OBJECTIVES:

To provide a summary of chemotherapy used in the management of malignant brain tumors, including a historical perspective, current standard therapies, and promising new therapies.

DATA SOURCES:

Published articles, research data, and reference books.

CONCLUSION:

Chemotherapy is used to treat several types of brain tumors, including primary central nervous system lymphomas, medulloblastomas, brain metastases, and malignant gliomas. New therapies, including cytostatic agents and molecular therapies, are being evaluated and used in the management of brain tumors.

IMPLICATIONS FOR NURSING PRACTICE:

It is essential for the oncology nurse to possess knowledge of the different types of brain tumors treated with chemotherapy, current chemotherapy regimens, new innovative therapies, and nursing management issues specific to this population.

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BRAIN TUMOR TREATMENT: CHEMOTHERAPY AND OTHER NEW DEVELOPMENTS

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MALIGNANT brain tumors are comprised of a number of different malignancies, including gliomas, medulloblastomas, primary central nervous system (CNS) lymphomas, and brain metastases. As a result of the multitude of tumors involving the CNS, the role of chemotherapy and the specific chemotherapeutic regimens are specific to the cell type of origin. Unfortunately, the role of chemotherapy in brain tumor patients is too often viewed as futile by health care professionals. The reality is that there are a number of distinct types of brain cancers within the brain, and the treatments and their outcomes vary greatly based on pathologic and histologic diagnosis. More recently, researchers are identifying new therapies based on increased knowledge of cellular and molecular biology. As these innovative therapies become more frequently used in the clinical setting, it is essential for the oncology nurse to understand these principles of therapy and the difference in these new agents compared with traditional cytotoxic chemotherapy.

Despite the differing treatment regimens, a shared issue among these CNS malignancies that affects the efficacy of chemotherapy and other systemically administered treatments reaching the tumor involves the blood-brain barrier (BBB). The BBB is a complex regulatory interface that impacts the potential effect that chemotherapy can have on a brain tumor. The BBB is composed of nonfenestrated capillary endothelial cells with tight intercellular junctions and it serves as a protective mechanism, making it difficult for certain agents to enter the CNS.[1] We know that some brain tumors produce BBB breakdown by the fact that gadolinium is seen in areas of tumor on magnetic resonance imaging studies,

and with this breakdown, systemically administered medications should have easier access reaching the brain. Some chemotherapy agents have difficulty crossing the BBB at effective dosages because of their molecular size or lipid insolubility. Administration of adequate dosages of chemotherapy to the brain can be limited by toxicities to the body, including bone marrow suppression, pulmonary, genitourinary gastrointestinal, hepatic and other systemic toxicities.

The remainder of this article reviews the use of chemotherapy in specific tumor types, including relevant historical uses, current standards of care, and new developments in the management of these patients. With gliomas accounting for 60% of all adult primary brain tumors, a large majority of brain tumor research lies within this area. Therefore, the review of glioma chemotherapy will provide increased depth, yet a comprehensive review will follow for primary CNS lymphoma, medulloblastomas, and brain metastases.

Primary CNS Lymphoma

Primary central nervous system lymphoma (PCNSL) is a rare, yet aggressive lymphoma that accounts for 4% of primary brain tumors, which is a noted increase in incidence compared with past decades.[2] PCNSL is defined as a lymphoma, usually B-cell, confined to the brain or spinal cord, without any systemic evidence of lymphoma. PCNSL is seen in both patients with and without AIDS, yet the natural history of the disease differs between these two populations.[3] Because of impaired immune function and high potential for opportunistic infections, chemotherapy is not a standard treatment for AIDS-related PCNSL. Therefore, the focus of this section is on chemotherapy for non-AIDS–related PCNSL.

PCNSL is most often detected on imaging studies as a contrast-enhancing lesion in the brain or spine parenchyma, yet PCNSL can also be seen as leptomeningeal disease or ocular lymphoma.[4] Although PCNSL is often evaluable only with a focal lesion on magnetic resonance imaging scan, it is considered a diffuse malignancy with the potential for spread throughout the CNS, requiring a "whole brain" treatment approach.

Whole brain radiation therapy (WBRT) has been the standard therapy for patients with PCNSL until recent studies using chemotherapeutic agents have shown more promising results.

While WBRT is able to provide initial complete response with radiographic imaging, these responses are not durable, resulting in rapid relapse with an overall median survival of less than 18 months.[5] Additionally, patients who undergo WBRT can experience significant neurotoxicity, especially in the elderly population, a subpopulation that is more frequently affected with PCNSL.[6] Because of the rapid rate of relapse and neurotoxicity associated with WBRT, chemotherapeutic treatment options have been and are continuing to be actively pursued. Popular strategies being evaluated include chemotherapy in combination with cranial irradiation, chemotherapy-only regimens, and other novel means of providing dose-intensive chemotherapy treatment, including blood-barrier disruption and autologous stem cell transplantation.

Combination chemotherapy with radiation has been evaluated by numerous researchers, resulting in more promising outcomes. A recent multi-centered phase II trial evaluated a treatment regimen consisting of high-dose intravenous methotrexate, procarbazine, vincristine, and intrathecal methotrexate, followed by WBRT, and completed with high-dose cytarabine. This complex treatment regimen resulted in a 94% response rate following induction therapy. Additionally, a median progression-free survival (PFS) of 24 months and an overall survival of almost 37 months were obtained.[7] The concern with these combination regimens is that neurotoxicity persists, similar to experiences of patients treated with WBRT alone; in this particular study, 15% of patients were found to have severe delayed neurotoxicity.[7]

Regimens consisting of high-dose chemotherapy with complete abandonment of up-front WBRT have also been evaluated. While many different chemotherapy agents and regimens have been considered, methotrexate is considered to be the most active agent in the treatment of PCNSL. The New Approaches to Brain Tumor Therapy, one of the National Institutes of Health-designated brain tumor consortiums, recently evaluated the use of high-dose methotrexate (8 gm/m^2) as initial treatment for PCNSL. Although data has not been published on overall survival, initial evaluation shows that median PFS was 13 months, and based on radiographic evaluation, 23 patients (74%) showed radiographic response with 12 complete responses (52%) and 5 partial responses (22%).[8] The evident benefit in the chemotherapy-alone

regimens is absence of late-onset neurotoxicity associated with WBRT. Despite the use of adjuvant chemotherapy, patients with PCNSL will frequently need to go on to receive cranial irradiation at the time of relapse; yet postponement of this toxic therapy can delay or prevent these devastating neurologic complications.

Other novel treatment techniques have been evaluated in an effort to deliver larger dosages of chemotherapy to the brain. These efforts include both blood-brain barrier disruption (BBBD) and autologous peripheral stem cell transplantation. BBBD has been studied in depth by researchers at Oregon Health Sciences University, along with other participating research centers. Reversible BBBD is achieved by intra-arterial infusion of hypertonic mannitol, allowing administration of dose-intensive chemotherapy. The role of BBBD has been studied in PCNSL at the time of initial diagnosis and recurrence. While some results have been promising, such as an estimated 42% 5-year survival,[9] this therapy entails complex administration requirements, the need for intensive care monitoring, and the potential for significant toxicity. High-dose chemotherapy with autologous stem cell transplantation continues to be evaluated; yet at this time, it is not clear that it provides an increased survival benefit. Additionally, the risk of severe toxicity exists, with this risk most significant in older patients.[10,11]

While a newly defined standard of care has not been agreed upon within the neuro-oncology community, there has been a trend away from WBRT and a move toward systemic chemotherapy for the adjuvant treatment of PCNSL. This shift in therapy has been associated with an increase in survival, along with a significant reduction in neurotoxicity when whole-brain radiation is avoided. Yet questions still exist. Ultimately, a decision needs to be made whether radiotherapy needs to be administered adjuvantly along with chemotherapy despite the negative sequelae or reserved for use in patients with relapsed disease.

Medulloblastoma

Medulloblastoma is the most common pediatric CNS malignancy, yet it occurs with much less frequency in the adult population. Medulloblastomas account for approximately 1% of malignant brain tumors in adults.[2] Because of the rare occurrence of medulloblastomas in the adult pop-

ulation, the vast majority of our treatment recommendations are taken from clinical research performed in the pediatric setting. Additionally, an attempt at gathering more information in adult medulloblastomas has been made through retrospective analyses of adult medulloblastoma patients, yet the downfalls in these evaluations include small sample size, evaluation over extended time intervals, and the use of heterogeneous treatment modalities.[12]

The standard therapy for medulloblastoma includes surgery with attempt at gross total resection, followed by craniospinal radiotherapy with a radiation boost to the tumor bed (posterior fossa). Adjuvant chemotherapy is advantageous in patients who are considered high risk, which is most frequently defined as (1) measurable residual disease within the posterior fossa, or (2) metastatic disease (abnormal enhancement involving the cerebellum, subarachnoid space, third or lateral ventricles, or extraneural disease).[13] The role of chemotherapy in "low or standard-risk patients" is not as clearly understood and continues to be evaluated in both the pediatric and adult setting.

Various chemotherapeutic regimens have been evaluated, with the most common treatment regimens including multiple chemotherapeutic agents. Several agents that have been evaluated and thought to be active in medulloblastomas include lomustine (CCNU), cyclophosphamide, vincristine, cisplatin, carboplatin, and etoposide.[14] Chemotherapy is used both as neoadjuvant and adjuvant treatment in high-risk patients at the time of initial diagnosis. In the event of recurrence, chemotherapy is typically used as salvage therapy, regardless of risk category.

Chemotherapy in Brain Metastases

Metastatic brain tumors are the most common cerebral tumors, occurring with a higher incidence than all primary brain tumors combined. On autopsy, 25% of patients with systemic cancer are found to have intracranial metastases.[15] Traditionally, surgery to accessible tumors and whole-brain irradiation are the standard treatment options for brain metastases, and recently the role of stereotactic radiosurgery has provided another promising treatment alternative. Chemotherapy is not frequently used for the management of metastatic brain tumors, but there are distinct settings were chemotherapy provides known benefit. It is clear that the BBB is breached

with brain metastases because they present as contrast-enhancing lesions on magnetic resonance imaging, suggesting that certain chemotherapy agents should be able to effectively reach the brain. While the accessibility of the BBB has an impact, the chemosensitivity of the primary tumor appears to be more predictive of responsiveness for brain metastases.[16]

Brain metastases from small cell lung cancer (SCLC) appears to be particularly chemosensitive compared with other systemic malignancies. Non–small cell lung cancer (NSCLC), choriocarcinomas, and breast cancers also have reports of beneficial response to chemotherapy.[16] In addition, while metastatic malignant melanoma has traditionally been considered nonresponsive to chemotherapy, recent studies with temozolomide have shown activity in melanoma, NSCLC, and other primary tumors.[17,18] Results of a recent phase II study in patients with metastatic melanoma showed activity with the combination of temozolomide and thalidomide; 31% of patients (12 of 38) had measurable benefit, although median survival remained poor at less than 10 months.[19]

The use of molecular therapy is being evaluated with various solid tumors, and in select cases, a beneficial response has been identified in the management of NSCLC brain metastases. Iressa (gefinitib; AstraZeneca, Wilmington, DE), an epidermal growth factor receptor inhibitor, received approval by the US Food and Drug Administration in 2003 for the treatment of recurrent NSCLC. While registration trials were ongoing, an Expanded Access Program was developed to make gefinitib available to patients with relapsed NSCLC who did not meet the study criteria for the formal registration trials. This program allowed many NSCLC patients with brain metastases to receive gefinitib. Gefinitib showed encouraging results, with many published case reports of NSCLC patients with brain metastases experiencing both radiologic and clinical response with improvement in neurologic function.[20,21]

MALIGNANT GLIOMAS

Malignant gliomas are the most common and typically the most aggressive primary tumor seen in the CNS. Glial tumors are composed of astrocytomas, oligodendrogliomas, anaplastic oligoastrocytomas (AO), ependymomas, and glioblastoma multiforme (GBM), and account for over 60% of primary brain tumors. Despite significant evaluation with laboratory and clinical research, the benefit of chemotherapy in this deadly tumor type, particularly in GBM, has long been debated. Yet recently there has been confirmative data that has provided much-needed results to support the use of adjuvant chemotherapy in glioblastoma multiforme.

Surgery and external-beam radiation therapy are considered the standard of care for the initial treatment of high-grade glioma. Historically, the use of chemotherapy has only shown minimal, if any, benefit in the treatment of high-grade gliomas, and therefore, its use has been strongly questioned within the medical community. To further support the futility of chemotherapy in high-grade gliomas, the Medical Research Council recently found no significant benefit in overall survival when evaluating the use of adjuvant chemotherapy. The Medical Research Council published findings from a large multi-institution, randomized trial evaluating the use of PCV (procarbazine, CCNU, and vincristine) chemotherapy following radiation therapy, with an overall median survival less than 10 months compared with patients who received radiation alone who had an overall survival of 9.5 months.[22]

Despite these discouraging results, there have been more optimistic research findings that support the use of chemotherapy in the management of malignant gliomas. Two different meta-analyses have shown a modest, yet significant survival benefit in patients with malignant gliomas who received radiation and chemotherapy, versus patients who received radiation therapy only.[23,24] Specific to the adjuvant setting, results from a recent phase II, multi-institution trial provide convincing data to support the role of adjuvant chemotherapy in the management of malignant gliomas. The study evaluated the efficacy of concomitant radiation therapy and temozolomide followed by adjuvant temozolomide in patients with newly diagnosed GBMs. Results from this study showed a median survival of 16 months, which far exceeds the expected median survival of 9 to 12 months in GBM.[25] There are criticisms of this trial, regarding median age, Karnofsky performance status, and extent of resection. Nonetheless, the results of this study provide definitive support for the use of adjuvant chemotherapy in the most aggressive tumor type, GBM, which historically has been considered nonresponsive to chemotherapy.

Most recently the EORTC (European Organization for Research and Treatment of Cancer and the NCIC (National Cancer Institutes of Canada presented multicentered phase III randomized trial data confirming the benefit of temozolomide chemotherapy in the adjuvant setting. The EORTC/NCIC study compared newly diagnosed GBM patients who were randomized to receive radiation therapy alone versus radiation therapy with concurrent temozolomide, followed with up to 6 cycles of adjuvant temozolomide. The data showed a statistically significant benefit in median survival; patients treated with radiotherapy alone had a median survival of 12 months versus 15 months in patients treated with radiotherapy with temozolomide. Additionally, 2-year survival data was collected with 8% of persons alive at 2 years who had received radiotherapy alone, in comparison to more than a quarter (26%) of the patients who received the radiotherapy with temozolomide.[26] The temozolomide chemotherapy agent was administered both in the concurrent and adjuvant setting, therefore future studies will be needed to clarify if the benefit truly lies in the combination of concurrent and adjuvant administration or by solely adding adjuvant chemotherapy following radiation therapy. Overall, this trial has provided pivotal information for the neuro-oncology community to support the use of adjuvant chemotherapy for patients diagnosed with glioblastoma multiforme, more clearly defining the standard of care for this patient population.

Chemotherapy is used in both the adjuvant and recurrent setting in the management of malignant gliomas. In gliomas, alkylating agents, nitrosourea, and topoisomerase inhibitors are the most active cytotoxic agents. In the past decade, cytostatic agents have been added to treatment protocols for glioma patients, mainly in the recurrent setting. Cytostatic agents act by causing changes in the biology of the tumor cells without directly causing cell death. Below, the use of cytotoxic chemotherapy, cytostatic agents, and various combination regimens are reviewed, with clinical research cited to support the use of these agents.

Nitrosoureas

The nitrosoureas have the longest history of use and have traditionally been considered the most active chemotherapeutic agents for the treatment of malignant gliomas. The two most common nitrosoureas used in the management of malignant gliomas are carmustine (BCNU) and CCNU. Nitro-

soureas are lipid-soluble agents that are able to cross the BBB with greater ease than other agents. BCNU has mainly been evaluated as single-agent therapy, while most data with CCNU is in combination therapy, and will be discussed in greater detail in the next section. Nitrosoureas have been studied and are used in both adjuvant and recurrent disease. BCNU is given at a dosage of 150 to 200 mg/m^2 intravenously every 6 to 8 weeks, depending on if the patient has been pretreated. In the two meta-analyses, which showed survival benefit for patients who received radiotherapy plus chemotherapy, BCNU was the most common chemotherapy used.[23,24] The most common toxicities associated with the nitrosoureas include myelosuppression, fatigue, nausea, vomiting, and the risk of drug-induced pulmonary fibrosis increases with cumulative dosages.

PCV (Procarbazine, CCNU, Vincristine)

PCV has a long history in the management of malignant gliomas. Until recently, this chemotherapy regimen was thought to be superior to BCNU in treating patients with anaplastic astrocytomas and anaplastic AOs in the adjuvant setting.[27] Yet, findings from a recent retrospective review showed no superiority in survival for patients receiving PCV over single-agent BCNU therapy.[28] The PCV regimen is based on a 6-week cycle where procarbazine is given at a dosage of 60 mg/m^2/day daily from day 8 to 21, CCNU 110 mg/m^2 on day 1, and vincristine 1.4 mg/m^2 intravenous push on day 14 and day 29, typically, with a maximum of six courses of PCV. Potential side effects include myelosuppression, nausea, vomiting, peripheral neuropathy secondary to vincristine, and pulmonary fibrosis secondary to CCNU. No more than six cycles of PCV should be given and CCNU should not be used if another nitrosourea-based therapy was given adjuvantly, because of the potential for irreversible myelosuppression and pulmonary toxicity from cumulative doses of nitrosoureas. Single-agent procarbazine and single-agent CCNU are also possible treatment options in the recurrent setting.[29,30]

Temozolomide

Temozolomide (Temodar; Schering Corp, Kenilworth, NJ) is the first oral chemotherapy agent to be approved by the US Food and Drug Administration for use in the treatment of malignant gliomas in the past 20 years. Temozolomide was approved in 1999 for use in patients with anaplastic

astrocytomas who have failed prior treatment with a nitrosourea and procarbazine, yet is clinically being used in both the adjuvant and recurrent setting for patients with both grade 3 and 4 malignant gliomas. Temozolomide, a methylating agent, is an oral chemotherapeutic agent that is commonly administered according to one of the following regimens. The most common regimen used is given at a dose of 150 to 200 mg/m^2 daily for 5 days, followed by a 23-day rest. Temozolomide can be administered for up to 24 months if there is no evidence of tumor progression during this interval. The alternate regimen that has been evaluated in the setting of concurrent radiation therapy is low-dose temozolomide at 75 mg/m^2 daily during radiation therapy, followed by a 4-week rest, and then the earlier mentioned 150 to 200 mg/m^2 regimen is resumed 4 weeks after the cessation of radiotherapy.

In the adjuvant setting, the concurrent temozolomide and radiation study by Stupp et al[25] provides the most encouraging evidence of temozolomide's benefit for adjuvant therapy in glioblastoma patients. Additionally, there are ongoing studies to confirm the use of temozolomide in upfront setting. The use of temozolomide at tumor recurrence also has well-documented support. A multicentered trial showed a 22% overall response rate (complete or partial response) in patients with refractory anaplastic astrocytomas.[31] A phase III study evaluated the use of procarbazine compared with temozolomide in GBM patients at first relapse. This trial resulted in valuable information regarding survival as well as toxicity of the therapy. The 6-month PFS was 21% for patients receiving temozolomide compared with 8% in patients receiving single-agent procarbazine.[32] Patients taking temozolomide experienced improved quality of life at 6 months compared with procarbazine group and this is likely influenced by the difference in PFS at 6 months.[33] While temozolomide is generally well-tolerated, potential side effects include myelosuppression, nausea, vomiting, rash, constipation. and fatigue.

Carboplatin

Carboplatin is a platinum-based alkylating agent that interferes with DNA replication by causing DNA cross-linkage. Carboplatin is administered intravenously at a dose of 5 to 7 area under the curve units once every 3 to 4 weeks, depending on the patient's prior chemotherapy history. Carboplatin is primarily used in patients with recurrent disease, with several phase II studies showing activity in recurrent malignant gliomas. Response rates (partial response or stable disease) ranged from 29% to 50% with a median time to progression ranging from 8 to 19 weeks, suggesting marginal responses to carboplatin.[34-36] Neutropenia and thrombocytopenia were the dose-limiting toxicities; therefore blood counts need to be followed closely. Other side effects include anemia, nausea, vomiting, fatigue, and the potential for peripheral neuropathy with cumulative doses.

Irinotecan

Irinotecan (Camptosar; Pfizer Inc, New York, NY) is a semi-synthetic analogue of camptothecin, an alkaloid extract from the Chinese tree camptotheca acuminata. Irinotecan shows antitumor activity by interacting with topoisomerase I, resulting in DNA double-strand breaks. Irinotecan is administered intravenously and there are various treatment schedules, with the most common regimen in malignant gliomas being 300 to 350 mg/m^2 intravenously every 3 weeks. Additionally, it was shown that enzyme-inducing anticonvulsants affect the metabolism of the irinotecan, and therefore larger dosages are required in this patient population to obtain efficacy.[37] Irinotecan has been evaluated in the recurrent setting and has shown activity in a subset of patients with recurrent malignant gliomas. In phase II studies, partial responses of 14% to 15% were shown, along with stable disease ranging from 14% to 55%.[37,38] Unfortunately, similar to other chemotherapy options, these responses have not proven to be durable, as seen with a median time to tumor progression as short as 6 weeks.[37]

Irinotecan and temozolomide is a new combination chemotherapy regimen currently being evaluated for the treatment of recurrent GBMs, with initial evaluation providing promising results. Preliminary analysis of this combination therapy showed impressive outcomes, with an initial response rate of 25% partial responders and 50% stable disease, in addition to a 38% 6-month PFS. Based on these results, future studies are being developed to provide further information regarding this potentially beneficial combination.[39]

Etoposide

Etoposide is a cell-cycle–specific agent generally reserved for use in glioma patients with recurrent disease.[40] Etoposide works by causing single-strand breaks in DNA and prevents mitosis by inhibiting DNS synthesis. Etoposide can be given

both orally and intravenously, yet because of its limited access to dividing cells, it is thought that continual oral administration is superior. Response rates have been reported as high as 42%, yet unfortunately durability is lacking, as seen with the median time to tumor progression of only 8.8 weeks.[41] Oral etoposide is typically given at a dosage of 50 mg/m^2 daily for 21 days. Alopecia, myelosuppression, nausea, vomiting, and fatigue are common side effects related to etoposide.

Cytostatic Agents

The role of cytostatic agents in the treatment of high-grade gliomas has become more prominent over the past decade. Recent laboratory and clinical research have identified new cytostatic treatments that work by various mechanisms of action, including differentiation, angiogenesis inhibition, and inhibition of protein kinase activity. These new cytostatic agents have provided the field of neuro-oncology with additional treatment options in a disease with limited options.

Tamoxifen. Tamoxifen is an oral agent that traditionally has been used to treat estrogen-receptive breast cancers, providing tumor control caused by the blockade of estrogen receptors. Tamoxifen is a cytostatic agent thought to work by an entirely different mechanism of action in gliomas. Tamoxifen used at high dosages (approximately 4 to 8 times the standard dose in breast cancer) causes inhibition of protein kinase C to occur, resulting in regulation of glioma cell growth by modulating intracellular signal transduction. Studies have shown that 17% to 25% of patients experienced partial responses, with an additional 19% to 46% of patients having stable disease.[42,43] Tamoxifen is generally prescribed at a dose of 160 mg daily for women and 200 mg daily for men. Tamoxifen is generally very well tolerated, yet toxicities include an increased risk of deep venous thrombosis, endometrial changes, menopausal symptoms, retinopathy, and fatigue. The potential for thrombotic events concerns for glioma patients, because their risk may be compounded by their disease and by associated neurologic deficits resulting in immobility.

Cis-retinoic acid. Cis-retinoic acid (CRA) is a synthetic vitamin A analogue and functions as a differentiating agent in the treatment of malignant gliomas. Retinoic acids are capable of interfering with tumorigenesis by promoting cell differentiation in tumor cells, thus preventing the uncontrolled cell growth associated with tumors. Promo-

tion of differentiation can lead to apoptosis (programmed cell death). CRA is administered orally at a 100 mg/m^2/day for 21 days, followed by a 7-day break. The most common toxicities associated with high-dose CRA use are dermatologic complications. Additionally, elevated cholesterol, triglycerides, and liver enzymes can occur; therefore, liver enzymes and lipid panels need to be monitored at regular intervals. Teratogenic effects have been documented. Therefore, it is imperative that patients are educated on this risk and the need for effective forms of birth control. Finally, patients should be counseled to minimize other forms of vitamin A and retinols because of the known association between vitamin A ingestion and pseudotumor cerebri (idiopathic intracranial hypertension). Symptoms of pseudotumor cerebri mimic those of increased intracranial pressure secondary to tumor growth, making it difficult to differentiate between signs of tumor growth versus pseudotumor cerebri.

CRA has been studied in malignant gliomas as a single-agent cytostatic therapy and in combination with other cytotoxic chemotherapy agents. In a single-institution phase II study, patients with recurrent malignant gliomas were treated with single-agent CRA for 3 weeks, followed by 1-week rest. A 53% overall initial response rate occurred, with the majority of patients experiencing either a minor response or stable disease, supporting the fact that CRA provides cytostatic response.[44] Additionally, CRA has been evaluated with temozolomide for recurrent disease and has shown potential benefit in patients with malignant gliomas, primarily GBM patients. The combination of temozolomide and CRA resulted in 6-month PFS of 32%, versus 21% in patients who received single-agent temozolomide.[45]

Thalidomide. Thalidomide was originally developed in the 1960s as a sedative, and was commonly used in pregnant women for its beneficial sedative and antiemetic properties. Because of the development of birth defects, most significantly abnormal limb development, thalidomide was quickly removed from public use. Yet, over the past two decades, cancer researchers have evaluated its anti-angiogenic properties, leading to studies in malignant gliomas, as well as in other cancers. Because of the highly vascular nature of high-grade gliomas, angiogenesis inhibitors such as thalidomide have been evaluated. In a single-institution phase II study, single-agent thalidomide was evaluated; 16 of 36 patients had an

initial response with two complete responses, two partial responses, and 12 patients with stable disease. Unfortunately, median time to progression was only 10 weeks.[46] Thalidomide has been studied in malignant gliomas at doses ranging from 100 to 1,200 mg/day. The most frequent side effects associated with thalidomide include somnolence, constipation, peripheral neuropathy, and deep vein thrombosis.

An analog of thalidomide, CC-5013, which is thought to have similar angiogenesis inhibition, yet to be a significantly more potent cytostatic agent is currently being evaluated in phase I studies. There have been preliminary reports of tumor stabilization in glioblastoma patients receiving CC-5013, yet follow-up evaluation is needed to provide more information regarding the true potential of this thalidomide-like agent.[47]

Combination Therapies in Gliomas

The prior review of cytotoxic and cytostatic agents provides an overview of the most commonly prescribed medications that are commercially available for the treatment of malignant gliomas. For the most part, combination chemotherapy regimens have not been shown to be superior to single-agent regimens in the management of malignant gliomas. Alternatively, the combinations of cytotoxic and cytostatic agents are more commonly used in an effort to optimize therapeutic benefits. Because of the differing side-effect profiles between these two classes of medication, cytotoxic and cytostatic agents can safely be used in combination with an attempt to maximize efficacy without causing increased toxicity. Combinations that have been formally evaluated include temozolomide and CRA and BCNU and thalidomide,[43,48] yet in the clinical setting, many variations of these agents are combined.[40]

SPECIAL GLIOMA POPULATIONS

There are particular subtypes of gliomas that deserve special mention in relation to the role of chemotherapy. Patients with anaplastic AOs have been found to be remarkably sensitive to chemotherapy and carry a better prognosis when compared with other high-grade gliomas.[49,50] Approximately two thirds of patients with AO have positive responses to chemotherapy. The PCV regimen is the most commonly used in AO, yet recent studies also show that temozolomide pro-

vides significant responses among patients with anaplastic AOs.[51] Additionally, specific genetic alterations have been identified in a large population of AO patients. Genetic analysis has identified that the combined loss of chromosomes 1p and 19q is associated with both improved chemosensitivity and longer recurrence-free survival following chemotherapy.[52]

Low-grade gliomas are slow-growing tumors that primarily affect young adults. Unfortunately, the natural history of this disease suggests that tumor recurrence with transformation to a malignant glioma is the likely outcome.[53] Typically, treatment for low-grade glioma includes surgical intervention with or without radiation therapy, although controversy exists among these therapies. The role of chemotherapy has traditionally been reserved for the time of recurrence, at which point, the tumor is biologically behaving as a high-grade tumor, yet the role in the adjuvant setting is not as well-supported. In a prospective study, patients with low-grade astrocytomas with incomplete tumor resection were randomized to treatment with radiotherapy or radiotherapy plus CCNU chemotherapy. Results from this study showed no survival advantage for the patients who received chemotherapy, therefore undermining a significant role for adjuvant chemotherapy in low-grade astrocytomas.[54] Alternatively, adjuvant chemotherapy in low-grade AO appears to have more significant activity. A recent study using PCV chemotherapy has shown response rates as high as 52%, yet further follow-up is needed to understand the extent of overall benefit in regards to time to tumor recurrence and overall survival.[55]

MOLECULAR THERAPIES FOR GLIOMAS

Advances in molecular and cellular biology have increased our understanding of the process of oncogenesis. This knowledge has resulted in the development of novel cancer treatment approaches aimed at targeting specific steps with this process. Therapeutic benefits have already been seen with this type of directed therapy in other tumor types, such as lung cancer and chronic myelogenous leukemia.[56,57] The field of neuro-oncology is at the forefront of this research with targeted molecular therapy for a multitude of reasons. First, the benefit of traditional chemotherapeutic agents, particularly in glial tumors, remains suboptimal despite decades of research.

Additionally, malignant gliomas have distinct molecular abnormalities that can serve as targets for therapies. It is our hope that these targeted therapies will provide better treatment options in the future.

A large majority of clinical trials in gliomas are being conducted with this small-molecule therapy, which is aimed at interfering with intracellular signal transduction in various ways. Some of the most common targets for therapies that have been identified in gliomas include kinases, farnesyltransferase, and matrix metalloproteinases (MMPs). Molecular therapies directed at these cellular targets are being developed and evaluated with significant enthusiasm in glioma patients.

Protein kinase pathways are involved in the regulation of cell growth and have been implicated in the development of several cancers. Therapies developed to target protein kinases are directed at both cell-surface receptor sites, as well as specific steps within intracellular signaling pathways. The most active protein kinase pathways that have been identified in glioma cell growth include the Ras/MAP-kinase pathway and the P13-kinase (PTEN/Akt) pathway, in addition to the process of angiogenesis with VEGFR tyrosine kinase.

Amplification and mutation of EGFR (epidermal growth factor receptor) and PDGFR (platelet-derived growth factor receptor) along the MAP-kinase pathway have provided targets for directed therapies with several agents, including ZD1839 (gefinitib; Iressa), OSI774 (Tarceva, erlotinib; OSI Pharmaceuticals, Melville, NY) and STI-571 (Gleevec, imatinib; Novartis, Basel, Switzerland) that are being evaluated in malignant gliomas. EGFR has been heavily evaluated in both laboratory and clinical research because aberrations of EGFR are seen in high frequency in malignant gliomas; EGFR is overexpressed in up to 50% of GBMs.[58] Additionally, deletions and mutations of PTEN along the PI3-kinase (PTEN/Akt) pathway provide additional targets, with agents such as rapamyacin, CCI-779, and RAD-001. Finally, there have been a multitude of antiangiogenesis agents directed at VEGF (vascular endothelial growth factor) and its receptors, which are involved in the promotion of new vessel formation, therefore providing blood supply for tumor growth.

Another area of targeted molecular therapy in gliomas is farnesyltransferase inhibitors, which are primarily directed at the Ras proteins and the enzyme farnesyltransferase. Ras proteins are cell membrane-associated proteins that have been implicated in glioma growth. Ras proteins are responsible for cell signaling that results in various cellular effects, including proliferation, survival, and angiogenesis.[58] Farnesyltransferase enzymes are responsible for initiating the first step in the activation of Ras proteins (which affect cell signaling). This process of farnesylation is critical for Ras maturation and function. Farnesyltransferase inhibitors selectively block farnesylation, the activation of Ras proteins, and therefore interfere with cellular proliferation. R115777 is a farnesyltransferase inhibitor that has undergone initial studies in malignant gliomas, and continues to be evaluated.

Lastly, MMP inhibitors are being developed to prevent glioma cells from being able to invade and spread. One of the major roles of MMPs is to degrade the basement membrane and the extracellular matrix, resulting in an environment more conducive for tumor cells to invade and spread. MMPs are overexpressed in gliomas as well as other cancers. Therefore, MMP inhibitors, including Marimastat (British Biotech, Oxford, UK) and Prinomastat (Agouron Pharmaceuticals, San Diego, CA), are attempting to arrest tumor growth by interfering with this process.[59]

Identification of specific targets along cell-signaling pathways responsible for tumorigenesis has led to evaluation of these various molecular therapies (Table 1). As we learn more about molecular biology, it is evident that tumor growth is dependent on multiple signaling pathways for tumor cell proliferation and survival. While previous efforts have focused on single-agent therapy directed at specific target, in the future, combination therapies will be needed to inhibit multiple steps within these aberrant signal-transduction pathways.[59] Ultimately, as our understanding of cellular and molecular biology continues to grow, the tumor tissue and molecular features within the tissue along with traditional histopathologic findings will allow us to more accurately diagnose and treat gliomas, hopefully resulting in more efficacious therapies for the patient.

NURSING CONSIDERATIONS

The chemotherapeutic treatment options for brain tumor patients vary greatly based on specific tumor types. It is important for the oncology nurse to understand the multitude of CNS

TABLE 1.
Common Targets for Molecular Therapies in Gliomas[59]

Intracellular Targets	Function of Molecular Therapy	Examples of Experimental Therapies
MAP-kinase pathway		
EGFR	Inhibition of EGFR	OSI-774 (erlotinib)
		ZD-1839 (gefinitib)
PDGFR	Inhibition of PDGFR	STI-571 (imatinib)
P13-Kinase Pathway	Inhibition of mTor, an enzyme activated in this pathway	Rapamyacin
PTEN/mTor		CCI-779
		RAD-001
VEGF/VEGFR	Inhibition of new vessel formation	SU5416
		PTK787
Farnesyltransferase/ Ras proteins	Inhibition of farnesylation	R11577
MMPs	Inhibition of MMPs, arresting the process of tumor invasion	Marimastat
		Primostat

Abbreviations: MAP, mitogen-activated protein kinase pathway; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; PTEN, phosphatase and tensin homolog on chromosome 10; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; MMP, matrix metalloproteinase.

tumors, their standard treatments, and other novel therapies being evaluated, such as cytostatic and molecular therapies. Additionally, other patient care issues important to the brain tumor patient receiving chemotherapy include management of drug-induced toxicities and problems that arise from steroid use and antiepileptic therapy.

Management of Toxicities

Management of chemotherapy side effects in a brain tumor population calls for the same high standards of care that exist for the general oncology population, with careful attention to the management of myelosuppression, nausea, and vomiting. Because of the risk of intracranial infections and hemorrhages, close monitoring for neutropenia and thrombocytopenia is essential, as these risks can be greatly compounded by the effects of cytotoxic therapy.[60] Additionally, aggressive management of chemotherapy-induced nausea and vomiting is needed because it can lead to difficulty in recognizing signs of increased intracranial pressure. In addition, it can increase a patient"s risk of aspiration, and may result in missed doses of steroids and anticonvulsants, which all can lead to negative sequelae. The use of serotonin-reuptake inhibitors (eg, ondansetron, granisetron, dolasetron, palonosetron) should be used generously to minimize the potential for nausea and vomiting.[60]

As new cytostatic and molecular therapies are being developed, the common toxicities associated with cytotoxic therapy may not exist. Toxicity profiles with these new agents are in the process of being identified, requiring the careful assessment and innovative management of oncology nurses. For example, dermatologic and gastrointestinal effects have been associated with several of the EGFR inhibitors, while an increased risk of thromboembolic events has been associated with angiogenic inhibitors. The use of standardized assessment tools will be helpful in recognizing the toxicities that result from these therapies. As adverse effects are linked to specific therapies, the opportunity exists for oncology nurses to be instrumental in the development of appropriate symptom management specific to these therapies.

Issues Related to Dexamethasone Therapy

The use of steroids, such as dexamethasone, are common in brain tumor patients in an effort to control increased intracranial pressure and minimize the neurologic deficits that can occur because of a mass lesion in the brain. Unfortunately, the use of steroids comes with known risks, which can be compounded in patients on chemotherapy. Long-term steroid use causes immunosuppression, resulting in a reduction of

lymphocytes. Steroid-induced lymphopenia predisposes patients to serious infections, specifically including pneumocystis carinii pneumonia (PCP). Retrospective reviews of brain tumor patients showed that the development of PCP is associated with dexamethasone use, lymphopenia, and high-dose chemotherapy. Based on these results, prophylactic therapy is encouraged in all brain tumor patients with lymphopenia or prolonged dexamethasone therapy.[61] Agents used for PCP prophylaxis include trimethoprim-sulfamethoxazole, dapsone, and pentamadine, with trimethoprim-sulfamethoxazole generally considered first-line therapy.

Effect of Anticonvulsant Therapy on Metabolism of Chemotherapy

Patients with malignant brain tumors are frequently on anticonvulsant therapy for seizure control and prophylaxis. Certain anticonvulsants, such as phenytoin, carbamazepine, and phenobarbital, use the P-450 enzyme system, and as previously mentioned, can affect the metabolism of certain chemotherapy agents, resulting in subtherapeutic dosages administered to the patient.[37] Because of the effect of enzyme-inducing antiepileptic medication on chemotherapy metabolism, most recent clinical trials have a separate phase I (dose-finding) trial for patients taking antiepileptic medication.[62] As new cytostatic and molecular therapies are being evaluated, the interaction between these agents and antiseizure medications will need to be identified to allow for optimal dosing.

CONCLUSION

Malignant brain tumors include a variety of tumor types with specific chemotherapy regimens based on the pathologic diagnosis. All too often, health care professionals and the public consider chemotherapy treatments for brain tumor patients to be futile. Recent advances with chemotherapy trials have already provided patients with new treatment options that can extend survival and improve quality of life, with a decrease in potential toxicities. Additionally, the current focus on the use of cytostatic agents and small-molecule therapies provide a renewed optimism that these novel therapies will improve outcomes for patients with malignant brain tumors.

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