Computed tomography-defined sarcopenia: a novel independent predictor of mortality, chemotoxicity and complications in patients with cancer

Vickie E Baracos
Albert Cancer Foundation Chair in Palliative Medicine
University of Alberta
2015
Disclosures related to this presentation:

None
Outline:

1. What’s skeletal muscle got to do with it?
2. Precise and specific quantification of skeletal muscle in oncologic images
3. Sarcopenia (severe skeletal muscle depletion) and cancer outcomes
Definition and classification of cancer cachexia, an international consensus

Fearon K et al. Lancet Oncology 2011: 12(5):489-495

• a multi-factorial syndrome of involuntary weight loss

• Severity classified according to the rate of ongoing loss of weight in combination with the concurrent degree of depletion of energy stores and body protein mass

• characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass)
Central nervous system inflammation induces muscle atrophy via activation of the hypothalamic–pituitary–adrenal axis. 

Experimental Medicine, 2011; 208 (12) 2449-63


CRH Corticotropin-releasing hormone, ACTH adrenocorticotropic hormone; POMC Pro-opiomelanocortin
Image – based muscle quantification of lean and fat on axial CT images

Variation in muscle across individuals of identical height and weight

BMI = 30.0 kg/m²

Martin L et al. Cancer cachexia in the age of obesity, J Clinical Oncology 2013 31(12):1539-47
Variation in fat; identical muscle mass

Martin L et al. Cancer cachexia in the age of obesity, J Clinical Oncology 2013 31(12):1539-47
Precision imaging of skeletal muscle

Skeletal muscle index (cm²/m²) vs Body mass index (kg/m²)

- **b₁**: SMI 29.8 cm²/m², BMI 40.2 kg/m²
- **b₂**: SMI 29.8 cm²/m², BMI 28.1 kg/m²
- **b₃**: SMI 29.7 cm²/m², BMI 15.3 kg/m²
- **c₁**: SMI 33.7 cm²/m², BMI 29.5 kg/m²
- **c₂**: SMI 46.3 cm²/m², BMI 29.4 kg/m²
- **c₃**: SMI 58.3 cm²/m², BMI 29.4 kg/m²
Quantification of skeletal muscle mass

A general definition of sarcopenia:

>2 Standard Deviations below the mean musculature for young healthy adults

For an 80 kg man, <22 kg (32 kg is normal)
For a 70 kg woman, <13 kg (21 kg is normal)
Sarcopenia: a low level of muscle, characterized by statistically significant* increase in health risk (mortality, toxicity, physical disability).

*statistical test for a threshold value - i.e. Optimal stratification
• N=250, independent of age, disease stage and performance status
• 11 months vs 21 months median survival

- N=163, HCV (34%), alcohol (20%), autoimmune liver disease (13%), HBV (6%), and others (27%).

- Independently prognostic in a model including Child-Pugh and MELD scores (Model for End Stage Liver Disease)
Median overall survival, months

Multivariate p < 0.05 *, p < 0.005 **, p < 0.0005***

Hazard Ratio for death
Pathological fatty infiltration of muscle

A – Low Muscle Attenuation
Patient 1
Age: 64 years old
Body mass index: 23.5 kg/m²
Skeletal muscle index: 47.8 cm²/m²
Mean muscle attenuation = 18.5 HU

Intmuscular adipose tissue
-190 to -30 HU

Low attenuation muscle
1: 0 to +29 HU
2: -29 to 0 HU

B – High Muscle Attenuation
Patient 2
Age: 63 years old
Body mass index: 23.1 kg/m²
Skeletal muscle index: 46.7 cm²/m²
Mean muscle attenuation = 43.5 HU

Normal attenuation muscle
+29 to +150 HU
Correlation between psoas muscle radiodensity by tertile and disease-free survival ($P = 0.04$) and distant disease-free survival ($P = 0.0002$) in melanoma.

Sabel MS et al. Melanoma; Ann Surg Oncol (2011) 18:3579–3585
Median overall survival, months

Sabel Melanoma
Antoun RCC

Hazard Ratio for death

[Knijnenburg RCC]
Chu FL
Martin Lung Gl

Multivariate p < 0.05 *, p < 0.005 **, p < 0.0005***
Infection Risk in Sarcopenia, Multivariate Odds Ratio

Energy Appeal
Signals
Cytokines
Eicosanoids
Energy Fuels
Glucose
Amino acids

- Sepsis, liver transplant
- Infection, liver transplant
- Infection, colon cancer surgery
- Nosocomial infection, nursing home

Matsuda T et al. Liver Transpl. 2013 Dec 20
An old story: alterations in fat mass alters the distribution of lipophilic drugs [e.g. halothane, fentanyl]:


But......What about the partition of non-lipophilic agents in lean tissue compartment?
Possible antineoplastic drug partition in lean tissue?

Large variation in LBM within any BSA range

If a hypothetical drug were given to these patients at 1000 mg/m², assuming partition in LBM, then the dose / kg lean body mass would be:

- Average: 40.0 mg/kg LBM
- SD: 6.6
- Min: 24.7
- Max: 73.7
Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, Mackey JR, Koski S, Pituskin E, Sawyer MB


Metastatic breast ca, taxane – or anthracycline resistant.

1250 mg/m² capecitabine BID

Dose – limiting toxicity defined as ≥ grade 2 and resulting in interruption of treatment (dose reduction or dose delay)

P=0.039
## Body Composition as an Independent Determinant of 5-Fluorouracil – Based Chemotherapy Toxicity

Carla M.M. Prado,1,2 Vickie E. Baracos,1,2 Linda J. McCargar,2 Marina Mourtzakis,1 Karen E. Mulder,1 Tony Reiman,1 Charles A. Butts,1 Andrew G. Scarfe,1 and Michael B. Sawyer1

Clin Cancer Res 2007;13(11) June 1, 2007

<table>
<thead>
<tr>
<th></th>
<th>Muscular &lt;20 mg/kg LBM</th>
<th>Sarcopenic &gt;20 mg/kg LBM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose /m²</td>
<td>425</td>
<td>425</td>
<td></td>
</tr>
<tr>
<td>Dose / kg LBM</td>
<td>16.1 ± 2.3</td>
<td>21.2 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dose limiting toxicity %</td>
<td>52%</td>
<td>93%</td>
<td>0.005</td>
</tr>
<tr>
<td>BSA m²</td>
<td>1.7 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>0.954</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.4 ± 17.2</td>
<td>69.3 ± 17.5</td>
<td>0.896</td>
</tr>
<tr>
<td>LBM, kg</td>
<td>41.3 ± 8.3</td>
<td>35.0 ± 3.9</td>
<td>0.011</td>
</tr>
</tbody>
</table>
Lean body mass as an independent determinant of dose limiting toxicity and neuropathy in patients with metastatic colon cancer treated with FOLFOX regimens.
Ali R et al, Cancer Medicine, in press 2015.

<table>
<thead>
<tr>
<th></th>
<th>Oxaliplatin Dose / kg LBM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 3.09 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Muscular</td>
</tr>
<tr>
<td>n</td>
<td>17</td>
</tr>
<tr>
<td>% male</td>
<td>16 (94.1%)</td>
</tr>
<tr>
<td>Lean Body Mass (kg)</td>
<td>55.5 ± 6.7</td>
</tr>
<tr>
<td>Oxaliplatin (mg/kg LBM)</td>
<td>2.86 ± 0.16</td>
</tr>
<tr>
<td>5FU (mg/kg LBM)</td>
<td>94.3 ± 5.5</td>
</tr>
<tr>
<td>Dose-limiting-toxicity; 1st 4 cycles, n (%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Early dose-limiting neuropathy, n (%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Possible antineoplastic drug partition in lean tissue?

Large variation in LBM within any body weight range

If a hypothetical drug were given to all of these patients at **800 mg flat dose**, then the dose per kg lean body mass would be:

- **Average**: 18.0 mg/kg LBM
- **Standard deviation**: 4.0
- **Min**: 9.1
- **Max**: 32.8

Lean body mass (kg)  
CT-defined
Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma

S. Antoun1*, V. E. Baracos2*, L. Birdsell2, B. Escudier3 & M. B. Sawyer2

1Department of Supportive Care, Institut Gustave Roussy, Villejuif, France; 2Department of Oncology, University of Alberta, Edmonton, Canada and 3Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France

Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients

O Huillard1, O Mir1, M Peyromaure2, C Tlemsani1, J Giroux1, P Boudou-Rouquette1, S Ropert1, N Barry Delongchamps2, M Zerbib2 and F Goldwasser1

Chemotherapy is reduced >20% or terminated in sarcopenic patients, due to excess toxicity, p<0.05

Dose-limiting toxicity, %

Colon, FOLFOX
Colon, 5 fluorouracil
Colon, FOLFIRI
Colon, FOLFOX
Lung, gem & vin
Phase I
Thyroid, vandetanib
Liver, sorafenib
Renal, sunitinib
Renal, sunitinib
Renal, sorafenib
Breast, capecitabine

Normal
Sarcopenic

A few preliminary pharmacokinetic data
Sarcopenia Predicts Early Dose-Limiting Toxicities and Pharmacokinetics of Sorafenib in Patients with Hepatocellular Carcinoma

Olivier Mir¹,²*, Romain Coriat¹,³, Benoît Blanchet¹,⁴, Jean-Philippe Durand¹, Pascaline Boudou-Rouquette¹, Judith Michels¹, Stanislas Ropert¹, Michel Vidal⁴, Stanislas Pol⁵, Stanislas Chaussade³, François Goldwasser¹

¹ Centre for Research on Angiogenesis Inhibitors (CERIA), Department of Medical Oncology, Cochin Teaching Hospital, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, ² Department of Clinical Pharmacology, Cochin Teaching Hospital, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, ³ Department of Gastro-Enterology, Cochin Teaching Hospital, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, ⁴ Laboratory of Pharmacology and Toxicology, Cochin Teaching Hospital, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, ⁵ Department of Hepatology and INSERM U1016, Cochin Teaching Hospital, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France
**All Dose Limiting Toxicities (DLT)**

- **Sarcopenic**
  - Incidence of DLT (%): 80

- **Non-sarcopenic**
  - Incidence of DLT (%): 20

*p < 0.0006*

**Diarrhea (grade 3/4)**

- **Sarcopenic**
  - Incidence of DLT (%): 40

- **Non-sarcopenic**
  - Incidence of DLT (%): 10

*p < 0.05*
Sarcopenic patients have ~ twice higher sorafenib AUC


<table>
<thead>
<tr>
<th></th>
<th>Sarcopenic</th>
<th>Non sarcopenic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median adjusted dose</td>
<td>102.4</td>
<td>53.7</td>
<td>0.013</td>
</tr>
<tr>
<td>for AUC (mg/l.h) on</td>
<td>48.0-137.8</td>
<td>24.5-74.5</td>
<td></td>
</tr>
<tr>
<td>day 28.</td>
<td>Range</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Patients with DLT</th>
<th>Patients without DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median adjusted dose</td>
<td>106.4</td>
<td>56.7</td>
</tr>
<tr>
<td>for AUC (mg/l.h) on</td>
<td>48-177.8</td>
<td>24.5-136.7</td>
</tr>
<tr>
<td>day 28.</td>
<td>Range</td>
<td></td>
</tr>
</tbody>
</table>
The lean body mass \((p<0.0001)\) and a polymorphism in the ABCG2 transporter \((421C>A)\) \((p=0.014)\) were 2 independent parameters accounting for the variability of composite (sunitinib + SU12662) exposure (AUC).
Lean body mass is correlated with dose-normalized composite (sunitinib + SU12662) exposure (AUC) in patients with renal cell carcinoma.

Spearman’s rho = 0.239
p < 0.0001
Potential reversibility of sarcopenia in patients with advanced cancer
In patients with advanced stages of cancer, the capacity for muscle protein anabolism is....?
(True or False)

A. Largely disabled due to old age, poor nutritional status, deconditioning, inflammation, cancer, and comorbid conditions.
Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial

Enobosarm is an orally active small molecule agonist of the skeletal muscle androgen receptor.

Mean absolute change from baseline to day 113 in stair climb time and power
Discussion

• Methods in place, radiologists not quite on board
• Current patient populations [radiologic] body habitus, cachexic→ obese, sarcopenic→muscular
• Emerging evidence suggests that a high dose per kg lean body mass exceeds the tolerance of some [sarcopenic or sarcopenic obese] patients; could muscular patients tolerate higher doses?
• Sarcopenic person is generally unfit.
• Muscle loss may be reversible
• Need more new prospective work on outcomes, pharmacokinetics, intervention.