Geriatric factors associated with 3-month mortality and severe chemotherapy toxicities in older patients with metastatic non-small-cell lung cancer: ESOGIA-GFPC-GECP 08-02 Study

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BACKGROUND

- In Europe, almost half of NSCLC patients are 75 years or older.
- Despite recent progress made with targeted therapies and immunotherapy, chemotherapy retains an important role.
- Evaluate the individual benefit-risk balance of chemotherapy for older patients is crucial.

Geriatric assessment (GA)

- Recently, two randomized trials reported that GA-guided intervention reduced chemotherapy-induced toxicity rates.
- CARG (at 3 months).
- GAIN.
- GA tools are used to predict:
  1. Death (Kebuloah, IFCC, 2018).
  2. Estimate risk of death at 100 days in older cancer patients.
- CReMA profiles (ADL, CARG).

OBJECTIVE

Identify geriatric prognostic factors associated with 3-month mortality and chemotherapy safety for older patients (≥75 years) with metastatic non-small cell lung cancer (mNSCLC).

METHODS

- Population: Patients ≥75 years old with stage III NSCLC about to receive first-line therapy.
- Exclusion criteria: severe concurrent disorders, PS > 2, active malignancy within the past 5 years, symptomatic brain metastases and bronchoalveolar, neuroendocrine, or composite cancer histology.

OUTCOMES

1-Month mortality

9-month mortality

Secondary endpoint: severity grade 3-4 or <5 CARG (Common Terminology Criteria for Adverse Events version 4.0).

EXPLANATORY VARIABLES

- Demographics: Smoking Status, Performance Status (PS), Geriatric tools (see Table 1).
- Biological markers: hemoglobin, total cholesterol, lactate dehydrogenase, C-reactive protein, Aluminemia.

STATISTICAL ANALYSIS

- Cox proportional hazards (survival) and logistic regression (toxicity) models, adjusted for treatment group, number of chemotherapy cytoxen and cycle, and included randomization arm as a strata.
- For all endpoints, the variables with p < 0.20 in univariate analyses were further examined in multivariate analyses. Separate models were run to account for correlated variables in order to estimate the proper effect of each variable.

RESULTS

- ESOGIA trial enrolled 404 patients to 45 French and Spanish centers (14 university hospitals, 4 cancer centers, and 27 community hospitals).
- All patients underwent GA.
- Median follow-up was 4.5 (range 0–36.7) months.

Table 1: Baseline characteristics of the 492 ESOGIA-trial participants.

Characteristic | Value
--- | ---
Age (years) | n = 492
Mean ± SD | 77 ± 7.4
Male sex | n = 492
Mean ± SD | 366 ± 7.2
Smoker status (n = 492) | Nemover-smokers
Nemover-smokers | 70 (20.4)
Former smokers | 60 (19.3)
Current smokers | 233 (63.9)
Randomized to geriatric assessment arm (n = 492) | 242 (49.1)
Treatment (n = 492) | Docetaxel monotherapy
Best supportive care | 239 (48.5)
Chemotherapy doublet | 56 (11.4)
Carboplatin doublet | 198 (40.8)
Carboplatin monotherapy | 50 (10.1)
Carbopentomod | 148 (30.0)
Performance status (PS) (n = 492) |
1 | 400 (81.2)
2 | 93 (18.8)
Activities of Daily Living score (n = 492) | 71 (14.4)
Instrumental Activities of Daily Living score (n = 492) | 4 | 302 (77.4)
5 | 92 (18.5)
Mini-Mental State Examination score (n = 223) (n = 492) | 78 (71.4)
Cut-off and Go Death Test (GDT) (n = 492) | Altered | 122 (24.9)
Continuous (n = 492) | 420 (95.1)
Falls during the last year (n = 492) | 74 (15.2)
Geriatric Depression Scale 5 score (n = 492) | 1-3 | 416 (84.4)
Staging (n = 492) | 2-3 | 61 (12.4)
4 | 15 (3.2)
Loss of appetite (n = 492) | 65 (13.2)
Recent Weight Loss (BRL) (kg/cycle) (n = 492) | 270 (57.7)
Body mass index kg/m² (n = 492) | 21.6–24.9 | 195 (38.6)
≥25 | 180 (37.2)
Carcinoma Comorbidity Index (CCI) score (n = 492) | 0-1 | 375 (76.1)
≥2 | 119 (23.9)

VALUES ARE EXPRESSED AS NUMBER (%) OR MEAN (SD) OR MEDIAN (IQR).

3-Month Mortality

- 3-month OS: 70.6% 95% CI: 69.7–71.5%
- Univariate analysis: male sex, PS = 2, anemia, IADL ≤ 2/4, MMSE ≤ 25, CDDS ≤ 2, abnormal GUC, loss of appetite, BRL ≤ 10 kg, ALB ≤ 30 g/L, and elevated LDH and CRP concentrations.
- Multivariate analyses: male sex, PS = 2, IADL ≤ 2/4, abnormal GUC, mobility, BRL ≤ 10 kg, anemia, CRP ≥ ALB ≤ 30 mg/L, and LDH ≥ 484 U/L.
- An interaction was found between weight loss and several IADL deficiencies (IADL ≤ 2/4).

Table 2: Multivariate analysis of clinical factors associated with grade 3-4 or 0-1 chemotherapy-induced toxicities in 475 patients given chemotherapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>IADL ≤ 2/4</td>
<td>1.90 (1.99–3.44)</td>
<td>0.053</td>
</tr>
<tr>
<td>CCI ≥ 3</td>
<td>1.06 (1.09–1.15)</td>
<td>0.038</td>
</tr>
<tr>
<td>Falls during the last year</td>
<td>0.99 (0.91–1.07)</td>
<td>0.67</td>
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DISCUSSION AND CONCLUSION

1- Geriatric factors predicting patient’s 3-month mortality

- Interaction between recent weight loss ≥ 5% and dependency in major daily activity in older patients with mNSCLC.
- Malnutrition of cancer patients is an already well-established prognostic factor.
- Concerning the degree of autonomy (AIDS, IADL, and ICD), published findings are contradictory.
- Comorbidities would rather have an impact at intermediate term.

2- Geriatric factors predicting chemotherapy toxicity

- Comorbidities are not included in CARG or CRASH score but their predictive value for chemotherapy might be stronger in real-life settings.
- Autonomy and recent falls are included respectively in the CARG and the CRASH score. Our study was probably underpowered to find these toxicities.
- The models identification of geriatric factors associated with toxicity remained poor, which clearly highlights the difficulties to predict these toxicities.

LIMITATIONS

- A selection of the study population was undertaken in ESOGIA, but in a pragmatic way, with few exclusion criteria and from a large number of centers.
- GA was done by the oncologist treating the patient. However, the clinicians participating in the ESOGIA trial were trained in how to conduct the GA.
- Extrapolation of the findings to clinical practice is restricted in real-life by the evolution and access to geriatric expertise.

In conclusion, the combined effect of dependence, weight loss and mobility were the main geriatric factors associated with 3-month mortality of patients ≥70 years with mNSCLC whose management was decided after GA. Concerning chemotherapy toxicity, it will be necessary to seek out other factors to evaluate the CRASH risk, a major outcome determinant in this population.