Neurofibromatosis Clinical Trial Consortium

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Abstract
Neurofibromatosis type 1 and type 2, affecting both children and adults, often result in devastating complications. The rapid unravelling of the genetic underpinnings of these unique disorders has led to the development of novel therapies, especially molecular-targeted therapies. To facilitate clinical trial development, the Neurofibromatosis Clinical Trial Consortium (NFCTC) was established in 2006 by the Department of Defense. Over the past decade, the Consortium has successfully completed studies for children and adults with neurofibromatosis type 1 and plexiform neurofibromas, neurocognitive challenges, low-grade gliomas, and malignant peripheral nerve sheath tumors. In addition, a study for children and adults with neurofibromatosis type 2 and acoustic schwannomas is near completion. The NFCTC has now been expanded to 19 sites in the United States and Australia. Mechanisms have been put in place to work closely with other consortia, foundations, and industry to expeditiously translate preclinical discoveries into clinical trials.

Keywords
brain tumor, cognition, genetics, neuroimaging, ophthalmology, treatment

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Neurofibromatosis type 1 (NF1) and type 2 (NF2) are genetically distinct disorders that cause a multitude of disease manifestations.1 Affecting both children and adults, these 2 diseases and other phenotypically similar conditions, such as schwannomatosis, often result in devastating complications that, until recently, were believed in great part to be untreatable.1 The rapid unravelling of the genetic underpinnings of these unique disorders has led to the hope that novel therapies, especially molecular-targeted treatments, could result in more effective means to treat the associated complications.2

A major obstacle in developing disease and condition-specific treatments has been the lack of established mechanisms to facilitate clinical investigations in these rare conditions.2 In an attempt to fill this void, the Neurofibromatosis Clinical Trials Consortium (NFCTC) was established in 2006 by the Department of Defense (DoD). The NFCTC was by intent a multidisciplinary effort, mandating that institutions with expertise both in the management of neurofibromatosis and in conducting clinical trials work together to expedite the development of biologically based clinical and, if possible, translational, therapeutic trials. This consortium, which has been in continuous operation since inception, has conducted multiple clinical trials in various manifestations of NF1 and NF2. The overall organization of the Consortium, its guiding principles, accomplishments, and challenges are reviewed in this manuscript. Also, future plans, now that funding has been confirmed for 2017-2022, are summarized.

Consortium Goals and Initiation
After a series of meetings in 2005 between members of the DoD and physicians with expertise in both neurofibromatosis and in pediatric clinical trial conduct, a planning grant was supported by the DoD to develop the Consortium. In 2007 the NFCTC was formally opened and included 9 member institutions and an Operations Center at the University of Alabama at

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Table 1. Clinical Trial Sites of NFCTC.

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Affiliate</th>
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<tr>
<td>University of Alabama at Birmingham**</td>
<td>Children’s Healthcare of Atlanta</td>
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<tr>
<td>Boston/Harvard Center, Boston Children’s, Dana Farber**</td>
<td>Massachusetts General Hospital</td>
</tr>
<tr>
<td>Children’s Hospital of Los Angeles</td>
<td>University of California at Los Angeles</td>
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<tr>
<td>Children’s National Health System**</td>
<td>Johns Hopkins Hospital</td>
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<tr>
<td>Children’s Hospital at Westmead (Sydney)</td>
<td>Murdoch Children’s Research Unit (Melbourne)</td>
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<tr>
<td>Cincinnati Children’s Hospital**</td>
<td>Lurie Children’s Hospital</td>
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<tr>
<td>National Cancer Institute**</td>
<td>University of Pennsylvania**</td>
</tr>
<tr>
<td>New York University Medical Center</td>
<td>University of Utah</td>
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<td>University of Chicago**</td>
<td>Washington University at St. Louis**</td>
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**Original site.

Birmingham (see Table 1). Both the Operations Center and the individual institutional sites were chosen competitively. The goals of the Consortium have remained the development of biologically-based, prospective clinical trials for children and adults with NF1 and NF2. In its original conception, the NFCTC was primarily focused on pediatric-aged patients, but before formal initiation, an additional adult focus was mandated. As the Consortium has evolved, the charge has been expanded to developing clinical trials for patients with schwannomatosis. In addition to developing these clinical trials, the Consortium is to establish and validate end points for judging the effectiveness of therapeutic interventions in patients with these conditions and to disseminate information on the progress of these clinical trials to the neurofibromatosis and related clinical and family/patient communities. The NFCTC is chartered to build an infrastructure that ensures high-quality data accrual, and compliance with regulatory and ethical requirements. By design, it was not the province of the NFCTC to undertake preclinical studies, but rather to collaborate closely with scientists performing such studies and to facilitate the translation of laboratory advances into clinical studies. It was expected that other organizations and foundations would fund the necessary preclinical work. The NFCTC was not designed as a “closed” entity and it welcomed proposals from investigators from institutions outside the member institutions of the Consortium, creating the opportunities for outside institutions to participate in clinical trials they proposed, along with other Consortium members. Soon after creation of the Consortium, a steering committee composed of the grant Principal Investigator, the Director of the Operations Office, the Group Chair, and the Principal Investigators of the chosen sites were charged to develop the methodology to facilitate the development of critically needed clinical trials.

Table 2. Clinical Trials Committees of the NFCTC.

<table>
<thead>
<tr>
<th>NF 1</th>
<th>NF 2</th>
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<tr>
<td>Neurocognitive (NF1)</td>
<td>Schwannomatosis</td>
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<td>Plexiform Neurofibromas (NF1)</td>
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<td>Low-Grade Gliomas (NF1)</td>
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<td>Malignant Peripheral Nerve Sheath (NF1)</td>
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<td>Bone (NF1)</td>
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<td>NF 2</td>
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Site Selection

Following approval of the planning grant proposal, the DoD and its Congressionally Directed Medical Research Programs (CDMRP) created an expert panel to evaluate and choose sites for the NFCTC. This competitive process evaluated sites on multiple criteria, including organization and multidisciplinary nature of the existing NF1 and NF2 programs, number of active patients with NF1 and NF2 seen at the site, clinical research experience of the site in performing prospective clinical trials, and available infrastructure to safely carry out site responsibilities including data capture and institutional review board (IRB) activities. Based on this review, 9 sites were chosen, as noted in Table 1. All original sites were in the United States. Soon after the Consortium was formed, an additional site (Children’s Hospital at Westmead in Sydney, Australia) was added as a full-time member.

As the Consortium evolved, concern was raised that the initial sites were not geographically balanced and also did not have the volume of patients to expeditiously perform all of the trials needed to meet the mandates outlined. The sites initially chosen primarily cared for pediatric-aged patients, and over time it became clear that the mandate from the DoD, which included performing studies that involved adult patients with NF1 and NF2, as well as to explore the potential of conducting trials in schwannomatosis, required more access to adult-age patients. Through a second competitive process, the NFCTC added 4 additional sites as outlined in Table 1 and also allowed sites to add geographically close collaborating sites to better serve the adult population.

As of 2016 there are 19 patient recruitment sites (Table 1), which include the original 9 sites, 2 sites in Australia, 3 sites that were added by a subsequent competitive site selection process, and 5 additional sites that were added as affiliates to the existing sites. The present number of sites and their location, although not fully overcoming geographic imbalances, has allowed the NFCTC to successfully conduct multiple clinical trials.

Clinical Trial Development

The primary objective of the NFCTC is to perform well-conceived, biologically based clinical and translational trials for children and adults with NF1 and NF2. To facilitate the development of such trials, the Consortium initially created multiple committees that were charged with developing and prioritizing trials for specific NF manifestations (see Table 2). By vote of the site PIs, it was decided that 3 areas of investigation would be initially prioritized: neurocognitive challenges of children with
NF1; plexiform neurofibromas in children and adults with NF1; and intracranial gliomas in patients with NF. However, this decision would not preclude the development of additional studies for other manifestations of these diseases.

As outlined in Table 2, soon after the initial 3 committees were convened, additional clinical trial committees were organized to develop studies for other manifestations of neurofibromatosis, including malignant peripheral nerve sheath tumors, tibial dysplasia (bone), and complications of NF2. To aid in the development of the protocols, multiple discipline committees, as noted in Table 3 were created and as mandated, by the bylaws of the NFCTC, the discipline committees were to review and approve proposed protocols before they were baled by the site PIs for final approval. Also, to aid the Consortium and ensure appropriate use of data management and NFCTC resources, a series of administrative committees (bylaws, publications, site evaluation, quality assurance and membership) were created.

In the first 5 years of the Consortium, protocols for NF1-associated neurocognitive issues, plexiform neurofibromas, and visual pathway gliomas were opened. In collaboration with Sarcoma Alliance for Research through Collaboration (SARC), an additional study for adults and children with malignant peripheral nerve sheath tumors was begun. The protocols, which were developed and opened, had to receive independent approval by the DoD and its CDMRP. Because each of the protocols dealt with a different facet of neurofibromatosis, it was required that the CDMRP create individual expert panels to scientifically review the protocols. Once a protocol is approved, it also must receive approval by local Institutional Review Boards, and the ongoing trials are monitored by an independent Data and Safety Monitoring Board.

In the second 5 years of the grant cycle, an External Review Committee (ERC), per the recommendation of the CDMRP, was created and was composed of experts in neurofibromatosis and in the conduct of clinical trials. The ERC was charged with reviewing the scientific rationale and the feasibility of proposed studies, prior to submission to the DoD for final approval. The DoD would rely on the ERC for scientific review and, if approved by the ERC, the DoD’s review would focus on ethical issues and consent processes, as well as the financial implications of the study to the Consortium.

Summary of Consortium Accomplishments and Future Plans

Since its inception, the NFCTC has initiated and completed multiple prospective studies. A summary of the studies undertaken, their results, lessons learned, and future plans are described below.

Plexiform Neurofibromas

A major priority for the NFCTC was to develop prospective studies for children with NF1 and plexiform neurofibromas. Plexiform neurofibromas are one of the most common manifestations of NF1, occurring in at least 40% of those with the condition. These tumors are thought to be predominantly congenital. They grow along the length of nerves, may be extremely large, and are composed of neoplastic Schwann cells, as well as fibroblasts, perineurial cells, and mast cells. Plexiform neurofibromas are a major cause of NF1-related morbidity. They may result in disfigurement, impairment of nerve or contiguous organ function, and pain. The hallmark cell involved in plexiform neurofibroma growth is the neoplastic Schwann cell, which lacks NF1 gene expression.

The neurobiology of plexiform neurofibromas is complicated, as the loss of neurofibromin results in activation of the RAS protein, which initiates a cascade of signaling events in the RAS/MAPK pathway, as well as possible activation of the P13K/AKT signaling pathway. These pathways are molecular targets, as is mTOR, a kinase acting downstream of P13 K, which plays a role in cellular catabolism, anabolism, and survival. Other cooperating events thought to be important for plexiform neurofibroma development and growth include increased expression of multiple growth factors, including EGF, PDGFR, and VEGF. c-KIT receptor kinase is also thought to be important in plexiform neurofibroma development, especially in large lesions that have recruited mast cells. The development of transgenic mouse models of NF-associated plexiform neurofibromas has made it possible to better elucidate the molecular drivers of plexiform neurofibromas and to evaluate the potential efficacy of novel agents. Such investigations have allowed for a more rational prioritization of which molecularly targeted drugs should be initially studied in clinical trials.

A major obstacle in the development of clinical trials for NF1-associated plexiform neurofibromas was the lack of clear objective measures to evaluate the efficacy of the agent chosen. Plexiform neurofibromas are notoriously difficult to evaluate radiographically, as they are irregular and are often widely infiltrative. Standard neuroradiographic measures, such as unidirectional or bidirectional measurements, may be misleading. A major advance for prospective clinical trials development within the Consortium for plexiform neurofibromas was the validation, at the National Cancer Institute, of a semi-automated measure of plexiform volume. This technique, utilizing non-enhanced STIR images, allowed for reproducible objective measures of plexiform neurofibroma growth and response to therapy. Natural history studies and prior ineffective clinical trials provided a baseline for studies evaluating the efficacy of any agents to alter time to progression for tumors that were documented to be growing prior to initiation of study. Other parameters of drug efficacy, such as impact on

Table 3. Discipline Committees of NFCTC.

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<th>Discipline Committees of NFCTC</th>
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<td>Biology</td>
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<td>Radiology/Neuroradiology</td>
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<td>Pharmacology</td>
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<td>Quality-of-Life</td>
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<td>Neuropsychology</td>
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neurologic function, pain, and quality of life, were included as secondary objectives on NFCTC prospective studies. The NFCTC also attempted to develop trials that incorporated biomarkers and pharmacodynamic endpoints as tertiary or exploratory endpoints.

The initial trial for plexiform neurofibromas undertaken by the NFCTC was a phase II study of the mTOR inhibitor sirolimus (rapamycin, NCT 00634270). This drug was chosen based on evidence of mTOR pathway activation in human NF1-associated plexiform neurofibroma explants and genetically engineered mouse models. In this study, 2 arms were prospectively evaluated: (1) for those patients with progressive plexiform neurofibromas at the time of study entry, documented by at least 2 prior MRI scans, time to progression was chosen as the primary outcome measure; and (2) for those patients with symptomatic but unproven radiographically progressive lesions, radiographic objective response was chosen as the primary outcome measure, since it was not believed that time to progression was a valid outcome measure in those without documented recent growth. All radiographic studies were volumetrically analyzed at the NCI on standardized images obtained at each site.

For the stratum of the study which assessed patients with progressive lesions, 49 patients, a median of 7.9 years of age at the time of diagnosis (range 3-45.4 years), were enrolled, and included 17 patients with lesions of the trunk, 12 with head and neck lesions, 8 with neck and chest lesions, and 7 with trunk/extremity. The study took nearly 5 years to complete, given both the restriction in the eligibility criteria of documented progression before study entry and use of a time-to-progression end point. The median time to progression of patients receiving sirolimus was 15.4 months, which was statistically longer than the 11.9 months seen on the historical control arm. Time to progression was not influenced by sirolimus trough blood concentrations. For this subgroup of patients, radiographic response was a secondary outcome measure, and no patient had a partial response; the maximum decrease in the plexiform neurofibroma volume seen was 17% in one patient. Overall, approximately one-third of patients had some degree (usually minor) of tumor size reduction, as measured by volume analysis. There was no significant change in self-reported quality of life, as measured by the PedsQL scale, and there was no significant change in the subjects’ self-reports of pain. Toxicity of the drug was relatively mild.

In the second stratum, in 13 subjects (only 12 received the study drug) with nonprogressive symptomatic lesions, no subject was noted to have a documented partial response and the study was halted as per the first formal stopping rule for the study. Interestingly, on self-report, there was a significant improvement in the mean scores of emotional and school domains from baseline to 6 months of treatment. Three patients did have a meaningful decrease in pain, although there was no statistically significant change from baseline for the group as a whole.

Of note, both arms of the study used centralized, real-time, pharmacokinetically guided dosing of sirolimus to maintain blood concentrations in a target range, and provided important information on the population pharmacokinetics of sirolimus and the changes in sirolimus metabolite formation with age in children with NF1.

Lessons Learned
In addition to the results of the study, other important conclusions could be drawn from the initial studies the NFCTC undertook for plexiform neurofibromas. First, prospective studies could be done across multiple centers within the Consortium using standardized centrally analyzed radiographic outcome measures and other functional measures of outcome. Studies that utilized time to progression as an outcome measure were, by design, longer duration studies, limiting the number of studies that could be conducted by the Consortium because of financial and logistic considerations. As this study was undertaken without an industry partner and, although sirolimus was commercially available, the cost associated with providing drug became rate limiting for the NFCTC’s ability to mount other trials, because the NFCTC had a fixed budget. For the NFCTC to more rapidly complete trials, it was decided that going forward, tumor response would be used as the primary outcome measure rather than time to progression free. Also, industry partners were to be sought for subsequent trials.

Second Generation of Studies
Based on preclinical data obtained in genetically engineered mouse experiments, 2 trials were begun by the NFCTC for plexiform neurofibromas after completion of the sirolimus trial. The studies were designed essentially identically to allow for a comparison between trials, and used radiographic objective response, as measured by centralized radiographic volumetric review, as the primary outcome measure. One study was a phase II study of a MEK inhibitor (NCT 02096471). The second was a phase II setting of a multiple receptor tyrosine kinase (MET, VEGFR2, c-KIT, RET) inhibitor (cabozantinib; NCT 0210136). Both trials had built in a priori success hurdles to minimize the exposure of ineffective drugs to patients, if the initial data were inconsistent with a minimally clinically acceptable response rate of 25%. Both studies passed the first phase study hurdle of objective responses in the first cohort of patients entered on the trials. Similar to the sirolimus study, secondary endpoints included overall quality of life and pain assessments. Unlike the experience with the sirolimus study for patients with plexiform neurofibromas, these 2 trials completed enrollment faster than predicted, and more than 40 patients were entered on the 2 trials within 2 years. Results of these trials are pending, but should be available within 3 years of study initiation. Both studies were done in collaboration with industry (which provided the drugs), making the studies more financially feasible for the NFCTC. A limitation of the MEK and cabozantinib studies was that the studies were limited to patients 16 years of age or older at time of study entry. This is
because of the lack of pediatric phase I dosage-data with the drugs chosen.

**Future Trials**

There are future studies planned for the patients with NF1 and plexiform neurofibromas. For the multiple receptor kinase inhibitor drug, given that pediatric safety data now exists for children, a second cohort of patients between the ages of 3 and 16 is to be studied. In addition, because of the increasing enthusiasm and positive early experience over the efficacy of the MEK inhibitors for plexiform neurofibromas, a phase II trial with an alternative MEK inhibitor is also planned, initially in patients 16 years or older, but to be extended also in those between 3 and 16 as soon as phase I pediatric data are available (study in progress). Another study to be performed through independent FDA funding, which will involve multiple Consortium sites, is a phase II trial of imatinib mesylate in patients with symptomatic airway neurofibromas, utilizing functional outcome measures as the primary determinant of efficacy.12

**Neurocognitive Disorders**

Neurocognitive deficits and associated academic failure are challenges for more than 70% of children with NF1.13 The types of cognitive issues these children face are variable and include attention deficits, difficulties in executive functions, visual spatial deficits, and language deficiencies. Genetically modified mouse models, utilizing heterozygous inactivating NF1 mutations, have been used not only to model the underlying biology of the cognitive issues in NF1, but also to explore if pharmacologic intervention could ameliorate or reverse some of these deficits.14,15 In one modeling system, decreased levels of neurofibromin not only resulted in hyperactivation of the RAS signaling cascade, but also increased GABAergic neurotransmission and reduced synaptic plasticity. Behavioral studies, in this mouse model, demonstrated that these molecular changes were associated with impaired spatial learning and attention. Focusing on the abnormalities in GABAergic neurotransmission, preclinical studies demonstrated that lovastatin, which plays a role in regulation of RAS signaling, reversed deficits in both attention and spatial learning. This became the basis of the randomized trial undertaken by the NFCTC.

The study undertaken by the NFCTC was designed to determine if treatment with 16 weeks of lovastatin would result in improved attention and visual spatial learning (NCT 00853580). For eligibility on the study, children had to be between 8 and 15 years of age at time of screening and have impaired performance on at least one of the primary outcome measures. A total of 272 children were screened, and 126 were excluded primarily because of lack of defined impairment on one of the primary outcome measures; other factors, such as Intelligence Quotient less than 70, also made screened patients ineligible.16 One hundred forty-six were randomized to either lovastatin or placebo. Lovastatin was found to have no significant effect on either primary outcome measure.

As an ancillary to this study, an investigation was completed assessing the utility of a novel technique to assess visual spatial learning, the arena maze.17 The arena maze is designed to be a human analogue of the Morris water maze test widely used in mouse studies to assess visual spatial learning. The results are pending.

**Lessons Learned**

The completion of this study, actually the first implemented by the NFCTC, demonstrated that neurocognitive studies could be done on a Consortium-wide basis. Mimicking the preclinical results from the mouse experiments was found to be much more difficult than expected, as identification of patients with the specific type of learning disability that paralleled the mouse phenotype resulted in nearly as many children being excluded from the study after screening as those who could be randomized on the trial. The use of a standardized computerized test to assess outcome was found to be feasible on a Consortium-wide basis, but required a significant amount of training and delayed startup at some sites, and data management was difficult because of the proprietary nature of the program and changes over time to export the data from the program. To complete this study, other non-Consortium sites were recruited, but it took so long to get IRB approval and site training completed, that the additional sites did not accrue a significant number of patients before study completion. Overall, this study, which was to be completed and reported within 3 to 4 years, began in 2009 and results were not fully reportable until 2015.

**Future Plans**

Because of the lack of efficacy of lovastatin, future trials with this drug, in combination with other agents, which were initially planned, are not to be undertaken. At this point, no Consortium-wide cognitive trial is under way. Based on the positive experience of performing prospective randomized clinical trials in this patient population utilizing computerized tests of outcome, a limited-site pilot study comparing the efficacy of stimulant medication to stimulant plus cognitive computerized training to improve attention, is under way. If positive, this study could lead to a Consortium-wide effort. A rationale for the stimulant trial comes from an alternative genetically engineered mouse model of NF mice with learning disabilities that demonstrated low levels of striatal dopamine, suggesting that neurofibromin is a positive regulator of dopamine homeostasis.18 It identified the dopaminergic system as a potential therapeutic target and lends credence to use of drugs such as methylphenidate, which inhibits the uptake of the dopamine and noradrenaline and ameliorates some of the behavioral impairments in the mouse model.

In addition, utilizing the cognitive battery evaluated in the NFCTC lovastatin trial, another limited site pilot is using computerized assessments of learning and memory to assess patients before and after treatment on MEK inhibitor studies.
These include children entered on studies designed for plexiform neurofibromas and visual pathways gliomas currently under way through NFCTC sites.

**Low-Grade Glioma**

Low-grade gliomas, predominantly pilocytic astrocytomas, are the most common central nervous system tumor arising in children with NF1.2,19 The majority occurs in the visual pathway and may affect the optic nerve and chiasm, often with contiguous involvement of the optic tracks and radiations. Separation of low-grade gliomas from areas of focal abnormal signal intensity can be difficult, and it is often arbitrary. In addition, there are patients who develop symptomatic low-grade gliomas outside the visual pathway, including the brainstem. The majority of low-grade gliomas in children with NF1 are diagnosed without tissue confirmation. Radiation therapy, a frequent form of treatment for gliomas that cannot be surgically resected in patients without NF1, is avoided whenever possible in children with NF1 because of the concerns of mutagenesis, vascular damage, and neurocognitive and neuroendocrine sequelae.20-22

Chemotherapy has been the primary modality of treatment for symptomatic progressive low-grade gliomas in children with NF1, and the carboplatin and vincristine regimen has been used successfully to control tumor growth for the past 3 decades.23 However, 30% to 40% of patients with NF1 and low-grade gliomas will develop progressive disease after completion of chemotherapy. In addition, there is increasing evidence that treatment with chemotherapy, although effective in causing tumor radiographic stability and/or regression, may not result in functional stability.24 There is no standard salvage chemotherapy regimen for those who fail first-line treatment. As outlined in the discussion of the treatment of plexiform neurofibromas, the increased understanding of the molecular disarrangements in patients with NF1 and results of studies in genetically engineered mouse models have suggested that molecular-targeted therapies may be effective for those patients with recurrent disease failing initial treatment with chemotherapy and possibly an alternative to chemotherapy in newly diagnosed patients.

The first glioma study undertaken in this condition by the NFCTC was a phase II study of everolimus (RAD001) for children with NF1 and chemotherapy-refractory radiographically progressive low-grade gliomas (NCT 01158651). Everolimus is a second-generation mTOR inhibitor and has already been utilized widely for patients with tuberous sclerosis and giant cell astrocytomas with great efficacy.25 This study began in February 2011 and accrued 23 patients. Overall, the study was done efficiently, although there was some initial delay in identifying patients with recurrent progressive (by imaging) low-grade gliomas. This study is presently in the last stages of data analysis. The RAD001 study was done in collaboration with industry, freeing up other resources for the NFCTC.

A second study, which has just begun, is a phase I/II study of a novel MEK-inhibitor (MEK162) for children with recurrent low-grade gliomas (NCT02285439). In this trial, the NFCTC is joining forces with an industry sponsored trial, which also encompasses patients without NF1 and low-grade gliomas and other RAS pathway-activated tumors. This phase I portion of the trial is expected to accrue between 12 and 36 patients, with and without NF1, to determine the phase II dose. After successful completion of the phase I component of the study, a stratum for children with NF1 and low-grade gliomas is to accrue 20 patients between 1 and 18 years of age.

**Lessons Learned**

The completed and just-initiated studies in children with low-grade gliomas have demonstrated that the Consortium can mount such studies successfully. Accrual on the everolimus study was somewhat slow; however, accrual for the MEK-inhibitor study, for which there is a tremendous amount of enthusiasm, has been rapid, suggesting that greater enthusiasm for a drug by investigators and patients will allow more rapid completion of the study. Also, just as was the case for treatment of plexiform neurofibromas, it was crucial to partner with industry so as not to cripple the financial flexibility of the NFCTC. Furthermore, being part of a larger study where resources of the NFCTC are being used synergistically with the resources available from the larger industry-sponsored study is not only financially sound but also speeds protocol development; a completely new study did not need to be developed, but rather the NF1 stratum was added to an ongoing study.

One major concern about the studies undertaken to date, as well as essentially all studies that have been performed in pediatric low-grade gliomas, including those with tumors of the visual pathway, is the continued use of radiographic response as the primary outcome measure. With increasing evidence that there may be a dissociation between radiographic response and clinical improvement and the understanding that a significant number of patients will lose some degree of vision despite apparently successful treatment based on imaging, there is clearly a need to focus on functional outcomes. For children with visual pathway gliomas, the most important functional measure is vision, not only acuity but visual fields. Finally, even with reliance on radiographic response as the primary outcome measure, there are limitations, because no widely accepted valid automated or semi-automated volumetric approach has been developed for these often infiltrative and irregularly shaped lesions; there continues to be reliance on largest bidirectional area measurements for the primary outcome measure. Better neuroradiographic measures are also needed.

**Malignant Peripheral Nerve Sheath Tumors**

Malignant peripheral nerve sheath tumors are a relatively infrequent complication of NF1 in the childhood years, and become a more common devastating issue in late adolescence and young adulthood.26,27 It is believed that the vast majority of
malignant peripheral nerve sheath tumors in children and adults with NF1 arise from congenital plexiform neurofibromas, and the lifetime risk for malignant peripheral nerve sheath tumor transformation for patients with NF1 and plexiform neurofibromas is between 8% and 13%. Approximately one-half of all malignant peripheral nerve sheath tumors will develop in children and adults with NF1.

Patients with NF1 have a lower response rate to adjuvant therapy than those without NF1 and poorer overall survival; 5-year survival is approximately 30% for those with NF1 who develop such lesions.\textsuperscript{26-28} Although there is consensus that complete surgical resection is the optimal first step in management for patients with malignant peripheral nerve sheath tumors, given the locations of such tumors and their infiltrative nature, this is often not possible.

An approach taken by the NFCTC is to partner with an international sarcoma therapy cooperative group, SARC, to do studies in combination. Also, the NFCTC has worked closely with the Children’s Tumor Foundation-sponsored NF Preclinical Consortium to identify possible effective biologic agents.

The first study undertaken by the NFCTC was a trial performed by the NFCTC in collaboration with SARC evaluating bevacizumab and everolimus (NCT01661283).\textsuperscript{29,30} This trial of an antiangiogenesis agent coupled with an mTOR inhibitor has been completed and responses were seen, as 3 of 25 either had a radiographic response or stable disease for at least 4 months on treatment; however, the rate of response was not considered to be adequate to consider the drug combination “active.”

The second study undertaken by the NFCTC and SARC was a trial evaluating the combination of an HSP90 inhibitor (ganeptesib) and the mTOR inhibitor sirolimus (NCT02008877). This study was based on preclinical data demonstrating that the drugs in combination were synergistic. Although the drug combination was well tolerated, of the first 10 patients enrolled on the study, none met criteria for radiographic benefit and the study was closed.

**Lessons Learned**

The results of these studies demonstrated that collaboration between the NFCTC and an international organization such as SARC can facilitate the development and completion of trials. Involving industry sponsors also made such studies easier to perform. Data could be shared between the 2 consortiums and was cost effective. Also, these studies showed the challenges in translating preclinical work to clinical success.

**Future Studies**

Work is continuing in a collaborative fashion between the NF Preclinical Consortium, SARC, and the NFCTC to develop and open trials for children with NF1 and malignant peripheral nerve sheath tumors. A study that has already been approved and partially funded is a phase II trial of an MEK inhibitor in combination with a dual mTOR kinase inhibitor. This combination of drugs has demonstrated substantial activity in a transgenic model of NF1 malignant peripheral nerve sheath tumors. Other combination studies, including those involving bromodomain inhibitors and histone deacetylase inhibitors are under consideration.

**Tibial Dysplasia**

Although osseous complications are relatively common in NF1, it was initially believed by the NFCTC that, because of the relative infrequency of any one complication and the difficulty in developing rational therapeutic questions for these complications, studies could not be undertaken.\textsuperscript{2,31-33} The Bone Committee of NFCTC took this as a challenge and focused on the significant problem of tibial dysplasia/tibial pseudarthrosis—a condition that affects between 2% and 5% of children with NF1. This condition usually presents with bowing of the tibia and/or fibula, often progresses to fracture, and results after healing in refracture; nonunion (pseudarthrosis) occurs in as high as two-thirds of patients. Preliminary evidence has demonstrated that placement of rhBMP-2-saturated collagen sponges around the tibial defect site improved the rate of healing and reduced the numbers of refractures. Based on this information, the NFCTC has recently launched a randomized phase II study to assess differences in bone union between those treated with rhBMP-2 compared with those who have standard surgical intervention (NCT 02718131).

**Lessons Learned**

The development of this study has taken more than 5 years from conception to inception. It was initially believed that the Consortium’s patient resources, despite the multiple sites involved, were not adequate to perform this type of study in a reasonable period of time. It was also unclear if the Consortium members had the type of relationships needed with the orthopedic surgeons at their institution to pursue this type of study. The Consortium, through its Bone Committee, reached out to orthopedists throughout the world to develop a working consortium that involved not only the NFCTC sites but additional international sites to perform this trial. This study has been discussed and promoted at pediatric orthopedic meetings around the world to build enthusiasm to complete this study. This type of leveraging of the NFCTC to perform such studies is a critical role for the Consortium and one that helps it fulfill its mandate.

In addition, the use of worldwide sites poses a number of challenges for a Consortium, including funding, drug distribution, regulatory issues, and multiple layers of approvals. Adding 5 sites can incur costs of thousands of dollars over the life of the study. A single IRB for all trials may greatly reduce the time to initiation of studies and reduce costs, but it is unclear whether this single IRB, as recommended by NIH, will be accepted by international sites.
Future Studies

Future trials may focus on the use of an antiresorptive agent such as pamidronate to prevent excessive resorption by overactive bone osteoclasts. Studies will be dependent on the ability of the NFCTC to accrue successfully on the tibial pseudoarthrosis study.

Neurofibromatosis Type 2 and Acoustic Schwannomas

A mandate of the NFCTC is to develop clinical trials for patients with NF2. The neurobiology of NF2 is still being unraveled; however, preliminary clinical experience demonstrated that the antiangiogenesis agent bevacizumab was remarkably effective in adults, causing hearing stabilization and improvement in those with progressive vestibular schwannomas and NF2.2,34-36

Building on this exciting finding, the NFCTC is conducting a phase II trial of bevacizumab for children and adults with NF2 and progressive vestibular schwannomas (NCT 01767792). This study, which began in 2011, has taken a relatively long time to accrue patients. The study utilizes strict entry criteria selecting patients only with documented abnormal word recognition scores. In this study, clinical response is assessed by both audiologic testing and MRI; however, the primary objective of this trial is determination of hearing response 24 weeks after treatment with bevacizumab. Secondary objectives are to determine the safety and long-term tolerability of bevacizumab in this patient population, to determine the radiographic response, and to determine the durability of hearing preservation.

Lessons Learned

This is the first study in NF1 or NF2 patients with tumors undertaken by the Consortium utilizing a primary functional outcome measure. This is an extremely important step for the Consortium and one that took additional training to mount. Further, to do this study appropriately, not only was there a need for cooperation between industry (as a sponsor) and the Consortium but also relationships had to be built with adult NF2 groups and patient and parent groups to facilitate the needed accrual.

Future Studies

Following completion of the study other agents will be evaluated. These include the possible use of everolimus, the mTOR inhibitor, in isolation or in combination with lapatinib, a FDA approved EGFR inhibitor.2,37,38 Lapatinib, may also be utilized as a single agent as pulse therapy. It is unclear whether these above approaches will be also used in combination with bevacizumab, pending results of the bevacizumab study.

Schwannomatosis

Schwannomatosis is a rare disorder resulting in the development of schwannomas throughout the body. In contrast to patients with NF2, patients with this condition do not develop bilateral vestibular schwannomas. The predominant presentation of those with schwannomatosis is severe tumor-related pain. A major challenge for treatment of this condition will be employment of a valid objective measure of benefit. It is hoped that the NFCTC will open a clinical trial for patients with schwannomatosis within the next 2 years.

Conclusion

Thus, over the past 10 years the NFCTC has matured and evolved into a more effective means to develop, open, and complete clinical investigations for children and adults with NF1 and NF2. For patients with NF1, multiple clinical trials have been opened in important disease manifestation, including plexiform neurofibromas, gliomas, and neurocognitive challenges. In both plexiform neurofibromas and visual pathway gliomas, second-generation studies are already under way, some near completion. Working closely with SARC, multiple studies have been performed and are being planned for children and young adults with malignant peripheral nerve sheath tumors. Even a tibial dysplasia therapeutic study has been begun by the Consortium in collaboration with other institutions around the world. The NFCTC’s first study for patients with NF2, investigating the efficacy of bevacizumab to stabilize and improve hearing in those with acoustic schwannomas, is near completion and other studies are planned. The NFCTC is also actively exploring the possibility of opening studies for patients with schwannomatosis. Although many challenges remain ahead, the NFCTC has attempted to meet the needs of patients with NF1, NF2, and schwannomatosis by expanding and working closely with other consortia, industry, and foundations to facilitate the rapid translation of the evolving biologic understanding of these conditions into clinical trials. The NFCTC has now been refunded for a third 5-year period extending into 2022, which will allow the development of even more potentially effective means to treat these crippling and, at times, life-threatening manifestations of neurofibromatosis.

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Ethical Approval

All studies must be approved by the IRB at the University of Alabama, Birmingham (the operations system), as well as all the participating sites. In addition, all protocols are approved by the Department of Defuse IRB and ethics office.

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