Breast cancer patients treated with intrathoracic therapy for leptomeningeal metastases: characteristics and validation of prognostic models in a large real-life database

**Background**
- Leptomeningeal metastasis (LM) in metastatic breast cancer (MBC) has high rates of morbidity and mortality.
- Large-scale data are scarce and strong evidence of benefit from treatment options is missing.

**Objectives**
- To describe the largest-to-date real-life population of MBC patients treated with IT therapy and to evaluate prognostic models.

**Conclusions**
- The outcome of MBC pts treated with IT therapy for LM remains poor (median OS 4.5 months) with no significant difference between 2008-2016, but 25.6% of pts lived over 1 year.
- Concomitant systemic therapy may offer a survival advantage that was maintained in HR+/HER2- patients, regardless of whether chemotherapy or endocrine therapy was used.
- Patients treated with IT methotrexate may have a better outcome than those treated with IT cytarabine or thioprox.
- The Curie score and the Breast-GPA were IT prognostic in our treated pts.

**Methods**
- The French nationwide Epidemiological Strategy and Medical Economics (EMSE) MBC database (NCT03375511) is an ambispective cohort collecting data from all consecutive patients (pts) that initiated treatment for MBC in one of the 18 French Comprehensive Cancer Centers since 2008.
- We selected female pts included between 2008 and 2016, who received IT therapy with methotrexate, thiopeta or cytarabine, at any time during the course of their disease.
- We used IT models to construct prognostic models.
- Two other models were fitted (starting from the date of IT therapy initiation) using previously published prognostic scores, the “simplified” Curie score, and Breast-GPA.

**Results**
- 162 of 168 (96.3%) treated pts were included in the analysis. No update was noted using the Kaplan-Meier method.
- IT therapy was significantly associated with better overall survival (OS) (HR 1.88, 95% CI 1.28-2.72, p < 0.001).
- RFS at 6 months was significantly prolonged in treated pts (HR 1.30, 95% CI 1.04-1.63, p=0.02).

**Table 1. Characteristics of patients treated or not with IT therapy**

<table>
<thead>
<tr>
<th>Feature</th>
<th>No IT therapy</th>
<th>N (%)</th>
<th>IT therapy</th>
<th>N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at MBC diagnosis (years)</td>
<td>65 (69.5%)</td>
<td>52 (44.4%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic type</td>
<td>Metastatic (85%)</td>
<td>72 (61.7%)</td>
<td>86 (71.0%)</td>
<td>0.115</td>
<td></td>
</tr>
<tr>
<td>Primary tumor site</td>
<td>Breast (94.4%)</td>
<td>93 (79.3%)</td>
<td>95 (80.1%)</td>
<td>0.330</td>
<td></td>
</tr>
<tr>
<td>BC subtype</td>
<td>HR+/HER2-</td>
<td>13,982 (48.8%)</td>
<td>13,656 (53.5%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>0 (5.1%)</td>
<td>13,982 (48.8%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td>77 (1.8%)</td>
<td>13,982 (48.8%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0A</td>
<td>20 (0.3%)</td>
<td>13,982 (48.8%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Cox multivariable model for OS in the complete database**

<table>
<thead>
<tr>
<th>Feature</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age over 60</td>
<td>1.36</td>
<td>(1.11-1.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment line ≥2</td>
<td>1.28</td>
<td>(1.06-1.55)</td>
<td>0.013</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>2.0</td>
<td>(1.48-2.67)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 1. OS in 168 IT treated pts according to BC subtype**

**Figure 2. OS in 168 IT treated pts according to the IT agent**

**Treatment modalities**
- The majority of our selected IT-treated patients (55.1%) received concomitant systemic therapy, while only 12.5% received concomitant RT. The preferred IT agent was methotrexate (66%).

**Outcome**
- Median OS from IT therapy initiation was 4.5 months (95% CI 3.8-5.6) and 1-year OS rate was 25.6%. Median OS according to BC subtype are presented in Figure 1.
- No significant difference in OS was noted between pts treated between 2012-2016 versus 2008-2012 (unadjusted HR=0.99 [0.74-1.32], p=0.947).

**Prognostic factors**
- Triple-negative subtype, treatment line ≥ 3, ≥ 3 metastatic sites, and IT therapy with cytarabine or thioprox were significantly associated with worse OS by multivariate analysis. While concomitant systemic therapy was associated with better OS (Table 2, Figure 1-3).
- No difference in OS was observed between patients with HR+/HER2- tumors treated with endocrine therapy versus chemotherapy backbone (unadjusted HR=1.07 [95% CI 0.62-1.86], p=0.811) (Figure 4).

**Prognostic scores**
- Both Curie and Breast-GPA scores had modest C-index of 0.57 but group stratification according to these scores was significantly prognostic in our study population (Figure 5-6).

**Reference**