Focus on central nervous system neoplasia

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Introduction, epidemiology, and etiology

Twenty thousand new primary central nervous system (CNS) neoplasms are diagnosed each year in the United States. CNS tumors are the second most frequent malignancy of childhood, and their incidence in adults increases with advancing age. Importantly, cancers of the CNS are among the most devastating of human malignancies, affecting the organ that defines the "self," often severely compromising quality of life (Louis et al., 2000). There are dozens of different types of CNS neoplasms recognized by the World Health Organization (WHO). Malignant gliomas of the cerebral hemispheres in adults and medulloblastomas of the cerebellum in children are the most common and most studied of primary malignancies and are reviewed here.

Malignant gliomas are so named because tumor cells phenotypically resemble normal glia; nonetheless, the tumors may arise from pleuripotential precursors. Malignant gliomas are classified as astrocytomas, oligodendrogliomas, and oligoastrocytomas and are histologically graded as WHO II, III, or IV. The most aggressive, grade IV, astrocytoma is referred to as glioblastoma. Medulloblastomas, which are thought to arise by malignant transformation of cerebellar granular cell progenitors, have a poorly differentiated histologic appearance, are all WHO grade IV and are staged according to the extent of disease.

Although the cause of most CNS neoplasms remains enigmatic, certain associations are evident. Epidemiologic studies, in both adults and children, have linked exposure to ionizing radiation and the subsequent development of CNS tumors. Gliomas and medulloblastomas also occur in rare families, implicating a genetic etiology in some cases. Malignant gliomas arise in association with neurofibromatosis type 1, as well as with the Li-Fraumeni and Turcot syndromes. Medulloblastomas occur in Turcot and Gorlin syndromes.

Conventional diagnostics and therapeutics

Adults with gliomas present with seizures, headaches, or focal neurological deficits (DeAngelis, 2001). Neuroimaging with magnetic resonance (MR) is essential for localization. Surgery is required for sampling and is a component of therapy; however, because hemispheric gliomas always infiltrate the surrounding brain, surgical resection is seldom curative. Pathological examination establishes tumor type and grade, with subsequent therapy dependent on these parameters. Survival is determined by many interrelated biological and therapeutic variables. In general, younger age, oligodendroglial subtype, lower grade, extensive resection, radiotherapy, and chemosensitivity predict longer survival. Patients with these favorable prognostic factors may live 20 years or more. In contrast, elderly patients with unresectable grade IV astrocytic gliomas live about six months despite radiotherapy, and such tumors are rarely chemosensitive. This extreme heterogeneity suggests that malignant glioma is many diseases, each with its own behavior and therapeutic requirements. Over the years, many new therapies have been tried, sometimes with much fanfare, but to date these have failed. Current therapies—surgery, radiation, and chemotherapy—are helpful and becoming safer, but the prospect that any combination of contemporary treatments can be curative now seems remote.

Children with medulloblastoma typically present with signs and symptoms attributable to a posterior fossa mass, including headache and vomiting from obstructive hydrocephalus, ataxia, and cranial nerve deficits (Packer et al., 1999). MR scanning reveals a cerebellar mass, with metastatic spread in about one-third of cases. Because of the tendency to disseminate, therapy consists of attempted surgical resection, external beam radiation to the entire neuraxis with a boost to the tumor bed, and multidrug chemotherapy for approximately one year. Histological features do not reliably predict behavior, although rare variants may follow more favorable or more aggressive courses. Prognostic staging is based on age, extent of surgical resection, and the presence of metastases. The overall 5-year survival of good risk patients is approximately 80% and about 65% for poor risk. However, life-altering cognitive, growth, and neuroendocrine deficits occur in the majority of survivors due in large part to the aggressive therapy that is necessary for tumor control. Consequently, as for malignant glioma, new therapeutic approaches are required.

The genetic basis of glioma and medulloblastoma tumorigenesis

Genetic analyses of gliomas in adults have demonstrated alterations characteristic of specific tumor subtypes and grades (Figure 1; Kleihues and Cavenee, 2000). The earliest known changes in astrocytomas have involved inactivating mutations of *TP53* as well as overexpression of the platelet-derived growth factor (PDGF) and PDGF receptor, and less commonly allelic loss of chromosome 22q. The progression to grade III astrocytoma is associated with inactivation of the p16-cdk4-pRb pathway as well as allelic loss of 19q. Further progression to grade IV (i.e., glioblastoma) occurs with loss of chromosome 10, sometimes with PTEN inactivation, and with amplification, rearrangement, and overexpression of the epidermal growth factor receptor (*EGFR*) gene. Oligodendroglial tumors commonly demonstrate allelic loss of 1p and 19q. As oligodendrogliomas become grade III lesions, they too undergo inactivation of the p16 pathway and may lose chromosome 10 and amplify *EGFR*. Oligoastrocytomas have histological features of both astrocytoma and oligodendroglioma, but are genotypically unambiguous, harboring the molecular signature of either oligodendroglioma or astrocytoma (Figure 1; Kleihues and Cavenee, 2000).

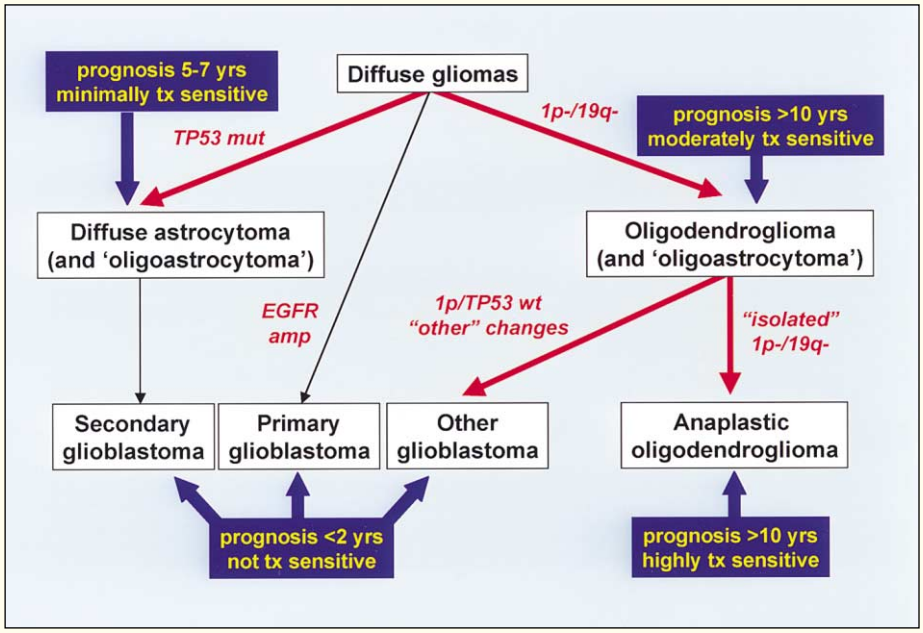

Figure 1. Traditional and molecular approaches to malignant glioma classification

Traditional histopathology classifies diffuse gliomas as astrocytomas, oligodendrogliomas, or oligoastrocytomas and assigns grades with anaplastic oligodendrogliomas and glioblastomas representing the high-grade lesions. Since particular genetic events (red italics) are associated with tumor histology, such as TP53 mutations in astrocytic tumors and 1p/19q loss in oligodendrogliomas, it is likely that genotyping will eventually classify tumors (bold red arrows). For instance, so-called oligoastrocytomas will be classified as either astrocytoma or oligodendroglioma. In addition, anaplastic oligodendrogliomas will be defined by a certain genotype, and other histologically similar tumors could be grouped with the glioblastomas. A combined histological-genetic approach would divide the tumors into clinically relevant groups with respect to survival and response to therapy (blue boxes). Abbreviations: TP53 mut, TP53 mutation; EGFR amp, EGFR amplification; $1p^{-}/19q^{-}$, allelic losses of 1p and 19q; prognosis values are estimates of median survival; tx, treatment.

The most common genetic alterations in medulloblastomas are loss of 17p distal to *TP53* and isochromosome 17q (Figure 2; Biegel, 1999; Kleihues and Cavenee, 2000). Insights into specific genetic pathways altered in these tumors have been provided by two inherited disorders: Gorlin syndrome, due to germline mutation of the Shh receptor *PTCH*, and Turcot syndrome, caused by mutation of either *APC* or DNA mismatch repair genes. About 10%–20% of sporadic tumors, typically of the desmoplastic variant, have been found to have mutations of genes in the Shh-PTCH-SMO pathway. Mutations related to Wnt-β-catenin-APC have also been documented but are rare. Molecular genetic assays have been clinically helpful in distinguishing medulloblastomas from the histologically similar but clinically distinct atypical teratoid/rhabdoid tumors that have 22q loss and *INI1/SNF5* mutations (Figure 2).

Molecular subsets of gliomas and medulloblastomas

Genotyping is beginning to influence treatment decisions (Figure 1). The case for molecular diagnosis as a guide to therapy is especially robust for oligodendroglioma (Cairncross et al., 1998; Ino et al., 2001; Smith et al., 2000). Approximately 60% of anaplastic oligodendrogliomas respond to a chemotherapy regimen called PCV (procarbazine, CCNU, and vincristine) (Cairncross et al., 1994). Those patients whose tumors have 1p loss essentially always respond to PCV, and those with combined 1p and 19q loss that lack other detectable alterations have durable responses and long survival times (over 10 years). In contrast, those whose tumors lack these genetic alterations but harbor others such as EGFR amplification rarely respond to PCV in a durable manner and have short survivals (less than 2 years). Hence, genotyping can direct the former group (1p loss) to initial PCV instead of radiotherapy, which is sometimes neurotoxic; the latter group (1p intact) can forego the unpleasantness and myelosuppression of PCV in favor of radiotherapy, which causes few side effects in patients with short survival times. It remains to be shown if 1p and 19q loss will also predict response to temozolomide, a new chemotherapeutic agent with antiglioma activity and a more favorable side-effect profile than PCV (Yung et al., 1999).

Glioblastomas can be divided into those with TP53 mutations and those with *EGFR* amplification, events which appear mutually exclusive (Figure 1; Kleihues and Cavenee, 2000). Patients whose glioblastomas have *TP53* mutations are often so-called secondary glioblastomas, in which glioblastoma has arisen in a prior lower grade astrocytoma, typically in younger adult patients. *TP53* mutations are also common in glioblastomas having many giant cells. *EGFR* gene amplification, on the other hand, typically occurs in so-called primary (or "de novo") glioblastomas, which appear to arise quite suddenly in older adult patients, as well as in small cell glioblastomas (Burger et al., 2001). Those high-grade astrocytic tumors with *EGFR* amplification and/or overrepresentation of chromosome 7 may follow more aggressive clinical courses and be less responsive to radiotherapy than glioblastomas with *TP53* mutations, but such differences do not yet influence clinical management (Barker et al., 2001; Kunwar et al., 2001; Smith et al., 2001). Moreover, it has not yet been possible to identify a molecular marker for the rare high-grade astrocytic gliomas that are cured by existing brain tumor therapies.

In the past decade, several developmentally regulated genes have been identified as markers that are associated with medulloblastoma outcome (Figure 2). Expression of the neurotrophin-3 receptor, *TrkC*, is associated with favorable clinical outcome (Segal et al., 1994). Increased expression of the neuregulin receptors *erbB2* and *erbB4* and of *c-myc*, however, are highly correlated with poor outcome (Gilbertson et al., 1997; Herms et al., 2000). Gene expression profiling with DNA oligonucleotide microarrays predicts favorable outcome for tumors expressing genes characteristic of cerebellar differentiation or encoding extracellular matrix proteins. In contrast, poor outcome is associated with expression of genes related to cell proliferation, multidrug resistance, and ribosomal biogenesis (Pomeroy et al., 2002). Expression profiles associated with metastasis include platelet-derived growth factor receptor α (*PDGFRA*) and genes in the ras/MAPK signaling pathway (MacDonald et al., 2001)

Animal models

A major recent advance in neurooncology has been the ability

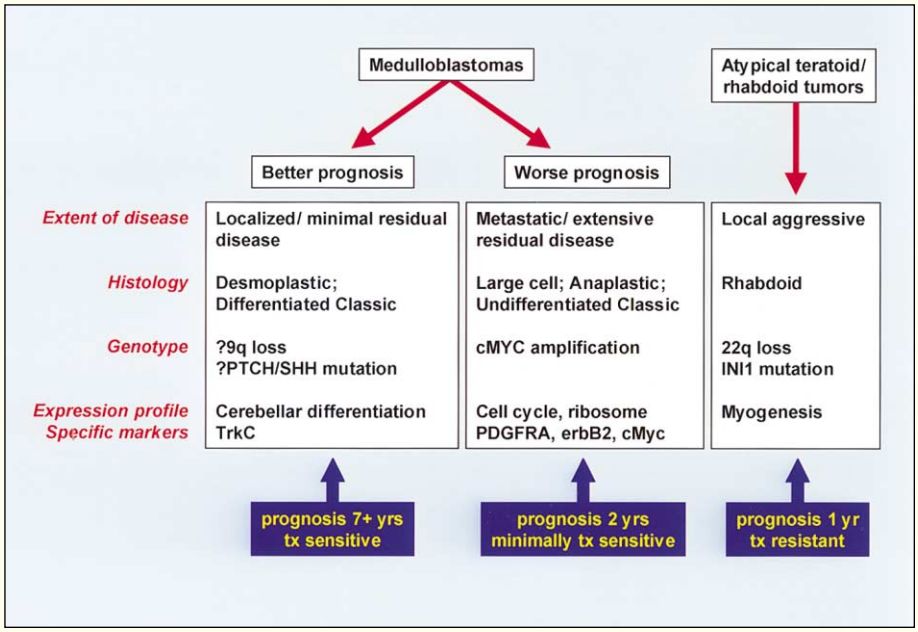

Figure 2. Traditional and molecular approaches to medulloblastoma classification

Medulloblastomas can be reliably distinguished from the histologically similar but clinically distinct atypical teratoid/rhabdoid tumors by characteristic genetic differences. In addition, medulloblastomas can be divided into better and worse prognosis cases by extent of disease, histopathology, genotype, and expression profiles. The exact prognostic importance of combinations of these parameters remains to be determined, and the given values (blue boxes) are therefore only rough approximations. See text for details.

to model glioma and medulloblastoma in mice using transgenic technologies (Holland, 2001; Wechsler-Reya and Scott, 2001). Such models now, for the first time, faithfully replicate the cardinal histological features of glioma—particularly glioblastoma—including white and gray matter invasion, vascular proliferation, and necrosis with tumor cell palisades. Such glioma models could be valuable for understanding the pathways responsible for glial tumorigenesis and for identifying novel therapeutic targets and also hold future promise for preclinical testing of novel therapies, especially when the transgenic alterations mimic those pathways deregulated in human gliomas (Holland, 2001). Mice with targeted mutation of the murine homolog of *PTCH* develop medulloblastomas, again offering a powerful tool for investigating dysregulated genetic pathways important in human medulloblastoma and potentially for preclinical trials (Wechsler-Reya and Scott, 2001).

New targets and novel therapies

The identification of molecular signatures that guide the use of existing therapies for individual patients—maximizing benefit and minimizing toxicity—is an important development in neurooncology, but the emergence of safe, curative treatments will require a deeper understanding of glioma and medulloblastoma biology. With such knowledge will come rationally designed, efficacious brain tumor therapies, analogous to STI571, the synthetic kinase inhibitor that reverses chronic myelogenous leukemia (CML) (Maura et al., 2002).

Broadly speaking, new therapies for CNS tumors can be anticipated in three arenas: (1) signal transduction blockade, (2) cell cycle control restoration, or (3) "effector" molecule inhibition. Activation of EGFR, PDGF, and ras signaling in high-grade astrocytomas suggests utility for inhibitors of receptor protein tyrosine kinases, farnesyltransferases, or protein kinase C pathways; such drugs are currently being evaluated in phase I/II malignant glioma trials. The association of poor medulloblastoma outcome with PDGFRA, ras/MAP kinase signaling, and ribosomal protein expression also provides a rational basis for signal transduction inhibitors in medulloblastoma treatment. Moreover, specific and potent blockers of Shh signaling have been identified and are being developed for clinical use, which could be of particular value for desmoplastic medulloblastomas (Taipale et al., 2000).

Inactivation of the p16 and p53 pathways argues that loss of cell cycle control contributes to gliomagenesis. Virally mediated gene transfer of functional p16, Rb, or p53, and mTOR inhibition with rapamycin analogs to restore the G1/S checkpoint are other examples of glioma therapies under development. Glioma cells synthesize matrix-degrading metalloproteinases and angiogenic molecules such as vascular endothelial growth factor (VEGF). These effector molecules contribute to invasion and vascular proliferation, cardinal features of malignant glioma histopathology. Reversing these behaviors with targeted inhibitors, some of which are now under study, may have therapeutic benefits. Oncolytic viruses—to deliver "chemosensitizing" genes and to lyse proliferating cells (e.g., attenuated herpes viruses)—have also entered clinical testing. Nonetheless, the tendency for human gliomas to invade widely and for medulloblastomas to metastasize could be significant obstacles to the effective delivery of such oncolytic viruses.

Future challenges

Advances in developmental neurobiology will no doubt augment our understanding of brain tumorigenesis, and there is a need for integration of developmental neurobiology with neuro-oncology (Louis et al., 2000). Indeed, from a therapeutic perspective, it may be especially important to understand early events. If STI571 for CML is any guide, new brain tumor therapies may be most effective when administered at an earlier stage in the neoplastic process, thus targeting critical tumor maintenance mechanisms (Maura et al., 2002). This, however, raises the thorny problem of early detection of brain tumors, with its technical and social challenges. In addition, a better understanding of the unique immunological environment of the CNS and of the biology of the blood-brain barrier will be important to the development and delivery of effective new therapies for glioma and medulloblastoma (Louis et al., 2000). Last, but certainly not least, improvement in the quality of life of patients suffering with CNS neoplasms is a goal of the highest priority.

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References

Barker, F.G., 2nd, Simmons, M.L., Chang, S.M., Prados, M.D., Larson, D.A., Sneed, P.K., Wara, W.M., Berger, M.S., Chen, P., Israel, M.A., and Aldape, K.D. (2001). EGFR overexpression and radiation response in glioblastoma multiforme. Int. J. Radiat. Oncol. Biol. Phys. *51*, 410–418.

Biegel, J.A. (1999). Cytogenetics and molecular genetics of childhood brain tumors. Neuro-oncol. *1*, 139–151.

Burger, P.C., Pearl, D.K., Aldape, K., Yates, A.J., Scheithauer, B.W., Passe, S.M., Jenkins, R.B., and James, C.D. (2001). Small cell architecture—a histological equivalent of EGFR amplification in glioblastoma multiforme? J. Neuropathol. Exp. Neurol. *60*, 1099–1104.

Cairncross, J.G., Macdonald, D., Ludwin, S., Lee, D., Cascino, T., Buckner, J., Fulton, D., Dropcho, E., Stewart, D., Schold, C., et al. (1994). Chemotherapy for anaplastic oligodendroglioma. J. Clin. Oncol. *12*, 2013–2021.

Cairncross, J.G., Ueki, K., Zlatescu, M.C., Lisle, D.K., Finkelstein, D.M., Hammond, R.R., Silver, J.S., Stark, P.C., Macdonald, D.R., Ino, Y., et al. (1998). Specific chromosomal losses predict chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J. Natl. Cancer Inst. *90*, 1473–1479.

DeAngelis, L.M. (2001). Brain tumors. N. Engl. J. Med. *344*, 114–123.

Gilbertson, R., Perry, R., Kelly, P., Pearson, A., and Lunec, J. (1997). Prognostic significance of HER2 and HER4 coexpression in childhood medulloblastoma. Cancer Res. *57*, 3272–3280.

Herms, J., Neidt, I., Luscher, B., Sommer, A., Schurmann, P., Schroder, T., Bergmann, M., Wilken, B., Probst-Cousin, S., Hernaiz-Driever, P., et al. (2000). C-MYC expression in medulloblastoma and its prognostic value. Int. J. Cancer *89*, 395–402.

Holland, E.C. (2001). Gliomagenesis: genetic alterations and mouse models. Nat. Rev. Genet. *2*, 120–129.

Ino, Y., Betensky, R.A., Zlatescu, M.C., Sasaki, H., Macdonald, D.R., Stemmer-Rachamimov, A.O., Ramsay, D.A., Cairncross, J.G., and Louis, D.N. (2001). Molecular subtypes of anaplastic oligodendroglioma: implications for patient management at diagnosis. Clin. Cancer Res. *7*, 839–845.

Kleihues, P., and Cavenee, W.K. (2000). World Health Organization Classification of Tumours of the Nervous System (Lyon: WHO/IARC).

Kunwar, S., Mohapatra, G., Bollen, A., Lamborn, K.R., Prados, M., and Feuerstein, B.G. (2001). Genetic subgroups of anaplastic astrocytomas correlate with patient age and survival. Cancer Res. *61*, 7683–7688.

Louis, D.N., Posner, J.B., Jacobs, T., and Kaplan, R. (2000). Report of the brain tumor progress review group. http://prg.nci.nih.gov/brain/finalreport.html.

MacDonald, T.J., Brown, K.M., LaFleur, B., Peterson, K., Lawlor, C., Chen, Y., Packer, R.J., Cogen, P., and Stephan, D.A. (2001). Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease. Nat. Genet. *29*, 143–152.

Maura, M.J., O'Dwyer, M., Heinrich, M.C., and Druker, B.J. (2002). STI571: a paradigm of new agents for cancer therapeutics. J. Clin. Oncol. *20*, 325–334.

Packer, R.J., Cogen, P., Vezina, G., and Rorke, L.B. (1999). Medulloblastoma: clinical and biologic aspects. Neuro-oncol. *1*, 232–250.

Pomeroy, S.L., Tamayo, P., Gaasenbeek, M., Sturla, L.M., Angelo, M., McLaughlin, M.E., Kim, J.Y., Goumnerova, L.C., Black, P.M., Lau, C., et al. (2002). Prediction of central nervous system embryonal tumour outcome based on gene expression. Nature *415*, 436–442.

Segal, R.A., Goumnerova, L.C., Kwon, Y.K., Stiles, C.D., and Pomeroy, S.L. (1994). Expression of the neurotrophin receptor TrkC is linked to a favorable outcome in medulloblastoma. Proc. Natl. Acad. Sci. USA *91*, 12867–12871.

Smith, J.S., Perry, A., Borell, T.J., Lee, H.K., O'Fallon, J., Hosek, S.M., Kimmel, D., Yates, A., Burger, P.C., Scheithauer, B.W., and Jenkins, R.B. (2000). Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. J. Clin. Oncol. *18*, 636–645.

Smith, J.S., Tachibana, I., Passe, S.M., Huntley, B.K., Borell, T.J., Iturria, N., O'Fallon, J.R., Schaefer, P.L., Scheithauer, B.W., James, C.D., et al. (2001). PTEN mutation, EGFR amplification, and outcome in patients with anaplastic astrocytoma and glioblastoma multiforme. J. Natl. Cancer Inst. *93*, 1246–1256.

Taipale, J., Chen, J., Cooper, M., Wang, B., Mann, R., Milenkovic, L., Scott, M., and Beachy, P. (2000). Effects of oncogenic mutations in Smoothened and Patched can be reversed by cyclopamine. Nature *406*, 1005–1009.

Wechsler-Reya, R., and Scott, M.P. (2001). The developmental biology of brain tumors. Annu. Rev. Neurosci. *24*, 385–428.

Yung, W.K., Prados, M.D., Yaya-Tur, R., Rosenfeld, S.S., Brada, M., Friedman, H.S., Albright, R., Olson, J., Chang, S.M., O'Neill, A.M., et al. (1999). Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. J. Clin. Oncol. *17*, 2762–2771.