12 Applications in Malignant Brain Tumors

Carsten Nieder and Mark R. Gilbert

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12.1 Introduction

Primary brain tumors are a very heterogeneous group of diseases arising from different cells of origin showing characteristic age distributions. The World Health Organization (WHO) has recently published an updated classification system, reviewed, for example, by (Fuller and Perry 2001). Virtually all of these tumors represent <2% of all cancers in most western countries. The treatment recommendations take into account the differences between pediatric and adult patients, and, when applicable, the different grades of the disease. One has to discriminate, for example, between histological tumor types that arise localized and unifocal, types that might present as either unifocal or multifocal central nervous system (CNS) disease, and types that are rarely limited to just one site. In contrast, tumor presentation outside of the CNS is exceedingly uncommon, even in the presence of cerebrospinal fluid (CSF) dissemination; therefore, based on the pattern of spread, the treatment volume might vary from the primary site alone to the whole cranio-spinal axis.

Chemotherapy with different sequentially or simultaneously administered agents can be used to enhance the effect of local treatment aiming either at additive cell kill or true radiosensitization, to defer intense, potentially toxic local treatment in vulnerable subgroups, or to treat distant tumor sites based on the principle of spatial cooperation. In general, primary brain tumors are not curable by chemotherapy alone; however, certain histological groups with better response to chemotherapy as well as radiotherapy have been defined, e.g., medulloblastoma. The main prerequisites of successful chemotherapy are sensitivity of the tumor cells to the mechanisms of the drug and sufficient drug exposure. The key issues of tumor heterogeneity with primary and acquired resistance as well as pharmacokinetics, pharmacodynamics, and tumor microenvironment deserve particular attention because of several facts that are specific for CNS tumors. First of all, the intact blood-brain barrier (BBB) prevents access to the brain for several compounds. Even in areas of BBB disturbance, as present, for example, in high-grade glioma, the effects of contemporary drug treatment are not fully satisfactory; thus, achieving therapeutic concentrations in distal, seemingly intact areas that also are known to contain infiltrating tumor cells remains an enormous challenge. Various strategies of modified application or increased dose have been explored, including intraarterial, intrathecal, and intratumoral delivery as well as disruption of the BBB. Furthermore, many patients with brain tumors are able to metabolize chemotherapy drugs and receptor tyrosine kinase (RTK) inhibitors more rapidly than other tumor

C. Nieder, MD
Department of Radiation Oncology, Klinikum Rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, 81675 Munich, Germany
M. R. Gilbert, MD
Department of Neuro-Oncology, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA

patients because of concomitant enzyme-inducing medications that are necessary to treat or prevent seizures. Phenytoin, carbamazepine, and phenobarbital induce hepatic cytochrome P450 enzymes, resulting, e.g., in higher maximum tolerated drug doses. Decreased drug effectiveness has been postulated from corticosteroid treatment. Radiological assessment of the effectiveness of chemotherapy might be difficult, especially in high-grade glioma after intensive pre-treatment (Vos et al. 2003). Many groups combine radiological with clinical findings, as published by (McDonald et al. 1990).

The need for chemotherapy administration is less obvious when local control rates are very high and toxicity from local treatment is uncommon as is, for example, the case in stereotactic radiosurgery (SRS) for WHO grade-II meningioma; however, in diffusely infiltrating high-grade glioma, combined modality treatment has gained increasing acceptance because intensified radiotherapy approaches are limited by normal tissue complications and have not resulted in satisfactory long-term control rates to date. In summary, brain tumors, especially those with high-grade histological features, present unique therapeutic challenges because of their location, aggressive biological behavior, and diffuse, infiltrative growth. Both the tumor and its treatment often result in profound changes in quality of life. Failure of local treatment is still the most common feature in several disease types; thus, improvement of long-term survival rates likely requires substantial refinements of combined-modality therapy.

12.2 Astrocytoma

12.2.1 Histology and Prognosis

Astrocytic neoplasms can be classified as low-grade (II) or high-grade (≥III) tumors. Further local progression or high-grade transformation is common. The most malignant type, glioblastoma multiforme (GBM), or WHO grade-IV glioma, tends to occur in 50- to 70-year-old patients, whereas the less malignant forms develop at least a decade earlier. The different types of astrocytoma can also be found in children. Pediatric patients are best treated in the context of appropriate cooperative group trials. (A detailed description of their treatment protocols is beyond the scope of this chapter.) Median survival time is limited to approximately 10–15 months for GBM and up to 30–50 months for anaplastic astrocytoma (AA) or WHO grade-III astrocytoma. Anaplastic astrocytoma is histologically characterized by its increased cellularity and mitotic activity, whereas GBM shows additional necrosis or endothelial proliferation. Mixed anaplastic oligoastrocytoma (MOA) and particularly pure anaplastic oligodendroglioma (AOD) represent more favorable histological groups with better response to chemotherapy as well as radiotherapy. Survival after relapse and second-line treatment of high-grade astrocytoma is usually in the range of 6–8 months while median time to further progression was 14 weeks in over 1400 patients treated with different regimens (Huncharek and Muscat 1998). Whereas the prognosis of low-grade pilocytic astrocytoma is favorable after surgical resection alone, most WHO grade-II infiltrating astrocytomas will eventually fail and require radiotherapy.

Tumor suppressor gene inactivation and oncogene activation and overexpression play a part, along with alterations in cell-cycle progression, abnormalities in signal transduction pathways, glial cell invasion, and angiogenesis, in the development of glioma. Prognosis is determined by several patient-associated factors (age, performance status, neurological function, symptom indices, and duration), tumor location and grade, as well as treatment-related factors such as surgical resectability or residual tumor volume (Laws et al. 2003). Less consistently reported factors include necessity for corticosteroids (or dose), duration of symptoms, or tumor side (frontal more favorable; Curran et al. 1993; Simpson et al. 1993). Curran et al. (1993) analyzed the survival of more than 1500 patients with high-grade glioma in the Radiation Therapy Oncology Group (RTOG) database and found that five variables (duration of symptoms, mental status, age at diagnosis, tumor grade, and postoperative performance status) defined six patient subgroups with distinct prognoses (median overall survival (OS) from 5 to 59 months. Proliferative activity measured, for example, by variants of the Ki-67 antibody was found to correlate to WHO grade, but not to OS, in multivariate analysis adjusted for the clinically established prognostic variables (reviewed by Stemmer-Rachamimov and Louis 1997). The same holds true for p53 immunostaining or presence of *p53* gene mutations (Nieder et al. 2000a). Expression of PAI-1, $p27^{Kip1}$(a cell-cycle regulator), alterations in the *MMAC/PTEN* gene, and epidermal growth factor receptor (EGFR) amplification in GBM have been