Review Article

**Emerging Therapies in CNS Metastasis**

**Abstract:** Leptomeningeal carcinomatosis (LC) is a rare but devastating manifestation of cancer that has undergone metastatic spread to the cerebrospinal fluid and leptomeninges. The most common malignancies associated with LC are melanoma, breast, and lung cancers. LC severely influences morbidity and mortality, with a mean survival time of 2-6 months. Although characterized nearly 150 years ago, LC remains incurable as there are limited therapeutic options, and there is a considerable risk of treatment-related toxicities. Hence, there is an urgent need for thorough characterization of disease pathogenesis to determine novel therapeutic targets and strategies to reduce LC burden. Here, we review the current understanding of the molecular landscape of this disease and highlight recent advances in LC diagnosis and therapy.



**Graphical Abstract.** (A) Interaction between the breast cancer cell-secreted cytokine GM-CSF and the OPC-derived protein TPP1 within the leptomeningeal environment modulates Her2+LC growth and metastasis. (B) Derivation of primary Lepto cells, their implant in the PDX mouse model, isolation of cells, and subsequent culture to carry out the drug screen assay.

**Keywords:** Leptomeningeal carcinomatosis; HER2+ breast cancer; metastasis; targeted-therapy; GM-CSF; KDM4A/4C

Background

Leptomeningeal carcinomatosis (LC), also known as “leptomeningeal metastasis,” is an ominous cancer complication in which tumor cells metastasize to the meninges covering the brain and spinal cord1. Some studies suggest that tumor cells migrate to leptomeninges either through hematogenous spread or as an extension of preceding tumor lesions2-4, which become dispersed through the neuroaxis via cerebrospinal fluid (CSF). Approximately 5% of patients with malignant tumors suffer from LC5. Although any malignancy can metastasize to the leptomeninges, the most common solid tumors for leptomeningeal spreading include breast, lung, melanoma, gastrointestinal and primary central nervous system tumors6-9, with breast cancer, particularly the HER2+ subtype, the most common etiology, followed by small cell lung cancer and melanoma10,11. The prognosis of LC is usually poor, though there exists heterogeneity in final consequences contingent on the primary tumor type and therapeutic response. The interval between initial cancer diagnosis and LC manifestation is also longer for breast cancers than for other solid tumors12: the median time between initial diagnosis of breast cancer and then LC is ~3.5 years13,14, while that for lung cancer-derived LC is a year or less15.

Clinical Features and Diagnostics

LC diagnosis is challenging, as the initial indications and symptoms seen in many patients are non-specific Also, 1/3 of patients with LC are asymptomatic12. Some typical clinical manifestations reported in LC patients include cranial nerve palsies, headache, confusion, cognitive impairment, seizures, cerebral disturbances, ataxia, ischemia, infarction, behavioral changes, limb weakness, gait abnormalities, bladder and bowel dysfunction, nausea, vomiting, and somnolence16,17. Despite advancements in diagnostic technologies, LC prognosis is poor, with a median overall survival of lower than 3 months4,18.

The most common standard for LC diagnosis includes high-resolution magnetic resonance imaging (MRI) of the brain and spine followed by examination of the CSF via lumbar puncture18-20. MRI may detect findings indicating pial enhancement, nodularity along with nodular disease, neural enhancement, or white matter changes and should be performed prior to lumbar puncture, as puncture-mediated meningeal irritation could lead to false-positive MRI results. Also, occurrence of any intracranial disease or bleeding diathesis should be considered before performing lumbar puncture, as the latter may lead to cerebral herniation, meningitis, and bleeding in epidural or subdural spaces. Notably, CSF cytology is positive in only half of the cases: thus false-negative results should not be ruled out. Repeated spinal fluid analyses up to 3 times in cytology-negative but clinically suspicious patients are likely to yield 90% positive cytology21. Furthermore, high CSF white blood cell (WBC) counts, elevated CSF opening pressure, elevated CSF protein levels, and low CSF glucose levels can further confirm LC diagnosis in CSF cytology-negative patients22.

Comparative analyses of expression levels of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER-2) not only aid in evaluating breast cancer prognosis but have also been utilized as an assessment factor in systemic chemotherapy23. However, in the case of LC, determination of the status of hormone receptors and HER-2 has yielded inconsistent conclusions. Some studies report an association between hormone receptor positivity and more prolonged survival, while others do not 24-26. Other studies indicate that HER2-overexpressing breast tumors show a higher incidence of CNS metastasis and LC than other molecular subtypes27-30. Importantly, although HER2+ breast tumors show a higher incidence of LC and treatment with the anti-HER2 monoclonal antibody trastuzumab delays LC development (15.2 versus 9.9 months)31,32, HER2 expression levels do not influence overall survival of LC, and HER2+LC remains incurable17,33-35.

Technological advancements have significantly improved LC diagnostics. Recently, CSF tumor markers have been suggested as diagnostic tools for LC18,36. For example, deviant expression of biomarkers such as vascular endothelial growth factor (VEGF), CYFRA 21-1, neuron-specific enolase, or carcinoembryonic antigen in CSF often accompanies a diagnosis of LC37. Also, next-generation sequencing of CSF-derived, cell-free circulating tumor DNA has revealed tumor-specific somatic mutations and may offer an advantage for early detection38. Proteomic analysis of CSF also can differentiate patients with LC from those without either LC or breast cancer. NMR metabolomics is now employed to diagnose LC resulting from lung adenocarcinoma39.

Current Treatment Strategies and Potential Future Therapies

The blood-brain barrier constrains both conventional chemotherapy and targeted therapies used to treat LC40. Tight junctions between astrocytes that constitute the blood-brain barrier prevent large-sized toxins, including chemotherapeutic drugs, from entering the cerebrospinal fluid and accessing the CNS. In addition, a blood-CSF barrier consisting of the choroid plexus and the arachnoid membrane is widely distributed; the choroid plexus is rich in the vasculature and the primary site of CSF production. The route of CSF flow plays a determining role in targeted drug entry into the CNS41,42. The challenge faced in the efficient drug delivery to the CNS has encouraged the consideration of multiple approaches, though each technique has its limitations and associated side effects. Majorly, the current standard of care for LC management is multidisciplinary and includes radiotherapy (RT) and intrathecal chemotherapy (ITC) (Table 1).

***Radiotherapy:***Fractionated RT is beneficial for the palliative management of symptoms and may relieve pain at sites of nerve root compression. RT likely facilitates the distribution of IT chemotherapy, particularly in bulky LC where the reach of ITC is limited36. Usually, conventional palliative dose fractionation schedules are followed, with methods including focal brain/spinal radiotherapy, whole brain radiotherapy, and craniospinal irradiation (CSI). A study by Pan et al.43 was carried out on 59 patients with LC from various solid tumors who received concomitant treatment of methotrexate and dexamethasone (ITC) and IF-RT (whole brain and/or spinal canal RT)44. The clinical response rate was assessed as the primary while overall survival (OS), and safety were evaluated as the secondary endpoints. Overall, the response of 51 patients was recorded with OS ranging from 1.4–36.7 months, a median of 6.8 months. Notably, 8 patients either showed no signs of neurological improvement or had deteriorative neurological symptoms, with overall survival ranging between 0.4 -18.5 months and a median of 2.8 months. Thus, levels of clinical response significantly correlated with the trend of OS. Treatment-related adverse events included radiotherapy-associated skin and mucosa damage, bone-marrow depression, MTX-induced mucosal injuries, lumber radiculitis, and neurotoxicity. The authors observed beneficial outcomes in patients with clinical responses and those that completed the concomitant therapy. ITC, in concomitance with radiotherapy, extended the remission of neurological signals and augmented OS, thereby contributing to improving life for patients with disease-related issues44.

***IV chemotherapy:***At high doses, commonly used drugs such as methotrexate confer survival benefits over radiation45. However, IV methotrexate occasionally leads to systemic side effects, including mucositis, bone-marrow suppression, and nephrotoxicity, which necessitates regular in-patient observance to monitor clearance and thus adversely affects a patient’s quality of life. A study by Kapke et al reported the beneficial effect of high-dose intravenous methotrexate on the metastatic breast cancer with leptomeningeal disease45. The study included a 71-year-old female who had records of ulcerative colitis in the past. Later, she was diagnosed to develop invasive ductal carcinoma (ER-positive, PR-positive, and HER2-negative). Her inital treatment were helpful and included dexamethasone and palliative radiation therapy to the cervical and lumbar spine. Thereafter, she was administered intravenous HD-MTX in combination with leucovorin rescue to achieve plasma methotrexate levels of <0.1 µM. This chemotherapeutic treatment regimen reduced her palpable breast mass, and her CSF cytology turned negative for the tumor. With extensive advantages accomplished in 7 months, the patient was switched from HD-MTX to capecitabine. However, owing to the adverse effects arising from capecitabine treatment, it was discontinued and the patient was transitioned and tested for other drug combinations, including anastrozole alone for 7 months, palbociclib with anastrozole for five months, exemestane plus palbociclib, abemaciclib with fulvestrant for 7 months, fulvestrant alone for seven months. MRI demonstrated stable osseous, CNS, and leptomeningeal but progressive liver ailment. After that, she received paclitaxel chemotherapy for a considerably long duration, with no significant dose-limiting noxiousness. Overall, she has endured systemic therapy for nearly 54 months involving first-line HD-MTX and preserved an admirable life condition.

***IT chemotherapy:*** These therapies injected directly into the CSF space (intrathecal) offer advantages as they can be administered in an ambulatory setting and circumvent restraints of drug delivery beyond the blood-brain barrier to some extent. Commonly used agents include methotrexate, cytarabine, thiotepa, and sustained-release liposomal cytarabine36. The major drawback of IT chemotherapy relates to its toxicity and delivery reliant on the CSF circulation. Aseptic/chemical meningitis is a common toxicity associated with IT chemotherapy, leading to acute headaches, nausea, and vomiting. Dexamethasone/steroid treatment can efficiently control the incidence of ventriculitis. Other rare but severe toxicities associated with IT chemotherapy include infectious meningitis, seizure, myelosuppression, and leukoencephalopathy18,26,36. A case study was reported wherein a 38-year-old patient was diagnosed with stage III-A breast cancer (T3N2MO) that had eventually led to leptomeningeal metastases. She was administered capecitabine (twice daily) in conjunction with whole-brain radiotherapy. Additionally, she received intrathecal methotrexate and cytarabine (five doses, twice weekly). Cytological advances were observed, and overall improvement in the quality of the patient’s life was reported. Progression-free survival was 6 months, after that, she was administered weekly paclitaxel and capecitabine that led to some clinical improvement for another 6 months, when the tumor become aggressive and uncurable46. Efficient delivery of paclitaxel to the tumor sites is often affected due to its poor solubility and permeability. Towards this, success has been achieved with the use of paclitaxel (Ptx)-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles (Ptx-PLGA-Nps)47-49.

***Systemic chemotherapy*:** Pioneering studies report improved survival benefits with systemic chemotherapy, as it bypasses delivery restrictions associated with ITC and treats the primary tumor and nodular type LC36,50. Identification of measurable concentrations of systemically administered chemotherapeutic agents within the CNS indicates possible disruption of the integrity of blood-CSF by certain chemotherapeutic agents50,51. Gaviani et al. presented a report of a 51-year-old woman diagnosed with leptomeningeal carcinomatosis from breast carcinoma and administered intrathecal chemotherapy with liposomal cytarabine (DepoCyte). In the study, the patient tolerated the intrathecal methotrexate, presented a typical hematological profile, CSF normalization, prolonged complete MRI response, and with no neurological toxicities52. Another study by Nakashima et al53 demonstrated a case of patient who developed meningeal carcinomatosis from ALK-positive lung adenocarcinoma and had previously been treated with alectinib and brigatinib as first and second line setting. Of note, lorlatinib administration as the third-line setting proved beneficial as it significantly improved the LC-related symptoms, including disturbance of consciousness and diplopia, with no adverse events. Likewise, another case study that included a 44-year-old woman diagnosed with leptomeningeal carcinomatosis arising from HER2+ breast cancer is being presented. Administration of trastuzumab and capecitabine resolved all her neurological symptoms54. However, ten months later, multiple brain metastases appeared. Hence, further studies are essential to validate the antitumor efficacy of trastuzumab and capecitabine. Onishi et al. reported a case study of a 45-year-old woman with HER2(-)/HER1 (-) breast cancer who had experienced a radical mastectomy and was afterward treated with radiation and chemotherapy55. However, in the next few years, she developed brain metastases with meningitis and was administered lapatinib. Notably, her symptoms disappeared within a month, and even she did well without a catheter. CT and MRI examination revealed a positive response and recovery in the brain metastases and meningitis. After nine months, based on CT scan, MRI reports and stability in serum carcinoembryonic antigen levels, lapatinib treatment was stopped. Lapatinib cessation resulted in the relapse of brain metastases, and meningitis carcinomatosis reappeared; in addition, upper limb skin metastases appeared. So, the treatment was started again and that helped the patient lead a good life. Thus, lapatinib was suggested as a therapeutic approach for meningitis carcinomatosis.

***Targeted therapy:*** Currently used targeted therapies include biomarker-driven therapies, biosimilars, antibody-drug conjugates, and other small molecules. For example, bevacizumab (a VEGF inhibitor) and dabrafenib (a BRAF inhibitor) have shown effectiveness against LC derived from melanoma56. Likewise, IT trastuzumab treatment has demonstrated efficacy against LC from HER-2-positive breast cancer, and this effect has been supported by clinical trials57,58. Mastens et al presented a case study of a 31-year-old woman with a stage IV (ER+PR-HER2+) ductal tumor metastasizing to bone and liver59. The patient underwent trastuzumab systemic chemotherapy, radical mastectomy plus radiotherapy. However, as later MRI imaging identified brain metastases patient underwent surgery and was transitioned to capecitabine and lapatinib. The occurrence of new metastases continued, and hence the patient was started with trastuzumab and methotrexate dosage delivered via the Ommaya reservoir. The IT therapy treatment regimen was well-tolerated, resulting in negative CSF cytology and sustained improvement. Another study by Ferrario et al. presented a case of a 31-year-old woman with a ER-PR-HER2+ invasive ductal carcinoma who had underwent a combination of adjuvant chemotherapeutic drugs (doxorubicin, cyclophosphamide, followed by paclitaxel), radiotherapy and surgery60. Following the occurrence of liver metastases, she was treated with carboplatin, paclitaxel and trastuzumab, and then capecitabine and trastuzumab which yielded beneficial response for 14 months, when MRI imaging identified the occurrence of diffuse leptomeningeal metastases. She was initiated with the intrathecal treatment of trastuzumab and methotrexate delivered via omaya ventricular Ommaya reservoir, which was well tolerated and overall prolonged the survival.

 Erlotinib and gefitinib treatments have more positive effects (enhanced overall survival) against EGFR-mutant non-small lung cancer56. Notably, pulsatile drug or dual therapy has shown promising results for patients who progressed to LC while being treated with EGFR targets for primary malignancy56. Anaplastic lymphoma kinase (ALK) inhibitors are also effective against LC derived from NSCLC with ALK rearrangements and are being evaluated in clinical trials53,61. A very recent study presented a case of a patient who had ALK-positive lung adenocarcinoma (cT3N3M1b: stage IVA). As the first and second-line settings, she was administered second-generation ALK inhibitors, alectinib and brigatinib, respectively. After a period of 30 months of treatment with brigatinib, a diffuse and linear enhancement along the cerebellar folia was observed upon the contrast-enhanced MRI examination of the brain. As she developed meningeal carcinomatosis, lorlatinib treatment was commenced in a third-line setting. Notably, there were no adverse effects, and various indications of meningitis, including disturbance of consciousness and diplopia, showed marked improvement, and the patient had a disease-free survival. Thus, Lorlatinib, which has been designed as a third-generation ALK inhibitor and with improved penetration in the central nervous system, exerts beneficial antitumor effects on tumors resistant to first- and/or second-generation ALK inhibitors. An upregulation of VEGF levels has been reported in patients with leptomeningeal carcinomatosis, and it relates to a poor prognosis62,63. A pilot case study by Wu et al assessed the effectiveness of BEEP that included anti-VEGF therapy (bevacizumab) in combination with chemotherapy (etoposide and cisplatin) in breast cancer patients with leptomeningeal carcinomatosis64. The study included 8 patients aged 30 - 65 years who have received prior chemotherapy therapy plus surgery, radiotherapy, or intrathecal chemotherapy for leptomeningeal metastases. The authors reported that 3 patients withdrew, and the study reported the conclusion from a total of 5 patients. Notably, three patients were receptive, demonstrating the malignant cells desertion in CSF, overall betterment in the neurological condition, and no symptoms of systemic advancement64.

Tumor cells expresses immune-checkpoint ligands, including cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death-ligand 1 (PD-L1), and hence successfully evade the protective immune response. Immune checkpoint inhibitors (ICIs) foster anti-tumoral responses by targeting the interaction between these immune-suppressive ligands and cytotoxic T-cells65. Some studies have highlighted the safety and efficacy of using ICIs in LC patients, resulting in enhanced survival and improved quality of life65. However, the simultaneous steroid application contributed to the poor survival. Effective against LC are immunotherapeutic agents such as nivolumab, ipilimumab, and pembrolizumab. Intrathecal delivery of IL-2 or tumor-infiltrating lymphocytes (TILs) has been assessed in LC; however, prospective studies are needed before considering these regimens in a treatment plan1,66 .

**Table 1.** Drugs currently under consideration as LC treatment, their route of administration, and current status. .

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| **S.No.** | **Drug/s**  | **Delivery Method** | **Clinical trial** | **Reference** |
| 1. | Methotrexate, Prednisolone | Ommaya reservoir |  | Yoshida et al.67 |
| 2. | Bevacizumab combined with etoposide and cisplatin | Systemic Infusion | Phase II | Wu et al.64 |
| 3. | Methotrexate | Systemic Infusion | Phase I | Tetef et al.68 |
| 4. | Trastazumab | Intrathecal | Phase I and Phase II | Bonneau et al.69,70 |
| 5. | Lapatinib, Capacitabine | Systemic Infusion | Phase I | Morikawa et al.71,72 |
| 6. | Thiotepa, Methotrexate, Hydrocortisone | Intrathecal | Phase II | Orlando et al.73 |
| 7. | Methotrexate, dexamethasone, fractionated radiation | Intrathecal | Phase II | Pan et al.43 |
| 8.  | Methotrexate, Depocyt, Liposomal cytarabine | Intrathecal | Phase II | Mrugala et al.74 |
| 9. | Pembrolizumab | Systemic Infusion | Phase II | Brastianos et al.75 |
| 10. | ANG1005, paclitaxel, Angiopep-2 | Systemic Infusion | Phase II | Kumthekar et al.76 |
| 11. | Methotrexate and fractionated radiation | Intrathecal | Phase III | Boogerd et al.77 |
| 12. | Liposomal cytarabine | Systemic Infusion | Phase III | Le Rhun et al.78,79 |
| 13. | Erlotinib | Systemic Infusion |  | Ji et al.80 |
| 14. | Trastuzumab, liposomal cytarabine, methotrexate | Intrathecal |  | Mego M et al.81 |
| 15. | Trastuzumab, and Capecitabine | Systemic Infusion |  | Shigekawa et al.54 |
| 16. | Trastuzumab, methotrexate | Intrathecal |  | Stemmler et al.82,83 |
| 17. | Trastuzumab | Intrathecal |  | Oliviera et al.84 |
| 18. | Fractionated radiation, liposomal cytarabine | Systemic Infusion |  | Glas et al.85 |
| 19. | Lapatinib | Systemic Infusion |  | Onishi et al.55 |
| 20. | Capecitabine |  |  | Ekenel et al.86 |
| 21. | Capecitabine + fractionated radiation, methotrexate, liposomal cytarabine | Intrathecal |  | Carmona-Bayonas et al.46 |
| 22. | Liposomal cytarabine | Systemic Infusion |  | Gaviani et al.52,87 |

Additional strategies are under investigation to exploit the unique features of the choroid plexus to optimize the delivery of pharmaceutical agents to the CSF. Chimeric antigen receptor (CAR)-based T-cell immunotherapy is being actively investigated to treat solid tumors, including HER2+ cancers. Our group's efforts led to the development of a second-generation HER2-specific CAR T-cell to treat breast cancer that metastasized to the brain88. In addition, the therapeutic efficacy of local intratumoral and regional intraventricular delivery of HER2-CAR T cells was assessed. To evaluate the HER2 specificity and CARdependent effector activities, we compared two intracellular costimulatory domains (4-1BB and CD28) contained by the CAR construct. Notably, HER2-CAR T cells possessing 4-1BB intracellular costimulatory domain demonstrated lessened but antigen specific cytokine production, improved tumor killing, and lowered T-cell exhaustion while it enhanced the antigen-dependent proliferative capacity as against the CD28-possessing HER2-CARs. In addition, the therapeutic efficacy of local intratumoral and regional intraventricular delivery of HER2-CAR T cells was assessed. HER2-CART cells delivered *i.c.v.* (0.5 x 106) led to a full recession of tumors; on the other hand, *i.v.* delivery of a 10-fold greater dose mediated limited tumor regression. Overall, our study demonstrated beneficial results of intraventricular delivery of 4-1BB-containing HER2-CAR T cells for the treatment of breast cancer patients with brain metastasis88.

***Ommaya reservoir****:* Also called an Ommaya shunt, the Ommaya reservoir is a ventricular access device that facilitates recurrent delivery of chemotherapeutic drugs without performing a lumbar puncture and allows CSF sampling for the dose titration and consistent intrathecal drug administrations89,90. The Ommaya shunt provides prolonged access to CSF and has eased the administration of antineoplastic, antimicrobial, or analgesic medications into the intrathecal space. Thus, using Ommaya reservoir facilitates repeated CSF sampling and chemotherapy to be administered right into the cerebral ventricles, and is not dependent on the CSF flow from the lumbar to the cranial regions. No special care is required for the Ommaya reservoir, which can remain in place for years90. Yoshida et al reported a study with 58 patients having LC67, and they were treated with both methotrexate and prednisolone using Ommaya reservoir, in conjunction with cytosine arabinoside for 4 doses of methotrexate. They reported clinical improvement in CSF cytology in 36 of 58 patients. They suggested that this regimen is likely to be beneficial and would improvise the neurologic condition of LC patients. Around 1980s, safety issues arising because of CNS infections and neurological complications resulted in a drop of the application of Ommaya reservoirs for CNS leukemia. Currently, they are primarily employed in cases with abnormal CNS anatomy, where access to the lumbar spine is challenging and for curing pediatric brain tumors. Furthermore, advancement in neurosurgery technologies and perioperative imaging has facilitated substantially reducing the probability of Ommaya-catheter misplacement and therefore has improved the benefits of drug delivery using Ommaya reservoir. In fact, a study by Steinherz et al reported that patients on alternate cycles of intrathecal and intraventricular chemotherapeutic drug administration had preferred the application of Ommaya reservoir90,91.

Alternative Approaches:

Despite the strategies summarized above, LC treatment options remain limited, and there is an unmet need to understand molecular mechanisms underlying CNS metastasis and determine what promotes HER2+ breast cancer cell proliferation in the acellular, protein and cytokine-poor leptomeningeal environment. To address these challenges, we recently generated and characterized primary HER2+LC patient-derived (Lepto) cell lines92 (Graphical Abstract). For this, fresh HER2+ nodular HER2+ LC tissues obtained surgically for pathological confirmation of HER2+ LC were dissociated into single cells by mechanical and enzymatic methods and then expanded on collagen-coated plates in media supplemented with hCSF. Three primary Lepto lines (Lepto1, Lepto2 and Lepto3) were derived, expanded and cultured on collagen-coated plates in hCSF-supplemented media, and then production was scaled up to produce a master cryobanked batch of low-passage primary Lepto cells used for analysis28,92.

These cells preserve the spatial preference for the leptomeningeal surface, mimicking the scenario in human patients. Lepto lines demonstrated the unique spinal cord migration functionality *in vivo*, as do HER2+ LC tumor cells. Lepto1-3 cells showed more rapid proliferative and enhanced tumorsphere-forming ability than other breast cancer cells. Furthermore, relative to other breast cancer (SK-BR3 and BT-474) cells, a small number of Lepto1-3 cells were required for tumor seeding *in vivo*. Moreover, intracardiac injection of Lepto cells into NOD/SCID mice promoted brain and spinal cord metastasis. Mice co-implanted with Lepto cells (on day 0) and OPCs (on day 7 or day 14) showed significantly decreased tumor growth based on BLI relative to non-OPC injected control animals bearing Lepto tumors and prolonged survival.

Furthermore, histopathologic analyses of H&E-stained axial and sagittal sections of the spinal cord and brain of Lepto bearing NOD/SCID mice injected with no OPCs or OPCs revealed a marked reduction in levels of Lepto derived tumors. Thus, oligodendrocyte progenitor cells (OPCs), the most abundant cells in white matter, inhibit Lepto cell growth *in vitro* and *in vivo*, restricting their spread beyond leptomeninges92. Additionally, primary Lepto lines showed an upregulated expression of the lysine demethylases (KDMs) KDM4A and KDM4C and were found to release the cytokine GMCSF, which acts as an oncogenic driver of  HER2+LC92. Mechanistic analysis has revealed that the OPC-derived factor TPP1 proteolytically degrades GMCSF, antagonizing HER2+ LC growth. Intrathecal delivery of anti-GMCSF antibodies plus a pan-Aurora kinase inhibitor synergistically inhibited GMCSF, reducing HER2+ LC growth *in vivo*. Conversely, GMCSF overexpression conferred survival benefits to HER2+ LC cells.

Furthermore, to identify targetable vulnerabilities, our group has evaluated the epigenome of HER2+ LC tumors. Accordingly, tumorspheres derived from Lepto1 cells were utilized to screen a library of 181 small molecule drugs that target epigenetic factors for compounds that are known to inhibit primary tumorsphere formation. Notably, LC cells showed selective sensitivity to the Jumonji demethylase inhibitor JIB-04, which decreased primary HER2+ LC cell viability, tumorsphere formation, regrowth, and invasion *in vitro*. JIB04 treatment of Lepto lines 1-3 reduced cell viability with more rapid kinetics than that seen in HER2+ or HER2- lines (specifically within 24 hours) and showed dose and time-dependent effects. Furthermore, treating patient-derived xenograft mouse models with a KDM4A/4C inhibitor hampered tumor growth and prolonged survival. Kaplan–Meyer analyses demonstrated that JIB04 treatment significantly prolonged survival relative to controls. Thus, JIB04 is effective in controlling HER2+ LC tumor growth of Lepto lines in NOD/SCID mouse models. In summary, *in vitro* and *in vivo* analysis illustrates the oncogenic function of KDM4A/4C and GM-CSF signaling in LC and suggests novel treatment strategies28. Studies from our laboratory also assessed the resistance of Lepto cells to various chemotherapeutic drugs. It was interesting to observe that when compared to the breast cancer cells (BT-474 or SK-BR3)s, Lepto cells displayed enhanced resistance to methotrexate (one of the most frequently employed intrathecal chemotherapy drugs). In addition, Lepto cells also showed elevated chemoresistance to Lapatinib, Trastuzumab, and Cytarabine when compared to other breast cancer cells (BT-474 or SK-BR3). Hence, HER2+CD326+CD49f- Lepto cells not only serve as the prototype of nodular HER2+ LC tissues but also established a prevailing CSC (CD44+CD24-) phenotype and characteristics, including drug resistance, aggressiveness, and strong ability to generate tumorspheres.

Pioneering work from the laboratory of Joan Massague has shown that metastasis of breast cancer to the brain requires factors that extravasate through non-fenestrated capillaries and specific enhancers that cross the blood-brain barrier to mediate brain colonization. This group conducted a gene expression and functional analysis using clinical samples and cells that had infiltrated the brain of patients with advanced disease. They found that cyclooxygenase 2, the epidermal growth factor receptor (EGFR) ligand HBEGF, and the alpha2,6-sialyltransferase ST6GALNAC5 function to mediate cancer cell passage through the blood-brain barrier93. Prostaglandin produced during inflammation increases blood-brain barrier penetrability, while HBEGF promotes cancer cell motility and invasiveness. The essential role of these genes in brain metastasis suggests they could be exploited and considered as therapeutic targets, although those approaches require further analysis and validation. Yet another study reported that pharmacological inhibition of cathepsin S decreased brain metastasis *in vivo.* Cathepsin S loss in tumor cells and macrophages compromised metastatic seeding and outgrowth, encouraging consideration of cathepsin S as a potential therapeutic target against brain metastasis94. Using HuMu arrays, authors have profiled stroma- and tumour-derived genes. Most importantly, cathepsin S displayed well-controlled stage- and cell-type-specific expression levels in brain metastases. Authors reported increased occurrence of tumour-derived cathepsin S in early brain metastases, while it lessened during late-stage metastases. Besides, stromal cathepsin S displayed an inverse relationship, i.e. elevated levels during late-stage brain metastases compared to the early-stages.

Conclusion:

LC is an unforeseen lethal outcome of systemic cancer spread. Her2+ breast cancer is the most common origin of LC and occurs when breast cancer cells metastasize to the brain and spinal cord lining. The poor prognosis of this ominous complication has been ascribed to the lack of our understanding of the mechanisms underlying HER2+ LC development and metastasis and the limited efficacy of treatments in the central nervous system. Current treatment strategies are mainly palliative and do not offer significant benefits in enhancing patient survival. Therefore, there is an urgent need to identify alternative strategies and druggable targets. In the present review, we have summarized currently available treatments and potential future therapies for LC derived from breast cancer. The neural-specific cross-talk between HER2+ LC tumors and OPCs found predominantly in white matter is particularly interesting. Recent *in vitro* and *in vivo* studies support the idea that administration or treatment with the protease TPP1, the selective pan-Aurora kinase inhibitor CCT13769, anti-GMCSF antibodies, or the KDM4A/4C lysine demethylase inhibitor JIB-04 decreases Her2+ LC tumor growth and prolongs animal survival28,92, and these analyses could lead to more effective therapies to treat Her2+ LC. However, more extensive prospective studies are essential to confirm effects of new targeted therapies. Also, sustained efforts to understand disease pathology is vital for developing efficacious treatment strategies.

**Future prospects:**

Management of HER2+ LC entails a multifaceted approach involving radiotherapy and intrathecal therapy; however, response rates to current treatment strategies are less than 20 percent. Advancement in the detection, analysis, quantification, and targeted treatment has the potential and will steer individualized therapies and management of LC. The advent of improvised diagnostic tools and technologies, including CSF CTC and ctDNA, will undoubtedly revolutionize the LC diagnosis and serve as a critical biomarker enabling monitoring the disease progression and behavior in response to drug treatment. Furthermore, these will enhance our insight into tumor genomics and hence is likely to open avenues for dedicated clinical protocols and personalized, targeted therapies and set the platform for a new clinical trial. Additionally, a detailed understanding of molecular mechanisms that govern HER2+ LC development, immune microenvironment characterization, and crosstalk between epigenetic modifiers are essential to discover novel therapeutic strategies for this devastating complication and will profoundly impact breast cancer therapy.

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