BACKGROUND AND OBJECTIVE

We reported in the ELY study (Boudou-Rouquette et al, Ebiomedicine 2021) that increased energy expenditure – so called hypermetabolism (HM) – is associated with decreased tumor response, reduced 6-month progression-free survival (PFS) and reduced overall survival (OS) in metastatic NSCLC patients (pts) treated with ICI. Here, we investigated whether to meet caloric requirements improves the sensitivity to ICI.

METHOD

We retrospectively included metastatic NSCLC pts without any actionable mutation treated with ICI monotherapy.

- Patients underwent a dietitian evaluation to quantify baseline caloric intake.
- Resting Energy Expenditure was measured (mREE) using indirect calorimetry.
- Theoretical RER (tRER) was calculated with the Harris & Benedict Formula.
- Statistical analysis included Kaplan-Meier estimates and Cox proportional hazards regression for PFS and OS.

- Hypermetabolism: mREE/tRER ≥ 110%.
- Normometabolism: mREE/tRER <110%.
- Caloric coverage: Caloric intake > 90% of estimated needs.

RESULTS

Average normometabolism vs. hypermetabolism (HM)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 162)</th>
<th>Group A (n = 84)</th>
<th>Group B (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (M/F)</td>
<td>1.8</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Cancer type</td>
<td>122 (75.3)</td>
<td>56 (67.1)</td>
<td>66 (78.6)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>31 (19.1)</td>
<td>17 (21.8)</td>
<td>14 (16.7)</td>
</tr>
<tr>
<td>Squamous Cell</td>
<td>9 (5.6)</td>
<td>5 (6.4)</td>
<td>4 (4.8)</td>
</tr>
<tr>
<td>ECOG PS (≤ 1)</td>
<td>84 (51.8)</td>
<td>38 (46.4)</td>
<td>46 (54.8)</td>
</tr>
<tr>
<td>ECOG PS (≥ 2)</td>
<td>42 (26.0)</td>
<td>30 (35.8)</td>
<td>32 (38.1)</td>
</tr>
<tr>
<td>Serum Albumin level, median [IQR]</td>
<td>38.0 [33.0 – 42.0]</td>
<td>36.5 [31.3 – 41.0]</td>
<td>39.0 [35.0 – 42.0]</td>
</tr>
</tbody>
</table>

The median OS reached 20.0 months in NM pts, vs. 6.8 in HM group (HR: 0.44 [0.30 – 0.63], p < 0.0001).

In HM patients, to reach caloric requirements was associated with an improved OS (HR: 0.58, 95%CI [0.35 – 0.95], p = 0.03).

- Median PFS was 4.3 vs. 1.9 months in groups A and B, respectively (HR: 0.49, 95%CI [0.31-0.80], p = 0.004).
- The PFS achieved in group A and in NM pts were similar (HR: 0.99, 95%CI [0.65-1.51], p = 0.95).

Half of patients were NM. Half of the HM patients did not meet their caloric needs.

PFS AND OS OF HM PTS WERE IMPROVED WHEN CALORIC NEEDS WERE MET

OBJECTIVE RESPONSE RATE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate HR [95%CI]</th>
<th>Multivariate HR [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A vs. Group B</td>
<td>0.49 [0.31 – 0.80]</td>
<td>0.004 [0.56 – 0.98]</td>
</tr>
<tr>
<td>NM vs. Group B</td>
<td>0.49 [0.33 – 0.73]</td>
<td>&lt; 0.001 [0.55 – 0.87]</td>
</tr>
<tr>
<td>PDLI TC &lt; 50% vs. ≥ 50%</td>
<td>0.63 [0.44 – 0.92]</td>
<td>0.02 [0.71 [0.48 – 1.04]</td>
</tr>
</tbody>
</table>

Smoking habit
- Former vs. Never
  - Group A: 0.52 [0.26 – 1.03]
  - Group B: 0.50 [0.24 – 1.04]
  - Multivariate: 0.06 [0.45 [0.21 – 0.96]

- ECOG PS ≥ 3 vs. < 3
  - Multivariate: 1.26 [0.71 – 2.23]
  - Multivariate: 0.44 [0.90 [0.50 – 1.78]

- Ser. albumin level
  - Multivariate: 0.96 [0.93 – 0.98]
  - Multivariate: 0.06 [0.93 [0.93 – 1.00]

The objective response rate in group A was similar the NM patients (p = 0.87).

DISCUSSION

- Hypermetabolism is predictive of ICI failure in NSCLC patients.
- Meeting caloric requirement is an effective way to overcome tumor resistance to ICI in this population.
- Thus, an accurate quantification of energy intake and expenditure to tailor nutritional support is paramount.

CONCLUSION

Energy supply is a critical determinant of the sensitivity to ICI in NSCLC pts. A randomized study to evaluate the benefit of early nutritional intervention in this setting is warranted.

Correspondence: manuela.tiako@aphp.fr, No COI to disclose.