Advances in the Systemic Treatment of Leptomeningeal Cancer

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Abstract: Leptomeningeal cancer (LMC), which refers to involvement of the cerebrospinal fluid by cancer cells, is a poor prognostic sign that complicates various solid malignancies. Treatment of LMC evolved around brain radiation, intrathecal therapy, and systemic chemotherapy, but response rates are unsatisfactory, and patients usually die from cancer progression. In this article, we review the history of the major therapeutic approaches used to treat LMC, and we expand on the promising new venues for applying biologic targeted agents to the treatment options utilized in LMC.

Introduction

Spread of malignant cells into the cerebrospinal fluid (CSF) is associated with later stages of cancer[1] and is unusual at diagnosis. The growth or presence of CSF malignancy has been called both *leptomeningeal cancer* (LMC) and *neoplastic meningitis*. The incidence of LMC in small cell lung cancer is 0.5% at diagnosis and 25% after 3 years of survival.[2,3] In patients with solid tumors, the median survival for untreated patients may be 4–6 weeks; with treatment, survival may be extended to 4–6 months.[4] Although there are many case reports of isolated responses to various therapies, very thorough reviews of the controlled trials in LMC have failed to define an optimum therapy.[4,5] The use of intrathecal (IT) chemotherapy, usually with central nervous system (CNS) radiation to bulky areas of disease, has been a common approach, but it has not made a large impact on survival and is associated with substantial neurologic toxicity.[4,5]

Among patients who have LMC from solid tumors, the most common primary cancers are breast, lung, melanoma, gastrointestinal tract, and adenocarcinoma of unknown primary origin. The probability of developing LMC is perhaps greatest for patients with melanoma (22–46% risk), small cell lung cancer (10–25% risk), and breast cancer (5% risk).[5] Most controlled trials of IT therapy have used methotrexate, arabinofuranosyl cytidine (Ara-C), liposomal Ara-C, or thiotepa. IT methotrexate and IT thiotepa were shown to have similar outcomes.[6] IT methotrexate has been combined with cytarabine, but this regimen had no benefit over methotrexate alone.[7] A study comparing IT methotrexate with IT liposomal cytarabine showed an improvement in meningitis-free survival for the liposomal Ara-C arm.[8]

The efforts to assess the efficacy of IT therapy are complicated by 1) the inclusion of multiple tumor types in most trials so that

a reasonable number of patients can be accrued, 2) the inclusion of lymphomatous meningitis in some studies along with solid tumors (lymphomatous disease may be more sensitive to chemotherapy), 3) the inclusion of patients with both brain and spinal involvement, who are likely to have different prognoses, and 4) the route of administration (lumbar puncture vs reservoir). By the time LMC develops, most patients will have tumors that were extensively exposed to other chemotherapy agents, and these tumors may be very resistant to further therapy.[9]

There is an extensive literature on IT methotrexate and IT cytosine arabinoside.[7,10-13] Two issues associated with IT therapy are the need to achieve adequate distribution of the drug and the need to reduce neurotoxicity. Furthermore, neurotoxicity may depend upon which agent is used, as well as the dose, schedule, and route of administration. Multiple lumbar punctures are associated more often with leaks in the lumbar area, with resultant nerve or cord damage.

The use of IT therapy may improve with newer agents. The paucity of systemic therapies that cross the blood-brain barrier previously led to a focus on IT therapy. However, in 1998, Siegal presented a thoughtful review focusing on the need to reconsider systemic therapy rather than more IT therapy.[14] A review by Bokstein and colleagues[15] found that systemic therapy and IT therapy of LMC had equivalent effects on overall survival. However, since that time, there have been newer agents developed that may make systemic therapy for LMC the treatment of choice. The goal of this review is to focus on newer options for systemic therapy.

Results and Toxicity of IT Therapy

LMC in patients with solid tumors is generally associated with a poor prognosis. One of the larger series, with 90 patients,[13] found a median survival of 5.8 months, with a range of 1–29 months. Prognosis may also vary by tumor type, although the survival by tumor type is not very well defined in the literature.[5] A recent article by Beauchesne[16] thoroughly reviewed the literature on IT therapy. This review quoted several randomized trials. In a trial of IT therapy with methotrexate versus thiotepa, the median survival was 15.9 weeks with methotrexate and 14.1 weeks with thiotepa (this trial included some lymphoma patients, which would improve prognosis).[16] In a trial comparing IT methotrexate versus methotrexate and cytarabine for LMC, the median survival with methotrexate alone was 12.1 weeks versus 7 weeks for the combination.[7] In a trial of liposomal Ara-C versus methotrexate, the median survival was approximately 105 days with liposomal Ara-C and 78 days with methotrexate.[8] In a comparison of IT therapy with systemic chemotherapy, the incidence of delayed neurologic complications was 20% with IT therapy versus 0% with systemic therapy.[15] These side effects included leukoencephalopathy, dementia, paresis, and seizures.

Newer agents such as rituximab (Rituxan, Genentech/Biogen Idec) and trastuzumab (Herceptin, Genentech) may be administered intrathecally, but such therapy would likely need to be given in conjunction with systemic therapy; if these agents are administered alone via the IT route, systemic disease would not be affected.[17]

Results of Systemic Therapy for LM Carcinoma

High-dose methotrexate has been reported to have some efficacy in treating LMC.[18,19] Tetef and coworkers reported on a nonrandomized trial of 13 patients with LMC from breast cancer, lung cancer, or osteosarcoma.[19] This dose-escalation study aimed to determine if a level of 1 uM could be achieved in the CNS. No patient had clearing of the tumor cells from the CSF, but 5 of the 9 breast cancer patients had already been exposed to methotrexate and were resistant to that agent. The final recommended regimen was a loading dose of 700 mg/m^2 and a 23-hour infusion of 2,800 mg/m^2, with leucovorin starting 6 hours from the end of the methotrexate infusion. Glant and associates[18] retrospectively reviewed patients who had received methotrexate 8 g/m^2 over 4 hours for LMC. Thirteen of the 16 patients treated with high-dose methotrexate had a complete cytologic response at 1 month. Median survival for the patients treated with high-dose methotrexate was 13.8 months, with 6 patients alive at 23–52 months. Among a comparison group treated at their institution with IT methotrexate, the median survival was 2.3 months. This comparison suggests that high-dose methotrexate could be more effective, but the patients had a variety of tumors, with more melanoma in the IT group and more chemosensitive-tumors in the high-dose methotrexate group. Another possible factor impacting survival is that the high-dose systemic methotrexate regimen would also treat systemic disease, whereas IT treatment would not.

A more recent trial of high-dose methotrexate for patients primarily with parenchymal and leptomeningeal breast cancer, or both, seemed to show a higher response rate for parenchymal lesions (33%) versus leptomeningeal disease (29%). The definition of response in leptomeningeal disease was less clearly defined.[20] There is a mention of at least 1 case of leptomeningeal breast cancer responding to pemetrexed (Alimta, Eli Lilly) intravenous chemotherapy.[17]

Capecitabine (Xeloda, Genentech) has been reported to have some efficacy in treating parenchymal brain metastases.[17] There has been a report of a patient with both

parenchymal and LMC breast cancer who experienced prolonged survival after treatment with CNS radiation and 3.7 years of capecitabine.[21] Ekenel and colleagues[22] reported clinical improvement with capecitabine therapy in patients with parenchymal brain metastases from breast cancer, including 3 patients with LMC. Two other studies, although not expressly addressing the question of LMC, have demonstrated the efficacy of treating brain metastases from breast cancer with lapatinib (Tykerb, GlaxoSmith-Kline) and capecitabine in HER-2 positive patients.[23,24]

Capecitabine has also been reported to have some efficacy in leptomeningeal and parenchymal brain metastases from lung cancer in at least 1 patient.[25] These studies suggest that some patients with LMC may respond to systemic therapy with capecitabine. However, the fact that capecitabine crosses the blood-brain barrier can also be reflected in its associated toxicity. Videnovic and associates[26] reported 5 cases of capecitabine-induced multifocal leukoencephalopathy and cited 3 other cases in the literature. Four of the 5 patients had liver metastases, and 2 had prior brain radiation or radiosurgery, but it is unclear if these factors are related.

Hormonal therapy for leptomeningeal breast cancer has been described in case reports. Boogerd and coworkers[27] reported on 2 breast cancer patients treated for LMC with primarily spinal column involvement. Both patients responded to tamoxifen and, possibly, other hormonal agents. Response was defined by neurologic improvement, but at least 1 of the patients had clearance of the malignant cells from the CSF. The prolonged control of the disease in these patients might reflect their estrogen-receptor status or the fact that patients with spinal involvement alone have a more favorable prognosis.[28] Ozdogan and colleagues described a breast cancer patient with primary brain involvement who had progressive neurologic signs despite prior brain radiation and IT methotrexate.[29] The patient experienced a progression-free survival of 16 months when treated with letrozole (Femara, Novartis).[29] Peroukides and associates[30] described a patient with estrogen-receptor breast cancer who had progressed on tamoxifen and developed LMC. She responded to letrozole therapy with continuation of IT methotrexate. Her survival was 36 months from the start of letrozole therapy. In prostate cancer, there has been a single case report of a patient with leptomeningeal prostate cancer who survived for more than 5 years with leuprolide therapy.[31] There were several letters to the editor regarding hormonal therapy of leptomeningeal breast cancer, with Chamberlain[32] suggesting that IT therapy is standard, but that one-third of treatment cycles of IT methotrexate are associated with aseptic meningitis, and Boogerd[27] indicating that, in his experience, half of longer term survivors who have had IT methotrexate may develop encephalopathy.

The small-molecule tyrosine kinase inhibitors erlotinib (Tarceva, Genentech/Astellas) and gefitinib (Iressa, AstraZeneca) have also been reported to have efficacy in leptomeningeal lung cancer. Stemmler and colleagues[33] described a patient with symptomatic brain metastases from lung cancer, whose CNS tumor improved with single-agent gefitinib therapy. This case report references 7 other studies of gefitinib in the treatment of brain metastases, including a study by Chiu and coworkers, which included 57 evaluable patients with lung cancer metastases.[34] These patients were not selected by epidermal growth-factor receptor (EGFR) mutation status. However, there are reports of patients with leptomeningeal lung cancer with documented EGFR mutations who responded to erlotinib and gefitinib.

Clarke and associates[35] described a patient who developed LMC from a non–small cell lung carcinoma that had previously progressed on standard daily dosing of erlotinib. This patient had a mutation, L858R, which confers sensitivity to EGFR tyrosine kinase inhibitors. She also had the T790M mutation, which is associated with resistance to the EGFR tyrosine kinase inhibitors. She was treated with a regimen of erlotinib 1,000 mg/weekly, then 1,200 mg/weekly. After receiving a ventriculoperitoneal shunt for hydrocephalus, she received erlotinib at a dose of up to 1,500 mg/weekly. Her response to this therapy was demonstrated by magnetic resonance imaging. The intermittent, high-dose administration of erlotinib achieved a higher CSF concentration than standard dosing and controlled this patient's LMC. Dhruva and Socinki described a patient with LMC from lung cancer who responded to an erlotinib regimen of 600 mg every 4 days.[36] The efficacy of standard-dose erlotinib would likely be less than the reported higher-dose regimens, due to insufficient CSF levels at standard doses.[35] Choong and associates[37] reported a response to standard-dose gefitinib, at 250 mg/daily, in a patient with LMC. Jackman and coworkers[38] described a patient who had developed LMC while on standard-dose gefitinib (250 mg/daily), who responded to increasing doses from 500 mg/daily to 750 mg/daily and up to 1,000 mg/daily. The patient had a cell line started from a pleural effusion, and Jackman and coworkers were able to determine the concentration necessary to inhibit the tumor, and they then measured the levels in the CSF as the dose was increased.

Three chemotherapeutic agents—temozolomide, ifosfamide, and topotecan (Hycamtin, GlaxoSmith-Kline)—have been demonstrated to cross the blood-brain barrier. There is not an extensive literature on their efficacy in LMC, but there are case reports suggesting that these agents may have some efficacy. Pietanza and associates had reported some response in 3 patients with small cell lung cancer who had previously undergone

brain irradiation.[39] Zauderer and colleagues reported at least brief responses in 2 patients with small cell lung cancer and LMC.[40] A trial of dose-dense temozolomide for the treatment of brain metastases in patients with melanoma, breast cancer, or lung cancer showed some response, but the duration of responses was transient even with this more intense regimen.[41] Segura and coworkers reported on 19 patients with LMC treated with temozolomide 100 mg/m^2 daily for 7 days out of 14. Two patients had a partial response.[42] Temozolomide alone does not appear promising for LMC. Temozolomide in combination with cisplatin has been reported to have efficacy in treating single cases of leptomeningeal melanoma[43] and leptomeningeal ethmoid sinus intestinal type–adenocarcinoma.[44] The more prolonged survival in these patients (the patient with melanoma lived for >1 year, and the patient with ethmoid sinus carcinoma lived for 10 months) suggests that combination therapy with temozolomide might provide better tumor control. A patient treated for leptomeningeal colorectal cancer with temozolomide, irinotecan, and bevacizumab (Avastin, Genentech) survived for about 6 months.[45]

Topotecan as a single agent has been reported to show efficacy in patients with brain metastases.[46,47] Topotecan was reported to have a CSF/plasma ratio of 30%, but this was after a 10 mg/m^2 dose, which is larger than the standard dose of 1.5 mg/m^2 daily for 5 days.[47] Its activity as a single agent in LMC was difficult to determine from the literature. There was a report of 5 patients with LMC treated with a combination of topotecan and ifosfamide.[48] Two of the 5 patients had some response, but they had also received IT methotrexate. The severe myelosuppression, with 1 death, associated with topotecan and ifosfamide in this trial makes it an unacceptable regimen at the dose and schedule tested. Topotecan was also administered intrathecally in a phase II trial by Groves and coworkers.[49] This treatment resulted in chemical meningitis in 32% of the cases. Overall survival was approximately 15 weeks.[49] Irinotecan alone has been associated with a survival of 13 months in a patient with leptomeningeal gastric cancer. Survival in this patient may have been limited more by stroke than the LMC.[50]

Other agents that may affect brain metastases and can cross the blood-brain barrier include lapatinib and bevacizumab. Although there are several trials of lapatinib and capecitabine (or lapatinib alone as induction therapy) in patients with brain metastases, the studies were not directed at treating leptomeningeal breast cancer.[23,24,51] There are studies examining the safety of using bevacizumab in patients with brain metastases.[52,53] Although the risk of hemorrhage may be acceptable, there is a paucity of data on its use in LMC. In a trial of bevacizumab with other agents for patients with lung cancer, the 2 patients who had LMC had progressive disease.[54]

Discussion

The treatment of LMC from solid tumors with IT therapy has generally not made a major impact on survival and often has negatively impacted quality of life. Arachnoiditis, complications of reservoir placement, paralysis, and encephalopathy may all occur with IT therapy, and rarely has any IT therapy alone led to a median survival of a year. Furthermore, with longer survival, IT therapy may lead to greater cumulative neurotoxicity.

Systemic therapy has previously been limited by the failure of many chemotherapeutic agents to cross the blood brain-barrier. In recent years, agents that cross into the CNS have been developed, including tyrosine kinase inhibitors (erlotinib, gefitinib), capecitabine, temozolomide, topotecan, irinotecan, bevacizumab, lapatinib, and pemetrexed (Alimta, Eli Lilly). Furthermore, older agents that cross the blood-brain barrier, such as high-dose methotrexate, carboplatin, and ifosfamide, remain available. It is possible, though not at all proven, that combination therapy may lead to more prolonged survival, but this possibility may just reflect the selection bias of case reports. Studies are also more difficult to evaluate when the numbers of patients are small and a variety of tumors is included.

It may only be possible to have clinical trials in LMC if treatment protocols are cancer-specific or there is stratification by cancer type, if treatment protocols can accrue nationally via the cooperative groups, and if we can accept that it may take longer to accrue enough patients with one tumor type to answer meaningful questions. Additionally, in this era of targeted therapy, testing of tumors for specific mutations might provide better insight into which patient subpopulation is expected to respond better to treatment.

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