A growing body of evidence suggests that high-grade gliomas in pediatric patients manifest properties that clearly distinguish them from their adult counterparts. Some of the most striking differences between them lie in their differential response to conventional treatment modalities. Whereas adjuvant chemotherapy has been shown to exert only a modest survival benefit when undertaken in adult patients, chemotherapy combined with surgery and radiotherapy is associated with a much more robust survival advantage in children. Several longitudinal cooperative group studies have demonstrated that in addition to the favorable response of childhood high-grade gliomas to chemotherapy, a significant correlation exists between the extent of resection and outcome. The authors of recent literature reviews focusing on adult patients have failed to demonstrate a similar association. Finally, it is becoming clearer that the difference between pediatric and adult high-grade gliomas extends well beyond clinical response to treatment and into the realm of molecular cytogenetics and the pathways that ultimately give rise to the adult and pediatric variants of these tumors. An unfortunate characteristic shared by pediatric and adult high-grade gliomas, however, is their universally poor prognosis: in children with GBM the 5-year survival rates range from 5 to 15%, whereas those with AA fare slightly better, with a 20 to 40% long-term cumulative survival probability.

The purpose of this brief review is to summarize the epidemiology, clinical presentation, histopathological features, treatment principles, and outcome of pediatric malignant gliomas. The characteristics of childhood and adult high-grade gliomas will be compared and contrasted wherever possible. We will conclude this article with a discussion of some of the recent novel therapeutic strategies.

**PEDIATRIC HIGH-GRADE GLIOMAS**

**Epidemiological Features**

Precise estimates of the frequency of pediatric high-grade gliomas have been difficult to define, largely because of the tendency in earlier reports to misclassify various low-grade glioma variants under the diagnostic umbrella of high-grade lesions. As such, the validity of many older descriptive and clinical studies of cases reported as high-grade gliomas has been somewhat undermined, simply because of the pathological heterogeneity of the glial tumors that were studied. In more recent descriptive epidemiological studies, however, the authors have begun to clarify incidence and prevalence.

As in adults, the majority of primary supratentorial hemispheric tumors in children are gliomas. In contrast to adults, however, high-grade gliomas are significantly less common than low-grade lesions, comprising only 20% of all hemispheric gliomas in pediatric series. Overall, malignant gliomas represent approximately 6.5% of all newly diagnosed childhood intracranial neoplasms.
translates into an incidence of approximately two cases per million children annually.

No review of primary brain tumors, especially those occurring in children, would be complete without a discussion of putative genetic or environmental risk factors. Although clearly beyond the scope of the present discussion, it can safely be said that apart from some well-known genetic syndromes that predispose to the development of CNS tumors in general, there remains little consensus about the nature and relative magnitude of other risk factors specific to the development of childhood malignant gliomas.51

Patients with NF1 harbor a mutation in the neurofibromin gene located on chromosome 17q11.2. Neurofibromin has homology to the RAS–guanosine 5-triphosphatase–activating protein family and normally functions as a tumor suppressor gene. Although the most characteristic intracranial neoplasms in patients harboring this mutation are optic pathway and hypothalamic gliomas, cerebral hemispheric lesions develop in a small percentage of patients. Although low-grade lesions tend to develop in patients with NF1, high-grade tumors have also been reported (Fig. 1).41

Turcot syndrome comprises the rare association between colonic polyposis and intracranial neoplasms. This syndrome more than likely represents a collection of distinct disease entities caused by specific germline mutations in a variety of tumor suppressor genes, including the adenomatous polyposis coli gene and DNA mismatch repair genes such as hMLH1 and hPMS2.18,34 In patients with germline adenomatous polyposis coli mutations there is an increased incidence of medulloblastoma, whereas in those with mismatch repair gene mutations there is generally an increased incidence of gliomas.

Li-Fraumeni cancer syndrome, caused by germline mutations in the p53 tumor suppressor, also predisposes to the development of high-grade gliomas.25 A number of less common syndromes have also been linked anecdotally to the development of glial neoplasms, but a molecular basis for these associations has yet to be found.

The one environmental factor known to cause malignant gliomas in childhood is prior irradiation of the brain (Fig. 2). Children who have undergone irradiation in the treatment of prior low-grade gliomas may be particularly susceptible to the transformation of the lesion into a higher-grade neoplasm.

**Diagnostic Evaluation**

Whereas low-grade gliomas typically present with an insidious onset of symptoms suggestive of intracranial hypertension or a protracted history of seizures, symptoms of high-grade gliomas are typically far more abrupt, with rapidly progressive symptoms or signs of elevated intracranial pressure and/or a focal neurological deficit.1,31 Seizures as a mode of presentation of high-grade gliomas are less commonly observed than in the setting of low-grade tumors (in approximately 30% of children presenting with malignant gliomas). A significant minority of children, perhaps representing only 5 to 10% of those with these tumors, present because of a sudden deterioration in neurological status, often as the consequence of intratumoral hemorrhage.

Evidence of disseminated disease at presentation is rare in cases involving high-grade gliomas;16 this is in stark contrast to cases involving other malignant pediatric intracranial neoplasms such as supratentorial primitive neuroectodermal tumors.

There is no pathognomonic radiographic appearance that distinguishes the various malignant supratentorial hemispheric tumors from each other. High-grade gliomas typically display irregular or ring enhancement on cranial CT scanning, reflecting the breakdown of the blood–brain barrier or tumor neovascularity. The characteristic MR imaging–documented appearance of malignant gliomas is that of low intensity on T1-weighted sequences, cortical and white matter T2-signal hyperintensity, representing
infiltrating tumor and reactive vasogenic edema, and the aforementioned irregular pattern of contrast enhancement (Fig. 2). Because of the propensity for these lesions to grow rapidly, evidence of significant local mass effect is often seen. The neuroimaging differential diagnosis includes other malignant supratentorial hemispheric tumors, such as supratentorial primitive neuroectodermal tumors, ependymomas, and pleomorphic xanthoastrocytomas. Pleomorphic xanthoastrocytomas, of which approximately 20% have histological characteristics typical of classical malignant gliomas (see the following section), have a fairly unique neuroimaging appearance in that an enhancing solid component arising near the cortical surface is characteristically observed, in association with an underlying cyst.

Gadolinium-enhanced neuroimaging of the entire neuraxis should be performed only if there is a high index of suspicion for the presence of disseminated disease at the time of initial evaluation or if a competing diagnosis is highly considered in the differential of a child’s presenting complaint. Perhaps the best philosophy is to reserve such intensive neuroimaging intervention for the postoperative period, after a firm histopathological diagnosis has been established.

**Histopathological Characteristics**

Childhood malignant gliomas may be polar hemispheric tumors or midline, deep-seated lesions; they may be fairly well demarcated from adjacent normal brain or diffusely infiltrative. Grossly, they may show foci of cystic degeneration, hemorrhage, or necrosis.

Supratentorial high-grade gliomas are classically divided into two major subgroups, AA (Grade III) and GBM (Grade IV), based on the presence of characteristic microscopic features. According to the World Health Organization classification scheme, AAs are characterized by their focal or diffuse hypercellularity, nuclear atypia, nuclear pleomorphism, and the presence of mitotic figures, whereas GBMs exhibit vascular proliferation and/or necrosis in addition to the aforementioned features.

Because several less common glial neoplasms also exhibit histological features typical of the classic malignant gliomas (AA and GBM), they are also classified as malignant gliomas in contemporary grading schemes. Grade III oligodendrogial neoplasms have anaplastic features including frequent mitoses, necrosis, and vascular proliferation. Although typically characterized as low-grade, a subset of pleomorphic xanthoastrocytomas exhibit evidence of malignant transformation with necrosis, pronounced mitotic activity, and endothelial proliferation, and are consequently classified as high-grade gliomas. Similarly, evidence of increased mitotic activity, necrosis, and endothelial proliferation may be seen in a small proportion of gangliogliomas and juvenile pilocytic astrocytomas. Although these latter lesions undoubtedly display features that would lead to their being labeled as anaplastic under the World Health Organization classification, significant controversy still surrounds the issue of whether these tumors should be grouped with the other high-grade gliomas in view of their more indolent clinical behavior.

The outcome of children with malignant gliomas is highly dependent on tumor histology; in general, patients with GBM fare far worse than those with AA. In the contemporary literature, 5-year survival rates range from 5 to 15% for children with GBM and from 20 to 40% for those with AA. The authors of several studies have shown that high-grade gliomas other than the predominantly astrocytic AA and GBM are associated with a more favorable outcome. This may in part be a result of a greater sensitivity of anaplastic oligodendrogial cells in mixed tumors to conventional chemotherapeutic agents, such as the combination regimen of procarbazine, lomustine, and vincristine.

**Genetic Alterations and Molecular Pathogenesis**

There are key cytogenetic and molecular differences between adult and pediatric high-grade gliomas, these differences led to the hypothesis that the development of pediatric high-grade gliomas may follow pathways distinct from the traditional primary and secondary malignant glioma paradigm seen in adults. Moreover, a growing link between the molecular characteristics of these tumors and their biological behavior has fueled the search for clinically relevant molecular predictors of outcome.

In comparative genomic hybridization studies investigators have shown that the pattern of chromosomal aberrations differs between pediatric and adult high-grade gliomas, as well as between pediatric AA and pediatric GBM. Compared with their adult counterparts, childhood high-grade gliomas consistently display more frequent gains of chromosomes 1p, 2q, and 21q, as well as more frequent losses of chromosomes 6q, 11q, and 16q. Pediatric AAs were typified by changes including +5q, −6q, −9q, −12q, and −22q, whereas pediatric GBMs exhibited gains of chromosomes 1q, 3q, and 16p in addition to losses of chromosomes 8q and 17p. An overwhelming observation, apart from the specific chromosomal aberrations, was that a great deal of chromosomal imbalance exists in pediatric malignant gliomas, with multiple regions of abnormality. There is speculation that a high number of chromosomal aberrations may correlate with an aggressive biological phenotype.

In one of the recent investigations of microsatellite instability in high-grade gliomas, 27% of pediatric high-grade gliomas compared with 0% of those in adults displayed length alterations in the tandemly repeated nucleotide sequences (p < 0.001). Once again, the authors proposed a correlation between microsatellite instability and outcome.

Additional specific molecular alterations have been discovered that appear to have a stronger association with clinical outcome than the aforementioned chromosomal aberrations and evidence of microsatellite instability.

**Treatment of Malignant Glioma**

Until recently, the prognosis in children with malignant supratentorial gliomas had been dismal, with most patients dying within 3 years of diagnosis. Recent aggressive multimodality therapies involving radiotherapy and chemotherapy and founded on a protocol of aggressive resection have been investigated largely under the auspices of multiinstitutional cohorts of pediatric patients with high-grade gliomas (the CCG and POG collaborations); these investigators have reported more encouraging survival profiles.
Role of Surgery in Malignant Glioma

Aggressive resection, with the preservation of neural function, is the cornerstone of the contemporary management of pediatric malignant gliomas (Fig. 3). The goal of surgery is twofold: to obtain tissue for the establishment of an accurate histological diagnosis for the lesion and to achieve safe cytoreduction of the lesion. For reasonably well-circumscribed lesions, a gross-total resection should be the only operative goal, because the extent of tumor removal is positively correlated with long-term survival. In cases of more infiltrative lesions that prohibit a radical resection, either because they cross the midline or extensively invade critical functional areas of the brain, the goal instead becomes excision of as much tumor as is possible without causing undue neurological morbidity (Fig. 4). Advances in microsurgical technique, in conjunction with the ever-proliferating application of surgical adjuncts including frameless stereotactic guidance systems and other methods for functional mapping of critical brain areas, provide the treating surgeon with a means for the safe removal of tumors previously thought to be unresectable or resectable only with significant morbidity for the patient.

A relationship between the extent of resection and patient survival was first alluded to in the CCG-943 trial, in which investigators demonstrated improved survival in pediatric patients with GBM, treated with radio- and chemotherapy, in whom some degree of tumor, more substantial than a simple biopsy specimen, had been resected. A more robust conclusion emerged from the subsequent CCG-945 multiinstitutional randomized cohort. The principal aim of the CCG-945 trial was to evaluate the relative efficacy of two alternative chemotherapeutic regimens. The unique nature of this collaborative effort, however, in that data were prospectively recorded with respect to a number of potentially prognostic variables, allowed for the analysts to determine the precise influence of the extent of resection on survival. In children with malignant gliomas undergoing tumor resection of greater than 90%, the 5-year estimate of PFS was 35 ± 7%, whereas that in children undergoing less than 90% resection, the 5-year PFS rate was only 17 ± 4% (p = 0.006). The strength of the association was demonstrated both in the subgroup of patients with AA (> 90% resection 44 ± 11% compared with < 90% resection 22 ± 6% [p = 0.055]) and in the subgroup harboring GBM (> 90% resection 26 ± 9% compared with < 90% resection 4 ± 3% [p = 0.046]). A caveat involved in interpreting this data is that one must always be aware of the fact that it is impossible to exclude completely the possibility that those tumors possessing more favorable biological characteristics were inherently more amenable to near-complete extirpation. The more favorable outcome in such patients may therefore be partly attributable to these inherent biological characteristics rather than being solely a product of the more aggressive surgical intervention.

Adjuvant Therapy

Following maximum resection, children with high-grade gliomas routinely undergo radiotherapy targeting the tumor bed and a margin of surrounding brain; the dosing protocol is fairly standard (5000–6000 cGy in 25–30 fractions). Unfortunately, attempts to intensify radiotherapy administration by dose escalation (to a cumulative total dose of 7200 cGy) in conjunction with hyperfractionation have failed to improve outcome in the setting of high-grade gliomas. The use of low-intensity chemotherapy has repeatedly been shown to improve survival over that associated with surgery and radiotherapy alone. The first study to demonstrate this advantage was the CCG-943 trial, in which children were randomly allocated to receive radiotherapy followed by the pCV protocol or radiotherapy alone. In children in the combined radio- and chemotherapy arm the 5-year event-free survival was 46% compared with that of 18% in the radiotherapy-alone group. In the CCG-945 follow-up study to the previous trial, investigators tested the superiority of a more complex “eight-drugs-in-1-day” regimen over standard pCV chemotherapy in high-grade glioma patients undergoing surgery and radiotherapy. The more elaborate “eight-in-one” protocol did not confer an additional survival benefit over treatment in the
control arm, probably in large part due to the suboptimum dose intensity of several components of the “eight-in-one” regimen.

Based on these observations, the chemotherapeutic paradigm has shifted from enhancing the complexity of low-intensity regimens, such as the “eight-in-one” protocol used in CCG-945, to dose intensification involving a limited number of agents used in rational combinations. To this end, more intensive submyeloablative regimens have been studied in a neoadjuvant setting, as have myeloablative regimens in an adjuvant role.37

In the POG-9135 trial investigators compared the use of neoadjuvant cisplatin/carmustine to cyclophosphamide/vincristine in patients in whom high-grade gliomas were newly diagnosed; a 20% 5-year survival rate was observed in the cisplatin/carmustine group as compared with less than 5% in those treated with cyclophosphamide-vincristine (p < 0.05). In the three-arm CCG-9933 study participants investigated the neoadjuvant administration of three different alkylating agents administered in conjunction with etoposide (carboplatin/etoposide; etoposide/ifosfamide/mesna; and etoposide/cyclophosphamide/mesna) in patients with known postoperative residual disease. Rather than finding a significant beneficial effect of any of these regimens on overall survival, the investigators instead reported an unacceptably high rate of disease progression in all three treatment arms. (Unpublished data.) Similarly, in the POG-9431 study, designed to compare neoadjuvant procarbazine to topotecan, investigators noted insufficient activity of either agent to warrant further investigation.

In studies involving high-dose chemotherapy in conjunction with stem cell rescue authors have documented promising rates of long-term disease control but at the expense of significant morbidity and mortality as a consequence of the regimens themselves.17,29 Similar findings have led many investigators in this area to doubt the value of intensified chemotherapeutic regimens in improving long-term disease control rates, if they indeed appear to arise along with significant deleterious consequences to a child’s overall QOL.

For the time being, the PCV regimen first examined in the CCG-943 and -945 trials appears to be the standard against which other chemotherapeutic protocols will be evaluated in the future, both with respect to efficacy and toxicity profiles.

Prognostic Factors

Two key prognostic factors with respect to predicting outcome in pediatric high-grade glioma patients have already been discussed. There is a powerful association between the extent of resection and ultimate clinical outcome, as established in the CCG-943 and -945 studies.12,46,50 Furthermore, tumor histology is also a very strong predictor of outcome; children with GBM have consistently been shown to fare worse than those with AA who have been matched with respect to other prognostic variables.12,46 Despite these significant associations, however, the aforementioned clinical and histopathological features fail to predict adequately outcomes in children with malignant gliomas, indicating a need to identify relevant molecular markers of clinical tumor behavior that will guide subsequent therapeutic decision making. As noted previously, a number of cytogenetic and molecular factors have been associated with outcome; the two that will be discussed in greater detail here include p53 expression status38,39 and tumor proliferation index.50

In the CCG substudy B975 investigators were able to obtain tumor specimens in 170 of the 231 children enrolled in the larger CCG-945 study, making this collection of pathological specimens representing pediatric high-grade gliomas the largest ever assembled. Alterations in the p53 pathway were examined in this cohort. In children with tumors that displayed evidence of p53 overexpression and/or TP53 mutations, a significantly worse PFS was demonstrated than in those with tumors that lacked these features. The 5-year PFS rate was 44 ± 6% in the 74 children in whom there were low levels of p53 expression compared with 17 ± 6% in 41 patients with p53 overexpression (p = 0.0001).39 Additionally, it was found that abnormalities of p53 expression were far more common in GBMs (58%) than in AAs (26%) or other Grade III gliomas (p < 0.002). Despite the strong association between histology and p53 alterations, p53 expression status was found to be an independent predictor of outcome for each histological stratum (p = 0.005).39 Furthermore, an association was found between p53 expression status and patient age; in children younger than 3 years of age there was a significantly lower frequency of TP53 mutation than in older children.38 This finding has led to the suggestion that malignant gliomas in younger patients may arise via a molecular pathway not involving p53.

Proliferation index, as assessed by MIB-1 antibody labeling of the nuclear Ki-67 antigen, was also found to correlate highly with patient outcome. Ninety-eight tumors obtained in the larger CCG-945 study were assessed using this method. The 5-year PFS rate was 33 ± 7% in 43 patients in whom MIB-1 labeling indices were less than 18%, 22 ± 8% in the 27 in whom labeling indices were between 18 and 36%, and 11 ± 6% in the 28 patients in whom labeling indices were greater than 36% (p = 0.003).40 Consistent with the experience in those studies aimed at ascertaining p53 marker status was the finding that the MIB-1 labeling index was also significantly correlated with tumor histology. Nevertheless, the link between MIB-1 labeling index and outcome was a robust one: the significance of the association held even after the independent effects of tumor histology on outcome were accounted for (p = 0.004). Although the finding that tumors with a high proliferative activity as assessed by this method tended to be more biologically aggressive is not terribly surprising, it does point toward the need for a better understanding of the cell cycle so that it may be appropriately targeted in the search for novel therapeutic strategies aimed at controlling these notoriously aggressive tumors.

In addition to p53 expression status and proliferative index, a variety of other molecular markers are currently under intense investigation for their potential association with outcome in childhood malignant gliomas. Additionally, it is hoped that some of these markers will ultimately prove useful as a means for prospectively identifying those children in whom a given therapeutic approach would yield a favorable response, thus serving as a method for pretreatment “risk stratification”.37
The starting point for many of these studies arose from the well-documented association of certain molecular markers with disease progression in the setting of adult malignant gliomas. Epidermal growth factor receptor amplification PTEN (phosphatase and tensin homolog detected on chromosome 10) deletions, and alterations in specific cell cycle control genes including 14ARF are some representative examples of the pathways currently being studied.

It is fitting to conclude this section by reiterating a point so eloquently made by Pollack and colleagues:39,40 no marker has yet been able to identify a subset of pediatric malignant gliomas that have a truly “favorable” prognosis, as even among the subgroups of patients whose tumors possess “favorable” marker profiles, more than 60% eventually die of disease progression, despite provision of the best available conventional treatments.

Tumor Recurrence

At the time one first suspects tumor recurrence in a patient, a complete evaluation for the determination of relapse is warranted. Although pediatric malignant gliomas typically recur at the primary site, they may also spread via the subarachnoid space to noncontiguous CNS sites. Leptomeningeal dissemination has been observed in a small proportion of children with high-grade gliomas.11 Metastases outside the CNS have been reported but are extremely rare.

Often, a recurrence at the primary site may be amenable to additional locoregional therapy including resection or stereotactic radiosurgery. Experimental chemotherapeutic protocols may also be considered if local therapy is not feasible. Any further intervention, however, must be individualized on the basis of the initial tumor type, the length of time between initial treatment and recurrence of the lesion, and the overall clinical picture. Despite aggressive therapy aimed at controlling recurrent disease, the prognosis for long-term survival is not good. In the CCG-945 trial,12,50 nearly all children in whom recurrence developed after initial surgery, radiotherapy, and chemotherapy died within 1 year. In those who received no additional treatment, mean survival was less than 2 months; in those children who were in sufficiently good clinical condition to warrant further treatment, the mean survival despite additional conventional chemotherapy, with or without further surgery, was less than 9 months.

In the setting of recurrent disease, high-dose myeloablative chemotherapy (thiotepa combined with etoposide) and autologous stem cell rescue yielded a 4-year event-free survival rate of 22 ± 7% compared with 2 ± 1% in children in the CCG-945 study who underwent conventional chemotherapy at the time of recurrence.13 The survival advantage associated with this high-dose regimen applied in both patients with GBM (14 ± 8% in patients on the experimental high-dose regimen compared with 0% in those on conventional chemotherapy [p = 0.003]) and for those with AA (36 ± 13% in patients on the experimental high-dose regimen compared with 10 ± 5% in those on conventional chemotherapy, [p = 0.036]). The benefit of high dose chemotherapy with stem cell rescue, however, was observed only in patients receiving this treatment in whom minimal tumor burden was demonstrated following radical resection.

In terms of tumor recurrence, improvements in patient outcome will be dependent on implementing novel therapeutic approaches targeting the molecular pathways that are aberrantly activated in these tumors, finding new mechanisms to improve the potency of locally delivered therapies, and modifying the host immune response against the tumor by using vaccines and immunomodulatory therapies.

Outcome and Prognosis

Despite refinements in the multimodality management of patients with these tumors, the overall long-term survival probability for children with supratentorial malignant gliomas remains dismal, with PFS beyond 5 years occurring in fewer than 30%. The outcome in children with high-grade gliomas is generally more favorable than in adults, but it is uncertain whether this difference is caused by variations in tumor biology, the therapeutic strategies used, inherent tumor resectability, or other factors remaining to be elucidated.

In contemporary studies of novel therapeutic strategies there are two principal goals. The first is to develop new protocols designed to improve overall survival (some of the more promising of these new ventures are discussed in the subsequent section). The second, which should not be considered a secondary objective in any sense, involves reducing the morbidity associated with conventional therapy, thereby preserving a child’s QOL during the treatment phase.

A surgeon must be judicious when undertaking the resection of a malignant glioma; any potential envisioned gains arising from a more radical resection must be balanced against the chances of causing real neurological harm to the patient.

The routine use of radiotherapy in the overall management of pediatric high-grade gliomas is associated with the well-known risks of delayed cognitive and neuropsychological sequelae. Although these patients are typically not treated with whole-brain irradiation, the radiation fields required for optimum treatment of these lesions quite commonly encompass a significant territory of brain tissue, thereby subjecting patients to a similar risk of adverse neurocognitive consequences. Protocols are being evaluated in which the aim is to target more precisely the neoplastic tissue while minimizing the volume of normal brain irradiated. Moreover, in light of the often devastating consequences of cranial irradiation in very young children, considerable attention has been devoted to devising strategies that either delay or avoid radiotherapy entirely in this population, by first administering an extended course of intensive chemotherapy.

Neoadjuvant and adjuvant chemotherapeutic protocols subject patients to significant toxicity involving the hematopoietic system in particular but also to other general body systems. Conventional low-intensity regimens appear to be relatively well tolerated, but, as previously mentioned, high-dose myeloablative and submyeloablative regimens are associated with substantial morbidity and mortality rates.17,29 Clearly, such significant toxicity-related considerations must be taken into account when discussing potential alternative therapeutic strategies with a child’s caregivers. Suffice it to say that ongoing study is required to determine fully whether such novel approach-
es truly translate into meaningful improvements in overall survival and QOL.

Future Directions

The efficacy of surgery and radiotherapy in the management of pediatric supratentorial high-grade gliomas has been established. The results obtained in several of the cooperative group studies discussed in this review have supported the finding that the provision of adjuvant chemotherapy in addition to irradiation improves the probability of long-term event-free survival.\(^\text{12,26}\) As suggested by the proliferation of chemotherapeutic trials in recent years, however, the optimal treatment regimen for pediatric malignant gliomas has yet to be established.

It is anticipated that further gains in survival rates will be yielded by investigation of several novel management approaches. One field of intense investigation is the study of novel chemotherapeutic agents such as antiangiogenic factors targeted at the hypervascular phenotype of malignant gliomas,\(^\text{49}\) or pharmacological approaches designed to interfere with the signal transduction pathways gone awry in these lesions; potential investigational agents in this regard include epidermal growth factor receptor inhibitors\(^\text{19}\) and platelet-derived growth factor receptor inhibitors.\(^\text{22}\) Additional studies are being conducted to examine the effect of new combinations of drugs, optimization of chemotherapy dose intensity, and chemotherapeutic measures designed to enhance the efficacy of conventional radiotherapy (‘‘radiosensitizing’’ agents). Finally, new systems designed to enhance drug delivery to local sites are also at the forefront of research. Representative tactics include the following: antibody- or ligand-mediated targeting of tumor cell antigens with the intent of inciting a host immune response against the tumor,\(^\text{20}\) or delivery of a cytotoxic agent\(^\text{26}\) or radionuclide conjugate\(^\text{45}\) directly to the tumor; gene therapy involving toxin-producing viral vector constructs to induce selective killing of rapidly proliferating tumor cells;\(^\text{2}\) and cytokine-producing constructs designed to induce an active host immune response against the tumor.\(^\text{15}\) The practice of such studies will, of necessity, be predicated on the central, blinded review of pathological specimens so that direct comparisons between different study results can be made. It appears that the current standard against which these novel investigational agents will be compared will be the pCV protocol examined under the auspices of the CCG-945 multiinstitutional cohort.

CONCLUSIONS

Ongoing delineation of the basic molecular mechanisms at work in pediatric supratentorial high-grade gliomas will serve to fuel the search for specific targeted therapies directed against these very aggressive lesions. Furthermore, continual refinements to the contemporary multimodality treatment of these tumors are being made. Taken together, these advances set the stage for improving the future prospects of children in whom these malignant supratentorial gliomas are diagnosed, both with respect to survival and QOL.

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