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Treatment of Pediatric Brain Tumors

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Abstract

Over the past decades considerable advances have been made in neurosurgery, radiotherapy and chemotherapy resulting in improved survival and cure rates for children with brain tumors. Here we review four of the most common subtypes of pediatric brain tumors, low-grade and high-grade astrocytomas, medulloblastomas and ependymomas, highlighting their molecular features regarding their tumor biology and promising potential therapeutic targets that may hold promise for finding new “molecularly targeted” drugs. Importantly, appropriate clinical trial design will play a critical role in the evaluation of new and novel treatment approaches for pediatric brain tumors.

Introduction

The first successful treatment of a pediatric brain tumor dates back to 1879. Sir William Macewen, a Scottish surgeon, was the first to perform an intracranial surgical procedure to successfully remove a meningioma from a 14 year-old girl. Upon her death, eight years later, no tumor was found at autopsy, demonstrating that surgical cures of brain tumors were possible. Brain tumors are the most common form of solid tumor and the leading cause of death from solid tumors in children (SEER program 1975-1999). Since the late nineteenth century, there have been numerous technical advancements in neurosurgery, radiology, radiation therapy, chemotherapy and supportive care that have resulted in current 5 year survival rates of 73% for all pediatric brain tumors combined (SEER program 1975-1999).

Modern technology has impacted greatly on the practice of pediatric neurooncology. Neurosurgical procedures are safer and more effective with computer guided stereotaxis, laser dissection and intraoperative physiologic monitoring and imaging. More aggressive surgeries can be performed with less damage to the normal brain. High-resolution magnetic resonance imaging (MRI) now provides for a highly detailed view of the brain anatomy and is further enhanced by additional MRI technology such as magnetic resonance angiography, functional brain mapping and spectroscopy. Dynamic susceptibility-weighted, contrast-enhanced perfusion MR imaging can help differentiate more aggressive from low-grade tumors (Law et al., 2008). With modern radiation therapy, including intensity-modulated radiation therapy and proton beam irradiation, exposure of normal tissues can be significantly reduced. The development of effective chemotherapy regimens specifically tailored for children with brain tumors, including high dose chemotherapy with autologous stem-cell rescue, has had two major consequences. Initially, chemotherapy was used in an

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adjuvant fashion following surgery and radiation therapy and this has led to significant improvements in progression-free and overall survival for many patients with malignant CNS tumors such as medulloblastoma. It has also been used successfully in infants and children deemed too young to receive CNS radiotherapy, both with low-grade gliomas and embryonal malignancies such as medulloblastoma. Chemotherapy can help postpone or replace radiation therapy in this younger population, thus reducing or eliminating the long-term side-effects of radiation including neuro-cognitive decline, developmental delay and endocrine deficiencies. Lastly, advances in supportive care have allowed for more aggressive therapeutic approaches while reducing the treatment-related morbidity and mortality.

The overall 5-year survival statistic of 73% in pediatric brain tumor patients, however, represents a highly heterogeneous population, whose treatments and prognoses vary widely based on age, tumor location, size, histology and staging. While some patients can be considered cured after successful tumor resection, others will succumb to their disease despite maximal multimodal therapy including surgery, radiation and chemotherapy. Unfortunately, it is highly unlikely that further dose escalation or modification of chemotherapy regimens using traditional agents will drastically change outcomes. Traditional high-dose chemotherapy for the most part relies on inducing nonspecific DNA damage and triggering apoptosis in cancer cells. Typically, the therapeutic index, i.e. the ratio between toxic and effective dose, is narrow and significant side-effects therefore common. There may be a rationale for modifications of dose and schedule with traditional medications. A “metronomic” or daily dosing of several medications in low dosage is thought to target tumor endothelium as an anti-angiogenesis protocol (Kieran et al., 2005).

Tumor angiogenesis is the ability to form new blood vessels that support tumor growth, and is seen as a critical step in tumor development and progression (Jain, 2005; Kerbel, 2008). The efficacy of anti-angiogenic therapy (bevacizumab) in combination with chemotherapy for brain tumors has been established in pivotal adult trials for recurrent high-grade glioma (Vredenburgh et al., 2007), and a corresponding pediatric trial by the Pediatric Brain Tumor Consortium (PBTC) is ongoing. In addition to bevacizumab, a vascular endothelial growth factor (VEGF)-neutralizing monoclonal antibody and the first FDA-approved anti-angiogenic agent for the treatment of cancer, a large number of novel anti-angiogenic agents are currently being tested in clinical trials (Sato et al., 2007).

Although significant strides have been made in understanding some of the underlying molecular features driving tumorigenesis, successful “molecular targeted” therapy for pediatric brain tumors remains for the most part elusive and several challenges persist: There are a number of clinical challenges confronting the successful implementation of these smart molecules. Few specific genetic alterations have been identified that may be exploited to specifically target the neoplastic cells, particularly in the “non-malignant”, low-grade tumors. Many of the potential targets identified do not currently have corresponding drugs available that are safe or that have advanced to clinical testing. Traditional clinical phase trial designs in oncology were originally conceived to determine maximum tolerated doses and clinical anti-tumor efficacy of chemotherapy drugs, and this approach may not be appropriate for evaluating molecular targeted agents. The majority of molecular targeted agents are expected to work best when combined with traditional chemotherapy or radiotherapy, and for the most part, clinical experience in this regard is currently lacking. Since pediatric brain tumors are rare compared to the common types of adult brain tumors, the commercial incentive to develop specific targeted therapies for the pediatric community is reduced. At the same time, the number of pediatric patients with a specific tumor entity is limited and often not sufficiently large to support large randomized, controlled trials. Clinical research is further complicated by the fact that our increasing molecular knowledge

is likely to further subdivide tumor entities, resulting in ever smaller “homogeneous” groups of patients for study in clinical trials.

Here, we will review some of the more common types of pediatric brain tumors (low-grade and high-grade astrocytomas, medulloblastoma and ependymoma), highlighting their molecular features, promising potential therapeutic targets and target-specific drugs in development or clinical testing. In addition, clinical trial design-related issues incorporating novel therapeutic approaches will be discussed. Although immunotherapy approaches for the treatment of brain tumors are rapidly emerging and have shown some preliminary successes, this topic is beyond the scope of this paper and has been recently reviewed elsewhere (Kushen et al., 2007).

Pediatric Astrocytomas (Gliomas)

Low-grade astrocytomas comprise a heterogeneous group of pediatric tumors including juvenile pilocytic astrocytomas (JPAs, WHO grade I), low-grade diffuse astrocytomas, gangliogliomas, oligodendrogliomas and mixed oligo-astrocytomas (WHO grade II), (Watson et al., 2001).

Juvenile Pilocytic Astrocytoma

Juvenile pilocytic astrocytomas (JPAs) are generally well-circumscribed and slow-growing tumors. Cyst formation is common and often used as a diagnostic feature. JPAs are the most common pediatric brain tumors, comprising 21% of tumors in children aged 0–14 years and 16% of tumors in those aged 15–19 years. JPAs are located most commonly within the cerebellar hemispheres, but also occur in the hypothalamus/optic pathway, the thalamic/basal ganglia region, the cerebral hemispheres and brain stem. Tumors also can be frequently found in the spinal cord. JPAs are often diagnosed in patients with neurofibromatosis type I (NF1), a genetic susceptibility syndrome with inactivation of the tumor-suppressor gene NF1 (*neurofibromin*). Involvement of the optic nerve is a classic finding, such that 15% of NF1 patients develop JPAs (Lewis et al., 1984) and one-third of patients with JPA have NF1 when the tumor is located in the optic nerve.

When complete tumor excision is achieved, no further therapy is required and relapse is rare (Watson et al., 2001). In many patients, however, a full resection may not be possible secondary to tumor size and/or location, thus limiting the extent of surgery due to the risk of causing unacceptable neurological deficits. A number of chemotherapy regimens as well as radiotherapy have been found to be effective treatment for residual and recurrent tumors, but are typically non-curative and carry significant risks and side-effects. Radiation therapy is usually reserved for patients who have exhausted chemotherapeutic and surgical options.

Several cytogenetic studies have been performed on JPAs to identify common chromosomal changes by fluorescence in situ hybridization (FISH), single nucleotide polymorphic (SNP) allele arrays, metaphase comparative genomic hybridization (CGH) and microarray CGH (aCGH). A recent aCGH study (Jones et al., 2006) of 44 JPAs showed that 64% of the tumors appeared to have a normal karyotype, consistent with prior reports (Sanoudou et al., 2000; Shlomit et al., 2000; Wong et al., 2005). Chromosomal gains of chromosomes 5 and 7 were most frequently observed, followed by chromosomes 6, 11, 15, and 20 (>10% of cases). When patients were grouped by age, those tumors from patients less than 15 years of age had none or only one chromosomal change versus those from patients >15 years of age where tumors contained multiple chromosomal changes. In a recent report, amplification of a tumor suppressor gene, HIPK2, a homeobox-interacting protein kinase, was noted in the chromosomal band 7q34 using aCGH in 60% (6 of 10) of JPAs and confirmed in an independent data set where 43% (26 of 61) of JPAs had HIPK2 amplifications (Deshmukh

et al., 2008). Overexpression of HIPK2 in the U87 glioma cell line increased cell growth consistent with its putative role as a tumor suppressor gene. Another, more recent aCGH study of 53 JPAs confirmed the gain of chromosomes 5 and 7, together with frequent amplification at chromosome band 7q34 (Pfister et al., 2008b). However, the gene identified was the protooncogene BRAF that was duplicated in 53% (28 of 53) of JPAs compared with 15% (2 of 13) of diffuse astrocytomas. *In vitro* studies blocking BRAF gene expression with shRNA or inhibiting phosphorylation of BRAF by the MEK1/2 small molecule inhibitor U0126 prevented proliferation of astrocytic cell lines concomitant with cell cycle arrest in G₂/M phase (Pfister et al., 2008a). These studies implicated BRAF in the important MAPK signaling pathway that has been previously identified in gliomas (Jeuken et al., 2007). Thus, BRAF duplication may be a novel mechanism underlying activation of the MAPK pathway in JPAs, and could be exploited therapeutically.

Abnormalities in the p53 and Rb tumor suppressor pathways have not been detected in JPAs and thus do not appear to play a role in the evolution of JPA tumors compared with other high-grade astrocytomas, where these two genetic pathways do play important roles (Cheng et al., 2000; Ishii et al., 1998; Willert et al., 1995).

JPAs occurring in NF1 patients are genetically and molecularly distinct, with loss of NF1 expression resulting in constitutive activation of RAS and the downstream mTOR signaling pathway (Dasgupta et al., 2005). Similarly, sporadic JPAs that generally do not have a loss of NF1, show frequent activation of the mTOR pathway, albeit through different mechanisms (Sharma et al., 2005). Although gene expression profiling of JPAs has revealed distinct genetic signatures related to NF1-status and brain region of origin, no specific expression signatures were found that correlated with clinical behavior, including aggressiveness or risk of recurrence.

Gene expression profiling of JPAs through the use of cDNA microarrays, suppression subtractive hybridization (SSH) and quantitative real-time PCR (qRT-PCR), has demonstrated a number of differentially expressed genes compared with diffuse astrocytomas (WHO grade II) and high-grade gliomas (Colin et al., 2006; Huang et al., 2000; Wong et al., 2005; Zhang et al., 2008). JPAs maintain high expression of major histocompatibility complex genes such as HLA-DR α (Huang et al., 2005), that are known to be downregulated in tumor specimens containing invading glioma tumor cells (Zagzag et al., 2005). They also showed high levels of expression of TIMP1 and TIMP2, inhibitors of metalloproteinases that promote cell invasion (Huang et al., 2005). In addition, JPAs show activation of genes involved in cell adhesion, cell proliferation and neurogenesis (Wong et al., 2005). A recent study comparing high-grade gliomas with JPAs identified 5 genes related to invasion and angiogenesis, including fibronectin, osteopontin and YKL-40, that were preferentially expressed in high-grade gliomas over JPAs (Colin et al., 2006). In contrast, *high* levels of YKL-40 expression were consistently detected in JPAs (10 of 10) using qRT-PCR (Zhang et al., 2008). YKL-40 is thought to play a role in proliferation and differentiation as well as angiogenesis, but its role in astrocytoma biology remains to be defined. Taken together, the genetics of JPAs to date support its biologic behavior as a slow growing, non-infiltrative, relatively benign pediatric tumor that can be cured with surgical resection. Currently, there are no reliable molecular prognostic criteria that can be used to predict the natural course or patient response to chemotherapy.

Diffuse Intrinsic Pontine Glioma

Brainstem tumors account for 10–20% of all pediatric tumors and diffuse intrinsic pontine gliomas (DIPG) represent 80% of all brainstem tumors (Recinos et al., 2007). DIPG remains one of the most lethal pediatric brain tumors with three year survival rates in the 5–10% range. The peak incidence is between five and ten years of age and the diagnosis can be

made based on the clinical history and MRI findings. Histologically, most DIPGs are classified as either grade II fibrillary or grade III–IV high-grade gliomas (anaplastic astrocytomas or glioblastomas), although biopsies are not required for diagnosis and therefore not performed routinely.

Genetic alterations for DIPG are not as well documented compared with other types of astrocytic tumors, partly due to the fact that little tissue is available for analysis. However, molecular analysis of limited numbers of tumor samples indicates that the frequency of p53 mutations appears to be higher in brainstem gliomas compared with non-brainstem gliomas (Cheng et al., 1999; Louis et al., 1993). Overexpression of EGFR, including amplifications, is common and has been correlated with tumor grade (Gilbertson et al., 2003).

Radiotherapy remains the mainstay of therapy for DIPGs and although most patients will respond initially, eventual tumor progression is inevitable (Recinos et al., 2007). Unfortunately, attempts at improving survival through addition of chemotherapy, including high-dose chemotherapy, have not achieved a better overall survival (Massimino et al., 2008). An ongoing clinical trial from the Children's Oncology Group (COG) evaluates the efficacy of the radiosensitizer Motaxefin-Gadolinium (Ford et al., 2007) in patients with newly diagnosed DIPG. In two recently completed phase I/II trials from the Pediatric Brain Tumor Consortium (PBTCT), radiation therapy was combined with gefitinib, a selective EGFR inhibitor and tipifarnib, a farnesyl transferase inhibitor. A phase I trial of vandetanib, a multi-tyrosine kinase inhibitor (VEGFR, EGFR, RET) and concomitant radiotherapy is currently ongoing. In a recent series, the anti-EGFR monoclonal antibody, nimotuzumab was used on 22 pediatric patients with recurrent pontine gliomas and stable disease or partial remission were seen in 10 patients (Bode et al., 2007). These encouraging results have prompted a larger, international phase II trial which is ongoing. DIPG remains one of the most frustrating diseases in pediatric oncology and novel, more effective treatments are urgently needed.

Medulloblastoma

Medulloblastomas are malignant, invasive tumors of the cerebellum occurring preferentially in young children. The peak age at diagnosis is 7 years with over 70% of tumors observed in children less than 16 years of age. Medulloblastoma patients are currently stratified into two groups: standard-risk and high-risk. High-risk patients are those <3 years of age or having a residual tumor mass after surgery of >1.5 cm², or metastatic disease at diagnosis (Packer et al., 2003). The use of multi-agent chemotherapy has allowed for the use of reduced-dose craniospinal radiotherapy (CSRT) to 24 Gy with improved cure rates, reflected by a >80% event-free survival in standard-risk patients. For other than standard-risk medulloblastoma, the dose of CSRT is 36 Gy with a boost dose to the primary tumor to 54 Gy followed by adjuvant chemotherapy. The 5-year event free survival rates for high risk disease is 60%.

Several different cytogenetic techniques, such as CGH, FISH, aCGH and spectral karyotyping have identified isochromosome 17q as the most common cytogenetic abnormality in medulloblastomas which is present in 30–40% of tumors (Biegel, 1997; Bigner et al., 1988; Griffin et al., 1988; Lo et al., 2007b). However, no association between chromosome 17 abnormalities and overall survival was found. In terms of genome-wide copy numbers, medulloblastomas harbor gains in chromosomes 4, 7, 8, 9 and 18, and losses in chromosomes 1, 2, 8, 10, 11, 16 and 19 in >20% (Lo et al., 2007b), consistent with the findings from other studies using CGH to detect chromosomal abnormalities (Eberhart, 2007; Rickert and Paulus, 2004). Amplifications of several MYC genes including MYCL, MYCN and MYCC are frequently detected in medulloblastomas, and they are generally associated with poor prognosis (Lamont et al., 2004; Lo et al., 2007b).

Three additional molecular signaling pathways have been implicated in the pathogenesis of medulloblastomas: Hedgehog, Wnt and Notch. Approximately 8% of sporadic medulloblastomas have inactivating mutations in the PTCH gene, which is an inhibitor of the Hedgehog signaling pathway and plays an important role in cerebellar development (Fogarty et al., 2005; Marino, 2005). Gene expression profiling results have supported the notion that Hedgehog signaling plays a role in a subset of medulloblastomas, particularly the desmoplastic/nodular subtype (Pomeroy et al., 2002; Thompson et al., 2006). The Wnt pathway is activated in 10% of sporadic medulloblastomas through mutations in β -catenin that activate Wnt signaling by removing critical inhibitory phosphorylation sites (Zurawel et al., 1998). Use of immunohistochemistry has been shown to detect nuclear accumulation of β -catenin in 18-25% of medulloblastomas (Eberhart et al., 2000), and the presence of this biomarker indicating activation of the Wnt signaling pathway predicts a favorable outcome (Ellison et al., 2005). Most recently, gene expression profiling identified “gene expression signatures” that classified medulloblastomas into five distinct groups, including two groups that either had aberrant Hedgehog signaling or Wnt signaling (Thompson et al., 2006). Clinically relevant subclassifications of medulloblastoma patients via gene expression profiling could lead to patient selection for clinical trials with tumor-specific molecular targeted therapies. Finally, the Notch signaling pathway, which plays an important role in maintenance of neural stem cells (Eberhart, 2007), has also been implicated in the development of medulloblastomas by gene expression profiling and SSH studies which identified genes, such as Notch 2, that are amplified and overexpressed in approximately 15% of cases (Fan et al., 2004; Yokota et al., 2004). The use of Notch pathway inhibitors, such as that inhibiting the release of a soluble form of the Notch receptor by γ -secretase, has been shown to inhibit the growth of medulloblastoma cells (Fan et al., 2004). Enzymes such as ADAM10, a disintegrin-metalloproteinase, that processes membrane bound receptor molecules into soluble proteins, including EGFR, Erb4 and Notch receptors, have become a recent focus for development of targeted therapeutics (Moss et al., 2008).

Several recent comprehensive studies screening for chromosomal abnormalities and/or using array based gene expression profiling have been identified target genes and prognostic markers, in addition to those already mentioned above, that could be used to as prognostic factors for risk stratification or therapeutic targets. In otherwise standard-risk medulloblastoma patients stratified by age >3 years and without metastatic disease, gain of 1q was significantly associated with poor survival (Lo et al., 2007a). An enzyme, hMOF, involved in histone acetylation, a process that is important for global regulation of gene transcription, cell proliferation, and response to DNA damage was shown to be downregulated in 40% (72 of 180) of medulloblastomas. Loss of gene expression was detected by immunohistochemistry more frequently in anaplastic and classic medulloblastomas compared with those with desmoplastic histology (Pfister et al., 2008b). Importantly, hMOF expression levels stratified patients into two risk groups associated with survival outcome and should be considered as a potential prognostic biomarker in the near future. Lastly, the gain of chromosome 7 is a frequent occurrence in medulloblastomas. The collagen gene COL1A2 encoding the alpha subunit of type I collagen was identified by microarray analysis and shown by immunohistochemistry to be overexpressed in a panel of 17 medulloblastomas specimens (Liang et al., 2008). One hypothesis for type I collagen expression in medulloblastomas may be its role in angiogenesis and blood vessel formation, since these tumors are highly vascular in nature. A small molecule inhibitor of collagen I synthesis, halofuginone, has been shown to inhibit neovascularization by blocking tubule formation by endothelial cells *in vitro* and tumor growth in an animal model (Abramovitch et al., 1999; Elkin et al., 2000). These results indicate a potential for targeting collagen I synthesis to limit angiogenic processes within the tumor and affect the clinical behavior of the tumor as well as improve patient outcome.

Ependymoma

Ependymomas are generally slow growing, well-circumscribed tumors that arise predominately infratentorially in children with a peak incidence of 6 years of age. They account for 10% of all pediatric tumors and approximately 30% of tumors in children <3 years of age (SEER data). Histopathological diagnosis and grading can be difficult, with frequent disagreement among neuropathologists. Furthermore, the impact of tumor histology on outcome remains controversial (Perilongo et al., 1997; Robertson et al., 1998; Schiffer et al., 1991). Complete surgical resection remains the single most important predictor of relapse-free and overall survival (Robertson et al., 1998; Timmermann et al., 2000). Radiotherapy is the standard adjuvant treatment, at least for older children, while the use of adjuvant standard-dose chemotherapy has not resulted in significantly improved outcomes and high-dose chemotherapy approaches to avoid radiation-therapy in young children have been disappointing (Zacharoulis et al., 2007). Involved field post-op radiotherapy is given to patients with localized residual disease in the cerebral hemispheres or posterior fossa but is deferred for patients with a gross total resection in the cerebral hemispheres or spinal cord.

Using metaphase CGH analysis, several genetic aberrations have been detected in ependymomas involving gains and losses of several chromosomes that can vary in different studies but commonly include gains of 1q, 5, 7, 8, 9, 18 and 19 and losses of 3 and 6 (Dyer et al., 2002; Pezzolo et al., 2008). Importantly, the gain of 1q is a common finding associated with a poor prognosis not only in ependymoma (Dyer et al., 2002; Mendrzyk et al., 2006) and medulloblastoma, but also other pediatric tumors, including neuroblastoma, Wilms' tumor and Ewing's sarcoma. To date, the gene(s) located on the region 1q25 that is gained in these malignancies has not been identified. In contrast, a better prognosis has been associated with the loss of the region 6q25.3 in patients with anaplastic ependymomas (Monoranu et al., 2008).

CGH studies have defined at least three distinct genetic patterns among ependymoma patients (Dyer et al., 2002; Mendrzyk et al., 2006). The group of patients <3 years of age showed few chromosomal changes compared with those >3 years of age. A second group showed several chromosomal imbalances together with a nonrandom gain or loss of chromosomes. A third group showed a balanced chromosome profile that occurred in tumors in children <3 years of age, suggesting that these tumors developed by a different genetic pathway compared with tumors arising in older children. However, one study of 20 pediatric ependymomas found that tumors in patients <3 years of age were characterized by structural chromosome rearrangements (Pezzolo et al., 2008). Further studies will be required to resolve these discordant findings.

Gene expression profiling has identified “gene expression signatures” showing the involvement of both the Notch and Hedgehog signaling pathways in subsets of ependymomas (Modena et al., 2006; Taylor et al., 2005). Similar to medulloblastoma, where these same pathways are activated, small molecule inhibitors, such as cyclopamine or HhAntag-691 (a benzimidazole) could be exploited to control tumor growth by inhibiting gene expression in the Hedgehog signaling pathway, such as Gli1 (Romer and Curran, 2005).

At least two independent studies have shown overexpression of human telomere reverse transcriptase (hTERT, located at 5p15.33) is a strong prognostic factor in ependymomas for poor survival (Mendrzyk et al., 2006; Tabori et al., 2006). In addition, inhibition of telomerase may be a future therapeutic target. Tumors need to maintain their telomeres in order to replicate chromosomes and thus reactivate the telomerase enzyme, whereas normal cells do not contain this active enzyme (Shay and Wright, 2005). Inhibitors of tankyrase and telomerase have been successfully used in cell culture to induce shortening of telomeres

such that tumor cells entered proliferation crisis and died (Seimiya et al., 2005). This novel therapeutic approach could be an effective anti-cancer therapy.

Lastly, ependymomas have shown frequent gains and amplification of EGFR, located at 7p11.2 (Mendrzyk et al., 2006). Overexpression of EGFR was an independent prognostic marker of poor survival. Several agents targeting EGFR are currently in clinical trials, such as the tyrosine kinase inhibitors erlotinib and gefitinib, and the monoclonal anti-EGFR antibody C225 (cetuximab) (Milano et al., 2008). The role of these agents in the treatment of EGFR-positive ependymomas, in combination with other chemotherapy and/or radiotherapy regimens, remains to be defined.

Clinical Trials Issues for Molecular Targeted Agents

The traditional clinical phase I trial design was originally conceived to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of cytotoxic drugs. The use of this model for molecular targeted agents has been called into question, since for these drugs, the minimum target inhibiting dose (MTID) may be more relevant in regard to biologic effect and positive treatment response (Korn, 2004). The use of pharmacodynamic, or phase 0, studies has been proposed as an efficient way to determine the molecular effects of targeted agents in a small group of patients before proceeding to advanced trials (Rojo et al., 2007). In phase II, or small efficacy trials, alternative endpoints, such as time to progression (TTP) are increasingly being used to facilitate the successful selection of active molecular agents that may have cytostatic rather than cytotoxic activity (Morabito et al., 2006). In addition, significant efforts are being made to identify surrogate markers, such as molecular imaging techniques and non-tumor tissue analysis, to help screen for effective treatments more rapidly (Curran et al., 2006). However, careful validation of such alternative strategies is necessary to avoid misleading conclusions. Well-designed, randomized placebo-controlled phase III trials remain the gold standard to prove clinical efficacy of any drug, including molecular targeted agents. However, the relatively small number of pediatric patients with brain tumors clearly limits the feasibility of adequately statistically powered phase III trials, particularly for the rare disease entities. Furthermore, the presence of unrecognized molecular heterogeneity can lead to falsely rejecting a treatment that is effective in a subgroup of patients and underscores the need for careful, molecular target-oriented patient selection rather than simply disease-selection. A recent analysis has identified positive predictive factors for successful phase III trials based on preceding phase II data for molecular targeted agents. These characteristics included multiple (versus single) institution participation and pharmaceutical company sponsorship, which may be in part explained by publication bias. Interestingly, the magnitude of the phase II response rates were not independently predictive of the phase III results in this analysis, although another study found that overall response rates did positively correlate with subsequent FDA approval (El-Maraghi and Eisenhauer, 2008).

Conclusions and Future Perspectives

Through advances in neurosurgery, radiotherapy and chemotherapy, significant progress has been made in the treatment of pediatric brain tumors over the past decades. While survival and cure rates have improved, the treatment-related morbidity remains high and significant long-term sequelae are common. Our growing knowledge of the tumor biology of pediatric brain tumors holds promise for finding new “molecular targeted” drugs that may augment, supplement or even replace conventional chemotherapy and radiotherapy. Rigorous and well-designed clinical trials will be needed to evaluate the safety and efficacy of these new approaches.

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