Abstract. Background/Aim: Prolonged overall survival (OS) has been reported for selected patients with leptomeningeal metastases (LM). The management and treatment of such patients is poorly-described. We report our experience on breast cancer (BC)-associated LM and patients with prolonged survival. Patients and Methods: Eleven patients with BC and LM had an OS >12 months in which treatment is described. Results: Combined intra-cerebro spinal fluid (CSF) and systemic treatment were administered until disease progression or toxicity in all but two patients. Involved-field radiotherapy was administered to two patients. Median OS in this selected cohort following LM diagnosis, was 21.0 (range=13-33.3) months. Conclusion: Prolonged OS but also prolonged responses can be observed in BC with LM. An individualized and multi-disciplinary approach is advised for the management of these patients.

The incidence of leptomeningeal metastasis (LM) will likely increase in the future due to improvement in the overall survival (OS) of patients with breast cancer (BC) as a consequence of chemotherapy utilization and of targeted agents with poor central nervous system (CNS) penetration. Notwithstanding a combined modality treatment, the prognosis of LM remains extremely poor. The median OS is 3.3 to 5 months in recent cohorts of patients with BC and LM, regardless of the choice of the intra-cerebro spinal fluid (CSF) chemotherapy agent and when combined with systemic treatment (2-7). The treatment goal of LM is to preserve the quality of life by stabilizing or improving neurological deficits and preventing neurological deterioration. However, the treatment for LM is not standardized as there are no randomized studies that have clearly defined the optimal management and treatment. A combination of intra-CSF chemotherapy, systemic therapy and CNS-directed radiotherapy (RT), when clinically-appropriate is often prescribed despite the lack of prospective trials (1, 8, 9). Treatment of LM is often continued until disease progression, toxicity or death of the patient. There are instances of prolonged survival in patients treated for LM, as approximately 15% of patients survive 12 months or longer, whatever the clinical characteristics may be, management and treatment of such patients is rarely described. Herein, we report and discuss our experience at a single institution for patients with BC-related LM, surviving 12 months or more.

Patients and Methods

Patients. All adult patients with BC and LM were retrospectively identified between January 2007 and July 2011. The following criteria for LM diagnosis were used: presence of malignant cells on CSF cytology or magnetic resonance imaging (MRI) consistent with CSF dissemination in the presence of LM neurological symptoms or signs. A total of 112 patients were identified. In this retrospective study, only patients with an OS >12 months were enumerated. Following approval by all regulatory bodies (approval number:
data that were collected prospectively, were analyzed retrospectively in patients with BC-related LM.

Treatment. Intra-CSF liposomal cytarabine (Mundipharma Inc., San Diego, California, USA) was used as initial therapy in all patients and was administered intra-CSF as 50 mg, every two weeks for a total of five treatments (induction phase), and in stable or improving patients then once every four weeks (maintenance phase) until disease progression, patient-determined discontinuance or toxicity. Dexamethasone, 6 mg orally once per day, was administered concurrently (on the day of treatment) and four days thereafter following intra-CSF drug administration to mitigate treatment-related chemical meningitis. Systemic treatment, when administered, was dependent upon the presence of progressive systemic disease, available salvage therapies and the general medical condition of the patient. CNS-directed RT was indicated for palliation of LM symptoms, to treat bulky disease defined radiographically, to correct CSF flow abnormalities defined by nuclear medicine CSF flow studies or for associated parenchymal brain metastases. Upon progression of LM treated with intra-CSF liposomal cytarabine, second line and third line intra-CSF chemotherapy (thiotepa and methotrexate, respectively) was offered when believed to be clinically indicated and to consenting patients.

Follow-up of the patients. Assessment of treatment included clinical neurological evaluation and cytological examination of CSF before each intra-CSF treatment. Entire-brain and spine MRI was obtained before treatment and every two to three months while on treatment. CSF sampling comprised at least 5 ml and was immediately submitted for cytospin, fixation and colouration. Radioisotope CSF flow studies were performed selectively in instances of suspected CSF flow-block (hydrocephaly, flow block suspected on MRI, CSF flow abnormalities defined by nuclear medicine CSF flow studies or for associated parenchymal brain metastases). Upon progression of LM treated with intra-CSF liposomal cytarabine, second line and third line intra-CSF chemotherapy (thiotepa and methotrexate, respectively) was offered when believed to be clinically indicated and to consenting patients.

Results
A total of 103 women with BC received intra-CSF liposomal cytarabine as first-line LM treatment. This cohort has been described in previous work of our group (7). At the time of the final analysis (November 2012), 97 patients had died. The median OS was 3.8 months (range=1 day-2.8 years). Thirty-six patients (35%) survived for more than six months and 11 (10%) more than 12 months. The longest survival of a patient with BC-related LM was 33.3 months.

Amongst patients with BC, LM and a greater than 12-months survival (a total of 11 patients), the median age at BC diagnosis was 39 (range=31-60) years. Histology was invasive ductal carcinoma in eight cases. Tumours were classified as estrogen receptors (ER)/progesterone (PR)-positive, human epidermal growth factor receptor-2 (HER2)-negative type in six cases, 'ER/PR negative, HER2 positive' type in three case and ER/PR/HER2-positive or ‘triple-negative type’ in one case. Histoprognostic grade was II in nine patients (Table I). LM and brain metastases were the site of first metastases in four patients. The median time-to-diagnosis of LM was 27.6 (range=1.5-238.0) months following establishment of BC. Patients were treated with a median of one (range=0-11) prior systemic chemotherapy and in the majority of cases adjuvant BC treatment. The median age at LM diagnosis was 46 (range=38-61) years. Initial Eastern Cooperative Oncology Group (ECOG) performance status (PS) at LM diagnosis was 0-2 in 10 patients and 3 in a single patient.

Neurological presentation included cranial nerve involvement (n=4), cerebellar signs (n=4), cerebral signs (n=2) and radiculo-spinal signs (n=2). Raised intracranial pressure (characterized by headaches, nausea and vomiting) was observed in three patients. There was no instance of LM-related encephalopathy. The median time between first symptoms and LM diagnosis was 2.4 (range=0.4-6.1) days. Standard CSF cytology showed the presence of malignant cells in six patients (median volume of CSF=7.5 mL, range=2-16). Median CSF protein content was 0.56 (range=0.07-5.81) g/ml. Only one patient had a completely normal CSF. Brain and entire-spine MRI was consistent with CSF dissemination in 11 patients. No bulky radiographic disease was observed, neither was CSF flow block suspected. Concomitant parenchymal brain metastases were present in seven patients, of whom one was previously treated with whole-brain radiotherapy. At the time of LM diagnosis, bone, liver and lung metastases were present in five, two and two cases, respectively.

All long surviving patients with BC-related LM (n=11) received initial treatment with a combination of intra-CSF liposomal cytarabine and systemic therapy. The median time from LM diagnosis to first intra-CSF treatment was 15 days (range=0-235). A ventricular access device (VAD) was implanted in 10 patients usually after stabilization of LM (time-to-implantation 1.5 months (range=0.2-25.3) months. A median number of 15 (range=4-16) liposomal cytarabine injections were administered. Concurrent systemic treatments included capecitabine (n=4), fluorouracil plus epirubicine with cyclophosphamide (n=3), paclitaxel (n=1), paclitaxel plus trastuzumab (n=1) and capecitabine plus lapatinib (n=1) and enantone plus exemestane (1 patient). Radiotherapy was administrated in 2 cases (n=1 each, posterior fossa only and whole-brain radiotherapy). Clinical, cytological and MRI
responses were observed after intra-CSF liposomal cytarabine and systemic treatment in nine, four and eight patients respectively. The median progression-free survival (PFS) after LM diagnosis was 7.6 (range=3.1-24.2) months. At first progression of LM, eight patients received second-line intra-CSF chemotherapy (thiotepa), that was combined with systemic treatment in five cases. ECOG PS in these eight patients was 0-2 in five cases and 3-4 in three cases. The median number of intra-CSF thiotepa injections was 16 (range=12-26). Systemic treatment included capecitabine plus lapatinib (n=2), docetaxel then vinorelbine (1 patient), capecitabine (n=1) and anastrozole (n=1). No patient received concomitant radiotherapy. Clinical, cytologic and MRI responses were observed in eight, three and four patients respectively. The median PFS following intra-CSF thiotepa therapy was 4.5 months (range=1.6–14.4). At the second progression of LM disease, six patients received a third-line of treatment. The ECOG PS for this group of patients was 2. Third-line LM directed therapy utilized intra-CSF methotrexate (n=6) and systemic therapy (n=4). The median number of intra-CSF methotrexate injections was 13 (range=7-14). Systemic treatment included capecitabine plus trastuzumab with lapatinib (2 patients), capecitabine, vinorelbine plus trastuzumab (n=1) and anastrozole (n=1). One patient received concomitant whole-brain RT for progressive brain metastases and lumbar RT for cauda equina-related symptoms. The median PFS after intra-CSF methotrexate was 4.3 (range=1.0-6.6) months.

At the time of final analysis, nine out of the total of 11 patients had died. Two patients were alive, 21.4 and 23.1 months, respectively, from the time of LM diagnosis. The median OS of the 11 long-surviving patients with BC-related LM was 21.0 (range=13–33.3) months. The median survival after second-line intra-CSF thiotepa was 11.24 (range=3.5-29.8) months and that after third-line intra-CSF methotrexate was 6.6 (range=2.0-13.6) months. The two patients with the longest control of BC-related LM survived with maintenance of neurological function and by reporting good quality of life. In both instances, intra-CSF chemotherapy or concomitant systemic treatments were stopped after one year. Both patients ultimately died of systemic cancer 29 and 33 months after LM diagnosis.

Discussion

In this cohort of 103 patients treated for BC-related LM patients, the median survival was 3.8 months and 11 patients (10%) survived for more than one year. Prolonged survival of patients with LM has been reported in the literature (2-6, 10-15) (Table II). In recent cohorts of BC-related LM, the median survival ranged from seven weeks to five months and the one-year survival varies from 7% to 24% (2-7, 11, 16, 17). Similarly to the current study, LM diagnosis has been based on the demonstration of malignant cells in the CSF (2, 5, 18), or on the basis of characteristic neurological signs and MRI findings (3, 4, 6, 7, 10).

Clinical characteristics. Among solid tumour cancer-related LM, BC is reported to have the best prognosis (19-23). In the current cohort the majority of BC was ER/PR-positive. Only a single patient had a triple-negative type of BC, generally believed to have the worst prognosis. The literature suggests that histology affects the risk of developing LM, with the highest risk being seen in the lobular subtype, an ER/PR-negative status or a triple-negative status (3, 4, 24-29). Notably, LM involvement, unlike parenchymal brain metastasis, is a relatively rare metastatic manifestation of HER2-positive tumours in CNS (3-5%) (3, 30). The literature is less clear with respect to the histology of BC and prognosis. In a cohort of 27 patients with BC-related LM, the majority of patients with a survival of six months or more had hormone receptor-positive BC (17). In the current cohort of 103 BC patients, triple-negative status was significantly associated with the poorest OS (7). According to the National Comprehensive Cancer Network and independently of primary tumor type, the initial PS, a reflection...
of neurological disease burden, bulky meningeal disease defined by CNS radiology, LM-related encephalopathy, the presence of CSF flow blocks defined by nuclear medicine CSF flow studies and the status of systemic disease are significant prognostic factors impacting on the outcome of patients with LM (31, 32). In addition, multivariate analysis in cohorts of patients with LM from various solid tumor types confirms the association between OS and the initial PS and suggests that age at LM diagnosis and the treatment modality (administration of systemic therapy) further impact survival (21-23, 33). The median age at LM diagnosis in the 11 patients with a prolonged survival in our study was similar although somewhat younger than those patients reported in the literature (46–53 years) (2-5, 7). Similarly, the initial ECOG PS at LM diagnosis was better in our long-surviving patients when compared to the entire cohort of 103 treated patients. In part this reflects a lower CNS disease burden further supported by the fact that none of the long-surviving patients presented with radiographically bulky disease, LM-related encephalopathy or hydrocephalus. In addition, the neurological deficits due to LM were less in the long-surviving group than in the larger cohort of 103 patients. Furthermore, the long-surviving patients were less pre-treated and more often presented with CNS metastasis as the site of first disease recurrence than in the larger cohort. This permitted a larger range of systemic therapies for long-surviving patients with BC-related LM. Other contemporary cohorts of BC-related LM suggest that the clinical and cytological responses are significantly associated with OS (2-6). In our long-surviving cohort, high rates of clinical, cytological and MRI responses were observed (9/11, 4/7 and 9/11, respectively). In addition, all long-surviving patients were initially treated with combination therapy, as well as the majority treated at the time of first or second LM recurrence.

Treatment. It is clinically challenging, to determine whom with LM to treat, as there are few guidelines to use as a reference. A description of long-surviving patients with LM is not available in the literature. The usual treatment of LM combines intra-

Table II. Median overall survival and proportion of patients with a survival of 12 months or more in cohorts of treated patients with leptomeningeal metastases from breast cancer.

<table>
<thead>
<tr>
<th>Description of cohorts</th>
<th>Median overall survival</th>
<th>One-year survival (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Our cohort (n=7), 2013</td>
<td>3.8 Months (range=1 day-2.8 years)</td>
<td>10%</td>
</tr>
<tr>
<td>103 patients from 2007 to 2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lara-Medina et al., (n=16) 2012</td>
<td>7 Weeks (95% CI, 2.3-11.6 weeks)</td>
<td>Not detailed</td>
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<tr>
<td>49 patients from 2003 to 2007</td>
<td></td>
<td></td>
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<tr>
<td>Meattini et al., (n=11), 2012</td>
<td>4.9 Months (range=0.3-27.7)</td>
<td>9%</td>
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<tr>
<td>33 patients from 2002 to 2010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al., (n=6), 2011</td>
<td>4.1 Months (range=2.2-5.8 months)</td>
<td>13.2%</td>
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<tr>
<td>68 patients from 1995 to 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Azevedo et al., (n=3), 2011</td>
<td>3.3 Months (range=0.03-90.4 months)</td>
<td>24.3%</td>
</tr>
<tr>
<td>60 patients from 2003 to 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gauthier et al., (n=4), 2010</td>
<td>4.5 Months (range=0-53 months) (entire cohort)</td>
<td>18%</td>
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<tr>
<td>91 patients from 2000 to 2007 (80 patients treated)</td>
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<td></td>
</tr>
<tr>
<td>Clatot et al., (n=5), 2009</td>
<td>150 Days (range=9-561 days)</td>
<td>Not detailed</td>
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<tr>
<td>24 patients from 1999 to 2008</td>
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<tr>
<td>Regierer et al., (n=17), 2008</td>
<td>9 Weeks (not detailed)</td>
<td>22%</td>
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<td>27 patients from 1998 to 2005</td>
<td></td>
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<tr>
<td>Rudnicka et al., (n=2), 2007</td>
<td>16 Weeks (1-402 weeks)</td>
<td>7%</td>
</tr>
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<td>67 patients from 2000 to 2005</td>
<td></td>
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<tr>
<td>Jaekle et al., (n=10), 2001</td>
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<td></td>
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<tr>
<td>53 patients from 1994 to 1999</td>
<td>12.6 Weeks (0-73.6)</td>
<td>19%</td>
</tr>
<tr>
<td>Chamberlain et al., (n=40), 1997</td>
<td>7.5 Months (1.5-16)</td>
<td>Not detailed</td>
</tr>
<tr>
<td>32 patients from 1986 to 1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fizazi et al., (n=29), 1996</td>
<td>67 Days (not detailed)</td>
<td>14.7%</td>
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<tr>
<td>68 patients from 1979 to 1994</td>
<td></td>
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<tr>
<td>Jayson et al., (n=41), 1994</td>
<td>77 Days (not detailed)</td>
<td>Not detailed</td>
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<td>35 patients from 1979 to 1992</td>
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<tr>
<td>Boogerd et al., (n=43), 1991</td>
<td>12 Weeks (not detailed)</td>
<td>11%</td>
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<tr>
<td>44 patients from 1978 to 1989</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clamon et al., (n=42), 1987</td>
<td>46 Days (not detailed)</td>
<td>23%</td>
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<tr>
<td>22 patients from 1977 to 1984</td>
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Author, reference, year of publication.
CSF chemotherapy and systemic therapy. Four intra-CSF therapies are mainly used (liposomal cytarabine, cytarabine, methotrexate and thiopeta). No significant difference in OS has been clearly demonstrated amongst these agents in comparative trials. It is customary at our centre to use intra-CSF liposomal cytarabine as first-line treatment as it has shown to improve PFS and results in a better quality of life when compared to intra-CSF methotrexate based on a single randomized study of solid tumor-related LM (34, 35). New intra-CSF agents, such as trastuzumab, are under evaluation for HER2-positive tumors and LM. Systemic chemotherapy when administered in the context of LM is dependent on the general medical status of the patient, previous treatment, available salvage therapies and the extent of systemic cancer. In the current study, all patients that were long survivors were treated with a new systemic therapy recognizing that co-administered systemic therapy is a prognostic factor in therapy of LM. In various contemporary cohorts of patients with BC and LM, systemic treatment was concomitantly associated in 33.8 to 78% of the cases (2, 3, 4, 6, 7, 16). The primary neurosurgical interventions in LM are ventriculoperitoneal shunting (VPS) for symptomatic hydrocephalus and placement of a VAD to facilitate administration of intra-CSF chemotherapy. In the current study, no patient in the long-surviving cohort manifested hydrocephalus or required placement of a VPS. In addition, the majority of patients were treated by way of a VAD. Ventricular, as opposed to lumbar, administration of chemotherapy has been demonstrated in a retrospective study to improve PFS in patients with solid tumor-related LM (36). The indications of CNS-directed RT are to palliate LM symptoms, treat bulky radiographic disease, correct CSF flow abnormalities or for associated parenchymal brain metastasis. RT-alone has not been shown to impact OS compared to best supportive care in patients with LM related to non-small cell lung cancer (37). In recent cohorts of patients with LM, RT was administered in 17 to 51% of all patients (2, 3, 4, 5, 7, 16). Despite multimodal treatment of LM, survival is of short duration. Treatment of LM is often administered until disease (neurological or systemic) progression, toxicity or patient-initiated discontinuance (2, 3, 4, 29). Some investigators have suggested LM-directed therapy to continue until normalization of CSF (2). A potential problem with intra-CSF chemotherapy of long duration is the possible emergence of treatment-related neurotoxicity. For example, an increased risk of delayed leuкоencephalopathy has been reported after intra-CSF methotrexate with cumulative doses of 150-170 mg without whole-brain RT, and even lower doses if intra-CSF methotrexate is combined with brain RT (38, 39). In a recent study, it was possible to administer intra-CSF methotrexate up to a CSF cumulative dose of 150 mg without apparent neurotoxicity (16). In other studies evaluating high-dose intra-CSF methotrexate, only two cases of periventricular hypodensity in 14 patients were observed and a median survival of four months was reported (5). It is customary at our centre to continue intra-CSF therapy until disease progression, a situation which occurred in 9/11 long-surviving patients with BC-related LM in the current study. It may be that prolonged duration of treatment as utilized here may in part account for prolonged survival in a subset of patients with BC and LM.

**Conclusion**

Prolonged OS may be observed in a subset of patients with LM. In patients with BC, long-surviving patients appear to be defined by relatively young age; ER/PR-positive tumors; limited prior therapy for systemic disease; LM as the site of first metastasis; good PS; lack of hydrocephalus; radiographic bulky disease; and LM-related encephalopathy; response to combined modality therapy and long duration of LM-directed therapy. The current study has limitations in that it is a retrospective analysis of patients with BC and LM and has selected patients with long survival, who were few in number. These long-standing survivors represent a highly select group of patients and it may be over-reaching to define a category of patients with BC and LM that permits prognostication as to survival. Nonetheless it appears there is a category of patients with LM that benefit from multimodal therapy and the current study attempts to characterize such patients. Clearly apparent from the current study is the unmet need for new therapeutics in managing this challenging CNS metastatic complication of cancer.

**Conflicts of Interest**

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Le Rhun et al: Prolonged Control of Leptomeningeal Metastases

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