1080P: Immune checkpoint blockade therapy affects circulating FLIP-expressing monocyte-myoelid-derived suppressor cells (M-MDSC) in non-prosger non-small cell lung cancer patients.

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Background

- Cancer cells affect the normal myelopoiesis favoring the generation of myeloid cells with immunosuppressive and inflammation-associated functions such as myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) able to support its growth and progression.

- Recently, we demonstrated that the antiapoptotic molecule cellular FLICE-inhibitory protein (c-FLIP) that functions as an important modulator of caspase-8 is crucial for the development of monocyte (M)-MDSCs.

- We speculated that immune checkpoint inhibitor (ICI)-based therapy could affect the FLIP-expressing monocyte myeloid cells frequencies and functions in non-prosger (NP) non-small cell lung cancer (NSCLC) patients.

Methods

- We enrolled 34 NSCLC patients: 16 patients received immunotherapy as the first line of treatment according to PD-L1 expression, 18 patients as second-line treatment.

- We collected blood samples at two time points: before ICI treatment (T0) and during the first clinical evaluation (T1). Circulating immune landscape was defined by multiparametric flow cytometry and systemic cytokine levels were tested by multiplex ELISA assay.

- Plasma samples were collected and stored at -80°C for cytokines quantification. Peripheral blood mononuclear cells (PBMCs) and CD14+ cells were isolated from NSCLC patient-derived whole blood and cryopreserved to evaluate c-FLIP expression and suppressive properties of monocytes, respectively. The suppressive activity of thawed monocytes was evaluated by proliferation assay through an in vitro culture of NSCLC-derived CD14+ cells with CD3/CD28-activated, Cell-Tape-labelled PBMCs isolated from bufy-coats at 3:1 ratio.

Patients’ population

Overall, 34 patients with advanced NSCLC who were treated with ICIs met the criteria for the analysis [Table 1]:

- 16 non-prosger (NP) pts
- 18 prosger (P) pts

Table 1. Clinical and biological characteristics of the population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NP (N=16)</th>
<th>P (N=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male: 16/20</td>
<td>12/16 (100%)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>72 (62-84)</td>
<td>72.5 (58-82)</td>
</tr>
<tr>
<td>FLICE/STAT1 expression level</td>
<td>72 (62-84)</td>
<td>72 (62-84)</td>
</tr>
<tr>
<td>Activity</td>
<td>0: 14/16 (87.5)</td>
<td>8/16 (50%)</td>
</tr>
<tr>
<td>1: 17/20 (85)</td>
<td>12/16 (75%)</td>
<td></td>
</tr>
<tr>
<td>2: 3/4 (75)</td>
<td>1/4 (25%)</td>
<td></td>
</tr>
<tr>
<td>Inhine</td>
<td>Never: 7/20 (35)</td>
<td>6/16 (37.5)</td>
</tr>
<tr>
<td>Former: 20/28 (71)</td>
<td>11/16 (68.7%)</td>
<td></td>
</tr>
<tr>
<td>Current: 7/4 (17.5)</td>
<td>2/4 (50%)</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>Adenocarcinoma: 20/25 (80)</td>
<td>11/16 (68.7)</td>
</tr>
<tr>
<td>Squamous Carcinoma: 4/25 (16)</td>
<td>9/16 (56.25)</td>
<td></td>
</tr>
<tr>
<td>DGRM Status</td>
<td>Mutated: 1/2 (50)</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td>Wild Type: 1 (97.1%)</td>
<td>16 (100%)</td>
<td></td>
</tr>
<tr>
<td>ICL1 percentage</td>
<td>&lt;1%: 3/4 (62.5)</td>
<td>1/4 (25%)</td>
</tr>
<tr>
<td>1%&lt;s≤10%: 15/16 (93.75%)</td>
<td>4/16 (25)</td>
<td></td>
</tr>
<tr>
<td>&gt;10%: 16/16 (100%)</td>
<td>12 (75%)</td>
<td></td>
</tr>
<tr>
<td>Immunotherapeutic Agent</td>
<td>Pembrolizumab: 16/16 (100%)</td>
<td>12/16 (75%)</td>
</tr>
<tr>
<td>Nivolumab: 16/16 (100%)</td>
<td>12/16 (75%)</td>
<td></td>
</tr>
<tr>
<td>Keytruda: 1 (6.25%)</td>
<td>1 (6.25%)</td>
<td></td>
</tr>
<tr>
<td>Line of immunotherapy</td>
<td>Induction: 15/16 (93.75%)</td>
<td>12/16 (75%)</td>
</tr>
<tr>
<td>Pro: 1/16 (6.25%)</td>
<td>4/16 (25%)</td>
<td></td>
</tr>
<tr>
<td>OSI</td>
<td>16 (100%)</td>
<td>12 (75%)</td>
</tr>
</tbody>
</table>

ICI immunotherapy affects the blood immune landscape in non-prosger NSCLC patients.

- Our results confirmed LIP1 as a predictive score for ICI treatment in patients with NSCLC [Figure 1].

- Using t-distributed stochastic neighbor embedding (t-SNE) analysis, we demonstrated that NP patients at T1 showed an increased frequency of specific subsets of T cells and a contraction of monocytes [Figure 2].

- Moreover, a reduction of IL-6 level was detected in NP patients after ICI treatment.

Results

ICI immunotherapy modifies immune-suppressive features of c-FLIP+ M-MDSCs.

- Interestingly, we identified a contraction of c-FLIP-expressing M-MDSCs in NP patients at T1 even if NP and prosger (P) patients had the same frequency of this circulating myeloid cell subset at T0.

- Monocytes isolated from both P and NP patients displayed similar immunosuppressive function at T0 but this pro-tumor activity was negatively influenced by c-FLIP-expressing cells contraction at T1 in NP patient cohort [Figure 3].

Conclusion

- To our knowledge, this is the first prospective study to evaluate the effects of ICI therapy on modulating MDSC-associated immunosuppression and inflammation.

- Our study sheds light on the effects of ICI on an MDSC subset in patients with NSCLC.

- FLIP-expressing monocyte enumeration may be considered, after validation, as an adjunctive tool for cancer immunotherapy since they effectively stratify progressors and non-progressors.

References


All authors declare no conflict of interests related to this study.

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