Chemotherapy and cerebral metastases: misperception or reality?

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✓Cerebral metastases remain a common complication among patients with cancer. Surgery and radiotherapy remain the principal therapeutic interventions. In contrast, the benefit of chemotherapy has long been viewed with skepticism. Nonetheless, as survival in cancer patients improves and the incidence of cerebral metastases increases, so does the demand for effective therapies. It is now recognized that the blood–brain barrier within metastases is permeable and thus allows entry of otherwise excluded drugs. Limited data have suggested that cerebral metastases have modest sensitivity to chemotherapy. Furthermore, novel agents and delivery strategies have been developed to facilitate central nervous system penetration. Nonetheless, data are limited by methodological flaws, including heterogeneous inclusion criteria, small sample sizes, lack of randomization, and inconsistencies in defined end points and response assessment criteria. Well-designed clinical trials are needed to address the effect of chemotherapy. Acceptable control arms must be established to measure the effect of chemotherapies. Standardized response criteria and disease-specific studies are essential.

KEY WORDS • cerebral metastasis • chemotherapy • carboplatin • cisplatin • gefitinib • targeted therapy • temozolomide

BRAIN METASTASES are the most common malignant tumors of the brain. Their incidence varies depending on the method of case ascertainment and can be as high as 30% during the course of a cancer patient's lifespan; the prevalence is even higher in autopsy series. This complication occurs more frequently as therapies for systemic disease improve and detection increases due to improved awareness and the ready availability of modern imaging techniques.⁵¹ The most common primary tumors to metastasize to the brain include melanoma and renal cell, lung, and breast carcinomas. Given their relatively greater incidence, however, breast and lung cancer account for most cases. Optimal treatment remains uncertain, although surgery (in select cases) and radiotherapy continue to be the primary treatment modalities. In contrast, chemotherapy has long been viewed with skepticism. Many chemotherapeutic agents have a limited ability to penetrate the BBB, which is impermeable to large, hydrophilic compounds. The concomitant use of corticosteroids as an antiemetic or therapy for tumor-related edema may further limit CNS penetration by “closing” the BBB. In addition, several common chemotherapeutics are substrates of efflux pumps, such as P-glycoprotein, that

actively extrude drugs from the CNS. Furthermore, brain metastases are often a late manifestation of cancer occurring at a time when patients have been extensively pretreated. Consequently, acquired chemoresistance is not unusual, and treatment may be poorly tolerated. Many of the tumors that commonly metastasize to the brain, such as NSCLC, melanoma, and renal cell carcinoma, are commonly resistant even to first-line chemotherapies.

Nonetheless, interest in chemotherapy for cerebral metastases is increasing. Despite significant improvements in technology, radiotherapy is not curative and is associated with putative long-term neurotoxicity.¹⁴ As cancer treatments have improved, the risk of brain metastases has increased. For example, the incidence of cerebral metastases has increased among women with HER-2/neu-expressing breast cancer responding to trastuzumab (see *Breast Cancer*). Among the advantages of chemotherapy is the simultaneous treatment of concomitant systemic disease. It is also now recognized that the BBB within the tumor is disrupted and therefore allows agents that may otherwise have been excluded to penetrate the tumor. In addition, novel small lipophilic chemotherapies that readily cross the BBB have been developed. Alternative delivery mechanisms that facilitate CNS entry of chemotherapies, such as intraarterial administration, chemotherapy-laden wafers, and iatrogenic BBB disruption, have also generated increased interest in chemotherapy.

There are limited data on chemotherapy for the management of brain metastases. Much of the data are confined to retrospective studies, small case series, and case

Abbreviations used in this paper: AGT = O₆-alkylguanine-DNA alkyltransferase; BBB = blood–brain barrier; CNS = central nervous system; CSF = cerebrospinal fluid; HER = human epidermal growth factor receptor; MTX = methotrexate; NSCLC = non–small cell lung cancer; SCLC = small cell lung cancer; WBRT = whole-brain radiotherapy.

TABLE 1
Preirradiation chemotherapy in patients with cerebral metastatic NSCLC*

Authors & Year	Treatment Regimen	No. of Patients	Response Rate (%)†	Stable Disease (%)
Franciosi et al., 1999	carboplatin, etoposide	43	30	34
Fujita et al., 2000	cisplatin, ifosfamide, irinotecan	28	50	46
Robinet et al., 2001	cisplatin, vinorelbine	76	27	NR
Bernardo et al., 2002	carboplatin, gemcitabine, vinorelbine	20	60	25
Cortes et al., 2003	cisplatin, paclitaxel + gemcitabine or vinorelbine	26	38	31
Quadvlieg et al., 2004	cisplatin, gemcitabine	40	64	5

* NR = not reported.

† Includes complete, partial, and minor responses.

reports. The clinical trials performed thus far have been small, and many have not been disease specific. Inclusion criteria have been heterogeneous and have included patients with various stages of disease and previous treatments. Authors of most trials evaluate chemotherapy as a salvage treatment used after radiotherapeutic options have been exhausted and disease has advanced. Study methodologies, including response criteria, have been inconsistent. The variety in the reported clinical trials makes comparisons of the individual regimens difficult.

LUNG CANCER

Lung cancer is the most frequently diagnosed form of cancer and the leading cause of cancer-related deaths. It is classified into small cell and non-small cell varieties, the latter being more common (80% of cases). Lung cancer accounts for approximately 39% of all cases of cerebral metastases.⁶⁵ The metastatic disease may be present at the time of patient presentation in 10% of cases. Cerebral metastases develop in 20 to 40% of patients during the course of the disease and represent a significant cause of morbidity.⁵⁰

Non-Small Cell Lung Cancer

Non-small cell lung cancer has limited sensitivity to chemotherapy. Platinum agents, principally cisplatin and carboplatin, are the most commonly used chemotherapeutics. Several authors have evaluated these agents, either as monotherapy or in combination with other agents, in the management of cerebral metastases. When used before radiotherapy, intracerebral response rates (partial and complete) of 27 to 50% have been reported for platinum-based regimens (Table 1).^{7,24,31,33,73} Robinet and colleagues⁷³ evaluated the timing of chemotherapy in patients with cerebral metastases caused by NSCLC. They randomized 114 patients to cisplatin and vinorelbine administered either before or concomitant with WBRT. Objective response rates (partial and complete; 27% compared with 33%), median progression-free survival (13 weeks compared with 11 weeks), overall survival (24 weeks compared with 21 weeks), and 6-month survival (46% compared with 40%) were similar between the two treatment arms (preirradiation chemotherapy and simultaneous treatment, respectively). Less is known about the effect of platinum agents (or other chemotherapies) in previously treated patients. Malacarne and associates⁵⁸ reported a response rate of 17% for carboplatin and etoposide in such patients,

which, not surprisingly, is lower than the rate in those less extensively treated. Three of nine evaluable patients with cerebral metastases from lung carcinoma treated using intraarterial carboplatin and intravenous etoposide responded to therapy.⁶⁴

Temozolomide is an oral methylating agent that can easily penetrate the CNS and is well tolerated, even among extensively pretreated patients. It appears to have limited activity against NSCLC, however. No objective responses to temozolomide monotherapy were recorded among 25 chemonaïve patients with NSCLC with or without cerebral metastases in a Phase II trial by the European Organization of Research and Treatment of Cancer group.²⁷ Reported cerebral metastases response rates in several Phase II studies of temozolomide monotherapy have been less than 10%.^{1,22,32,37,84} Temozolomide has also been combined with cisplatin (Table 2).²³ When temozolomide was combined with vinorelbine in a Phase I study, four and one patient had stable disease and a partial response, respectively, among 10 patients with NSCLC.⁶⁶

Temozolomide has also been administered together with WBRT. Verger and colleagues⁸⁹ randomized 82 patients with cerebral metastases (half of whom had a primary lung carcinoma) to WBRT with or without temozolomide. Radiographically demonstrated response rates and overall survival were similar between the two groups, although 90-day progression-free survival (54% compared with 72%) and death from cerebral metastases (69% compared with 41%) significantly favored the combination treatment arm. In a second randomized Phase II study of patients with cerebral metastases, adding temozolomide to WBRT improved the radiographically demonstrated response rate from 67 to 91%.⁴ In addition, 2 months following the completion of therapy, temozolomide-treated patients required less dexamethasone. Overall survival was again similar between the two groups. Improved radiographically demonstrated response rates were confirmed in a Phase III study by the same group: 53% for the combined treatment as opposed to 33% in those treated with radiation alone.³ The median survival was longer among those treated with temozolomide, although the difference was not statistically significant (8.3 compared with 6.3 months). Unfortunately, the authors of these studies did not report disease-specific outcomes. Studies are ongoing to further evaluate this treatment approach.

Recently, there has been growing interest in the use of targeted therapies in NSCLC. Erlotinib hydrochloride and gefitinib, small-molecule tyrosine kinase inhibitors selec-

TABLE 2
Phase II studies of temozolomide in pretreated patients with cerebral metastatic NSCLC

Authors & Year	Treatment Regimen	No. of Patients	Response Rate (%)	Stable Disease (%)
Abrey et al., 2001	standard temozolomide	22	9	36
Christodoulou et al., 2001	standard temozolomide	12	8	0
Friedman et al., 2003	dose-intense temozolomide	29	7	NR
Siena et al., 2003	dose-intense temozolomide	21	NR	24*
Christodoulou et al., 2005	temozolomide, cisplatin	32	18	NR

* Includes partial responses and stable disease.

tive for the epidermal growth factor receptor, have demonstrated activity in select patients with NSCLC. In particular, these agents have notable activity in tumors with a specific epidermal growth factor receptor mutation more common in Asian populations.⁸² The extent to which these agents penetrate the BBB is unknown. In a single-institution retrospective review of Japanese patients with refractory NSCLC treated with gefitinib, control of cerebral metastases was achieved in all 14 patients with this complication (including 43% of patients with objective responses).⁴⁶ In a prospective study of pretreated patients with NSCLC performed in Taiwan, the cerebral metastases response rate and disease control rate were 50 and 91%, respectively.²¹ Similar results were demonstrated in another small Japanese case series.⁶³ Gefitinib had comparable activity against intra- and extracranial lesions.^{21,63} These results are in contrast to those from a similar prospective study performed in Italy; in that study, the response and disease control rates were 10 and 27%, respectively.¹⁵ Although systematic studies of erlotinib have not been performed to date, case report data suggest that this agent has activity against cerebral metastatic NSCLC.²⁶ Larger trials of targeted therapies, either alone or in combination with other agents or radiotherapy, are warranted and ongoing.

Small Cell Lung Cancer

Relative to NSCLC, SCLC is more chemosensitive. Platinum-based therapies remain the most common regimens used. Fewer authors have evaluated the use of systemic chemotherapy for cerebral metastatic SCLC. The European Organization of Research and Treatment of Cancer group randomized 120 patients with newly diagnosed, untreated, SCLC-based brain metastases to teniposide with or without WBRT.⁶⁹ Response rates were significantly better (57 compared with 22%) and the time to progression longer in patients who had received WBRT. Treatment failure occurred less often among those randomized to the combined treatment (17 compared with 43%). Note, however, that systemic failure occurred more often among patients treated with WBRT alone. Overall survival was similar between the two groups, approximately 3.5 months. Seute and colleagues⁸¹ treated 24 patients with asymptomatic cerebral metastatic SCLC by using cyclophosphamide, doxorubicin, and etoposide in lieu of radiotherapy; 27% responded to treatment. All patients eventually became symptomatic from the CNS lesions. This result compares unfavorably with WBRT outcomes.⁸¹ In a Phase II study of pretreated patients with cerebral metastases, treatment with topotecan resulted in a 33% response

rate with an additional 23% of patients having stable disease.⁵⁴ The median time to progression was 3.9 months for those who responded to treatment, and myelotoxicity was common. Authors of other smaller studies of single-agent topotecan for cerebral metastases in pretreated patients with SCLC reported response rates of more than 50%.⁹⁰

CEREBRAL METASTATIC MELANOMA

Cerebral metastases are a common complication among patients with melanoma. The incidence, which varies based on the method of case ascertainment, is approximately 6 to 43%.²⁵ Melanoma is relatively chemoresistant. Many of the frequently used regimens, such as dacarbazine and biological therapies (interferon and interleukin), have limited activity within the CNS. Consequently, the CNS is a frequent site of treatment failure. Much of the recent chemotherapy data for cerebral metastatic melanoma are temozolomide based. In a Phase II study of patients with cerebral metastatic melanoma, 151 patients received temozolomide monotherapy in lieu of WBRT. Six percent of patients had a radiographically demonstrated response and 26% had stable disease. Progression-free survival, however, was short, approximately 1 month.² Similar results were reported by Schadendorf et al., who treated 45 patients with asymptomatic cerebral metastases with dose-intensified temozolomide. By 8 weeks posttreatment, 82% of patients had progressive disease.⁷⁹ Using a similar dose-intensive regimen, Siena et al. reported a control rate of 40% among 21 patients with cerebral metastatic melanoma.⁸⁴ In a subgroup analysis of other studies, authors found that two of four patients treated with temozolomide and cisplatin and one of two treated with temozolomide monotherapy realized at least stable disease.^{22,23} Responses have also been reported when temozolomide has been combined with thalidomide and docetaxel.^{6,47} Temozolomide has also been combined with WBRT. In a single-institution retrospective review, patients treated with WBRT and temozolomide had better overall survival than those treated with temozolomide alone (9 months compared with 5 months, respectively).⁴⁵ A Phase II trial of this therapeutic approach revealed a response rate of 9.7% with a short median progression-free survival of 2 months.⁵⁹ Alternatively, temozolomide has shown some promise as a preventative agent. When temozolomide was added to regimens with minimal CNS activity, the rate of subsequent cerebral metastases was decreased. More specifically, cerebral metastases developed in none of the 35 patients with systemic melanoma treated with temozolomide and interferon- α -2b while the

TABLE 3
Chemotherapy for cerebral metastatic breast cancer*

Authors & Year	Treatment Regimen	No. of Patients	Response Rate (%)	Stable Disease (%)
Franciosi et al., 1999	cisplatin, etoposide	56	38	21
Abrey et al., 2001	standard temozolomide	10	0	40
Christodoulou et al., 2001	standard temozolomide	4	0	0
Arena et al., 2003	metronomic temozolomide	19	10	NR
Friedman et al., 2003	dose-intensive temozolomide	15	0	NR
Siena et al., 2003	dose-intensive temozolomide	21	NR	19*
Christodoulou et al., 2005	temozolomide, cisplatin	15	40	NR
Lassman et al., 2005†	high-dose methotrexate	32‡	28	28

* Partial responses and stable disease reported together.

† Included patients with leptomeningeal metastases.

‡ Ninety-two percent of patients had breast cancer.

study treatment was administered. Once temozolomide was discontinued, however, 17% of patients demonstrated treatment failure in the brain.⁴⁸ Similarly, none of the responding patients receiving temozolomide, interferon- α 2, and interleukin-2 had cerebral metastases while on the treatment regimen.⁷⁵ In another Phase II study of temozolomide, interferon- α -2b, and interleukin-2, only 6% of patients demonstrated cerebral metastases while on the treatment. In contrast, cerebral metastatic melanoma developed in 33% of patients receiving a dacarbazine-based chemotherapy. After discontinuing treatment, cerebral metastases developed in 23% of temozolomide-treated patients.⁹² A decreased incidence of cerebral metastases after replacing dacarbazine with temozolomide has been noted elsewhere.⁶⁷ The question of whether temozolomide can protect the brain from metastases warrants further investigation given the limitations of available therapies for this complication.

BREAST CANCER

Approximately 20% of patients with breast cancer have cerebral metastases at autopsy, whereas the clinical diagnosis of cerebral metastases is made before death in 5 to 10% of patients. Given the high incidence of breast cancer among women, it accounts for a significant proportion of all brain metastases, approximately 17%.⁹ Furthermore, as systemic therapies for breast cancer improve, the incidence of cerebral metastases has increased. This fact is highlighted among women with HER-2/neu-positive breast cancer responding to trastuzumab. This recombinant monoclonal antibody is directed against HER-2, which is overexpressed in 20 to 30% of breast cancers. Despite the effectiveness of trastuzumab in the management of systemic breast cancer, it is not uncommon for this treatment to fail in the CNS. It is thought that the BBB prevents trastuzumab from adequately penetrating the CNS, thereby creating a sanctuary from this agent.

Breast cancer is relatively more sensitive to chemotherapy than are NSCLC and melanoma, although well-performed explorations of this treatment modality have yet to be completed. Rosner and colleagues⁷⁶ reported a response rate of 50% among 100 women treated with a variety of regimens typically used to treat breast cancer. Interestingly, many of the agents were thought to have poor BBB penetration (cyclophosphamide, doxorubicin, 5-fluorouracil, conventional-dose MTX, and vincristine). After

using similar regimens, Boogerd et al.¹⁰ reported a cerebral metastases response rate of 59%. Data from these reports suggest that chemotherapeutics may adequately penetrate the BBB to achieve cytotoxic concentrations within tumors. To date, several small studies of chemotherapy specifically administered for cerebral metastases have been published (Table 3).

Despite good BBB penetration, temozolomide has minimal activity against breast cancer. In a Phase II study by the National Cancer Institute of Canada-Clinical Trials Group, 19 patients with systemic breast cancer (including five with cerebral metastases) were treated with dose-intensive temozolomide; none of these patients responded to this treatment.⁸⁸ Similar disappointing results have been reported by other groups who evaluated temozolomide administered specifically for cerebral metastases (Table 3). The effect of temozolomide on cerebral metastases when combined with radiotherapy is unknown, as most studies have included only a small number of patients with breast cancer and the results were not reported separately. Temozolomide was combined with vinorelbine in a Phase I study in which one of six pretreated breast cancer patients had a partial response (an additional patient had stable disease). Temozolomide was also combined with capecitabine in a Phase I study in which 62% of patients realized at least stable disease, including 16% with a complete or partial response. Most patients were extensively pretreated.^{66,72} Both treatment regimens were well tolerated.

Doxorubicin, a standard agent incorporated into breast cancer protocols, has limited penetration of the CNS. When encapsulated in liposomes, however, its penetration of the BBB is augmented. In animal studies, a 15-fold increase in doxorubicin concentrations was detected in tumors stereotactically implanted into rat brains treated with liposomal-formulated doxorubicin compared with standard drug formulations. Cerebrospinal fluid drug levels measured in tumor-bearing animals were 10- to 30-fold higher after injection of liposomal-formulated doxorubicin compared with levels after injections of standard formulations.⁸³ When administered with temozolomide in 19 patients with cerebral metastases, most of which had been pretreated, liposomal doxorubicin resulted in a 37% response rate. Of the eight patients with breast cancer, three had a complete response (all had previously been treated with WBRT) and two had a partial response. Overall, patients with breast cancer accounted for five of the seven responses. Given the limited activity of temo-

zolomide against breast cancer, this finding suggests the liposomal doxorubicin may have promising activity in mitigating cerebral metastatic breast cancer.¹³ Further investigation is warranted.

Capecitabine, a well-tolerated oral prodrug of 5-fluorouracil, is currently approved by the Food and Drug Administration for refractory metastatic breast cancer. Authors of several case reports have suggested that it has activity in breast cancer patients with cerebral metastases.^{28,74,91} A Phase I study of capecitabine and temozolomide has now been completed in pretreated patients with cerebral metastatic breast cancer in whom an 18% response rate was reported.⁷² Lapatinib is a small-peptide, dual tyrosine kinase inhibitor of HER-2. In an open-label Phase III study, patients with HER-2/neu-positive breast cancer refractory to trastuzumab were treated with lapatinib and capecitabine; these patients had nearly double the progression-free survival of patients treated with capecitabine alone (8.5 compared with 4.5 months). Furthermore, the rate of cerebral failure was significantly lower.³⁴ In a Phase II study of lapatinib in patients with HER-2/neu-positive breast cancer in whom cerebral metastases had developed while on treatment with trastuzumab, five and three patients achieved a greater than 30% and 15 to 30% reduction in tumor burden, respectively, on volumetric analysis.⁵⁶ Additional prospective studies of these agents, either alone or in combination, are indicated, given that they seem to have activity against cerebral disease.

GERM CELL TUMORS

The effectiveness of chemotherapy has also been demonstrated in the management of cerebral metastases from other less common cancer types such as germ cell tumors, which are chemosensitive. Durable responses to mostly cisplatin-based regimens have been reported in series of patients with germ cell tumors. Most long-term responders are patients who presented with cerebral metastases; treatment of CNS relapse in patients previously treated with platinum-based regimens is less effective.²⁶

TREATMENT SENSITIZERS

Sensitizers to enhance the responsiveness of tumors to treatments have been explored in clinical trials.¹⁴ Most available modern data relate to the radiosensitizers motexafin Gd and RSR13 (efaproxiral). Motexafin Gd is a metalloporphyrin that selectively targets tumor cells after its intravenous administration. It acts by catalyzing the oxidation of a number of intracellular-reducing metabolites, thereby generating reactive oxygen species.⁷¹ Early Phase II data have shown encouraging response rates when motexafin Gd was administered concomitantly with radiotherapy. Authors of a Phase III study reported an improvement in the time to neurological progression, particularly in patients with NSCLC, who also had significantly less neurological death. There was no difference in overall survival.^{62,66} Data from a confirmatory study in patients with NSCLC, however, failed to confirm the benefit of motexafin Gd and WBRT, and future developments remain uncertain.

Efaproxiral is a small molecule that binds to hemoglo-

bin and decreases its affinity for O₂. Consequently, O₂ is released from hemoglobin, and tissue PO₂ is increased. Results of a Phase III study of WBRT plus supplemental O₂ with or without efaproxiral revealed encouraging activity in the subset of patients with breast cancer that had been treated with the study drug: overall survival increased from 4.6 to 8.7 months in these patients.⁸⁵ Currently, efaproxiral is being evaluated in a confirmatory study of patients with breast cancer.

Chemosensitizers have also been investigated with regard to overcoming chemoresistance. Resistance to methylating agents, such as temozolomide, is mediated through AGT, which removes methyl groups that mediate the drug's cytotoxicity. Note that AGT is encoded by *MGMT*, which is on chromosome 10. Epigenetic silencing of *MGMT* due to promoter hypermethylation has been associated with increased responsiveness to treatment. Strategies to inhibit *MGMT* expression or counteract AGT activity are being explored.

The base excision repair system is another mechanism of resistance to radiotherapy and chemotherapy. In a series of molecular reactions that involve poly(adenosine diphosphate-ribose) polymerase, damaged bases are removed and, ultimately, DNA is repaired.⁸⁶ Poly(adenosine diphosphate-ribose) polymerase inhibitors might sensitize tumors to treatment and are currently being investigated in clinical studies.⁵⁷

LEPTOMENINGEAL METASTASES

Leptomeningeal metastases represent another manifestation of systemic cancer. Non-small cell lung cancer, breast cancer, and melanoma are involved in most cases of this complication.¹⁶ Hematological malignancies also commonly relapse within the CSF.²⁰ If this metastatic disease is left untreated, the median patient survival is approximately 2 months. Even with aggressive therapy, the prognosis remains poor—approximately 4 to 6 months.⁶⁰ Unlike the case for cerebral metastases, for which radiotherapy and surgery are the principal therapeutic modalities, leptomeningeal metastases are managed mainly with chemotherapy, which is usually administered intrathecally via repeated lumbar punctures or a surgically placed, intraventricular Ommaya catheter. Lumbar puncture is inconvenient and uncomfortable for the patient, and chemotherapy administered via this route may not distribute as efficiently as that administered directly into the ventricle. Placement of an Ommaya reservoir requires a surgical procedure and is associated with short- and long-term complications including infection, hemorrhage, catheter malfunction, and pericatheter necrosis.¹⁹ The effectiveness of intrathecal chemotherapy depends on the flow dynamics of the CSF. In 61% of cases, as assessed by timed ventriculography studies, CSF flow was disturbed. In fewer than half of these patients was hydrocephalus detected on CT scanning.³⁹ Compared with patients without CSF flow abnormalities, survival was significantly worse, and neurological death rates were significantly greater when patients with such abnormalities were treated with intrathecal chemotherapy.^{18,39} In addition, neurotoxicity can occur in areas of trapped chemotherapy.^{39,61}

Perhaps one of the greatest limitations of intrathecal chemotherapy is the limited number of agents available

for intrathecal administration. To date, only two agents are commonly used: MTX and cytosine arabinoside. Traditionally, they have been given as single-dose injections 2 days per week during an induction phase. Depending on the response, the frequency of administration is tapered during a consolidation phase. The optimal duration of therapy is unknown. The short half-life and rapid clearance of these medications have generated concern that the exposure of tumor cells to cytotoxic levels of the drugs is insufficient, especially far from the injection site.²⁹ To overcome this obstacle, alternative treatment schedules have been devised in which the agent (usually MTX) is given on several consecutive days, thus ensuring a steady level of cytotoxic drug concentration.¹⁶ Such concentration-against-time schedules are more demanding on the patient. Alternatively, a liposomal formulation of cytosine arabinoside, Depocyt, has been developed; the use of this drug allows the frequency of treatments to be reduced to once every 2 weeks. The half-life of Depocyt is such that cytotoxic levels are maintained for 14 days. Other agents for intrathecal administration are currently under investigation, including rituximab (an anti-CD20 antibody) and trastuzumab (anti-HER-2 antibody).^{36,68,77,80}

Several authors have conducted retrospective and prospective trials evaluating the effectiveness of intrathecal therapy. Most trials differ in the inclusion criteria, treatment methods and schedules, and criteria for diagnosis and response; thus, comparisons of the results are difficult. Nonetheless, some conclusions can be drawn. Approximately 20 to 30% of patients die during early phases of treatment.^{8,11,49} The intrathecal agents all appear to have equal efficacy, although there is a trend toward better survival and a longer time to disease progression with Depocyt in the treatment of both solid and hematological tumors.^{40,41} Clinical response rates vary between 9 and 69%. Cytological response rates are approximately 25 to 50%. Melanoma and NSCLC are relatively more treatment resistant, whereas breast cancer, SCLC, and lymphomas are more responsive. The duration of response is short, and the median survival period remains only 4 to 5 months with aggressive therapy. Data from one study of MTX in patients with breast cancer has suggested a benefit from intrathecal therapy on a concentration-against-time schedule.³⁰ Most study data have failed to demonstrate a benefit when multiple agents were administered simultaneously,^{35,44} although in a small retrospective study Kim and colleagues noted improved survival and response rate among those treated with MTX, cytosine arabinoside, and hydrocortisone compared with those treated with MTX alone.⁵² Patients with normal CSF flow dynamics have better responses.^{17,18} Toxicity is similar among the agents, causing headache and nausea. Arachnoiditis is common and can be minimized with the administration of dexamethasone several days before and after intrathecal treatment.¹⁶ As the agents are cleared into the systemic circulation, systemic toxicity may occur. Intrathecal MTX is occasionally associated with mucositis and myelosuppression. Folinic acid is generally given in conjunction with MTX to minimize this complication.

Systemic chemotherapy may also have activity against leptomeningeal metastases. It has several advantages over intrathecal chemotherapy. Systemic chemotherapy will treat coexistent systemic disease, is not dependent on CSF

dynamics, and can be administered effectively in patients with CSF blocks. Chemotherapy administered systemically allows cytotoxic concentrations with bulky or intraparenchymal disease. A wide array of agents is available for systemic administration, and this method obviates an Ommaya reservoir or repeated lumbar punctures. As is the case in treating cerebral metastases, however, the BBB may limit CNS penetration of these agents.

Few studies have been performed on the use of systemic chemotherapy in the management of leptomeningeal metastases. Methotrexate administered at high doses achieves cytotoxic concentrations within the CNS.^{38,87} When MTX is administered with folinic acid rescue, systemic toxicity can be minimized. Authors of two studies have shown encouraging results with this regimen.^{38,55} Bokstein and colleagues compared patients prospectively treated in two separate trials differing only in the use of intrathecal chemotherapy. Its exclusion did not change the overall response to treatment, the median survival, or the proportion of long-term survivors. The rates of early and delayed intrathecal treatment-related complications were decreased significantly. Other study results have shown that the addition of systemic chemotherapy to intrathecal treatment can improve response rates. More recently, gefitinib and capecitabine have been shown to have activity against leptomeningeal metastases from NSCLC and breast cancer, respectively.^{36,43,53,78} More research is required to validate the use of systemic chemotherapy for the management of this complication.

ENHANCED CNS DELIVERY OF CHEMOTHERAPY

To circumvent the BBB, several alternative mechanisms of chemotherapy administration are being considered. The Food and Drug Administration has approved carmustine wafers for newly diagnosed glioblastomas multiforme. Such wafers are implanted within the surgical cavity at the time of tumor resection. Thus far, control rates of 100% have been reported for treated lesions.^{12,42} The obvious limitation of such an approach is that it may effectively treat only one aspect of a multicentric disease. The intraarterial administration of chemotherapy may facilitate penetration of the CNS by increasing the concentration of the delivered agent in the cerebral circulation. With this approach, the driving gradient across the BBB is optimized. Note, however, that intraarterial administration is more invasive and labor intensive, although available data suggest that it is safe when performed by experienced clinicians.⁶⁴ Iatrogenic BBB disruption, with osmotic agents or WBRT, may further augment BBB penetration.

CONCLUSIONS

Despite a long history of skepticism regarding chemotherapy for cerebral metastases, a growing body of evidence suggests that it may be an effective treatment modality. This issue will be increasingly relevant as therapies for non-CNS disease improve and the risk of CNS treatment failure increases. Several questions warrant further exploration. Do patients who require chemotherapy for systemic disease need to be treated with WBRT, or is chemotherapy alone sufficient? To what extent do individual chemotherapies penetrate the BBB in the setting of

intracranial disease? What is the effect of alternative methods of chemotherapy administration on outcome (for example, intraarterial chemotherapy, BBB disruption, convection-enhanced delivery, chemotherapy-impregnated wafers, and so forth)? Does liposomal encapsulation improve BBB penetration? Can chemotherapy prevent the development of cerebral metastases in high-risk patients? Can chemotherapy resistance be overcome with treatment sensitizers such as poly(adenosine diphosphate-ribose) polymerase inhibitors? Can the concomitant administration of chemotherapy and radiotherapy improve outcomes? Specifically, what is the role of temozolomide in patients with systemic cancer? The resolution of these and other issues will require well-designed clinical trials. Ideally, protocols should be disease specific and variables such as the extent of pretreatment, the presence of active systemic disease, and the concomitant use of corticosteroids should be controlled for. Studies should be adequately powered to allow appropriate statistical analysis. Optimal end points should be established, and clinical and radiographic response criteria standardized. It is well recognized that the majority of patients succumb to systemic disease rather than CNS failure; consequently, overall survival may not be the optimal end point. Furthermore, the quality of life and neurocognition, which are affected by the disease and its treatments, are increasingly being recognized as relevant in this population. Appropriate study control arms should be established; it is essential to consider these controls when determining the effectiveness of a therapy.

On the basis of the available data, it is difficult to establish recommendations for systemic chemotherapy for cerebral metastases. Before pursuing off-protocol therapies, patients must be educated regarding the extensive limitations of available data. In the absence of a clinical trial, it is reasonable in most circumstances to reserve chemotherapy as a salvage therapy following radiotherapy. Ideally, patients should be accrued to protocols and data collected in a systematic manner, to resolve many of the outstanding issues. It is also reasonable to minimize the use of corticosteroids to maximize the benefit of chemotherapy in patients with cerebral metastases.

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