

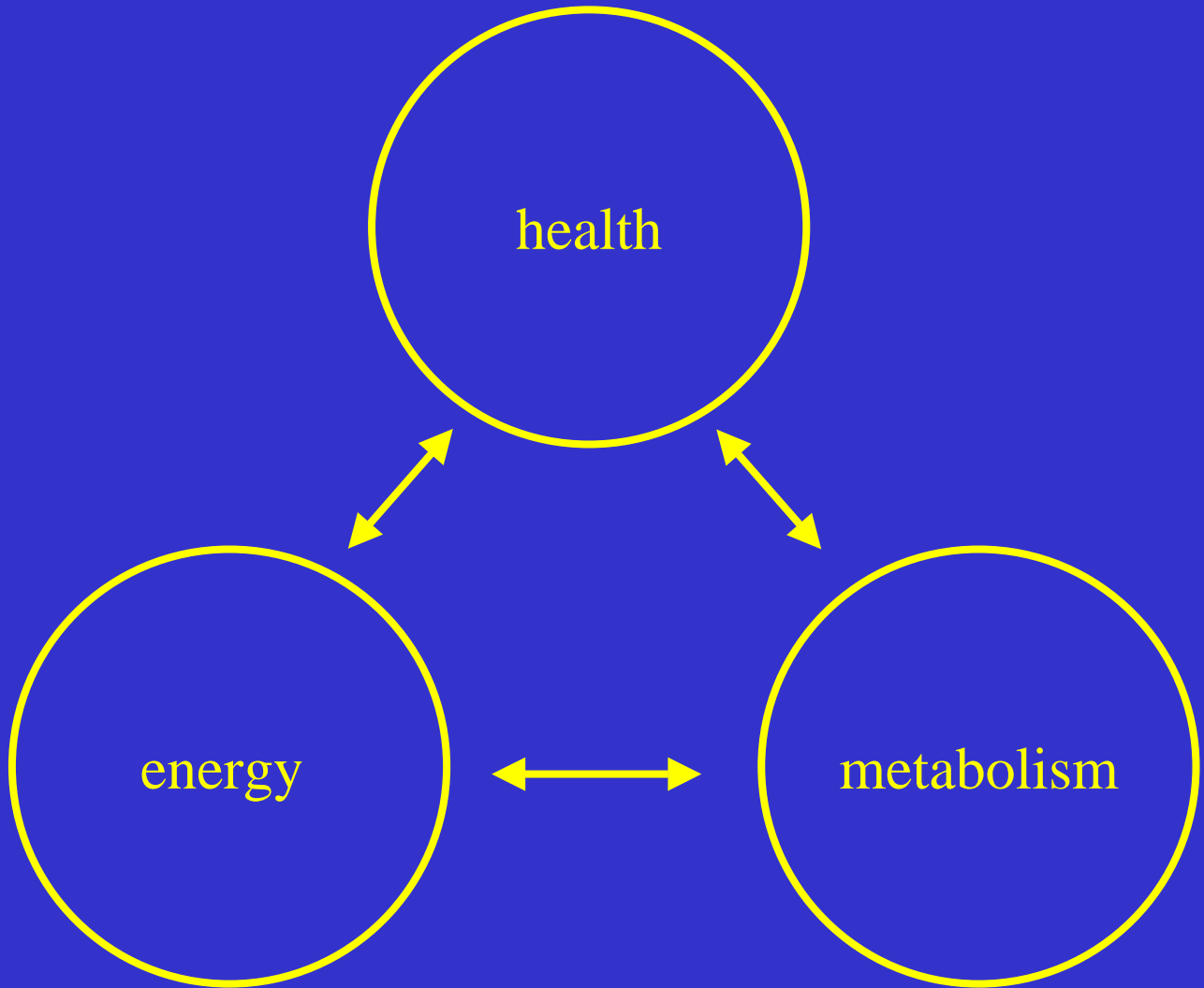
Carnitine and Cancer

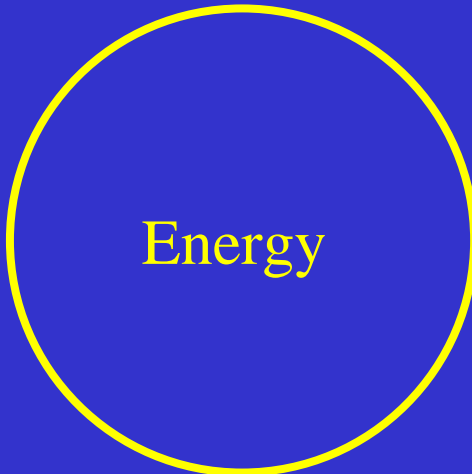
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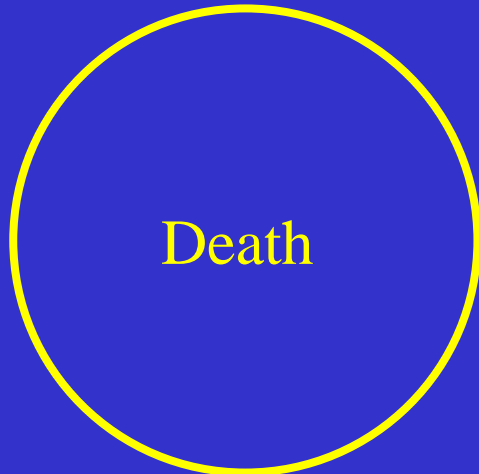
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Energy

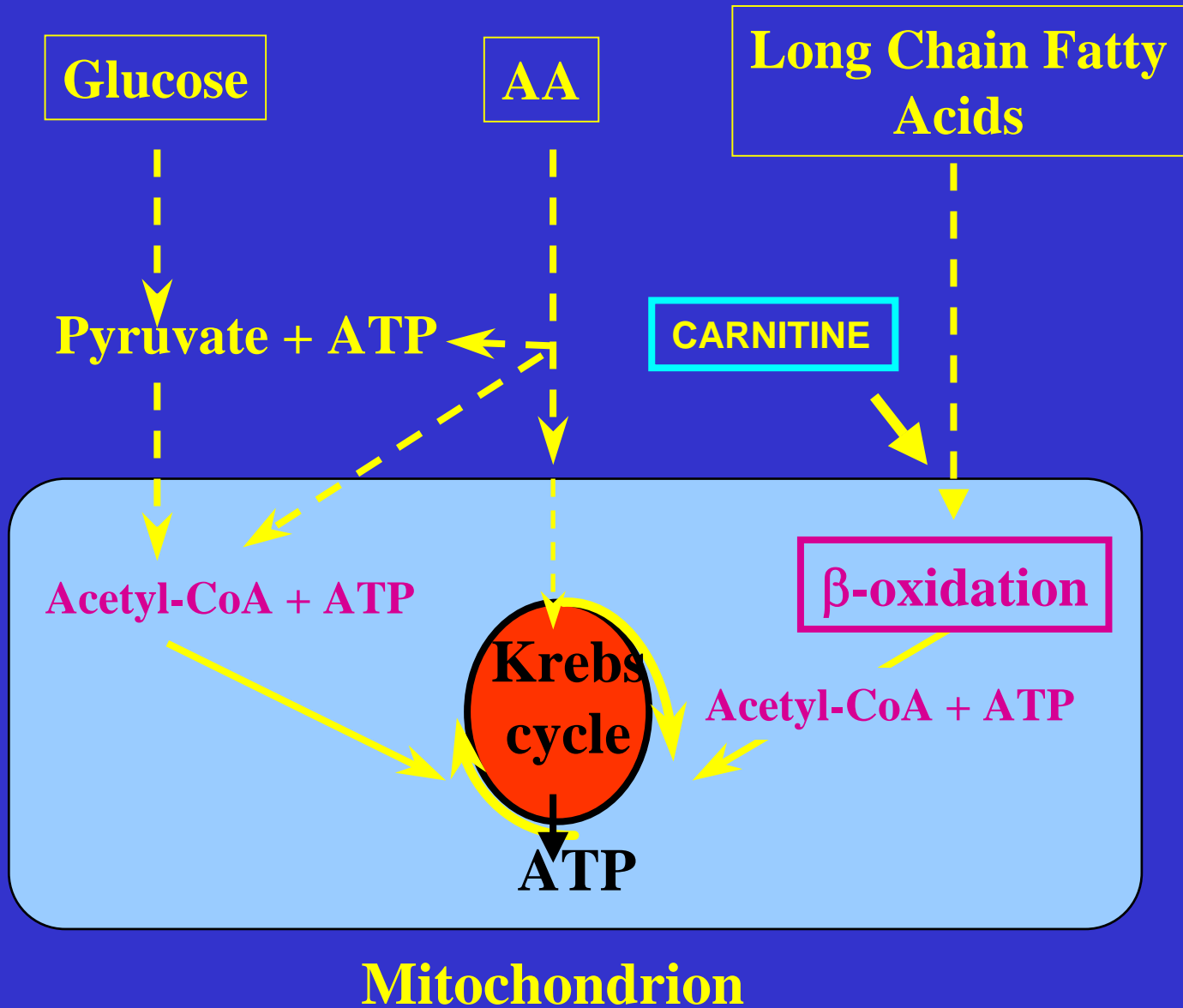


Death

Chronic diseases

- Renal failure
- Hepatic failure
- Cancer
- Heart Failure
- AIDS

Cellular Energy Sources



Why carnitine and cancer?

Poor nutrition

Carnitine metabolism

- Nausea/vomit
- Liver metastasis
- GI cancer
- Renal cancer, renal insufficiency

Cisplatin

Decreased glomerular filtration
Tubular damage

Ifosfamide

Dietary sources

- 75% of requirements
- red meat and dairy products

•Carnitine biosynthesis:

- 25% of requirements
- Most humans tissues:
trimethyl-LYS to butirobetaine
- Liver, kidney and brain:
from γ -butirobetaine

Cancer cells
Walker 256 sarcoma bearing rats
Decreased CPT-1 activity
Different CPT-2 enzyme isoform
Decreased fatty acid oxidation

Anthracycline antibiotic
Intercalates with DNA
Decreased free carnitine
Decreased free fatty acid oxidation
Decreased intracellular ATP content

Chronic myeloid leukemia patients.
Bone marrow cultures. Vs normal
voluntaries. No difference on
oncogenes, gross associated genes.
50 fold decrease expression rate of
CTP-1A and CTP-1B

Fatigue

Symptom management in cancer patients

Pain

Nausea/vomiting: chemotherapy, opioid induced

Encephalopathy

Opioid induce side effects:

itching

respiratory depression

hypotension

constipation

depression

anorexia

peripheral neuropathy: chemotherapy-induced, nutritional

Fatigue:

- prevalence: 78% (survey on 419 randomly selected cancer patients, 39% significantly affected their daily routine)

- 95% of patients with radiotherapy, chemotherapy, interleukins, α -interferon

Potential Predisposing Factors or Etiologies of Cancer Related Fatigue

Modified from Portenoy and Itri. *The oncologist* (1999)

• Physiologic

- Underlying disease
- Treatment of the disease

• *Chemotherapy*

• *Radiation therapy*

• Intercurrent systemic disorders

• *Anemia*

• *In*

Develops during course of chemotherapy

Improved by the time of next course

May not be present right after treatment

Cumulative

Worsens with time

Radiation of small parts of the body can cause severe fatigue

At least three months until it returns to baseline

Mild fatigue= 9-12 g/dl

Severe fatigue=<9 g/dl

Blood transfusion

Recombinant human erythropoietin

Open-label study in 2349 patients treated for 16 weeks shows increase in energy level, activity and quality of life.

expensive

not covered by most insurance companies

increased risk of stroke in cancer patients?

• Psychological

Increased urinary excretion of carnitine in patients treated with cisplatin

Hauberger W. et al. Eur J Pharmacol (1998) 54:503-8

Study design:

- 10 patients treated with cisplatin (50-180 mg/day)
- hydration during trial
- 5 patients treated with radiotherapy
- No other chemotherapeutic agent during the trial
- Serum and urinary carnitine (total-free-acyl) measured

Increased urinary excretion of carnitine in patients treated with cisplatin

Hauberger W. et al. Eur J Pharmacol (1998) 54:503-8

Urine determinations

| Treatment | Before Day-1 | During | | | After | |
|---------------------|-----------------|------------------|--------------------------|------------------|------------------|------------|
| | | Day 1 | Day2 | Day3 | Day+1 | Day+7 |
| Cisplatin | | | | | | |
| Free carnitine | 39.3(29.5) | 731 (523) | <u>919</u> (539) | 634 (243) | 406 (282) | 83.4(72.0) |
| Short-chain | 77.3(55.2) | 238 (163) | 212(113) | 190(115) | 200(135) | 99(44.3) |
| Total carnitine | 117(79) | 968 (478) | <u>1130</u> (602) | 824 (345) | 606 (348) | 182(105) |
| Radiotherapy | | | | | | |
| Free carnitine | 155(174) | 193(176) | 166(208) | ND | ND | ND |
| Short-chain | 173(72) | 127(29) | 133(40) | ND | ND | ND |
| Total carnitine | 328(230) | 320(195) | 300(229) | ND | ND | ND |

Bold =P<0.05 vs. day-1

Bold=P<0.05 vs. radiotherapy

Increased urinary excretion of carnitine in patients treated with cisplatin

Hauberger W. et al. Eur J Pharmacol (1998) 54:503-8

Increase in carnitine urinary excretion

- cisplatin induced tissue damage
- inhibition of carnitine reabsorption
- damage of proximal tubule
- good correlation between free carnitine and short chain acyl-carnitine

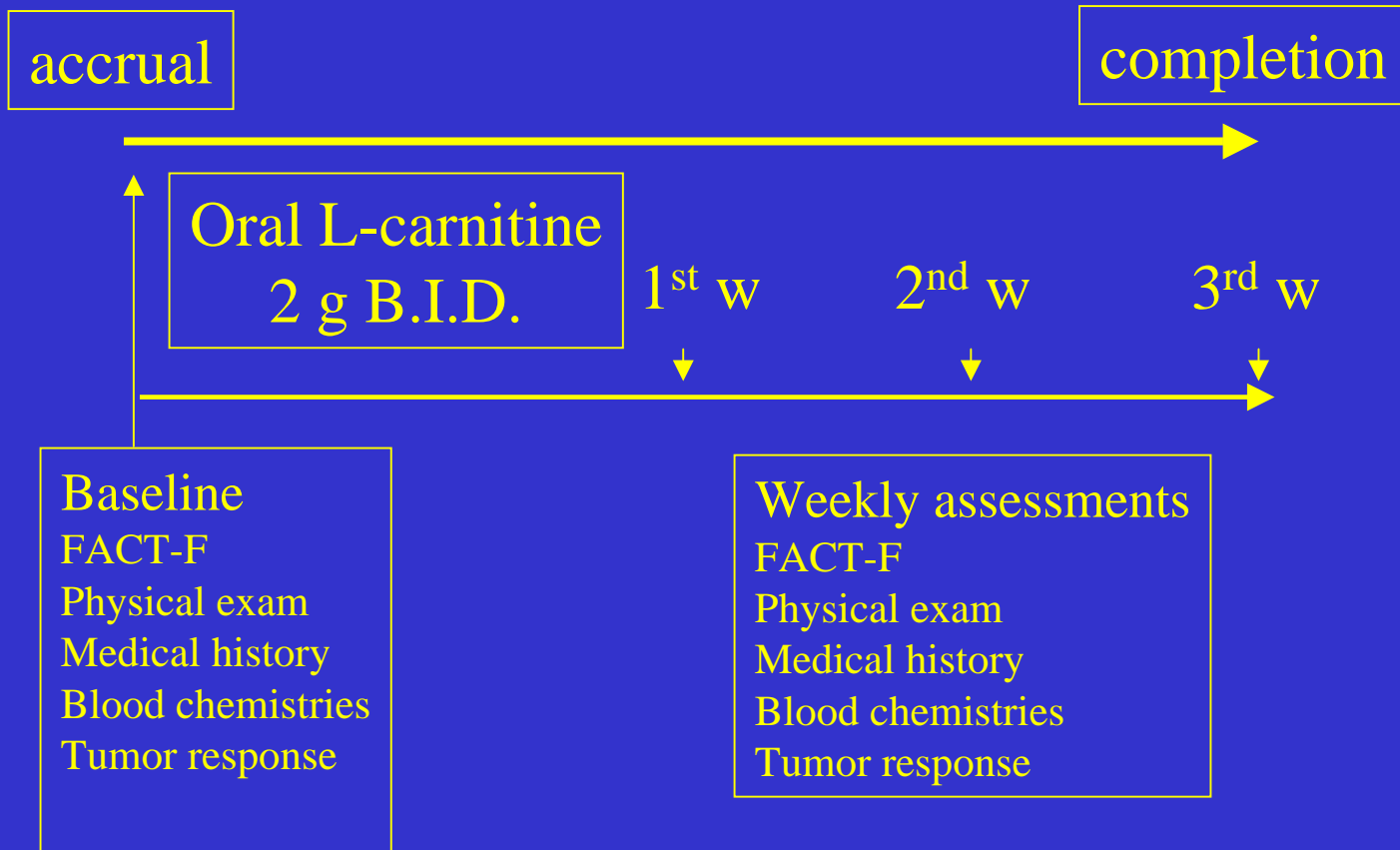
Increase in carnitine plasma levels

- release of intramuscular carnitine tissue damage.
- excretion of 1 mmol of carnitine/day would be equivalent to 500 g of tissue damage.

L-carnitine Supplementation for the Treatment of Chemotherapy Induced Fatigue

Graziano et al. Brit. J Cancer (2002)86,1854-7

Study design



L-carnitine Supplementation for the Treatment of Chemotherapy Induced Fatigue

Graziano et al. Brit. J Cancer (2002)86,1854-7

| | |
|--|------------|
| Number of patients | 50 |
| Sex | |
| male | 30 |
| Female | 30 |
| Median age in years (range) | 61 (45-70) |
| ECOG Performance Status | |
| 0 | 31 |
| 1 | 19 |
| Chemotherapy | |
| Cisplatin/gemcitabine | 22 |
| Cisplatin/epirubicin/fluorouracil | 16 |
| Cisplatin/etoposide | 04 |
| Cisplatin/taxol | 04 |
| Ifosfamide/adriamycin | 04 |
| Percent response rate to chemotherapy | |
| Non small cell lung cancer | 44 |
| Gastric cancer | 39 |
| Other | 25 |
| Timing of fatigue perception | |
| After 1 cycle | 20 |
| After 2 cycles | 30 |

L-carnitine Supplementation for the Treatment of Chemotherapy Induced Fatigue

Graziano et al. Brit. J Cancer (2002)86,1854-7

| Timing | Mean FACT-F (s.d.) | Mean Hb g/dl (s.d.) |
|---------------|--------------------|---------------------|
| Baseline | 19.7(±6.4) | 13.6(±0.6) |
| | <0.001 | p>0.05 |
| After 1 week | 34.9(±5.4) | 13.4(±0.5) |
| | p>0.05 | p>0.05 |
| After 2 weeks | 35.7(±5.5) | 13.0(±0.3) |
| | p>0.05 | p>0.05 |
| After 3 weeks | 36.5(±5.1) | 13.2(±0.5) |

I. L-carnitine supplementation in cancer patients with fatigue and carnitine deficiency.

Cruciani et. al. Preliminary data. Partially funded by NIH/NCCAM
5R21AT001025-02

Description: Open-label study. Safety and tolerability

Methods: Increasing doses of L-carnitine up to 4000 mg/day. Three groups completed: 250, 750 and 1250 mg/day liquid form. In the absence of side effects the following dose is started in a new group of patients.

Inclusion criteria:

- cancer and fatigue
- Karnofsky score >50
- At least one week of completion of chemotherapy
- Carnitine deficiency <35 $\mu\text{moles/L}$, <25 for females, and/or an acyl-carnitine/free ratio >0.4

Primary outcome: Fatigue

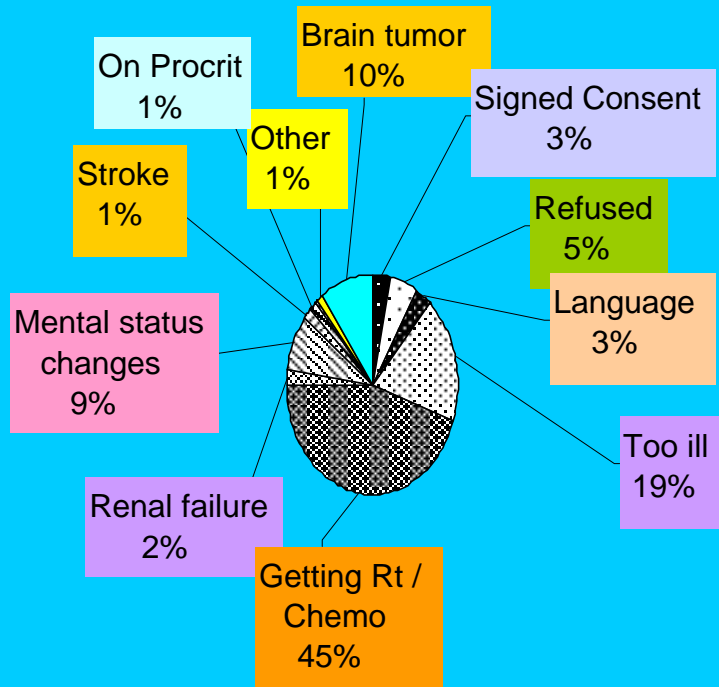
Secondary Outcomes: Depression, Quality of life, Performance status

Phase II Developmental Study on Fatigue in Terminal Cancer

Grant No. 5 R21 AT01025-02; R. Cruciani, PI

N = 529 Patients

L-carnitine in Advanced Cancer



L-carnitine supplementation in cancer patients with fatigue and carnitine deficiency.

| Pt | Date enrolled | Age/ Gender | Cancer Diagnosis | KPS | Faigue Report | Free L-carn | Total L-carn | Acyl L-carn | Eligibility status |
|--------|---------------|----------------|---------------------|-----|------------------|----------------|-----------------|-------------|-----------------------------|
| 1.UJ | 01/07/03 | 60M | Breast | 70 | severe | 24 | 33 | 0.375 (0.4) | Yes |
| 2. JW | 01/28/03 | 61M | Prostate | 50 | severe | 32 | 40 | 0.25 | Yes (didn't start) |
| 3. MR | 02/05/03 | 37M | Leukemia | 70 | moderate | 31 | 37 | 0.19 | Yes |
| 4.JF | 02/12/03 | 54M | Bladder | 70 | moderate | 26 | 32 | 0.23 | Yes |
| 5. JV | 02/21/03 | 34M | Anal | 70 | severe | 25 | 33 | 0.32 | Yes |
| 6.ML | 03/26/03 | 64F | Breast | 80 | severe | 19 | 26 | 0.36 | Yes |
| 7.PL | 03/26/03 | 61F | Breast | 70 | moderate | 21 | 29 | 0.38 | Yes (didn't start) |
| 8. RP | 03/12/03 | 83F | Lymphoma | 60 | severe | 42 | 48 | 0.14 | No |
| 9.TM | 05/09/03 | 55M | Lung | 60 | severe | 29 | 35 | 0.20 | Yes (incomplete) |
| 10. ME | 05/28/03 | 53F | Colon | 70 | severe | 23 | 28 | 0.21 | Yes |
| 11.LO | 05/23/03 | 67F | Breast | 60 | moderate | 18 | 23 | 0.27 | yes |
| 12.TM | 07/25/03 | 49F | Colon | 70 | moderate | 34 | 39 | 0.14 | No |
| 13.JC | 07/28/03 | 57F | Breast | 70 | moderate | 28 | 32 | 0.14 | No |
| 14. WL | 08/01/03 | 51M | Larynx | 70 | severe | 30 | 34 | 0.13 | Yes |
| 15. DF | 09/29/03 | 49F | Breast | 80 | severe | 11 | 12 | 0.09 | Yes |
| 16. RB | 10/15/03 | 67M | Prostate | 50 | severe | 18 | 28 | 0.55 | Yes (incomplete) |
| 17.JC | 11/03/03 | 64F | Breast | 70 | moderate | 31 | 36 | 0.16 | No |
| 18.TF | 11/21/03 | 67M | Lung | 50 | severe | 34 | 37 | 0.08 | Yes (protocol violation) |
| 19.JS | 12/01/03 | 73m | Acute leukemia | 50 | severe | 52 | 68 | 0.31 | No |
| 20. OI | 01/14/04 | 49m | Anal | 60 | severe | 25 | 35 | 0.04 | Yes (protocol violation) |
| 21. RS | 01/20/04 | 59m | Leukemia | 70 | moderate | 28 | 33 | 0.18 | Yes |
| 22.BJ | 03/10/04 | 64F | Lung | 60 | moderate | 22 | 27 | 0.22 | Yes (in progress) |

Effect of one week L-carnitine supplementation on fatigue in adult cancer patients with fatigue and carnitine deficiency.

| | Mean | N | Std. Dev | p-value |
|-------------|------|---|----------|---------|
| baseline | 69.4 | 8 | 14.0996 | |
| L-carnitine | 48.2 | 8 | 25.9557 | 0.16 |

Effect of one week L-carnitine supplementation on performance status (Karnofsky scores) in adult cancer patients with fatigue and carnitine deficiency.

| | Mean | N | Std. Dev | p-value |
|-------------|------|---|----------|---------|
| baseline | 72 | 8 | 4.4721 | |
| L-carnitine | 78 | 8 | 4.4721 | 0.07 |

Effect of one week L-carnitine supplementation on sleep in adult cancer patients with fatigue and carnitine deficiency.

| | Mean | N | Std. Dev | p-value |
|-------------|------|---|----------|---------|
| baseline | 10 | 8 | 4.3 | |
| L-carnitine | 6 | 8 | 3.5 | 0.24 |

Effect of one week L-carnitine supplementation on mood in adult cancer patients with fatigue and carnitine deficiency.

| | Mean | N | Std. Dev | p-value |
|-------------|------|---|----------|---------|
| baseline | 35 | 8 | 7.43 | |
| L-carnitine | 21 | 8 | 13.26 | 0.03 |

II. L-carnitine supplementation in cancer patients with fatigue and Carnitine deficiency. Randomized, Double blind, Placebo controlled.

Cruciani et. al. Preliminary data. NIHNCAM. 5R21AT001025-02

Description: Randomized, Double blind, Placebo-control.

Methods: 1500 mg L-carnitine liquid form B.I.D.

Inclusion criteria:

- cancer and fatigue
- Karnofsky score >50
- Carnitine deficiency <35 μ moles/L, <25 for females, or a ratio of acyl-carnitine (total-free)/free>0.4

Primary outcome: Fatigue

Secondary Outcomes: Depression, Quality of life, Performance status

III. ECOG. L-carnitine supplementation in cancer Patients with fatigue. Randomized, Double blind, Placebo controlled.

Cruciani et. al.

Description: Randomized, Double blind, Placebo controlled.

Methods: 1500 mg L-carnitine liquid form B.I.D.

Inclusion criteria:

- cancer and fatigue
- Karnofsky score >50

Primary outcome: Fatigue

Secondary Outcomes: Depression, Quality of life, Performance status

CONCLUSIONS

- **Fatigue is the most prominent symptom in cancer patients**
- **Carnitine metabolism is altered in cancer patients**
 - Metabolic Changes in normal cells
 - Metabolic changes in tumor cells
 - Chemotherapy
- **Future directions:**
 - Placebo-control studies
 - Long term effect of carnitine supplementation on tumor progression
 - Drug-drug interaction of antineoplastics and carnitine
 - Role of carnitine in symptoms other than fatigue (e.g. peripheral neuropathy)

Collaborators

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