Tumor-Macrophage Fusion Cells detected in the circulation of metastatic breast cancer patients is prognostic for rapid progression and death

ABSTRACT

Recently, it was described that macrophages and tumour cells can fuse to form tumour macrophage fusion cells (TMFs), detectable within primary tumours and patient’s (pts) circulation. However, there are multiple pathways and subsequent subtypes of TMFs with limited data on the various TMF types, commonality in blood, and their clinical relevance. Here we evaluated n=122 metastatic breast cancer (mBC) blood samples for CTCs & TMFs. We describe numerous types of TMFs with vastly different fusion phenotypes, including 1) partial (i.e. some membrane interaction & both cells retaining their original phenotypes), 2) homodimeric (i.e. both cells with fused membranes & sharing cytoplasm), 3) cannibalistic (i.e. CTC within a CD14+ macrophage & cells retaining their individual phenotypes), 4) binucleated (i.e. both cells completely merge & becoming one cell with dual expression phenotypes), and 5) hyperploid (i.e. multiple cells merge to form a large polyplloid cell). As CTCs & TMFs are isolated from a single blood sample, we evaluated both CTCs & TMF subtypes to determine their prognostic and predictive values for aggressiveness of disease.

MATERIALS & METHODS

We categorized and enumerated the 6 forms of CTCs/TMFs: 1) Partial, 2) Homodimeric, 3) Cannibalistic, 4) Binucleated, 5) Hyperploid, 6) and HyperEngorged. (Fig. 1) from a prospective pilot study using n=122 mBC pts that were starting new lines of treatment. Whole peripheral blood (7.5mL) was procured, filtered and stained using cytokeratin & CD45/CD14 to identify CTCs & TMFs. We compared the presence of the various types of TMFs & CTCs to pts’ progression-free survival (PFS) and overall survival (OS) hazard ratios (HRs), analyzed by censored univariate analysis based on RECIST v1.1 over 24 months.

RESULTS

CTCs were found in 39% of patients, partial fusion TMFs in 25%, homodimeric in 6%, cannibalistic in 0%, and hyperploid in 2%, & hyperfusion fusion cells (i.e. CAMLs) in 96%.

Neither CTCs alone, binucleated TMFs, nor hyperploid cells were prognostic for PFS or OS (Table 1).

TMFs with partial or homodimeric fusion were prognostic for worse PFS & OS (Table 1).

Combining patients with any TMFs into one group (minus hyperploid TMFs) was highly significant for worse PFS and OS (Figures 2 & 3).

CONCLUSIONS

The study of TMFs is relative limited and their existence is new in oncology.

We detected and described TMFs in the blood of mBC pts, demonstrating an association with poor clinical outcomes.

These data suggest a TMF involvement in the pathogenesis of cancer. Further understanding of their biology may be important in the study of tumorigenesis.

Table 1. Hazard ratio comparisons of CTCs, TMFs and CAMLs (Hyperploid fusion cells)

<table>
<thead>
<tr>
<th>HR/95% CI</th>
<th>p value</th>
<th>Any CTC</th>
<th>Partial Fusion TMF</th>
<th>Homodimeric TMF</th>
<th>Cannibalistic TMF</th>
<th>BINUCULATED TMF</th>
<th>Any TMF minus Hyperplody</th>
<th>Hyperplody (Any CAMLs)</th>
<th>HyperEngorged CAML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present vs Absent</td>
<td>47 vs 75</td>
<td>1.7 (1.1-2.7)</td>
<td>8.0 (1.9-34.2)</td>
<td>2.0 (0.1-21.1)</td>
<td>1.0</td>
<td>0.815</td>
<td>1.9 (0.1-28.6)</td>
<td>3.3 (1.9-5.8)</td>
<td>3.3 (1.1-10.2)</td>
</tr>
<tr>
<td>PFS</td>
<td>OS</td>
<td>0.0056</td>
<td>0.0015</td>
<td>0.36</td>
<td>0.0001</td>
<td>0.0735</td>
<td>0.0001</td>
<td>0.0015</td>
<td>1.5 (0.9-2.5)</td>
</tr>
<tr>
<td>31 vs 115</td>
<td>38 (98-7532.1)</td>
<td>74.8 (3.7-78.4)</td>
<td>1.9 (0.1-28.6)</td>
<td>3.3 (1.9-5.8)</td>
<td>3.3 (1.1-10.2)</td>
<td>1.5 (0.9-2.5)</td>
<td>0.0001</td>
<td>0.0015</td>
<td>1.5 (0.9-2.5)</td>
</tr>
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</table>

Figure 1. Diagram of the Different TMF Subtypes and Images of TMFs from Metastatic Breast Cancer Patient’s Blood

Figure 2. PFS of Patients with Any TMFs

Figure 3. OS of Patients with Any TMFs

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