurrent use.

Glutathione cont'd

- Yet the *CA* Journal article does not discuss the issue of cisplatin toxicity, including its notorious ototoxicity, nor does it mention the simple solution of giving patients undergoing cisplatin treatment supplemental glutathione, which has now been shown in a number of randomized trials to be an effective technique.

Vaginal dryness

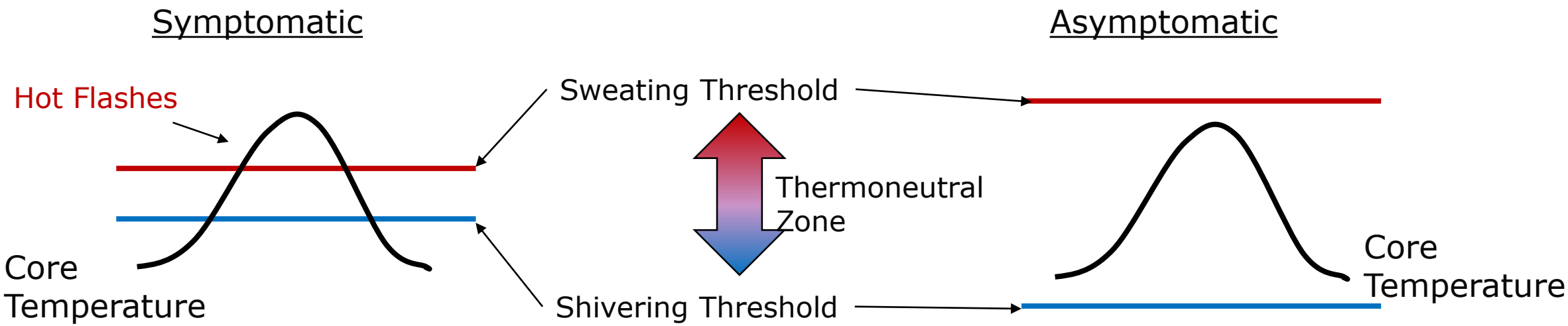
- Coconut oil or any dense oil will help
  - Organic is not expensive
- DHEA vaginal suppositories – may help but very limited study
- Estriol vaginal cream – Still estrogenic with few studies especially in breast cancer. At .25mg twice weekly little change was seen in serum estrogen levels
- Gynecol Endocrinol. 2010 Jun;26(6):404-12. doi: 10.3109/09513591003632258
- Hyaluronic acid with vitamins E, A, and aloe vaginal cream – Compounded by me.

Vasomotor symptoms

- Typically treated with antidepressants
- Recommended options for women with concerns or contraindications relating to estrogen-containing treatments include prescription progestogens, venlafaxine, paroxetine, fluoxetine, or gabapentin.
  - From a preliminary study by NAMS
- Relizen – a new product worth considering
  - A purified pollen extract

The Pathophysiology of Vasomotor Symptoms

The "Sweating Threshold"



- Appearance of hot flashes coincides with estrogen withdrawal, but estrogen levels do not differ between symptomatic and asymptomatic women[1]
- Hot flashes are triggered by small elevations in core body temperature acting within a reduced thermoneutral zone in symptomatic menopausal women[1]
- Elevated central noradrenergic activation narrows the thermoneutral zone; an acute increase in brain noradrenergic activation is associated with the onset of hot flashes[2]

1. Archer et. Al. "Menopausal hot flushes and night sweats: Where are we now?" Climacteric 2011; 14: 515-528.
2. Freedman RR. "Pathophysiology and treatment of menopausal hot flashes." Seminars in Reproductive Medicine 2005; 23(2): 117-25.

Treatment Landscape for Vasomotor Symptoms

Current Treatment Landscape

A variety of treatment options exist, but a treatment gap remains for the patients who cannot take these products or prefer not to

Options	Considerations	Treatment Gap
Hormone Replacement Therapy (HRT)	▪ Highly effective ▪ Controversial since WHI; patients may refuse treatment with HRT ▪ Percent of women aged 50-59 using HT has declined significantly: 38.3% (2000) → 6.7% (2010)[1]	▪ Known, suspected, or history of breast / uterine cancer except in appropriately selected patients ▪ History of stroke or MI ▪ Smokers ▪ High blood pressure
SSRIs	▪ Black box warning for suicidal thoughts ▪ Inconclusive efficacy ▪ Discontinuation can result in withdrawal-like symptoms	▪ May not be appropriate for breast cancer patients (inhibitor of CYP2D6 and blocks tamoxifen conversion to active metabolite, endoxifen)[4]
Phytoestrogens	▪ Inconclusive efficacy[2] ▪ Limited acceptance	▪ May not be appropriate for cancer patients (Work on estrogen pathways)[3]

In 2000, close to 130 million HRT/ERT prescriptions were filled in the U.S., compared to 38 million prescriptions in 2010, suggesting that demand exists **for an alternative[5]**

1.Lobo RA. Where are we 10 years after the Women's Health Initiative?. *J Clin Endocrinol Metab.* 2013;98(5):1771-80.
2.Newton KM. "The Herbal Alternatives for Menopause (HALT) Study," *Maturitas*, 2005 Oct.
3.Espie M. "How can hot flashes be managed effectively and without risk?" *Cancers Au Feminin* 2013.
4.Orleans RJ, Li L, Kim MJ, et al. FDA Approval of Paroxetine for Menopausal Hot Flushes. *N Engl J Med* 2014; 370:1777-1779
5.IMS Data, 2000 – 2010.

How do we know that Relizen is non-estrogenic?

Non-Estrogenic Mechanism of Action

- An *in vivo* examination of the uterotropic effect of Relizen's active ingredient in immature female rats did not show any estrogenic effect
- Relizen's active ingredient demonstrated no increase in uterine weight in immature female rats after repeated oral administrations, even at doses as high as 100 times the normal daily dose

Relizen has no estrogen-mediated effect

Hellström, A.C., and J. Muntzing. "The pollen extract [Relizen] – a nonestrogenic alternative to hormone therapy in women with menopausal symptoms." *Menopause* 2012; 19(7): 825-829.

What do we know about Relizen's impact on breast cancer cells?

No Stimulation of Breast Cancer Cells

- An E-Screen *in vitro* test was performed using MCF-7 cells, an immortalized human breast carcinoma cell line that endogenously expresses estrogen receptors
- In comparison to 17-beta estradiol, Relizen did not stimulate the proliferation of MCF-7 breast tumor cells

Relizen does not stimulate proliferation of MCF-7 breast cancer cells

Munoz, E. *Effect of a PE-F/A on estrogenic activity*. VivaCell Biotechnology GmbH. Internal report. July 2012.

Does Relizen impact the metabolism of tamoxifen?

No Inhibition of Tamoxifen Metabolism

- An *in vitro* study analyzed inhibition of the CYP2D6 system in human liver microsomes using high daily doses of Relizen's active ingredient
- Relizen showed little to no inhibition of the CYP2D6 system, even up to a concentration of 5 times the suggested daily dose

Relizen does not inhibit tamoxifen's metabolic pathway in CYP2D6 human pooled liver microsomes

Goldstein SR, Espié M, Druckmann R. Does Relizen, a non-hormonal treatment for vasomotor symptoms, inhibit the CYP2D6 Enzyme System? *Menopause.* 2014; 21(12): 1320-1369.

Why do they say "No Herbs"?

- As much as we know about herbs is as much as we don't know.
- During therapy these herbs can change blood levels of your chemotherapy either up or down.
  - Many induce liver enzymes and through similar pathways that the chemotherapy uses to both function and to be eliminated
  - It is well known that the cytochrome (CYP) P450 enzyme system is involved in drug metabolism of many medications used in clinical practice and have been implicated in the causing clinically relevant drug-drug interactions.[1,2] There are a number of CYP450 enzymes involved in mediating drug interactions and commonly include CYP1A2, 2C9, 2C19, 2D6, and 3A4.[1] Of these CYP enzymes, CYP3A4 is not only the most prevalent CYP enzyme in the liver, but is used by more than 50% of medications on the market for their metabolism and elimination from the body.

HERBS AND INTERACTIONS

Medicinal Plant and parts used	Scientific name	Major constituents	Mechanism of drug interactions	Candidates for interactions	LE	Reference
Cranberry (fruit extract)	*Vaccinium macrocarpon*	Anthocyanins, flavonoids	Inhibition of CYP enzymes and P-gp	Warfarin, CYP1A2, 2C9, and 3A4 substrates	4	Li et al. (2009), Kim et al. (2010b), Roberts and Flanagan (2011), Hamann et al. (2011)
Dong quai (root)	*Angelica sinensis*	Flavonoids, coumarins	Inhibition of CYP1A2, 3A4, and P-gp	CYP substrates	3	Scott and Elmer (2002), Tang et al. (2006), Sevior et al. (2010)
Gan cao (root)	*Glycyrrhiza uralensis*	Glycyrrhizin	CYP2C9 and 3A4 induction	Warfarin, Lidocaine, CYP2C9, and 3A4 substrates	2	Mu et al. (2006), Tang et al. (2009)
Garlic (bulb)	*Allium sativum*	Allicin, phytoncide	CYP 3A4 and P-gp induction	Saquinavir, warfarin, CYP2D6, and 3A4 substrates	4	Markowitz et al. (2003a), Cox et al. (2006), Berginc and Kristl (2012)
Germander (leaves)	*Teucrium chamaedrys*	Saponins, flavonoids, diterpenoids	Production of toxic CYP3A4-induced metabolites	CYP3A4 inducers like Phenobarbital, rifampicin	3	De Berardinis et al. (2000), Savvidou et al. (2007)
Ginseng (root)	*Panax ginseng*	Ginsenosides	Inhibition and induction of CYP2C9, 2C19, 2D6, and 3A4 activity	Imatinib, CYP2E1, and 2D6 substrates	4	Gurley et al. (2005a), Bilgi et al. (2010), Malati et al. (2011)
Grape seed (seed oil)	*Vitis vinifera*	Proanthocyanidin, resveratrol	Decreased CYP2C19, 2D6, and 3A4 activity	CYP2C19, 2D6, and 3A4 substrates	4	Nishikawa et al. (2004)
Kava kava (root)	*Piper methysticum*	Kavalactones	Decreased CYP1A2, 2D6, 2E1, and 3A4 activity	CYP substrates	4	Gurley et al. (2005b), Teschke (2010), Sarris et al. (2011)
Liquorice (root)	*Glycyrrhiza glabra*	Inhalant	Inhibition of CYP2B6, 2C9 and 3A4	CYP2B6, 2C9 and 3A4 substrates	4	Kent et al. (2002), Al-Deeb et al. (2010), Methlie et al. (2011)
St John's wort (aerial parts)	*Hypericum perforatum*	Hyperforin, hypericin, flavonoids	Inhibition and induction of CYP and P-gp	Orally administered CYP substrates	4	Hu et al. (2005), Hafner et al. (2009), Lau et al. (2011)

LE, level of evidence.

NATURAL MEDICINES – INHIBITORS OF CYP3A4 ©2009 Pharmacology Weekly		
Common Name	**Ingredient or Plant Name**	**Type of Inhibition**
Bidara laut	*Strychnos ligustrina*	Mechanism-based inhibitor of CYP3A4
Black Cohosh	*Cimicifuga racemosa*	Inhibition of CYP3A4 enzyme
Cat's claw	*Uncaria tomentosa*	Inhibition of CYP3A4 enzyme
Chamomile	*Matricaria chamomilla*	Inhibition of CYP3A4 enzyme
Cubeb Berry extract	*Piper cubeba*	Appears to be the methylenedioxyphenyl lignan compounds found in extract; mechanism-based inhibition of CYP3A4
Echinacea (aka., Black sampson Coneflower)	*Echinacea angustifolia*	Not known
Evodia fruit extract	*Evodiae Fructus*	Appears to be the rutaecarpine and limonin compounds
Goldenseal	*Hydrastis canadensis*	Inhibition of CYP3A4 enzyme
Grapefruit juice	*Citrus paradisii*	Appears to be from furanocoumarin compounds
Kabab chini	*Piper cubeba*	Appears to be the methylenedioxyphenyl lignan compounds found in extract; mechanism-based inhibition of CYP3A4
Kayu manis	*Cinnamomum burmani*	Mechanism-based inhibitor of CYP3A4
Licorice	*Glycyrrhiza glabra*	Inhibition of CYP3A4 enzyme
Neem	*Azadirachta indica*	
Puyang tincture	*Zingiber aromaticum*	Appears to be the kaempferol glycosides and kaempferol derivatives found in tincture. Appears to be mechanism-based inhibition of CYP3A4
Red Wine	Resveratrol	Mechanism-based inhibitor of CYP3A4
Saunf	*Foeniculum vulgare*	Mechanism-based inhibitor of CY3A4
Schisandra fruit extract	*Schisandra chinensis*	Thought to be from Gomicin C
White pepper	*Piper nigrum*	Mechanism-based inhibitor of CY3A4
Wild cherry	*Trifolium pratense*	Not known

"Chemo Brain"

- Consequences of chemobrain upon quality and quantity of life.

  - Depression
  - Concentration difficulties
  - Problem with multi-tasking
  - Memory
  - Moodiness
  - Fatigue
  - Brain-fog-awareness
  - Sleep difficulties

- "…they (the studies) consistently suggest that between approximately 15% and 25% of chemotherapy-treated breast cancer patients will have evidence of cognitive dysfunction some years after chemotherapy, compared to about 10% of breast cancer survivors who did not receive chemotherapy…"

- Clin Breast Cancer. 2002 Dec;3 Suppl 3:S116-20.
  Effects of epoetin alfa on cognitive function, mood, asthenia, and quality of life in women with breast cancer undergoing adjuvant chemotherapy.
  O'Shaughnessy JA. Baylor Sammons Cancer Center, US Oncology, Dallas, Texas 75246, USA. Joyce.O'Shaughnessy@USOncology.com

Advanced brain imaging techniques

- Directly or indirectly assess many of these mechanisms
  - Very limited application of these tools in studies
  - Morphometric magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), and MR spectroscopy (MRS) are noninvasive techniques that could yield important complementary data regarding the nature of neural changes after chemotherapy
  - Electrophysiological studies and targeted molecular imaging with positron emission tomography (PET) could also provide unique information.

Biochemical testing can reveal nutritional abnormalities

- Malonyldialdehyde – dozens of antioxidants
- Glutathione reductase – selenium, glutathione, etc.
- Ascorbic acid/dehydroascorbit acid levels – vitamin C
- Homocysteine/methylmalonic acid: B6, B12, folic acid
- C-reactive protein – vitamin E, etc.
- Vitamin D (25-D3 and 1, 25 D3) – Vitamin D analogues
- Essential fatty acids – omega 3, and omega 6
- Phosphotidylcholine, phosphotidylserine – choline, serine, lecithin, etc.
- Neurotransmitter imbalances – glycine, GABA, tryptophane, etc.
- B-vitamins – B1, B2, B3, B5, B6, biotin, folic acid, B12, etc.
- Selenium
- Magnesium
- Zinc
- Autonomic nervous system dysfunction

Other testing

- Detoxification assays
- Hormonal assays
- Antioxidant assays
- Vitamin assays
- Mineral assays
- Neuro-degenerative markers
  - CRP
  - Homocysteine
  - Fibrinogen
  - Others

Brain Protecting

- Omega 3 fatty acids
- L-carnitine
- B-vitamins
- Antioxidants
- Bio-identical Hormones
  - Testosterone
  - Growth hormone
  - Other hormones

Drug-Induced Nutrient Depletion

- Almost half the drugs used in clinical practice have documented nutrient depleting effects.
- Co-enzyme Q10, folic acid, B2, B6, Mg, Zn are nutrients most likely to be depleted.
- Mechanisms include impaired absorption or bioactivation; increased excretion, nausea, anorexia or diarrhea (common side effects of cancer therapies).

Anthracyclines

- Available agents include:

- Daunorubicin (Daunomycin)
- Daunorubicin (liposomal)
- Doxorubicin (Adriamycin)
- Doxorubicin (liposomal)
- Epirubicin
- Idarubicin
- Valrubicin, used only to treat bladder cancer
- Mitoxantrone, anthracycline analog

Anthracyclines Plus L-theanine (5-N-ethyl glutamine)

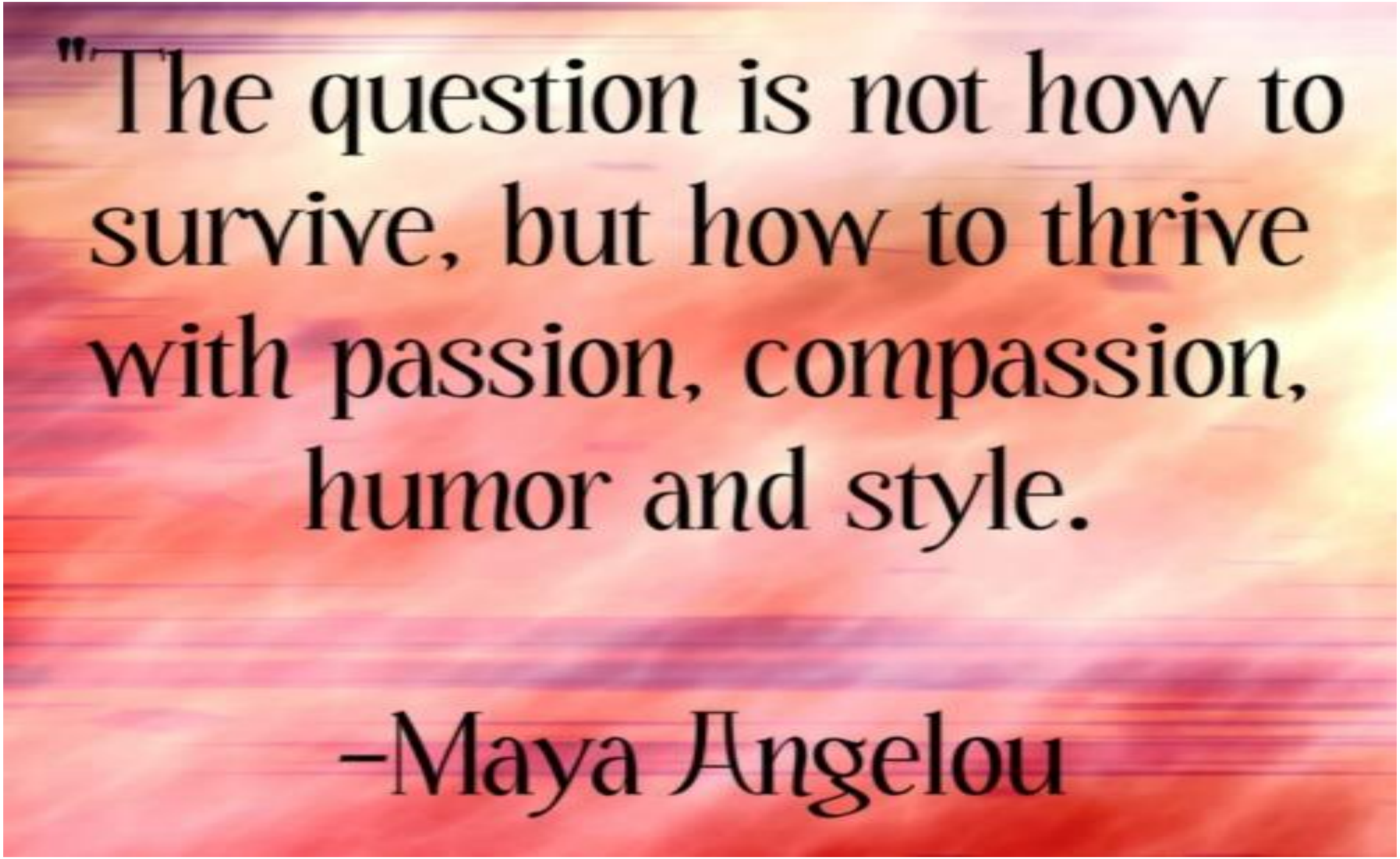
- Rodents: L-Theanine, a unique amino acid found in green tea, enhances the efficacy and decreases toxicity of doxorubicin and idarubicin.
- Theanine inhibits glutamate-mediated doxorubicin efflux, only in cancer cells.
- In normal cells, theanine increases intracellular glutamate and glutathione levels and does not increase doxorubicin concentration.

Anthracyclines plus DHA

- Rats: DHA from algae increases the sensitivity of mammary tumors to epirubicin (and to radiotherapy).
- DHA pretreatment decreases tumor vascularity.
- Effects of DHA are reversed by vitamin E in a dose-dependent fashion.

Conclusions

- Antioxidants and other supplements can reduce side effects
- They can increase effectiveness of chemotherapy and radiotherapy.
- Which supplements to use is dependent on what chemotherapy is being given
- Successful use is dose dependent
- This is a very complicated subject
- **Careful guidance is required and the improper use can REDUCE effectiveness of therapy**


"The question is not how to survive, but how to thrive with passion, compassion, humor and style.
-Maya Angelou