Validation of the Institut Curie simplified prognostic score for breast cancer meningeal carcinomatosis

Breast cancer is the leading nonhematologic cause of meningeal carcinomatosis (MC), an unusual metastatic site. Its treatment generally relies on intrathecally and/or systematically delivered chemotherapy, combined with radiotherapy or surgery when needed. However, the overall survival (OS) of patients with proven MC is short, generally no longer than 6 months after the diagnosis of MC [1]. A retrospective study on 91 breast cancer MC diagnosed and treated homogeneously by a high-dose intrathecal methotrexate regimen [2] at the Institut Curie (Paris, France) from 2000 to 2007 has been recently reported [3]. This study retrieved four adverse independent prognostic factors at MC diagnosis: performance status (PS) of three to four, elevated Cyfra 21-1 marker in the cerebrospinal fluid (CSF), negative hormone receptors (HR) status and more than three previous chemotherapy lines for metastatic disease. Two prognostic scores were derived from these results, based on the number of adverse prognostic factors: the complete score included the four prognostic factors, whereas the simplified score did not include CSF Cyfra 21-1 as its dosage is not made routinely in this setting. Both prognostic scores allowed to classify patients into three groups with poor, intermediate and good prognosis (median OS of 2, 4 and 12 months, respectively). These scores required further validation.

A retrospective validation of the simplified prognostic score has been conducted in patients diagnosed with breast cancer MC at the Institut Jules Bordet (Brussels, Belgium) after approval of the local ethic committee. Briefly, the electronic file of each of the 926 patients who underwent CSF cytological analysis from 01/2000 to 07/2010 were screened manually for MC diagnosis (tumor cells in CSF): 88 patients had both breast...
cancer and MC, 9 of them being not included in the analysis (patients treated in another institution or diagnosed with another stage IV cancer). For the remaining 79 patients, PS, HR status and number of previous chemotherapy lines at MC diagnosis were obtained in their electronic medical files, together with their OS from the time of MC diagnosis (66 deaths and 13 censored). First-line intrathecal treatments were as follow: liposomal cytarabine ($n = 27$ patients), methotrexate ($n = 24$), thiotepa ($n = 1$), no intrathecal treatment ($n = 15$) and unknown ($n = 12$, insufficiently documented in the supporting medical records). Other treatment modalities were mainly radiotherapy ($n = 26$) and systemic chemotherapy ($n = 16$). OS curve is shown in Figure 1A (median 2.6 months).

A multivariate analysis confirmed the independent role of each prognostic factor included in the simplified score (Table 1). This score was calculated individually, each adverse prognostic factor being scored as 1 point, leading to a total score ranging from 0 to 3. OS curves according to the simplified score are shown in Figure 1B ($P < 0.0001$): median OS were 1.1, 2.0 and 6.5 months, respectively, in the poor ($n = 21$ patients), intermediate ($n = 26$ patients) and good ($n = 20$ patients) prognostic group. Similar results were obtained after excluding the 12 patients with unknown treatment ($P < 0.0001$).

Interestingly, these curves looked very similar to those reported initially [3], with ~25% of ‘long-term survivors’ (OS > 1 year) in the good prognostic group.

In this retrospective study, the simplified prognostic score has been therefore validated, although treatment modalities were different and did not systematically rely on intrathecally delivered chemotherapy. Although clinically relevant, the simplified score may be not specific to MC as it relies on three prognostic factors validated in the whole metastatic setting. Our study call for further prospective validation of the simplified score and comparison to the complete prognostic score, which may be more specific as it includes tumor marker in the CSF. Further validated score may be used in this heterogeneous population to stratify patients in future therapeutic trials.

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disclosure

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Table 1. Patients characteristics and prognostic value (overall survival)

<table>
<thead>
<tr>
<th>Performance status &gt; 2</th>
<th>Patients/patients assessed (%)</th>
<th>Univariate analysis, $P$ value</th>
<th>Multivariate analysis, RR (95% CI), $P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30/67 (45)</td>
<td>&lt;0.0001</td>
<td>4.3 (2.3–8.2), &lt;0.0001</td>
</tr>
<tr>
<td>&gt; 3 prior lines of chemotherapy</td>
<td>16/76 (21)</td>
<td>0.001</td>
<td>2.5 (1.2–5.3), 0.009</td>
</tr>
<tr>
<td>Negative hormone receptors status</td>
<td>27/79 (34)</td>
<td>0.03</td>
<td>2.2 (1.2–4.0), 0.007</td>
</tr>
</tbody>
</table>

Cl, confidence interval; RR, relative risk.

Figure 1. Overall survival (OS) of patients diagnosed with MC. (A) OS of the whole Institut Bordet cohort. (B) Simplified prognostic score applied to the Institut Bordet cohort.
references


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