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Head's Up on the Treatment of Malignant Glioma Patients

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Primarily brain tumors are rare. As a consequence, oncology nurses may not be familiar with the spectrum of diagnoses within this group and the impact that diagnosis has on prognosis and treatment of these tumors. Although typically associated with a poor prognosis, recent advances have been made in the diagnosis and treatment for these tumors that generates great optimism for continued improvements in patient outcomes. This article will provide an update and review of the care and treatment of patients with the most common type of tumor, glial malignancies.

Primary brain tumors are those that arise from the constituent elements of the central nervous system. Relatively uncommon, it was estimated that 51,410 new cases of primary nonmalignant and malignant brain tumors were diagnosed in 2007 (Central Brain Tumor Registry of the United States [CBTRUS], 2008). Primary malignant tumors represent a substantial proportion of these tumors, with 22,070 new cases diagnosed in the United States in 2007 (12,010 in men, 10,060 in women). This number represented 1.36% of all cancers diagnosed each year. However, an estimated 12,930 deaths will be attributed to primary brain tumors in the United States, representing 2.5% of all cancer deaths (American Cancer Society [ACS], 2009). Primary tumors are not only associated with significant mortality, but patients often have devastating neurologic complications that may influence their quality of life (Drappatz, Schiff, Kesari, Norden, & Wen, 2007; Lovely, 1998). Any intracranial tumor, regardless of the degree of malignancy, can potentially invade or displace critical brain areas, resulting in neurologic compromise or even death.

Historically, the true incidence of primary brain tumors may have been under-reported, primarily as a consequence of tumor registries not including low-grade tumors in incidence data. Primary brain tumors

also are thought to be increasing in frequency, primarily in older adults (Fisher, Schwartzbaum, Wrensch, & Wiemels, 2007). Although an absolute increase in the incidence is possible, alternative reasons for the increase include improved neuroimaging techniques (increasing the rate of discovery), better patient access to specialized care leading to more accurate diagnoses, changing attitudes toward the care of older adults, both increasing longevity and encouraging medical intervention, as well as a true increase in incidence secondary to exposure to environmental carcinogens (Wen & Kesari, 2008).

The exact etiology of primary brain tumors is not known. Less than 5% of all primary tumors are associated with specific genetic disorders, such as neurofibromatosis, tuberous sclerosis, Turcot syndrome, and von-Hippel Lindau disease (Fisher et al., 2007). Exposure to ionizing radiation is the only definitive risk factor for the development of primary brain tumors (Bondy et al., 2008; Ron et al., 1988; Sadetzki, Modan, Chetrit, & Freedman, 2000). Recently, an inverse association between self-reported allergic conditions and the occurrence of gliomas has been reported (Bondy et al.; Scheurer et al., 2008). In addition, acquired immunosuppression, from either the use of immunosuppressive agents or HIV infection, is associated with an increased incidence of primary central nervous system lymphoma (Schabet, 1999; Schiff, Suman, Yang, Rocca, & O'Neill, 1998). There is reported increased incidence in relation to certain occupations, including manufacturing of synthetic rubber, petrochemical, aeronautics, drug manufacturing, nuclear energy, and precision metal work (Bondy et al.). However, the causative exposure in these occupations has not been fully defined. Recent investigations have focused on the association between exposure to extremely low-frequency electromagnetic fields, including exposure from cellular phones and the development of a primary brain tumor. Despite several large scale epidemiology studies, to date, no definitive association

has been reported (Kan, Simonsen, Lyon, & Kestle, 2008; Lahkola et al., 2007; Schoemaker et al., 2005).

Classification

Primary brain tumors are classified according to the presumed cell of origin. Several classification systems have been developed; however, the World Health Organization (WHO) system is the most widely used. In the WHO system, a primary brain tumor is first classified by its cell of origin and then a grade is designated based on cellular characteristics that likely correlate with the degree of malignancy (Louis et al., 2007). The typical TNM (tumor, node, metastases) system does not apply because these tumors rarely spread outside of the central nervous system. Instead, grading assesses the degree of aggressiveness of tumor cells by evaluating anaplasia, invasiveness, and proliferative (mitotic) activity. There are seven recognized general categories of central nervous system tumors, including tumors of neuroepithelial tissue, germ cell tumors, tumors of cranial and paraspinal nerves, tumors of the meninges, lymphomas and hemapoietic neoplasms, tumors of the sellar region, and metastatic tumors (Louis et al.).

The most common group of tumors of neuroepithelial tissue is the gliomas, accounting for 36% of all primary CNS tumors and 81% of malignant tumors (CBTRUS, 2008). Table 1 provides the WHO classification of glial tumors. The majority of gliomas are astrocytomas. Astrocytomas are classified as low-grade (WHO grade II), anaplastic (WHO grade III), and glioblastoma (WHO grade IV). Glioblastoma accounts for 50% of all gliomas, making it the most frequent primary malignant tumor (CBTRUS). These tumors are characterized by increased mitosis, cellular atypia, and either necrosis, neovascularization, or both.

Glioblastomas can further be classified as primary, occurring *de novo*, or secondary, developing as a consequence of continued malignant transformation from

a lower grade glioma (Furnari et al., 2007; Ohgaki & Kleihues, 2007; Wen & Kesari, 2008). This malignant transformation results from a sequential accumulation of genetic aberrations and dysregulation of growth-factor signaling pathways, as outlined in Figure 1 (Furnari et al.; Wen & Kesari). *De novo* glioblastoma is typically characterized by mutations and amplification of epidermal growth factor receptors (EGFR), loss of heterozygosity of chromosome 10 q, deletion of the phosphatase and tensin homologue on chromosome 10 (PTEN), and p16 deletion. Secondary glioblastomas are characterized by overexpression of the platelet-derived growth factor receptor, loss of heterozygosity of chromosome 10 q, abnormalities in the p15 and retinoblastoma (RB) pathways, and mutations in the TP53 tumor suppressor gene (Furnari et al., 2007). Current research efforts are focusing on the cellular origin of these tumor cells and further classification of tumors based on these cellular characteristics that may allow for further delineation of tumor types and responsiveness to therapies.

Recently, identifications of specific molecular markers that confer improved responsiveness to therapy and prediction of survival have been reported. In patients with oligodendroglioma, losses of chromosome 1 p and 19 q are correlated with higher chemosensitivity and better prognosis (Bromberg & van den Bent, 2009; Ueki et al., 2002). This test is now routinely performed in patients with oligodendroglioma and anaplastic oligodendroglioma. Studies are ongoing evaluating the use of this marker in stratification of treatment and further evaluation of outcome.

Diagnosis and Treatment

Most patients present with either an acute neurologic event, such as a seizure, or more protracted development of neurologic symptoms, such as problems with word finding or progression of the severity of headaches over time (Lovely, 2004). Symptoms are often

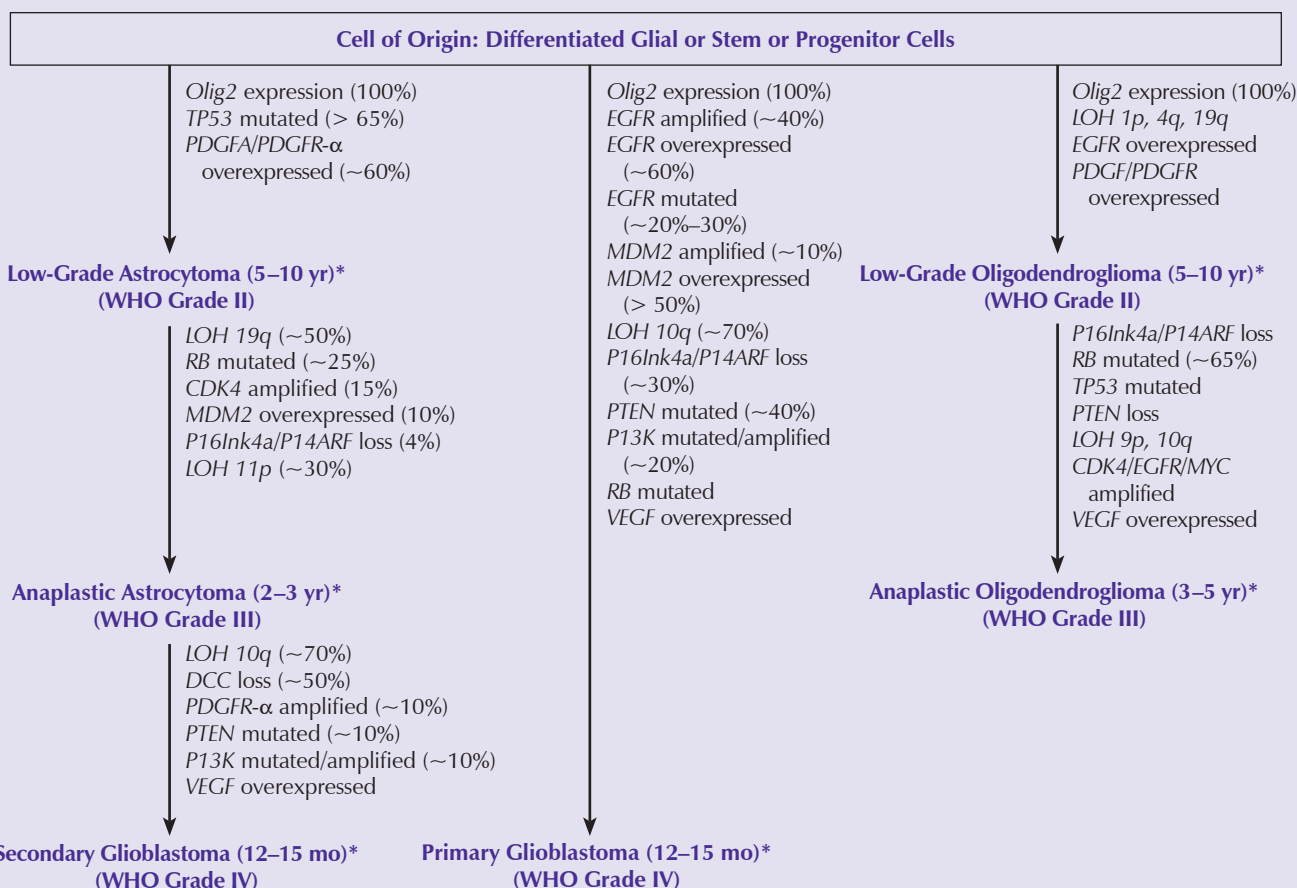
classified into generalized symptoms associated with increased intracranial pressure or focal symptoms resulting either directly from tumor invasion or pressure on specific neuroanatomic areas. Patients presenting with increased intracranial pressure may develop symptoms such as headaches, seizures, and reduced level of consciousness (Lee & Armstrong, 2008). These patients often require emergency evaluation and management.

Initial recognition of a brain tumor is based on neuroimaging. Magnetic resonance imaging (MRI) with ferromagnetic contrast is the gold standard,

Table 1. World Health Organization Tumor Classification

Tumor Grade	Astrocytic Tumors	Oligoastrocytic Tumors	Oligodendroglial Tumors
I	Subependymal giant cell astrocytoma; pilocytic astrocytoma	–	–
II	Diffuse astrocytoma; pleomorphic xanthoastrocytoma	Oligoastrocytoma	Oligodendroglioma
III	Anaplastic astrocytoma	Anaplastic oligoastrocytoma	Anaplastic oligodendroglioma
IV	Glioblastoma; giant cell glioblastoma; gliosarcoma	–	–

Note. Based on information from Louis et al., 2007.



Note. Genetic and chromosomal alterations involved in the development of the three main types of malignant gliomas (primary and secondary glioblastomas and anaplastic oligodendroglioma) are shown. Oligodendrocyte transcription factor 2 (*Olig2*) and vascular endothelial growth factor (*VEGF*) are expressed in all high-grade gliomas. Median lengths of survival (*) are shown. A slash indicates one or the other or both. *DCC* denotes deleted in colorectal carcinoma, *EGFR* epidermal growth factor receptor, *LOH* loss of heterozygosity, *MDM2* murine double minute 2, *PDGF* platelet-derived growth factor, *PDGFR* platelet-derived growth factor receptor, *P13K* phosphatidylinositol 3-kinase, *PTEN* phosphatase and tensin homologue, and *RB* retinoblastoma.

Figure 1. Pathways in the Development of Gliomas

Note. From "Malignant Gliomas in Adults," by P.Y. Wen and S. Kesari, 2008, *New England Journal of Medicine*, 359(5), p. 494. Copyright 2008 by the Massachusetts Medical Society. All rights reserved. Reprinted with permission.

providing superior detail both of brain anatomy and extent of tumor compared to computed tomography (Armstrong, Cohen, Weinberg, & Gilbert, 2004). Glioblastoma characteristically appear as a ring-enhancing lesion with a rim of contrast enhancement surrounding an area of necrosis. However, it is recognized that these tumors can be nonenhancing or have heterogenous enhancement, particularly in secondary tumors. The tumor is infiltrative, and that tumor is also present in the surrounding brain. Although there can be a characteristic imaging appearance, obtaining tissue is necessary to make a definitive diagnosis in almost all cases. Therefore, either biopsy or tumor removal is performed unless the tumor is in eloquent brain (parts of the brain that control function such as senses, speech, and motor function) or comorbid conditions preclude surgery (Bohan & Glass-Macenska, 2004; Simon & Schramm, 2009).

Surgery

Surgery serves multiple purposes in patients with glial tumors, including obtaining tissue for diagnosis, improving neurologic function, or preventing impending herniation or neurologic compromise (Cardis et al., 2007). However, surgery for any of the malignant gliomas is never curative. Remaining in the brain are infiltrating microscopic tumor, often referred to by patients as "roots or tentacles," that are not detectable on MRI. Therefore, for most glial tumors, the surgeon can never "get it all." The role of surgery has not been evaluated in a randomized trial comparing outcome in patients undergoing surgery versus biopsy. However, there are studies that support the role of extensive resection as an important component in patient management. Lacroix et al. (2001) did perform a retrospective review reporting that if patients undergo a 90% resection, there

is a significant improvement—13 versus 8.8 months median survival ($p < 0.001$).

The surgical approach is dependent on several factors, including the size and location of the lesion, association with the frontal cortex, association with edema or herniation, whether the lesion is focal or multifocal, and whether margins are delineated or diffuse (Jackson et al., 2001; Ryken, Frankel, Julien, & Olson, 2008). In general, neurosurgeons will perform the maximum resection possible without resulting in neurologic compromise. Removal of tumor is important to reduce intracranial pressure and tumor-induced mass effect and improve neurologic function, but the primary purpose is to obtain tissue for diagnosis. Because of the heterogeneous nature of these lesions, it is critically important to obtain enough tissue to make an accurate diagnosis. A review of 81 cases of biopsy followed by resection reported that 38% of diagnoses changed with results of the tumor resection (most commonly an increase in tumor grade), resection altered prognosis in 49% of patients, and resection altered the treatment plan in 33% (Jackson et al.).

There are several new techniques used intraoperatively to enhance the extent of resection without neurologic compromise. These include awake craniotomy, functional imaging, and use of intraoperative MRI (Simon & Schramm, 2009). The primary goal of these technologies is to extend the amount of tumor tissue that can be safely removed. The impact of these techniques on patient outcome is still under investigation.

In addition to tumor removal, local therapies can be introduced at the time of tumor resection. Historically, direct application of treatment, including chemotherapy and radiation therapy, has been attempted with minimal impact on survival (Gonzalez & Gilbert, 2005; Westphal et al., 2003). Gliadel, a polymer impregnated with BCNU (carmustine), has been approved for use in newly diagnosed patients with glioblastomas, with improvement in survival when compared to placebo (hazard ratio = 0.73, $p < 0.05$) (Westphal et al.). However, when only patients with glioblastomas were included in the analysis, not the full patient population included in the intent-to-treat analysis, the study did not reach statistical significance. Thus, the use in patients at the time of initial tumor resection remains controversial (Gonzalez & Gilbert).

Radiation Therapy

Radiation therapy is often used as the initial postoperative treatment for malignant gliomas. Level 1 evidence (evidence obtained from a properly designed randomized trial) of the efficacy of radiation therapy exists for WHO grade III and IV tumors (Walker et al., 1978). Early studies reported a substantial impact on survival when compared to surgery alone, extending survival from 3–6 months to 9–12 months (Walker et al.). For glial tumors, the use of local radiation therapy had the same impact

on survival with less toxicity than whole brain radiation therapy. Therefore, radiation treatment using a local field has become the standard of care (Hancock & Burrow, 2004). Intensive dosing and use of radiosensitizers have not shown to be beneficial (Chang, Khuntia, Robins, & Mehta, 2007). The current standard for malignant glioma patients is 60 Gy delivered in 2 Gy fractions to the gross total volume plus a 2–3 cm margin (Chang et al., 2007). For patients with grade I or II lesions, this dose has not been shown to improve survival either in place of standard fractionated radiation therapy or in addition to it (Souhami et al., 2004).

New radiation therapy techniques and technology are under evaluation. These include using advanced imaging technology such as positron-emission tomography scans or magnetic resonance spectroscopy to determine treatment field, use of conformal planning with intensity modulated radiation therapy, and use of proton beam radiation therapy (Chang et al., 2007). These techniques may improve the efficacy of the radiation while decreasing treatment exposure to normal brain parenchyma. However, there are no studies that provide definitive evidence that these technologies improve survival or decrease treatment-related toxicity. Therefore, studies should continue to fully assess the impact of these modalities.

Chemotherapy

Historically, conventional systemic chemotherapy has several limitations when used to treat glial tumors. These include poor drug penetration into tumor (as a result of blood-brain barrier, hypoxia, and intracranial pressure), systemic toxicity, drug-drug interactions (e.g., corticosteroids, anticonvulsants), and intrinsic resistance of brain tumors (Gonzalez & Gilbert, 2005). Alkylating agents such as BCNU and CCNU (lomustine) have exhibited the best response rate in these tumors, with 20%–35% of newly diagnosed patients demonstrating objective responses. However, a meta-analysis of studies containing chemotherapy in patients with newly diagnosed glioblastoma reported only a very modest impact on survival (Fine, Dear, Loeffler, Black, & Canellos, 1993).

In 2005, Stupp et al. reported the first level 1 evidence of the benefit of temozolomide in addition to radiation therapy in patients with newly diagnosed glial tumors. The treatment regimen, consisting of 75 mg/m² of temozolomide daily during radiation therapy followed by 200 mg/m² five out of every 28 days for six months to one year demonstrated a significant survival advantage (14.6 months versus 12.1 months) compared with external beam radiation treatment alone. In a subgroup of patients, 06-methylguanine methyltransferase (MGMT) promoter methylation was associated with improved progression-free and overall survival (Hegi et al., 2005; Stupp et al., 2009). MGMT is a DNA repair enzyme that, when the promoter region of the gene is methylated,

gene expression is blocked and less MGMT enzyme is produced, making the tumor cell less able to repair damage caused by alkylating agents such as temozolomide. A recently published analysis of the two-year and five-year survival data confirmed this improvement in overall survival for those with methylated MGMT (survival of 27% versus 11% at two years and 10% versus 2% at five years [hazard ratio = 0.6; 95% CI = 0.5–0.7; $p < 0.0001$]) (Stupp et al., 2009). Current studies validated the association of MGMT methylation and outcome in a larger sample as well as evaluating the impact of dose intensification of the adjuvant arm (Stupp et al., 2006).

Chemotherapy for patients with grade II or III gliomas remains controversial. For patients with grade II tumors who have undergone a complete resection, treatment may include observation, fractionated external beam radiation therapy, or the consideration of chemotherapy (Duran & Raizer, 2007). No study to date has shown a survival benefit for the use of chemotherapy alone or when chemotherapy is added to radiation therapy for treatment of grade II gliomas. Because of the reported chemosensitivity of patients with oligodendroglial tumors, chemotherapy is often prescribed to patients with

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these tumors, and studies are currently underway evaluating response to these therapies (Graham & Cloughesy, 2004; Van den Bent, Reni, Gatta, & Vecht, 2008). For patients with anaplastic astrocytoma, standard treatment approaches include a maximal safe resection followed by radiation therapy. The use of chemotherapy in the adjuvant setting also has not been shown to confer a survival benefit in this population (Graham & Cloughesy; Wen & Kesari, 2008).

Treatment at Recurrence

To date, there are no standard treatments for glial malignancies at recurrence (Gilbert et al., 2009). In May 2009, the U.S. Food and Drug Administration granted accelerated approval for the use of bevacizumab for the treatment of patients with GBM who have recurred after standard treatment, representing the first approved treatment for recurrent GBM in over 10 years. Participation in clinical trials should be encouraged at this stage of the illness. In the United States, repeat tumor resection may be performed to confirm tumor

progression and relieve neurologic symptoms (Bohan & Glass-Macinka, 2004). This is increasingly important because of the recognition of worsened imaging soon after completion of chemoradiation, which may be a consequence of pseudoprogression (Brandes, Tosoni, et al., 2008; Chamberlain, Glantz, Chalmers, Van Horn, & Sloan, 2007). This effect, in which the enhancement of size of the lesion initially increases as a result of early necrosis, may occur in up to 30% of patients treated with concurrent chemoradiation (Chamberlain et al.). Recently, it has been reported that it occurs more commonly in patients with methylated MGMT and may confer improved survival for patients experiencing it (Brandes, Franceschi, et al., 2008).

Phase II data indicate modest efficacy to a variety of therapies, including dose-dense temozolomide, other alkylating agents, irinotecan, and PCV (procarbazine, CCNU, and vincristine) (Gonzalez & Gilbert, 2005; Graham & Cloughesy, 2004). Antiangiogenic treatments are undergoing extensive evaluation. Bevacizumab, a humanized monoclonal antibody against the vascular endothelial growth factor (VEGF), has been the most widely studied antiangiogenic agent in malignant gliomas. Vredenburgh et al. (2007) reported evidence of activity in recurrent malignant glioma to the combination of bevacizumab and irinotecan. Other studies have demonstrated similar results (Chamberlain, 2009; Desjardins et al., 2005). However, there are some concerns about potential toxicity, such as wound healing problems and intestinal perforation (Chamberlain; Zuniga et al., 2009). In addition, classic metrics of efficacy in brain tumor studies may be misleading. Inhibition of VEGF by bevacizumab may repair blood-brain barrier dysfunction, leading to a decrease in IV contrast leakage into tumor. This may be erroneously interpreted as tumor response, thereby possibly accounting for a component of the reported high response rates (Chamberlain). Studies are currently underway to evaluate the impact of this therapy in recurrent disease as well as the addition to radiation and temozolomide in newly diagnosed patients with glial tumors.

New Paradigms

Developing effective new treatments for malignant gliomas has proven to be very challenging. Intensified therapy, even to the degree requiring bone marrow or stem cell transplantation, has not shown significant improvements in survival. The heterogeneity of these tumors remains one of the major hurdles. Despite similar histopathologic appearance, the underlying molecular changes that resulted in the cancer formation vary greatly from tumor to tumor (Sathornsumetee & Rich, 2008). Therefore, a particular therapy may prove very beneficial to a subpopulation of patients but have only a modest response rate overall for the entire population. There are currently many initiatives to extensively characterize

malignant gliomas so that specific molecular profiles that predict treatment response can be developed. This will hopefully lend itself to optimizing selection of therapy for individual patients.

An immediate challenge is to build on the results of the chemoradiation treatment regimen from the study by Stupp et al. (2006). One of the approaches is to use biologic agents to treat these tumors. Many of the molecular abnormalities are known to deregulate signal transduction pathways that are involved in maintaining normal homeostasis or confer malignant properties, such as self-sustained proliferations, resistance to apoptotic stimuli, tissue invasion, and the ability to form and sustain new blood vessels (Mason & Cairncross, 2008). New treatment approaches targeting these signal transduction pathways are currently being evaluated and are designed to alter tumor behavior (Mason & Cairncross; Sathornsumetee et al., 2008). It may not result in tumor destruction, but rather may control tumor growth or allow apoptosis. There are a plethora of approaches currently under investigation. These include inhibition of growth factor signaling pathways (such as epidermal growth factor pathway, platelet-derived growth factor pathway, VEGF pathway, and others (Sathornsumetee et al.).

The use of biologic agents uses agents that are designed to modulate a specific signaling event thought to have a critical role in the survival, proliferation, or invasion of a specific cancer. This approach is not specific to glial tumors. In oncology, this approach includes the use of imatinib in treatment of chronic myelogenous leukemia. The complicating factor for glial tumors is that there are several pathways thought to be critical to influencing tumor growth, including EGFR, VEGF, FTI (farnesyl transferase inhibitor), PTEN/P13K, and platelet-derived growth factor receptor (Sathornsumetee et al., 2008). Unlike chronic leukemia, several of these pathways are ac-

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tive in most glial tumors and there may be cross-linkages among pathways. This results in the tumor using a different pathway if one is shut down or inhibited by therapy. As a result, agents that target multiple pathways or the use of multiple agents will most likely be needed to retard tumor growth (Sathornsumetee & Rich, 2008).

It is now recognized that improvements in survival for patients with glial tumors may occur in a stepwise fashion, with no one treatment leading to a cure. Ongoing studies will hopefully build on the foundation of

treatment for all grades of glial tumors. While these new therapies may represent innovations in treatment, they have generated several issues that have further complicated evaluation of treatment. One issue is that these newer agents often do not result in tumor shrinkage. Therefore, the definition of response has been controversial. Additionally, other agents, such as VEGF inhibitors, result in significant reductions in contrast enhancement, but often nonenhancing tumors continue to progress, or the patient continues to decline neurologically despite an apparent "improvement on MRI." Other treatments result in initial worsening of contrast enhancement, termed "pseudoprogression," that is difficult to distinguish from progressing tumor. The use of improved molecular analysis of individual tumors in conjunction with targeted approaches will hopefully result in significant improvements in overall survival.

Supportive Care

As treatment continues to advance, there are several supportive care issues that can significantly affect quality of life and even hasten patient death if not well controlled. These include use of corticosteroids, the occurrence of thrombosis, and neurologic events and deficits, such as seizures and cognitive deficits.

Corticosteroids: Glial tumors often result in brain edema causing neurologic compromise. Corticosteroids have been shown to reduce symptoms and improve life expectancy. There is not a standard dose or type of steroids that is used. Typical doses range from 2 mg–24 mg of dexamethasone (Wen & Kesari, 2008). Typically, the lowest dose possible to control symptoms should be used, and tapering should occur as soon as tolerated. Chronic use of steroids can result in significant side effects, including muscle weakness, poor wound healing, risk of infection, and bone loss resulting in fractures.

Seizures: Seizures occur in 50%–70% of patients with low-grade gliomas and 20%–30% of patients with glioblastoma (Armstrong, Kanusky, & Gilbert, 2003; Westcarth & Armstrong, 2007). Tumor location is important because tumors involving the cerebellum and brainstem are not associated with seizure occurrence. The use of prophylactic anticonvulsants in patients with cerebral lesions is controversial. The American Academy of Neurology performed a meta-analysis and reported no benefit to their use (Glantz et al., 2000). However, the studies included had several limitations, and some clinicians continue to use prophylaxis, particularly in superficial lesions or those associated with hemorrhage, which are thought to confer higher risk of seizures (Stevens, 2006). Certain anticonvulsants, including phenytoin, phenobarbital, and carbamazepine, can alter the metabolism of chemotherapy (Chang et al., 2001, 2008; Gilbert et al., 2003; Loghin et al., 2007). Therefore, their use is often avoided or patients are changed to a

nonenzyme-inducing anticonvulsant, such as levacetam (Wen & Kesari, 2008).

Unlike epilepsy, seizures in the person with a glial tumor can result in transient or permanent deficits or even death (Armstrong et al., 2003). Therefore, management goals should include amelioration of all seizures if possible. Appropriate education on seizure management at home should be undertaken. If the patient experiences a prolonged seizure or multiple seizures without recovery, emergency measures should be undertaken to prevent injury or death.

Cognitive deficits and fatigue: Cognitive deficits occur frequently in patients with glial tumors as a result of the tumor, therapy, depression, or concurrent medications, such as anticonvulsants (Wen & Kesari, 2008). Use of neurocognitive testing to fully evaluate deficits and counseling for depression is imperative for overall patient management. Use of psychostimulants, such as methylphenidate, may improve attention and reduce abulia (loss of the ability to make decisions or act independently) (Litofsky & Resnick, 2009; Meyers, Weitzner, Valentine, & Levin, 1998; Wen & Kesari, 2008). Depression has been estimated to occur in nearly 50% of patients with glioblastomas (Litofsky & Resnick). Providing adequate psychosocial support and consideration of pharmacotherapy in appropriate patients is an important challenge that has not been fully evaluated for impact on patient outcome.

Thrombosis: Development of deep vein thrombosis is a recognized complication in patients with glial tumors, with reported incidence as high as 40% (Marras, Geerts, & Perry, 2000; Sciacca et al., 2004). Risks include reduced mobility in some patients, but hypercoagulability is associated with the tumor itself and any patient is at risk (Marras et al., 2000; Wen & Kesari, 2008). Often, classic symptoms, such as pain and erythema, are masked as a result of the use of corticosteroids. Evaluation of the lower extremities with Doppler ultrasound or use of high-resolution computed tomography and d-dimer are indicated in any patient suspected of having a thrombosis (Gerber, Grossman, & Streiff, 2006; Wagman et al., 2008). Anticoagulation can be safely administered, although risk of bleeding can occur and the patient should

be monitored carefully. If anticoagulation is stopped, re-embolization can occur because of the underlying hypercoagulable state (Catt, Chalmers, & Fallowfield, 2008; Gerber et al., 2006).

Despite the advances discussed previously, most patients with glial tumors will die of their disease. In caring for patients, it is important to provide information regarding the diagnosis and prognosis while still maintaining hope. Involvement of a caregiver early in the course of the disease is important in establishing support for the patient (Catt et al., 2008). Early and ongoing discussion may lessen the anxiety related to the uncertainty of prognosis and help maintain the trust and credibility of the health care providers. Good symptom control throughout the illness will improve the patient's quality of life but also improve the patient's legacy and the caregiver's memories (Faithfull, Cook, & Lucas, 2005).

Conclusion

There have been significant advances in the diagnosis and management of patients with glial tumors over the last decade. Current efforts will lead to a better understanding of the tumor biology and identify specific targets within the tumor that may result in improved tumor control. This paradigm shift will have a major impact on brain tumor treatment strategies in the near and distant future.



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References

- American Cancer Society. (2009). *Cancer facts and figures, 2009*. Atlanta, GA: Author.
- Armstrong, T.S., Cohen, M.Z., Weinberg, J., & Gilbert, M.R. (2004). Imaging techniques in neuro-oncology. *Seminars in Oncology Nursing*, 20(4), 231–239.
- Armstrong, T.S., Kanusky, J.T., & Gilbert, M.R. (2003). Seize the moment to learn about epilepsy in people with cancer. *Clinical Journal of Oncology Nursing*, 7(2), 163–169.
- Bohan, E., & Glass-Macinka, D. (2004). Surgical management of patients with primary brain tumors. *Seminars in Oncology Nursing*, 20(4), 240–252.
- Bondy, M.L., Scheurer, M.E., Malmer, B., Barnholtz-Sloan, J.S., Davis, F.G., Il'yasova, D., et al. (2008). Brain tumor epidemiology: Consensus from the Brain Tumor Epidemiology Consortium. *Cancer*, 113(7, Suppl.), 1953–1968.
- Brandes, A.A., Franceschi, E., Tosoni, A., Blatt, V., Pession, A., Tallini, G., et al. (2008). MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. *Journal of Clinical Oncology*, 26(13), 2192–2197.
- Brandes, A.A., Tosoni, A., Spagnoli, F., Frezza, G., Leonardi, M., Calbucci, F., et al. (2008). Disease progression or pseudoprogression after concomitant radiochemotherapy treatment: Pitfalls in neuro-oncology. *Neuro-Oncology*, 10(3), 361–367.
- Bromberg, J.E., & van den Bent, M.J. (2009). Oligodendrogliomas: Molecular biology and treatment. *Oncologist*, 14(2), 155–163.

- Cardis, E., Richardson, L., Deltour, I., Armstrong, B., Feychting, M., Johansen, C., et al. (2007). The INTERPHONE study: Design, epidemiological methods, and description of the study population. *European Journal of Epidemiology*, 22(9), 647–664.
- Catt, S., Chalmers, A., & Fallowfield, L. (2008). Psychosocial and supportive-care needs in high-grade glioma. *Lancet Oncology*, 9(9), 884–891.
- Central Brain Tumor Registry of the United States. (2008). *Statistical report: Primary brain tumors in the United States, 2000–2004*. Hinsdale, IL: Author.
- Chamberlain, M.C. (2009). Bevacizumab for recurrent malignant gliomas: Efficacy, toxicity, and patterns of recurrence. *Neurology*, 72(8), 772–774.
- Chamberlain, M.C., Glantz, M.J., Chalmers, L., Van Horn, A., & Sloan, A.E. (2007). Early necrosis following concurrent Temodar and radiotherapy in patients with glioblastoma. *Journal of Neuro-Oncology*, 82(1), 81–83.
- Chang, J.E., Khuntia, D., Robins, H.I., & Mehta, M.P. (2007). Radiotherapy and radiosensitizers in the treatment of glioblastoma multiforme. *Clinical Advances in Hematology Oncology*, 5(11), 894–902, 907–815.
- Chang, S.M., Kuhn, J.G., Robins, H.I., Schold, S.C., Jr., Spence, A.M., Berger, M.S., et al. (2001). A Phase II study of paclitaxel in patients with recurrent malignant glioma using different doses depending upon the concomitant use of anticonvulsants: A North American Brain Tumor Consortium report. *Cancer*, 91(2), 417–422.
- Chang, S.M., Lamborn, K.R., Kuhn, J.G., Yung, W.K., Gilbert, M.R., Wen, P.Y., et al. (2008). Neuro-oncology clinical trial design for targeted therapies: Lessons learned from the North American Brain Tumor Consortium. *Neuro-Oncology*, 10(4), 631–642.
- Desjardins, A., Rich, J.N., Quinn, J.A., Vredenburgh, J., Gururangan, S., Sathornsumetee, S., et al. (2005). Chemotherapy and novel therapeutic approaches in malignant glioma. *Frontiers in Bioscience*, 10, 2645–2668.
- Drappatz, J., Schiff, D., Kesari, S., Norden, A.D., & Wen, P.Y. (2007). Medical management of brain tumor patients. *Neurologic Clinics*, 25(4), 1035–1071.
- Duran, I., & Raizer, J.J. (2007). Low-grade gliomas: Management issues. *Expert Review of Anticancer Therapy*, 7(12, Suppl.), S15–S21.
- Faithfull, S., Cook, K., & Lucas, C. (2005). Palliative care of patients with a primary malignant brain tumor: Case review of service use and support provided. *Palliative Medicine*, 19(7), 545–550.
- Fine, H.A., Dear, K.B., Loeffler, J.S., Black, P.M., & Canellos, G.P. (1993). Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer*, 71(8), 2585–2597.
- Fisher, J.L., Schwartzbaum, J.A., Wrensch, M., & Wiemels, J.L. (2007). Epidemiology of brain tumors. *Neurologic Clinics*, 25(4), 867–890.
- Furnari, F.B., Fenton, T., Bachoo, R.M., Mukasa, A., Stommel, J.M., Stegh, A., et al. (2007). Malignant astrocytic glioma: Genetics, biology, and paths to treatment. *Genes and Development*, 21(21), 2683–2710.
- Gerber, D.E., Grossman, S.A., & Streiff, M.B. (2006). Management of venous thromboembolism in patients with primary and metastatic brain tumors. *Journal of Clinical Oncology*, 24(8), 1310–1318.
- Gilbert, M.R., Supko, J.G., Batchelor, T., Lesser, G., Fisher, J.D., Piantadosi, S., et al. (2003). Phase I clinical and pharmacokinetic study of irinotecan in adults with recurrent malignant glioma. *Clinical Cancer Research*, 9(8), 2940–2949.
- Gilbert, S.J., Singhrao, S.K., Khan, I.M., Gonzalez, L.G., Thomson, B.M., Burdon, D., et al. (2009). Enhanced tissue integration during cartilage repair in vitro can be achieved by inhibiting chondrocyte death at the wound edge. *Tissue Engineering. Part A*, 15(7), 1739–1749.
- Glantz, M.J., Cole, B.F., Forsyth, P.A., Recht, L.D., Wen, P.Y., Chamberlain, M.C., et al. (2000). Practice parameter: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 54(10), 1886–1893.
- Gonzalez, J., & Gilbert, M.R. (2005). Treatment of astrocytomas. *Current Opinions in Neurology*, 18(6), 632–638.
- Graham, C.A., & Cloughesy, T.F. (2004). Brain tumor treatment: Chemotherapy and other new developments. *Seminars in Oncology Nursing*, 20(4), 260–272.
- Hancock, C.M., & Burrow, M.A. (2004). The role of radiation therapy in the treatment of central nervous system tumors. *Seminars in Oncology Nursing*, 20(4), 253–259.
- Hegi, M.E., Diserens, A.C., Gorlia, T., Hamou, M.F., de Tribolet, N., Weller, M., et al. (2005). MGMT gene silencing and benefit from temozolomide in glioblastoma. *New England Journal of Medicine*, 352(10), 997–1003.
- Jackson, R.J., Fuller, G.N., Abi-Said, D., Lang, F.F., Gokaslan, Z.L., Shi, W.M., et al. (2001). Limitations of stereotactic biopsy in the initial management of gliomas. *Neuro-Oncology*, 3(3), 193–200.
- Kan, P., Simonsen, S.E., Lyon, J.L., & Kestle, J.R. (2008). Cellular phone use and brain tumor: A meta-analysis. *Journal of Neuro-Oncology*, 86(1), 71–78.
- Lacroix, M., Abi-Said, D., Fourney, D.R., Gokaslan, Z.L., Shi, W., DeMonte, F., et al. (2001). A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival. *Journal of Neurosurgery*, 95(2), 190–198.
- Lahkola, A., Auvinen, A., Raitanen, J., Schoemaker, M.J., Christensen, H.C., Feychting, M., et al. (2007). Mobile phone use and risk of glioma in five North European countries. *International Journal of Cancer*, 120(8), 1769–1775.
- Lee, E.L., & Armstrong, T.S. (2008). Increased intracranial pressure. *Clinical Journal of Oncology Nursing*, 12(1), 37–41.
- Litofsky, N.S., & Resnick, A.G. (2009). The relationships between depression and brain tumors. *Journal of Neuro-Oncology*. [Epub ahead of print].
- Loghini, M.E., Prados, M.D., Wen, P., Junck, L., Lieberman, F., Fine, H., et al. (2007). Phase I study of temozolomide and irinotecan for recurrent malignant gliomas in patients receiving enzyme-inducing antiepileptic drugs: A North American Brain Tumor Consortium study. *Clinical Cancer Research*, 13(23), 7133–7138.
- Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavenee, W.K., Burger, P.C., Jouvet, A., et al. (2007). The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathologica*, 114(2), 97–109.
- Lovely, M.P. (1998). Quality of life of brain tumor patients. *Seminars in Oncology Nursing*, 14(1), 73–80.
- Lovely, M.P. (2004). Symptom management of brain tumor patients. *Seminars in Oncology Nursing*, 20(4), 273–283.
- Marras, L.C., Geerts, W.H., & Perry, J.R. (2000). The risk of venous thromboembolism is increased throughout the course of malignant glioma: An evidence-based review. *Cancer*, 89(3), 640–646.
- Mason, W.P., & Cairncross, J.G. (2008). Invited article: The expanding impact of molecular biology on the diagnosis and treatment of gliomas. *Neurology*, 71(5), 365–373.
- Meyers, C.A., Weitzner, M.A., Valentine, A.D., & Levin, V.A. (1998). Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. *Journal of Clinical Oncology*, 16(7), 2522–2527.
- Ohgaki, H., & Kleihues, P. (2007). Genetic pathways to primary and secondary glioblastoma. *American Journal of Pathology*, 170(5), 1445–1453.
- Ron, E., Modan, B., Boice, J.D., Jr., Alfandary, E., Stovall, M., Chetrit, A., et al. (1988). Tumors of the brain and nervous system after radiotherapy in childhood. *New England Journal of Medicine*, 319(16), 1033–1039.
- Ryken, T.C., Frankel, B., Julien, T., & Olson, J.J. (2008). Surgical management of newly diagnosed glioblastoma in adults: Role of cytoreductive surgery. *Journal of Neuro-Oncology*, 89(3), 271–286.
- Sadetzki, S., Modan, B., Chetrit, A., & Freedman, L. (2000). An iatrogenic epidemic of benign meningioma. *American Journal of Epidemiology*, 151(3), 266–272.
- Sathornsumetee, S., Cao, Y., Marcello, J.E., Herndon, J.E., 2nd, McLendon, R.E., Desjardins, A., et al. (2008). Tumor angiogenic and hypoxic profiles predict radiographic response and survival in malignant astrocytoma patients treated with bevacizumab and irinotecan. *Journal of Clinical Oncology*, 26(2), 271–278.
- Sathornsumetee, S., & Rich, J.N. (2008). Designer therapies for

- glioblastoma multiforme. *Annals of the New York Academy of Science*, 1142, 108–132.
- Schabet, M. (1999). Epidemiology of primary CNS lymphoma. *Journal of Neuro-Oncology*, 43(3), 199–201.
- Scheurer, M.E., El-Zein, R., Thompson, P.A., Aldape, K.D., Levin, V.A., Gilbert, M.R., et al. (2008). Long-term anti-inflammatory and antihistamine medication use and adult glioma risk. *Cancer Epidemiology, Biomarkers, and Prevention*, 17(5), 1277–1281.
- Schiff, D., Suman, V.J., Yang, P., Rocca, W.A., & O'Neill, B.P. (1998). Risk factors for primary central nervous system lymphoma: A case-control study. *Cancer*, 82(5), 975–982.
- Schoemaker, M.J., Swerdlow, A.J., Ahlbom, A., Auvinen, A., Blaasaas, K.G., Cardis, E., et al. (2005). Mobile phone use and risk of acoustic neuroma: Results of the Interphone Case-Control Study in five North European countries. *British Journal of Cancer*, 93(7), 842–848.
- Sciacca, F.L., Ciusani, E., Silvani, A., Corsini, E., Frigerio, S., Pogliani, S., et al. (2004). Genetic and plasma markers of venous thromboembolism in patients with high grade glioma. *Clinical Cancer Research*, 10(4), 1312–1317.
- Simon, M., & Schramm, J. (2009). Surgical management of intracranial gliomas. *Recent Results in Cancer Research*, 171, 105–124.
- Souhami, L., Seiferheld, W., Brachman, D., Podgorsak, E.B., Werner-Wasik, M., Lustig, R., et al. (2004). Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: Report of Radiation Therapy Oncology Group 93–05 protocol. *International Journal of Radiation Oncology, Biology, and Physics*, 60(3), 853–860.
- Stevens, G.H. (2006). Antiepileptic therapy in patients with central nervous system malignancies. *Current Neurology and Neuroscience Reports*, 6(4), 311–318.
- Stupp, R., Hegi, M.E., Mason, W.P., van den Bent, M.J., Taphoorn, M.J., Janzer, R.C., et al. (2009). Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: Five-year analysis of the EORTC-NCIC trial. *Lancet Oncology*, 10(5), 459–466.
- Stupp, R., Hegi, M.E., van den Bent, M.J., Mason, W.P., Weller, M., Mirimanoff, R.O., et al. (2006). Changing paradigms—An update on the multidisciplinary management of malignant glioma. *Oncologist*, 11(2), 165–180.
- Stupp, R., Mason, W.P., van den Bent, M.J., Weller, M., Fisher, B., Taphoorn, M.J., et al. (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *New England Journal of Medicine*, 352(10), 987–996.
- Ueki, K., Nishikawa, R., Nakazato, Y., Hirose, T., Hirato, J., Funada, N., et al. (2002). Correlation of histology and molecular genetic analysis of 1p, 19q, 10q, TP53, EGFR, CDK4, and CDKN2A in 91 astrocytic and oligodendroglial tumors. *Clinical Cancer Research*, 8(1), 196–201.
- U.S. Food and Drug Administration. (2009). FDA approves drug for treatment of aggressive brain cancer. Retrieved August 12, 2009, from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm152295.htm>
- Van den Bent, M.J., Reni, M., Gatta, G., & Vecht, C. (2008). Oligodendroglioma. *Critical Reviews in Oncology/Hematology*, 66(3), 262–272.
- Vredenburgh, J.J., Desjardins, A., Herndon, J.E., 2nd, Dowell, J.M., Reardon, D.A., Quinn, J.A., et al. (2007). Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. *Clinical Cancer Research*, 13(4), 1253–1259.
- Wagman, L.D., Baird, M.F., Bennett, C.L., Bockenstedt, P.L., Cataland, S.R., Fanikos, J., et al. (2008). Venous thromboembolic disease. NCCN. Clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, 6(8), 716–753.
- Walker, M.D., Alexander, E., Jr., Hunt, W.E., MacCarty, C.S., Mahaley, M.S., Jr., Mealey, J., Jr., et al. (1978). Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. *Journal of Neurosurgery*, 49(3), 333–343.
- Wen, P.Y., & Kesari, S. (2008). Malignant gliomas in adults. *New England Journal of Medicine*, 359(5), 492–507.
- Westcarth, L., & Armstrong, T. (2007). Seizures in people with cancer. *Clinical Journal of Oncology Nursing*, 11(1), 33–37.
- Westphal, M., Hilt, D.C., Bortey, E., Delavault, P., Olivares, R., Warnke, P.C., et al. (2003). A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro-Oncology*, 5(2), 79–88.
- Zuniga, R.M., Torcuator, R., Jain, R., Anderson, J., Doyle, T., Ellika, S., et al. (2009). Efficacy, safety and patterns of response and recurrence in patients with recurrent high-grade gliomas treated with bevacizumab plus irinotecan. *Journal of Neuro-Oncology*, 91(3), 329–336.