M.A. Hayat *Editor*

Tumors of the Central Nervous System

Volume 2
Gliomas: Glioblastoma (Part 2)

Springer

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Gliomas: Glioblastoma (Part 2)

Edited by

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"Although touched by technology, surgical pathology always has been, and remains, an art. Surgical pathologists, like all artists, depict in their artwork (surgical pathology reports) their interactions with nature: emotions, observations, and knowledge are all integrated. The resulting artwork is a poor record of complex phenomena."

Richard J. Reed MD

Preface

The primary objective of this series, *Tumors of the Central Nervous System*, is to present the readers with the most up-to-date information on the initiation, progression, recurrence, metastasis, and treatment of the CNS tumors. As in volume 1, volume 2 has discussed in detail biomarkers and diagnosis of gliomas, especially glioblastoma. The role of a large number of biomarkers in the diagnosis of glioblastoma is included. Advantages and limitations of the use of biomarkers for diagnosis are presented. The role of *TP53* gene mutation in the initiation and progression of glioblastoma is presented as well as germline mutations of this gene. Role of oncogenes and tumor suppressor genes is also discussed. Also, is discussed the role of specific genes in the resistance to drug therapy.

The importance of the use of imaging modalities (e.g., PET, CT, MRI, and SPECT) in clinical diagnosis, treatment assessment, and recurrence determination is pointed out. It is well established that early diagnosis is the key to cancer "cure". Prognosis is highly dependent on the stage of the disease. Thus, a simple and reliable screening method would be of tremendous advantage. Imaging techniques in clinical practice are used for the staging of tumors, detection of tumor recurrence, monitoring of efficacy of therapy, and differentiation between malignant and benign tissues. In this volume, use of PET in diagnosing glioma and in assessment of biological target volume in high-grade glioma patients is explained. Also is discussed the use of MRI in glioma surgery.

Present and future therapeutic drugs for malignant gliomas are described. The efficacy of several drugs, such as cyclosporine, interferon, heparin, and cannabinoids in treating glioblastoma is explained. Effectiveness of therapies, such as resection, radiation, chemotherapy, and immunotherapy, against high-grade gliomas is detailed. Therapy for recurrent high-grade glioma with bevacizumab and irinotecan is presented. Use of dendritic cell therapy and adenoviral vectors for glioblastoma is discussed. Brainstem gliomas are also described, so is tumor-associated epilepsy.

This work consists of 37 chapters that were contributed by 101 authors representing 16 countries. The high quality of each manuscript made my work as the editor an easy one. Strictly uniform style of manuscript writing has been accomplished. The results are presented in the form of both black-and-white and color images and diagrams.

I am indebted to the contributors for their promptness in accepting my suggestions, and appreciate their dedication and hard work in sharing their knowledge and expertise with the readers. Each chapter provides unique individual, practical knowledge based on the expertise of a large number of researches and physicians. A vast medical

field such as tumors of the CNS can be discussed adequately only by a large number of experts. It is my hope that this volume will be published expediously.

I am thankful to Dr. Dawood Farahi, Dr. Kristie Reilly, and Mr. Philip Connelly for recognizing the importance of scholarship in an institution of higher education, and providing resources for completing this project.

Union, New Jersey M.A. Hayat
September 2010

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Chapter 1

Introduction

M.A. Hayat

In developed countries cancer is the second leading cause of death exceeded only by cardiovascular diseases. There are more than 100 types of cancers that can inflict any part of the body. In 2005, 7.6 million people died of cancer, which constitutes 13% of the 58 million deaths worldwide. In the global population exceeding 6 billion in the year 2002, there were approximately 10.9 million new cancer cases, 6.7 million cancer deaths, and 22.4 million surviving from cancer diagnosed in the previous 5 years. In 2020, it is expected that the world's population will increase to 7.5 billion, with 15 million new cancer cases and 12 million cancer deaths. Approximately, 1.4 million new cases of cancer and 550,000 cancer deaths were reported in the United States in 2008 (Am. Cancer Soc.), These data amount to ~1500 deaths caused by cancer every day in the United States. In 2006 an estimated 19,000 new cases of brain tumors and 13,000 deaths were reported in the United States. This figure accounts for ~1.4% of all cancer cases and 2.3% of all cancer cases that cause death. More than 10,000 Americans die annually from glioblastoma. Survival for this disease has not changed much in three decades. Since 1970, the number of cancer survivors has increased four-fold, with cancer survivors representing ~3.5% of the United States population and 5-years survival rates increasing into the 60% range. These raises invite issues related to long-term and late effects of cancer treatment and the realization that cancer survivors represent ~16% of all new primary cancers.

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Glioblastoma

Gliomas can arise either spontaneously (primary glioma) or can progress from a lower-grade to a higher-grade (glioblastoma) of tumor. Malignant glioma is the most common tumor of the CNS, and glioblastoma is the most malignant form. Glioblastoma is characterized by rapid, highly invasive growth, extensive neovascularisation, and high mortality. The key reason for the lack of successful therapy is the infiltration of single tumor cells into the surrounding brain parenchyma cells, preventing complete glioblastoma resection. This process is facilitated by two related processes: (1) angiogenesis, the sprouting of new blood vessels from preexisting vasculature in response to external chemical stimulation, and (2) vasculogenesis, the reorganization of randomly distributed cells into a blood vessel network. Tumor cells can also acquire blood supply through other ways to escape conventional antiangiogenesis. In other words, blood vessels are formed by tumor cells instead of endothelial cells. This novel concept in tumor vascularization is termed as vasculogenic mimicry, which is the ability of aggressive tumor cells to express endothelium-associated genes and form extracellular matrix-rich vasculogenic-like networks in three-dimensional culture. Such networks recapitulate embryonic vasculogenesis, and have been observed in human aggressive tumors such as glioblastoma (El Hallani et al., 2010, and Chapter 11, in this volume).

Glioblastoma can be divided into two subtypes based on amplication and mutation of different genes, and characterization of molecular pathways has opened new venues to targeted therapies based on the individual genetic signature of the tumor (Ohgaki and

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Kleihues, 2007). Two main subtypes on the basis of genetic differences are: (1) Primary glioblastomas typically occur in patients alder than 50 years of age, and are characterized by epidermal growth factor receptor (EGFR) amplification and mutations, loss of heterozygosity of chromosome log, deletion of the phosphatase and tension homologue on chromosome 10 (PTEN), and p16 deletion. (2) Secondary glioblastomas occur in younger patients as low-grade or anaplastic astrocytomas that are transformed over a period of several years into glioblastoma multiforme. Secondary glioblastomas are much less common than primary glioblastoma, and are characterized by mutations in the *TP53* tumor suppressor gene, overexpression of the platelet-derived growth factor receptor (PDGFR), abnormalities in the *p16* and retinoblastoma (Rb) pathways, and loss of heterozygosity of chromosome loq.

Although glioblastoma is the most common and aggressive type of glioma and has the poorest survival, a small percentage of patients survive longer than the established median. Identification of genetic variants that influence long term survival of such patients may provide insight into tumor biology and treatment. A recent study by Liu et al. (2010) indicates that polymorphisms in the *LIG4, BTBD2, HMGA2,* and *RTEL1* genes are associated with the survival of glioblastoma patients. *LIG4* and *BTBD2* are predictors of short-term survival, while *CCDC26, HMGA2,* and *RTEL1* are predictors of long-term survival. In general, older patients (>50 years) have the worst survival (1.2 years), while younger patients may show a median survival-term of 7.8 years. These genes are known to be involved in the double strand break repair pathway.

It is known that glioblastoma responds poorly to conventional therapies. Glioblastoma cells thrive despite an irregular blood supply and a frequently hypoxic microenvironment. Compensatory mechanisms, including glucose uptake and glycolytic activity, are enhanced in these tumors. In other words, glioblastoma cells, posses sufficient glycolytic capacity (more than that in normal brain tissue), supporting their migration even without mitochondrial involvement (Beckner et al., 1990) A recent study has identified ATP citrate lyase (ACLY) as a positive regulator of glycolysis in glioblastomas (Beckner et al., 2010). ACLY can be targeted to suppress hypoxic cell migration and invasion, and restore glycolytic inhibition. This inhibition of hypotoxic tumor cells potentially complement antiangiogenesis therapies that compromise the blood supply to tumor cells.

Treatment

The three most common treatments are resection, radiation, and chemotherapy, or a combination of these methods. According to Sandmair et al. (2000), when radiation is utilized following surgical resectioning of the tumor, the median survival time may increase from 14 to 40 weeks. Maximal resection of brain glioma is usually the first or second treatment choice. Radiation is the alternative treatment. The goal is to maximize the effectiveness of resection, while minimize the operative risk. To accomplish this goal is not easy. Active migration of glioblastoma cells through the narrow extracellular spaces in the brain makes them elusive targets for surgical management. Glioma cells are "self-propelled", and are able to adjust their shape and volume rapidly as they invade the brain parenchyma. The infiltrative nature of malignant gliomas results in poor demarcation of malignant boundaries. Another reason is the frequent location of supratentorial gliomas near or within eloquent areas. Consequently, the advantage of maximal resection in all cases is controversial. Image-guided surgery utilizing fluorescence with 5-aminolevulinic acid, neuronavigation, and intraoperative MRI has enabled more complete resectioning of contrast-enhancing tumors (Stummer et al., 2006; Nimsky et al., 2006)

Chemotherapy in conjunction with surgery and radiation can increase the estimated survival of patients by 10.1% at 1 year and 8.6% at 2 years, but these rates apply to lower-grade glioma tumors. The current recommended chemotherapeutic agent is alkylating drug temozolomide. The 2-year survival rate of patients with newly diagnosed glioblastoma treated with radiotherapy and temozolomide is 26.5%, compared with 10.4% for radiotherapy alone (Stupp et al., 2005).

Telozolomide also exerts antitumor affects by impairing angiogenic process. In vitro and in vivo studies have shown antiangiogenic activity by this drug even when it is used alone (Mathieu et al., 2008). The efficacy can be further enhanced by combining this treatment with bevacizumab; the later also has an antiangiogenic effect, although with a different mechanism of action. Antiangiogenic compounds

also increase the therapeutic benefits of radiotherapy (Nieder et al., 2006). A phase 2 pilot study of bevacizumab in combination with telozolomide and regional radiotherapy for the treatment of patients with newly diagnosed glioblastoma recently reported that toxicities were acceptable to continue enrollment and a preliminary analysis of efficacy showed encouraging mean progression-free survival (Lai et al., 2008). It is concluded that a range of side-effects, including post-therapeutic neurological deterioration, can commonly or uncommonly are experienced by patients undergoing chemotherapy.

To overcome some of the limitations mentioned above, intraoperative eletrostimulation can be used (Duffau, 2007, also, see Chapter 22, in this volume). The purpose is to understand the interindividual anatomical-functional variability in the case of glioma patients. In order to tailor the resection for each patient, it is mandatory to study the cortical functional organization, the affective connectivity, and the potentiality for brain plasticity.

Another limitation is the innate inter individual prognostic variability encountered among malignant glioma patients. This limitation can be overcome by carrying out analysis of prognostic factors, which can predict the outcome of a therapy among diagnosed malignant glioma patients. Such an information can affect the design and conduct of clinical trials in the case of patients with recurrent glioma. Phase II trials play a critical role in the assessment of novel therapeutic approaches.

Factors associated with an increased risk of death are old age (50 years or older), lower karnofsky performance score (<80), initial and on study histological data of glioblastoma multiforme, corticosteroid use, shorter time from original diagnosis to recurrence, and tumor outside frontal lobe (Carson et al., 2007). However, patients differ with respect to their characteristics, including age, performance status, histological data, time from initial diagnosis to recurrence, exact location of tumor, whether the tumor is resectable, number and type of prior therapies, and use of concomitant medication (e.g., anticonvulsants). Thus, patients with recurrent gliomas have significantly different prognoses depending on their characteristics including those mentioned above.

The importance of the role of immune-signaling in the regulation and function of resident neural stem cells in the CNS is beginning to be understood (Carpentier and Palmer, 2009). The complexity of the immune signaling becomes apparent considering that some aspects of this signaling are beneficial by promoting intrinsic plasticity and replacement of injured cells, while others inhibit the regenerative response that might restore or replace neural networks lost in disease. The broad implication is that tissue environment may influence the activity and fate of endogenous or transplanted neural stem cells. Immunotherapy alone or in combination with other treatments has also been tried with some success. For example, bevacizumab has shown some promise for recurrent glioblastoma, although recurrence is common following treatment with this antibody. Thus, this treatment is transient.

Another approach is to develop novel drugs that target glioblastoma cells. Role of Na^+/K^+-ATPAse (the sodium pump, a membrane protein) in the migration of glioblastoma cells is interesting. It has been shown that the α1 subunit of the ubiquitous sodium pump is over-expressed in glioblastoma (Lefranc et al., 2008). This study demonstrates that UNBS1450 drug, a cardionolide compound that inhibits sodium pump, impairs glioblastoma cell migration through disorganization of the actin cytoskeleton and has potent proautophagic effects on glioblastoma cell lines. Thus, sodium pump may prove to be another useful target for drug development against this disease. The importance of prior laboratory prediction of individual drug response cannot be overemphasized. Drug sensitivity is determined by multiple genes and accessibility to the target tumor. The complexity of mechanisms involved in drug sensitivity becomes apparent, considering that gene expression profile in response to drug exposure vary considerably among individuals even for the same drug or regimen and tumor type.

It is known that gliomas, in their proliferative stage, are highly vascularized tumors, and their persistence and growth depend on the pathological formation of new capillary blood vessels. Thus, angiogenesis inhibition is an efficient therapeutic strategy for treating malignant gliomas. However, the benefit of current anti-angiogenic agents has been at best modest. Reasons for limited effectiveness of such agents include their short circulating half-life, dose-limiting toxicity, and the noninvasive methods to monitor anti-angiogenic therapies in vivo (van Eekelen et al., 2010). Recently, these authors have engineered and characterized a secretable form of antiangiogenic

thrombospondin-1 (TSP-1) that targets the vascular component of gliomas and reduces tumor blood vessel density, resulting in the inhibition of tumor progression and increased survival of mice bearing highly malignant human gliomas. A large number of standard and novel treatments against malignant gliomas are discussed by other authors in this and volume 1 of this series.

Glioblastoma tumors containing CD133-positive cells display strong capability of resistance to chemotherapy (temozolomide, carboplatin, VP16, and Taxol) (Liu et al., 2006). Brain cancer stem cells (CSCs) with such resistance also show a higher expression of drug resistance genes (e.g., BCRPI) and DNA mismatch repair genes (e.g., MGMT) as well as antiapoptotic proteins (e.g., Bcl-2). Growing evidence also indicates that CD133-posiotive CSCs show higher expression of mRNA levels of inhibitors of apoptotic proteins such as IAPs (Liu et al., 2006). Based on this and other evidence it can be concluded that apoptotic pathways contribute to resistance of CD133-posiotive to chemotherapy and medical radiation. Thus, CD133-positive cells can be considered as a marker for glioblastoma CSCs that can be targeted either biochemically or immunologically without harming normal brain tissue stem cells.

One approach to treat glioblastoma is to induce differentiation of CD133 brain tumor cells, critically weakening their tumor-forming ability. Piccirillo et al. (2006) have shown that bone morphogenetic proteins (BMPs) prompt the differentiation of such cells. This study demonstrated that the BMP-treated tumor cells engrafted into mice were more mature and less invasive, and CD133 cells could not be recovered from these small tumors. The implication is that a differentiation-promoting agent (BMP) is a potential treatment for brain tumors. This experimental approach is ripe for further testing.

As stated earlier, CD133 (prominin-1) has been proposed as a marker for brain tumor-initiating cells. However, a recent study shows that tumorigenic potential also exists among $CD133^{-}$ cells to form tumors (Prestegarden et al., 2010). Nestin glial fibrillary acidic protein and neuron-specific enolase markers were expressed in $CD133^{-}$ cells. It seems that the ability to form tumors maybe a general trait associated with different glioma cell phenotypes, rather than a property limited to an exclusive subpopulation of glioma stem cells.

Nevertheless, targeting CSCs pathways will ultimately prove to be an effective therapeutic strategy against malignant gliomas. In order to accomplish this goal, it is necessary to understand and link cellular, molecular, genetic, and epigenetic mechanisms to compare the similarities and differences between normal neural stem cells and glioblastoma-initiating stem cells.

The relevant question is whether chemoresistance of glioblastoma stem cells is due to reduced drug uptake or due to drug efflux. An in vivo study indicates that neither of these two alternatives is fully applicable to answer this question (Eramo et al., 2006). According to this study, drug resistance by glioblastoma stem cells depends on the abnormalities of the cell death pathways such as overexpression of antiapoptotic factor or silencing of key death effectors. In other words, the altered expression of apoptosis related proteins renders normal neural stem cells strongly resistant to death receptor ligands and inflammatory cytokines. More extensive studies are required to fully understand the mechanisms of chemoresistance by glioblastoma stem cells.

As indicated earlier, cerebral glioma shows the highest incidence rate among malignant intracranial tumors, and the therapeutic efficacy of surgery, radiotherapy, and chemotherapy for the former are not satisfactory, and these tumors show a tendency to recur after the treatments. Many drugs exert their anticancer actions only after entering the cells, but some drug-resistant tumor cells can prevent the drugs from penetrating and thus avoid being destroyed. Ultrasound can increase the intracellular bioaccumulation of drugs by increasing the membrane permeability in tumor cells and thus reducing the thereshold values of cell death (Deckers et al., 2008).

Currently, inducing tumor cell death is considered the endpoint in most nonsurgical therapies, but there is increasing evidence that different death modes of tumor cells have different effects on the functions of immune cells, especially macrophages. Macrophages play important roles in the occurrence and development of tumors. Recently, Xu et al. (2009) studied the effects of ultrasound on the cell death induced by arsenic trioxide, and the secondary activation of macrophages; this study was carried out using rat glioma cell line C6. Arsenic trioxide has been approved by the FDA for the treatment of refractory leukemia. Kim et al. (2008) have also used arsenic

trioxide for sensitizing human glioma cells. It seems that ultrasound synergisticulary enhances the cell death effect by promoting arsenic trioxide entry into the cell line C6, and macrophages are activated by the killed C6 cells (Xu et al., 2009). This study provides a theoretical basis for the clinical use of this drug and ultrasound in glioma treatment.

Because conventional treatments are not very effective against glioblastoma, there is an urgent need to develop novel, effective therapeutic strategies against this disease. One such therapy involves the role played by brain tumor-derived stem cells (BTSC) and neural stem cells (NSC) in cancer initiation and progression (Germano et al., 2010). BTSC are a small subpopulation of cancer cells having similarities, such as self-renewal, multipotency, and relative quiescence. BTSC originate from a population of endogenous NSC. It is thought that BTSC play a crucial role in the recurrence of primary brain tumors and treatment resistance. Therapies targeting BTSC might be more effective in treating this disease.

One of the new treatments to improve patient survival is targeting cancer stem cells that contain higher NOTCH activity. The NOTCH signaling pathway regulates stem cells in the brain. It has been shown that the NOTCH pathway blockade depletes stem-like cells in the glioblastoma, suggesting the usefulness of using NOTCH inhibitors (e.g., γ-secretase) as chemotherapeutic reagents to target cancer stem cells (Fan et al., 2010). Another critical role of NOTCH signaling is that it promotes radio resistance of glioma stem cells (Wang et al., 2009). Thus, inhibition of this signaling holds promise to improve the efficiency of current radiotherapy in glioma therapy.

Glioblastoma Multiforme

Glioblastoma multiforme is the most common primary intrinsic brain tumor of adulthood, and the most malignant glioma subtype. Although significant advances have taken place during the last 25 years in the basic understanding of tumor pathogenesis, the median survival of patients has increased only 3.3 months (from 11.3 to 14.6 months). This poor prognosis is due to the near inevitability of the recurrence of the tumor in spite of the initial use of maximal safe surgical resection, radiotherapy, and chemotherapy. Under the circumstances, additional systemic and local therapies, as well as repeat surgery, are considered; these therapies have potential benefits and risks, especially resulting from surgery.

Surgery does provide benefits, such as immediate decrease in tumor burden and improvement of tumor-related neurologic symptoms and deficits. A potential risk is the exacerbation or new onset of the same, as well as a temporary or permanent exclusion from other therapies. In addition, potential injury to the M1 and M2 segments of the middle cerebral artery can result in damage to the eloquent brain regions they supply (Park et al., 2010).

In the light of risks and uncertainity involved in the outcome of the reoperation, these patients deserve to know their treatment options. In the past, studies have been carried out assessing the outcome of reoperation of patients with recurrent glioblastoma multiforme (Ammirati et al., 1987). However, such studies did not establish guidelines for providing preoperative advice to patients considering reoperation. Recently, Park et al. (2010) have devised a preoperative scale that predicts survival after resurgery for recurrent glioblastoma multiforme. This scale identifies patients likely to have poor, intermediate, or good relative outcomes after surgical resection of the recurrent tumor. On the basis of this scale, survival benefit and the attendant risk can be evaluated, on case-by-case basis, from surgery. Because surgery is not curative, it is important to identify potentially effective treatments with minimal risk.

Medical Imaging

A large of imaging modalities, including computed tomography (CT), position emission tomography (PET), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and single photon emission computed tomography (SPECT), are being routinely used for diagnosis, treatment, and assessment of treatments (Hayat, 2008). Combined PET/CT is a well-established approach that has been extensively validated in routine clinical practice; CT provides anatomical information, while PET contributes functional information. The introduction of PET/CT was a revolutionary milestone in clinical imaging. However, because the effective radiation

dose is the sum of the doses from PET and CT, this combined examination (particularly diagnostic one requiring high resolution CT) results in increased patient exposure and a higher theoretical radiation-induced cancer risk than that with PET or CT alone. Understandably, but unfortunately, the acceptance of a treatment by patients is much higher when the information primarily addresses the benefits than the risk.

A more recently emerging therapeutic modality for glioblastoma consists of boron neutron capture protocol (Yamamoto et al., 2008). This technique theoretically allows tumor-selective destruction, while sparing normal tissue, even when the cells have microscopically spread to the surrounding normal brain. The tumor cell selective irradiation depends on the nuclear reaction between the stable isotope of boron (^{10}B) and thermal neutrons, which release α and ^{7}Li particles within a limited path length through the boron neutron capture reaction, ^{10}B (n,α) ^{7}Li. The selectivity depends on the dose from the boron neutron capture reaction, i.e., the accumulation of boron-10 in tumor cells. Prospective randomized clinical trials are needed to confirm the efficacy of this modality.

Risk of Medical Radiation

At the outset it is pointed out that although radiation therapy has been the standard treatment of glioblastoma for four decades, it is only transiently effective, and offers no lasting cure. Medical radiation fails in the long run because it cannot kill the subpopulation of CD133 tumor-initiating cells. Although many nuclear medicine and radiological procedures are safe, there is still the need to justify these procedures on the basis of a favorable risk: benefit ratio. Hazards associated with medical radiation exposure do exist. Radiation, for example, may induce necrosis at doses of 60 Gy and above. The recent dramatic increase in the number of diagnostic medical procedures and nuclear medicine procedures has resulted in a very significant increase in cumulative exposure to radiation and related risk of carcinogenesis. In the United States in 2006, ∼377 million diagnostic and interventional radiological examinations and 18.6 million nuclear medicine examinations were performed (Mettler et al., 2009). Among the diagnostic nuclear medicine procedures, cardiac studies followed by bone scanning are the most frequent nuclear medicine procedures. Approximately, 12% of all radiological procedures and 50% of nuclear medicine procedures carried out worldwide are performed in the United States (Salvatori and Lucignani, 2010). These startling findings underline the pressing need to optimize and justify all exposures of patients to medical ionizing radiation.

Starting from last decade, there has been a substantial increase in the use of PET/CT in children. In all patients, especially in children, it is crucial to keep radiation doses as low as is clinically feasible. It is known that some children who undergo medical radiation, are prone to develop cancer or heart disease later in life. Medical radiation protection has implication for a range of persons: patients, medical, technical, and nursing staff, friends, relatives, caregivers, and members of the public.

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Part I
Biomarkers and Diagnosis

Chapter 2

Gliomagenesis: Advantages and Limitations of Biomarkers

Michel Wager, Lucie Karayan-Tapon, and Christian-Jacques Larsen

Abstract During the last years, spectacular progress in the field of molecular biology raised the hope that it might replace or at least improve significantly the World Health Organization classification of tumors of the central nervous system. Although up to now, this has not been the case, a few biomarkers have found their place as prognostic factors for certain tumor types on the one hand, and as predictive factors of response to treatments on the other hand. The present chapter will deal with the following tumor types: astrocytic tumors (including Diffuse astrocytoma, Anaplastic astrocytoma, Glioblastoma, and Pilocytic astrocytoma), Oligodendroglial tumours (including Oligodendroglioma and Anaplastic oligodendroglioma), and mixed gliomas (including Oligoastrocytoma and Anaplastic oligodendroglioma). The current biomarkers are not decision-making parameters on a case by case basis, but they have progressively emerged as cornerstone indicators as far as stratification in clinical studies is concerned. As a consequence, during therapeutic trials, it can be considered that groups of patients whose biomarkers anticipate a poor response to standard treatment might be offered the opportunity of innovative therapies. In this context, the most recent developments of molecular biology culminating in integrated molecular analysis of tumors and the possibilities offered by neurosphere cultures established from glioblastoma multiforme that recapitulate the tumor allow to anticipate a growing importance of a series of new biomarker in the years to come.

Keywords Biomarkers · Gliomagenesis · Gliomas · Genomic analysis · Kinase · Tumor grade

Introduction

This chapter will focus on adult gliomas only. The authors think that gliomas in children and adults are quiet different entities that should be considered separately. This conviction relies on clinical reasons on the one hand, because, as compared to adult gliomas, tumors in children are of lower prevalence, more often low grade at diagnosis, and tumor progression to higher grades arise later in the course of the disease. Furthermore, their anatomical distribution is different from that in the adult. Available biologic data also tend to distinguish these two periods of life: three of the main ways of gliomagenesis in adults – PI3-kinase/Akt/PTEN, p53/MDM2/p14 ARF, Rb/CyclinD1/CD4/p16 CyclinD1 Rb/CyclinD1/CD4/p16INK4A CD4 seem only rarely involved in children gliomas, quite as EGFr's amplification (Tamber et al., 2006).

Grade I glioma, i.e. pilocytic astrocytomas, is a truly benign lesion that can be cured by total surgical removal. This tumor will be only quickly evoked in this chapter. Indeed, every aspect of this tumor – clinical presentation and imaging features, principles of treatment and outcome – distinguish it from adult diffuse gliomas, and its place in the World Health Organization (WHO) classification can be considered a historic inheritance.

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