Children's Tumor Foundation

NF FORUM

5/6/09

This is the fifth installment in a series of articles recapping the Children's Tumor Foundation's 2009 NF Forum - a patient and family medical symposium. This was the inaugural year of the Forum and more than 180 attendees descended on Washington D.C. from April 3-5, for the event. **Continue reading below for previous installments.**

Thank you to all who attended. We hope to see you, and many new faces, again next year!

We gratefully acknowledge the support of The Jeff Gordon Foundation that made this meeting possible.

A panel of foremost experts on NF research and clinical care took questions from attendees eager to learn about NF as it applied to them and/or their loved ones. Below is a transcript from the Q&A session.

Q: Will there be drugs that are broadly effective in NF1 tumors, bone etc.?
A: We hope it is that simple. For example in cancer, many tumor types respond to the same drug. However a drug that works on a tumor does not work on e.g. learning disabilities. Looking ahead it may be that a 'cocktail' of multiple drugs is needed to manage tumors or different aspects of NF.

Q: Would it work to put neurofibromin (NF1 protein) back into a cell as a therapy?
A: Unfortunately this is more complex than it sounds. First of all NF1 protein is very large making these experiments tricky. Also, you would have to know you are reintroducing the protein into the right cell. There is a drug in development called PTC124 that 'reads through' genetic defects called nonsense mutations and can actually restore a cell's protein-making. However even if this works in NF it might only benefit a subset of NF patients since there are so many different types of NF mutations.

Q: Have clinical trials been held up by a lack of patients enrolling? Should patients be more openly sharing information with each other on their trial experiences?
A: Regarding enrollment, organizing the Clinical Trials Consortium has really helped to identify more patients, and patient registries including the one in development by the Children's Tumor Foundation will also be a huge help in identifying patients. Some trials are more difficult to fill for example if a tumor is rare. In terms of patient privacy, a wide open blog for information sharing about trial participation is not a good idea.

Q: Many patients do not have insurance or access to quality care. Can the physicians comment as to what NF advocates can do in informing and lobbying the new administration?
A: There are many NF patients that end up underserved. This is a fundamental flaw of the medical system and hospitals are at a breaking point in terms of caring for the uninsured. Physicians will be told by their boss what they can and cannot do procedure-wise: and what the hospital will and will not cover. Patients need to lobby. However bear in mind if there is only a very small approved reimbursement for the hospital they will not do the procedure. Hospital bills are very complex.

Q: Since NF is such a complicated disorder, where is the best place for me to get care? Should we travel to a specialist center or can we just see our local doctor?
A: Where possible it is best to seek care at one of the multidisciplinary NF Clinics across the country, these are listed on the Foundation's web site [www.ctf.org]. If this is geographically a long way for you, it is always possible for your local doctor to work in conjunction with such a clinic to coordinate your day to day care, while making regular visits to the NF Clinic.

Q: In a family where parents have NF, and their children appear to be unaffected by NF, how can we be sure the children do not have NF?
A: In an adult, this can be confirmed clinically. In a child, where symptoms of NF might still develop even if not yet apparent, genetic testing is required.

Q: My son has been told he is lacking in executive reasoning – what is this?
A: This means that you may be smart and even have a very high IQ – but not know what to do with the information, how to organize and plan time. It is believed this is related to ADHD - a part of the brain called the prefrontal cortex is involved. It is important to know this is unrelated to IQ. The good news is you can improve executive function – there are many books about organizing and planning time.

Q: What are the long term effects of Lovastatin on the liver?
A: As yet we do not know. There are children with familial hyperlipidemia who have been taking Lovastatin for a long time and those kids do not have liver issues. However, we don't yet know how individuals without familial hyperlipidemia will do on long-term Lovastatin. That will be monitored in the Phase II clinical trial.

Q: For six year old children behind in maturity versus their peers, should we hold them back for a year of school until they mature further? Or is it best to have them advance with their peer group?
A: Hold them back and allow them to mature. At 6 years old the academic demands are small, but it is critical to allow them to develop social skills for their age group. Holding kids back one grade level at this age is unlikely to impact on their academic progress in the long term but will allow them to mature socially and in the long term may help their learning disabilities.

Q: Is there a link between NF1 and stroke?
A: In NF1, the walls of blood vessels – including those in the brain - can be weakened and this may affect the risk of stroke.

Q: In a patient with multiple types of NF pain, is there any nerve functional assessment test that can be done to better understand it?
A: Unfortunately not. The nerve tests that can be done look not at pain, but at electricity and function in nerve pathways that regulate normal types of sensation and also motor function.

Q: Is any research being done into non-traditional therapies for NF pain?
A: Not at this time. However there is now an NIH institute dedicated to studying non-traditional therapies so we may see an increase in this area.

5/5/09
NF Forum Recap, Part IV

Dr. Cynthia Hingtgen (Director of a Foundation NFCN Affiliate Clinic at Indiana University) addressed the complex issue of pain – what causes it and how it can be managed. Acute pain - such as from an appendix surgery - is usually manageable. In contrast chronic pain such as neuropathic pain and inflammatory pain are more difficult to tackle.

The first thing to remember is that pain can be good as it serves as a warning that something is wrong. In NF, new onset of pain in a tumor is usually a warning sign, and could signal that a benign tumor is becoming malignant; a cutaneous neurofibroma may be rubbing; or that there is some overall tumor disturbance. In Schwannomatosis, pain is actually the diagnostic characteristic of the disorder.

Unfortunately there are no quick solutions for the treatment of chronic NF pain. A variety of drugs are used - anticonvulsants, antidepressants, non-steroidal anti inflammatory drugs and opioids. While none of these drugs were developed specifically for pain management, they happen to block some of the signals in the nervous system that cause pain. At best however these offer temporary relief. Many patients have turned to non-drug clinical approaches such as nerve block, surgery or electrostimulation. Though not doctor prescribed, many patients also utilize non-medicine approaches such as acupuncture, biofeedback, counseling, hypnosis, magnets and exercise therapy. These approaches may offer some benefit and should be kept in mind.

Looking ahead we are hoping to identify biological drug therapies for NF related pain in the same way that biological drug therapies are being developed for tumors treatment. This is a challenging field as there are very few pain researchers working in NF, or NF researchers working in pain. Nevertheless it is possible that studying the biology of NF pain and finding

biologically targeted therapies could teach us about how pain in general could be managed.

5/4/09

NF Forum Recap, Part III

Living and Coping with NF: Challenges and Resources for Families

Moderator, Sandra Cushner–Weinstein (Children's National Medical Center) led a panel including Dr. Viskochil, Dr. Korf, Dr. Yohay, Dr. Blakeley, Dr. Belzberg, Kathleen Berentsen (Genetic Counselor and Children's Tumor Foundation Clinical Programs Coordinator), NF parent advocates Jill Markland and Patti Hurst, and two teens living with NF1, Katie and Raquel. The panel discussion provided a few points of insight:

• It is important that a child not see NF as their legacy, but to be empowered. Believe in your child and help them to believe in themselves and you will help them accomplish their goals. The disorder does affect the whole family and the family can provide vital support.

• A major question is when to tell the child he/she has NF. In general there was agreement that earlier is better to tell a child they have NF, and that more details can be provided to the child as they get older and can comprehend. It was agreed that keeping information back will probably cause more issues later. For many parents it is a question of just 'knowing the right time'. Remember NF unfolds over a lifetime and individuals will deal with it very differently. Get the child engaged in understanding NF. Make sure they know what signs to look for, changes in their body that might be NF related.

• Educate your child's friends and teachers – this can not only open up your child's life but lead to their school doing NF fundraisers and awareness. Educate the school nurse with brochures such as the Foundation's "Guide for Educators', 'About NF1/NF2', 'About NF1 Learning Disabilities', etc. Preparing brief written personalized material to share with teachers and others can be helpful – a mini -biography of your child and his/her special needs. People want to know but often don't want to ask and this makes it easier.

• Sending kids with NF to camp (such as the one organized by the Foundation each summer) for many kids can be an empowering moment – for many this will be the first opportunity to meet other kids with NF and to not have to explain what NF is on meeting new people. The Foundation's YouthConnect, an online chat forum meets weekly throughout the year and is kind

of a ‘year round camp’. Empower them by engaging them directly in supporting NF research and awareness through activities like NF Endurance Team or Racing4Research.

• The doctors commented on how they help patients live successfully. When giving a new diagnosis of NF1, provide as much information as possible. Arm the family with knowledge. However place the NF facts in perspective; often patients read about things that will not happen and in a sense have too much information; put their mind at rest. It is important to identify an NF care team you are confident in; this may include a larger NF center working closely with your local doctor. Confidence in your NF care team will help with the uncertainty of NF.

4/22/09
NF Forum Recap, Part II

NF1 Tumor Clinical Trial Updates

Dr. Roger Packer (Director of the Foundation’s NF Clinic Network (NFCN), Affiliate Clinic at Children’s National Medical Center) described a major step forward for NF trials: the formation of the NF Phase II Clinical Trials Consortium comprising 9 institutions and funded by the Congressionally Directed Medical Research Program for Neurofibromatosis (CDMRP NFRP).This Consortium is focused on developing trials for tumors of NF1 (plexiforms, optic glioma and malignant peripheral nerve sheath tumors) as well as learning disabilities.

One quarter of NF1 patients have plexiform tumors and this tumor type is the first focus of the Consortium. Currently surgery is the main treatment approach but many plexiforms cannot be removed by surgery and can cause major health issues such as compressing organs. Though they can be extensive, plexiforms can now be measured volumetrically to better monitor their growth and response to clinical therapies.

A few drugs have been tested in previous plexiform clinical trials (thalidomide, farnesyl transferase inhibitors, and pirfenidone) and though none have been successful, these studies

have made it easier to design future NF1 clinical trials. Currently open plexiform trials include Gleevec and AZD2171, both biological drug therapies showing early promise. The first trial of the Consortium is a Phase II trial of rapamycin for plexiform tumors, opened in early 2008. Patient recruitment has been moderately simple through the 9 Consortium sites - enrollment is now complete. Rapamycin has shown some promise in another NF-like disorder, tuberous sclerosis, and there is reasonable hope it may be effective in NF1.

The next tumor trial for the Consortium will be for optic pathway glioma, a tumor affecting around 10% of NF1 patients.

In addition, a Consortium trial will shortly be underway for learning disabilities. (described below).

NF1 Learning Disabilities Clinical Trials Update

Dr. Maria Acosta (a neurologist with the CTF-NFCN Affiliate Clinic at Children's National Medical Center) provided an update on clinical trials for NF1-related learning disabilities. Learning disabilities affect the whole family as well as the individual. It is estimated that two-thirds of persons with NF1 have some cognitive challenges but this could be as high as 90% based on European studies. This might include not only learning disabilities but motor coordination and clumsiness. 60% of children with NF1 related learning disabilities meet the description of having attention deficit and hyperactivity disorder (ADHD). It may be easier to share your child's challenges with a teacher as ADHD-like, since they will most likely be more familiar with ADHD than NF1. In addition there is legislation providing resources for kids with ADHD and these could be accessed for NF1 (see http://www.chadd.org/ for more information).

A Phase II clinical trial of Lovastatin for NF1-related learning disabilities for 150 children under 18 will begin in May 2009 under the Phase II Clinical Trials Consortium. A Phase I safety study of Lovastatin primarily looked at drug safety, however a few participants' parents have reported their child responded positively to the drug with improved behavior and as a result those children have remained on Lovastatin at the parents' request. However, other children on the Phase I trial reported no difference. The Phase II trial will include analysis of drug pharmacokinetics - to see if the drug is acting differently in different people and if this relates to results seen. We are learning more about what drugs may work in NF1-related learning disabilities; other clinical trials will follow; and different drugs may work for different individuals. Another natural history study is following babies from birth onward to get a better understanding of how and when learning disabilities might be detected in NF1. However it could be many years before these are widely prescribed for NF1. A key focus

must be on improving quality of life for kids with NF1-related learning disabilities and focus on what they do well.

NF2 Clinical Trial Updates

Dr. Jaishri Blakeley (Director of the Foundation's NFCN Affiliate Clinic at Johns Hopkins University) looked back to the Foundation's NF2 Clinical Trials Planning Workshop held in October 2007, at which time there was no clear path forward for how best to do NF2 clinical trials. Until very recently NF2 specific trials were not available; NF2 patients only had the opportunity to enroll in general trials for brain tumor. However a patient advocate at the October 2007 meeting, Ms. Michie O'Day, deaf from NF2 related surgeries, compared NF2 trial planning to the building of the National Cathedral in Washington, DC noting that the Cathedral was built over 100 years, with multiple
architects and designers involved, many of whom never saw it completed. She hoped we would reach our goal in 10 years instead of 100. Dr. Blakeley was delighted that only 18 months after the Foundation's Workshop,
NF2 trials are underway including our newly funded clinical trial she is heading.

NF2 can lead to a variety of tumors; vestibular schwannoma (VS), meningioma, peripheral schwannoma and ependymoma. VS is the main cause of NF2 disability and therefore the primary focus of initial clinical trials. The Foundation funded Clinical Trial Award to Dr. Blakeley will test Tykerb (Lapatinib) in VS. The trial will open in May. 2
0 patients will be enrolled, 10 with NF2 VS and 10 with sporadic VS. Glaxo Smith Kline is providing drug and technical support for this CTF trial. Tykerb has shown efficacy in breast cancer and much is known about its biology. This is a Phase 0 trial meaning that patients receive drug prior to surgery; after surgery tumors are analyzed to see if the drug hit the target. If Lapatinib shows promise it will be moved to Phase II trials in NF2 and could potentially move rapidly to pediatric trials.

Another NF2 trial, funded by CDMRP NFRP, will commence shortly at Harvard/MGH. This Phase II trial tests PTC-299 in vestibular schwannomas. PTC-299 is a new drug in from PTC Therapeutics that targets blood vessel growth – essentially 'starving' the tumor. A report from Harvard/MGH at our 2008 NF Conference showed a small number of NF2 patients responding to the drug Avastin (another 'tumor starving' drug) with VS shrinkage and even some regained hearing. The PTC-299 trial will accept patients under 18 years old and includes travel funding. A trial is currently open for testing Sutent (Sunitinib) in meningioma - this trial is particularly interested in recruiting NF2 patients. Another trial is open for testing Tykerb in

combination with temozolomide as a treatment for ependymoma.

In summary we are now firmly in the age of biological drug therapies for NF2. Looking ahead a goal is to be able to offer clinical trial options to as many patients as possible, whether these are retrospective/natural history studies, observational studies, pilot clinical trials, or full scale clinical trials.

For the latest update on current clinical trials and research studies, visit www.clinicaltrials.gov and search 'neurofibromatosis'. You should talk to your doctor or clinic coordinator, or visit www.ctf.org
or contact the Children's Tumor Foundation.

4/15/09
NF Forum, Part I

Dr. Kim Hunter-Schaedle (Chief Scientific Officer, Children's Tumor Foundation) presented an overview of Foundation research, medical programs and accomplishments toward identifying effective drug treatments and improving clinical care for NF. Dr. Hunter-Schaedle announced the recipients of the Foundation's first two Clinical Trials Awards – one to Dr. Jaishri Blakeley (Johns Hopkins University) to assess Tykerb in NF2 vestibular schwannomas; and one to Dr. Aerang Kim, Dr. Brigitte Widemann (National Cancer Institute) and Dr. Bruce Korf (University of Alabama at Birmingham) to expand an ongoing trial of Sorafenib in NF1 plexiform neurofibromas. Dr. Hunter-Schaedle then went on to discuss the significant progress of the Foundation's Drug Discovery Initiative and NF Preclinical Consortium (which has drug collaboration with Novartis) which are moving closer to identifying candidate NF therapies through testing drugs in cells and mice. Finally, Dr. Hunter-Schaedle discussed the Children's Tumor Foundation NF Clinic Network which now includes 38 clinics across the United States and continues to grow. As a result of these programs, Foundation grant investments in 2008 were close to $3 million!

What Is a Clinical Trial and Should I Enroll?

Dr. Bruce Korf, the Children's Tumor Foundation's Chairman of Medical Affairs, and Director of an NF Clinic Network Affiliate Clinic at the University of Alabama at Birmingham, presented on the topic of 'What Is a Clinical Trial, and Should I Enroll'? Due to significant research progress, NF clinical trials are now moving forward that use both existing drugs (those currently marketed to treat other disorders and diseases) and new drugs (those not marketed but still in development by biotechnology and pharmaceutical companies).

Drugs progress through a number of clinical trial phases. Phase I trials –the first step of putting drugs into humans, to assess drug safety – require 20-80 patients be recruited. Phase II trials expand on safety and begin to look at drug efficacy; these require 100-300 patients. Phase III trials expand efficacy studies, look for side effects, compare the new drug to those currently prescribed for the disorder or disease, and require 1,000-3,000 patients. Phase IV trials monitor the drug once it is marketed and prescribed to look for long-term effects.

Depending on the phase, clinical trials may include a placebo arm – patients receive a sugar pill that looks exactly like the drug pill but contains no drug. If you enroll in a trial with a placebo arm you will be randomly assigned to one arm or the other. The physician may or may not know if you are in the drug or placebo arm. Once the study has advanced to where the test drug is deemed safe and effective, placebo arm patients may 'crossover' and start receiving the active drug.

If you apply to be in a clinical trial, you may or may not be accepted, based on 'inclusion' and 'exclusion' criteria that may include age, sex, or a variety of physical characteristics such as tumor type, size and location. If you are not accepted on a trial, it is important to recognize that this does not mean you are being 'deprived' of a drug just of participating in the trial – if we knew for sure the drug would work, it would not be in a clinical trial.

Participation in a trial requires informed consent: you must legally be informed about potential benefits and risks of the trial. For children too young to sign informed consent there is a process called informed assent with parental consent. Trial benefits may include the drug being effective, or, simply, the fact that you are contributing to advancement of scientific knowledge. Risks may include pain, inconvenience of taking drug, etc. You will also be notified of options instead of participating in the trial e.g. chemotherapy or surgery. Expenses you may incur in the trial e.g. travel, or hospitalization for rare side effects may not be covered either by the trial or your insurance. You will be informed of this. Even after signing informed consent, you may withdraw from the trial at any time. Finally you will be provided with your results at the end of the trial.