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Comprehensive Profiling of Metaplastic Breast Carcinoma Reveals Frequent Over-Expression of PD-L1

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Comprehensive Profiling of Metaplastic Breast Carcinoma Reveals Frequent Over-Expression of PD-L1

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Abstract (updated)
Background: Metaplastic breast carcinoma (MBC) is a rare subtype of breast carcinoma less responsive to conventional chemotherapy relative to usual breast carcinomas such as ductal and lobular breast cancers. MBC usually clusters with triple negative breast cancer (TNBC), but MBCs portray a worse prognosis in comparison with TNBC. Published studies investigating MBCs for specific biomarkers of therapy response are rare and limited by the methodological approaches.

Methods: 297 samples (MBC (n=75), triple-negative breast cancer of no-special-type (TNBC-NOS, n=106), HER2-positive breast cancers (n=32) and luminal (ER+/Her2- breast cancers (n=84)). The samples were profiled using direct sequencing analysis ([Illumina MiSeq Next Generation Sequencing (NGS)]) using formalin-fixed paraffin embedded tissue blocks. Immunohistochemistry for PD-L1 (SP142, Spring Bioscience) and PD-1 (EH12, Pharmingen) was performed using automated procedures.

Results (updated)
Mean age of patients: 57 years (range, 35-93 years).

Histology: MBCs exhibited various morphologic features including squamous, myoepithelial, spindle, and rhabdoid morphology with heterologous elements: bone (n=3) and cartilage (n=22 cases).

ER, PR and HER2 status were available for 71 patients; 63 cases (89%) of MBCs exhibited triple negative phenotype.

Overall PD-L1 positivity among 75 metaplastic breast carcinomas was 46%, highest of all types.

Background
Metaplastic breast carcinoma (MBC) encompasses a group of mammary neoplasms characterized by differentiation of the neoplastic epithelium into squamous or mesenchymal cells (1). It is less responsive to conventional chemotherapy compared to the usual ductal and lobular breast carcinomas (2). In molecular terms, MBC usually clusters with triple negative (ER-/PR-/HER2-) breast cancer (TNBC), but MBCs portray a worse prognosis in comparison with TNBC. Published studies investigating MBCs for specific biomarkers of therapy response are rare and limited by the methodological approaches (3, 4).

Methods
The study included 297 samples [MBC (n=75), triple-negative breast cancer of no-special-type (TNBC-NOS, n=106), HER2-positive breast cancers (n=32) and luminal (ER+/Her2- breast cancers (n=84)]. The samples were profiled using direct sequencing analysis ([Illumina MiSeq Next Generation Sequencing (NGS)]) using formalin-fixed paraffin embedded tissue blocks. Immunohistochemistry for PD-L1 (SP142, Spring Bioscience) and PD-1 (EH12, Pharmingen) was performed using automated procedures.

Results
Mean age of patients: 57 years (range, 35-93 years).

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Overall PD-L1 positivity among 75 metaplastic breast carcinomas was 46%, highest of all types.

Conclusion:
Comprehensive profiling of metaplastic carcinoma 72 MBCs were tested by NGS of which 57 cases had interpretable results. Mutations were detected in 16 out of 45 tested genes affecting 48 out 75 metaplastic carcinomas (84%).

TP53 mutation was the most frequent mutation (32/57, 56%). In 20 cases, TP53 was the sole mutation detected in the tumor tissue while in the remaining 12 cases other mutations co-occurred. PIK3CA mutation was the second most commonly observed mutation (13/72, 23%) while HRAS mutations were detected in 4 cases (7%), STK11 in 3 cases (5%), FBXW7, PTEN, c-MET and JAK3 in two cases, respectively (4%).

None of the cases harbored EGFR mutation.

Conclusions
Metaplastic carcinomas are characterized by increased PD-L1 expression in carcinoma cells, and PD-1 expression in TILs, which can be exploited in clinical trials utilizing immune check point inhibitors in this hard-to-treat subtype of breast cancer.

Comprehensive mutational profiling of MBC revealed predominant of TP53 and PIK3CA mutations and a wild type EGFR expression.

Figure 1A, 1B. Despite various morphologic appearances (A, C) of metaplastic carcinomas, strong PD-L1 overexpression (B, D) was observed in nearly 50% of the cases.

When any of the pathways studied were blocked by various inhibitors, PD-L1 expression was decreased. Inhibitors were tested at a concentration of 10 µM. Columns show mean and SEM for triplicate experiments.

Overall PD-L1 positivity among 75 metaplastic breast carcinomas was 46%, highest of all types.

Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>PD-L1 status</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metaplastic carcinoma</td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td>TNBC NOS</td>
<td>93 (91%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>HER2+</td>
<td>30 (94%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Luminal carcinoma</td>
<td>79 (94%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Total</td>
<td>241 (83%)</td>
<td>49 (17%)</td>
</tr>
</tbody>
</table>

Table 2.

<table>
<thead>
<tr>
<th>Type</th>
<th>(PD-L1+/TIL+)</th>
<th>(PD-L1+/TIL-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>29 (40.8%)</td>
<td>14 (19.7%)</td>
</tr>
<tr>
<td>Type 2</td>
<td>4 (5.6%)</td>
<td>24 (33.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>71 (100%)</td>
<td>71 (100%)</td>
</tr>
</tbody>
</table>

Mutational profiling of metaplastic carcinoma