Detection and evaluation of the role of sarcopenia in elderly patients with cancer treated with chemotherapy. ONCOSARCO Project. Preliminary results


Unit of Cancer in the Elderly

Medical Oncology Department. Hospital General Virgen de la Luz de Cuenca. SPAIN
Cancer in the elderly

Risk (%)

Age

Male
Female

0-39
40-59
60-79

1.6
8.2
33.7

1.9
9.2
22.2

American Society of Cancer, 2000
The final objective is to arrange the best treatment to the selected elderly cancer patient. Better than age, FRAILTY

WHO?
Concept of frailty

INDEPENDENT elderly...

...BUT...FRAIL elderly...

constipation
traumatism
change in the medication
infection
hospitalization

DEPENDENT

Prevalence of frailty in Europe

CGA: a tool to take decisions

Balducci L. Cancer Control 2007 (14):1
Frailty. The Fried criteria

Fried criteria: ≥3 of the following conditions:
- Unintentional weight loss.
- Weakness.
- Self-reported exhaustion.
- Slow walking speed.
- Low physical activity.

Table 1. Operationalizing a Phenotype of Frailty

<table>
<thead>
<tr>
<th><strong>A. Characteristics of Frailty</strong></th>
<th><strong>B. Cardiovascular Health Study Measure</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Shrinking: Weight loss</td>
<td>Baseline: &gt;10 lbs lost unintentionally in</td>
</tr>
<tr>
<td>(unintentional)</td>
<td>prior year</td>
</tr>
<tr>
<td>Sarcopenia (loss</td>
<td></td>
</tr>
<tr>
<td>of muscle mass)</td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>Grip strength: lowest 20% (by gender, body</td>
</tr>
<tr>
<td></td>
<td>mass index)</td>
</tr>
<tr>
<td>Poor endurance; Exhaustion</td>
<td>“Exhaustion” (self-report)</td>
</tr>
<tr>
<td>Slowness</td>
<td>Walking time/15 feet: slowest 20% (by</td>
</tr>
<tr>
<td></td>
<td>gender, height)</td>
</tr>
<tr>
<td>Low activity</td>
<td>Kcals/week: lowest 20%</td>
</tr>
<tr>
<td></td>
<td>males: &lt;383 Kcals/week</td>
</tr>
<tr>
<td></td>
<td>females: &lt;270 Kcals/week</td>
</tr>
</tbody>
</table>

C. Presence of Frailty

Positive for frailty phenotype: ≥3 criteria present
Intermediate or prefrail: 1 or 2 criteria present

Fried L. J Gerontol (Medical Sciences) 2001;56a(3): M146-M156
Definition of sarcopenia

30% in >70 years

Table 1. Criteria for the diagnosis of sarcopenia

<table>
<thead>
<tr>
<th>Diagnosis is based on documentation of criterion 1 plus (criterion 2 or criterion 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low muscle mass</td>
</tr>
<tr>
<td>2. Low muscle strength</td>
</tr>
<tr>
<td>3. Low physical performance</td>
</tr>
</tbody>
</table>

The European Working Group on Sarcopenia in Older People (EWGSOP)
Sarcopenia and cancer

- **Toxicity** of treatment:
  - **Chemotherapy**:
    - Capecitabine in breast cancer (Prado, 2009).
    - Chemotherapy in metastatic colorectal cancer (Barret, 2014).
    - Phase I trials (Cousin, 2014).
  - **Targeted treatments**:
    - Sunitinib in renal cancer (Huillard, 2013; Cushen, 2014).
    - Sorafenib in renal cancer (Antoun, 2010).

- **Predictor of response** to oncologic treatment:
  - A worse response to neoadjuvant chemotherapy in women with breast cancer (Del Fabbro, 2012).
  - Shorter time to tumor progression in metastatic breast cancer treated with capecitabine (Prado, 2009).

- **Events after surgery**:
  - Mortality after cystectomy after radical cystectomy (Psutka, 2014; Payton, 2014; Smith, 2014).
  - Adverse postoperative outcome after colorectal cancer surgery (Reisinger, 2014).

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Objectives

- To assess the role of sarcopenia as a **predictor of tolerance and toxicity** to chemotherapy in elderly patients with diagnosis of cancer.

- To identify which of these parameters, sarcopenia or frailty, is **the best tool to predict tolerance to chemotherapy** in elderly patients diagnosed with cancer.

- To determine the **normal values** of many variables related to “Muscle mass”, “Muscle strength” and “Physical performance” in Cuenca, SPAIN.
Material and Methods
Design and study population

- **Study subjects:** ≥70 years.
  - Diagnosis of cancer (any type and any stage).
  - Unit of Cancer in the Elderly. Medical Oncology Department. Hospital General Virgen de la Luz in Cuenca.
- Selection of patients:
  - Treatment with chemotherapy.
  - To sign informed consent previous to the inclusion.
  - Not been hospitalized two weeks prior to the inclusion in this project.
- **Study design:** prospective cohort study.
  - The baseline visits were held from January 2013 to January 2014.
  - The recruitmen will extend until January 2015. These are the preliminary results after the first year of the project.
  - The initial interview and the different tests, were carried out at the Unit of Cancer in the Elderly by the main investigator.
  - At the beginning of every cycle, and during 4 months, it was collected information regarding outcome variables.
Study variables (I)

**Socio-demographic variables:**
- Age.
- Sex.
- Cultural level:
  - No reading nor writing.
  - Reading and writing.
  - Primary or advanced studies.
- Marital status:
  - Married.
  - Widowed.
  - Single.
  - Divorced.

**Variables related to the tumor:**
- Kind of tumor:
  - Breast cancer.
  - Digestive trac tumors.
  - Lung cancer.
  - Urologic/prostate cancer.
  - Others.
- Tumoral stage:
  - Stage I-III.
  - Stage IV.
- Chemotherapy:
  - Mono or polichemotherapy.
  - Name of the scheme.
Covariables:
- Variables related to sarcopenia:
  - Muscle mass
  - Muscle strength
  - Physical performance
  - Method of evaluation

- Impedanciometer (Biolectric impedance analysis-BIA, Tanita BC-420, Japan)
- Dynamometer (JAMAR ® Hand dynamometer; Baseline Analog Hydraulic Push-Pull dynamometer (12-0393))
- Chronometer

**Variables**
- Skeletal Muscle Mass total (SMMI-T)
- SMMI-SSMMI-I
- Hand grip
- Hip flexion
- Knee extension strength
- Gait speed
- Sit-to-stand chair

Variables related to frailty:
- Poor energy and endurance (Self-reported exhaustion).
- Slowness.
- Low physical activity level.
- Weakness (grip strength).
- Unintentional weight loss.

Study variables (II)
- **Muscle mass**: SMMI-T ♂ <8,87 kg/m²; ♂ <6,42 kg/m²
- **Muscle strength**: Hand grip ♂ <30 kg; ♂ <20 kg
- **Physical performance**: Gait speed ≤0,8 m/s

- **Unintentional weight loss** (loss of weigh over 4 kg in last year).
- **Weakness** (hand grip depending ot the normal values in our population).
- **Self-reported exhaustion** (in the last week, how many days have you felt that everything you do is an effort; in the last week, how many times you do not feel like doing anything?).
- **Slow walking speed** (>7 sec in men ≤173 cm in heigh or in women ≤159 cm; or >6 sec in men >173 cm or women >159 cm).
- **Low physical activity** (<383 kcal/week in men; <270 kcal/week in women).

Fried L. J Gerontol (Medical Sciences) 2001;56ª(3): M146-M156
Study variables (III)

**Outcomes variables:**

- **Severe toxicity: YES, NO:**
  - Mortality for chemotherapy: YES, NO.
  - Hospitalization for chemotherapy: YES, NO.
  - Early discontinuation of chemotherapy: YES, NO.
  - Institutionalization: YES, NO.
  - Hematologic toxicity grade 4 or non hematologic toxicity grade 3 or 4 (Common Toxicity Criteria NCI-CTC Version 2.0; 30 abril 1999): YES, NO.
Sample size

- Bilateral test.
- Alpha risk 5%; betha risk 10% (power 90%).
- Sarcopenia: 30%.
- Toxicity of chemotherapy:
  - In non sarcopenic patients: 20%.
  - In sarcopenic patients: 50%.

Macro \texttt{INSize}
Type=Co2R

\begin{align*}
N1 \text{ (sarcopenic patients)} &= 41 \\
N0 \text{ (non sarcopenic patients)} &= 94
\end{align*}

After Fleiss correction method
A descriptive analysis will be performed of the characteristics of the sample. It will be calculated the percentage of subjects meeting frailty criteria (Fried). It will be calculated the percentage of patients meeting sarcopenia criteria (EWGSOP).

Logistic regression (adjusted by sex and age): To analyze which variables related to sarcopenia, are associated to risk of severe toxicity of chemotherapy.

Statistical analysis

Logistic regression (adjusted by sex and age): To analyze which model is associated to severe toxicity of chemotherapy:

- The model of sarcopenia as defined by the European group (EWGSOP);
- The model of sarcopenia as defined by the previous logistic regression;
- The model of frailty as defined by Linda Fried.
The investigation meets the standards of the Helsinki declaration concerning investigation with human subjects.

The study was approved by the Hospital General Virgen de la Luz de Cuenca Ethics Committee.

All participants signed an informed consent form prior to inclusion in the study.
Results
Characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
<td><strong>N</strong>=54 (January 2013-January 2014)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Mean: 73.2 y (SD 4.6)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>56.3%</td>
</tr>
<tr>
<td><strong>Charlson</strong></td>
<td>1.78 points (hypertension and diabetes)</td>
</tr>
<tr>
<td><strong>Married</strong></td>
<td>N=24; Single: N=5</td>
</tr>
<tr>
<td><strong>No read no write</strong></td>
<td>N=2; High education: N=5</td>
</tr>
<tr>
<td><strong>ECOG</strong></td>
<td>ECOG 0: 42.7%; ECOG 2: 53.5%; ECOG 3: 3.8%</td>
</tr>
</tbody>
</table>
Types of tumors

- **Gastro-intestinal**
  - Colon cancer: N=12
  - Rectal cancer: N=4
  - Gastric cancer: N=2
  - Pancreas cancer: N=1
  - Ampulloma tumor: N=1

- **Gynecological/Breast**
  - Breast cancer: N=6
  - Ovarian cancer: N=2
  - Endometrial cancer: N=1

- **Urological/Prostate**
  - Prostate cancer: N=4
  - Bladder cancer: N=2

- **Other**
  - Lung: N=9 (17%)

- **Others**
  - N=4
Tumoral stage

- Stage II: 4 (7.4%)
- Stage III: 21 (38.9%)
- Stage IV: 29 (53.7%)
Classification by Balducci

- Group 1: 29 (53.7%)
- Group 2: 20; 37%
- Group 3: 5; 9.3%

Initial reduced dose in 25 cases (46.3%)
Schemes of chemotherapy

- Raltitrexed-oxaliplatin: N=3.
- XELOX: N=3.
- Carboplatin-gemcitabine: N=2.
- Carboplatin-vinorelbine: N=1.
- FOLFIRI: N=2.
- Oxaliplatin-gemcitabine: N=1.
- Capecitabine-vinorelbine: N=1.
- Cisplatin-5FU: N=3.

- Capecitabine: N=4.
- Paclitaxel: N=5.
- 5-fluorouracile: N=1.
- Docetaxel: N=4.
- Gemcitabine: N=2.
- Irinotecan: N=2.
- Temozolomide: N=2.

- Monotherapy
- Polichemotherapy

20; 37%
34; 63%
### Variables related to sarcopenia and frailty

<table>
<thead>
<tr>
<th>Variables</th>
<th>N=54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>86.6 kg (SD 10.7)</td>
</tr>
<tr>
<td>Muscle mass</td>
<td>SMMI-T: 8.814 kg/m2 (SD 12.801)</td>
</tr>
<tr>
<td></td>
<td>SMMI-S: 8.014 kg/m2 (SD 1.001)</td>
</tr>
<tr>
<td></td>
<td>SMMI-I: 4.897 kg/m2 (SD 2.425)</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>Hand grip: 9.75 kg</td>
</tr>
<tr>
<td></td>
<td>Hip flexion: 5.75 kg (SD 6.77)</td>
</tr>
<tr>
<td></td>
<td>Knee extension: 6.25 kg (SD 2.31)</td>
</tr>
<tr>
<td>Physical performance</td>
<td>Gait speed: 1.021 m/s (SD 0.721)</td>
</tr>
<tr>
<td></td>
<td>Sit-to-stand chair: 20.21 sec (SD 7.634)</td>
</tr>
</tbody>
</table>

Sarcopenia: N=25 (46.3%).
Frailty: N=5 (9.3%).
Outcome variables (16 events)

- Death: 10 patients died during the treatment, but none of them died because of chemotherapy (tumor progression in 7 cases; age-related comorbidities in 3 cases).
- Delays: 5; 31%
- Suspension: 6; 38%
- Dose reduction: 1; 6%
- Institutionalization: 0; 0%
- Hospitalization: 3; 19%
- Severe toxicity: 0; 0%

10 patients died during the treatment, but none of them died because of chemotherapy (tumor progression in 7 cases; age-related comorbidities in 3 cases).

No cases of institutionalization.

Median of reductions: 1.21 times

H toxicity G4, N=3 (afebrile neutropenia)
NH toxicity G3, N=2
NH toxicity G4, N=1 (severe mucositis)
Conclusions
Conclusions

- Elderly cancer patients are frequently sarcopenic patients (46.3% in our series).
- For the moment, we only have the descriptive results of the study, as recruitment is active until January 2015. At the moment, 16 final events have occurred (29.6%).
- Hematologic or not hematologic severe toxicities are usual in this group of patients (11%) and in 16.7% of cases (38% of the final events/outcome variables), it is necessary to stop, delay or reduce the dose of chemotherapy.
- The final results of this project could clarify the importance of sarcopenia in elderly patients diagnosed with cancer.

- This project has been awarded by the Mutua Madrileña (2012).
- This project has also been awarded as a top national project on Geriatrics by the Spanish Society of Geriatrics and Gerontology (2012).