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Children's Oncology Group's 2013 Blueprint for Research: Central Nervous System Tumors

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Abstract

In the US, approximately 2,500 children are diagnosed annually with brain tumors. Their survival ranges from >90% to <10%. For children with medulloblastoma, the most common malignant brain tumor, 5-year survival ranges from >80% (standard-risk) to 60% (high-risk). For those with high-grade gliomas (HGGs) including diffuse intrinsic pontine gliomas, 5-year survival remains <10%. Sixty-five percent patients with ependymoma are cured after surgery and radiation therapy depending on the degree of resection and histopathology of the tumor. Phase II trials for brain tumors will investigate agents that act on cMET, PDGFRA, or EZH2 in HGG, DIPG, or medulloblastoma, respectively. Phase III trials will explore risk-based therapy stratification guided by molecular and clinical traits of children with medulloblastoma or ependymoma.

Keywords

ependymoma; high-grade glioma and diffuse intrinsic pontine glioma; medulloblastoma

INTRODUCTION

The landscape for pediatric brain tumor biology and treatment is undergoing a rapid transition as data from several studies are discovering key pathways and genetic changes that are critical for tumor initiation and maintenance. The key challenge for clinical

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investigators engaged in neuro-oncology research is to harness this information and design clinical protocols with novel agents that will seek to cure patients with CNS malignancies in childhood.

STATE OF THE DISEASE—CLINICAL

Medulloblastoma

Overview and incidence—Medulloblastoma is the most common malignant brain tumor in childhood [1]. Medulloblastoma can arise from infancy through adulthood, with a peak incidence occurring around 6 years of age. Approximately 400–450 new pediatric patients (infants to 21 years of age) with medulloblastoma are diagnosed annually in North America. Medulloblastoma is the most widely studied pediatric brain tumor, and clinical protocols from the European Union and North America have contributed to major advances in the standard of care for patients with this disease.

Staging/stratification—Current medulloblastoma protocols use a clinical-staging system that essentially separates children with standard-risk disease from those with high-risk disease based on whether metastatic (M_{1-3}) disease or residual tumor ($> 1.5 \text{ cm}^2$) is present [2]. Tumor histology was recently introduced into the staging system, when patients with large cell/anaplastic histology were recognized as being at greater risk of disease relapse. Hence, medulloblastoma with large cell/anaplastic histology is now classified as high-risk disease [3].

A growing body of literature indicates that medulloblastoma consists of at least four distinct molecular disease entities: WNT, Hedgehog (HH), Group 3, and Group 4 [4–7]. These molecular diseases have distinct clinical and molecular features and different cure rates. Patients with WNT tumors have the most favorable outcomes, even when they present with metastatic disease. Those with Group 3 tumors with large cell/anaplastic histology and *MYCC/MYCN* amplification have a dismal prognosis with current therapy. Children with HH or Group 4 tumors have an intermediate prognosis [8].

Current outcome—Current therapy for medulloblastoma includes maximal safe surgical resection of the tumor, craniospinal irradiation (CSI) irradiation boost to the primary tumor bed for patients older than 3 years, and adjuvant chemotherapy. This approach cures more than 80% of patients with standard-risk disease. For standard-risk medulloblastoma, a systematic reduction of CSI from 36 to 23.4 Gy and weekly vincristine treatments is also an effective approach that results in less impairment of long-term neuro-cognitive functioning in children younger than 8 years [9]. Adjuvant chemotherapy regimens consisting of either cisplatin/vincristine/CCNU or cisplatin/vincristine/cyclophosphamide have resulted in excellent overall survival (OS) [10]. For patients with high-risk disease, data suggest that the addition of chemotherapy to higher-dose radiation (craniospinal dose of 36 Gy) and adjuvant chemotherapy may cure approximately 65% of patients [11].

High-Grade Glioma and Diffuse Intrinsic Pontine Glioma

Overview and incidence—High-grade glioma (HGG) which includes anaplastic astrocytoma (AA) and glioblastoma multi-forme (GBM) together with diffuse intrinsic

pontine glioma (DIPG) constitute approximately 25% of all pediatric brain tumors. HGGs are rarely seen in infancy, but their incidence increases with age; thus, adolescents have the highest incidence of HGG among the pediatric age groups. Patients with DIPG tend to have a dismal outcome. Tumors in other locations of the brain stem (i.e., mid-brain or medulla) are generally low-grade gliomas and associated with much better survival [12].

Staging/stratification—Treatment for HGGs does not involve stratification yet, because molecular traits have failed to identify prognostic features in the pediatric population with this disease. Clinical factors such as the extent of surgical resection and presence or absence of metastatic disease affect survival; patients who undergo gross total resection have a survival advantage. The diagnosis of DIPG is guided by a combination of clinical findings (i.e., cranial nerve palsy and long tract signs) and characteristic features on imaging studies [13]. However, no stratification scheme is currently used to select treatment for patients with DIPG [14].

Current outcome—Outcome for patients with HGG or DIPG is dismal with fewer than 10% of children GBM or DIPG surviving at 2 years from diagnosis. This statistic has not improved, despite the introduction of several agents that have demonstrated activity in adult tumors, most notably temozolomide [15,16]. Unfortunately, Phase II studies in the recurrent disease setting have not identified any agents with sufficient activity to warrant inclusion in treatment regimens for patients with newly diagnosed HGG or DIPG. Temozolomide based regimens in pediatric patients with recurrent HGGs also have not been as effective as they are in adults with this disease [17].

Ependymoma

Overview and incidence—Ependymoma accounts for 8–10% of all pediatric brain tumors and is the third most common brain tumor in children [1,18]. Ependymoma can arise in the supratentorial brain, posterior fossa, or spinal cord. In adults, this disease accounts for 4% of brain tumors and most ependymomas arise in the spine. Cure rates for ependymoma have improved over time, with the recognition that extent of surgical resection is a crucial prognostic feature [19]. Other key prognostic factors of ependymoma have been identified in large cohort studies of the tumor's molecular features [20–24].

Staging/stratification—Extent of surgical resection remains a crucial factor that affects long-term disease control in patients with ependymoma [25,26]. Metastatic disease is present in <5% of patients at diagnosis, and it is associated with a dismal outcome [27]. Although earlier studies reported various effects of tumor histology on disease outcome, a consensus on this question has emerged, and a comprehensive stratification system has been proposed that groups patients into low-risk or high-risk treatment groups [22,28]. In future clinical trials, a version of this classification system will probably be used to treat patients.

Current outcome—Surgical resection and adjuvant radiotherapy cure approximately 65% of patients with ependymoma [29]. Almost 25% of infants can be cured with surgical resection of the tumor and postsurgical chemotherapy without the use of radiation [30,31]. Most of patients with recurrent disease are not curable, but they can experience prolonged

disease-free intervals after repeat surgical resection and chemotherapy and/or irradiation [32,33]. This approach has not been tested in a prospective trial, but small single-institution series have documented prolonged periods of disease control [34].

STATE OF THE DISEASE—BIOLOGICAL

Molecular Targets

Medulloblastoma—The most logical molecular target for medulloblastoma that has emerged after a decade of preclinical work is the Smoothened (SMO) antagonists which are specific to the HH-subtype of the disease [35–41]. Phase I testing has been completed for the GDC 0449 trial through the Pediatric Brain Tumor Consortium, and Phase II protocols for children and adults are near completion.

Whole-genome sequencing (WGS) of medulloblastoma has revealed several additional targets that are subgroup-specific [42,43]. The most actionable target is the *EZH2* gene, which contributes to maintaining the stem cell state of tumor progenitor cells [44]. Novel *EZH2* inhibitors are currently being developed. Additional molecular targets need further validation in preclinical models of the subtypes of medulloblastoma. [45–49].

High-grade glioma—WGS has revealed mutations in the chromatin-remodeling gene *H3F3A* in 44% of pediatric patients with HGG. The majority (86%) of tumors that have *H3F3A* mutations also carry *ATRX-DAXX/P53* mutations. These tumors are mostly glioblastomas and are present in children and young adults [50]. Tumors that harbor *H3F3A/ATRX-DAXX/P53* mutations are strongly associated with alternative lengthening of telomeres and a specific gene expression profile [50]. Thus, finding suitable targets for drug development will be a priority for the next generation of HGG studies.

Diffuse intrinsic pontine glioma—Similar to findings in HGG, WGS revealed potential gain-of-function mutations in *H3F3A* and *HIST1H3B* in 78% of DIPG tumors [51]. GWS of samples obtained from autopsied DIPG tissue also revealed recurrent amplifications of *PDGFRA*, *cMET*, and focal amplifications of cell-cycle regulatory genes controlling the retinoblastoma protein phosphorylation, hence identifying potential that could be exploited by novel therapy [52,53].

Ependymoma—Using a cross-species genomics approach, Johnson et al. [54] discovered that ependymoma comprises at least nine molecularly distinct diseases. They also found that supratentorial ependymoma is largely driven by the amplification of the *EPHB2* gene. Witt et al. [23] also described two distinct subgroups of posterior fossa ependymoma that have prognostically distinct clinical and pathologic features.

RECENT FINDINGS

Medulloblastoma

Standard-risk medulloblastoma—The COG A9961 protocol enrolled 421 (379 eligible) patients with standard-risk medulloblastoma between December 1996 and December 2000. All patients received weekly vincristine during radiotherapy, reduced-dose

CSI (23.4 Gy), and a boost of 32.4 Gy to the entire posterior fossa. Upon completion of radiotherapy, patients were randomized to either a cyclophosphamide- or CCNU-containing adjuvant chemo-therapy regimen. More than 80% of children can be cured with this therapy, and the adjuvant chemotherapy regimen did not affect outcome [10]. This study has served as the basis of the current COG trial (ACNS0331), in which patients who are older than 3 years and younger than 8 years are randomized to receive 18 or 23.4 Gy CSI. Additionally, all patients receive a radiation boost to the entire posterior fossa or the tumor bed with a 2-cm margin (using conformal radiation therapy treatment planning and delivery techniques). This latter study has had robust accrual and is close to meeting its planned total patient accrual. European investigators just published their prospective trial comparing the event free survival (EFS) and OS for 340 standard-risk medulloblastoma between hyperfractionated radiotherapy (HFRT) and standard conventional radiotherapy (STRT). At a median follow up of 4.8 years (0–1–8.3 years) the EFS and OS rates were not significantly different between the two treatment arms: 5-year EFS was $77 \pm 4\%$ in the STRT and $78 \pm 4\%$ in the HFRT cohort; the corresponding OS was $87 \pm 3\%$ and $85 \pm 3\%$, respectively [55]. The European investigators are currently pursuing a prospective protocol that will adjust therapy according to clinical and molecular risk for the standard-risk patients.

High-risk medulloblastoma—The COG 99701 protocol enrolled 161 eligible patients, 81 of whom had high-risk medulloblastoma. This Phase I/II study included concurrent administration of CSI and carboplatin as a potential radio-sensitizer. Vincristine was also included in the regimen. The study demonstrated that administering carboplatin with CSI was safe and could potentially improve OS and EFS for patients with high-risk disease at presentation [11]. This study is the basis of the current high-risk medulloblastoma study in COG (ACNS0332), in which the effect of adding carboplatin to CSI is being studied in a prospective, randomized manner. Other investigators in the US and Europe [56,57] have also documented a survival for high-risk medulloblastoma with an EFS of 70% with the use of neo adjuvant chemotherapy, higher dose radiation therapy, given either by standard fractionation or hyperfractionation, and adjuvant chemo-therapy that consists of higher doses of chemotherapy with stem cell rescue.

High-Grade Glioma

Initial treatment typically consists of surgery followed by radiotherapy combined with chemotherapy. European investigators evaluated the effect of adjuvant chemotherapy following surgery in children <5 years of age to avoid the use of radiation therapy until relapse/progression [58,59]. The COG conducted a series of studies to determine the efficacy of temozolomide administered concurrently with CSI and after radiotherapy in children with HGGs (ACNS0126). Despite data in adults demonstrating efficacy of temozolomide in a subset of patients with mismatch-repair deficiency, the results of ACNS0126 did not demonstrate a survival advantage over historic controls [16,60]. In a subsequent COG study (ACNS0423); CCNU was administered with temozolomide after radiotherapy to determine the impact on OS. Unfortunately, no improvement in survival was noted compared to that seen in the ACNS0126 trial (Jakacki RJ—personal communication).

The current COG study, ACNS0822, is designed to ascertain the best outcome among three multimodality regimens and a bevacizumab-based adjuvant chemotherapy regimen.

Diffuse Intrinsic Pontine Glioma

Sequential clinical studies using different therapeutic strategies have been conducted in an effort to improve the survival of patients with DIPG. The addition of temozolomide during and after radiotherapy did not affect OS or EFS of patients with DIPG (ACNS0126) [15]. Motexafin-gadolinium used concurrently with involved-field irradiation was tested in a prospective Phase II study and failed to show efficacy (ACNS0222) [61]. The current COG study, ACNS0927, is also using a combined modality approach using a histone deacetylase (HDAC) inhibitor during and after radiotherapy in patients with newly diagnosed DIPG.

Ependymoma

The COG completed a large prospective trial for newly diagnosed ependymoma (ACNS0121) that enrolled 378 (355 eligible) patients from August 2003 to November 2007. The study sought to document the local control and patterns of failure for localized ependymoma treated with 3D conformal radiotherapy using an anatomically defined 1.0-cm clinical target volume. Data from the ACNS0121 protocol have documented 5-year EFS of $55 \pm 6\%$ and a 5-year OS of $86 \pm 2\%$. The study demonstrated that the extent of surgical resection was a key factor that influenced disease control in patients with ependymoma, irrespective of histology. Patients who underwent partial surgical resection had 3-year EFS of $41 \pm 7\%$, as compared to $73 \pm 4\%$ for those who had either a near-total resection (i.e., $<5 \text{ mm}^2$ residual tumor) or macroscopic gross total resection of any grade or location of ependymoma. COG investigators have initiated a biology study (ACNS11B1) which should confirm in a uniformly treated population prognostic factors identified by various group, including the Europeans. This will underpin risk assignment and potentially therapy in the next front line clinical trial. The current COG trial (ACNS0831) builds on the ACNS0121 trial and will determine the impact of chemotherapy on EFS and OS of patients with localized ependymoma treated with 3D conformal radiotherapy and randomized to receive adjuvant chemotherapy. Investigators in Europe will soon embark on a prospective study that will test several different adjuvant chemotherapy regimens following surgery and radiation therapy for newly diagnosed patients with ependymoma.

STRATEGIC APPROACH: TARGETED THERAPY

Medulloblastoma

Newly diagnosed disease—The most well established target for treating medulloblastoma is the SMO receptor in the HH-subgroup. The use of a SMO inhibitor has shown transient efficacy in a single published case report [41]. WNT-subgroup patients have an excellent cure rate in both European and U.S. studies [56,62]. Thus, this subgroup will be targeted for a judicious reduction of therapy that maintains the high cure rate but reduces the long-term deleterious effects of combined-modality therapy. Patients with aggressive subtypes of medulloblastoma (*MYC* amplification, large cell/anaplastic histology, or metastatic disease) will need effective targeted therapies to improve their cure rates.

Relapsed disease—Patients with relapsed medulloblastoma have a dismal prognosis. The current study (ACNS0821) is a randomized trial comparing effectiveness of the combination of irinotecan and temozolomide with that of the same drugs combined with bevacizumab. The impact of this regimen on OS of patients with recurrent medulloblastoma will be determined. The next generation of COG trials for recurrent medulloblastoma will include therapies that are specific to each molecular subtype of the disease.

Trial design strategies—Clinical investigators will pursue prospective trials that will stratify the treatment of patients with newly diagnosed medulloblastoma on the basis of their molecular features and clinical risks, and target each subgroup with the appropriate therapeutic strategy. COG investigators are currently conducting studies on tumor tissues that were collected during the ACNS0331 and ACNS0332 protocols to determine the outcome of those patients based on the molecular features. The results of these studies will be used to generate historic outcome data against which the next generation of clinical trials will be compared. Due to the small number of patients in each medulloblastoma molecular subgroup, randomized Phase III studies will not be possible. However, Phase II studies comparing the outcomes of current patients with those of historic controls should have adequate power to detect differences in survival and establish baseline outcomes for future prospective randomized trials.

High-Grade Glioma and Diffuse Intrinsic Pontine Glioma

Newly diagnosed disease—Drugs that effectively treat HGG and DIPG have been elusive. Several reports have been published on new target genes in pediatric HGG and DIPGs that present attractive targets for the next generation of prospective HGG and DIPG studies [50–53,63].

Relapsed disease—Investigators in North America and Europe have formed a preclinical consortium to share reagents (cell lines, xenografts, snap-frozen tumor tissue) to facilitate high-throughput screening (HTS) of novel compounds. Drugs that show activity in the screens will be tested against human orthotopic xenografts and undergo extensive preclinical pharmacokinetic and pharmacodynamic (PK/PD) testing. Candidate drugs that have a favorable PK/ PD profile and demonstrate activity in orthotopic xenografts will be prioritized for testing in patients with recurrent disease. This strategy maximizes the chances of finding effective therapeutic options for these incurable tumors. Pseudo-progression of disease remains a considerable problem in selecting the appropriate patient population for relapsed HGG trials, but improved imaging is utilized to improve the selection process.

Trial design strategies—Well-designed Phase II trials with early stopping rules that test the efficacy of new agents, as measured by 6-month OS, will be a priority for patients with newly diagnosed or relapsed disease. Conduct of these studies will be limited by the availability of suitable novel agents from either the NCI Cancer Therapy Evaluation Program's portfolio or through industry partnerships.

Ependymoma

Newly diagnosed disease—Targeted therapies for patients with newly diagnosed ependymoma are currently not ready for clinical implementation. Investigators in the Collaborative Ependymoma Research Network are currently developing preclinical data using subgroup-specific genetically engineered mouse models (GEMM). HTS against these models may generate lead compounds for clinical testing. An HTS against *EPHB2*-driven ependymoma has suggested that PLK and IGFR1 inhibitors, bortezomib, and 5-fluorouracil, have potential activity against the disease [64].

Relapsed disease—In the ACNS1021 trial, COG investigators are testing the efficacy of sunitinib in patients with recurrent ependymoma. Lapatinib (an EGFR inhibitor), which has been tested in a Pediatric Brain Tumor Consortium trial, did not show any efficacy in relapsed ependymoma [65]. There is a paucity of agents for which preclinical results justify testing clinically. Preliminary data suggest that telomerase inhibitors may have a role in a subset of patients with ependymoma [66].

KEY TRIALS TO BE PURSUED

Medulloblastoma

Pivotal phase III trials—Over the next 3 years, the strategy for medulloblastoma trials in North America and Europe may involve a series of smaller pilot studies that use novel therapies targeted toward specific molecular subtypes of the disease rather than large Phase III trials. This is especially the case for patients with Group 3 tumors who have a dismal prognosis. Therapeutic strategies that appear promising in the pilot studies could potentially be further studied in a Phase III setting.

Randomized phase II studies and prioritization strategy—The next generation of medulloblastoma studies will be subgroup-specific, randomized Phase II studies; thus, these studies will address only patients with Group 4 tumors, as this tumor subset is the most common type of the disease. Priority will be given to introducing novel agents that have demonstrated activity in pre-clinical testing (e.g., in genetically engineered mouse models or subgroup-specific orthotopic xenografts) and have a favorable PK/ PD profile that is relevant to pediatric patients with medulloblastoma.

High-Grade Glioma and Diffuse Intrinsic Pontine Glioma

Pivotal phase III trials and randomized phase II trials—In regard to HGG and DIPG trials, the strategy in North America will be to design Phase II studies with the proviso to advance the promising treatments to Phase III randomized trials. The current ACNS0822 protocol is a 3-arm, Phase II randomization of patients with newly diagnosed disease. If patients in either of the two experimental treatment arms experience improved survival, compared to that seen in patients on the standard treatment arm, then the study will proceed to a randomized Phase III study. This strategy is an efficient way to rule out ineffective combinations and select agents with promising activity.

Ependymoma

Phase III trials—COG is currently conducting a randomized Phase III trial of newly diagnosed patients with ependymoma that is determining the efficacy of adjuvant chemotherapy following surgery and irradiation therapy. This trial will require another 3–4 years of accrual to meet its goal of 400 eligible patients. The SIOP consortium will also be conducting a prospective study that will test the efficacy of several adjuvant chemotherapy regimens following surgery and irradiation therapy. During this time period, new agents will most likely emerge from Phase II studies to test in future Phase III trials.

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