Critical Reviews in Oncology / Hematology 135 (2019) 85–94

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

Leptomeningeal carcinomatosis in patients with breast cancer

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ARTICLE INFO

Keywords:
Leptomeningeal carcinomatosis
Leptomeningeal metastasis
Neoplastic meningitis
Breast cancer

ABSTRACT

Leptomeningeal carcinomatosis (LC) is defined as infiltration of the leptomeninges by metastatic carcinoma, a relatively uncommon but devastating complication of many malignancies. Although only 5% of patients with breast cancer develop leptomeningeal involvement, it remains the most common etiology of LC. It can occur as a late-stage complication of systemic progression or present as the first sign of metastatic disease, with or without parenchymal brain metastases. Lobular carcinomas have a higher propensity to metastasize into the meninges when compared to ductal carcinoma, especially the triple-negative subtype, which usually is associated with a shorter interval between metastatic breast cancer diagnosis and the development of LC. Prognosis remains poor, with median survival of 4 months for patients receiving state-of-the-art treatment. The main factors associated with survival are performance status at diagnosis, CSF protein level and triple-negative subtype. Headache is commonly the first clinical presentation of LC, and the diagnostic workup usually requires CSF-cytological analysis and or/MRI. The current management of LC consists of a combination of intra-CSF chemotherapy, systemic therapy, radiotherapy and/or best-supportive care. The standard intra-CSF chemotherapy regimen is methotrexate. Radiotherapy is used for relieving obstruction points on CSF-outflow channels due to ependymal nodules, tumor deposits or bulky disease. Objective responses have been reported with intrathecal administration of trastuzumab for HER2-positive disease, yet this strategy is still under investigation. Further prospective trials are needed to better address the impact of these treatment modalities on overall survival and quality of life.

1. Introduction

Metastases to the central nervous system in patients with breast cancer can cause substantial morbidity and mortality (Huang et al., 2018). They may occur either within the brain parenchyma, along the leptomeninges, or both (Sekhar et al., 2017).

Leptomeningeal carcinomatosis (LC) is defined as leptomeningeal infiltration, including the pia mater, arachnoid and subarachnoid space from a solid primary tumor. It is a rare complication of breast cancer, with an incidence rate of approximately 5% (Corbin and Nagpal, 2016; Gauthier et al., 2010; Kokkoris, 1983). Considering the high incidence of breast cancer worldwide, in absolute numbers it constitutes the most common etiology of LC. It presents concurrently with brain metastasis in breast cancer in 14% of the cases (de Azevedo et al., 2011).

2. Methodology

We performed a comprehensive systematic literature search in PubMed (Cochrane, Scopus, Embase and Medline) with key-words such as “leptomeningeal carcinomatosis AND breast cancer” = total of 265 citations or “leptomeningeal metastasis AND breast cancer = 182 citations”, or “neoplastic meningitis AND breast cancer = 272 citations”. The final search was performed in May 2018. Articles in languages other than English, duplicated articles, articles referring to etiologies of leptomeningeal disease other than breast cancer and articles considered not relevant to this review (not focused on leptomeningeal disease) were excluded. Inclusion criteria allowed retrospective and prospective studies published in English with the key words cited before. A total of 107 studies met our inclusion criteria and were included for quantitative synthesis (Fig. 1).

3. Breast cancer subtype and leptomeningeal carcinomatosis

A predisposition to LC of lobular histological type is well established and described by many authors, accounting for approximately 35% of the LC associated with breast cancer. However, our literature review demonstrated that the rate of parenchymal brain metastasis in lobular carcinoma is only about 7%. This suggests a propensity for leptomeningeal dissemination of this subtype even in the absence of cerebral metastasis (Abouharb et al., 2014; Niwińska et al., 2013). A possible

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https://doi.org/10.1016/j.critrevonc.2019.01.020
Received 15 August 2018; Received in revised form 26 January 2019; Accepted 26 January 2019

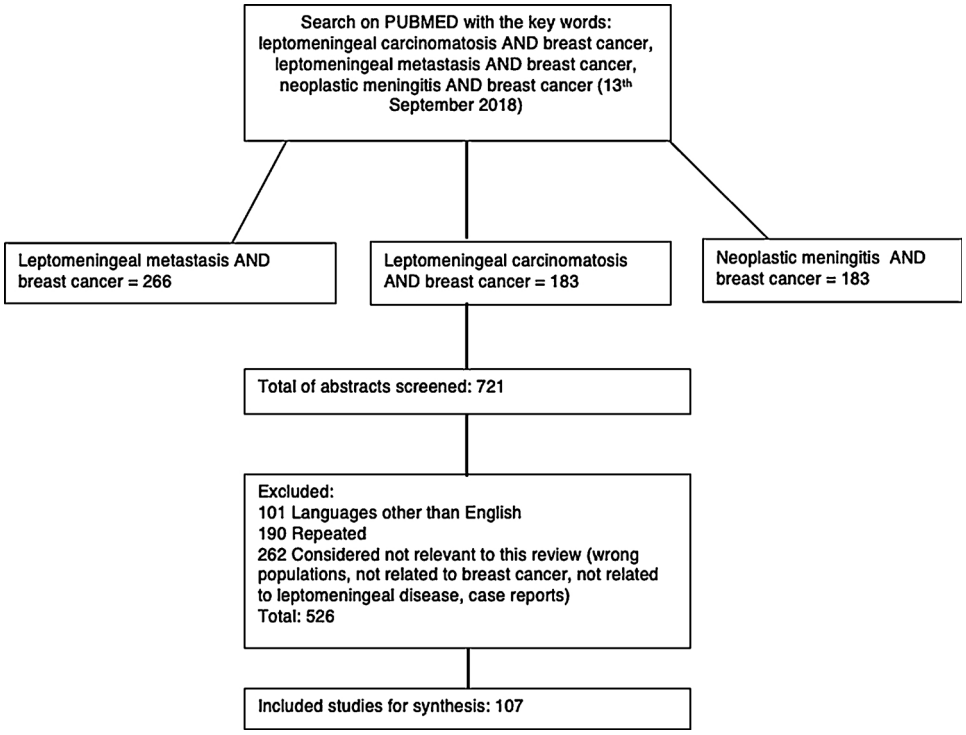

Fig. 1. Summary of evidence search and selection.

explanation for this predisposition exhibited by lobular carcinoma to metastasize to the meninges are the changes in cell adhesion molecules found in this subtype.

It is well known that the E-Cadherin-catenin complex is vital for the maintenance of normal and tumoral cytoarchithereture and also a necessary mediator of cell-cell adhesion (Petrova et al., 2016). In many primary tumors with invasive properties, intercellular adhesion is reduced, and tumor clones fail to adhere to one another, becoming disorganized, and able to separate from the primary tumor mass. Decreased expression of the E-cadherin-catenin complex has been correlated with invasion, metastasis and unfavorable prognosis (Corso et al., 2018; Petrova et al., 2016). It was first demonstrated in a mouse model of pancreatic cancer in which disruption of the expression of E-cadherin led to early invasion and metastasis (Batistatou et al., 2009). It is reported that the majority of invasive lobular breast cancer (around 90%) express complete E-cadherin loss (Corso et al., 2018). Autopsy data, from one retrospective cohort of metastatic breast cancer patients revealed an incidence of LC in infiltrating lobular breast carcinoma of 14% compared with 1% of infiltrating ductal breast carcinoma (Lamovec and Zidar, 1991).

The proportion of patients with LC also differs according to molecular subtypes. The most commonly described molecular breast cancer subtype associated with LC is triple-negative: approximately 40% of LC are related to triple-negative breast cancer. The median interval of time from breast cancer diagnosis to LC is usually counted in years and it ranges between 2 and 7 years as reported in retrospective series (Gauthier et al., 2010; Yust-Katz et al., 2013). Commonly, LC presents as a late-stage complication of breast cancer, and is diagnosed in patients with active and progressive systemic disease in up to 70% of cases (Sacco et al., 2016). The time to development of LC seems to be influenced by the hormone receptor status. LC in triple-negative disease develops after a significantly shorter time from the diagnosis of breast cancer than other subtypes. There are also reports of LC as initial presentation of primary breast cancer and as the first site of metastatic disease in triple-negative subtypes (Sacco et al., 2016; Yust-Katz et al., 2013).

Although HER-2-positive disease is known to have a propensity to cerebral metastasis this association is not directly translated to LC. Retrospective data shows that HER-2-positive disease is less frequent than luminal and triple-negative subtypes in patients with LC, accounting for approximately 10–15% of the cases (Abouharb et al., 2014; de Azevedo et al., 2011; Park et al., 2010). A 14% prevalence of concurrent LC at the time of brain metastasis diagnosis has been reported in a HER-2-positive breast cancer cohort (Yust-Katz et al., 2013). Patients with HER-2+ subtype and brain metastasis have a favorable prognosis compared with other subtypes. However, in patients with leptomeningeal disease there is no significant difference in overall survival between HER-2+ and hormonal receptor+/HER-2-negative subtypes. The HER-2 status concordance rate between metastatic breast cancer cells in CSF and primary tissue is known to be very high (up to 95%) (Park et al., 2010). There is also evidence that the molecular profiling of tumor cells in cerebrospinal fluid matched primary tumors from metastatic breast cancer patients (Magbanua et al., 2013).

4. Pathogenesis: how does breast cancer reach the leptomeninges?

The possible pathways by which cancer cells reach the leptomeninges have been extensively discussed in the literature. Such dissemination may occur by hematogenous spread through the arterial or venous circulation, or endoneural, perineural, perivascular of lymphatic spread. In large cohorts, brain metastases were associated with LC in 33–54% of the cases (de Azevedo et al., 2011; Gauthier et al., 2010; Lara-Medina et al., 2012; Le Rhun et al., 2013; Lee et al., 2011; Niwińska et al., 2013; Rudnicka et al., 2007; Yust-Katz et al., 2013). It is more frequently seen in patients with parenchymal brain metastasis located in the posterior fossa or patients that underwent neurosurgery with opening of the ventricular system for resection of cerebellar lesions (Ha et al., 2017; Ojerholm et al., 2014). Retrospective data suggests that whole brain radiotherapy (WBRT) after resection of breast cancer brain metastases could reduce the incidence of LC when compared to partial radiotherapy to the tumor bed (Johnson et al., 2016; Ojerholm et al., 2014). In another large cohort of patients with brain metastasis the incidence of LC was higher in patients treated with

surgery followed by stereotactic radiosurgery than in patients treated with radiosurgery alone (Ma et al., 2018).

In the absence of parenchymal central nervous system (CNS) metastases, the most common prognostic factor for dissemination is the presence of bone metastases, especially vertebral or paravertebral lesions (Johnson et al., 2016; Kokkoris, 1983). Cancer cells may reach the bones neighboring the CNS via venous or arterial channels. They may then infiltrate the leptomeninges by direct extension or spread along the perivascular spaces of the intravertebral veins and paravertebral venous plexus (Chen et al., 2015; Kokkoris, 1983).

5. Prognosis

Although LC from breast cancer has the best prognosis when compared to LC secondary to other malignancies, it still carries a poor prognosis, with a median overall survival (OS) of approximately 4 weeks, that can be prolonged to 4 months in some patients with aggressive multimodal treatment (Chen et al., 2015; Huang et al., 2018; Meattini et al., 2012). Several factors have been identified as possible predictors of survival: the most commonly described in the literature include performance status, CSF protein levels, degree of neurologic deficit, age at diagnosis and triple-negative subtype (Jo et al., 2013; Lara-Medina et al., 2012; Morikawa et al., 2017; Nayar et al., 2017; Niwińska et al., 2018; Palma et al., 2013; Torrejón et al., 2013; Yust-Katz et al., 2013). Although the prognosis is poor, there are some patients who present survival > 6 months. The one year survival rate described in the literature is around 20% (Clatot et al., 2009; Morikawa et al., 2017). Gauthier et al., proposed a specific prognostic score (Table 1) for patients with breast cancer leptomeningeal metastasis that correlates performance status, more than three chemotherapy regimens before LC diagnosis, negative hormone receptor status and high Cyfra 21-1 level in CSF with overall survival (Gauthier et al., 2010). Knowledge of these potential factors associated with prognosis and overall survival could inform bedside treatment decisions identifying a subgroup of patients who are candidates for an intensive management approach (Comte et al., 2013; Gauthier et al., 2010). Another score (INDEX score) was recently suggested by Niwinska et al., that correlates overall survival with older age, performance status, luminal subtype, and the treatment intensity delivered to the patient. Patients classified as having bad prognosis presented a median overall survival of 1.5 months compared to patients with good prognosis who experienced a median overall survival of 9.6 months (Niwińska et al., 2018).

6. Clinical features

Leptomeningeal carcinomatosis can present a large variety of clinical features turning the diagnosis oftentimes tricky. The symptoms arise according to the area of the CNS involved by the malignant cells (Hyun et al., 2016; Le Rhun et al., 2017a). Some of the often seen signs and symptoms include: headache, radicular pain, cranial nerve deficits, visual disturbances, hearing loss, seizures and causa equine syndrome. Another possible clinical presentation is a new onset of a psychiatric disorder (Le Rhun and Galanis, 2016; Zairi et al., 2012). Direct compression and invasion of brain parenchyma, involvement of CNS vessels leading to ischemia, metabolic strain, and disruption of the blood-brain barrier are some of the physiopathologic mechanisms responsible for the clinical course (de Azevedo et al., 2011; Hyun et al., 2016; Le Rhun et al., 2013; Le Rhun et al., 2017a). Nausea, vomiting, positional headaches and even somnolence are symptoms related to obstructive or communicative hydrocephalus that may occur in more than half of the patients with LC due to damage of the CSF flow. Approximately 80% of the patients are symptomatic at the moment of diagnosis, and the main complaint is headache (Le Rhun et al., 2017a). The clinical findings may be subtle initially, and many times are dismissed, especially in patients who are clinically ill and known to have metastatic disease. However, the symptoms tend to progress quickly in severity and evolve reflecting multifocal involvement of the neural axis Patients with already known metastatic breast cancer that develop such neurologic signs are highly suspicious for leptomeningeal carcinomatosis (Le Rhun and Galanis, 2016; Zairi et al., 2012).

7. Diagnostic workup

The diagnosis of LC remains difficult and is established by the presence of malignant cells in the CSF or, in the absence of malignant cells in the CSF, by concomitant characteristic clinical symptoms or signs and typical MRI findings (Altundag et al., 2007; Le Rhun et al., 2017b; Nayar et al., 2017; Yu et al., 2001).

The gold standard for the diagnosis of LC remains the demonstration of tumor cells on CSF which is positive in up to 60% of the patients (Lee et al., 2015). However; the sensitivity of CSF cytology in solid tumors is somewhat limited and may be adversely impacted by limited sample size or delays in processing. Repeating the CSF cytology up to 3 times increases the sensitivity to above 90%. Each CSF collection should draw 5–10 ml to ensure sufficient amount for analysis. Hemorrhagic contamination should be avoided, and the sample should be processed within 30 min after sampling (Glantz et al., 1998; Le Rhun et al., 2017a; Nayar et al., 2017).

In the absence of the presence of pathologic cells in the CSF analysis, indirect signs and CSF alterations are observed in more than 90% of the patients with leptomeningeal disease including increased opening pressure (> 200 mm H_2O) in 21–42%, increased CSF leukocyte count (> 4 mm^{-3}) in 48–77%, elevated protein (> 50 mg/dl) in 56–91% and decreased glucose (< 60 mg/dl) in 22–63% (Le Rhun et al., 2017a; Li

Table 1
Prognostic scores and overall survival results in patients with leptomeningeal carcinomatosis from breast cancer.

Score	Variables (pontuation)	Classification	Medium overall survival
Curie score Gauthier et al. (2010)	Hormone receptor status (negative = 1 and positive = 0) Previous chemotherapy lines (> three lines = 1; ≤ three lines = 0) Initial Cyfra 21-1 level in cerebrospinal fluid (> 4 ng/ml = 1)	Group A: 0–1 points Group B: 2 points Group C: 3 or 4 points	Group A: 12 months Group B: 4 months Group C: 2 months
Index score Niwińska et al. (2018)	Age at diagnosis (< 53 years = 1; > 53 = 0) Karnowsky performance status (KPS > 70 = 1; < 70 = 0) Luminal biological type (ER/PR+; HER2−) (Yes = 1; No = 0) Radiotherapy (Yes = 2; No = 0) Intrathecal treatment (Yes = 1; No = 0) Systemic treatment (Yes = 2; No = 0)	Formula: 7+ (age at diagnosis) – (KPS) – (luminal) – (2× RT) – (intrathecal) – (2× systemic) Group A (formula = 1) Group B (formula = 2) Group C (formula = 3–4) Group D (formula = 5–8)	Group A: 9.6 months Group B: 6.9 months Group C: 3.9 months Group D: 1.5 months

et al., 2018; Yust-Katz et al., 2013).

About 70–80% of patients with leptomeningeal disease present abnormalities on image scans. The imaging modality of choice for the diagnosis is high quality, T1-weighted magnetic resonance imaging (MRI) with gadolinium contrast, which has been shown to be more sensitive compared to contrast-enhanced CT. The study must include images of the brain and spine as leptomeningeal disease can impact the entire neuroaxis (Chang and Lo, 2003; Le Rhun et al., 2017a; Nayar et al., 2017). Characteristic MRI findings include sulcal enhancement or obliteration, linear ependymal enhancement, cranial nerve root enhancement and leptomeningeal enhancing nodules, notably of the cauda equine (Collie et al., 1999; Watanabe et al., 1993). Whenever possible, cerebrospinal MRI should be obtained before lumbar puncture or ventricular shunt placement because these procedures usually promote an enhancement of meningeal contrast and might lead to a false-positive image interpretation. Cranial computed tomography is reserved to patients who present contraindications for MRI and it is mainly useful to identify nodular disease (Chamberlain et al., 1990; Glantz et al., 1998; Le Rhun et al., 2017a; Yust-Katz et al., 2013).

Around 30–70% of the patients might develop obstruction of the CSF flow. CSF flow studies that utilize Indium-111 DTPA of Technetium-99m labeled albumin present higher sensitivity than conventional MRI and can better characterize the location of obstructive hydrocephalus, allowing for palliative intervention with focused radiotherapy. However, routine analysis of CSF flow for prognostic evaluation remains a rare practice among clinicians (Le Rhun et al., 2017a; Zairi et al., 2012). The use of PET-CT is not recommended for the diagnosis of LC although it has been reported in cases where F-18 F-FDG PET/CT study helped in the diagnosis of LC (Nuvoli et al., 2018; Ortapamuk and Demir, 2017; Short et al., 2019).

Rhun et al. conducted a web-based survey questioning about the diagnosis and treatment patterns for patients with leptomeningeal metastasis from solid tumors across 26 countries in Europe. Diagnosis and treatment decisions for patients with leptomeningeal metastasis from solid tumors varied widely across Europe suggesting the need for standardization of diagnosis and evaluation tools as well as controlled studies to improve the level of evidence for all therapeutic approaches to LC (Le Rhun et al., 2017b).

8. Treatment

There is currently no generally accepted standard of care in the treatment of breast cancer LC. The current management of LC consists of a combination of intra-CSF chemotherapy, systemic therapy, radiotherapy or best-supportive care and should be individualized on a case by case (Dawood and Gonzalez-Angulo, 2013; Dudani et al., 2016; Kim et al., 2012; Le Rhun et al., 2017b; Lin et al., 2017; Niwińska et al., 2018; Singh et al., 2013).

Treatment decisions are influenced by the individual's functional status, ability and willingness to receive additional treatment, and extent of active systemic (extracranial) disease. The prognostic factors and scores previously cited could help better selecting patients for aggressive treatment (Gauthier et al., 2010). In some patients, the diagnosis of LC is the final event of the disease and compels providers and patients to pursue palliative care, especially when it is accompanied by a dramatic clinical decline (Fusco et al., 2013).

9. Treatment implications of the blood-brain barrier (BBB) and the Blood-CSF barrier

One important point about the treatment of LC is that the traditional chemotherapy and targeted therapies utilized to treat systemic disease are limited by the blood-brain barrier (BBB). The tight junctions between the astrocytes of the BBB protect the brain from accidental toxins, but in doing so also shield the brain from intentional toxins, like chemotherapy (Bartsch et al., 2013). Most chemotherapy drugs are too large to pass from the blood into the cerebrospinal fluid and access the CNS. Drug efflux pumps, such as Pgp, that line the BBB work to actively transport toxic substances, including drugs, out of the brain, contributing to further drug resistance in the CNS (Bowman and Kumthekar, 2018; Le Rhun et al., 2017a; Scott et al., 2016).

Besides of the BBB, the homeostasis of the brain also depends of the blood-CSF barrier. The blood-CSF barrier is widely distributed and, with its large supply of transporters, it could represent an efficient alternative route for chemotherapy and target drugs entry into the CNS (Johanson et al., 2005). This barrier is composed of the choroid plexus and the arachnoid membrane (Deeken and Loscher, 2007). The choroid plexus which is the primary site of CSF production, is composed of a rich capillary bed, pia mater, and epithelial cells (Boire et al., 2017; Shapiro et al., 2009). Drugs that penetrate the lateral ventricle choroid plexus can follow the CSF bulk flow in the ventricular system and then become in contact with all the region of the brain (Johanson et al., 2005; Redzic et al., 2005). Although it accounts for only 0.2% of brain weight, the choroid plexus is necessary for adequate nutrition and function of the brain as well as many other additional functions including renal regulation, hepatic metabolism, immune cell sinalization, endocrine regulation, maintenance of osmotic balance, and regulation of trophic factors (Johanson et al., 2005). The choroid plexus is composed by a heterogeneous population of cells and a diverse complement of cellular proteins (Deeken and Loscher, 2007).

There are strategies under investigation to optimize the delivery of pharmaceutical agents to the CSF harnessing the unique features and mechanisms presented by the choroid plexus: (1) the transport of antitumor agents between the blood and CSF (for example, prolactin receptor localized in the blood-CSF barrier but not the BBB) (Mangurian et al., 1992), (2) the Na^+/ascorbate cotransporter that is unique to the blood-CSF barrier (Angelow et al., 2003), (3) viruses that infect promptly the choroid plexus epithelium (Petito, 2004), (4) leukocyte traffic across the choroid plexus (Kivisäkk et al., 2003). In principle, researchers could also develop strategies to prevent access of tumor cells into the CSF by blocking choroid plexus cell-surface markers to which tumor cells are attracted. There is a recent work published by Boiere et al. addressing the complement component 3 (C3a), which is produced in the choroid plexus by cancer cells in animal models and also confirmed in patients with leptomeningeal metastasis from breast cancer. According to this research, C3a receptor activation allows entry of plasma growth factors into the CSF stimulating leptomeningeal metastasis. Interruption of the C3a receptor signaling blocks leptomeningeal metastasis in mice models (Boire et al., 2017). Future explorations of the multivariate functions of the choroid plexus may become a potential pathway for the development of novel approaches to CSF-targeted therapy.

10. Treatment modalities

10.1. Intrathecal chemotherapy

For all the reasons mentioned above, the idea of administering treatment directly into the subarachnoid space is the theoretical purpose behind intrathecal (IT) chemotherapy (Tetef et al., 2000).

IT and/or intraventricular chemotherapy has become a standard approach for patients with LC in many institutions. It has been studied prospectively and retrospectively. Most data come from observational studies, primarily retrospective. Until now, no prospective trial has demonstrated that IT prolongs overall survival in LC (Heo et al., 2017; Lee et al., 2017). Boogerd et al. published a small randomized study demonstrating that the addition of IT chemotherapy to systemic treatment and involved field radiotherapy didn't lead to a survival benefit or improved neurologic response (Boogerd et al., 2004). On the other hand, there is a considerable number of retrospective cohorts showing clinical, cytological and imaging response as well as some reports of complete response with IT chemotherapy (Table 2). Three options of IT

Table 2
Summary of retrospective cohort's results of leptomeningeal metastases in breast cancer patients.

First author/year	Number of patients with LC	Breast cancer subtype distribution	Treatment	Medium overall survival
Lara-Medina et al. (2012)	49	ER positive 20% PR positive 27% HER-2 positive 20% TNBC 39%	IT chemotherapy 59% Systemic chemotherapy 45% Radiotherapy 51%	7 weeks 14 weeks for patients that received IT chemotherapy
Yust-Katz et al. (2013)	103	HR positive 55.3% HER-2 positive 22.8% TNBC 22.8%	IT chemotherapy 55% Systemic chemotherapy 36% Radiotherapy 52%	4.27 months 24 patients surviving more than one year
Gauthier et al. (2010)	91	ER positive 70% PR positive 44% HER-2 positive 10% TNBC 21%	IT chemotherapy 87% Systemic chemotherapy 78% Radiotherapy 29%	4.5 months
Niwińska et al. (2018)	187	HR positive 56% HER-2 positive 19% TNBC 37%	IT chemotherapy 68% Systemic chemotherapy 56% Radiotherapy 56% Hormonal therapy 17%	4.2 months
Le Rhun et al. (2013)	103	ER positive 61% PR positive 44% HER-2 positive % TNBC 23%	IT chemotherapy 100% Systemic chemotherapy 44% Radiotherapy 13.6% Hormonal therapy 15%	3.8 months
Torrejón et al. (2013)	38	ER positive 60% PR positive 34% HER-2 positive 26% TNBC 23%	Systemic chemotherapy 52% Radiotherapy 80%	2.6 months
de Azevedo et al. (2011)	60	ER positive 51% PR positive 43% HER-2 positive 15% TNBC 30%	IT chemotherapy 68% Systemic chemotherapy 21% Radiotherapy 36%	3.3 months
Morikawa et al. (2017)	318	HR positive 44% HER-2 positive 26% TNBC 26%	IT chemotherapy 14% systemic chemotherapy 20% Radiotherapy 64%	3.5 months
Almajed et al. (2016)	19	ER positive 53% PR positive 33% HER-2 positive 20% TNBC 40%	Not reported	2 months
Jo et al. (2013)	95	HR positive 25% HER-2 positive 15% TNBC 53%	IT chemotherapy 82% Systemic chemotherapy 48% Radiotherapy 52%	3.3 months
Lee et al. (2011)	68	HR positive 35% HER-2 positive 27% TNBC 36%	IT chemotherapy 68% Systemic chemotherapy 33% Radiotherapy 72%	4.1 months
Comte et al. (2013)	66	HR positive 68% HER-2 positive 16% TNBC 13%	IT chemotherapy 100% Systemic chemotherapy 80% Radiotherapy 23% Hormonal therapy 14%	4.5 months
Meattini et al. (2012)	33	HR positive 60% TNBC 39% HER-2 16%	IT chemotherapy 12% Systemic chemotherapy 18% Radiotherapy 53%	5.4 months
Heo et al. (2017)	38	HR 62% HER-2 positive 25% TNBC 29%	Chemotherapy 31.6% Radiotherapy 44% Suportive care 18%	4.0 months

chemotherapy are commonly described in the literature: methotrexate, cytarabine, including liposomal cytarabine, and thiotepa (Table 3) (Chahal et al., 2015; Comte et al., 2013; Fizazi et al., 1996; Glas et al., 2008; Laakmann et al., 2017; Meissner and Addeo, 2016; Niwińska et al., 2015; Ongerboer de Visser et al., 1983). The administration of intra-CSF chemotherapy may be done through repeated lumbar puncture or preferably through a subgaleal reservoir and intraventricular catheter (Le Rhun et al., 2017a). The use of a ventricular access device is safe and improves patient's comfort and compliance with CSF directed therapy (Zairi et al., 2015). Before each intra-CSF injection, the same amount of volume should be removed. A sample for CSF analysis should also be collected right before each dose of IT-chemotherapy. Intra-CSF pharmacotherapy should not be recommended in patients with symptomatic hydrocephalus or with obstructive gross disease (de Azevedo et al., 2011; Gauthier et al., 2010; Le Rhun et al., 2017a). For selected patients, in this situation (obstructive hydrocephalus) a ventriculoperitoneal cerebrospinal fluid shunting can be considered after a CSF flow study (Lin et al., 2011).

A prospective randomized trial with 95 patients compared the efficacy and safety of IT methotrexate and thiotepa in patients with previously untreated neoplastic meningitis, with no difference between the two arms (Grossman et al., 1993). Combinations of intraventricular therapy have also been tested with no clear survival or clinical benefit and increased toxicity (Groves et al., 2008; Kim et al., 2003). Another prospective phase II trial reported that administration of IT topotecan is feasible but provides no additional benefit over other IT therapies with more side effects (Groves et al., 2008). For this reasons, the intrathecal regimen of choice adopted by most institutions consists of methotrexate monotherapy or combined with radiotherapy (Le Rhun et al., 2017a; Pan et al., 2016).

Case reports and retrospective series have demonstrated efficacy and safety of IT-trastuzumab for patients with HER-2-positive disease, some with positive and optimistic results (Bonneau et al., 2018; Groves et al., 2008; Hitchins et al., 1987; Kim et al., 2003; Lu et al., 2015; Mego et al., 2011; Pan et al., 2016; Park et al., 2016; Platini et al., 2006; Pluchart et al., 2016; Zagouri et al., 2013). This strategy is still under

Table 3
Standard intra-CSF chemotherapy regimens.

IT-chemotherapy agent	Half life in CSF	Posology	CSF cytologic clearance	Observations
Methotrexate (MTX)	4.5–8 h	10–12 mg twice a week for four weeks (induction phase) 10–12 mg weekly for 4–8 weeks Maintenance regimen: 10–12 mg monthly	20–60%	Can used in conjunction with radiation therapy Continuous exposure to low systemic concentrations of MTX can lead to absorption by choroid plexus and cause severe myelosuppression
Cytarabine (liposomal preferred)	14–21 days	50 mg IT every 2 weeks for 8 weeks Maintenance regimen: 50 mg monthly	33%	Increased incidence of chemical meningitis - should be administered orally (4 mg twice daily) for a total of 5 days. Other neurologic complications: encephalopathy, seizures, myelopathy, and a pseudotumor cerebri-like syndrome.
Thiotepa	3–4 h	10 mg IT twice a weekly for 4 weeks 10 mg IT weekly for 4 weeks Maintenance regimen: 10 mg monthly	30%	

investigation in two prospective trials (NCR01325207, NCT01373710).

10.2. Radiotherapy

Radiotherapy is another alternative of treatment, especially used to treat nodular disease and symptomatic cerebral or spinal sites (Le Rhun et al., 2017a). Normalization of CSF flow can be achieved with focal radiotherapy in 30% of the patients with spinal blocks and in 50% of patients with intracranial blocks. This strategy prior to IT-chemotherapy may enhance the efficacy and reduce the toxicity of intra-CSF therapy (Pan et al., 2016; Souchon et al., 2010). Patients with poor performance status are usually treated with isolated WBRT or best supportive care (Dawood and Gonzalez-Angulo, 2013; Gani et al., 2012; Heo et al., 2017; Maur et al., 2017).

10.3. Systemic treatment

No prospective trials have been reported on systemic treatment specific for LC, but retrospective series suggest some activity of systemic chemotherapy. Various regimens have been described with clinical and imaging response including capecitabine (Tanaka et al., 2013), cyclophosphamide, 5-fluorouracil (5-FU), methotrexate (TX), vincristine, cisplatin, etoposide, vinorelbine, gemcitabine, carboplatin and paclitaxel (Le Rhun et al., 2017a; Stebel, 2012; Yust-Katz et al., 2013). Most of the centers administer systemic treatment concurrent or after intrathecal treatment. Table 2 summarizes the treatment of choice of retrospective cohorts with median overall survival results. There are also case reports showing efficacy and response of hormonal therapy for patients with LC (Almajed et al., 2016; Navarro Martín et al., 2005; Ozdogan et al., 2003). The use of lapatinib in a patient with LC HER-2-positive breast cancer has been reported previously (Lavaud et al., 2016; Onishi et al., 2011). Trastuzumab emtansine (T-DM1) has been described active after trastuzumab progression in LC. Ricciardi et al. reported a case of complete response of LC after T-DM1 concomitant with WBRT with CR lasting over 13 months and complete resolution of neurological symptoms with no need of corticosteroid use (Ricciardi et al., 2018).

Bevacizumab has also been studied and might potentiate the chemotherapeutic effects in breast cancer patients with LC. This evidence comes from retrospective and small prospective cohorts and still has no clear survival benefit (Chen et al., 2016; Wu et al., 2015).

According to previously reported data, patients who achieve cytologic response (CSF cytology without neoplastic cells after treatment) present clinical improvement and better survival (Bartsch et al., 2013).

The fact that most of the current data regarding the treatment of LC comes from retrospective series and there is limited high-quality evidence regarding optimal treatment of LC related to breast cancer makes it hard to determine if the longer survival described for patients who underwent treatment is indeed the result of the treatment itself or due to the good initial clinical characteristics of the patients able to tolerate such therapy (selection bias). Further prospective trials are urgently needed to better address the impact of the available treatment modalities in overall survival and quality of life in patients with LC related to breast cancer (Scott et al., 2016).

11. Final considerations

LC from breast cancer causes serious morbidity and carries a poor prognosis. Without treatment this condition leads do death within 4–6 weeks. It presents differences in time to presentation and prognosis in each molecular breast cancer subtype. Investigation with imaging studies (cerebrospinal MRI) and CSF analyses should start as soon as the patient presents suggestive clinical signs. The choice of treatment should consider prognostic evaluation and multidisciplinary discussion. Radiotherapy is preferred for bulky or obstructive disease. IT/IV treatment with or without systemic treatment is safe and should be

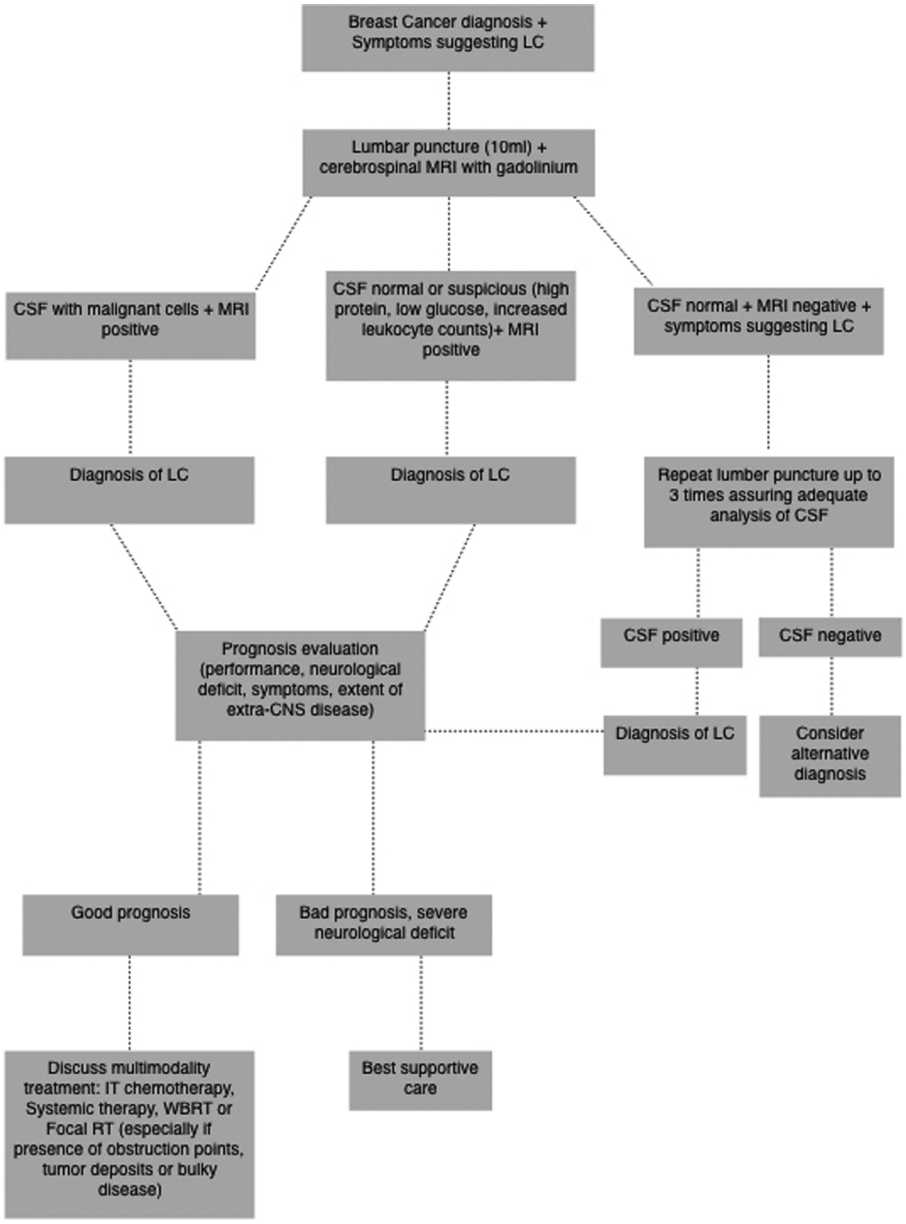

Fig. 2. Diagnosis and treatment workup of leptomeningeal carcinomatosis in patients with breast cancer.

reserved for patients with good prognosis. Fig. 2 summarizes diagnosis and treatment recommendations. Future research should focus on larger prospective studies regarding treatment options for LC and also the role of targeted therapies in this scenario.

Funding

None.

Conflicts of interest

The authors of this manuscript declare no conflict of interests.

Acknowledgements

We are thankful to ASCO's Virtual Mentor program for pairing a young oncologist in training in Brazil with a senior oncologist from an American Center to work together on this manuscript

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