Carnitine and Cancer

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Beth Israel Medical Center, N.Y., N. Y.
Chronic diseases

- Renal failure
- Hepatic failure
- Cancer
- Heart Failure
- AIDS
Cellular Energy Sources

- Glucose
- AA
- Long Chain Fatty Acids

Pyruvate + ATP

Acetyl-CoA + ATP

CARNITINE

β-oxidation

Krebs cycle

Mitochondrion
Why carnitine and cancer?

Carnitine metabolism

Carnitine biosynthesis:
- 25% of requirements
- Most humans tissues: trimethyl-lys to betaoxobetaine
- Liver, kidney and brain: from γ-betaoxobetaine

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

Cisplatin
- Decreased glomerular filtration
- Tubular damage

Ifosfamide

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

Dietary sources
- 75% of requirements
- Red meat and dairy products

Fatigue

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

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

Carnitine and cancer

Chloroacetylcoa

TCA intrinsic toxicity

Taxol
- Promotes microtubule formation

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

Bone marrow toxicity
- Urinary tract toxicity

Cisplatin

Walker 256 sarcoma bearing rats

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- Red meat and dairy products

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Walker 256 sarcoma bearing rats

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Cancer cells

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

Chronic myeloid leukemia patients.
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
    - Infection
    - Pulmonary disorders
    - Hepatic failure
    - Heart Failure
    - Renal Insufficiency
    - Malnutrition
  - Sleep disorders
  - Lack of exercise
  - Chronic pain
  - Opioids

- **Psychological**

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 erithropoyetin
  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?
Increased urinary excretion of carnitine in patients treated with cisplatin

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


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Before Day-1</th>
<th>During Day 1</th>
<th>During Day 2</th>
<th>During Day 3</th>
<th>After Day+1</th>
<th>After Day+7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free carnitine</td>
<td>39.3(29.5)</td>
<td><strong>731</strong>(523)</td>
<td><strong>919</strong>(539)</td>
<td>634(243)</td>
<td>406(282)</td>
<td>83.4(72.0)</td>
</tr>
<tr>
<td>Short-chain</td>
<td>77.3(55.2)</td>
<td>238(163)</td>
<td>212(113)</td>
<td>190(115)</td>
<td>200(135)</td>
<td>99(44.3)</td>
</tr>
<tr>
<td>Total carnitine</td>
<td>117(79)</td>
<td><strong>968</strong>(478)</td>
<td><strong>1130</strong>(602)</td>
<td><strong>824</strong>(345)</td>
<td><strong>606</strong>(348)</td>
<td>182(105)</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free carnitine</td>
<td>155(174)</td>
<td>193(176)</td>
<td>166(208)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Short-chain</td>
<td>173(72)</td>
<td>127(29)</td>
<td>133(40)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Total carnitine</td>
<td>328(230)</td>
<td>320(195)</td>
<td>300(229)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Bold = P<0.05 vs. day-1
Bold = P<0.05 vs. radiotherapy
Increased urinary excretion of carnitine in patients treated with cisplatin

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

**Study design**

- **accrual**
- **Oral L-carnitine**
  - 2 g B.I.D.
  - 1st w
  - 2nd w
  - 3rd w
- **completion**

**Baseline**
- FACT-F
- Physical exam
- Medical history
- Blood chemistries
- Tumor response

**Weekly assessments**
- FACT-F
- Physical exam
- Medical history
- Blood chemistries
- Tumor response
L-carnitine Supplementation for the Treatment of Chemotherapy Induced Fatigue  

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>30</td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>61 (45-70)</td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Cisplatin/gemcitabine</td>
<td>22</td>
</tr>
<tr>
<td>Cisplatin/epirubicin/fluorouracil</td>
<td>16</td>
</tr>
<tr>
<td>Cisplatin/etoposide</td>
<td>04</td>
</tr>
<tr>
<td>Cisplatin/taxol</td>
<td>04</td>
</tr>
<tr>
<td>Ifosfamide/adriamycin</td>
<td>04</td>
</tr>
<tr>
<td>Percent response rate to chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Non small cell lung cancer</td>
<td>44</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>39</td>
</tr>
<tr>
<td>Other</td>
<td>25</td>
</tr>
<tr>
<td>Timing of fatigue perception</td>
<td></td>
</tr>
<tr>
<td>After 1 cycle</td>
<td>20</td>
</tr>
<tr>
<td>After 2 cycles</td>
<td>30</td>
</tr>
</tbody>
</table>
### L-carnitine Supplementation for the Treatment of Chemotherapy Induced Fatigue


<table>
<thead>
<tr>
<th>Timing</th>
<th>Mean FACT-F (s.d.)</th>
<th>Mean Hb g/dl (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>19.7(±6.4)</td>
<td>13.6(±0.6)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001 p&gt;0.05</td>
<td></td>
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<tr>
<td>After 1 week</td>
<td>34.9(±5.4)</td>
<td>13.4(±0.5)</td>
</tr>
<tr>
<td></td>
<td>p&gt;0.05 p&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>After 2 weeks</td>
<td>35.7(±5.5)</td>
<td>13.0(±0.3)</td>
</tr>
<tr>
<td></td>
<td>p&gt;0.05 p&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>After 3 weeks</td>
<td>36.5(±5.1)</td>
<td>13.2(±0.5)</td>
</tr>
</tbody>
</table>
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 μmoles/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

- Getting Rt / Chemo: 45%
- Refused: 5%
- Signed Consent: 3%
- Too ill: 19%
- Language: 3%
- Mental status changes: 9%
- Renal failure: 2%
- Stroke: 1%
- On Procrit: 1%
- Brain tumor: 10%
- Other: 1%
- Too ill: 19%
L-carnitine supplementation in cancer patients with fatigue and carnitine deficiency.

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

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>N</th>
<th>Std. Dev</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>69.4</td>
<td>8</td>
<td>14.0996</td>
<td>0.16</td>
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<tr>
<td>L-carnitine</td>
<td>48.2</td>
<td>8</td>
<td>25.9557</td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>N</th>
<th>Std. Dev</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>72</td>
<td>8</td>
<td>4.4721</td>
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<tr>
<td>L-carnitine</td>
<td>78</td>
<td>8</td>
<td>4.4721</td>
<td>0.07</td>
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</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>N</th>
<th>Std. Dev</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>10</td>
<td>8</td>
<td>4.3</td>
<td>0.24</td>
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<tr>
<td>L-carnitine</td>
<td>6</td>
<td>8</td>
<td>3.5</td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>N</th>
<th>Std. Dev</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>35</td>
<td>8</td>
<td>7.43</td>
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<tr>
<td>L-carnitine</td>
<td>21</td>
<td>8</td>
<td>13.26</td>
<td>0.03</td>
</tr>
</tbody>
</table>
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 µmoles/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

Bruce Culleney, MD.
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Albert Einstein College of Medicine, Bronx, NY.

Ella Dvorkin, CSW.
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Stephan Malamud, MD.
Cancer Center, Beth Israel Medical Center, NY, NY.

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Beth Israel Medical Center, NY, NY.