Leptomeningeal Metastasis: Challenges in Diagnosis and Treatment

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Abstract

As therapeutic options and supportive care for the treatment of neoplastic disease have improved, there has been an associated increase in the incidence of leptomeningeal disease. In this review, the clinical presentation, natural history, diagnostic evaluation, and treatment options for this often devastating sequela of solid tumors, lymphoma, and leukemia will be summarized. The therapeutic efficacy of ionizing radiation, systemic agents, and intrathecal drugs will be examined from the existing literature. Additionally the pathophysiology, which in part defines the therapeutic limitations in approaching this patient population, will be discussed in order to assist in individualized clinical decision making.

Keywords

leptomeningeal metastasis; carcinomatous meningitis; treatment; diagnosis

INTRODUCTION

Leptomeningeal metastases (LM) are emerging as a more frequent clinical situation in oncology. The rising incidence is likely the result of prolonged survival due to improved supportive care and chemotherapy regimens, and the failure of currently available systemic agents to penetrate the blood-brain, the blood-CSF and the brain-CSF barriers [1, 2]. Improved diagnostic imaging techniques are also a contributing factor in this rise in incidence of leptomeningeal disease [2].

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LM usually presents in patients with widely-metastatic and progressive cancer (70%), but it can occasionally be the first manifestation of cancer (5–10%), sometimes even in the absence of detectable systemic disease [3, 4]. LM is more common in patients with lymphoma, leukemia, breast cancer, lung cancer, and melanoma [4–6]. Other less common malignancies associated with a high risk of developing LM are medulloblastomal/PNET and posterior fossa high-grade gliomas, although this latter observation is somewhat contentious [1].

The prognosis is generally poor once symptomatic LM develops, with some heterogeneity in outcomes depending on the primary tumor type and response to treatment. There have been few advances in the treatment of LM in the past several decades; further laboratory and clinical research is needed to improve the quality of life and survival of these patients.

CLINICAL PRESENTATION

The classic presentation of LM is the development of multifocal neurological deficits in the setting of advanced cancer. Symptoms and clinical signs are frequently the result of the relatively acute onset of debilitating neurologic deficits affecting various motor/sensory functions and possibly cognitive function. Reported outcomes of LM from solid tumors have indicated high rates of progression to death within 4 to 6 weeks without therapy [7].

Symptoms and signs of LM are referable to the specific neural structures involved with the tumor and can be organized into three groups [6]:

1. Cerebral involvement is most commonly manifested by development of headaches. Nausea, encephalopathy, seizures and communicating hydrocephalus can also be observed.

2. Cranial nerve involvement may lead to unilateral or bilateral deficits of cranial nerve roots, with frequently observed complications including diplopia, hearing loss, facial numbness and decreased visual acuity.

3. Spinal involvement with compromise of the spinal cord and nerve roots may result in extremity weakness, paresthesias and/or pain.

Pathophysiology

The leptomeninges (as distinct from the pachymeninges, which refers to the dura) consist of the arachnoid and pia mater and form the boundaries of the subarachnoid space, separated from each other by fine trabeculae and the cerebrospinal fluid (CSF).

Achieving systemic control of the primary cancer is crucial to the prevention of leptomeningeal spread of cancer. There are different proposed mechanisms of tumor spread into the leptomeninges. Tumor cells may reach the leptomeninges by hematogenous spread to the vessels of the arachnoid or choroid plexus, direct extension from parenchymal, dural and bone-based metastases and/or via perineural route along cranial nerves to finally enter the subarachnoid space [I, 8]. The CSF may also be a sanctuary site, where tumor cells are relatively protected from the immune surveillance that is present outside of the central nervous system (CNS). For example, in various hematologic malignancies (e.g., childhood acute lymphocytic leukemia), high rates of occult CSF involvement have been reported within the sanctuary site of the CNS. Recognition of the CNS as a site of occult disease involvement in high-risk hematologic malignancies has resulted in the institution of CNS prophylaxis in some patients as part of systemic therapy, achieved by incorporation of systemic chemotherapy with adequate CNS penetration and routine administration of intrathecal chemotherapy. In many of the pediatric acute lymphocytic leukemia (ALL) protocols which may be used for treatment of young adults, prophylactic cranial

radiotherapy is recommended for high-risk patients. These modifications to the therapeutic approaches in high-risk hematologic diseases such as ALL have resulted in the observed decrease in the incidence of CNS relapse from as high as 66 to approximately 5% [9].

Diagnostic Tools and Considerations

Identifying CSF involvement early in the course of the disease at a time when tumor burden is minimal likely represents the time frame during which therapeutic maneuvers may be most efficacious [2].

CSF

Definite diagnosis of LM can be established by direct examination of the CSF or by characteristic changes evident on imaging modalities such as magnetic resonance imaging (MRI). There are, however, presentations in which a high degree of clinical suspicion may warrant further evaluation with other techniques described in detail below.

Examination of the CSF should include measurement of the opening pressure, cell count, protein, and glucose in addition to sampling for direct cytologic examination. The cytology specimen should ideally contain 5 to 10ml of CSF and should be processed promptly. Although cytologic evaluation of the CSF is frequently performed in cases of suspected LM, the morphologic examination of the CSF fails to demonstrate malignant cells in up to 45% of patients [6, 10]. If the initial cytology is negative for malignant cells, repeat samples improve the yield to approximately 90% after the third lumbar puncture [6]. A negative cytology after three lumbar punctures does not rule out the diagnosis of LM in the context of other positive testing, such as an MRI with characteristic findings and other CSF testing described below. Ultimately, clinical judgment will be essential to guide and establish a diagnosis.

An elevated opening pressure, elevated protein level and/or decreased glucose level may also be indicators of CSF involvement by malignant cells.

Other tests that have been studied in the CSF of patients with suspected LM with varying sensitivity and specificity include tumor markers such as carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), β -human chorionic gonadotrophin (β -HCG), and monoclonal immunoglobulins elaborated from multiple myeloma. Specific tumor markers identified in the CSF, especially if higher than in serum, in the appropriate clinical context can assist in the diagnosis of LM [11].

Other nonspecific markers include β -glucoronidase, β -microglobulin and isoenzyme V of lactate dehydogenase (LDH) that are frequently elevated in patients with LM. This is most commonly seen with a diagnosis of leukemia and lymphoma, but can also be seen in patients with a variety of other acute or chronic inflammatory and/or infectious processes involving the leptomeninges [2].

In patients with leukemia or lymphoma with non-diagnostic cytology, additional laboratory testing of the CSF samples by immunohistochemistry, flow cytometry and/or polymerase chain reaction (e.g. analysis of immunoglobulin heavy chain gene rearrangements) may further increase the diagnostic yield.

Flow cytometry is considered more sensitive than cytology for the detection of hematologic malignant cells in the CSF [12]. In a prospective study by Hegde *et al.* [12], CSF was assessed by flow cytometry and cytology in 51 newly diagnosed and 9 treated/relapsed aggressive B-cell lymphomas at risk for CNS involvement. The high-risk lymphomas included in the analysis were AIDS-related lymphomas, Burkitt lymphomas, and diffuse

large B cell lymphomas with extranodal sites of disease. Among 51 newly diagnosed patients, 11 (22%) had occult CSF involvement. All 11 were detected by flow cytometry, but only 1 by cytology (P =.002). Among the 9 treated patients, CSF involvement was detected by flow cytometry alone in 2, and also confirmed by cytology in 1 case. Chemistry and cell counts (performed on CSF) were similar in patients with and without CSF lymphoma. This suggests that patients with high-risk lymphoma should also undergo CSF evaluation by flow cytometry..

It is still unclear, however, whether positive flow cytometry in the setting of negative cytology has clinical implications. A retrospective study from the Netherlands was performed comparing the diagnostic value of flow cytometry and cytology in the detection of LM in hematologic malignancies [13]. This large retrospective review included 1,054 samples in 219 hematologic malignancy patients collected from 2001–2004, with 68% of samples collected from patients with B-cell lymphoproliferative diseases. These data showed that the sensitivity of flow cytometry in the detection of LM is two to three times greater than that of cytology. Almost 50% of patients had CSF involvement diagnosed by flow cytometry in the setting of negative cytology. There were four patients who had positive cytology in the setting of negative flow cytometry and these were associated with pleocytosis and clinical symptoms suggestive of higher disease burden. These patients had a worse prognosis, and thus, cytology still has a role in the diagnosis of LM and may have prognostic significance.

Although flow cytometry is a feasible and attractive option for hematologic malignancies, this technique is not applicable to the large number of patients at risk for LM in the setting of solid tumors. Identification of specific biomarkers of disease measurable in the CNS, specifically in the setting of solid tumors, may allow for earlier diagnosis of occult CNS involvement and treatment. Preclinical evidence suggests the possible relevance of SDF-l and VEGF in the homing and neoangiogenesis of metastases. Groves *et al.* [14] measured these molecules in the CSF of melanoma, breast, and lung cancer patients being evaluated for LM. CSF samples from 89 patients (41 with breast cancer, 35 with lung cancer and 13 with melanoma) were analyzed. Twenty-five percent (22/89) of all samples were positive for malignant cells; 20% from breast cancer, 29% from lung cancer and 31 % from melanoma. CSF VEGF levels were available from 83 patients, and were elevated (>20 pg/ml) in *15/22* (68%) of patients with positive CSF cytology and normal (<20 pg/ml) in 59/61 (97%) of patients with negative CSF cytology. The two patients with negative CSF cytology who also had elevated CSF VEGF levels had MRI evidence of LM. CSF SDF-l levels were available from 81 patients, and were elevated (>950 pg/ml) in 11/18 (61%) of patients with positive CSF cytology and normal (<950 pg/ml) in 57/63 (90%) of patients with negative CSF cytology. In this study, elevated CSF levels of VEGF were sensitive and highly specific for the diagnosis of LM from breast cancer, lung cancer and melanoma. CSF SDF-l levels provided less additive diagnostic information to that already provided by CSF VEGF levels [14].

Relationship of CSF to the Blood-Brain-Barrier (BBB)

The mechanisms by which drugs achieve access to the CNS are complex. Although frequently these mechanisms are described inclusively as penetration of the blood-brain barrier, these actually represent distinct processes involving a true blood-brain barrier (BBB) and a separate blood-CSF barrier. Concentration of most drugs is greater in the brain than the CSF, which in effect creates a physiological gradient between the two compartments. The flow of CSF through the ventricular system and over the surface of the brain provides a "depot" that reduces the steady-state concentration of a molecule penetrating into the brain and CSF. This "depot effect" is greater the slower a drug moves, which makes it particularly important for large lipid-soluble drugs [15].

It should also be noted that fluctuations in the BBB occur with administration of therapy for LM. Ott *et al.* [16] described a small series of patients evaluated by positron tomography (PET) imaging which included 2 patients undergoing chemotherapy and radiation for primary CNS lymphoma compared with 3 control patients (with diagnoses including astrocytoma and dysgerminoma). Serial 68-GaEDTA PET scans were performed weekly until completion of chemoradiation, with observed reconstitution of the BBB to normal values within 5 weeks from the beginning of treatment. Although there is a paucity of data directly measuring the degree of BBB disruption with LM and reconstitution with subsequent therapy, there is clear indirect clinical experience to this effect. For example, responses have been observed with systemic administration of single-agent rituximab (a monoclonal antibody against CD20) in the treatment of relapsed lymphoma with CNS involvement [17]. Without some degree of BBB disruption, penetration and activity of this large molecule would not be feasible as steady state concentrations of rituximab measured in the CSF are typically 0.1 % of those observed in the serum [18].

Imaging

Gadolinium-enhanced multiplanar MRI is the preferred imaging modality in suspected cases of LM, as MRI is more sensitive for imaging the neuraxis than computed tomography (CT) imaging [19]. However, when a contraindication to MRI exists, CT with myelography is an alternative with similar quality for evaluation of the spine in patients with LM [4]. MRI of the entire craniospinal axis is an important initial step in the evaluation of a patient with suspected LM. If cranial nerve involvement is suspected, thin cuts through the brain should also be performed. Cranial MRI readings consistent with LM include ependymal, dural, and leptomeningeal enhancement and communicating hydrocephalus. Spinal MRI may reveal linear or nodular enhancement of the cord and thickening of lumbosacral roots. Neuroimaging readings in cases of LM are more likely to be abnormal in solid tumor than hematologic malignancies (i.e., 90% vs. 55%, respectively) [5].

Ideally, the patency of the CSF pathways should be evaluated via a radionuclide cisternogram (usually ^{111}Indium-DTPA), specifically if intra- CSF therapy is being considered. Practically, however, this is not common practice at many centers if there is no obvious blockage of CSF flow by MRI. Disrupted CSF flow is reported in 31–61 % of patient with LM [20, 21]. The presence of CSF obstruction not otherwise corrected has prognostic implications and interferes with uniform distribution of intra-CSF chemotherapy.

The diagnosis of LM can be a challenging, and requires careful investigation through a combination of clinical history and examination, imaging studies, and laboratory data. As CSF cytology will be positive in some cases of normal imaging and vice-versa, both tests are useful for evaluation of clinically suspected LM [22]. MRI provides detailed anatomic information that may be of particular benefit in localizing areas of disease for directed radiotherapy.

Treatment

Treatment decisions regarding LM are usually made in the context of progressive systemic tumor, CNS metastases, and limited life expectancy. Thus, if treatment of LM is initiated, it is necessarily palliative with the objective of preserving neurological performance and improving quality of life. Determination of suitable candidates for treatment of LM is complicated by the lack of a uniform approach and treatment of LM.

For patients with high performance status, absent or minimal fixed neurological deficits, and limited tumor burden, treatment should target the entire neuraxis because of the multifocal involvement of the CNS. Current therapies include involved field radiotherapy to

symptomatic or bulky sites plus chemotherapy (intra-CSF, systemic, or both) in selected cases, or craniospinal radiotherapy, or intra-CSF chemotherapy. Palliative care/hospice is recommended for the patients with poor performance status and multiple fixed neurological deficits, unless patients have highly responsive malignancies such as small cell lung cancer or lymphoma.

Corticosteroids are used to treat symptoms associated with LM related to spinal cord compression and/or increased intracranial pressure, although their beneficial effects are temporary and associated with adverse side effects. In patients with symptomatic hydrocephalus, placement of a ventriculoperitoneal shunt is a reasonable palliative approach [23]. Shunt placement carries the risk of systemic seeding and may be complicated by valve failure. However, these risks are typically justified in the context of quality of life issues in a patient population with a relatively poor prognosis.

Despite the lack of a standard approach for this disease, chemotherapy and radiotherapy play important roles in the management of LM. Relative to immunotherapy, it is of interest to note that intra-CSF alpha interferon has been tested in the setting of LM. Most recently, Chamberlain [24] reported a series of 22 patients including 2 melanoma patients and a variety of other solid tumors and hematologic malignancies. Toxicity was considerable with a 60% incidence of arachnoiditis, as well as a chronic fatigue syndrome in 90% of patients. Activity with intra-CSF alpha interferon in combination with chemotherapy and/or radiotherapy was modest.

Radiotherapy

External beam radiotherapy is indicated and beneficial for patients with LM with large tumor burden, including parenchymal brain metastasis, sites of symptomatic disease, or CSF flow obstruction [25].

External beam radiotherapy is often administered to symptomatic sites and to areas of bulky leptomeningeal metastases even if asymptomatic because intra-CSF chemotherapy does not penetrate beyond two to three millimeters from the tumor-CSF interface [26]. While treatment schedules vary, patients receiving focal palliative radiotherapy for LM usually receive a total of 24–30 Gy in 8–15 fractions. Pain is the symptom that appears to be most responsive to this modality. Focal radiotherapy usually does not result in complete neurologic recovery, with the exception of those patients with radiosensitive cancers such as leukemia, lymphoma or less frequently breast cancer [26].

Since LM is frequently a disseminated disease, craniospinal irradiation (CSI) can be considered in selected cases. This technique treats the entire craniospinal axis and frequently is utilized with high rates of success in other malignant diseases of the craniospinal axis, such as medulloblastoma and CNS germinoma [25]. Herrmann *et al.* [27] evaluated the efficacy and feasibility of CSI with and without intrathecal chemotherapy in 16 patients with LM in solid tumors. The overall median survival was 12 weeks; patients receiving CSI alone had a median survival of 8 weeks, compared to 16 weeks for those receiving both methotrexate (MTX) and CSI. Over two-thirds of patients had regression of their neurological symptoms during or within days after radiotherapy was completed. However, approximately one third of patients developed significant myelosuppression, and dysphagia, mucositis and nausea were common [27]. These side effects may be manageable with supportive care and should not preclude the use of CSI in selected cases. Because of the complicated set-up of CSI, the associated toxicities, and incurable nature of LM, most clinicians favor focal radiation instead of CSI.

Focal radiation to sites of obstruction may lead to reversal of obstructive flow patterns; however, many would consider this a relative contraindication to intra-CSF therapy. In this regard, patients with CSF flow obstruction refractory to site of obstruction therapy are predicted to have rapid leptomeningeal disease progression and poor survival [20]. Based on prior experience with involved field radiotherapy in 16 patients with LM from NSCLC and abnormal CSF flow, Chamberlain favors radiotherapy to bulky sites as initial treatment for such patients [3, 28].

Chemotherapy

Most chemotherapy regimens fail to penetrate the CSF in therapeutic concentrations. High-dose intravenous methotrexate (MTX), cytarabine, and thiotepa are exceptions and have the advantage of achieving a more homogeneous CSF distribution. Systemic chemotherapy has been reported to successfully treat LM, but no data from randomized trials exist to support this approach [29–31]. However, many patients cannot tolerate these regimens due to the presence of adverse factors at the time of LM diagnosis and the toxicity of therapy. These drugs may, however, be considered in chemotherapy-sensitive tumors, e.g. breast cancer, germ cell, hematologic malignancies, and small cell lung cancer. For example, approaches to LM in lymphoma are extrapolated from the primary CNS lymphoma literature describing improved outcomes with high-dose methotrexate based regimens [32, 33]. With regard to CNS lymphoma, Neuwelt *et al.* have used primary chemotherapy with osmotic disruption of the BBB with the intent of eliminating radiotherapy and minimizing the toxicity that can be associated with systemic chemotherapy. Survival results obtained with this approach have been encouraging [34].

Intra-CSF chemotherapy, given either via lumbar puncture (LP) or Ommaya reservoir, targets the entire CSF and can be used for nonbulky LM with relatively low systemic toxicity. An Ommaya reservoir (an implanted subcutaneous subgaleal device connected to a catheter terminating in the lateral ventricle) is generally preferred over LP because it allows more homogeneous distribution of intra-CSF chemotherapy. In the study by Shapiro *et al.* [35], administration by Ommaya reservoir more reliably produced adequate CSF distribution compared to administration by LP, which occasionally caused epidural and subdural leakage. As frequent administrations are necessary with most intra-CSF chemotherapy (due to drug half-life), drug delivery can be done easily with the assistance of the reservoir with less patient discomfort. It can also be useful for CSF sampling to evaluate response to therapy, although some regard sampling via LP to be more accurate. However, it is associated with adverse effects in 9% of patients, which include infection, incorrect catheter tip placement, or reservoir defect [36]. Before the administration of intrathecal chemotherapy (ITC) via LP, the patency of the CSF pathways must be evaluated via radionuclide cisternogram, since CSF obstruction interferes with its uniform distribution.

Four chemotherapentic agents can be applied for intraCSF therapy: methotrexate, thiotepa, cytarabine (Ara-C) and liposomal Ara-C. No randomized controlled trials have proven a significant benefit of one intra-CSF chemotherapy over another, except in lymphomatous meningitis, where liposomal Ara-C is more beneficial than standard Ara-C [37].

An evidence-based review of the efficacy of intrathecal chemotherapy in the treatment of LM revealed that there is only weak suggestion of improved clinical outcomes [38]. Parenthetically, when reviewing the literature on intrathecal chemotherapy, the reader should be cautious in interpreting outcome data from studies in which solid tumor results are combined with those derived from lymphoma patients. Data from randomized trials with intra-CSF chemotherapy are presented in Table 1. Review of these data regarding outcomes in solid tumor patients is very sobering. For example, in the study by Shapiro *et al.* [39], progression-free survival is so poor, that it essentially represents the time to next evaluation.

There are several potential explanations for these poor results. The most obvious relates to underlying drug sensitivity (e.g., one would not expect most solid tumors to respond to Ara-C). Blockage of CSF flow discussed above is common, and may alter potential effectiveness of intra-CSF chemotherapy. Radionuclide ventriculography in patients with LM has demonstrated that as many as 70% have ventricular outlet obstructions, abnormal flow in the spinal canal, or impaired flow over the cortical convexities [40, 41].

Intra-CSF chemotherapy can only treat the thin monolayer of cells adjacent to the CSF, and therefore has little effect on nodular areas and other areas of bulky disease. Bulkier areas of disease rely on neovascularization for continued growth, and chemotherapy agents with good CNS penetration will be more effective in treating these disease sites than agents administered via the intrathecal route [2, 7]. Given the limitations of chemotherapy in the treatment of LM in solid tumors, many oncologists consider involved field radiotherapy to be a reasonable initial approach for palliative treatment of LM in solid tumors [3, 28]. In selective hematologic malignancies, systemic chemotherapy (i.e., high-dose methotrexate) or intra-CSF chemotherapy may be considered, although palliative radiotherapy may be a more feasible option in a large subset of these patients as well.

Methotrexate (MTX), a folate anti-metabolite, is the most frequently used agent [2]. It is given twice a week by intrathecal or intraventricular bolus injection. Cytotoxic levels are maintained for up to 48 hours after each dose [35]. Potential toxicities include acute arachnoiditis, mucositis, and myelosuppression, which can potentially be minimized with systemic administration of folinic acid. In addition, MTX induced cerebritis may be difficult to distinguish from progressive LM, with hallmarks of drug-induced cerebritis including a clinical worsening of neurologic sigus and symptoms and an increase in CSF protein. To minimize the risk of drug-induced cerebritis, many practitioners will administer approximately 30 mg of intra-CSF hydrocortisone without preservative immediately post intra-CSF chemotherapy. Additionally, necrotizing leukoencephalopathy, especially when MTX is administered following radiotherapy, is a feared complication [42]. Although the risk of MTX-induced leukoencephalopathy is less defined with MTX administered only via the intra-CSF route, the severe complications noted in long-term survivors of high-dose systemic methotrexate based therapy warrants concern. For example, among 12 patients over the age of 60 with an observed median survival of greater than 2 years following high-dose methotrexate systemic chemotherapy and whole brain irradiation for primary CNS lymphoma, the risk of severe and debilitating neurotoxicity from leukoencephalopathy was greater than 70% [32].

Thiotepa, an alkylating ethyleneimine compound, is most commonly given two to three times per week as a bolus injection [43]. The CSF half-life is short and therefore it is not commonly used in the clinical setting. Hematologic toxicity can be observed following intra-CSF administration.

Ara-C, a pyrimidine nucleoside analogue, is used more commonly to treat leukemic or lymphomatous meningitis. It has a half-life of 3–4 hours in the CSF and achieves cytotoxic levels in the CSF only for a short time [44]. Administration of liposomal Ara-C extends the CSF half-life to 141 hours, allowing administration once every 2 weeks, an important quality of life issue for patients [45]. Liposomal Ara-C is approved for the treatment of lymphomatous meningitis. A phase III study performed by Glantz *et al.* randomized patients with LM due to solid tumors to intra-CSF administration of lyposomal Ara-C versus MTX and found no difference in overall survival, response or duration of response. There was an improvement in time to neurological progression for liposomal Ara-C, but the criteria for neurological progression, in our opinion, were subjective. Interestingly, neither the Mini-Mental Status Exam score nor the KPS changed significantly between baseline and the end

of the induction period in either treatment arm, nor was there a significant change in either measure when looked at separately for responders and nonresponders, regardless of treatment assignment [45, 46].

No evidence-based data exists regarding the optimal duration of intra-CSF chemotherapy in LM. Patients may continue therapy according to tolerability and response to therapy. CSF for cytology should be obtained prior to each dose in order to monitor response to therapy along with periodic imaging as needed.

INNOVATIVE CHEMOTHERAPEUTIC APPROACHES

Capecitabine

Capecitabine, an oral pro-drug of fluorouracil, has been given to women with metastatic breast cancer with LM with observation of responses and clinical improvement [50, 51].

There is also increasing interest in the combination of capecitabine plus lapatinib due to their know synergy and CNS activity. In the study by Geyer *et al.* [52], CNS disease developed in fewer women with HER2 positive metastatic breast cancer treated with the combination of capecitabine/lapatinib (n=4) compared with those receiving capecitabine monotherapy (n= 11). However, given the small number of patients, this difference was not statistically significant [52]. Another study which included a similar patient population also - suggests capecitabine and lapatinib provides clinical benefit to patients with progressive brain metastasis from HER-2 positive breast cancer [53]. It is logical that this combination would be efficacious in such LM patients and further studies are warranted.

Temozolomide

Temozolomide, an oral alkylator, reaches CSF levels approximately 20% of those in plasma [5]. In a small phase II study of temozolomide in LM [54], patients received 75 mg/m^2 daily for 6 continuous weeks, followed by a 4 week break. Temozolomide was well tolerated, although no responses were seen. However, treated patients demonstrated maintenance of quality-of-life for up to 20 weeks. Additional data suggest the potential role of temozolomide as a radiosensitizing agent [55], and these properties warrant further investigation in the setting of LM given the already established role of involved-field radiotherapy to bulky or symptomatic leptomeningeal disease sites. Relative to this, the Radiation Therapy Oncology Group is considering a randomized study of LM in non-small lung cancer comparing involved field radiation with and without temozolomide.

Topotecan

Topotecan, a topoisomerase I inhibitor, was recently tested in the phase II setting in patients with primarily breast, lung, and brain tumors and did not demonstrate significant benefit over conventional intra-CSF therapies [56].

Etoposide

Etoposide, a topoisomerase II inhibitor, has been used for intra-CSF therapy, predominantly in children. A small phase II trial in adults showed activity similar to other intra-CSF drugs with a cytological response of about 25% [57].

TARGETED THERAPIES

Trastuzumab

Little is known so far about the pharmacokinetics and activity of trastuzumab (monoclonal antibody directed against HER2) in the CNS. A previous publication suggested that

trastuzumab does not penetrate the CSF in sufficient levels [58]. There have been several case reports in the literature of intra-CSF administration of trastuzumab for HER2 overexpressing breast cancer-related LM [59–62], with varied results.

An ongoing study with intra-CSF trastuzumab in patients with LM from breast cancer or primary brain tumor demonstrated that intra-CSF trastuzumab can be safely administered (20–60 mg per dose, either weekly or every other week) [63]. Two of the four patients with breast cancer (both HER-2 +) are responding clinically and cytologically 4 and 14 weeks after initiating treatment. The patient with medulloblastoma (also HER-2+) continues to respond clinically and cytologically after 6 weeks. Seven of 11 patients with GBM have responded (two cytologically, two radiographically, all seven clinically), with response durations ranging from 4 to 12+ weeks. There were no adverse events related to the intra-CSF trastuzumab. Final results are pending but HER2 status may predict response.

Lapatinib

Data indicate that lapatinib (a tyrosine kinase inhibitor of HER2 and epidermal growth factor receptor) crosses the blood-brain barrier providing a clear rationale for testing lapatinib in patients with CNS metastases [64]. As described previously, there is increasing interest in combining lapatinib with chemotherapy, such as capecitabine, due to its CNS activity in HER-2 + breast cancer [52, 53].

Rituximab

Rituximab, a humanized monoclonal antibody against CD-20, has limited penetration into the leptomeningeal space when administered intravenously. A phase I study of intraventricular rituximab in patients with recurrent CNS and intraocular lymphoma revealed that intra-CSF rituximab (10–50mg) is feasible and effective [65]. Rapid craniospinal axis distribution was demonstrated. Cytologic responses were detected in 6 of 10 patients; including four patients achieving a complete cytologic response. Two patients experienced improvement in intraocular NHL and one exhibited resolution of parenchymal NHL. Toxicity was mild and self-limited, with the most frequently observed toxicities consisting of hypertension (reproducible with repeat drug exposure at the highest dose level of 50 mg), transient diplopia, nausea, and vomiting. As most toxicities occurred at the 50 mg dose level, the recommended intra-CSF dose of rituximab based on these data is 10–20 mg.

Rituximab via ventricular reservoir (25 mg twice per week) has also been studied in combination with liposomal Ara-C in 14 patients with recurrent lymphomatous meningitis [66]. Best responses to treatment included 10 partial responses and the combination did not appear to have any additive toxicity.

Hormonal Therapy

The penetration of tamoxifen and aromatase inhibitors into the CSF has scarcely been investigated. There are a few published case reports of patients with metastatic hormone-responsive breast cancer with LM that suggest hormone therapy may be effective with an acceptable toxicity profile in a selective group of patients [67–69].

Radioimmunotherapy

Tumor selective radioimmunotherapy strategies may represent a novel means of LM treatment. Radiolabeled antibodies have an advantage over "naked" antibodies (e.g., rituximab,trastuzumab) because of the lack of effector cells and complement in the CSF.

The radioimmunotherapy agent 131-iodine-3F8 was investigated in a phase I study of 15 patients with leptomeningeal spread of tumor [70]. The 3F8 is a murine immunoglobulin C3

antibody against the protein GD2, which is expressed in many primary CNS tumors and some normal neural tissues. An understanding of GD2 expression in solid tumors is evolving. Previous experience has shown responses in metastatic neuroblastoma treated with intravenous 3F8 [71] and the combination of 3F8 with 131-iodine has resulted in novel imaging techniques in neuroblastoma [72].

The phase I experience with 131-iodine-3F8 involved intra-Ommaya administration of drug at escalating dose levels. Although most cases were primary CNS tumors with LM spread, one patient had LM spread of metastatic melanoma. Three patients achieved objective responses by imaging, and the patient with melanoma had evidence of decreased LM enhancement on MRI with treatment. The agent was well tolerated with mild and self-limited toxicities of fever, nausea, vomiting, headaches, and possible chemical meningitis [70]. These promising data are the basis for ongoing investigation of this agent in the phase II setting. Further evaluation may lead to a better understanding of feasibility and efficacy of radioimmunotherapy in the setting of metastatic solid tumors with LM involvement.

Prognosis

Prognosis and life expectancy varies according to tumor type and perforroance status. The cause of death in patients with LM is progressive systemic disease in 10–64% of patients, neurological tumor progression in 15–87% or treatment-related toxicity in 0–15% [4]. Patients with lymphoma or breast cancer may have longer survival, and have good response to treatment. Clinical assessment with risk stratification should play an important role in determining therapy options based on prognosis for patients with LM.

CONCLUSION

LM is a neurologically devastating and rapidly fatal late complication of cancer. All current therapeutic options are palliative in nature with the goal of stabilizing disease and delaying further complications. Future trials are warranted to determine the effects of treatment on quality of life and control of neurological symptoms

Acknowledgments

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Table 1

Randomized Clinical Trials in LM[1]

Trial	Design	Outcome
Grossman et al.[45]	IT MTX versus thio-TEPA (59 patients; solid tumors and lymphoma)	Median survival, 15.9 (MTX) versus 14.1 weeks (thio-TEPA)
Hitchins et al.[46]	IT MTX versus MTX + CYT (44 patients; solid tumors and lymphoma)	Median survival, 12 (MTX) versus 7 weeks (MTX+CYT
Glantz et al.[43]	LS-CYT versus MTX (61 patients; solid tumors)	Overall survival, 105 (LS-CYT) versus 78 days (MTX), difference not significant
Glantz et al.[35]	LS-CYT versus CYT (28 patients; lymphoma)	Overall survival, 99.5 (lLS-CYT) versus 63 days (CYT), difference not significant. Cytologic response rate 71% (LS-CYT) versus 15%
Boogerd et al.[47]	IT versus no IT therapy, but systemic therapy and RT were given in both arms (35 patients; breast cancer)	Median survival, 18.3 (IT) versus 30.3 weeks (no IT)
Shapiro et al.[37]	Lymphoma (25 patients)	LS-CYT versus all MTX and CYT-treated patients combined: PFS 35 versus 43 days (not significant)
	LS-CYT versus CYT	LS-CYT versus MTX: PFS 35 versus 37.5 days (not significant)
	Solid tumors (103 patients), LS-CYT versus MTX	LS-CYT versus CYT: PFS 34 versus 50 days, cytologic remission rate 33.3% versus 16.7% (both not significant)

Abbreviations: IT, intrathecal; LM, leptomeningeal metastasis; MTX, methotrexate; CYT, cytarabine; LS-CYT, liposomal cytarabine; PFS, progression-free survival; RT, radiotherapy.