Mitosis in circulating tumor cells and its prognostic significance in late stage breast cancer

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ABSTRACT

It has been well documented that enumeration of Circulating Tumor Cells (CTCs) isolated from the peripheral blood of breast cancer patients can be used as a prognostic indicator of survival. CTC identification typically relies on immunohistochemical stains used in an absent/present method (i.e. CK+ / EpCAM+/CD45-). However, this methodology for identification of CTCs is highly subjective, and histological cytology remains the standard identifier of cancer cells. We expand upon our work regarding the cytological criteria of CTCs, Adams et al., Cytometry 20151, to determine if pathological grading criteria can be applied to CTCs. We report the assessment for overall survival of 36 late stage breast cancer patients in relation to CTC number and presence of active mitosis.

INTRODUCTION

CTCs are cells that originate from a primary solid tumor and are found transiting the circulatory system. CTC enumeration can be used to monitor therapy response and predict outcome.1,4 However, CTC subtyping can be relied upon immunostaining presence/absence, rather than the more standardized histopathological identification.2 Low pressure microfiltration using CellSieve™ microfilters is a technique shown to isolate patient CTCs, while retaining the fine morphological detail required for histopathology1,2. High resolution morphology can identify CTC subtypes, i.e. apoptotic CTCs, highly pleomorphic CTCs, and CTCs in active mitosis. Aggressive phenotypes are associated with CTC population in mitosis. Subtyping by phenotypic determinates may aid in identifying CTCs cellular status for diagnosis, prognosis and therapy determination.1,4

RESULTS

PDCTCs were found in 83% (30 of 36) of patient samples tested. 23 of 36 patients (64%) had ≥5 PDCTCs with a median survival of >24 months. 13 of 36 patients (36%) had ≥5 PDCTCs with a median survival of 10.0 months, Hazard ratio was 5.2. Mitotic PDCTCs were found in 36% of patient samples tested. 23 of 36 patients (64%) had 0 mitotic PDCTCs, median survival of >24 months. 13 of 36 patients (36%) had ≥1 mitotic PDCTCs, median survival of 5.7 months. Hazard ratio was 11.1.

CONCLUSIONS

• Low pressure microfiltration captures CTCs while retaining fine cellular features, such as mitosis.
• Mitotic CTCs are relatively common in aggressive late stage breast cancer patients.
• Stratification of breast cancer patients based on CTCs is a prognostic indicator of survival.
• Prognostic value is dramatically increased by subtyping CTCs based on their mitotic index.
• CTC subtypes indicate definable traits that can be exploited for personalized treatment of cancer.

References


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Table 1: Prediction table with the hazard ratios, confidence intervals and p-values for the patient populations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>1 mitotic CTC vs 0 mitotic CTC</td>
<td>11.1</td>
<td>3.1-39.7</td>
<td>&lt;0.001</td>
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<tr>
<td>≥5 CTC vs &lt;5 CTC</td>
<td>5.2</td>
<td>1.6-16.5</td>
<td>0.005</td>
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<tr>
<td>ER/PR positive vs negative</td>
<td>1.3</td>
<td>0.5-3.7</td>
<td>0.174</td>
</tr>
<tr>
<td>HER2 positive vs negative</td>
<td>1.8</td>
<td>0.6-5.7</td>
<td>0.289</td>
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<tr>
<td>Hormone positive vs negative</td>
<td>4.0</td>
<td>1.4-11.2</td>
<td>0.009</td>
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