Breast cancer patients treated with intrathecal therapy for leptomeningeal metastases in a large real-life database

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**INTRODUCTION**

Leptomeningeal metastasis (LM) is a rare and feared cancer complication, occurring in 5%-10% of solid cancers, most frequently in breast cancer (BC), lung cancer and melanoma. The incidence of LM has been historically reported to be up to 5% in BC and is rising as patients live longer and with improvement of technologies and availability of neuroaxis imaging.1-3 This incidence could be underestimated due to the difficulty of diagnosis and the relatively high frequency of false-negative results.3 LM is associated with high morbidity and mortality. Patients usually develop debilitating neurological symptoms, affecting their quality of life and, although patients with LM...
from BC have longer survival relative to other solid malignancies, the median overall survival (OS) ranges between 1.5 and 4.5 months, even despite active multimodal treatment.2-4 Poor survival together with advanced progressive systemic disease in most patients5 and absence of validated response criteria6 make it difficult to implement prospective studies. To date, very few randomized trials have been conducted on patients with LM, mostly based on heterogeneous histologies and endpoints.1,7 Consequently, in the absence of strong evidence, treatment guidelines are based on expert opinion and consist of intrathecal (IT) therapy for most patients (methotrexate, cytarabine and thiotepa being the most commonly used drugs), systemic therapy, with a strong emphasis on regimen modification at LM diagnosis, and radiotherapy (RT) in the presence of symptomatic nodular disease.1,3,8 As neither of these treatment modalities has demonstrated significant benefit in OS in randomized trials,1 considerable heterogeneity of diagnostic and treatment strategies was observed among clinicians across Europe in a recent survey, reflecting the many unresolved controversies concerning these issues.9 However, only 10% of clinicians declared that IT therapy was never part of the treatment strategy.9 To assist clinicians’ decisions in this challenging setting, previous efforts have been made to stratify patients into prognostic groups according to their characteristics and to identify those patients most likely to benefit from aggressive multimodal treatment,8,10-14 but, unfortunately, the performance of these models remains uncertain.

The objectives of our study were to report the characteristics and outcomes of patients with metastatic BC (MBC) receiving IT therapy for LM and to evaluate prognostic models in a nationwide real-life cohort. In addition to its large scale, this cohort has the enormous advantage of following all consecutive patients treated for MBC, enabling us to compare patients who developed LM and needed IT therapy, at some point in time, with the rest of the MBC population.

MATERIALS AND METHODS

Study design, patients and data collection

This was a retrospective analysis focusing on MBC patients with LM treated with IT therapy in the French nationwide Epidemiological Strategy and Medical Economics (ESME) MBC database (NCT03275311).15

The present analysis was approved by an independent ethics committee (Comité de Protection des Personnes Sud-Est II-2015-79). No formal dedicated informed consent was required, but all patients had approved the reuse of their electronically recorded data. In compliance with French regulations, the ESME MBC database was authorized by the French data protection authority (Registration ID 1704113 and authorization No. DE-2013-117). Moreover, in compliance with the applicable European regulations, complementary authorization was obtained on 14 October 2019 regarding the ESME research data warehouse.

For this study, we selected female patients included in the ESME MBC cohort between 2008 and 2016, who received IT therapy with methotrexate, cytarabine or cytarabine (either standard or liposomal) at any time during the course of their disease, as a proxy for LM, as our data did not allow the distinction between LM and brain metastases among central nervous system (CNS) lesions. Other details on study design, patients and data collection can be found in Supplementary Materials and methods, available at https://doi.org/10.1016/j.esmoop.2021.100150.

Objectives

The primary objective of this study was to assess the outcomes of MBC patients treated with IT therapy for LM and the primary endpoint was the median OS, defined as the time (in months) from the start date of IT therapy to the date of death from any cause. Secondary objectives and endpoints are detailed in Supplementary Materials and methods, available at https://doi.org/10.1016/j.esmoop.2021.100150.

Statistical analysis

Cox proportional hazards models were used to identify prognostic factors for OS and were expressed as hazard ratios with their 95% confidence intervals (CIs). Two other models were fitted using previously published prognostic scores.10,16

The ‘simplified’ Curie score10 was developed on a single-institutional population that included all BC patients with LM between 2000 and 2007. Negative prognostic factors were hormone receptor (HR)-negative status (versus positive), Eastern Cooperative Oncology Group (ECOG) performance status (PS) 3-4 (versus 0-2) and previous chemotherapy lines >3 (versus ≤3 lines). For the purposes of validation, missing data for PS were imputed to PS 3-4 because patients with missing PS had similar survival to those with PS 3-4. Patients could have a score of 0, 1, 2 or 3, according to the sum of negative prognostic factors present (+1 each). Because of the small number of patients with score 3 (n = 8), we stratified our patients into three risk groups, with scores of 0, 1 and 2-3, respectively.

The Breast-graded prognostic assessment (GPA) score16 was initially constructed for BC patients with brain metastases based on Karnofsky Performance Status (KPS), ‘genetic subtype’ and age. Missing data for PS were imputed to KPS 60, as these patients had an intermediate univariate OS, between those of patients with KPS ≤50 and KPS 70-80. Patients with missing data for BC subtype (n = 21) had Breast-GPA NA (not available). Details on the methods of conversion of ECOG PS to KPS and allocation of points according to prognostic factors are described in Supplementary Materials and methods (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100150). Because only two patients had a Breast-GPA score of 3.5-4.0, they were grouped with those with a Breast-GPA score of 2.5-3.0 and patients were therefore
stratified into three classes, with Breast-GPA scores of 0.0-1.0, 1.5-2.0 and 2.5-4.0, respectively.

The performance of all models was assessed in terms of discrimination and calibration. Risk group stratification was also evaluated for the two previously published scores. The significance level alpha was fixed at two-sided 5% and all analyses were carried out using R software (version 3.6.1; R Foundation for Statistical Analysis, Vienna, Austria). Other statistical details are presented as Supplementary Materials and Methods, available at https://doi.org/10.1016/j.esmoop.2021.100150.

RESULTS

Patient characteristics

Between 2008 and 2016, 22 266 female MBC patients were included in the ESME database. The median follow-up of the whole population was 24.6 months (range 3.1-100.3). Among them, 327 patients (1.47%) received IT therapy at some time during the course of their disease. Fifteen patients had missing data concerning the treatment line and were excluded. Our final study sample therefore consisted of 312 patients (Figure 1).

Patients included in our study sample, compared with nonselected patients, were younger (median age: 52 years versus 61 years at MBC diagnosis, \( P < 0.001 \)) and more often had lobular histology (23.4% versus 12.7%, \( P < 0.001 \)) and triple-negative (TN) subtype (24.7% versus 13.3%, \( P < 0.001 \); Table 1).

The characteristics of our selected patients and details regarding therapies received for LM are also reported in Table 1. The median time to MBC was 30.5 months (interquartile range (IQR) 1.7-85.5], while 27.9% of patients had at least three other metastatic sites in addition to leptomeningeal metastases, and 43.6% had liver metastases. The majority (52%) had received at least two previous treatment lines, and 21.5% of patients were receiving at least three other metastatic sites in addition to leptomeningeal metastases, and 43.6% had liver metastases. The majority (52%) had received at least two previous treatment lines, and 21.5% of patients were receiving at least their fifth treatment line at initiation of IT therapy.

The IT agents most frequently used were methotrexate (in 66% of patients), followed by cytarabine (29.2%) and thiotepa (4.8%). The median interval between MBC diagnosis and initiation of IT therapy was 15.7 months (IQR 5.7-35.9). Patients received IT therapy for a median duration of 8.6 weeks [IQR 3.3-20.5; these data were available for 182 patients (58.3%)]. Fifty-five percent of patients received concomitant systemic therapy, which consisted of chemotherapy, targeted therapy (using, in the decreasing order of frequency, trastuzumab, lapatinib, bevacizumab and palbociclib), endocrine therapy or combinations of these systemic agents. Only a minority (12.5%) of patients received RT for LM, whole-brain RT (10.3%) or stereotactic RT (2.2%).

Survival analysis

With a median follow-up of 24.6 months (min = 3.1/max = 100.3), 59/312 patients (18.9%) were still alive. Median OS was 4.5 months (95% CI 3.8-5.6), with estimated survival rates of 42.4% (95% CI 37.1-48.6) at 6 months and 25.6% (95% CI 20.8-31.5) at 1 year (Figure 2A). During follow-up, 90.1% of patients experienced an event.

In multivariable analysis, compared with HR+/HER2− subtype as reference, TN subtype was associated with a significantly poorer OS (hazard ratio 1.81, 95% CI 1.32-2.47, \( P < 0.001 \)), while HER2 + subtype was equivalent (hazard ratio 0.92, 95% CI 0.62-1.38; Table 2). Median OS was 5.1 months (95% CI 4.1-7.3) for HR+/HER2−, 5.6 months (95% CI 2.9-11.6) for HER2 + and 3.0 months (95% CI 1.7-5.1) for TN BC patients, respectively, \( P < 0.0001 \) (Figure 2B).

Patients with poor PS of 3-4 had significantly worse survival than patients with PS of 0-1 on univariate analysis (median OS of 4.1 months versus 7.3 months, unadjusted hazard ratio 1.84, 95% CI 1.18-2.88; \( P = 0.014 \)). In multivariable analysis that also incorporated the type of IT therapy and the presence of concomitant systemic therapy, PS did not reach statistical significance (\( P = 0.20 \)). More extensive systemic disease (\( \geq 3 \) metastatic sites except for CNS) was also associated with worse OS (hazard ratio 1.33, 95% CI 1.01-1.74; \( P < 0.001 \)).

Multivariable analysis of the impact of specific IT agents showed that administration of cytarabine or thiotepa resulted in significantly worse OS of 3.5 months, versus 5.2 months for methotrexate (adjusted hazard ratio 1.68, 95% CI 1.28-2.22; \( P < 0.001 \); Table 2, Figure 2C).

Concomitant systemic therapy was associated with significantly better OS, increasing from 2.3 months (95% CI 1.7-3.8) without systemic therapy to 6.9 months (95% CI 6.0-10.3) with at least one systemic therapy, and was a strong prognostic factor in our final multivariable model.
The following characteristics are reported for our selected population at
Histologic type, BC subtype, Age at MBC diagnosis, years

| Feature                                      | Group of patients | P value |
|----------------------------------------------|-------------------|---------|
| Time to MBC diagnosis, n (%)                 | Nonselected       | Selected|
| <6 months (de novo)                          | 6543 (29.8)       | 87 (27.9)       | 0.052 |
| 6-24 months                                  | 2728 (12.4)       | 52 (16.7)       |       |
| 24-60 months                                 | 4339 (19.8)       | 69 (22.1)       |       |
| >60 months                                   | 8275 (37.7)       | 102 (32.7)      |       |
| NA                                           | 54 (0.3)          | 2 (0.6)         |       |
| ECOG performance status, Liver metastasis, n|                   |           |       |
| HR-/+ HER2−                                  | 13 562 (61.8)     | 168 (53.8)      | <0.001|
| HER2+                                       | 3995 (18.2)       | 47 (15.1)       |       |
| Triple negative                              | 2908 (13.3)       | 77 (24.7)       |       |
| NA                                           | 1474 (6.7)        | 20 (6.4)        |       |
| Invasive carcinoma of no special type        | 16 217 (73.9)     | 206 (66.0)      | <0.001|
| Invasive lobular carcinoma                   | 2777 (12.7)       | 73 (23.4)       |       |
| Other                                        | 2521 (11.5)       | 23 (7.4)        |       |
| NA                                           | 424 (1.9)         | 10 (3.2)        |       |
| BC subtype, n (%)                           |                   |           |       |
| HR-/+                                         | 4382 (20.0)       | 94 (30.1)       | <0.001|
| HER2+                                       | 17 131 (78.0)     | 208 (66.7)      |       |
| NA                                           | 426 (2.0)         | 10 (3.2)        |       |

The following characteristics are reported for our selected population at
initiation of IT therapy

| Feature                                      | Group of patients | P value |
|----------------------------------------------|-------------------|---------|
| Previous CNS local therapy, n (%)            |                   |         |
| WBRT                                         | 64 (20.5)         |         |
| Stereotactic RT                              | 19 (6.1)          |         |
| Surgery                                      | 14 (4.5)          |         |
| Number of metastatic sites (excluding CNS), n|                   |         |
| <3                                           | 160 (51.3)        |         |
| ≥3                                           | 152 (48.7)        |         |
| Liver metastasis, n (%)                      |                   |         |
| No                                           | 176 (56.4)        |         |
| Yes                                          | 136 (43.6)        |         |
| Treatment line, n (%)                        |                   |         |
| Line 1                                       | 62 (19.9)         |         |
| Line 2                                       | 88 (28.2)         |         |
| Line 3                                       | 58 (18.6)         |         |
| Line 4                                       | 37 (11.9)         |         |
| Line 5 and more                              | 67 (21.5)         |         |
| ECOG performance status, n (%)               |                   |         |
| PS 0-1                                       | 49 (15.7)         |         |
| PS 2                                         | 42 (13.5)         |         |
| PS 3-4                                       | 48 (15.4)         |         |
| PS NA                                        | 173 (55.4)        |         |
| Intrathecal agent, n (%)                     |                   |         |
| Methotrexate                                 | 206 (66)          |         |
| Cytarabine                                   | 91 (29.2)         |         |
| Thiopeta                                     | 15 (4.8)          |         |
| Concomitant systemic therapy, n (%)          |                   |         |
| Yes                                          | 172 (55.1)        |         |
| No                                           | 140 (44.9)        |         |
| Type of systemic therapy, n (%)              |                   |         |
| Chemotherapy or targeted therapy backbone    | 151 (48.4)        |         |
| Endocrine therapy alone                      | 21 (6.7)          |         |
| Concomitant radiotherapy for LM, n (%)       |                   |         |
| WBRT                                         | 32 (10.3)         |         |
| Stereotactic RT                              | 7 (2.2)           |         |
| No RT                                        | 273 (87.5)        |         |

Continued
When applied to the study patients, the Curie score was significantly prognostic for OS. In our cohort, 12.8% of patients (n = 40) had a Curie score = 0 and median OS of 13.2 months (95% CI 6.1-17.5), 39.4% of patients (n = 123) had score = 1 and median OS of 5.0 months (95% CI 3.9-7.8) and 47.8% of patients (n = 149) had score = 2-3 and median OS = 3.5 months (95% CI 2.5-4.6), P < 0.001 (Figure 3A, Table 2). Patients with a Curie score = 2-3 had significantly longer OS than those with a Curie score = 0 (unadjusted hazard ratio 2.13, 95% CI 1.43-3.19; P < 0.001; Table 2).

The Breast-GPA score showed a similar performance in this cohort, with a C-index also of 0.57 (Supplementary Figure S2C, available at https://doi.org/10.1016/j.esmoop.2021.100150) and good calibration at 3 months, better than that observed at 6 or 12 months (Supplementary Figure S3C, available at https://doi.org/10.1016/j.esmoop.2021.100150). The Breast-GPA risk group stratification was also prognostic in our patients. Patients with a Breast-GPA score = 2.5-4.0 had significantly better OS than those with a Breast-GPA score = 0.0-1.0 [median OS of 7.3 months (95% CI 4.5-13.7) versus 3.2 months (95% CI 1.7-5.2), unadjusted hazard ratio 0.46, 95% CI 0.31-0.68; P < 0.001]. Similarly, patients with a Breast-GPA score = 1.5-2.0 had a better OS [median OS of 4.5 months (95% CI 3.7-6.3)] than those with a Breast-GPA score = 0.0-1.0 [unadjusted hazard ratio 0.6, 95% CI 0.45-0.82; P < 0.001; Figure 3B, Table 2].

DISCUSSION

IT therapy is recommended by current guidelines for the vast majority of patients with LM3,8 and is widely used in clinical practice.4,9 We conducted a retrospective analysis of the largest-to-date cohort of BC patients with LM treated with IT therapy. This population was extracted from a contemporary real-life nationwide cohort of MBC patients followed from the time of metastatic relapse, which allowed us to compare the characteristics of these patients with those of the general MBC population, confining however our main analysis exclusively to patients treated with IT.

The predisposition of BC with lobular histology to metastasize to the leptomeninges has been described in the literature10,17 as a specificity of LM, as opposed to brain metastases. Consistent with these data, we also found a
higher prevalence of lobular histology in our selected population compared with the general population of MBC patients\textsuperscript{18} or even with the MBC population with any type of CNS metastases in the ESME database.\textsuperscript{19} BC subtypes also have different propensities to metastasize to the leptomeninges compared with brain parenchyma. We observed a higher prevalence of LM in TN BC, but not in HER2\textsuperscript{+} tumours (despite the higher prevalence of brain metastases\textsuperscript{20}), in line with previous reports.\textsuperscript{10,21}

Interestingly, \textasciitilde20\% of our selected patients had LM at the time of metastatic relapse, while the majority of patients had been heavily pretreated and had extensive systemic disease at LM diagnosis, confirming previous data.\textsuperscript{5,10}

Survival in our population, with a median OS of 4.5 months, was in the range or even better than that previously reported in other studies (e.g. 7 weeks,\textsuperscript{12} 3.5 months,\textsuperscript{22} 3.9 months,\textsuperscript{13} 17 weeks,\textsuperscript{21} 4.5 months,\textsuperscript{10} or pooled median OS of 14.9-18.1 weeks in the review by Scott

### Table 2. Univariate and multivariable analyses of overall survival in patients treated with IT therapy

| Categories                                      | N   | Hazard ratio | 95% CI | P value   | Hazard ratio | 95% CI | P value   |
|------------------------------------------------|-----|--------------|--------|-----------|--------------|--------|-----------|
| IT therapy initiation period                   |     |              |        |           |              |        |           |
| 2008-2012                                      | 74  | 1            |        | 0.947     |              |        |           |
| 2012-2018                                      | 238 | 0.99         | 0.74-1.32 | 0.618     |
| Age at MBC, years                              |     |              |        |           |              |        |           |
| <55                                            | 175 | 1            |        |           |              |        |           |
| \geq 55                                        | 137 | 0.94         | 0.73-1.20 |           |
| Time to MBC, months                            |     |              |        |           |              |        |           |
| <6                                             | 87  | 1            |        |           |              |        |           |
| 6-24                                           | 52  | 1.03         | 0.71-1.50 |           |
| 24-60                                          | 69  | 0.85         | 0.60-1.22 |           |
| \geq 60                                        | 102 | 0.77         | 0.56-1.07 |           |
| ECOG performance status at initiation of IT therapy |     |              |        |           |              |        |           |
| PS 0-1                                         | 49  | 1            |        | 0.014     | 1            |        |           |
| PS 2                                           | 42  | 0.95         | 0.58-1.55 | 0.95      |
| PS 3-4                                         | 48  | 1.84         | 1.18-2.88 | 1.47      |
| PS NA                                          | 173 | 1.39         | 0.97-1.98 | 1.3       |
| BC subtype                                     |     |              |        |           |              |        |           |
| HR+/HER2−                                      | 168 | 1            | <0.001 |           |              | <0.001 |
| HER2+                                          | 47  | 0.96         | 0.65-1.42 | 0.92      |
| TN                                             | 77  | 1.87         | 1.39-2.51 | 1.81      |
| NA                                             | 20  | 1.43         | 0.88-2.32 | 1.12      |
| Number of metastatic sites (excluding CNS) at initiation of IT therapy |     |              |        |           |              |        |           |
| <3                                             | 160 | 1            |        | 0.088     | 1            | <0.001 |
| \geq 3                                         | 152 | 1.24         | 0.97-1.59 | 1.33      |
| Treatment line at initiation of IT therapy      |     |              |        |           |              |        |           |
| Line 1                                         | 62  | 1            |        | 0.04      | 1            | <0.001 |
| Line 2                                         | 88  | 1.52         | 1.06-2.18 | 1.44      |
| Line \geq 3                                    | 162 | 1.74         | 1.24-2.45 | 1.88      |
| Concomitant systemic therapy                    |     |              |        |           |              |        |           |
| No                                             | 140 | 1            | <0.001 | 1         | <0.001       |
| Yes                                            | 172 | 0.50         | 0.38-0.64 | 0.47      |
| Intrathecal agent                              |     |              |        |           |              |        |           |
| Methotrexate                                    | 206 | 1            | 0.051  | 1         | <0.001       |
| Cytarabine/Thiotepa                            | 106 | 1.29         | 1.16-1.78 | 1.68      |
| Concomitant RT                                  |     |              |        |           |              |        |           |
| No                                             | 273 | 1            |        |           |              |        | 0.748     |
| Yes                                            | 39  | 0.94         | 0.66-1.35 |           |

Univariate Cox model for the scores evaluated

| Curie score\textsuperscript{a} | N | Hazard ratio | 95% CI | P value   |
|---------------------------------|---|--------------|--------|-----------|
| 0                               | 40 | 1            |        | <0.001    |
| 1                               | 123| 1.31         | 0.87-1.98 |           |
| 2-3                             | 149| 2.13         | 1.43-3.19 |           |
| Breast-GPA\textsuperscript{c}   |     |              |        |           |
| 0.0-1.0                         | 74 | 1            |        | <0.001    |
| 1.5-2.0                         | 154| 0.6          | 0.45-0.82 |           |
| 2.5-4.0                         | 63 | 0.46         | 0.31-0.68 |           |

\textsuperscript{a} Because only eight patients had a Curie score of 3 and only four patients had a Breast-GPA score of 3.5-4.0, these patients were grouped with patients with a Curie score of 2 and a Breast-GPA score of 2.5-3.0, respectively.

\textsuperscript{b} Twenty-one patients had Breast-GPA NA due to missing data for BC subtype.

| BC, breast cancer; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; GPA, graded prognostic assessment; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IT, intrathecal; MBC, metastatic breast cancer; NA, not available; PS, performance status; RT, radiotherapy; TN, triple negative.

\section*{References}

1. Carausu M, et al. ESMO Open 2021; 6(3):100150.

2. Scott J, et al. J Clin Oncol 2018; 36(20):2091-2099.

3. Jatoi I, et al. J Clin Oncol 2013; 31(26):3257-3263.

4. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

5. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

6. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

7. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

8. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

9. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

10. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

11. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

12. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

13. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

14. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

15. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

16. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

17. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

18. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

19. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

20. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.

21. Tselepis CD, et al. J Clin Oncol 2013; 31(11):1324-1330.
et al.\textsuperscript{15}). Although, in most of the cited studies, IT therapy was used for the majority of patients, it should be noted that a limitation in this comparison is our selection of only those patients treated with IT therapy. Besides, in our study, the median OS was defined as starting from the date of IT therapy initiation and not from the date of LM diagnosis. Nevertheless, the outcome of these patients remains disappointingly poor. We also did not find any significant difference in the outcome of patients treated between 2008 and 2012 compared with that of patients treated between 2012 and 2016. However, 25% patients in our study survived for >1 year, a higher percentage than that usually reported\textsuperscript{4,21,22} and only equal to the rate reported in patients treated with a high-dose IT methotrexate regimen in the study by Gauthier et al.\textsuperscript{10} This finding suggests a relatively consistent group of patients with a potential for better survival, who might benefit from more intensive therapy.

Significant prognostic factors in multivariable analysis were BC subtype, the number of treatment lines at initiation of IT therapy, the number of other non-CNS metastatic sites, the presence of concomitant systemic therapy and the IT agent used. The respective model (with the addition of ECOG PS) showed a relatively good performance in terms of discriminative and predictive abilities, better than those of the two previously published scores validated in our cohort. Current guidelines recommend patient stratification before choosing the treatment strategy and acknowledge that more individualized prognostic tools remain an unmet need for these patients.\textsuperscript{18} We chose to validate in our cohort two previously published prognostic scores, the simplified Curie score, developed in a population with BC and LM, the majority of them treated with IT methotrexate,\textsuperscript{10} and the Breast-GPA, initially developed for BC patients with brain metastases,\textsuperscript{16} but which has also been recently evaluated for BC patients with LM.\textsuperscript{14} We confirmed in our cohort the prognostic role of the two scores, which mainly differ in terms of the number of previous treatment lines and age. However, these scores both had a low C-index (<0.6) in our cohort. This is the first time that the C-index of the Curie score has been evaluated,\textsuperscript{10,11} while a higher C-index has been observed with the Breast-GPA in a smaller cohort.\textsuperscript{14} These low C-indexes for these scores, when applied to our cohort, could be explained by the limitations of this study, as many patients presented missing data for PS at the time of initiation of IT therapy and no data were available concerning concomitant brain metastases. It should also be noted that the PS in our patients was evaluated by the ECOG scale and not the Karnofsky scale and, in order to evaluate the Breast-GPA score, we had to convert one scale to the other, with the inherent limitations. Another major limitation of this study is that other prognostic factors previously shown to have an impact on survival were not available, such as cerebrospinal fluid biochemistry\textsuperscript{10,12,23} or cytology,\textsuperscript{13} magnetic resonance imaging aspect,\textsuperscript{8,13} neurological symptoms\textsuperscript{8,12} or response to treatment\textsuperscript{10} (reviewed in\textsuperscript{1}).

The present study suggests that OS could be improved by concomitant systemic therapy (except in TN subtype) and the use of IT methotrexate (rather than cytarabine or thiopeta). There is little strong evidence from randomized trials concerning the benefit of a specific treatment modality in this population.\textsuperscript{24,25} However, data from many retrospective studies underpin the correlation of systemic therapy\textsuperscript{1,10,12,26} or a combination of IT and systemic therapies\textsuperscript{4,11,22} with better outcomes, and systemic therapy is recommended by EANO-ESMO guidelines.\textsuperscript{9} Interestingly, we found no significant difference in terms of survival between patients treated exclusively with endocrine therapy versus patients who received a chemotherapy backbone. To date, evidence for the activity of endocrine agents in LM is mainly

![Figure 3. Kaplan-Meier plots for overall survival according to (A) Curie score (0 versus 1 versus 2-3, log-rank \( P < 0.0001 \)) and (B) Breast-GPA-designated risk groups (0.0-1.0 versus 1.5-2.0 versus 2.5-4.0, log-rank \( P = 0.00011 \)). Patients were grouped in classes according to each score, as described in the ‘Materials and methods’ section. CI, confidence interval; GPA, graded prognostic assessment.](https://doi.org/10.1016/j.esmoop.2021.100150)
based on case reports. Most of the previous randomized or observational studies (reviewed in) did not find any significant difference in terms of survival between the various IT agents, except for two older reports of better neurological progression-free survival and quality-of-life-adjusted survival with liposomal cytarabine compared with standard methotrexate in patients with LM from solid tumours. Nevertheless, we should mention as caveats of our analysis the absence of information on treatment regimens (i.e. standard versus high-dose methotrexate), cytarabine formulation and of course the retrospective design that limited our analysis of all possible confounders. However, these data need to be validated in an independent cohort.

Similar to previous studies, RT for LM was not associated with increased survival, but it was used considerably less frequently than previously described. However, the role of RT in LM consists of alleviating symptoms, mostly in nodular or bulky disease, parameters that could not be assessed from our database.

In conclusion, we described and compared the characteristics and outcomes of the largest cohort of MBC with LM treated with IT therapy, associated with poor OS. However, we identified a subgroup of patients with survival >1 year and showed that 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 also have a better outcome than those treated with IT cytarabine or thiotepa. We also validated two previously published prognostic scores that might help to guide oncologists in the indication for IT and/or systemic therapy.

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REFERENCES

1. Le Rhun E, Preusser M, van den Bent M, Andratschke N, Weller M. How we treat patients with leptomeningeal metastases. ESMO Open. 2019;4(suppl 2):e000507.
2. Saadeh F, Boire A. Leptomeningeal disease and the role of intrathecal therapy. In: Ramakrishna R, Magge RS, Baaj AA, Kniely JPS, editors. Central Nervous System Metastases: Diagnosis and Treatment. Manhattan New York: Springer International Publishing; 2020:169-186.
3. Le Rhun E, Weller M, Brandsma D, et al. EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. Ann Oncol. 2017;28:iv84-iv99.
4. Scott BJ, Oberheim-Bush NA, Kesari S. Leptomeningeal metastasis in breast cancer — a systematic review. Oncotarget. 2015;7(4):3740-3747.
5. Taillibert S, Chamberlain MC. Leptomeningeal metastasis. Handb Clin Neurol. 2018;149:169-204.
6. Le Rhun E, Devos P, Boulanger T, et al. The RANO Leptomeningeal Metastasis Group proposal to assess response to treatment: lack of feasibility and clinical utility and a revised proposal. Neuro Oncol. 2019;21(5):648-658.
7. Chamberlain M, Soffietti R, Raizer J, et al. Leptomeningeal metastasis: a response assessment in neuro-oncology critical review of endpoints and response criteria of published randomized clinical trials. Neuro Oncol. 2014;16(9):1176-1185.
8. National Comprehensive Cancer Network. Central Nervous System Cancers (Version 3.2020). 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/cns_blocks.pdf. Accessed July 5, 2020.
9. Le Rhun E, Rudá R, Devos P, et al. Diagnosis and treatment patterns for patients with leptomeningeal metastasis from solid tumors across Europe. J Neuro Oncol. 2017;133(2):419-427.
10. Gauthier H, Guilhaume MN, Bidad FC, et al. Survival of breast cancer patients with meningeal carcinomatosis. Ann Oncol. 2010;21(11):2183-2187.
11. Bidad F-C, Lossignol D, Larsimont D, Piccart M, Awada A. Validation of the Institut Curie simplified prognostic score for breast cancer meningeal carcinomatosis. Ann Oncol. 2011;22(2):480-482.
12. Lara-Medina F, Crismatt A, Villarreal-Garza C, et al. Clinical features and prognostic factors in patients with carcinomatous meningitis secondary to breast cancer. *Breast J*. 2012;18(3):233-241.

13. Le Rhun E, Devos P, Weller J, et al. Prognostic validation and clinical implications of the EANO ESMO classification of leptomeningeal metastasis from solid tumors. *Neuro Oncol*. 2020;noaa298. https://doi.org/10.1093/neuonc/noaa298.

14. Ratosa I, Znidaric T. Breast cancer patients with leptomeningeal carcinomatosis: treatment results and validation of prognostic indexes. *Eur J Cancer*. 2020;138:565.

15. Pérol D, Robain M, Arveux P, et al. The ongoing French metastatic breast cancer (MBC) cohort: the example-based methodology of the Epidemiological Strategy and Medical Economics (ESME). *BMJ Open*. 2019;9(2):e023568.

16. Sperduto PW, Kased N, Roberge D, et al. The effect of tumor subtype on survival and the graded prognostic assessment (GPA) for patients with breast cancer and brain metastases. *Int J Radiat Oncol Biol Phys*. 2012;82(5):2111-2117.

17. Niwińska A, Rudnicka H, Murawska M. Breast cancer leptomeningeal metastasis: propensity of breast cancer subtypes for leptomeninges and the analysis of factors influencing survival. *Med Oncol*. 2013;30(1):408.

18. Deluche E, Antoine A, Bachelot T, et al. Contemporary outcomes of metastatic breast cancer among 22,000 women from the multicentre ESME cohort 2008-2016. *Eur J Cancer*. 2020;129:60-70.

19. Darlix A, Louvel G, Fraisse J, et al. Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a large multicentre real-life cohort. *Br J Cancer*. 2019;121(12):991-1000.

20. Koniali L, Hadjisavvas A, Constantinidou A, et al. Risk factors for breast cancer brain metastases: a systematic review. *Oncotarget*. 2020;11(6):650-669.

21. Niwińska A, Pogoda K, Michalski W, Kunkiel M, Jagiello-Gruszfeld A. Determinants of prolonged survival for breast cancer patient groups with leptomeningeal metastasis (LM). *J Neuro Oncol*. 2018;138(1):191-198.

22. Morikawa A, Jordan L, Rozner R, et al. Characteristics and outcomes of patients with breast cancer with leptomeningeal metastasis. *Clin Breast Cancer*. 2017;17(1):23-28.

23. Griguolo G, Pouderoux S, Dieci MV, et al. Clinicopathological and treatment-associated prognostic factors in patients with breast cancer leptomeningeal metastases in relation to tumor biology. *Oncologist*. 2018;23(1):1289-1299.

24. Booger W, van den Bent MJ, Koehler PJ, et al. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomised study. *Eur J Cancer*. 2004;40(18):2726-2733.

25. Le Rhun E, Wallet J, Mailliez A, et al. Intrathecal liposomal cytarabine plus systemic therapy versus systemic chemotherapy alone for newly diagnosed leptomeningeal metastasis from breast cancer. *Neuro Oncol*. 2020;22(4):524-538.

26. Niwińska A, Rudnicka H, Murawska M. Breast cancer leptomeningeal metastasis: the results of combined treatment and the comparison of methotrexate and liposomal cytarabine as intra-cerebrospinal fluid chemotherapy. *Clin Breast Cancer*. 2015;15(1):66-72.

27. Le Rhun E, Taillibert S, Zairi F, et al. A retrospective case series of 103 consecutive patients with leptomeningeal metastasis and breast cancer. *J Neuro Oncol*. 2013;113(1):83-92.

28. Almajed MM, Esfahani K, Pelmus M, Panasconi L. Complete response and long-term survival of leptomeningeal carcinomatosis from breast cancer with maintenance endocrine therapy. *Case Reports*. 2016;2016.bcr2016215525.

29. Glantz MJ, Jaeckle KA, Chamberlain MC, et al. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. *Clin Cancer Res*. 1999;5(11):3394-3402.

30. Cole BF, Glantz MJ, Jaeckle KA, Chamberlain MC, Mackowiak Ji. Quality-of-life-adjusted survival comparison of sustained-release cytosine arabinoside versus intrathecal methotrexate for treatment of solid tumor neoplastic meningitis. *Cancer*. 2003;97(12):3053-3060.