Review

Biology and treatment of gliomas

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Summary. This review discusses some of the recent advances in glioma research and treatment. Our understanding of the characteristics of these tumors has been strengthened by the application of molecular biologic and genetic techniques to pathologic grading and therapy outcome. Newer attempts to correlate imaging modalities to pathologic grading are also discussed. It is anticipated that these developments will strengthen our ability to design improved treatment strategies, an essential goal inasmuch as current treatment schemes have limited benefit. More work needs to be done to understand the biology of these tumors especially the complex interactions of their cytokine expression, multiplicity of genetic abnormalities, and their local environment. Only then will be able to develop improved therapeutic interventions.

Keywords: chemotherapy, glioma, astrocytoma, glioblastoma, ependymoma, oligodendroglioma, radiotherapy, surgery, cytokines

Introduction

The worldwide incidence of gliomas has increased over the last few years, most noticeably in the elderly. This is likely due to both an increase in our ability to detect these malignancies with newer imaging methods and an absolute rise in incidence. The dismal record of success in the treatment of these tumors makes glioma research imperative if we are to see improvement. The advent of molecular genetics brings hope as it increases our ability to study gliomas and thus gain insight into their genesis, phenotypic diversity, and behavior and, ultimately, to develop new treatment strategies.

In this review we will discuss areas of progress in the laboratory and clinical management over the last several years and relate these findings to our current clinical understanding. Past reviews provide additional detailed accounts regarding the state of clinical and basic research into gliomas [1–4].

Histology

The pathologic grading of gliomas has been the subject of heated debate. Various classification schemes have been advanced with no universal standard yet adopted. This controversy leads to continued confusion regarding the interpretation of treatment response and malignant growth potential as tumors are not always placed into uniform and comparable categories. Classically, the system advanced by Kernohan [5] divided these neoplasms into four grades. Later grading systems combined several features into a three-grade system which has gained increasing favor [6].

Recently, Daumas-Duport et al. [7, 8] proposed a modification of previous grading schemes, which relied on histologic criteria that included nuclear atypia, mitosis, endothelial proliferation and necrosis as differentiating features. Daumas-Duport assigned a point system to these histologic variables: Grade 1 tumors had none of the above features, Grade 2 had one feature, Grade 3 had two features and Grade 4 had three or more features. In their initial evaluation, this grouping led to distinct median survival curves [8], but a subsequent review of 251 cases at the Massachusetts General Hospital found no statistical difference in survival between grade 2 and 3 [9]. The only significant predictor of survival for malignant gliomas was found to be necrosis, agreeing with previous grading systems [10]. A three tiered system of well differentiated astrocytoma, anaplastic astrocytoma and glioblastoma multiforme represents the most practical means for grading these tumors.

Any histologic grading system will suffer if insufficient or unrepresentative biopsy material is submitted for evaluation; this is especially true for gliomas, which have considerable intratumoral heterogeneity [11–14]. This heterogeneity (reflected in the name given to the most malignant member of the gliomas, glioblastoma multiforme) within a given tumor plagues their evaluation whether by histology, immunochemistry, molecular genetics and troubles clinical evaluation by diagnostic imaging techniques.

Radiology

Even with the advances of computed tomographic (CT) scanning and nuclear magnetic resonance imaging
(MRI), the main advantage of scanning is to define the tumor boundaries and distinguishing tumor from edema and blood. While some inferences about the biologic behavior of tumors may be made from these studies, accurate evaluation demands biopsy. The previously held opinion that non-contrast enhancing tumors are uniformly of a less malignant histologic phenotype has been disputed [19].

When stereotactic frames are used in concert with these powerful imaging techniques, lesions may be sampled even when their location would have made any open surgical approach fraught with hazard [15–18]. The heterogeneity of gliomas, however, makes interpretation of the small samples obtained with stereotactic biopsy unreliable and the wise clinician should be aware of sampling errors from such biopsies. Given the advantage of tumor bulk reduction, particularly if greater than 90% removal is feasible, an open procedure is preferable when non-eloquent regions of the brain are involved. Stereotactic biopsy at the very least is warranted in the vast majority of cases to secure a diagnosis of malignancy.

Several studies have found that radiographically defined tumor margins do not correlate with histologically confirmed tumor margins [11, 15]. In an autopsy study utilizing CT correlation, histologically confirmed tumor was found outside the radiographically defined contrast enhancing tumor and peritumoral 'edema' edge [13]. Greene et al. studied CT and NMR images with CT-guided stereotactic biopsies and found, at the time of initial surgery, tumor up to 1.5 cm outside radiographically abnormal areas [15]. Current neuroradiographic techniques remain only approximate in delineating the extent of disease.

Newer techniques are currently under study to improve the non-surgical evaluation of tumor infiltration. Positron emission tomography (PET) allows the study of glioma metabolic activity by evaluation of glucose ([18F]-fluoro-2-deoxyglucose), amino acid ([11C]-methionine), or oxygen metabolism [20–22]. PET scanning has been used to correlate areas of high metabolic activity (as indicated by increased glucose or methionine uptake) with extent and grade tumor [13, 23]. Indeed some argue that PET scanning is superior to CT evaluation [20, 24]. Patronas et al., for example, found that increased uptake of [18F]-fluoro-2-deoxyglucose (FDG) by tumor corresponded to decreased survival time [25]. There are also reports that changes in intensity of FDG uptake may correspond to alterations in the biology of the tumor in vivo [22]. These physiologic studies are presently hampered by poor resolution when compared to CT or NMR. Technical difficulties such as the expense of the hardware, the need for arterial blood sampling and on site cyclotron generated reagents limit PET's present clinical applications.

Single photon emission computed tomography (SPECT) with 99mTc-halothallium is another physiologic scanning method which is believed to work by exploiting differences in Na+/K+ pump activity between malignant and benign tissues. Studies with this technique are in their infancy but they may play a role in assessing malignancy of tumors [33] and, like PET scanning, may prove useful in identifying radiation necrosis from tumor recurrence, but without the technical problems that hamper wide clinical use of PET scanning. Other reagents such as Tc99m MIBI (Cardiolite) are also being assessed for use with SPECT in identifying tumor.

### Proliferation markers

Conventional imaging techniques and histologic review alone are insufficient measures of tumor growth potential and outcome. Tumor cell proliferative markers are being used increasingly to predict tumor growth potential. One of the more studied markers is bromodeoxyuridine (BUDR), a halopyrimidine that competes with thymidine for tumor cell uptake and incorporation by S-phase cells. In cell kinetic studies, BUDR is infused into patients shortly before surgery and the percentage of BUDR-labeled cells in surgical specimens is evaluated using specific monoclonal antibodies to BUDR incorporated into DNA [26–28]. This allows the clinician to establish which tumors have a faster rate of cell division. Hoshino et al. [26] found that histologically more malignant appearing tumors have a higher percentage of BUDR labeled cells. Hoshino et al. [26] LaBrousse et al. [29] found that BUDR labeling may correlate better with survival than histologic grade.

Other techniques are currently under study, including a silver colloid staining technique that evaluates nuclear of DNA organization [30]. A correlation has been found between nuclear regions stained by this technique, appearance of histologic malignancy, and prognosis. Burger et al. have found that higher nuclear staining of gliomas with the KI-67 antibody seems to correspond with more malignant histologic appearance and faster growth characteristics [31]. As a bridge between the evaluation of histologic labeling and neuroradiologic imaging, on group is studying the use of [18F]-fluoro-2-deoxyuridine, which can be used both as a histologic marker and a PET scan marker [32].

### Heterogeneity

One difficulty in relating in vitro models of malignant gliomas to the in situ environment is the instability of cell lines [34]. Several changes in cell morphology after multiple passages have been found including changes in expression of protein receptors (platelet derived growth factor receptor (PGDF-R), epidermal growth factor receptor (EGF-R), etc.) chromosome loss (22, 10) and changes in cytokine expression (see below) [35–37]. Chromosomal changes may also affect the ability to establish a cell culture from a glioma biopsy [38–40].

The heterogeneity of these tumors also makes in
Cell markers

The pathologic evaluation of brain tumors can frustrate the most experienced neuropathologist. The use of marker proteins and immunohistochemical methods can assist in pathologic diagnosis, supplementing traditional histologic stains and at times making unnecessary ultrastructural evaluations.

Although tumors differ within and between each other with respect to these markers, there has been little attempt to correlate their level of expression with clinical outcome. The histochemical markers commonly used at present include glial fibrillary acidic protein (GFAP), S-100 protein, synaptophysin, neuron-specific enolase, and vimentin. Synaptophysin and neuro-specific enolase are expressed primarily in primitive neuroectodermal tumors and have been said to differentiate these tumors from gliomas.

Of these marker, GFAP appears to be more specific for gliomas. GFAP is a 55-kd protein monomer that can form intrachain disulfide cross-links. It is present in astrocytomas and oligodendrogliomas and less so in neurofibromas, medulloblastomas, and ependymomas. Its presence in primitive neuroectodermal tumors underscores the pluripotent differentiation of these tumors. It is believed that GFAP is expressed in cells reacting to their local environment. In fact, the first isolation of GFAP was from a multiple sclerosis plaque, which perhaps represents a reaction to a localized insult. Using antisense oligomers, Weinstein et al. found GFAP to be required for astrocytic reaction to neurons. There may be a coordinated biological interaction between GFAP, vimentin, and S-100.

Recently, the human GFAP gene has been cloned and its chromosomal location identified as 17q21. GFAP has also been found to be expressed in gliomas with low levels of fibronectin gene transcription and expression. A correlation between GFAP mRNA levels and PDGFα receptor mRNA, but not PDGFβ receptor mRNA, was found as well. S-100, a 25 kd protein composed of two similar subunits, forms heterodimers and homodimers and is believed to be a calcium-binding protein expressed in the cell nucleus. S-100 is expressed in a wide variety of CNS tumors as well as many non-central nervous system tumors, mostly schwannomas and neurofibromas. Because of S-100's wide expression in CNS tumors its usefulness lay mainly in its ability to identify the gliomatous portions of gliosarcomas and it may help to distinguish astrocytomas (GFAP and S-100 positive) from oligodendrogliomas (less strongly GFAP positive but still S-100 positive).

Unfortunately, none of the glioma markers are sufficiently reliable to be used to grade gliomas, reflect differentiation, or indicate lineage of astrocytomas, oligodendrogliomas, or ependymomas. The lack of specific markers for most CNS tumors reflects their complex heterogenous biology.

Molecular biology

Little is understood regarding the generation of malignant gliomas and the progression (if operant) from more 'benign' forms (such as the juvenile pilocytic astrocytoma) to astrocytoma and glioblastoma multiforme. Whether tumors are initiated from a normal cell to form a malignant variant by sequential steps beginning with the slower growing tumors and subsequently evolving to a glioblastoma or can be genetically altered to an aggressive phenotype directly from the normal cell remains to be determined; it seems likely to both scenarios are operant.

The application of molecular biological techniques to gliomas has greatly increased our understanding of changes that lead to their creation. It is believed that oncogenes and tumor suppressor genes exert a balanced control on cell growth. For example, the p53 gene system appears to suppress cell growth, while aberrant forms of the gene allow cell proliferation and stimulate growth. Several families of oncogenes may be involved in malignant glioma development. Many of the receptors for the factors believed involved in glioma tumorigenesis have structural homologies, including an extracellular binding domain, a transmembrane domain and an intracellular domain that possesses tyrosine kinase activity.
The EGF-receptor (EGF-R) protein has been found to be similar to the erb-B oncogene (vide infra). The EGF-R is overexpressed in a large number of gliomas, most of them phenotypically glioblastoma multiforme [65, 66]. This occurs through gene amplification and increased RNA transcription of the EGF-R. There appear to be intra- and inter-tumoral differences [67], which suggests that EGF-R overexpression is related to a late evolution of a more malignant phenotype. The biological result of EGF-R overexpression is unknown, and EGF-R overexpression has not been found to correlate with survival.

It is known that the EGF-R has an integral protein tyrosine kinase that become active with receptor stimulation [64]. This would be expected to increase protein phosphorylation and, in turn, cell division. The stimulation of the EGF-R could be via autocrine stimulation, altered protein confirmation, or increased protein production. In some cases over-expression of EGF-leads to cellular transformation, but only after receptor activation [66]. Furthermore, this amplification, while a heterogeneous response in tumors, appears to result from a loss of a specific coding sequence [68].

Recently, expression of a structurally altered EGF-R was found in a glioblastoma cell line [69]. This protein, termed p190, appears to be structurally similar to the EGF-R and has similar phosphorylation sites. This analogue is distinct from the erb-B-oncogene. The erb-B-2 gene arises as a result of a point mutation [70] of the EGF-R gene; this alteration in the gene product leads to increased expression and cell growth [71]. Of further note is the finding that the EGF-R maps to chromosome 7, commonly overexpressed in glioblastoma.

The EGF-R is bound by transforming growth factor alpha (TGFα). This protein is a single amino acid chain of molecular weight 5,600 [72]. TGFα appears to bind the EGF-R in an autocrine fashion and has been found to be present in glial tumors of various histologic appearances [73, 74]. The expression of TGFα may be the result of genetic alterations of glioma cells at an earlier stage of malignant evolution. Eventually the over-expression of EGF-R may then accelerate tumor growth. Recent work has demonstrated gene amplification of EGF-R in higher grade gliomas but not in lower grades [75].

Elevated levels of TGFα have been found in the urine of glioma patients [76] in amounts correlating with the degree of malignancy. One case of reduction of TGFα levels in the urine following cyto-reductive surgery has been reported [77].

Transforming growth factor beta (TGFβ) is a 25 kd disulfide-linked protein with the novel feature that it can stimulate or inhibit cell growth and is secreted by glioblastoma cells [78, 79]. It has been shown that TGFβ has suppressive effects on lymphocyte function, specifically the IL-2 mediated generation of tumor-infiltrating lymphocytes [80]. Thus TGFβ may play a role in the suppression of the immune response to astrocytic tumors.

We do not yet, however, understand the activation of TGFβ. In vitro it is cleaved from a protopolypeptide by the use of plasmin or treatment in an acidic environment (pH 3.1 or lower) [81, 82]. Furthermore we do not understand how this activation can occur in the CNS environment. Perhaps it is secreted by glialoma cells and activated by contact with vascular endothelial cells [83]. The interaction of TGFβ with the vascular system may cause significant alteration of immune responses via changes in the blood coagulation cascade [84–86]. Work has begun on blocking the production of TGFβ with in vitro glioma cell cultures to test these theories [87].

TGFβ has also been shown to alter the expression of the c-sis oncogene [88]. This gene encodes the β chain of platelet derived growth factor (PDGF) which is composed of two heterologous dimers (AB). Each chain has at least 80% homology with the other and heterodimers and homodimers have been found. PDGF is involved in glial evolution [89], and two receptors, PDGF-R-A and PDGF-R-B, are known. Malignant gliomas secrete the PDGF protein in all of its dimer forms (AA, BB, AB) with PDGF-A chain having the highest level of expression [73]. The half life of the PDGF-B-mRNA is not prolonged in glioma cells, indicating gene transcript stability may not play a role in glioma initiation or progression [90].

Fibroblast growth factors (FGF) are heparin-associating proteins with mitogenic and angiogenic activity. The basic form (bFGF) has been found in glioma cells along with high-affinity bFGF receptors [91, 92]. In addition, tumors of increasing malignant grade appear to possess relatively higher levels of bFGF, apparently localized to subadjacent vascular areas [93, 94]. However, other researchers have found increased levels of PDGF-A chain and PDGF-R in this same cell membrane region [95]; and further studies have demonstrated increased levels of TGFα in these areas [96]. Addition of antisense oligonucleotide primers to block transcription of bFGF were found to inhibit growth of a glioma cell culture line, but not growth of a nontransformed human glia culture line [97].

**Treatment**

Malignant gliomas can present as a single lesion or as multifocal lesions, but rarely will either metastasize outside the CNS. The incidence of multifocal gliomas is higher than previously believed and ranges from 5% in anaplastic gliomas to approximately 13% in glioblastoma multiforme. Moreover, multifocal gliomas appear to be associated with a high incidence of secondary malignancies, indicating a genetic predisposition (A. P. Kyritsis, personal communication, 1992). The prognosis of the multifocal gliomas as a group is very poor with a median survival time of only 6 months after diagnosis.

Most clinical trials are directed towards treatment of
the malignant forms of brain tumors, e.g. anaplastic astrocytoma and glioblastoma. It is not completely established at present if treatment of the low-grade astrocytomas improves survival. The median survival time of patients with glioblastoma multiforme is between 8 and 13 months and for anaplastic gliomas between 20 and 36 months depending on treatment [98]. Covariates that influence survival are histologic type and grade tumor, proliferative index, post-surgical tumor volume, age of patient, performance status, and type of chemotherapy used. In general, the prognosis is favorable if the patient is young, histologic necrosis is absent, the proliferative (labeling) index is low, and the tumor volume is minimal [98–103]. Current therapy of malignant gliomas includes surgery, radiation therapy and chemotherapy.

**Surgery and radiotherapy**

Although the conclusion is still questioned, complete or near complete surgical extirpation of the tumor prior to radiotherapy or chemotherapy seems to improve survival [101–104]. From a practical viewpoint, surgical reduction of at least 90% of tumor volume (more than 1 log of cells) is required for an increase in survival attributable to surgery.

Radiotherapy is one of the more effective treatment modalities for malignant gliomas. Originally it consisted of whole-brain radiation but later it became evident that this approach resulted in unnecessary CNS toxicity, since the tumor tends to recur within 3 cm of its original margins in most instances [104–108]. Whether radiation is given by whole brain or limited field portals, conventional fractionation is 1.7–2.0 Gy fractions per day, five days a week to a total of 60 Gy. In current practice, this treatment covers the tumor bed and a 2–3 cm margin based on CT enhancement and probably 2 cm based on MRI enhancement.

Other fractionation schedules evaluated include hyperfractionation to a higher than normal total dose and accelerated fractionation to a more conventional total radiation dose in a shorter period of time. The former has been used with moderate success against brainstem gliomas [109]. However, a randomized study by the Brain Tumor Cooperative Group in 557 patients with cerebral gliomas showed no advantage of hyperfractionated radiotherapy plus carmustine over conventional radiotherapy plus carmustine [110]. Accelerated fractionation is believed to enhance the radiation effect since the tumor cells are less resistant to frequent radiation fractions than normal brain cells [111, 112].

Another recent modification is the use of radiosensitizers or radiopotentiators in order to enhance the radiation effect. Included are hypoxic cell sensitizers such as misonidazole and fluosol, halogenated pyrimidines such as bromodeoxyuridine and iododeoxyuridine, and platinum analogues. The jury is still out on the benefit of these agents with radiotherapy in patients with malignant gliomas.

For selected patients with recurrent malignant gliomas interstitial brachytherapy with stereotactic implantation of radioisotope seeds prolongs survival but decreases the quality of life since a high percentage of these patients become steroid dependent and need reoperation for removal of radiation necrosis [113]. As adjuvant therapy to extend beam radiotherapy, brachytherapy’s benefits are limited to patients with glioblastoma multiforme [114]. In the adjuvant setting chronic steroid usage and reoperation may be responsible for some of the benefit attributed to brachytherapy.

**Chemotherapy**

Adjuvant chemotherapy following surgery can be given before, during or after radiotherapy [115, 116]. Most reports are of chemotherapy after radiotherapy. Most of the drugs used have produced either no benefit or short-lasting response. Drug treatment failures have been attributed to poor drug delivery, a low tumor growth fraction, low immunogenicity of the tumor cells, and cellular resistance and heterogeneity. In general, drug delivery is poor in the normal brain area adjacent to the tumor (an area that exhibits microscopic tumor cell infiltration), greater in the periphery of the tumor bulk, and low in central necrotic areas. Attempts to increase drug concentration in the tumor bed using intrarterial delivery with or without blood-brain barrier disruption with osmotic agents have been disappointing: these have increased brain and retinal toxicity and produced little or unconfirmed benefits in survival.

Currently there are efforts to enhance drug or radioisotope delivery to brain tumors using monoclonal antibodies as carriers. The limitation of this approach is nonspecific binding to other tissues and the immunogenicity of the antibodies, which will limit the number of times they can be used in a multicourse therapy regimen. Even polyclonal conjugates of radioisotopes have been considered as possible carriers to brain tumors [117]. This targeting technique is limited by concomitant high uptake to other vital organs such as kidneys, liver and spleen.

The heterogeneity of malignant gliomas and selection of resistant clones is another major limiting factor in the effectiveness of chemotherapy. For instance, it has been shown that BCNU-resistant cells demonstrate amplification of the multidrug resistant gene and increase in polyamine biosynthesis [118]. There is recent evidence that TGFβ may modulate multidrug transport in glioma cells [119]. Calcium channel blockers and calmodulin inhibitors can overcome multidrug resistance. The action of calcium channel blockers is obscure and unrelated to inhibition of calcium processes [120]. Verapamil, a calcium channel blocker, produced inhibition of glioblastoma growth in nude mice [121]. Human studies employing verapamil to augment chemother-
apy's effect are currently underway in several centers.

Patients with gliomas have generally depressed cell-mediated immunity [122], and their circulating T-lymphocytes have been found to be reduced [123]. There is evidence that the humoral responses are affected as well, but their exact implication is less clearly defined [124, 125]. Peripheral blood lymphocytes from patients with gliomas produced lower levels of IL-2. However, after incubation with IL-2, the lymphocytes exhibited higher natural killer activity and strong cytotoxicity, suggesting that IL-2 may be useful in adoptive immunotherapy [126].

Chief among the drugs used for brain tumor chemotherapy are the nitrosoureas. Most effective members of this family are drugs that are generally lipid soluble, less than 400 daltons, and can cross the blood-brain barrier readily. Carmustine (BCNU) administered as a single agent after surgery and radiotherapy was the first drug to improve survival of patients with malignant gliomas [99]. The combination of lomustine (CCNU), procarbazine, and vincristine (PCV) has been reported to be superior in treating anaplastic gliomas producing a median survival time of 36 months compared with 19 months for carmustine [127]. PCV appeared superior to carmustine, however, the increased survival was not significantly different in glioblastoma patients. Unfortunately, in most glioblastoma trials, the survival curves for all but the longest surviving 30% of patients has not changed over the past two decades of clinical trials.

A large randomized trial found no advantage of streptozotocin, a 1-methyl-1-nitrosourea combined with glucose, over BCNU [110]. In another randomized study, there were no significant differences among BCNU, BCNU alternating with procarbazine, or BCNU with hydroxyurea alternating with procarbazine and VM-26 (teniposide) [128]. Simultaneous use of ifosfamide during radiation therapy followed by BCNU in a non-randomized trial of 75 patients resulted in a median survival time of 15.4 months for glioblastomas and 21.4 months for anaplastic astrocytomas [129].

Aggressive therapeutic regimens have been disappointing in malignant gliomas. The 'eight drugs in one day' chemotherapy, which involves administration of methylprednisolone, vincristine, CCNU, procarbazine, hydroxyurea, cisplatin, cytosine arabinoside and the imidazole carboxamide the same day, failed to improve survival compared with BCNU alone and in addition had increased toxicity [130]. Administration of high doses of BCNU (900–1050 mg/m² IV) combined with autologous bone marrow transplantation [131–133] also resulted in increased pulmonary and liver toxicity with only marginal additional survival benefit. Similar disappointing results followed intracarotid administration of either BCNU or ACNU for the treatment of glioblastoma multiforme [134, 135].

Patients with recurrent or progressive malignant glioma have been shown to respond to a variety of anticancer agents but few respond with complete resolution and disappearance of radiographically demonstrated tumor. Some patients respond to several successive and different forms of chemotherapy before succumbing to the tumor. Of the many reasons for chemotherapy failure tumor cell resistance and limitations in drug delivery are likely to be the most significant.

Treatment with high-dose cyclophosphamide and vincristine of 5 patients with recurrent glioblastoma and 6 with recurrent anaplastic astrocytoma produced partial response or stable disease in 3 and 5 patients, respectively. The median time to progression (MTP) was 4 months in the glioblastoma and 28 months in the anaplastic astrocytoma groups [136]. Addition of benzimidazole to CCNU produced no advantage in 42 patients with anaplastic astrocytoma [137]. Combination of trifluoperazine, a calmodulin inhibitor with bleomycin was tried against recurrent malignant glioma in phase II trial but showed no benefit [138].

Two chemotherapeutic agents, efllornithine (DFMO) and procarbazine, have shown activity against recurrent gliomas. Efllornithine, a specific polyamine inhibitor, has been tested in several trials and shown to be effective in over 50% of recurrent astrocytomas in combination with either mitoguazone or carmustine. The effect of glioblastomas was less pronounced, with only 20% of patients showing stable disease [139–140]. Efllornithine was currently tested as a single agent for recurrent gliomas. Preliminary evaluation indicated that approximately 45% of anaplastic glioma patients either responded or stabilized for a median duration of nearly a year (48 weeks); results for glioblastomas were less convincing (V. A. Levin et al., submitted).

Procarbazine, a methylhydrazine derivative, has been active as a single agent against recurrent glioma [141, 142]. In a recent study procarbazine produced partial response or stable disease in approximately 50% of patients. The median time to progression for responding patients was 13 months [143].

Carboplatin, a new generation heavy metal compound that inhibits DNA synthesis, had a 40% response rate in glioblastomas and 57% in anaplastic astrocytomas with median time to progression of 20 and 21 weeks, respectively [144]. A combination of mechlorethamine, vincristine and procarbazine appeared also to be active in recurrent glioma with 52% response and stable disease and median time to progression of 42 weeks [145].

Therapy with interferon-beta resulted in 50% response and stable disease in both glioblastomas and anaplastic astrocytomas with median time to progression of 18 and 16 weeks, respectively [146]. The interferon response rate is impressive, but the lack of durable responses makes its continued use problematic. Interferon-alpha with BCNU is being evaluated currently as initial post-radiotherapy chemotherapy by the North Central Cooperative Group.

Finally, intratumoral infusion of chemotherapy is another approach being tested. Continuous infusion of methotrexate intratumorally via multiple catheters was tested in a pilot study and found to be technically fea-
sible without significant side effects [147]. Interstitial chemotherapy with biodegradable polymers containing BCNU after maximal surgery is currently being evaluated as a means of delivering high drug concentration to tumor with limited toxicity [148].

Conclusions

Malignant cerebral gliomas, like most solid cancers, are variably resistant to treatment because of inadequate drug delivery, systemic toxicity, inherent tumor cell resistance to drugs, and limited immunologic surveillance. Specific considerations for gliomas are that: 1) the blood-brain barrier restricts the delivery of chemotherapy to certain areas of tumor; 2) cellular heterogeneity is widespread with prominent drug and radiation resistant clones appearing to survive treatment; and 3) defects in immune surveillance and response limit live and dead tumor cell removal.

Gross total resection (greater than one log reduction) of the malignant glioma when possible has favorable effects on survival and quality of life.

Radiotherapy is, in general, a beneficial form of palliation. In addition to conventional dose fractionation, schedules of hyperfractionated, accelerated hyperfractionated, brachytherapy, brachytherapy and hyperthermy, and stereotactic radiosurgery are under investigation.

Chemotherapy of malignant gliomas, although failing to produce cure or substantial numbers of long-term survivors, has played an important role in the treatment of primary brain tumors. Many chemotherapeutic agents have been tried alone or in combination in malignant gliomas. BCNU has been the main drug used for both glioblastomas and anaplastic astrocytomas. Further studies will likely validate the superiority of the combination of CCNU, procarbazine, and vincristine (PCV) for the treatment of anaplastic gliomas and replace BCNU monotherpay for these tumors. In recurrent tumors, chemotherapy is less effective, although procarbazine, eflornithine, high-dose cyclophosphamide, vincristine, carboplatin, and interferon-beta are known active agents in addition to the nitrosoureas.

Finally, other approaches are currently being tested to: 1) enhance drug delivery to tumor with monoclonal antibodies; 2) counteract drug resistance with use of calcium channel blockers; 3) develop drugs to block unique tumor-specific enzymes; and 4) potentiate the immune response.

Intense laboratory research is currently being conducted to investigate the genetic abnormalities of malignant gliomas, the interaction of oncogenes with suppressor genes, and the specific protein cascades that lead to oncogenesis. The first steps in understanding the transformation of glial cells to neoplastic gliomas has been taken. As we learn more about oncogenes and suppressor genes and the subsequent cascades of stimulatory and inhibitory proteins and cytokines they control, we will be able pharmacologically manipulate these interactions and slow tumor growth. Examples recently advocated are to use biologic differentiation agents [149] to induce the reversion of the malignant cell back to a more normal phenotype and the insertion of modified gene elements utilizing retroviruses that will alter glioma growth and phenotype [150].

Other factors that would help in the treatment of these tumors are an improved ability to define the extent of disease, which would allow a more exact evaluation of tumor volume, cell proliferation, and early tumor recurrence. Comparisons of histologic parameters to growth control factors and other cytokines that may alter the ability of the body to respond to these tumors may lead to further improvements in survival.

At this point, the histologic grading and radiographic appearance of these tumors remains a poor approximation of their true phenotypic appearance and malignant potential. We must understand the genetic changes that allow glioma genesis and support glioma tumor growth. We do not, as yet, understand how the currently defined clinical methods of evaluation will be affected by our increasing knowledge of cellular mechanisms of these tumors and their ability to escape detection. As we learn more through laboratory research, the evaluation of these tumors through markers of cellular proteins and proliferative potential become increasingly important, while the histologic and radiographic appearance of glioma may well assume a lesser role. Eventually we should be able to design better chemotherapy programs which will stop the great suffering and loss of life due to this malignancy.

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Book review


This book is part of a series, entitled Cancer Treatment and Research, which provides annual or biannual updates on current oncology literature concerning specific topics. This volume is essentially focused on mechanisms of resistance to alkylating agents including cispalatinum and natural products.

Certainly the study of drug resistance is in the process of rapid evolution and a frequent updating of relevant molecular and biological findings and results of clinical applications is of great interest. With respect to basic mechanisms, this volume is particularly interesting on DNA repair, DNA-topoisomerase enzymes and multi-drug resistance. It contains several chapters on these topics, ranging from basic genetic and biochemical mechanisms to clinical applications.

Specific mechanisms of resistance to antimetabolites are not reviewed in detail; only one chapter covers some aspects of the phenomenon of gene amplification, one which is certainly relevant in the mechanisms of resistance to most antimetabolites.

All of the authors are prominent scientists who have made major contributions to this field, and many reviews by the same authors are already available in specialized oncology journals. Nevertheless, a collection of these reviews in one volume can be useful to students, scientists and clinicians involved in this area of research.

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