The Rational Use of Nutritional Supplements/ Nutraceuticals for Cancer Supportive Care

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Why Nutraceuticals?

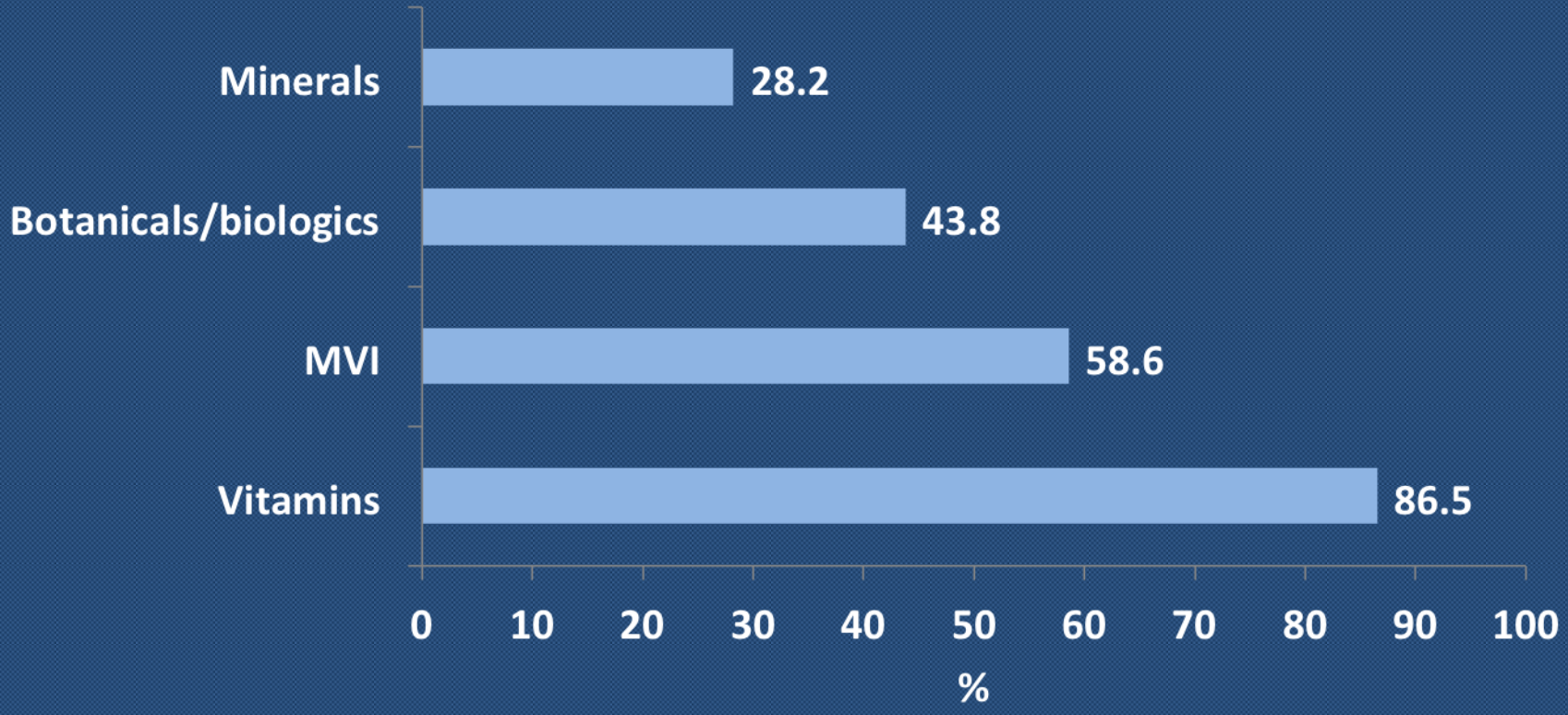
- Patients with cancer desire to be active participants in their care
- Patients with cancer want to:
  - Combat the cancer
  - Manage cancer symptoms
  - Cope with cancer treatment side effects
- Patients with cancer have access to OTC vitamins, minerals, and herbal supplements

Patient with Too Many Bags

- Asked by oncologist to see patient
- Being treated for early stage E+ breast cancer on Tamoxifen
- Recent increase in LFT's (2-3x's ULN)- concerned that Tamoxifen may be cause
- Patient admitted on direct questioning to taking some dietary supplements
- Arrived at our meeting with 3 shopping bags full

Unsupervised Use of Nutritional Supplements by Patients With Cancer

237 of 820 patients (29.1%) receiving chemotherapy or radiation therapy use nutritional supplements NOT prescribed by their physician



MVI, multivitamin.

Kumar NB, et al. *Cancer Control.* 2002;9:236-243.

Safety of Herbal Products

If what is on the label of an herbal medicine is what is in the container, “toxicity” is rarely encountered.

Norman R. Farnsworth, Ph.D. (1999)

Launch Products

Product	Positioning
CogniQOL	Improvement of cognitive function; Lymphedema
DaxibeQOL	Cachexia, Sarcopenia
FemQOL	Hormone suppression induced night sweats
FolaQOL	Anti-folate induced toxicity
InflaQOL	Anti-inflammatory
LymphaQOL	Breast cancer-associated upper extremity lymphedema
MucosaQOL	Stomatitis, lower GI toxicity Taxane induced neuropathy
MyoQOL	Anthracycline induced cardiotoxicity; Fatigue
NeuroQOL	Chemo induced neurotoxicity; Fatigue
NutraQOL	Immune-balancing, physical and mental well being; Febrile Neutropenia
RadoQOL	Post radiation cerebral edema

Launch Products

Product	Positioning
ProbioQOL	Correction of imbalance in intestinal flora in cancer patients due to antibiotics and chemo; Diarrhea
ErythroQOL	Cancer associated anemia
VitaQOL	Cancer associated vitamin and mineral deficiency or support

Breast Cancer: Case One

- 45 y/o pre-menopausal female has recently intentionally lost 15# and palpated a mass in LUQ of her breast
- Tumor characteristics imaging & biopsy
  - E 3+ P2+ Hr2-
  - 1.5 cm MBR 7/9
  - Questionable peri-neural invasion
- Lumpectomy w/ SN biopsy
  - 1/3 nodes +
  - Surgical specimen similar to biopsy

Breast Cancer: Case One

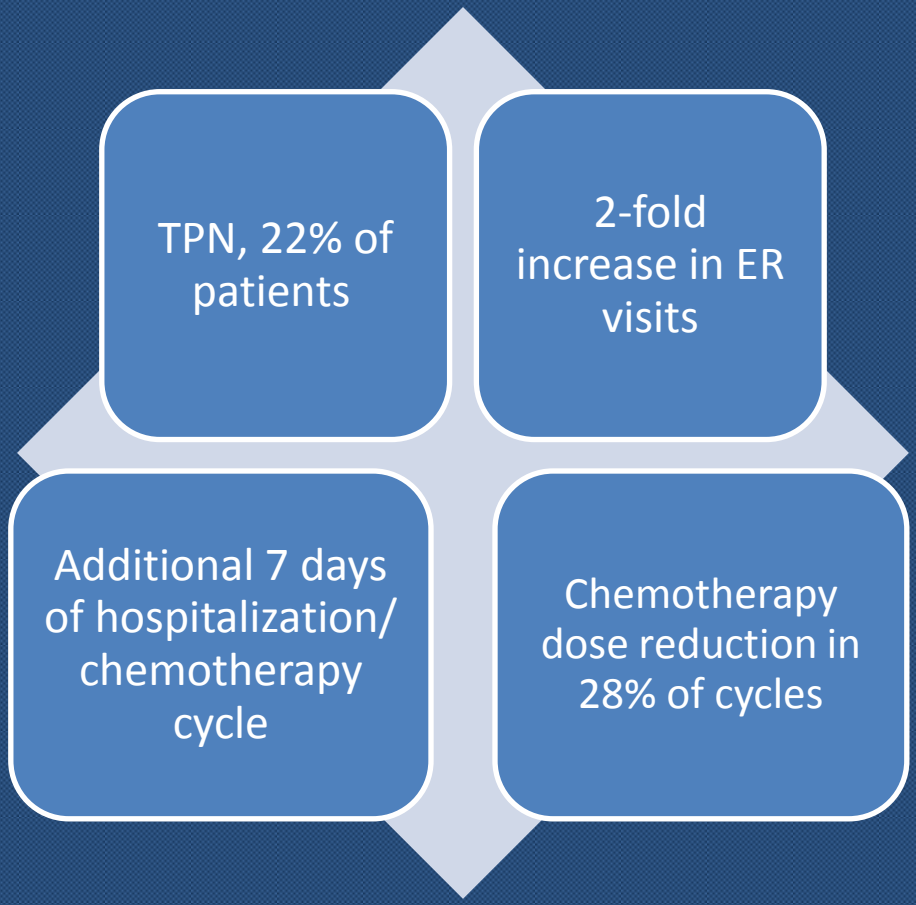
- PE: unremarkable except for
  - BP 145/80
  - Ht Wt BMI 28
  - Well healing scars in left breast and axilla
- Social Hx: Married, Teaches music (violin)

Chemotherapy selected Taxotere Cytoxan in the usual doses followed by 5 years tamoxifen

What side effects do you anticipate for this patient during chemo and with tamoxifen ?

Mucositis/Stomatitis: Burden of Disease

Grade 3 or 4 oral mucositis in patients with solid tumors associated with increased healthcare costs and dose reductions

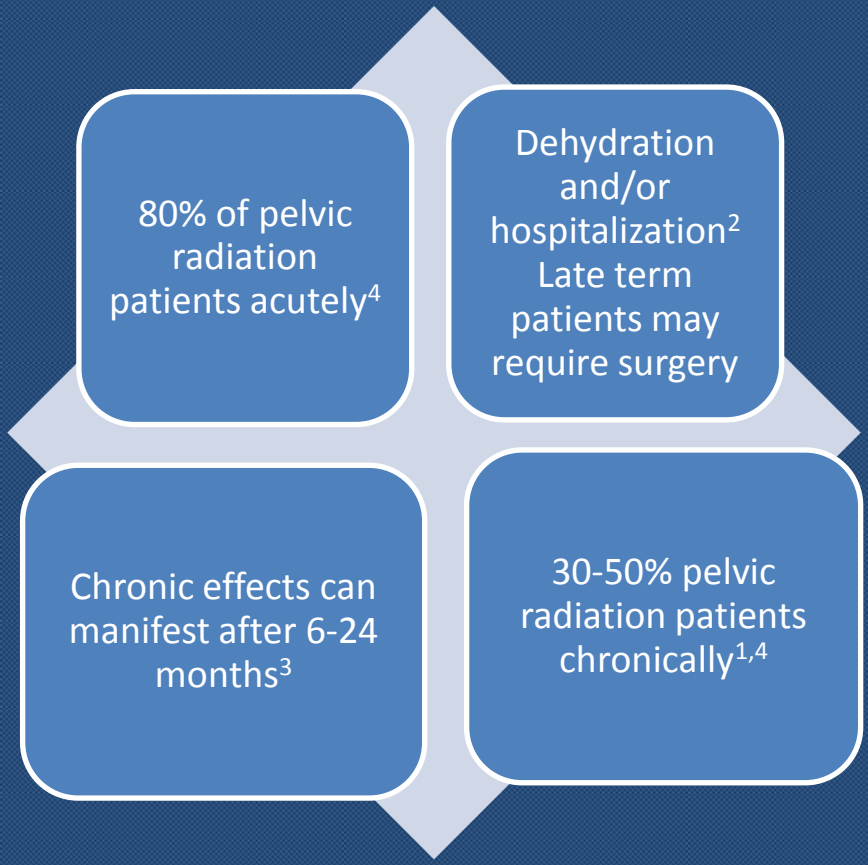


TPN, total parenteral nutrition.

NCCN Task Force Report. *JNCCN*. 2008;6(suppl 1):S1–S21.

Radiation-Induced Diarrhea: Burden of Disease

Radiation induced bowel injury causes diarrhea acutely and late effects may cause severe impacts on QOL.



1. Andreyev HJ, et al. *Int J Radiat Oncol Biol Phys*. 2005;62:1464–1471.
2. Kozelsky TF, et al. *J Clin Oncol*. 2003;21:1669-1674.
3. Vasudeva R, et al. Medscape. http://emedicine.medscape.com/article/180084-overview. Accessed March 13, 2012.
4. Abayomi J, et al. *European J Oncol Nurs.* 2009; 13(4):262-7

Modulation of Intestinal Function by Dietary Factors.

GLUTAMINE

-Preferred fuel for eneterocytes
-Precursor GSH
-Modulate Heat Shock Protein response
-Regulate apoptosis/ proliferation signaling
-Modulating intestinal & systemic immunity

OMEGA 3 FATTY ACIDS

-Attenuate inflammatory injury
-Modulate intestinal immunity
-Modify lymphocyte number
-Improve gut barrier function
-Modulate gut microbiota

DECREASING INJURY

PRO/PRE-BIOTICS

-Reverse micorbiota disruption
-Modulate intestinal immune system
-Enhance production of SCFA
-Enhance production of intestinotrophic hormones
-Boost gut barrier function
-Modulate drug metabolism via modification key bacteria

Xue H et al. JPEN J Parenter Enteral Nutr 2011;35:74-90

Glutamine Effect on Oral Mucositis

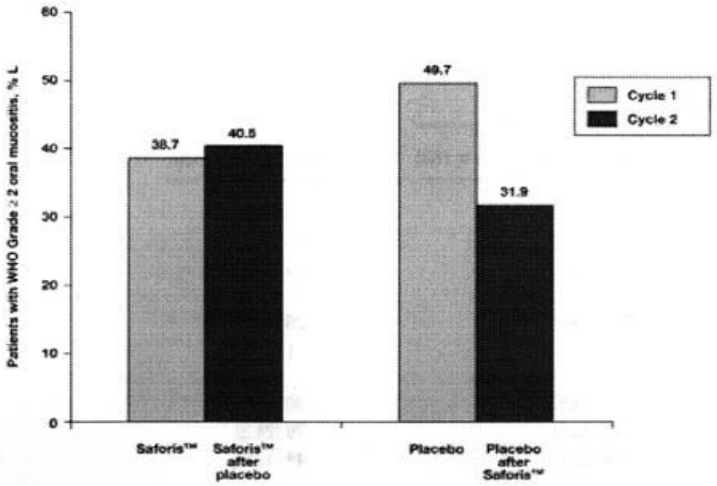


FIGURE 3. Percentage of patients responding to treatment with Saforis versus placebo in Treatment Cycles 1 and 2.

TABLE 3
Maximum Severity of Oral Mucositis by Treatment Group in Treatment Cycle 1

Maximum WHO grade	Patients, n (%) Saforis (n = 163)	Placebo (n = 163)	P
0	52 (31.9)	50 (30.7)	.042*
1	48 (29.4)	32 (19.6)	
2	61 (37.4)	70 (42.9)	
3	2 (1.2)	11 (6.7)	.005†

WHO indicates World Health Organization.
* Overall shift in the distribution of maximum oral mucositis grade using the Wilcoxon rank-sum test, adjusted for center.
† Cochran-Mantel-Haenszel test, adjusted for center.

TABLE 4
Oral Mucositis Assessment Scale

	Treatment Cycle 1 Intervention Saforis (n = 163)	Placebo (n = 163)	P
Oral mucositis score, mean (SD)	0.22 (0.29)	0.26 (0.34)	.200
Worst ulceration score, mean (SD)	0.23 (0.39)	0.32 (0.45)	.013*
Ulceration score >0, n (%)	63 (38.7)	81 (49.7)	.025†

SD indicates standard deviation.
* From analysis of variance with terms for center and treatment.
† From Cochran-Mantel-Haenszel test adjusted for center.

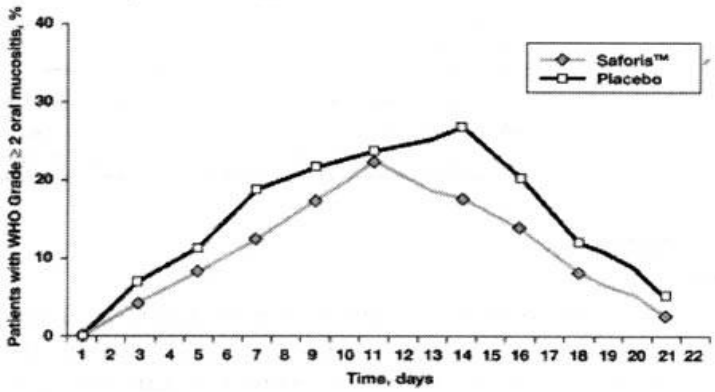


FIGURE 4. Percentage of patients with World Health Organization (WHO) grade ≥2 oral mucositis at each time point during Treatment Cycle 1 by treatment group.

with the placebo group (97.5% vs 91.9%; $P = .039$). No treatment differences were observed with respect to

Peterson DE et al. Cancer 2007; 109:322-31.

Glutamine & Chemotherapy Diarrhea

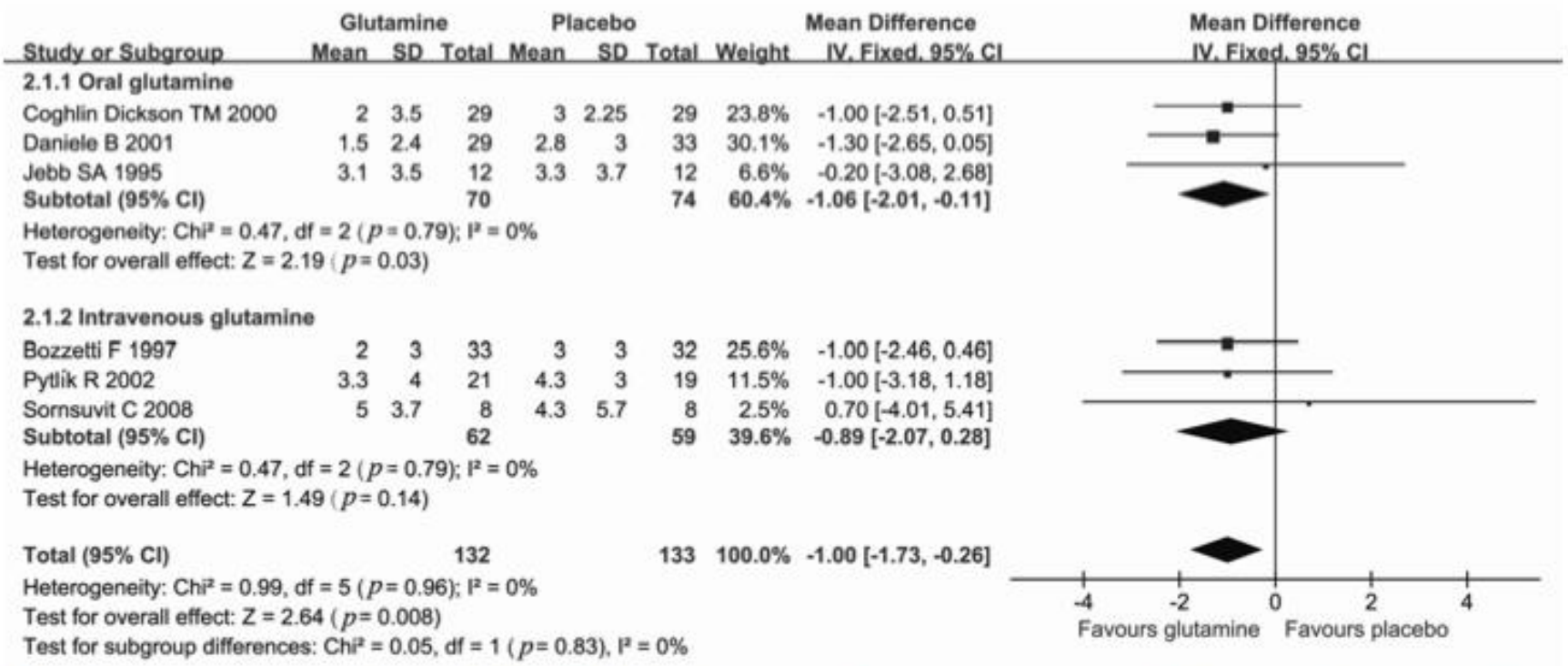


Figure 1. Meta-analysis of the duration of diarrhea in randomized controlled trials comparing glutamine and placebo. The results revealed a benefit of glutamine in reducing the duration of diarrhea, particularly in the oral glutamine subgroup. CI, confidence interval. Chi^2, Chi-square.

Sun J et al. Asia Pac J Clin Nutr 2012; 21(3):380-5.

Support for Mucositis & Enteritis

- Glutamine 20 gm/day 1-7 chemotherapy cycle
- Fish oil containing 750-1200 mg EPA + DHA
  - Hold for platelets less than 75,000
  - Caution using with anti-platelet or anticoagulant drugs
- Probitoics 1 or 2 doses per day
- Include prebiotic & probiotic foods in diet

Black Cohosh Extract

For Management of Hot Flashes, Sweating, Other Symptoms Related to Hormonal Suppression

Black Cohosh & Breast Cancer: Safety & Efficacy

- 136 breast cancer pts after surgery, radiation & adjuvant chemotherapy (age 35-50); Groups equivalent for tumor stage & therapy
- Open label trial
- Tamoxifen +/- BCE (Klimadynon)20 mg/d
- Asessment: HF number & severity
- Outcome (1 yr):
  - 50% patients free of hot flashes
  - Severe hot flashes (24% BCE vs 74% Us care)
  - No significant ADE occurred in either group

Munoz GH et al. *Maturitas* 2003; 44 Suppl 1: 859-565.

Black Cohosh Laboratory Studies

	Parameter	Week 0 (mean ± SD)	Week 52 (mean ± SD)	Difference (mean ± SD)	*P*
Hormones	17β-estradiol (pg/mL)[a]	19.86 ± 9.38	22.66 ± 50.35	2.81 ± 50.38	Sig.
	FSH (mU/mL)[b]	75.05 ± 27.36	68.86 ± 33.44	−6.19 ± 29.45	Sig.
	LH (mU/mL)[a]	31.79 ± 11.48	29.64 ± 13.26	−2.15 ± 11.85	Sig.
Lipids	Cholesterol total (mg/dL)	202.91 ± 26.41	216.06 ± 36.07	13.15 ± 37.28	Sig.
	HDL (mg/dL)	64.28 ± 12.60	71.38 ± 15.52	7.11 ± 12.65	Sig.
	LDL (mg/dL)	124.14 ± 22.59	132.10 ± 30.25	7.96 ± 31.47	Sig.
	Triglycerides (mg/dL)	110.47 ± 38.75	138.93 ± 85.03	28.46 ± 84.55	Sig.
Clinical chemistry	SGOT (U/L)	21.78 ± 10.37	31.47 ± 11.67	9.69 ± 13.77	Sig.
	SGPT (U/L)	25.21 ± 11.53	28.48 ± 35.22	3.27 ± 35.53	Sig.
	γ-GT (U/L)	26.61 ± 17.47	27.44 ± 31.54	0.83 ± 32.84	NS
	Bilirubin total (mg/dL)	0.51 ± 0.25	0.56 ± 0.29	0.05 ± 0.25	Sig.
	Uric acid (mg/dL)	4.42 ± 1.19	4.42 ± 1.10	0.00 ± 1.12	NS
	Glucose (mg/dL)	98.46 ± 13.42	100.62 ± 27.78	2.16 ± 28.84	NS
Hemostasis	INR	1.01 ± 0.11	0.96 ± 0.26	−0.05 ± 0.27	Sig.

FSH, follicle-stimulating hormone; LH, luteinizing hormone HDL, high-density lipoprotein; LDL, low-density protein; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; γ-GT, gamma-glutamyl transferase; INR, international normalized ratio; Sig., significant; NS, not significant.

[a]Values below the lower limit of quantification were replaced by lower limit of quantification value.

[b]Values above the upper limit of quantification were replaced by upper limit of quantification value.

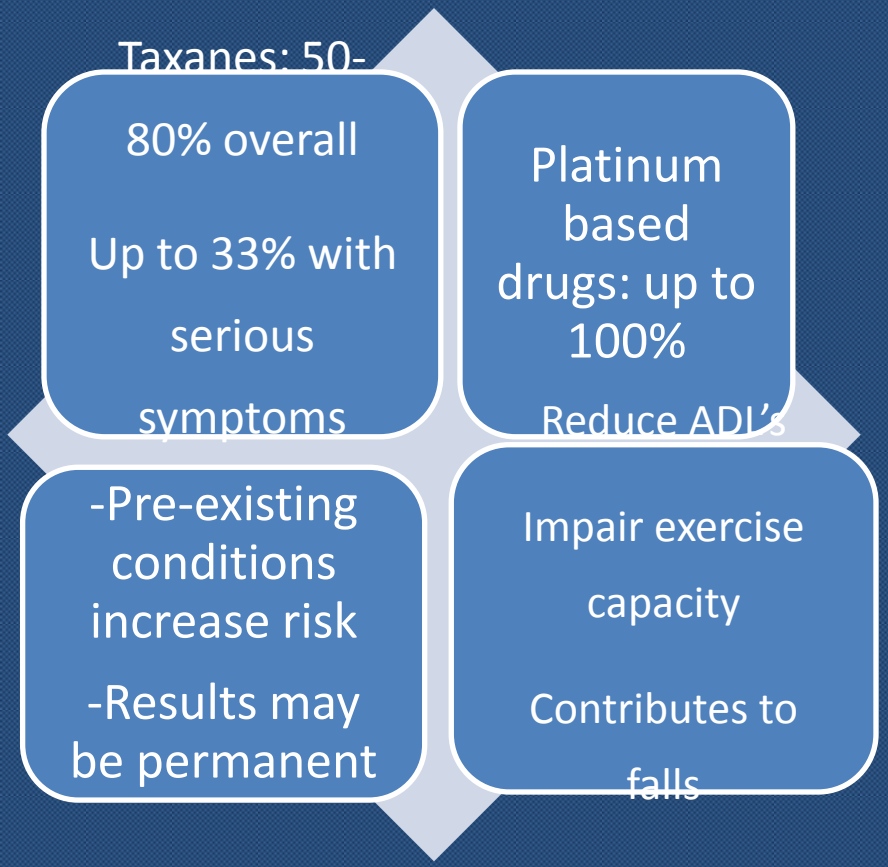
Raus K et al. *Menopause* 2006. 13:678-691.

Breast Cancer Case Two

- How would your dietary supplement recommendations change if the patient in case one was 65 with a history of diabetes and sciatica?
- What would you recommend to reduce the toxicity of her radiation?

Chemotherapy Induced Neuropathy: Burden of Disease

Often results in dose reductions or early discontinuation of therapy



1. Stubblefield MD, et al. J Natl Compr Canc Netw. 2009; 7 (suppl 5): S1-S26. (NCCN Task Force Report)
2. Malil B et a. Current Neurol Neurosci Rep, 2008; 8:56-65.
3. Wolf S et al. European J Cancer, 2008; 44: 1507-1515.

Glutamine: Clinical Study

Adult Oxaliplatin and 5-FU: Beneficial Effects

Study	Patients & Design	Glutamine Dose	Outcomes
Wang et al 2007	Randomized study Metastatic colon or rectal cancer patients in Taipei (N = 86 patients; glutamine=42, control=44) Excluded patients with pre-existing neuropathy or diabetes No calcium or magnesium infusion allowed Primary outcomes: •Prevention or decrease of neuropathy Chemo: Oxaliplatin 85 mg/m^2 days 1 and 15 + folinic acid 20 mg/m^2 and 5-FU 500 mg/m^2 bolus days 1, 8, and 15 every 28 days	15 g BID x 7 days every 2 wks beginning on day of oxaliplatin infusion	Glutamine decreased •Grade 1–2 sensory neuropathy after 2 cycles (16.7% vs 38.6%; *P*=.04) •Grade 1–2 sensory neuropathy (26.2% vs 36.4%) and grade 3–4 (4.8% vs 18.2%; *P*=.05) after 4 cycles •Grade 3–4 sensory neuropathy (11.9% vs 31.8%; *P*=.04) after 6 cycles •Incidence of acute, transient peripheral nerve hyperexcitability (33.3% vs 56.8%; *P*=.03) •Interference with ADL (16.7% vs 40.9%; *P*=.02) •Percentage of patients requiring dose reductions (7.1% vs 27.3%; *P*=.02) Glutamine did not affect treatment response (*P*=.9) or survival time (*P*=.79) No difference in impaired nerve conduction (*P*=.68) Study weakness: not placebo controlled

Toxicity graded using NCI CTCAE v2.0.

ADL, activities of daily living; BID, twice daily; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Wang WS, et al. *Oncologist*. 2007;12:312-319.

Support for Peripheral Neuropathy

- Glutamine 20 gm/ day 1-7 of chemotherapy cycle
  - Can increase to maximum of 30 grams QD
- Acetyl-L-carnitine 500 mg-1 gm TID
- Alpha-lipoic acid 600 mg BID to TID
- B complex (low doses often contained in multivitamins)

Glutamine Safety

- Hepatic encephalopathy & renal insufficiency- limit protein
- Glutamine precursor of glutamate (excitatory neurotransmitter) theoretically contribute mania
- MSG hypersensitivity- theoretical interaction
- Warburg effect- paradoxical response cellular level vs. whole organism

MucosaQOL

Indications: Mucositis, Neuropathy, Enteritis

L-Glutamine

5-gram stick-packs, peach flavor

Recommended Use: ***1-2 stick-packs in water TID***– swish and swallow

4-7 days during chemotherapy

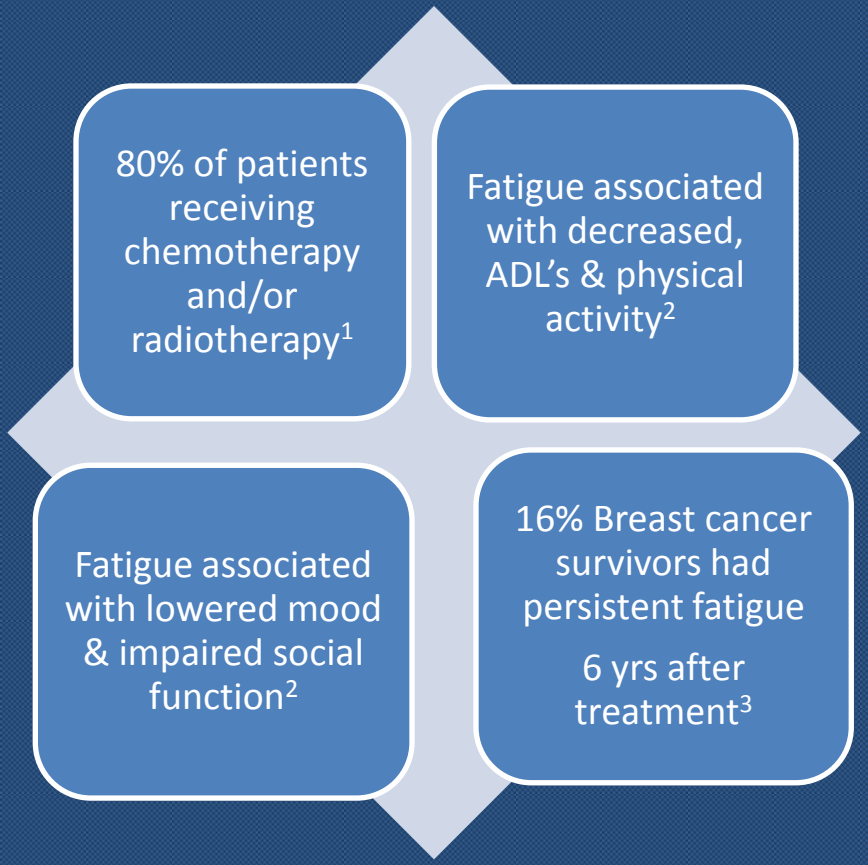
May increase to every day for symptom relief

Advanced Cancer: Case Three

- 78 y/o woman presents with NSCC of lung metastatic to liver
- She is currently undergoing salvage chemotherapy with carboplatin
- Her major complaint now is fatigue
- She reports a recent 20# weight loss
- She never smoked

Cancer Related Fatigue: Burden of Disease

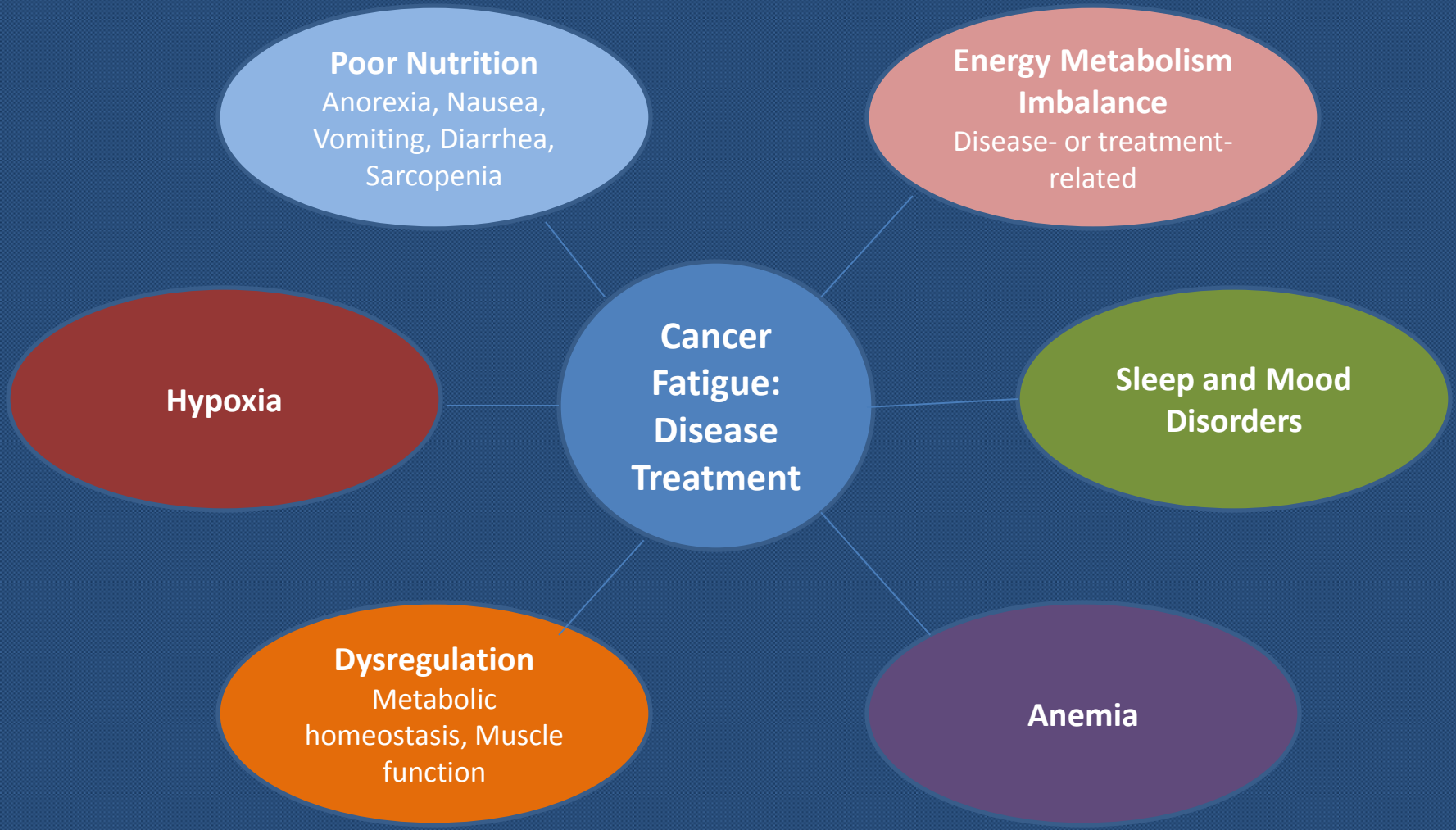
Cancer related fatigue causes marked impacts on QOL and is often under recognized or considered inevitable.



1. NCCN, National Comprehensive Cancer Network.NCCN. Cancer-Related Fatigue, NCCN Guidelines Version 1.2012.
2. Donovan KA et al. Psychoonocology 2012; Apr 30. doi: 10.1002/pon.3085. [Epub ahead of print]
3. Schmitz KH et al. Cancer, 2012; 118 (Suppl): 2217-25.

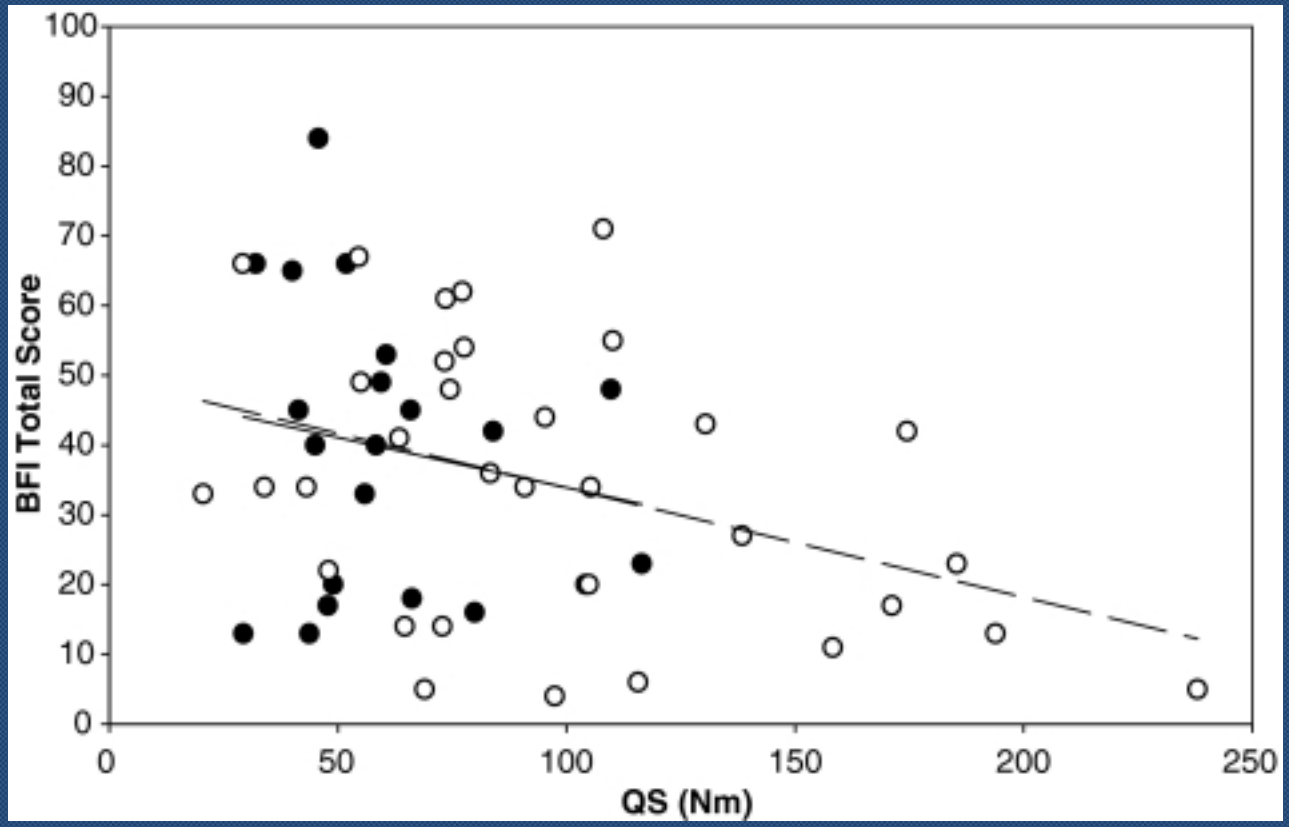
Cancer-Related Fatigue: Proposed Mechanisms

The multifactorial pathophysiology of cancer-related fatigue is not fully understood



Gramignano G, et al. *Nutrition.* 2006;22:136-145.

Advanced Cancer: Case Three



Correlation between isokinetic (60˚ /s) quadriceps extension strength (*QS*) and the Brief Fatigue Inventory (*BFI*) in male (*dotted line*, *n*=33) and female (*solid line*, *n*=24) patients with newly diagnosed advanced cancer

Carnitine: Clinical Studies

Effect on Fatigue/QOL/Nutrition/Function

Study	Patients & Design	Carnitine Dose	Outcomes
Gramignano et al 2006	Open-label, non-randomized study Patients with advanced cancer who developed fatigue, high ROS blood levels, or both (N = 12) Primary outcomes • Fatigue (MFSI-SF) • Quality of Life (QOL-OS; EQ-$5D_{vas}$) • Nutrition/function (LBM, appetite, grip strength) • Laboratory variables (ROS, PIC, CRP, leptin)	Oral L-carnitine • 2 g, TID x 4 wks	Fatigue decreased • MFSI-SF: t_0, 25.40 vs wk 4, 12.05; *P* <.001 Quality of life improved • QOL-OS: t_0, 54.30 vs wk 4, 36.80; *P* <.05 • EQ-$5D_{vas}$: t_0, 50.58 vs wk 4, 73.33; *P* <.001 Nutrition/function improved • LBM: t_0, 38 kg vs wk 4, 40.39 kg; *P* <.05 • Significantly improved appetite • No difference in grip strength Laboratory variables • Reduced CRP: t_0, 0.97 ng/mL vs wk 4, 0.59 ng/mL; *P*=.05

CRP, C-reactive protein; EQ-$5D_{vas}$, EuroQol visual analog scale; IL, interleukin; LBM, lean body mass; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; PIC, proinflammatory cytokines (IL-6, IL-1, TNF-α); QOL, quality of life; QOL-OS, quality of life-oxidative stress questionnaire; ROS, reactive oxygen species; t_0, baseline ;TID, thrice daily; TNF-α, tumor necrosis factor-alpha.

Gramignano G, et al. *Nutrition.* 2006;22:136-145.

Support for Cancer Fatigue

- Acetyl-L-carnitine 2 gm BID to TID
- Co-enzyme Q 10 100 mg BID
- Branch chain amino acids 6.6 grams BID
- Dietary changes to stabilize blood sugar
- Additional protein
- Normalize sleep (melatonin 3- 10 mg QHS)
- Exercise
- Yoga

Carnitine: Safety

- Adults: no toxicity at doses up to 30 g/day[1,2]
  - Pediatrics: appears safe in doses up to 0.65g/kg/day in children ages 2–21 years[3]
- No significant side effects reported in any study
  - One report of insomnia[1]
  - Four patients reported mild nausea[2,3]
- Warfarin
  - Due to the known interaction between L-carnitine and acenocoumarol, L-carnitine and acetyl-L-carnitine should be used cautiously in patients taking warfarin
- L-carnitine inhibits thyroid hormone uptake by target cell nuclei[4]
  - An increase in seizure frequency or severity has been reported in people with a history of seizures who have received oral or intravenous L-carnitine[5]

1. Maestri A, et al. *Tumori.* 2005;91:135-138.
2. Bianchi, et al. *Eur J Cancer.* 2005;41:1746-1750.
3. Cruciani RA, et al. *J Pain Sympt Manag.* 2006;32:551-559.
4. Benvenga, et al. *Ann NY Acad Sci.* 2004;1033:158-167.
5. Carnitor [package insert]. Gaithersburg, MD: Sigma-tau Pharmaceuticals, Inc; 2007.

NeuroQOL (acetyl-L-carnitine)

Indications: Neuropathy, Fatigue, QOL

500 mg per capsule

Recommended Use: 2 capsules TID

May be used up to 6g/day

FemQOL:

Indications: Menopausal symptoms

Standardized Isopropanolic Black Cohosh Extract

20 mg per capsule

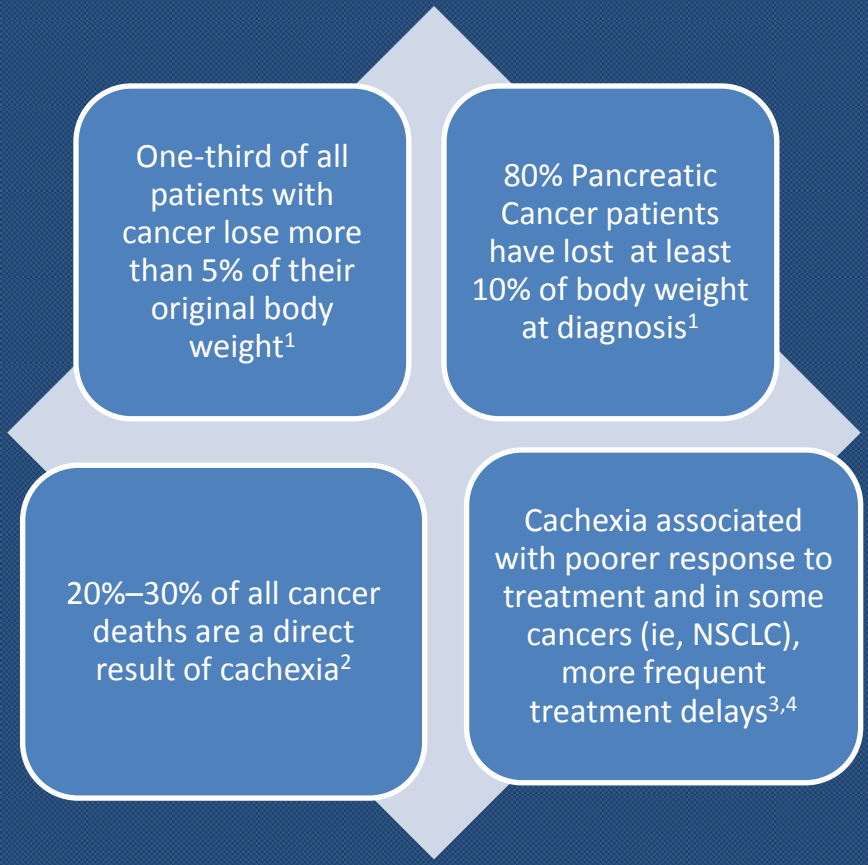
Recommended Use: 1 capsule BID

Pancreatic Cancer: Case Four

- Patient is a 55 y/o male presenting initially with a 20 pound unintentional weight loss. He weighed 235 three months ago and now weighs 216 pounds.
- He was diagnosed with a locally advanced pancreatic tumor
- He is starting on FOLFIRI

Cachexia & Sarcopenia: Burden of Disease

Cachexia, anorexia and sarcopenia impair patient response to treatment and significantly affect prognosis.



1. Fearon KCH. *Eur J Cancer*. 2008;44:1124-1132.
2. Penet MF, et al. *Current Opin Support Palliat Care.* 2011;5:327-333.
3. Dewys WD, et al. *Am J Med.* 1980;69:491-497.
4. Ross PJ, et al. *Br J Cancer.* 2004;90:1905-1911.

Effect of Weight Loss on Median Survival in Cancer Patients

- The clinical course of cancer is adversely affected by weight loss
- Results from case record analysis (N = 3047) of 12 ECOG chemotherapy trials

	Median Survival (Wk)				
Tumor	No WL	0–5% WL	5–10% WL	>10% WL	*P* value
NSCLC	20	17	13	11	<.01
Prostate	46	30	18	9	<.05
Colorectal	43	27	15	20	<.01

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; WL, weight loss.
Dewys WD, et al. *Am J Med.* 1980;69:491-497.

Cachexia Syndrome

- In and of itself, weight loss does not fully describe or define cachexia
- Three factors relate to adverse patient function and prognosis:
  - Weight loss (≥ 10%)
  - Reduced food intake (≤ 1500 kcal/day)
  - Systemic inflammation (C-reactive protein ≥ 10 mg/L)

Fearon KC, et al. *Am J Clin Nutr.* 2006:83:1345-1350.

Nutritional/Functional and Quality of Life Before and After Treatment With AA Supplementation

Parameters	Baseline	Post-treatment	*P* value[a]
Grip strength (kg)	**28.2 ± 9.5**	**30.4 ± 9.2**	**.0001**
Weight (kg)	53.1 ± 10.6	54.2 ± 11.1	.056
BMI	19.7 ± 2.8	19.8 ± 2.9	.119
Lean body mass (kg) (bioimpedence)	41.2 ± 8.3	42.6 ± 6.7	.221
Fatigue (MFSI-SF)	25 ± 8.1	22 ± 7.3	.181

[a]Calculated by Student *t* test for paired data.
BMI, body mass index; MFSI-SF QoL, multidimensional fatigue symptom inventory-short form quality of life.
Madeddu C, et al. *Mediterr J Nutr Metab*. 2010;3:165-172.

Nonsignificant Changes Before VS After Amino Acid Supplementation

Parameters	Baseline	After Treatment	*P* value
Hemoglobin (g/dL)	10.7 ± 1.5	11.2 ± 1.6	.894
Absolute lymphocyte count ($1\ \mu l^{-1}$)	1473 ± 559	1673 ± 872	.284
C-reactive protein	24.7 ± 18.1	17 ± 11.4	.066
IL-6 (pg/mL)	21.3 ± 16.4	13.7 ± 4	.157
TNF-α (pg/mL)	22.1 ± 11.9	19.5 ± 7.6	.526
Leptin (ng/mL)	3.6 ± 4.5	10.8 ± 11.7	.052

Differences between means calculated by Student *t* test for paired data;.
IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha.
Madeddu C, et al. *Mediterr J Nutr Metab*. 2010;3:165-172.

Support for Cachexia

- Branch chain amino acids 6.6 gm BID to TID
- Curcumin
  - 3-6 gm BID (unformulated to improve absorption)
  - 1-2 gm BID (formulated to improve absorption)
- Fish oil 1200 – 2000 gm EPA + DHA BID
- Appetite stimulation
- Increase oral protein intake

Safety of Oral Amino Acid in Cancer Patients

- Madeddu, 2010[1]
  - No toxicity of any grade nor adverse events for any patient observed
- Cangiano, 1996[2]
  - No discontinuations related to trial
  - Authors conclude that BCAAs may be used safely in cancer patients with anorexia
- May provide an additional hypoglycemic effect in patients receiving anti-diabetic medications
- Toxicity in rare diseases
  - Amyotrophic lateral sclerosis
  - Branched-chain ketoaciduria

1. Madeddu C, et al. *Mediterr J Nutr Metab*. 2010;3:165-172.
2. Cangiano C, et al. *J Natl Cancer Inst*. 1996;88:550-552.

DaxibeQOL

Indications: Cachexia; Anorexia; Sarcopenia

Essential Amino Acid Supplement
For Musculoskeletal Support

6.6 g per Sachet
Recommended Use: **1-2 sachets daily**

InflaQOL

Indications: Radiosensitiizing; anti-inflammatory

Curcumin Phytosome

500 mg per capsule

Suggested Use: 2-3 capsules bid

Colon Cancer: Case Five

- 62 y/o African American male with iron deficiency anemia discovered on routine physical required for work (commercial truck driver)
- FHx: MGF developed colon cancer at 70 yrs
- Pt has never had colonoscopy & “hates doctors”
- Pt is assymptomatic but stool guiac + for blood

Colon Cancer: Case Five

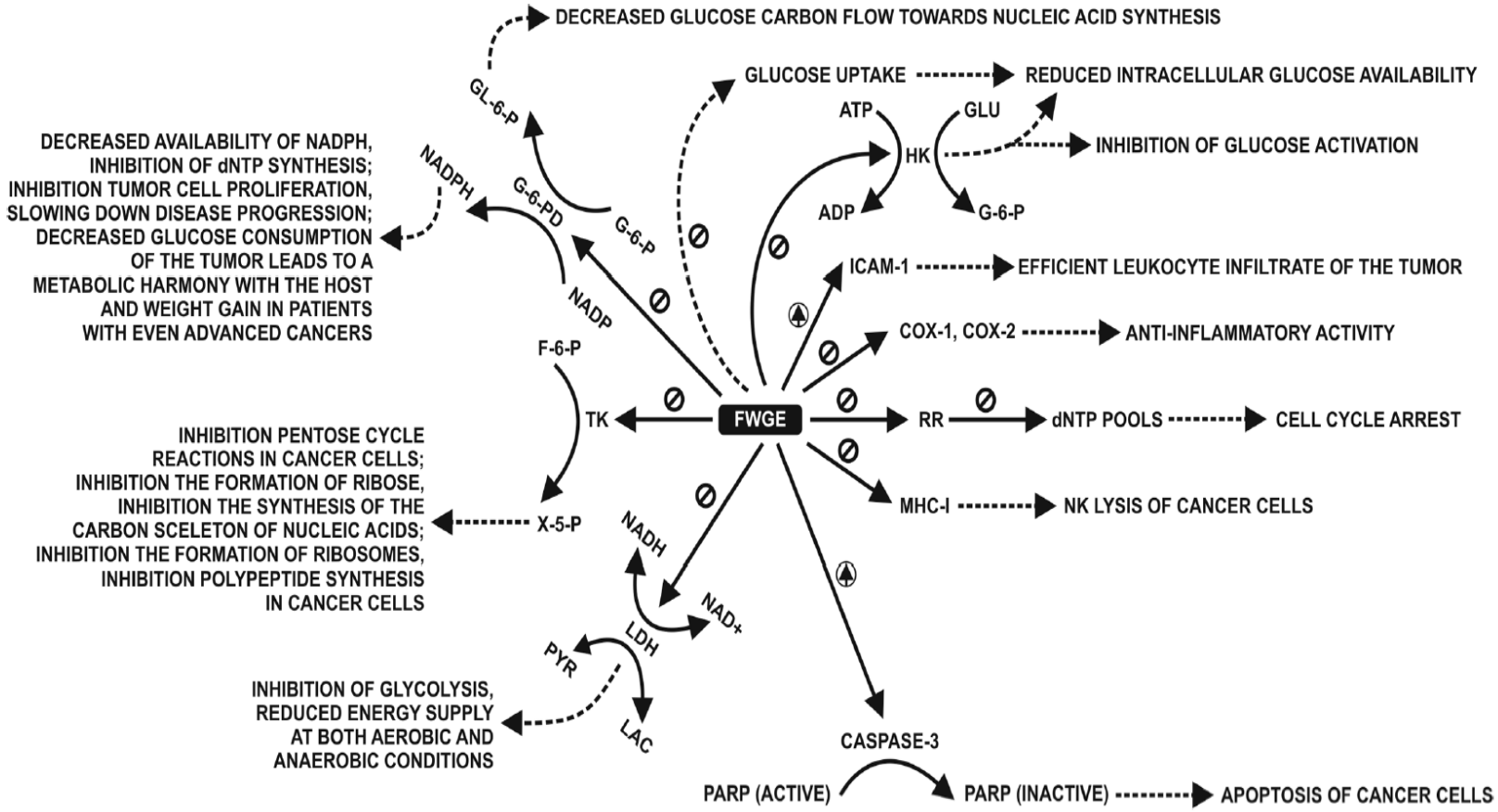
- Colonoscopy reveals fungating mass in Right ascending colon
- Surgery reveals 5.5 cm adenocarcinoma partially through the muscularis
- Lymph nodes: 5/10 local nodes positive
- Stage III B
- FolFox chemo therapy for 6 months

Colon Cancer: Case Five

- What would improve this patients response to chemotherapy?
- What side effects do you anticipate from his chemotherapy?
- What issues are you concerned about based on his race?
- What would you recommend to reduce his risk of recurrence?

Use of Freeze-dried Wheat Germ Extract for the Supportive Care of Cancer Patients

FWGE Mechanism: How Does It Work?



Squamous Cell Carcinoma of the Oral Cavity

1 and 5 Year FWGE Treatment Results

1-Year	FWGE		Control		Significancy
	23		22		-
Deaths	0	0.0%	1	4.5%	NS
Local relapse	1	4.3%	12	54.5%	*P*<.001
Metastasis	1	4.3%	4	22.7%	NS (Nearly significant)
Disease Progression	2	8.7%	13	59.1%	*P*<.001

5-Year Survival

FWGE: 17 Patients (74%)

Control: 10 Patients (45.5%)

P<.05

FWGE, fermented wheat germ extract.

Barabas J, Nemeth Z. *Orv Hetil.* 2006;147:1709-1711.

Adjuvant FWGE (NutraQOL) Improves Overall Survival in High Risk Skin Melanoma Patients

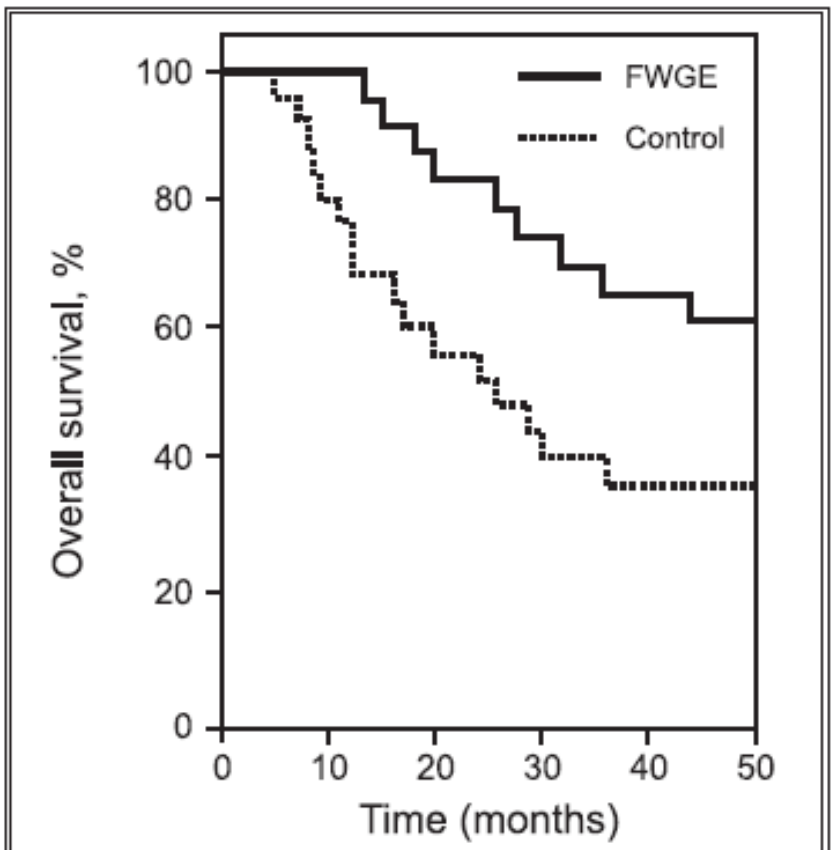


Figure 2. Kaplan-Meier estimate of the cumulative probability of overall survival in stage III skin melanoma patients. Log-rank test: chi-square [1] = 4.72; $p = 0.0298$.

FWGE, fermented wheat germ extract.

Demidov, et al. *Cancer Biotherapy & Radiopharmaceuticals.* 2008;23:477-482.

Colorectal Cancer: Point Analysis

In colorectal cancer, following surgery, compared with SOC alone, SOC plus FWGE results in:

- 82% reduction in new recurrences ($P<.01$)
- 67% reduction in metastasis ($P<.01$)
- 62% reduction in deaths ($P<.01$)

"FWGE has supportive value in the treatment of the colorectal cancer"

FWGE, fermented wheat germ extract; SOC, standard of care.

Jakab, et al. *Br J Cancer.* 2003;89:465-469.

FWGE Safety & Use

- No adverse effects reported in studies
- Clinical experience
  - Occasional mild gastroentestinal distress
  - No increased distress in gluten intolerant patients
- Separate dose from all medication
- Take on a completely empty stomach for one hour before and after dose
- Do not expose to heat or take with hot beverages

FWGE, fermented wheat germ extract

NutraQOL

Indications: QOL, Febrile Neutropenia

Fermented Wheat Germ Extract

Orange flavor

5.5 gram sachets

Recommended Use: 1 sachet daily

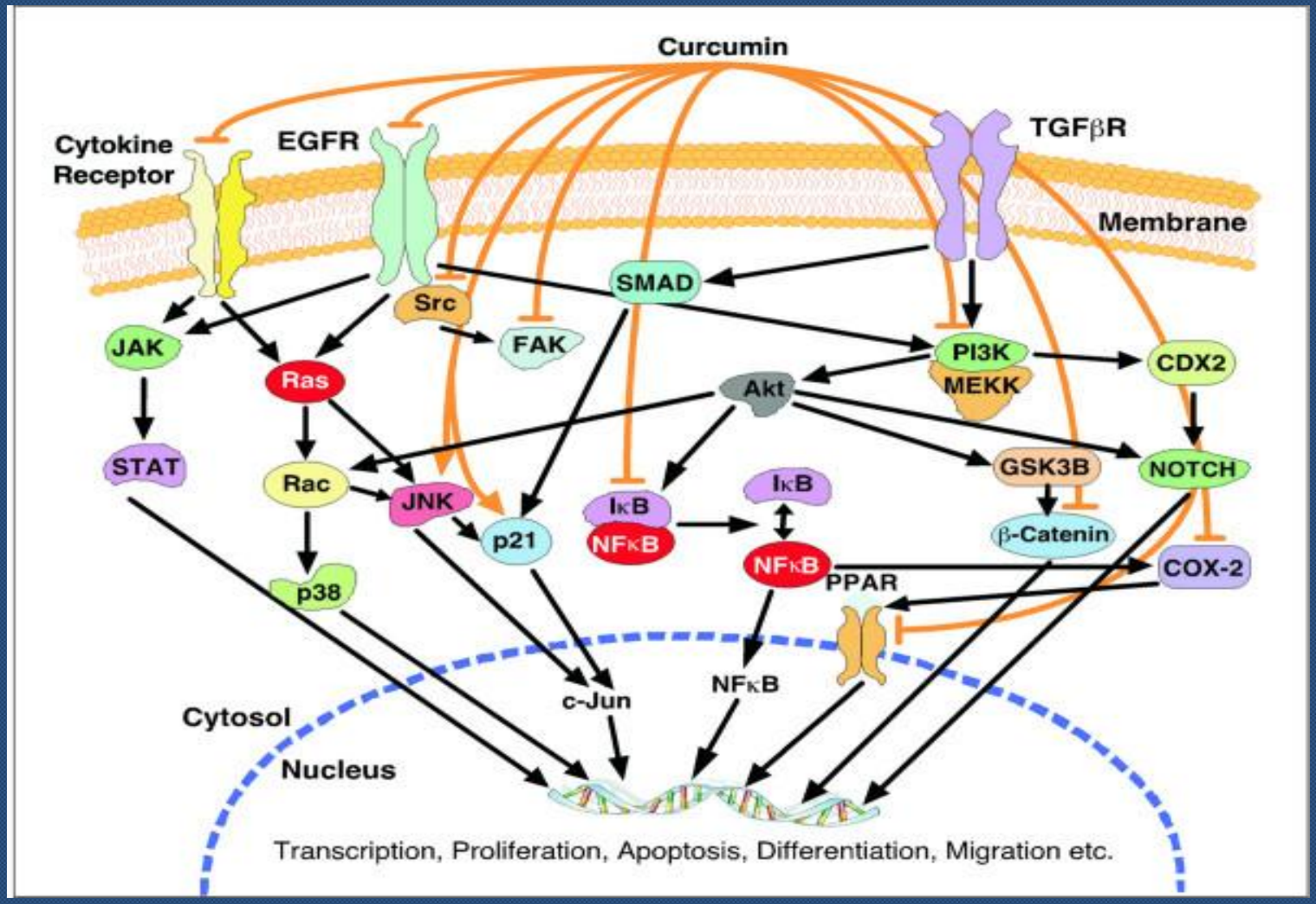
Inflammation and Cancer

Inflammation & Prognosis

- Adenocarcinoma of Pancreas after surgery
  - *CRP < 10= median survival 21.5 months; > 10= 8.4 months (p=0.015)*[1]
- Prostate cancer survival 10 yrs after intital dx & trx
  - *CRP predicted overall survival & prostate cancer specific survival (HR 1.80 [1.01-3.52] p < 0.05)*[2]
- Gastro-esophageal cancer survival after surgery
  - *CRP < 10= median survival 79 months; > 10= 19 months (HR:3.53 [1.88-36.64]; p<0.001);* [3]
- Breast cancer survival in HEAL study
  - *CRP decreased overall survival HR 2.27 [1.27-4.08; p=.002] & trend towards decreased disease free survival (p=.07)*[4]

1. Jamieson NB et al. *Br J Cancer* 2005, 92:21-23.
2. McArdle PA et al. *Urol Int* 2010, Apr 15 Epub.
3. Crumley AB et al. *Br J Cancer* 2006, 94:1568-1571.
4. Pierce BL et al. *J Clin Oncol* 2009, 27:3437-3444.

Molecular Targets of Curcumin



Curcumin: Anticancer Studies

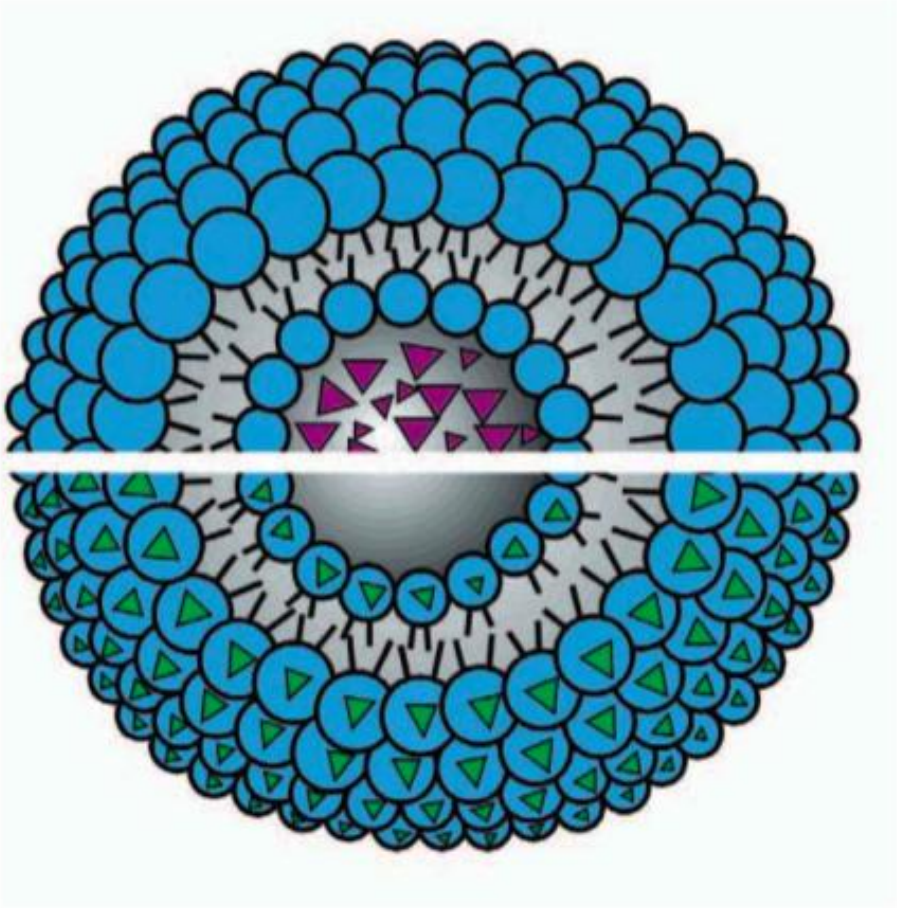
Pancreatic Cancer

Study	Patients & Design	Curcumin Dose	Curcumin Outcomes
Kanai et al 2011[1]	Phase I/II study in patients with GEM-resistant advanced disease (N = 21) Chemo: GEM-based Outcomes: Efficacy, safety, and feasibility	8 g/d	• Well tolerated • 100% treatment completion rate • Stable disease rate: 28% • Median survival: 161 d (95% CI, 109–223 d) • One-year survival: 19% (95% CI, 4.4%–41.4%) • Improvement in patient-reported cancer- or CT-related symptoms (eg, fatigue, pain, constipation)
Epelbaum et al 2010[2]	Open-label phase II in patients with untreated locally advanced or metastatic disease (N = 17) Chemo: GEM Outcomes: Efficacy and safety	4 g/d BID until disease progression, death, or severe toxicity	• Grade 2–3 GI toxicity in 8 patients • Toxicity-related discontinuation: 29% • CBR: 40% • Local control rate: 45.5% • Median TTP: 2.5 mo (range: 1–12) • Median OS: 5 mo (range: 1–24)
Dhillon et al 2008[3]	Open-label phase II study in patients with histologically-confirmed disease (N = 21) No chemo Outcomes: Efficacy and safety	8 g/d for ≥ 8 wk	• No treatment-related toxic effects • Stable disease for > 18 mo (n = 1) • Dramatic but transient tumor response (n = 1) • Stable weight and improved well being for 8 mo despite progression in nontarget lesions (n = 1)

BID, twice daily; CBR, clinical benefit response; CI, confidence interval; CT, chemotherapy; GEM, gemcitabine; GI, gastrointestinal; OS, overall survival; TTP, time to progression.

1. Kanai M, et al. *Cancer Chemother Pharmacol.* 2011;68:157-164; 2. Epelbaum R, et al. *Nutrition and Cancer*. 2010;62:1137-1141; 3. Dhillon N, et al. *Clin Cancer Res*. 2008;14:4491-4499.

LIPOSOME

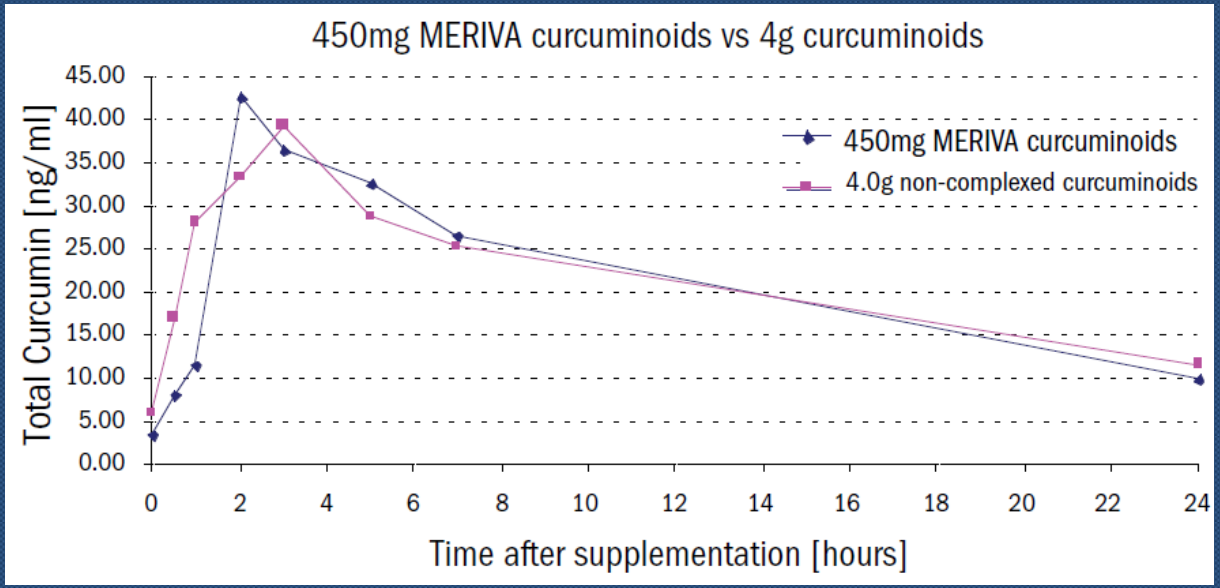


PHYTOSOME

- Water soluble free drug
- Phosphatidylcoline
- Phosphatidylcoline-drug complex

Phosphatidylcholine-Curcumin Complex: Pharmacokinetics

- In rat study, PC-curcumin complex Cmax and AUC were 5-times higher than unbound curcumin[1]
- Small unpublished, single-dose trial demonstrated 450 mg of PC-curcumin complex absorbed as efficiently as 4000 mg unbound *C. longa* extract (95% curcumin)[2]



AUC, area under the plasma concentration time curve; Cmax, maximum plasma concentration; PC-curcumin, phosphatidylcholine-curcumin complex.

1.Marczylo TH . *Cancer Chemother Pharmacol.* 2007;60:171-177.
2.Jurenka J. *Altern Med Rev.* 2009;14:141-153.

Curcumin

Gastrointestinal Disorders: Ulcerative Colitis

Patients & Design	Dose	Outcomes
Randomized, double-blind, placebo-controlled multicenter trial of curcumin as maintenance therapy for patients in Japan with quiescent UC (N = 89) All patients received: SZ (1–3 g/d; median 2 g/d) or mesalamine (1.5–3 g/d; median 2.25 g/d) Outcomes: •CAI •EI	Curcumin 1 g BID (n=43) or placebo (n=39) x 6 mo Patients continued on SZ or mesalamine for an additional 6 mo	• Relapse rate lower in curcumin group vs control (4.6% vs 20.5%; *P*=.04) • Mean CAI in curcumin group improved from 1.3 at baseline to 1 at 6 mo (*P*=.038) • Mean CAI in placebo deteriorated from 1 at baseline to 2.2 at 6 mo (*P*=.0003) • Patients in curcumin group had improved EI (1.3 at baseline vs 0.8 at 6 mo; *P*=.0001)

BID, twice daily; CAI, clinical activity index; EI, endoscopic index; SZ, sulfasalazine; UC, ulcerative colitis.

Hanai H, et al. *Clin Gastroenterol Hepatol.* 2006;4:1502-1506.

Curcumin: General Safety

- Curcumin is well tolerated in patients at doses up to 12,000 mg/d[1-8]
  - No maximum tolerated dose has been identified in humans[1]
- Side effects primarily NCI CTCAE toxicity grade 1–2 nausea and diarrhea[1-8]
  - May be secondary to bulky volume of tablets with higher doses
- Time of side effect onset varies by patient and could begin months after treatment initiation[1-8]
- Caution using with anti-coagulants & anti-platelets[9]

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

1. Lao CD, *BMC Complement Altern Med.* 2006;6:10; 2. Cheng AL,et al. *Anticancer Res*. 2001;21:2895-2900 ; 3. Hanai H, et al. *Clin Gastroenterol Hepatol*. 2006;4:1502-1506; 4. Sharma RA, et al. *Clin Cancer Res.* 2001;7:1894-1900; 5. Sharma RA, et al. *Clin Cancer Res.* 2004;10:6847-6854; 6. Garcea G, et al. *Cancer Epdemiol Biomarkers Prev*. 2005;14:120-125; 7. Deodhar SD, et al. *Indian J Med Res.* 1980;71:632-634; 8. Bundy R, et al. *J Altern Complement Med*. 2004;10:1015-1018. 9. Shah BH, et al. *Biochem Pharmacol.* 1999;58:1167-1172.

Curcumin: General Safety

Disease Interactions

Gallbladder Disease[1,2]

- Turmeric can cause gallbladder contractions
- Use with caution in patients with gallstones or gallbladder disease

Surgery[3]

- Due to its antiplatelet effects, turmeric may cause excessive bleeding if used perioperatively
- Consider discontinuing turmeric at least 2 weeks before elective surgical procedures
- No adverse event cases have been reported related to surgery

1. Balaji S, Chempakam B. *Food Chem Toxicol*. 2010;48:2951-2959.
2. Rasyid A, et al. *Asia Pacific J Clin Nutr*. 2002;11:314-318.
3. Shah BH, et al. *Biochem Pharmacol*. 1999;58:1167-1172.

InflaQOL

Indications: Radiosensitiizing; anti-inflammatory

Curcumin Phytosome

500 mg per capsule

Suggested Use: 2-3 capsules bid

Coenzyme Q10 in the Prevention of Anthracycline Toxicity & Cardiac Protection

Coenzyme Q10: Clinical Studies

Conclusions

- Randomized controlled trials with between-group analyses are lacking
- Optimum blood levels of CoQ10 for prevention of anthracycline-induced cardiotoxicity have not been defined
- An increase in serum CoQ10 levels requires supplementation with ~ 100 mg/d, but 3 studies used 90 mg/d
- CoQ10 may have a stabilizing effect on the heart
- CoQ10 effect on development of late or delayed cardiomyopathy unknown; no long-term follow-up
- Factors affecting bioavailability include
  - CoQ10 preparation used
  - Individual's age, sex, race, diet, and nutritional status
  - Stomach contents and alcohol consumption
- CoQ10 not associated with any toxicity in clinical trials

Roffe L, et al. *J Clin Oncol*. 2004;22:4418-4424.

Safety of Coenzyme Q10 in Cancer Patients

- No toxicities reported for daily intake up to 240 mg/d[1,2]
- Safety not established in pregnant or lactating women[2]
- Procoagulant effects; structurally similar to vitamin K[2]

1. Thibault A, et al. *Clin Cancer Res*. 1996;2:483-491.
2. Roffe L, et al. *J Clin Oncol*. 2004;22:4418-4424.

MyoQOL

Indications: Cardioprotective; Energy

Coenzyme Q10 - 100 mg per capsule

Crystal-free CoQ10 with superior absorption compared to other preparations.

Suggested use: 1 capsule BID

DermaQOL

Xenoestrogen Free Personal Care Products
Enhancing Quality of Life

DermaQOL

Product	Positioning
DermaQOL	Current Thorne organics skin line- shampoo, conditioner, body lotion, and soaps will be relabeled under OncoQOL- DermaQOL line Positioning For patients with breast cancer on anti-estrogens to minimize exogenous estrogens from skin products For patients with alopecia For patients with skin irritation die to disease or chemo
Shampoo, Conditioner, Lotion Shower gel, Lip balm, Aloe soap	Xenoestrogen free personal care products for patients with hormone receptor positive breast cancer or women at high risk for breast cancer
Sulfur Balsam soap	Cancer or chemo associated dermatitis
Aloe Spray	Acute Radiation dermatitis
Soothing Relief cream	Relief cream for rough skin areas. Use with Aloe Spray for radiation dermatitis

Summary & Discussion