Nutritional effects of cancer therapy and potential modulation of tumor growth

A. Laviano (IT)
Nutritional effects of cancer therapy and potential modulation of tumour growth

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Cocoa

- Theobroma cacao
- Drink of Gods (Xocoatl)
  - theo = God
  - broma = drink
- Mexico (Maya, Incas, Aztecs)
- Aphrodisiac
Learning Objectives

• Understanding the impact of anti-cancer therapies on nutritional status
• Understanding the negative role of caloric restriction/fasting on cancer patients’ nutritional status and outcome
• Discussing the inhibitory role of specific nutrients on tumour growth
• Discussing the role of specific nutrients in enhancing efficacy of anti-cancer therapies
Cancer Statistics, 2014

Rates are age adjusted to the 2000 US standard population. Incidence rates are adjusted for delays in reporting.

Siegel R et al. CA Cancer J Clin 2014; 64:9-29
Cancer Statistics, 2014


Siegel R et al. CA Cancer J Clin 2014; 64:9-29
Current limitations of anti-cancer strategies

- Too much focus on tumor cells, minimal on the human body attached to them (i.e., up to 40% of cancer patients receive chemotherapy in the last month of life, but ASCO quality standards recommend <10%).
- Excessive toxicity.
- High costs = financial toxicity of cancer (i.e., sipuleucel-T yields 4 month survival advantage in advanced prostate cancer at 93,000 USD per course of treatment).
- Questionable cost-effectiveness (i.e., new drugs approved after demonstration of survival extension by 15 days).
- Study design (i.e., survival as the ultimate outcome).
- Statistical analysis or “the seductive certainty of significance” (Nuzzo R. Nature 2014; 506:150-152).
Cancer treatment toxicity

• Non preventable factors
  - patient’s genetic background
  - pharmacokinetic & pharmacodynamic

• Preventable factors
  - dosage
  - timing
  - malnutrition
# Genetic Variants in Inflammation-Related Genes Are Associated with Radiation-Induced Toxicity Following Treatment for Non-Small Cell Lung Cancer

**Table 3.** Cumulative effect of unfavorable genotypes and radiation-induced toxicity risk.

<table>
<thead>
<tr>
<th>Number of Unfavorable Genotypes</th>
<th>Grade &lt;2 n</th>
<th>Grade ≥2 n</th>
<th>*HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esophagitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>49</td>
<td>11</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>14</td>
<td>3.71</td>
<td>1.53 to 8.99</td>
<td>0.004</td>
</tr>
<tr>
<td>≥5</td>
<td>16</td>
<td>42</td>
<td>8.85</td>
<td>4.19 to 18.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Phenomoniitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>41</td>
<td>1</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>17</td>
<td>13.30</td>
<td>1.72 to 102.94</td>
<td>0.013</td>
</tr>
<tr>
<td>≥4</td>
<td>15</td>
<td>20</td>
<td>69.42</td>
<td>8.62 to 558.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*adjusted for age, gender, pack years, clinical stage, performance status, treatment regimen, radiation type, and radiation dosage.

Unfavorable genotypes: IL6:rs1800795, IL16:rs11556218, TNF:rs1799724, PTGS2:rs20417.
PTGS2:rs5275, PTGS2:rs689470, IL4:rs1801275, IL10:rs1800872, IL10RA:rs3135932,
IL1B:rs16944, IL2RB:rs228942, IL8:rs4073, IL10RB:rs2834167, IL13:rs1800925, NOS2:rs2297518.

Unfavorable genotypes: IL1A:rs1800587, IL8:rs4073, TNF:rs1799724, TNFRSF1B:rs1061622.
MIF:rs755622, IL4:rs2243250, IL4:rs2070874, IL13:rs10800925, IL13:rs20541, NOS3:rs1799983, NFKBIA:rs1799983.
doi:10.1371/journal.pone.0012402.t003

Cancer treatment toxicity

• **Non preventable factors**
  - patient’s genetic background
  - pharmacokinetic & pharmacodynamic

• **Preventable factors**
  - dosage
  - timing
  - malnutrition (=cachexia → muscle loss)
Sarcopenia Predicts Early Dose-Limiting Toxicities and Pharmacokinetics of Sorafenib in Patients with Hepatocellular Carcinoma

Olivier Mir\textsuperscript{1,2}, Romain Coriat\textsuperscript{1,3}, Benoît Blanchet\textsuperscript{1,4}, Jean-Philippe Durand\textsuperscript{1}, Pascale Boudou-Rouquette\textsuperscript{1}, Judith Michels\textsuperscript{1}, Stanislas Ropert\textsuperscript{1}, Michel Vidal\textsuperscript{4}, Stanislas Pol\textsuperscript{2}, Stanislas Chaussade\textsuperscript{3}, François Goldwasser\textsuperscript{1}

\textbf{a} All dose-limiting toxicities (DLT)

\begin{center}
\begin{tabular}{c|c|c|c|c|c|c}
 & \multicolumn{2}{c}{Incidence of DLT (\%)} & \multicolumn{2}{c}{Incidence of DLT (\%)} & \multicolumn{2}{c}{Incidence of DLT (\%)} \\
 & Sarcopenic & Non-sarcopenic & Sarcopenic & Non-sarcopenic & Sarcopenic & Non-sarcopenic \\
\hline
& & & & & & \\
\end{tabular}
\end{center}

\textit{p}<0.0006

\textbf{b} Hand Foot Skin Reaction (grade 3/4)

\begin{center}
\begin{tabular}{c|c|c|c|c|c|c}
 & \multicolumn{2}{c}{Incidence of DLT (\%)} & \multicolumn{2}{c}{Incidence of DLT (\%)} & \multicolumn{2}{c}{Incidence of DLT (\%)} \\
 & Sarcopenic & Non-sarcopenic & Sarcopenic & Non-sarcopenic & Sarcopenic & Non-sarcopenic \\
\hline
& & & & & & \\
\textit{ns}
\end{tabular}
\end{center}

\textbf{c} Diarrhea (grade 3/4)

\begin{center}
\begin{tabular}{c|c|c|c|c|c|c}
 & \multicolumn{2}{c}{Incidence of DLT (\%)} & \multicolumn{2}{c}{Incidence of DLT (\%)} & \multicolumn{2}{c}{Incidence of DLT (\%)} \\
 & Sarcopenic & Non-sarcopenic & Sarcopenic & Non-sarcopenic & Sarcopenic & Non-sarcopenic \\
\hline
& & & & & & \\
\textit{p}<0.05
\end{tabular}
\end{center}

\textbf{d} Sorafenib AUC (mg\textsuperscript{\textbullet}/h/L)

\begin{center}
\begin{tabular}{c|c|c|c|c|c|c|c}
 & \multicolumn{2}{c}{Sorafenib AUC (mg\textsuperscript{\textbullet}/h/L)} & \multicolumn{2}{c}{Sorafenib AUC (mg\textsuperscript{\textbullet}/h/L)} & \multicolumn{2}{c}{Sorafenib AUC (mg\textsuperscript{\textbullet}/h/L)} \\
 & Sarcopenic & Non-Sarcopenic & Sarcopenic & Non-Sarcopenic & Sarcopenic & Non-Sarcopenic \\
\hline
& & & & & & \\
\end{tabular}
\end{center}

\textbf{PLO}S ONE 2012; 7 (5):e37563
Cancer Cachexia in the Age of Obesity: Skeletal Muscle Depletion Is a Powerful Prognostic Factor, Independent of Body Mass Index

- n = 1473 (lung or GI cancer, at presentation).
- BMI distribution: 17% obese, 35% overweight, 36% normal weight
- High weight loss, low muscle index, and low muscle attenuation are independent prognostic factors of survival.
- Survival model containing conventional variables (i.e., cancer diagnosis, stage, age, performance status) has c statistic of 0.73.
- Survival model including only BMI, weight loss, muscle index, and muscle attenuation has a c statistic of 0.92.

Martin L et al. J Clin Oncol 2013; 31:1539-1547
Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy\textsuperscript{1–3}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Graphs showing the effect of nutritional intervention on calorie intake (A) and protein intake (B) over time.}
\end{figure}

Anti-inflammatory mediators

Leukotrienes of 5 series, e.g. LTB₅, LTC₅, LTD₅

Leukotrienes of 4 series, e.g. LTB₄, LTC₄, LTD₄

EPA

Prostanoids of the 3 series, e.g. TXA₃, PGE₃, PGI₃

Prostanoids of the 2 series, e.g. TXA₂, PGE₂, PGI₂

AA

Lipoxygenase

Cyclooxygenase

Pro-inflammatory mediators
Nutritional Intervention With Fish Oil Provides a Benefit Over Standard of Care for Weight and Skeletal Muscle Mass in Patients With Nonsmall Cell Lung Cancer Receiving Chemotherapy

Table 2. Weight and Tissue Changes Quantified With CT Imaging From Baseline to After Chemotherapy in the Standard of Care, Fish Oil, and Reference Groups

<table>
<thead>
<tr>
<th>Changes</th>
<th>Standard of Care Group</th>
<th>Fish Oil Group</th>
<th>Reference Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change, kg</td>
<td>-2.3 ± 0.9</td>
<td>0.5 ± 1.0(^b)</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>Muscle rate of change, %/100 d</td>
<td>-6.8 ± 2.6</td>
<td>0.1 ± 1.6(^b)</td>
<td>-6.0 ± 0.9</td>
</tr>
<tr>
<td>IMAT rate of change, %/100 d</td>
<td>9.5 ± 5.2</td>
<td>-16.4 ± 13.9(^b)</td>
<td>11.1 ± 3.5</td>
</tr>
<tr>
<td>TAT rate of change, %/100 d</td>
<td>-3.9 ± 5.0</td>
<td>-5.0 ± 6.5</td>
<td>-6.0 ± 4.6</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; IMAT, intermuscular adipose tissue; TAT, total adipose tissue.

\(^a\) The number of patients varies because of images outside the viewing field. Results are shown as the mean ± standard error.

\(^b\) Significantly different from standard of care (\(P < .05\), using the two-sample Student t test.)

Murphy RA et al. Cancer 2011; 117:1775-82
Oral nutritional supplements containing n-3 polyunsaturated fatty acids affect quality of life and functional status in lung cancer patients during multimodality treatment: an RCT

BS van der Meij¹, JAE Langius¹, MD Spreeuwenberg², SM Slootmaker³, MA Paul⁴, EF Smit⁵ and PAM van Leeuwen⁶

Figure 1. Physical activity (daily PAM score) over time for the I and C groups. Values are mean ± s.d., baseline: n = 12 (I), n = 16 (C); week 3: n = 13 (I) and n = 17 (C); week 5: n = 8 (I), n = 13 (C). *P < 0.05, difference between the I and C group (analysed by generalised estimating equations, with baseline value and sex as covariate).
Normal protein anabolic response to hyperaminoacidemia in insulin-resistant patients with lung cancer cachexia

Aaron Winter, Jacqueline MacAdams, Stéphanie Chevalier

Fig. 3. Change in whole-body net leucine balance in response to the hyperinsulinemic, euglycemic, iso/hyperaminoacidemic clamp. Bars are means ± SEM. White bars: Controls; Black bars: NSCLC. Net balance = synthesis − breakdown. "p < 0.05 versus controls by ANCOVA with adjustment for the change in insulin.
Impact of cancer treatment on nutritional status

Dr. Stanley B. Burns’ cases (1800)
Influence of taste disorders on dietary behaviors in cancer patients under chemotherapy

Karla Sánchez-Lara	extsuperscript{1*}, Ricardo Sosa-Sánchez	extsuperscript{1}, Dan Green-Renner	extsuperscript{1}, Cindy Rodríguez	extsuperscript{1}, Alessandro Laviano	extsuperscript{2}, Daniel Motola-Kuba	extsuperscript{1}, Oscar Arrieta	extsuperscript{2}

Table 4 Median of sweet detection threshold vs. diet consumption in cancer patients in the second chemotherapy cycle

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>≥ 6.4 μmol/ml</th>
<th>&lt;6.4 μmol/ml</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories per Day</td>
<td>1,450 ± 833</td>
<td>1,970 ± 658</td>
<td>0.05</td>
</tr>
<tr>
<td>Proteins (g/day)</td>
<td>53 ± 32</td>
<td>74 ± 45</td>
<td>0.02</td>
</tr>
<tr>
<td>Carbohydrates (g/day)</td>
<td>167 ± 81</td>
<td>240 ± 84</td>
<td>0.04</td>
</tr>
<tr>
<td>Fat (g/day)</td>
<td>57 ± 33</td>
<td>82 ± 31</td>
<td>0.08</td>
</tr>
<tr>
<td>Zinc (mg/day)</td>
<td>9.6 ± 5.4</td>
<td>17 ± 7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

g = grams
mg = milligrams
μmol/ml = micromole/millimeter
* Mann-Whitney U test
Direct effects of doxorubicin on skeletal muscle contribute to fatigue

van Norren K et al. Br J Cancer 2009; 100:311-4
Evolution of body weight, muscle area, and adipose area during 6 months of treatment with sorafenib (gold; n = 48) vs placebo (blue; n = 32).

Antoun S et al. JCO 2010;28:1054-1060
Specific nutrients and tumour growth

• Do nutrients stimulate the growth of cancer cells? **Yes**

• Does nutritional support in cancer patients accelerate tumour growth in a clinically relevant manner? **Probably not**

• Do malnourished cancer patients live longer than wellnourished cancer patients? **No**
Brain tumor initiating cells adapt to restricted nutrition through preferential glucose uptake

Cancer cells interact with stroma cells to create an inflammatory microenvironment which supports proliferation of tumor cells.

Figure 1 | Extracellular tumour-microenvironment interactions. Examples of

Neutralizing Tumor-Promoting Chronic Inflammation: A Magic Bullet?

Lisa M. Coussens, Laurence Zitvogel, A. Karolina Palucka

Science 2013; 339:286-291
Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial

Supplementation With Fish Oil Increases First-Line Chemotherapy Efficacy in Patients With Advanced Nonsmall Cell Lung Cancer

Table 3. Chemotherapy Outcomes and Survival in the Standard of Care and Fish Oil Groups

<table>
<thead>
<tr>
<th></th>
<th>Standard of Care(^a)</th>
<th>Fish Oil(^b)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, no. (%)</td>
<td>8 (25.8)</td>
<td>9 (60.0)</td>
<td>.008</td>
</tr>
<tr>
<td>Clinical benefit, no. (%)</td>
<td>13 (41.9)</td>
<td>12 (80.0)</td>
<td>.02</td>
</tr>
<tr>
<td>Complete response, no. (%)</td>
<td>1 (3.2)</td>
<td>1 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Partial response, no. (%)</td>
<td>7 (22.6)</td>
<td>9 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Stable disease, no. (%)</td>
<td>5 (16.1)</td>
<td>2 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease, no. (%)</td>
<td>18 (58.1)</td>
<td>3 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Number of chemotherapy cycles received</td>
<td>3.0 ± 1.4</td>
<td>3.9 ± 0.9</td>
<td>.02</td>
</tr>
<tr>
<td>Time on chemotherapy, d</td>
<td>60.3 ± 31.1</td>
<td>78.9 ± 23.5</td>
<td>.05</td>
</tr>
<tr>
<td>1-Year survival (%)</td>
<td>38.7</td>
<td>60.0</td>
<td>.15</td>
</tr>
</tbody>
</table>

Mean ± standard deviation, two-sample t-test and \(\chi^2\)-test.
\(^a\) \(n = 31\).
\(^b\) \(n = 15\).

Murphy RA et al. Cancer 2011; 117:3774-3780
Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival\textsuperscript{1–5}

Nikki Buijs, Marian AE van Bokhorst-de van der Schueren, Jacqueline AE Langius, C Rene Leemans, Dirk J Kuik, Mechteld AR Vermeulen, and Paul AM van Leeuwen

**FIGURE 1.** Kaplan-Meier curve of the overall survival of severely malnourished patients with head and neck cancer after major surgery. The black line represents the arginine group ($n = 17$), and the dotted line represents the control group ($n = 15$).

**FIGURE 2.** Kaplan-Meier curve of locoregional recurrence-free survival in severely malnourished patients with head and neck cancer after major surgery. The black line represents the arginine group ($n = 17$), and the dotted line represents the control group ($n = 15$).

*A m J Clin Nutr 2010; 92:1151-1156*
## Caloric restriction and differential stress response in oncology

<table>
<thead>
<tr>
<th></th>
<th>Life-span increase</th>
<th>Beneficial health effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dietary restriction</td>
<td>Mutations/ drugs</td>
</tr>
<tr>
<td><strong>Yeast</strong></td>
<td>3-fold</td>
<td>10-fold (with starvation/DR)</td>
</tr>
<tr>
<td><strong>Worms</strong></td>
<td>2- to 3-fold</td>
<td>10-fold</td>
</tr>
<tr>
<td><strong>Flies</strong></td>
<td>2-fold</td>
<td>60-70%</td>
</tr>
<tr>
<td><strong>Mice</strong></td>
<td>30-50% (~100% in combination with DR)</td>
<td>30-50%</td>
</tr>
<tr>
<td><strong>Monkeys</strong></td>
<td>Trend noted</td>
<td>Not tested</td>
</tr>
<tr>
<td><strong>Humans</strong></td>
<td>Not determined</td>
<td>Not determined (GHR-deficient subjects reach old age)</td>
</tr>
</tbody>
</table>

*Fontana L et al. Science 2010; 328:321-326*
The Ratio of Macronutrients, Not Caloric Intake, Dictates Cardiometabolic Health, Aging, and Longevity in Ad Libitum-Fed Mice

Toxicity in Chemotherapy — When Less Is More
Alessandro Laviano, M.D., and Filippo Rossi Fanelli, M.D.

A Mice Fed Ad Libitum
- Normal cells
- Cancer cells
- Chemotherapy
- Destruction of normal cells
- Shrinkage of tumor volume
- Side effects, toxicity

B Mice Subjected to Short-Term Fasting
- Normal cells
- Cancer cells
- Fasting mimicking diet
- Differential stress resistance leads to activation of protective response
- Oncogenes prevent differential stress resistance
- Chemotherapy
- Decrease in side effects and toxicity
- Increase in objective response

The Ketogenic Diet Is an Effective Adjuvant to Radiation Therapy for the Treatment of Malignant Glioma

Palliative care reduces morbidity and mortality in cancer

Gabrielle B. Rocque and James F. Cleary

Key Messages

• By altering taste and smell, chemotherapy reduces food intake.
• Specific chemotherapeutic agents have a negative and direct impact on muscle mass.
• Caloric restriction in vulnerable individuals, like cancer patients receiving active anti-cancer therapies, may favour weight loss and cachexia.
• Omega-3 fatty acids have been shown to enhance the efficacy of chemotherapy, although these preliminary results need to be validated in larger trials.
“Quid est veritas?”
“What is the truth?”

“Vir qui adest”
“The man (=patient) in front of you”