Pre-diagnosis neutrophil-to-lymphocyte ratio and lung cancer mortality

Real-world outcomes of first-line Pembrolizumab MONOTHERAPY for PD-L1-positive (TPS≥50%) metastatic NSCLC

Dr. Juan Felipe Córdoba
Pre-diagnosis neutrophil-to-lymphocyte ratio and lung cancer mortality

BACKGROUND

- Inflammation is an established hallmark of cancer development and progression.
- The neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation.
  - NLR is associated with smoking status.
  - Increasing NLR is associated with increased mortality from many chronic diseases, including lung cancer.
- Most studies examine blood at diagnosis, which may reflect disease-related inflammation.
- Hematopoiesis is programmed through epigenetic changes, which enables blood cell proportion estimation from methylation data.
- We examined whether the inflammatory profile reflected by pre-diagnosis DNA methylation-derived NLR (mNLR) was associated with lung cancer mortality in a prospective study of heavy smokers.

METHODS

- 293 lung cancer cases from the CARET trial with:
  - >20 pack years
  - >6 years since quit
  - No occupational asbestos history
- Blood collected on average 4.1 years pre-diagnosis
- Cases were identified through 2005 and followed for mortality events until 2013
- DNA methylation assayed on the 850K CpG Illumina Epic array
- Pre-diagnosis mNLR was computed as the ratio of predicted granulocyte and lymphocyte proportions derived from DNA methylation signatures in whole blood
  - White blood cell mixture deconvolution (Koestler et al. 2017, CEPH)
  - mNLR is defined by quartiles indicating low (Q1) to high (Q4) systemic inflammation
- Assessed associations with pre-diagnosis mNLR and lung cancer-specific mortality using adjusted Cox proportional hazards models
  - Age, sex, race, smoking status, intervention arm, asbestos exposure, pack years smoked, time between blood draw and diagnosis
  - Stage stratifies (non-proportional baseline hazards)

RESULTS

Table 1. Characteristics of CARET lung cancer cases at blood draw

<table>
<thead>
<tr>
<th></th>
<th>All cases</th>
<th>Adenocarcinoma</th>
<th>Squamous cell</th>
<th>Small cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) or N (%)</td>
<td>(N=290)</td>
<td>(N=132)</td>
<td>(N=100)</td>
<td>(N=62)</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.1±5.6</td>
<td>64.2±5.3</td>
<td>64.3±5.5</td>
<td>63.5±6.1</td>
</tr>
<tr>
<td>Race (white)</td>
<td>282 (96)</td>
<td>125 (96)</td>
<td>93 (93)</td>
<td>56 (90)</td>
</tr>
<tr>
<td>Female</td>
<td>59 (20)</td>
<td>51 (40)</td>
<td>23 (23)</td>
<td>20 (32)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>188 (64)</td>
<td>88 (68)</td>
<td>76 (76)</td>
<td>36 (59)</td>
</tr>
<tr>
<td>Pack years</td>
<td>0.0±0.2</td>
<td>0.0±0.2</td>
<td>0.0±0.2</td>
<td>0.0±0.2</td>
</tr>
<tr>
<td>Years since quit smoking</td>
<td>23.4±2.3</td>
<td>23.4±2.3</td>
<td>23.4±2.3</td>
<td>23.4±2.3</td>
</tr>
<tr>
<td>Active intervention arm</td>
<td>107 (36)</td>
<td>55 (44)</td>
<td>32 (32)</td>
<td>19 (31)</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>51 (17)</td>
<td>19 (15)</td>
<td>21 (21)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Late stage (IIV)</td>
<td>215 (73)</td>
<td>65 (50)</td>
<td>62 (62)</td>
<td>59 (99)</td>
</tr>
<tr>
<td>Years from diagnosis to death or end of study period (2013)</td>
<td>4.3±2.4</td>
<td>4.3±2.4</td>
<td>4.3±2.4</td>
<td>4.3±2.4</td>
</tr>
<tr>
<td>Any death (through 2013)</td>
<td>294 (97)</td>
<td>115 (90)</td>
<td>98 (98)</td>
<td>96 (150)</td>
</tr>
<tr>
<td>Lung cancer-specific death (through 2013)</td>
<td>247 (84)</td>
<td>96 (75)</td>
<td>82 (82)</td>
<td>60 (107)</td>
</tr>
</tbody>
</table>

Figure 1. Hazard ratios for pre-diagnosis mNLR and mortality in lung cancer cases, overall and by histology

CONCLUSIONS

- An inflammatory response prior to diagnosis as indicated by higher mNLR levels may be associated with mortality in heavy smokers who go on to develop lung adenocarcinoma.
  - HR=2.0, 95% CI: 1.03-4.03 comparing mNLR Q4 to mNLR Q1.
    - We observed a statistically significant linear trend for increased risk of mortality with increasing mNLR quartiles (P=0.02).
    - Associations among adenocarcinoma cases were larger in magnitude for those who were younger at blood draw, younger at diagnosis, who had fewer than the median of pack year smoking history, and who were in the active intervention arm.
- We did not observe evidence for associations between mNLR and mortality for squamous cell or small cell lung cancer.
- Since indicators of survival may be used to guide treatment decisions and gauge response to treatment, further studies are needed to understand the potential clinical utility of pre-diagnosis mNLR.
Real-world outcomes of first-line Pembrolizumab MONOTHERAPY for PD-L1-positive (TPS≥50%) metastatic NSCLC

INTRODUCTION
- Pembrolizumab is a humanized IgG1 monoclonal antibody that blocks PD-1 and its ligand PD-L1.
- In the KEYNOTE-024 trial, Pembrolizumab significantly improved outcomes compared to docetaxel in patients with PD-L1-positive metastatic NSCLC.
- A subsequent trial,-Keynote-189, confirmed overall survival (OS) benefit with Pembrolizumab compared to docetaxel in a broader population of patients with advanced NSCLC with a PD-L1 expression score (TPS) of ≥50%.
- Pembrolizumab is currently approved for the first-line treatment of PD-L1-positive metastatic NSCLC.

OBJECTIVE
- To investigate the real-world outcomes of Pembrolizumab in the first-line setting in routine clinical practice in the United States (US) for PD-L1-positive metastatic NSCLC.

METHODS
- Study Design
  - Retrospective cohort study
  - Medical record review
- Study Population
  - adult patients with advanced NSCLC
  - PD-L1-positive status
  - Pembrolizumab as first-line treatment
- Study Sites
  - US sites

RESULTS
- Real-world outcomes of Pembrolizumab in first-line treatment of PD-L1-positive metastatic NSCLC
- OS: 13.5 months
- PFS: 5.5 months
- Survival benefit: 1.5 months
- Progression-free survival benefit: 3.5 months
- Overall response rate: 40.0%
- Complete response rate: 10.0%
- Duration of response: 10 months

CONCLUSIONS
- Pembrolizumab demonstrates real-world efficacy in first-line treatment of PD-L1-positive metastatic NSCLC.
- Real-world outcomes confirm the benefits observed in clinical trials.
- Pembrolizumab offers a treatment option for patients with PD-L1-positive metastatic NSCLC in routine clinical practice.

TABLE 1: Objective Response Rate (ORR) by PD-L1 TPS in the Real-World Setting

<table>
<thead>
<tr>
<th>TPS (%)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>40.0</td>
</tr>
<tr>
<td>&lt;50</td>
<td>20.0</td>
</tr>
</tbody>
</table>

TABLE 2: Progression-Free Survival (PFS) by PD-L1 TPS in the Real-World Setting

<table>
<thead>
<tr>
<th>TPS (%)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>5.5</td>
</tr>
<tr>
<td>&lt;50</td>
<td>3.0</td>
</tr>
</tbody>
</table>

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References

Initiatives científicas de Grupo Español de Cáncer de Pulmón Spanish Lung Cancer Group

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