

Treating Refractory NB

After just a few months of your child's treatments, you may finally feel like you are getting the hang of cancer treatment. Then you find out that your child is "refractory"—i.e., one of the 20-50% of high-risk NB cases that does not respond to treatment adequately during frontline treatment.¹ Once again, the wheels have come off the cart and you are bogged down in new information and emotions.

*In this chapter, parents who have dealt with refractory disease share some of the information and insights they have learned along the way. Our hope is that the experience of others who have been in your situation will be helpful as you navigate this new stage of your child's treatment. As always, parents' observations are just that, and **an experienced oncology team must always be your guide in medical matters.***

What does this mean for my child?

If you look up a definition of refractory, you will find it is "a condition that does not respond to treatment." However, in the world of NB, it is not that simple. Refractory NB may also be referred to as resistant, stable, or primary refractory disease. Your child may have had a very good partial response to treatment or only a very limited response -- there is a range of response that may be considered refractory. Keep in mind that "refractory" disease is different from "progressive" disease, in which the NB is not only **not** responding to treatment nor remaining stable, but is increasing or spreading despite treatment.

Whatever range of response has been seen, once your child has not responded to therapy as intended and is identified as refractory, he or she will no longer continue on the frontline protocol. It is time to consider alternatives. What this means is that you must become an even greater advocate for your child's medical care, be willing if necessary to consult with new doctors, and possibly even travel to new and distant places for treatment. It is important to keep in mind that each child responds differently and that a variety of new or improved treatments continually become available. There *are* long-term survivors whose once refractory disease was successfully treated with therapies that diverged from the "front-line" treatment the child had "failed." Your goal is to find that successful alternative path for your child.

What is the first step?

So, how do you find out the best path for your child without enrolling in medical school yourself? An oncologist with expertise and long experience in NB, and most importantly, someone with whom you feel comfortable and can place your trust, is the key resource in making your next treatment decision for your child. If you are not already being treated at a medical center that has doctors who specialize in NB, *now* is the time to make contact with such institutions. The trick is to do so quickly—time can be critical in fighting NB.

You should regard your child's primary oncologist as an invaluable resource when determining subsequent treatment options, even if you decide to consult with additional NB experts. It is necessary to take into full consideration whether the child has responded favorably in a manner that might suggest the pursuit of a specific treatment and also whether the child has any medical

conditions that might preclude a certain course of treatment. Having intimate knowledge of the child's specific response to date and his or her present condition, your child's primary oncologist is in a unique position to help.

However, sometimes even your child's primary oncologist may not be fully informed about newer options available for children with refractory disease, and it may be necessary for you to do some research yourself. Alternatively, you may feel being more informed will enable you to have a more meaningful discussion with the medical professionals. Whatever your rationale, your research may involve exploring online the protocols offered at other cancer centers; speaking to NB experts at other cancer centers; speaking to principal investigators of new clinical trials; and/or obtaining second opinions from one or more NB specialists based on their comprehensive examination of your child and his or her history. Many parents also speak with others whose refractory children have been treated on certain clinical trials; be mindful that every child is different and the experience of others may have limited relevance to your child's situation.

If you decide to get a second opinion, a list of NB specialists in the U.S. and their contact information may be found in **"Confronting the Diagnosis: U.S. NB Specialists."** (This is not a comprehensive list.) Do keep in mind that these are doctors known around the country and even the world, and some have a very large number of patients; they often receive dozens of calls and emails a day. Hence, you might not get a return call or email, or at least not as quickly as you wish – which is immediately! It is often helpful to speak with the doctor's secretary first and find out if the specific doctor prefers to be contacted first by email or phone and the best time to call.

Keep in mind that a doctor cannot give you an informed second opinion over the phone, and will need to examine your child and his history to advise you medically. You must take the responsibility of having copies of all your child's medical records sent to a consulting physician. This can take time and may also involve some frustrating administrative steps, so you should determine as soon as possible how to get copies of your child's medical records.

Indeed, once you have realized your child is refractory, beginning the next phase of treatment as soon as possible and avoiding progressive disease is crucial. Yet, you do not want to rush into a treatment that may preclude a different, equally promising trial. In the experience of many parents of children with refractory disease, there are two very important and related considerations to bear in mind when deciding on the next course of action.

On the one hand, you wish to identify the treatment that will knock out the disease this time around, keeping in mind that such decisions rarely constitute the elimination of all other options. In many instances the failure to respond to a specific treatment -- or even emotional, financial, or social considerations -- will dictate a "return to the drawing board" in your effort to find the best care. Hence, this is also an opportunity to identify and set aside some options for later consideration. But, on the other hand, your preferred choice of treatment may have the effect of precluding some others. In particular, choosing an extremely harsh option, with potentially damaging, long-term side-effects, may render the child ineligible for other subsequent treatments, either by doing irreparable harm to organs or blood counts, or by changing the biology of the disease. For example, the high-dose chemotherapy that often accompanies transplant may affect organ function; high-dose MIBG might result in long-term suppression of blood counts; and a particular chemotherapy regimen may cause the cancer cells to develop an immunity to that agent. It is crucial to identify the "opportunity costs" of the various possible treatments (see further discussion below). It is also important to plan ahead in order to make the best use of a stem cell harvest.

Investigating Available Protocols/Clinical Trials

NB protocols or trials are basically treatment options. Your induction chemotherapy or treatment regimen was a protocol used after initial diagnosis and staging of the disease. But whereas there is limited variation in "frontline" treatments around the country, treatment options for a child with

refractory disease are numerous and varied – and hence can be very confusing.

There are several centers that specialize in NB and some treatments may be available only at specific institutions. There are 14 hospitals across the countries that are affiliated with New Approaches in Neuroblastoma Treatment (NANT) (www.nant.org). NANT is a consortium of research institutions that share research protocols and support. Some trials may not be available at all of the NANT hospitals, but most will be. Another excellent resource is Memorial Sloan-Kettering Cancer Center (MSKCC, www.mskcc.org) in New York City. MSKCC has a team of several oncologists devoted to neuroblastoma and conducts research separate from NANT.

There is a wealth of information on the internet—but it is hard to pare down to a reasonable size. A good place to start is the websites from NANT, MSKCC, the National Cancer Institute <http://www.cancer.gov/CLINICALTRIALS> and the National Institutes of Health <http://clinicaltrials.gov>. On most sites you will find a listing for clinical trials. These trials will be listed under “Neuroblastoma” or “Solid Tumors.” Of course, on the NANT website, all of the trials are for NB.

You will find information organized in different ways, but should be able to determine which trials are currently open, why they think the drug/treatment/combination of drugs will work, what is being tested, and what results the drug has shown in the laboratory. Often the “consent forms” for the protocols can be read or downloaded from the internet. Each protocol will have specific eligibility criteria. Becoming familiar with eligibility criteria of trials is a good idea, so you know what items are often listed. Much of the information on the consent forms will be the same—basic information and disclaimers—but after you’ve looked at a few, you will be able to discern where the important information is. This information can help you determine whether or not the trial is targeting your child’s particular situation and whether your child would be eligible for it.

For example, some trials have been primarily successful in reducing bone marrow disease, while others may be considered better for bulky tumors. In each case, you must ask whether there is sound reason to suppose that a particular treatment might be beneficial to your child’s specific case and whether the potential for beneficial results outweighs the potential for further harm, either from progressive disease or side-effects. As noted, your child’s induction treatment for NB may have resulted in certain physical impairments such as hearing loss, kidney or heart damage. These effects are important to consider as you determine the next course of treatment. Any viable option almost surely *will* have some favorable factors as well as the potential for both short and long-term harm.

It is wise to contact the oncologist conducting the research or those most experienced with the treatment strategy, in order to get answers to your specific questions, including the potential benefits and detriments for your child’s specific case. In some cases, the data from previous clinical experience and scientific studies will provide clear support for the decision; in many cases the evidence is indirect and ambiguous. Anecdotal evidence of a favorable early response to a new, relatively benign treatment regimen (offering little harm to the child) may be all there is to go on in some cases. Do not be reluctant to ask probing questions of the doctors conducting the trials and get all the answers you need to make an informed decision.

Bottom line: you will need to discuss all possibilities with your child’s primary oncologist and any consulting NB specialist, but reading the trial documents and conducting additional research, including talking to other parents whose children have been treated on such trials, can help you form questions and be better prepared to advocate for the best individualized treatment for your child. You, as the parent, are empowered to direct the care of your child.

Clinical Trials

Whichever treatment you choose, it is likely to be a clinical trial of a newer drug than your child’s initial induction chemotherapy. Parents sometimes refer to these newer treatments as “experimental

treatments.” In the world of NB, each child’s cancer is unique and thus, all treatments, even induction chemotherapy, can be considered experimental. Unfortunately, there is no existing NB treatment at this time that all children respond to successfully.

Clinical trials fall into three categories – Phase I, Phase II and Phase III trials. The distinctions between these categories are spelled out in this Handbook in **“What is a Clinical Trial?”** In a nutshell, a Phase I trial is defined by the NCI as the first step in testing a new treatment in humans. Before being approved as a Phase I clinical trial, the treatment has had promising results in a lab setting (ie testing on NB cells grown in dishes and NB tumors in mice). The clinical trial is established to determine the maximum tolerated dosage and the best means by which a treatment is given (i.e. orally, intravenously, etc). Pediatric Phase I clinical trials usually involve drugs that already have an established maximum tolerated dose in adults, and dosage levels are based on approximately 80% of the maximum tolerated dose used in adults for other cancers (typically other solid tumors). A Phase I trial agent for NB may be a completely new drug, a drug that never been used for NB, or a new combination of available drugs.

Phase II trials are typically a refinement of a Phase I trial that showed some success in treating NB. The purpose of a Phase II trial is to determine the anti-cancer effectiveness of the maximum tolerated dose established for a drug in its Phase I trial.

Phase III trials compare the current “standard” treatment to a new treatment, randomizing patients to either the new or the standard treatment. Most (but not all) children with high-risk NB are treated at diagnosis on a Phase III trial.

As the parent of a refractory patient, you are likely to be choosing between Phase I and Phase II trials. For a discussion of what is involved in enrolling in a clinical trial, see **“What is a Clinical Trial.”** Enrolling in a trial is usually straightforward and the doctor will walk you through the paperwork. All clinical requirements, whether scans, blood work, etc will be managed by your oncology team. As a parent, it is wise to follow-up with your treating oncology team to ensure that any pre-trial tests are completed and sent to the trial coordinators in a timely manner. Any delays in obtaining pre-trial tests may delay treatment for your child. Repeating scans and tests that may have been done relatively recently can be an issue with insurance companies who don’t like to pay for duplication. However, most of the insurance issues can be worked out with a phone call and sometimes a letter from the doctor.

You will be required to authorize treatment under the chosen protocol and sign waivers that outline the risks associated with the treatment regimen. Unfortunately, all cancer treatment options pose some risk to your child – as does the cancer itself. The trick is –

- 1) understanding the risks,
- 2) determining whether those risks pose a greater risk to the health of your child versus the risk posed by NB, and
- 3) evaluating whether the new protocol may preclude your child from enrolling on subsequent protocols.

Depending on the age of your child, he or she may be asked to give “assent” as well. See **“What is a Clinical Trial.”**

Please know that your child can leave a trial early if it doesn’t appear to be the best course of treatment.

Maximizing the Options

As noted above, it is important to take the long view when deciding between trials. Some trials may prevent you from being treated with another drug/trial down the road, or some may have long periods of recovery with low counts and transfusions. Recently, it seems that many trials require

stem cells in reserve. With that in mind, it might be worth discussing whether or not harvesting stem cells (new or to add to your current supply) is possible, and if so can be done immediately. It can take longer if done later in the treatment cycle, and may not yield as many cells, but stem cells have been collected at non-traditional times.

Read the trial documents and consent forms carefully, and talk with your doctors about a possible series of treatments that will make the best use of the available treatments while not precluding the possibility of other effective treatments down the road. It may seem unimportant now, when the situation is so critical—but it is also worth considering and asking the doctors about side effects from the treatment that may affect hearing, cognitive, and/or physical development.

Unfortunately there are no simple answers. Once you are dealing with refractory NB, you will likely be consulting with new and different doctors, traveling far from home to treatment centers that have NB specialists, and at times making decisions based on a leap of faith. However, the more informed you are, the more comfortable you will feel that you have made the best possible choice for your child.

Other Considerations

While amassing medical and logistical information on the various treatment options that are available, attention should be given to other, more personal concerns. In addition to direct financial cost of treatment, there are a host of social, psychological, emotional and even spiritual considerations that may bear on the treatment choices. One of the most important considerations may be whether a treatment would be available through a local facility, or only through a regional medical center. If the treatment requires travel and extended out of town stays, then careful consideration must be given to time away from school, a caregiver's time away from work, time away from other family members, and even time away from the ordinary, everyday sort of activities that might provide for a sense of stability for the child. Whether absence from home is either temporary or long-term (some families choose to stay near remote treatment centers for months and even years), careful consideration must be given to the impact on marriage, family, income, and the child's social development. If possible, it may be helpful to discuss these concerns with families who have experienced the course you are considering. Some parents have found it valuable to have fairly clearly established and regularly reviewed "rules of disengagement" – i.e, an exit strategy that will determine when it might be best to return home and/or suspend certain treatment regimens.

Participation by your child in the process of determining the next step in treatment will depend on the child's age and the specific case. As noted above, depending on the age of your child, he or she may be asked at some institutions to give "assent" to enrollment in a clinical trial. Many parents feel it is important throughout the decision-making process to talk with their child in an age-appropriate manner about what he or she might anticipate in the treatment scenarios being considered. For example, it may be appropriate to discuss with the child that certain options will involve frequent travel, long periods away from school, pain, additional hairloss, time in isolation, or other "costs." Some children may have concerns that need to be aired; even where their fears cannot be entirely avoided, they can be acknowledged and legitimized. Often, due consideration can be given to even a very young child's concerns and wishes, thereby allowing the child a sense of significance and ownership in the process. Again, these are very personal matters and dependent on the individual situation.

The most important factor to remember throughout this entire process is that, *when a decision is made on the information available at the time, it is the best possible decision.* You should trust fully in your decision insofar as you regard it as providing the best possible opportunity for the child to flourish as you work together with your child's oncologists toward a cure. There is, of course, no guarantee. Decisions are always based on imperfect information; there will always be another new drug you could not have known about at the time, another factor that may or may not impact the list of potential costs and benefits. Whether or not things go as you might have planned (and, of course,

they almost never do), it is pure folly to suppose that you could have known that it would have been better to have pursued a different course. You can no more determine the outcome of a course of treatment that you chose against, than you can fully anticipate the course actually chosen. Would it have been better or worse? No one, not even that nagging voice in your own head, can say with any certainty. Because in reality hindsight is not 20/20, you must go on, trusting the resources presently available to you, never forgetting that you have done your very level best for your child.

Please contact info@cncfhope.org with any comments

¹ Kushner BH, Cheung NK. [Induction for high-risk neuroblastoma](#). *Pediatr Blood Cancer*. 2007 Sep;49(3):221-3. PMID: 17417798