Chemotherapy for Brain Tumors

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Traditionally, cytotoxic drugs have played a limited role in the treatment of brain tumors, but important advances in chemotherapy have occurred during the past decade. Certain central nervous system (CNS) malignancies are gradually, the treatment of adults and children with malignant brain tumor is improving. Structural and functional MRI and intraoperative cortical and subcortical mapping studies in awake patients are leading to safer, more complete resections, and, for most types of brain tumor, complete resection is associated with a substantially better outcome. As a consequence of CT- and MRI-guided stereotactic biopsy, unresectable tumors can be sampled safely and a precise diagnosis established in most instances. This greater diagnostic accuracy may lead, in some cases, to the selection of specific, more effective postoperative therapies.

New radiation therapy techniques, such as three-dimensional conformal radiotherapy and fractionated stereotactic radiotherapy, by limiting the volume of normal brain tissue irradiated, lessen the risk and severity of delayed neurotoxicity without sacrificing the tumor-controlling benefits of higher doses of radiation. In selected patients, stereotactic radiosurgery and interstitial radiotherapy (brachytherapy) permit intensive irradiation of small tumors in noneloquent regions of the brain. These methods enhance tumor control with acceptable or manageable toxic effects. With regard to medical management, the growing network of sophisticated physicians (eg, oncologists, pediatricians, neurologists) cognizant of the special problems and needs of adults and children with cancers of the nervous system, together with the emergence of multidisciplinary brain tumor treatment centers, is enhancing patient care.

Traditionally, cytotoxic drugs have had a limited role in the treatment of patients with malignant brain tumor, and progress in the development of truly effective systemic chemotherapies has been slow. However, important advances in the chemotherapy of malignant brain tumors have occurred during the past decade. In much the same way that surgical and radiotherapeutic techniques have become increasingly refined, so, too, has chemotherapy. It is now evident that the many types of central nervous system (CNS) malignancies differ in their response to cytotoxic drugs and that some CNS tumors, such as primary CNS lymphoma, medulloblastoma, oligodendrogloma, and intracranial germ-cell tumors, are remarkably chemosensitive. Within 10 years, it is likely that several classes of malignant brain tumor will be treated initially, primarily, or exclusively with systemic chemotherapy. This article will highlight advances in the chemotherapy of brain tumors, focusing on the chemosensitive CNS malignancies, but also will include some data on the potential use of cytotoxic and cytostatic chemotherapeutic agents in other, less chemosensitive tumors, such as glioblastomas and anaplastic astrocytomas. Lastly, a discussion of future directions that may hold promise, including high-dose chemotherapy with stem-cell rescue, blood-brain barrier disruption, and regional treatment using controlled-release biodegradable polymers, is included.

Primary CNS Lymphoma

Lymphomas of the brain parenchyma, usually of B-cell origin, were once considered rare tumors that occurred almost exclusively in older adults (ie, in patients > 60 years old). Now, however, they are being diagnosed increasingly in younger patients and those with iatrogenic or AIDS-associated chronic immunosuppression. An extensive search for an occult systemic lymphoma is unwarranted in most instances of CNS lymphoma, as these intermediate- or high-grade lymphomas rarely arise or spread systemically. Lesions may be single or multiple and may involve any region of the CNS, including the cerebral hemispheres, cerebellum, brainstem, or spinal cord. In an immunocompetent patient, the typical primary CNS lymphoma appears on MRI or CT as a discrete homogeneously enhancing lesion with little peritumoral edema or displacement of adjacent structures (ie, mass effect). In immunocompromised patients, particularly those with AIDS, CNS
lymphomas may be nonenhancing or have other atypical radiographic features. Primary CNS lymphomas often are periventricular in location, and, not surprisingly, at diagnosis neoplastic lymphocytes are found in the cerebrospinal fluid (CSF) in approximately one-third of cases.[1] Primary CNS lymphomas restricted to the leptomeninges also have been described. Ocular involvement is a unique feature of CNS lymphoma (not seen with other primary CNS malignancies), which occurs at diagnosis or subsequently in 20% of patients. Surgery is essential for diagnosis but has little therapeutic role in this diffusely infiltrating, multifocal neoplastic process. Many CNS lymphomas, perhaps 40%, are exquisitely corticosteroid-sensitive—a property that is advantageous therapeutically but can complicate the diagnostic process. Large tumors may regress completely in the time it takes to organize a stereotactic biopsy procedure. [2,3] If a primary CNS lymphoma is suspected, clinically or radiographically, and the patient is stable, corticosteroids should be withheld until the day of surgery, otherwise there may be no target for the surgeon or the tissue retrieved may be necrotic or nondiagnostic. Rapid tumor lysis, presumably via a steroid-initiated apoptotic cell death pathway, is another unique feature of primary CNS lymphoma. These tumors also are radiosensitive, and for many years whole-brain radiotherapy was the standard treatment. Radiation alone produced a complete clinical and radiographic response in 80% of patients. Although responsive to radiotherapy, most patients with primary CNS lymphoma died as a consequence of recurrent disease 12 to 18 months after initial treatment. Rare young immunocompetent patients with lymphoma enjoyed long-term survival with steroids and whole-brain radiation therapy, but serious neuropsychological and neuroendocrine toxicities due to radiation meant that permanent tumor control sometimes came at a high price.

Chemotherapy

After recurrent CNS lymphomas were observed to respond dramatically to methotrexate, CHOP (cyclophosphamide, doxorubicin HCl, Oncovin, and prednisone), CHOD (cyclophosphamide, doxorubicin HCl, Oncovin, and dexamethasone), BACOD (bleomycin, Adriamycin, cyclophosphamide, Oncovin, and dexamethasone) and PCV (procarbazine, CCNU, and vincristine), cytotoxic agents were added to radiotherapy and prescribed at diagnosis.[4-7] High-Dose Methotrexate—Although no standard chemotherapeutic regimen has emerged, among the most promising regimens is high-dose methotrexate. Methotrexate is neurotoxic in irradiated patients, causing a leukoencephalopathy, but is safe and effective when given neoadjuvantly. Neoadjuvant high-dose methotrexate has doubled the median survival time for patients with primary CNS lymphoma from 12 to 18 months to more than 40 months. Two patterns of failure may account for the particular success of the methotrexate-based chemotherapeutic strategies of DeAngelis et al[8] and Neuwelt et al[9]. First, early recurrences at distant brain sites have occurred with regimens that do not contain CNS-penetrating drugs (eg, CHOP, CHOD, and BACOD). Second, leptomeningeal recurrences have developed when initial treatment does not include intrathecal chemotherapy.[1,10,11] Thus, early treatment of subclinical, subradiographic, microscopic lymphoma behind an intact blood-brain barrier, remote from bulky lesions, and early treatment of the CSF compartment may be essential components of regimens with curative potential. DeAngelis et al use drugs that, except for vincristine, cross the blood-brain barrier and give intrathecal methotrexate (Table 1), while Neuwelt et al ensure drug delivery to the brain and CSF by transiently disrupting the blood-brain barrier with mannitol. Chamberlain et al[12] also have reported median survival times in excess of 40 months in patients treated with hydroxyurea plus radiation followed by PCV—another CNS-penetrating formula. Regimens Under Investigation—First-line regimens for systemic lymphoma, such as EDHAP (etoposide, dexamethasone, ara-C, and Platinol) or ADHAP (Adriamycin, dexamethasone, ara-C, and Platinol) followed by radiotherapy (with or without intrathecal methotrexate), are under evaluation. Two studies have examined drug combinations with superior antilymphoma activity but inferior brain and CSF penetration (CHOP and CHOD) followed by whole-brain radiation.[13,14] No improvement in survival was found over radiation therapy alone, and toxicity from chemotherapy was a significant problem. Regimens that incorporate better drugs for bulky disease but also treat microscopic disease and the CSF compartment with intravenous and intrathecal methotrexate have been proposed.[15] Immunocompromised patients with CNS lymphoma—may benefit from chemotherapy, but most respond poorly, tolerate treatment poorly, or succumb to opportunistic infections.[16] The role of chemotherapy for AIDS-related CNS lymphoma may evolve in the future as more effective therapies for the primary infection enable patients to live longer and tolerate more aggressive antineoplastic treatment.
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Current Role of Chemotherapy

It is likely that radiotherapy will be held in reserve for increasing numbers of patients with primary CNS lymphoma as medical oncologists strive to develop curative systemic regimens. Indeed, many complete responders to chemotherapy and elderly patients are now being treated with cytotoxic drugs alone.[11,17] Late sequelae of radiation therapy are a significant problem in the elderly, with radiation-induced dementia (occurring as early as 1 year after treatment) of particular concern.[8] Hence, regimens that do not include radiation therapy are especially valuable for older patients.

Medulloblastoma

Medulloblastomas of the cerebellum account for < 1% of adult brain tumors but are the most common CNS malignancy in children.[18] Histologically identical neoplasms arising elsewhere in the CNS are called primitive neuroectodermal tumors (PNETs).

Treatment begins with maximum safe resection, followed by staging. Staging is routine because, at diagnosis, medulloblastomas occasionally have metastasized to bone or other extraneural structures and commonly have seeded the leptomeninges.[19] Staging includes a postoperative MRI or CT scan to assess the completeness of surgical removal, a bone scan to exclude systemic metastases, and a gadolinium-enhanced spinal MRI and cytologic analysis of the CSF to assess the status of the leptomeninges.

The tendency for medulloblastomas to contaminate the CSF at an early stage has several important therapeutic implications: First, whenever possible, surgeons avoid ventriculoperitoneal shunting because intra-abdominal metastases may occur in patients with shunts. Second, with the exception of infants (see below), the entire neuraxis is irradiated at diagnosis.

Craniospinal irradiation is curative treatment in up to 50% of patients with medulloblastoma.[20] Unfortunately, whole-neuraxis radiotherapy has significant toxic effects, including intellectual impairment, short stature, endocrine failure and radiation-induced CNS tumors.[21] Infants and young children are especially vulnerable to these serious toxicities of craniospinal treatment.

Chemotherapy

After observations that recurrent medulloblastomas responded to a variety of cytotoxic drugs and regimens, including carmustine (BCNU [BiCNU]) or lomustine (CCNU [CeeNU]), vincristine, cisplatin (Platinol) or carboplatin (Paraplatin), cyclophosphamide (Cytoxan, Neosar), PCV, cisplatin plus etoposide , and cyclophosphamide plus vincristine, the combination of chemotherapy and craniospinal irradiation was prescribed at diagnosis in an effort to prolong tumor control and patient survival. In children, the initial adjuvant trials using vincristine and CCNU were disappointing overall, but subset analysis suggested that patients with advanced-stage medulloblastoma may benefit from adjuvant chemotherapy. [22,23] In adults, Bloom et al noted higher 5- and 10-year survival following adjuvant vincristine and CCNU.[24]

Treatment Recommendations

At present, whole-neuraxis radiation alone is recommended for patients > 3 years old with minimal residual tumor after surgery and no evidence of CSF or systemic dissemination; these patients are considered to be at average-risk for recurrence. The chemotherapy plus craniospinal treatment is recommended for patients with bulky leptomeningeal or disseminated disease, who are known to be at high-risk for recurrence.

The platinum-based cytotoxic regimen developed by Packer et al (Table 2) has emerged as the adjuvant chemotherapy regimen of choice for high-risk patients. Five-year survival rates in excess of 85% have been reported with this regimen.[25] In light of these extraordinary results, the role of adjuvant chemotherapy for standard-risk patients is under review; perhaps these patients also should be treated with adjuvant platinum-based chemotherapy.

For children < 3 years old, in whom the toxic effects of neuraxis treatment are profound, chemotherapy is recommended and radiation postponed until the CNS matures more fully.[19] Reducing or eliminating neuraxis radiotherapy is an important therapeutic goal for medulloblastoma and PNETs. However, a recent study of a decreased dose of neuraxis radiation was closed early because of an increased risk of early relapse.[26]

Oligodendroglioma

Oligodendrogliomas and mixed gliomas (ie, oligoastrocytomas) account for 5% to 15% of glial tumors. These tumors are thought to arise from a precursor cell committed to oligodendrogial differentiation. Typically, oligodendrogliomas present with seizures in young and middle-aged adults. Oligodendrogliomas may be low-grade and exceedingly indolent or high-grade (ie, anaplastic) and moderately aggressive. Median survival times exceed 10 years for patients with low-grade lesions.
and range from 2 to 5 years for those with high-grade oligodendrogliomas. As in astrocytic tumors, excellent performance status and young age are favorable prognostic factors in oligodendrogliomas.[27]

Surgery is the mainstay of initial treatment. Oligodendrogliomas frequently are amenable to radical resection and re-resection because the tumor/brain interface often is relatively well-delineated and 50% of these tumors are found in the frontal lobe. Until recently, postoperative radiotherapy was recommended for most patients with partially resected low-grade oligodendrogliomas and all patients with anaplastic tumors. However, the wisdom of the early use of radiation—a treatment that can be neurotoxic in long-term survivors—is being reevaluated in light of the recent recognition of the unusual chemosensitivity of oligodendrogliomas. Moreover, radiation oncologists have become more conservative in their recommendations now that earlier diagnosis by imaging has emphasized the indolent course of many oligodendrogliomas, at least initially.

Chemotherapy

Oncologists have known for many years that some gliomas respond to nitrosoureas and that some patients live longer as a consequence of adjuvant treatment, but they were unable to predict either benefit. Little progress occurred until Cairncross and Macdonald[28] observed that recurrent anaplastic oligodendrogliomas respond to therapy with PCV (Table 3). Subsequently, several groups reported that newly diagnosed aggressive tumors, mixed tumors, and symptomatic low-grade oligodendrogliomas also respond to PCV.[31-33] Oligodendrogliomas also have shown responses to other alkylators, including BCNU, CCNU, thiotepa, melphalan (Alkeran), dacarbazine (DTIC), and cisplatin-containing regimens.[34-37]

Although most aggressive or anaplastic oligodendrogliomas respond to PCV, some do not, or do so only transiently. In our experience, long-standing seizures, prior low-grade oligodendroglioma, and classic histopathology predict an excellent response, whereas rapidly evolving nonconvulsive symptoms, ring enhancement on MRI or CT, and uncertain or ambiguous pathology predict a poor response.[unpublished observations, 1997] Many of these poorly or briefly responsive tumors are monomorphic, glial fibrillary acidic protein (GFAP)-negative gliomas with large necrotic regions; some pathologists term these tumors grade 4 oligodendrogliomas, while others describe them as unclassifiable high-grade gliomas or glioblastomas.

Predicting response precisely may ultimately require oligodendroglioma-specific markers or molecular characterization of tumor tissue.

Unanswered Questions—Oligodendrogliomas are chemosensitive, but only time and experience will determine how PCV or other chemotherapy regimens can be used to the patient’s best advantage. For example, to assess the value of adjuvant chemotherapy, the Radiation Therapy Oncology Group (RTOG) has initiated a randomized trial comparing PCV plus radiation therapy vs radiation alone for patients with newly diagnosed pure and mixed anaplastic oligodendrogliomas. Other important questions to be answered include the following: Are there more effective, less toxic regimens than PCV? How can the treatment of recurrent tumor be improved? Are there effective salvage therapies post-PCV? Should low-grade oligodendrogliomas be treated with PCV, and if so, which ones and when? Will pulmonary insufficiency, second malignancies, or other serious side effects of chemotherapy occur in long-term survivors?

Undoubtedly, the trend over the next few years will be to postpone radiotherapy for patients with low-grade oligodendrogliomas. Attention will also likely be focused on the development of more effective, perhaps more intensive chemotherapy regimens for newly diagnosed patients with anaplastic tumors so that radiation can be postponed indefinitely for this group as well.

Germ-Cell Tumors

Germ-cell tumors of the CNS are rare cancers of children and young adults. Most of these tumors are diagnosed in the second or third decade of life in patients presenting with headaches, vomiting, papilledema, and vertical gaze palsies due to obstructive hydrocephalus and dorsal mid-brain compression. Subarachnoid spread to the anterior recess of the third ventricle may be evident at diagnosis, in which case, endocrine abnormalities due to hypothalamic or pituitary dysfunction may be present.

Germ-cell tumors of the CNS are of two types: germinomatous and nongerminomatous. The nongerminomatous neoplasms include choriocarcinomas, teratomas, yolk sac tumors, and endodermal sinus tumors. Histologically, these tumors are identical to germ-cell tumors arising in the gonads and mediastinum and, like systemic germ-cell tumors, may secrete alpha-fetoprotein and
beta-human chorionic gonadotropin. Germ-cell tumors of the CNS frequently seed the leptomeninges, necessitating postoperative staging by gadolinium-enhanced spinal MRI, CSF cytologic examination, and serum and CSF biochemistry for tumor markers. Pineal region tumors, such as these, are difficult to resect completely, but most can now be biopsied safely using MRI- or CT-guided stereotactic techniques. Wide local-field radiotherapy with or without spinal irradiation has been the mainstay of therapy. Germinomas are exquisitely radiosensitive. Many patients are cured with radiotherapy, and 5-year survival rates in excess of 80% are commonplace.[38] Nongerminomatous germ-cell tumors, on the other hand, are more refractory to radiation and rarely are cured by this modality alone.[39] Of necessity, radiation treatment fields are large and include the deep mid-line structures. Consequently, cognitive impairment, behavioral difficulties, and neuroendocrine failure are evident in many long-term survivors.

Chemotherapy

Single chemotherapeutic agents and combination regimens effective in testicular germ-cell tumors are now being used successfully to treat primary CNS germ-cell tumors. Responses to cisplatin, cyclophosphamide, doxorubicin, vincristine, bleomycin (Blenoxane), VAB-6 (cyclophosphamide, vinblastine, actinomycin, bleomycin, and cisplatin), and other drug combinations have been observed.[40] Using various cisplatin-based regimens alone, remissions lasting up to 3 years have been reported in patients with germinomas.[41,42] Nongerminomatous tumors also have been found to respond to cyclophosphamide, cisplatin plus etoposide, and other platinum-containing regimens.[43-45]

Current Role of Chemotherapy

Chemotherapy is rapidly becoming the initial treatment of choice for newly diagnosed patients with germ-cell tumors of the CNS. Balmaceda et al[46] recently achieved high rates of complete response without the use of radiotherapy in patients with both germinomas and nongerminomatous germ-cell tumors using the combination of carboplatin, etoposide, and bleomycin (Table 4). Given the remarkable success of systemic chemotherapy for testicular cancer, it is possible that curative cytotoxic regimens for germ-cell tumors of the CNS will emerge within the next 10 years.

Glioblastoma and Anaplastic Astrocytoma

Glioblastomas and anaplastic astrocytomas are the most common primary brain tumors of adults. Optimal treatment includes maximum safe resection and radiotherapy. The completeness of surgical removal is dictated largely by tumor location; for example, nondominant frontal lobe tumors can be debulked extensively, whereas tumors in the basal ganglia or thalamus cannot. Using a linear accelerator or cobalt unit, radiation is administered to a local field that includes the tumor and peritumoral tissue only. Tumor control may be enhanced somewhat by adjuvant stereotactic radiosurgery or adjuvant interstitial radiation (ie, brachytherapy) with radioactive iodine seeds. These approaches should be reserved for patients with small tumors in noneloquent regions of the brain and should be used sparingly until their beneficial effects have been established unequivocally by randomized control trials.

Treatment prolongs life but is seldom curative. Median survival is approximately 10 months for patients with glioblastoma and 2 to 3 years for those with anaplastic astrocytoma. Nonrandomized studies reporting longer survival times must be interpreted cautiously, as they may have excluded patients with unresectable tumors or other unfavorable prognostic factors, such as older age and poor performance status.

Chemotherapy

Glioblastomas and anaplastic astrocytomas sometimes respond to BCNU, CCNU, and other nitrosoureas; procarbazine (Matulane); and the new orally administered alkylating agent temozolomide (Temodol), but these tumors are substantially more resistant to chemotherapy than are lymphomas, medulloblastomas, oligodendrogliomas, or germ-cell tumors. Adjuvant chemotherapy with a nitrosourea or PCV may increase 1- and 2-year survival rates of patients with glioblastoma or anaplastic astrocytoma by up to 10%, as demonstrated by Fine et al[47] in a recent meta-analysis. However, fewer patients are receiving adjuvant treatment today than 10 years ago. Some believe that anaplastic astrocytomas are more responsive to chemotherapy than are glioblastomas and strongly recommend adjuvant PCV for young patients with high performance status and intermediate-grade gliomas.[48]

Waning enthusiasm for adjuvant chemotherapy reflects a hard-nosed reappraisal of the cost-benefit ratio of current cytotoxic treatment, not a lack of interest in systemic treatments for glioblastoma...
and anaplastic astrocytoma, which, in point of fact, is greater now than ever before. However, attention is shifting away from cytotoxic drugs to cytostatic compounds that block growth-signal transduction (eg, SU101), inhibit tumor cell invasion (eg, BB2516), and suppress angiogenesis (eg, thalidomide). Studies of these compounds are currently underway.

Ultimately, high-grade astrocytic tumors may be treated with a combination of traditional cytotoxic agents, such as BCNU, plus one or more of the cytostatic compounds currently under development.

**Ependymoma**

Ependymomas occur at all levels of the neuraxis. Intracranial tumors usually are found in the posterior fossa and are more common in children. Both low-grade and anaplastic ependymomas occasionally seed the leptomeninges.

Treatment includes surgical removal (if possible), staging by gadolinium-enhanced spinal MRI and CSF cytologic examination, and limited-field irradiation for tumors localized at diagnosis or craniospinal irradiation for disseminated disease.

The median duration of survival is 5 years for patients with intracranial tumors. Young age, supratentorial location, incomplete resection, anaplastic pathology, and early dissemination are poor prognostic indicators.

**Chemotherapy**

Standard initial therapy for older children and adults does not include chemotherapy, but platinum-based regimens have some antiependymoma activity.[49] Chemotherapy is being used increasingly to postpone radiation in infants and young children.

**Spinal Ependymomas**

Spinal ependymomas are more common in adults. Intramedullary spinal ependymomas often are circumscribed and can be removed surgically. Radiotherapy is recommended following incomplete resection. Myxopapillary ependymomas of the conus are difficult to resect and may require radiation, while those in the filum can be resected completely in most instances and require no further treatment.

At present, there is no role for chemotherapy in the treatment of either intramedullary or myxopapillary spinal ependymomas.

**Strategies for Improving the Efficacy of Cytotoxic Drugs**

**High-Dose Chemotherapy Plus Stem-Cell Support**

Currently, many highly chemosensitive and some moderately chemosensitive systemic malignancies are being treated with intensive chemotherapy followed by hematopoietic reconstitution using peripheral blood stem cells or bone marrow. This approach is based on laboratory and some clinical data suggesting that higher doses of chemotherapy will kill greater numbers of tumor cells and cure some patients whose tumors would have relapsed otherwise. This approach has been toxic, expensive, and ineffective for glioblastoma multiforme but is a clinical research strategy worth considering for the chemosensitive CNS malignancies (primary CNS lymphoma, medulloblastoma, anaplastic oligodendroglioma, and intracranial germ-cell tumors).

Enhanced drug delivery is one reason to consider a dose-intensive chemotherapeutic approach to treatment, but the risk of cognitive impairment and other serious neurotoxicities following successful tumor control by irradiation is the single most compelling argument supporting this approach. This is especially true for primary CNS lymphoma, medulloblastoma, and germ-cell tumors of the CNS, for which large, parallel, opposed radiation fields, whole-brain radiotherapy, or craniospinal irradiation is required. A less persuasive case can be made for high-dose therapy in anaplastic oligodendroglioma, for which less toxic, local-field conformal radiotherapy is possible in many instances.

**Blood-Brain Barrier Disruption**

Anatomically, the blood-brain barrier consists of tight junctions between vascular endothelial cells. Many chemotherapeutic agents will enter brain tumor tissue because blood vessels in the tumors have either a discontinuous endothelium or abnormal tight junctions. However, large, water-soluble, charged, or excessively protein-bound drugs are excluded by the blood brain-barrier, which may be partially or completely intact at the tumor-brain interface and beyond.

The blood-brain barrier is likely of no consequence when the goal of chemotherapy is palliative, ie, to shrink large symptomatic intracerebral neoplasms. However, circumventing the barrier is likely to be a critical step when chemotherapy regimens are highly effective and given with curative intent. Agents that cross the intact barrier, osmotic disruption of the barrier,[9] or transient opening of the barrier using bradykinin analogs, such as RMP-7,[50] may be essential elements of tomorrow’s curative chemotherapy regimens for brain tumors.
Regional Treatment
To enhance chemotherapy delivery to CNS malignancies and minimize systemic toxicities, methodologies have evolved for delivering cytotoxic agents directly to the tumor site. To date, intra-arterial and interstitial chemotherapy have proven to be less effective than hoped and more toxic than anticipated. [51,52]

Controlled-release biodegradable polymers may be a more promising approach. Two polyanhydride systems have been studied extensively: p(CPP-SA) for hydrophobic drugs, such as BCNU, and p(FAD-SA) for hydrophilic compounds and those susceptible to hydrolysis, such as methotrexate and cisplatin.[53,54] Brem et al[55] have established the safety of this methodology and have demonstrated in a recent randomized controlled trial that patients with recurrent malignant glioma live longer after reoperation and BCNU polymer implantation (Gliadel Wafer) than after reoperation and sham implantation. Future studies employing this technology will examine the utility of BCNU-polymer therapy in newly diagnosed patients, the efficacy and toxicity of escalating doses of BCNU, and the effects of other cytotoxic drugs delivered in this fashion.

New Agents
The search for effective systemic therapies for brain tumor continues on two fronts: more effective cytotoxic drugs and novel agents that impede angiogenesis, signal transduction, and glioma cell invasion. Temozolomide is a new oral cytotoxic agent with moderate side effects that cross-links DNA. It has produced partial response rates of 40% to 50% in newly diagnosed and recurrent high-grade astrocytomas.[56] Phase II and III studies of this drug alone and in combination with BCNU are underway or planned.

Classes of compounds that show promise include angiogenesis inhibitors (eg, thalidomide), protein kinase C inhibitors (eg, high-dose tamoxifen [Nolvadex]), topoisomerase inhibitors (eg, topotecan [Hycamtin]), platelet-derived growth factor (PDGF) receptor antagonists (eg, SU101), and cell differentiation agents (eg, phenylacetate).

Summary
Traditionally, cytotoxic drugs have had a limited role in the treatment of brain tumors. However, advances in the chemotherapy of brain tumors have occurred during the past decade. Certain brain tumors, including primary CNS lymphoma, medulloblastoma, oligodendroglioma, and intracranial germ-cell tumors, have been shown to be quite chemosensitive. The major therapeutic challenge remains malignant glioma, for which adjuvant chemotherapy has been of limited benefit. It is hoped that new drug delivery systems, such as controlled-release biodegradable polymers, and novel approaches, such as gene and immune modulation, will prove useful. Ultimately, true advances will depend on gaining a better understanding of these tumors at the cellular and molecular level.

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