



## Dealing with Relapse

The focus of this chapter is on relapse after treatment for *high-risk* neuroblastoma. As always in the case of NB, the guidance of an experienced doctor you trust is absolutely crucial, especially in the complex decisions involved in relapse treatment. However, your knowledge can be a valuable ally. The more you know, the easier it is to understand the issues presented by relapse, have a meaningful dialogue with your child's doctor, and make informed decisions about the many treatment options.

This chapter draws extensively from "Treatment of Relapsed and Refractory Neuroblastoma," authored by Drs. K. Matthay and B. Kushner, in the 2005 pediatric oncology text *Neuroblastoma* (Cheung & Cohn, eds). There is some overlap with the previous chapter in this Handbook on treating refractory disease, because both are "resistant disease" -- standard frontline therapy has failed and new treatments options are needed. However, whereas refractory disease is considered "progressive" only if NB spreads to new sites or the size of a lesion is increased, relapsed disease (also referred to as "recurrent" disease) is always progressive disease at discovery, because it has *increased* from "no evidence of disease." The length of the time of remission, the location and nature of the disease, the prior treatment, and many other factors must be considered to determine how to treat this new, recurrent disease.

### SOME BACKGROUND INFORMATION

**A Note on Low-Risk and Intermediate-Risk Cases.** The treatment strategies discussed here do not apply to relapse after low- or intermediate-risk NB. The incidence of relapse is less after successful treatment for low- or intermediate-risk NB. Localized relapse in low- and intermediate-risk cases can often be successfully treated by surgery. In the case of metastatic relapse after low- or intermediate-risk treatment, the child's relapse treatment is usually very similar to high-risk frontline therapy. However, some of the general observations that follow may be relevant as well for low- and intermediate-risk relapse cases.

**Risk of Relapse for High-Risk NB.** Phase III and pilot studies from the past 15 years have revealed long-term survival after high-risk treatment ranging from 25% to over 50%.<sup>1</sup> For example, follow-up of children with high-risk disease treated in 1991-1996 on clinical trial "CCG-3891" revealed nearly 60% long-term survival for the 50 children who reached remission and completed both transplant and six months of Accutane (13-*cis*-retinoic acid). In other words, about 40% relapsed after successful treatment.<sup>2</sup> Since then, the dose of induction chemo has been intensified, transplant regimens have changed, and additional treatments for minimal residual disease such as antibodies have often been used, so it may be that the risk of relapse after successful treatment is now lower. It is also encouraging to know that the risk of relapse decreases every year after successful frontline therapy since most relapses occur within two years after stem cell transplant or completing chemotherapy.<sup>3</sup>

**What causes relapse?** No one has determined what causes NB relapse after clinical remission. Theories for its cause include:

- re-introduction of NB cells in contaminated stem cells at rescue;
- NB cells “hiding” in sanctuary sites such as brain or testes; and
- NB cells becoming resistant during frontline therapy.

The recent results of a clinical trial (“COG-A3973”) comparing randomized patients receiving purged stem cells after transplant versus unpurged showed no difference in survival between the two groups, so contaminated stem cells are probably not the cause of most relapses.<sup>4</sup> Many researchers believe developing more effective treatments for minimal residual disease (MRD) will reduce the incidence of relapse in high-risk cases.<sup>5</sup>

By far the most common sites for relapse are bone and bone marrow, and sites not involved at first diagnosis (such as brain and lungs) are seen in up to 8% of relapsed children.<sup>6</sup>

**Monitoring after Frontline Treatment.** For about two years after finishing NB treatment, a child does follow-up tests and scans every three months, then every six months and eventually none; the schedule varies according to the institution and the particular case. It is certainly hard not to worry however far from treatment a child may be, because the symptoms of relapse can be similar to those of a host of childhood illnesses and conditions. Parents must continue to be vigilant -- but without being alarmist.

If your child has a complaint that persists over a few hours or days, depending on the symptom and its severity, naturally you should follow up with your pediatrician or your oncologist. Some parents recommend keeping a log of the child’s complaints (discreetly, without upsetting the child), because it is important to be able to describe the precise symptoms and their duration to the doctors. It may take time, but ideally you will develop a good working routine for dealing with your professional team (which should include a pediatrician informed about your child’s history) when you are troubled by your child’s symptoms. You are the person most familiar with your child, and your invaluable instincts should be given careful consideration by your medical team.

**Establishing Conclusive Evidence of Relapse.** Just as with first diagnosis, relapse is not always obvious. Some NB relapses have no symptoms and are discovered by routine follow-up tests and scans; others present with similar symptoms as seen at first diagnosis (pain, fever, fatigue, anemia, etc.) or with new symptoms not present before (as with headaches in brain relapses).

Worrisome symptoms may require an oncology clinic visit for a physical exam, often followed by a CBC and urine HVA/VMA tests, and possibly even scans. NB relapse must be absolutely *proven* before treatment can commence, because some secondary cancers can resemble NB, and correct treatment must be given. Tests that evidenced the child’s first diagnosis may no longer be reliable. One large German study found a relatively low incidence (54%) of abnormal HVA/VMA results at relapse<sup>7</sup>; occasionally relapsed NBs are MIBG-negative although previously MIBG-avid. Hence, other scans may be necessary, such as PET. See **“Getting through Tests and Scans.”** Biopsy of bone marrow or suspicious spots on scans is often done in cases where a bone scan or PET is positive but catecholamines are normal. The possibility of residual matured (harmless) tumor can further complicate the determination of whether relapse treatment is needed, so rescanning may be required after a few weeks to determine if the disease is growing and active.

If relapse is confirmed, many of the same staging, pathology and genetic tests done at first diagnosis are performed, as well as baseline tests for heart, hearing, and other organ function. If a biopsy is performed, tests for ALK mutation and other characteristics may be done. Since most treatment begins with some type of chemotherapy, a central venous access will be required. A port is often chosen rather than a Hickman or Broviac, depending on impending treatment choices. See **“Broviacs, Hickmans, Ports, etc.”**

**Beginning Relapse Treatment.** After the whirlwind of scans, tests, and line placement, most often “retrieval” chemotherapy is begun. Depending on the relapse scenario, children very often respond to chemo again, especially if relapse occurs after more than one year of remission.<sup>8</sup>

However, relapse after high-risk treatment is a different scenario from first diagnosis. Whereas at first diagnosis a well-defined road map of the frontline protocol is provided, there is generally no set treatment path for a relapsed child. The NB team will often present several optional treatments to parents and discuss the various benefits and disadvantages of each. Some doctors even list “no treatment” as one of the options. Doctors may discuss the possible timing of various subsequent treatments that will depend on the child’s response to the initial relapse chemo and on various personal considerations. In other words, relapse treatment is usually very individualized – and parents are generally expected to participate in the process of determining the particular treatment plan for their child.

Although perhaps less obvious, the considerations and analyses underlying relapse treatment are also different from those at first diagnosis. As Drs. K. Matthay and B. Kushner note in “Treatment of Relapsed and Refractory Neuroblastoma”:

*“The appropriate approach to the patient with recurrent or resistant neuroblastoma depends on the goals of the therapy. Although in previous studies the median survival for patients who relapsed after myeloablative therapy and bone marrow transplantation was only 3 months, with current multimodality approaches and judicious use of established as well as investigational agents, the survival can be prolonged for years,<sup>9</sup> and cure may be a possibility in some settings. Whether the goal is symptom palliation, prolongation of life, or complete remission depends on the timing and nature of the relapse, the prior therapy, and the tumor biology.”<sup>10</sup>*

To participate fully in such difficult treatment decisions, parents of a relapsed child must have a basic understanding of the underlying rationales for the various treatment paths, and the benefits and detriments of these treatments for their child’s specific case, both from a medical and a personal perspective. The following section will provide some general information on the various considerations to be weighed in determining relapse treatment – keeping in mind, of course, that the guidance of an experienced and trusted oncologist in these complex and difficult decisions is absolutely crucial.

## RELAPSE TREATMENT RATIONALE

Your doctor will take into consideration many factors when recommending treatment for relapse:

Age of child:

- ⇒ *less than one year*
- ⇒ *1-21 years*
- ⇒ *over 21*

How long the child was in remission after treatment:

- ⇒ *less than one year*
- ⇒ *1-2 years*
- ⇒ *long remission*

Where disease is located:

- ⇒ *at primary site*
- ⇒ *lung; liver*
- ⇒ *central nervous system (CNS)*
- ⇒ *distant sites (bone, marrow)*

How much disease (tumor burden):

- ⇒ *minimal or trace disease*
- ⇒ *many bone metastases or loaded bone marrow*
- ⇒ *bulky disease (soft tissue); many lymph nodes*

Rate of tumor growth:

- ⇒ *rapid progression*
- ⇒ *slow or stable disease*

Prior treatment history

- ⇒ *induction regimen (agents used)*
- ⇒ *number of stem cell transplants (SCTs)*
- ⇒ *local, targeted, or total body irradiation*
- ⇒ *antibodies*

Organ function:

- ⇒ *impaired kidney, liver, bone marrow function, hearing, etc*

Available stem cells:

- ⇒ *number of rescues stored*
- ⇒ *length of storage time*
- ⇒ *potential of another collection*

Changing characteristics of the child's NB, or new information:

- ⇒ *no longer MIBG-avid*
- ⇒ *chemo-resistance (loss of p53 function)*
- ⇒ *presence of ALK mutation; other mutations or expressions*

Goals of treatment:

- ⇒ *cure*
- ⇒ *prolonging life*
- ⇒ *quality of life*
- ⇒ *palliative care*

**Your child's specific situation may present options and/or limitations for certain treatments.**

A key factor is whether or not the NB still responds to chemotherapy. Having already been down that road, many parents want something new for their child, but the fact remains that chemo-sensitive NB will commonly be treated most successfully first with chemotherapy. However, the specific facts will be carefully considered. If a child had a certain chemo combination during induction, the oncologist may choose a different combination at relapse. If a child has recently undergone stem cell transplant, it is less likely high-dose chemo would be recommended due to the threat to bone marrow recovery and organ function; in contrast, a "late" relapse often allows for options of more aggressive therapy similar to frontline treatment. If, however, the NB is not responding to chemotherapy, then the oncologist will consider other treatment possibilities. Some children with very minimal bone marrow disease detected early may be a candidate for antibody therapy and/or retinoids or other combination therapies. There is a treatment specifically for isolated CNS or brain relapse at MSKCC in New York City, using an antibody called 8H9 and surgery in addition to chemo and radiation. Surgery may be recommended for certain local tumor recurrences, but some cases are not ideal for surgery, such as multiple masses in the liver.

**Treatments for relapse vary in approach and intensity.** Some or all of the elements of frontline treatment for high-risk neuroblastoma --chemotherapy, surgery, radiation, Accutane, or antibodies -- can potentially be used in the relapse setting, depending on the individual situation. Each of these treatments attack NB in a different way and with varying intensity.

The variety of intensity in treatment means there are weighty decisions to be made regarding treatments allowing good quality of life versus harsh treatments with potential to bring about cure or long term survival. There may be a sequence that starts out with harsh treatment, and then depending on the disease response, the child may move onto less aggressive treatments, or conversely, a child may respond to something lower dose at first, and then require harsher treatment later to elicit a response. Your child's oncologist must help you navigate this difficult dynamic, but

sometimes the decisions to be made are very personal. See discussion below regarding “maximizing your options” and “quality of life” considerations.

It is advisable to ask your oncologist about collecting stem cells (new or to add to your current supply) during the planning stage of relapse treatment, since the availability of stem cells can allow for treatments not otherwise possible.<sup>11</sup>

**Can we know what will actually work against my child’s NB?** Truth is, no one knows for certain. NB cells can change and lose functions that make them chemo-sensitive. It also appears that every child’s NB disease is unique. Research is ongoing in “personalized medicine,” with the long-term goal of someday being able to determine the most effective treatment for each child (understanding and use of these technologies is limited thus far). For example, one such “personalized medicine” effort is currently underway in the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC) led by Dr Giselle Sholler at the Van Andel Research Institute.<sup>12</sup>

There are no hard and fast rules, and currently relapse treatment relies on *educated* trial-and-error to see what works in each child. To reiterate, oncologists will recommend certain treatment options depending on all the variables in your child’s specific case. The treatments mentioned below are merely examples to illustrate how varied the choices can be; furthermore, treatment for relapsed children is an ever-changing landscape. *The guidance of an experienced oncologist through this complex landscape is crucial.*

**High-dose chemo/radiation.** Some treatments include high doses of chemotherapy or targeted radiation therapy, or a combination of the two, which may require stem cells for rescue. Examples of high dose chemotherapy combinations are ICE (ifosfamide, carboplatin, and etoposide) and CIT (carboplatin, irinotecan, temozolomide). High-dose choices can result in potentially long inpatient stays, and the children that respond well can usually continue on to milder therapies. <sup>131</sup>I MIBG radiation therapy, a type of “targeted” radiation using the radioactive iodine-131 isotope, has been used to treat more than 700 children with relapsed and refractory NB since the mid-1980s, and has the highest response rate against neuroblastoma for a single agent, with about 30% of children responding. The child must be MIBG-avid – i.e., NB shows up on the child’s MIBG scan. New trials include combining MIBG radiation therapy with chemotherapy. See “**MIBG Treatment**” for more information on treatment issues surrounding MIBG. “Hot antibodies” (3F8 antibodies with radioactive isotope <sup>131</sup>I attached, currently given in conjunction with Avastin) is another approach that has been tried at Memorial Sloan-Kettering. Allogeneic (donor) or cord blood transplants, and haplo-identical or donor NK cell therapies, albeit less common, are additional aggressive possible treatment options considered for relapse. Germans reported recently on a small series of relapsed NB that had second stem cell transplant – similar to repeating frontline treatment – and survival was improved in the second transplant group.<sup>13</sup>

**Medium-dose chemo.** Outpatient chemotherapy that is relatively easy on the blood counts is often chosen for certain relapse scenarios. One combination used frequently is topotecan and cyclophosphamide, which is usually administered IV at a clinic daily for one week out of every three or four weeks.<sup>14</sup> Topotecan with etoposide has been studied as a relapse regimen in Germany.<sup>15</sup> Another commonly used combination is irinotecan and temozolomide.<sup>16</sup> Irinotecan can be administered as an IV infusion daily for one or two weeks or taken orally, and temozolomide is an oral chemo taken in pill form daily for five days out of a three or four week cycle.

**Low-dose chemo.** Low-dose oral agents in pill form, such as topotecan, Cytoxan, temozolomide, or etoposide, may be used in some cases. These regimens are much easier on blood counts than high dose chemo so often transfusions and neutropenic fevers can be avoided. Occasionally combinations of oral chemos are used.

*Timing, dosage and form of the various chemotherapy regimens can vary per patient based on the specific medical and personal factors.*



**Targeted drugs (“small molecules”) and biologics.** These drugs employ different mechanisms from some common chemotherapy agents to destroy NB and sometimes are used in conjunction with medium- or low-dose chemo. Targeted drugs recently or currently being tested in clinical trials for relapsed or refractory neuroblastoma include inhibitors of certain NB cell functions and signals such as non-selective kinase inhibitor CEP-701<sup>17</sup> (dropped by pharmaceutical company, but other similar drugs are being explored), aurora A kinase inhibitor, and ALK inhibitor; HDAC inhibitors such as SAHA (vorinostat); inhibitors of blood vessels that support NB tumors— “anti-angiogenetic” agents, such as ABT-751<sup>18</sup>; and stimulators of “differentiation” or apoptosis of NB cells (to mature or cause their death) such as the retinoids fenretinide or Accutane.<sup>19</sup> Nifurtimox, an anti-protozoal drug, is being administered to patients along with chemotherapy in a trial to determine if it enhances the effectiveness of chemotherapy.<sup>20</sup> Some new drugs are attractive for their low toxicity profile and may cause relatively minor side effects, but toleration does vary. From the child’s perspective, the main advantage of low-dose regimens (chemo or targeted drugs) is allowing for near-normal activity.

**Immunological treatments – antibodies.** Monoclonal antibodies may be an option for some relapsed children, generally those with minimal disease. For example, MSKCC has been treating children with 3F8 antibodies since the mid-1980s as part of frontline treatment. There are currently several different trials using the 3F8 antibody, and recently a high-dose protocol has been initiated for children in remission after relapse. This antibody, made in mice, generally must be preceded by high-dose chemo to prevent premature formation of an immune response known as human anti-mouse antibody, or “HAMA.” St. Jude’s is producing a new “humanized” antibody hu14.18 to use with cytokines (immune stimulators). The ch14.18 antibody (*chimeric* refers to its part mouse and part human derivation) is available to relapsed and refractory children in Germany, and will be available to relapsed patients in the COG soon (a trial is currently planned), but some refractory cases with minimal detectable disease may be eligible immediately after stem cell transplant. Another humanized antibody trial for relapsed neuroblastoma will open in COG hospitals in 2011 using hu14.18-IL2 with GM-CSF and retinoic acid.

**Immunological treatments – vaccines and viruses.** Efforts are underway at several institutions to produce various vaccines against NB, intended primarily for those with minimal disease or in second remission. Current vaccine trials are studying various approaches. A study at MSKCC is trying to elicit B cell (antibody) responses to GD2 and GD3 similar to anti-GD2 antibodies, and a study at Penn State/Hershey is trying to generate cytotoxic (killing) T cell responses to the vaccine proteins. Another approach at Baylor uses a neuroblastoma cell line that has been genetically modified to release cytokines, which may help stimulate an immune response to the tumor. In 2010 the first trials using oncolytic viruses in children opened. This new treatment modality is very attractive because it is non-toxic and potentially very effective. Safety has been established in many adult trials, and recent results from some adult trials are showing promising effects against difficult solid tumors. Several early phase oncolytic virus trials for neuroblastoma are underway using reovirus (Reolysin), vaccinia (JX-594), herpes simplex (HSV1716), Newcastle disease, and Seneca Valley virus (NTX-010).<sup>22</sup>

Clinical trials open, and then occasionally close temporarily for safety review, and then open again. Contacting the principal investigator is the best way to know the status of a specific trial. See discussion of research into clinical trials, below.

**Second remission treatment issues.** With advances in treating relapsed NB, more children are able to reach NED (no evidence of disease) again. While this is very good news of course, it poses a unique treatment dilemma. Once a child relapses, the likelihood of another relapse is very high, and therefore continued treatment of some sort is usually advised. However, there is no consensus on what agents should be used or for what length of time, and few drugs are available for an oncologist to prescribe beyond low-dose oral chemo. The problem is that most clinical trials of new treatments for relapsed NB *require evidence of disease*. Possible options for relapsed children in second remission include Accutane, low-dose oral chemo in pill form (such as topotecan, Cytosar, etoposide,

temozolomide, thalidomide, Celebrex—separately or in various combinations), 3F8 antibody (requires high-dose chemo), and some vaccines. As more studies are planned to treat minimal residual disease (MRD) occasionally eligibility for “second or greater response” is included, such as the fenretinide trial.<sup>23</sup> Some treatments may be available for “NED after relapse” via “compassionate use” such as ABT-751. This is an important item for discussion with your child’s doctor.

**Special issues with late relapse.** While late relapses are rare, they have been observed and studied.<sup>24</sup> Relapse diagnosis at any point is devastating, but a “late” relapse (3 or more years after finishing frontline treatment) can be especially unexpected. Being thrust immediately into treatment decisions after a hiatus from keeping up with the developments in the treatment of NB can be overwhelming. Quickly obtaining records of cumulative doses of chemotherapy and radiation received during frontline treatment is very important. After late relapse a child can sometimes receive aggressive therapy again, similar to frontline treatment. Late relapses often demonstrate prolonged response to treatment.<sup>25</sup>

**Maximizing your child’s treatment options is an important part of the relapse decision process.** (This is also the case with refractory NB, hence very similar considerations are discussed in that chapter). Without knowing if the child will respond to any given treatment beforehand, it is wise to plan for more options later. This means looking at the eligibility criteria of trials and keeping a close eye on the child’s organ function. For example, the liver enzymes may be elevated and eliminate the child from a particular trial. Some trials do not allow prior allogeneic (donor) transplants or radiation to more than 25% of the bone marrow. Others require the availability of stored stem cells. There are many such criteria, and looking at all the possible trials (including those that may open in the near future) helps parents consider and determine the maximum possibilities.

In other words, 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; some may have long periods of recovery with low counts and transfusions; and some may have high risk of side effects that will rule out subsequent treatments. 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 later. 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.

**Weighing Quality of Life and Other Considerations.** Providing a child with maximum quality of life during relapse treatment without eliminating some promising “harsh” treatment may present difficult choices. Every parent wants a treatment that ultimately brings cure, but after already seeing the hardships of frontline therapy, parents and children understandably may gravitate to what is “easiest” of the promising choices given. One of the goals of relapse treatment is commonly “tolerability,” and researchers recognize this – the reason so many studies report something along the lines of “this combination was well tolerated in heavily-pretreated children with resistant neuroblastoma.”<sup>26</sup>

Moreover, attention may have to be given to some non-medical concerns. In addition to direct financial cost of treatment, there are a host of social, psychological, and emotional considerations that may bear on the treatment choices. For example, one important consideration may be whether a treatment would be available through a local facility, or only through a regional medical center. Many families have elected and successfully maintained a treatment “partnership” between their local oncologist and an NB specialist in another part of the country. If the treatment requires travel and extended out of town stays, then careful consideration must be given to balancing 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 a sense of stability for the child. Whether absence from home is temporary or long-term (some families choose to stay near

remote treatment centers for months and even years), consideration of the impact on marriage, family, income, and the child's social development may be wise. 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.

These are difficult issues indeed, and very personal in nature.

## **INVESTIGATING DOCTORS AND CLINICAL TRIALS**

Presented with such complex issues and decisions, it is not surprising most parents of relapsed children eventually find themselves doing research themselves. You may simply wish to understand better your child's situation and treatment options, or you may wish to bring more informed questions to your child's doctor about different treatment possibilities. Alternatively, you may feel your child's doctor is not sufficiently pro-active in exploring treatment options or is not fully informed about certain specific options available for children with relapsed disease.

Whatever the rationale, your research may involve exploring online the relapse protocols offered at other cancer centers; speaking to principal investigators (the oncologists heading up the research) 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 relapsed 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.

**Getting a Second Opinion.** If you are being treated at a medical center that sees very few cases of NB, you may decide upon your child's relapse that this is an appropriate point in the journey to get a second (or third) opinion.

For a list of NB specialists in the U.S. and their contact information, see "**Confronting the Diagnosis: US NB Specialists.**" (This is not a comprehensive list.) Keep in mind that some of these specialists treat a large number of patients, and they often receive dozens of calls and emails a day. It is advisable to speak with the doctor's secretary first and find out if the doctor prefers to be contacted first by email or phone and the best time to call.

***Also, a doctor cannot give you an informed second opinion over the phone or in an email!*** To recommend a course of treatment the consulting doctor will require:

- a complete treatment summary;
- recent medical records (such as scans and biopsies);
- a physical examination of your child; and
- possibly additional tests and scans.

You must take the responsibility to get a treatment summary completed by your child's current doctor and have copies of pertinent medical records sent to a consulting physician. This can take time and may require patience with some frustrating administrative delays.

Even if you decide to move your child's primary treatment to another center, your child's initial oncologist is an invaluable resource when weighing relapse treatment options. Having intimate knowledge of the child's specific history and his or her present condition, your child's initial oncologist is in a unique position to help you consult with additional NB experts as you seek new treatments for your child.



**Investigating available relapse treatments.** However knowledgeable your oncologist may be, you may decide yourself to investigate the available relapse treatments, in order to enhance your own understanding and comfort level. As noted, treatment options for a child with relapsed disease are numerous and varied, and there is much to investigate. The process is virtually identical to researching treatments for refractory NB, especially if the child has relapsed while still on treatment.

For starters, there is a wealth of information on the internet—but it can be daunting to sort through. Relapse NB trials can be found on these websites (using search mechanisms for recurrent neuroblastoma):

- New Approaches in Neuroblastoma Treatment (NANT), [www.nant.org](http://www.nant.org)
- National Cancer Institute, [www.cancer.gov/clinical\\_trials](http://www.cancer.gov/clinical_trials)
- National Institutes of Health, [clinicaltrials.gov](http://clinicaltrials.gov)

Institutional websites also list trials available only at their locations, so be sure to search websites of institutions of interest. Notable examples are Memorial Sloan-Kettering ([www.mskcc.org](http://www.mskcc.org)) and St Jude ([www.stjude.org](http://www.stjude.org)); also, some NANT institutions have their own trials that are NOT listed on the NANT website, such as CHOP, Boston Children's, and others.

By contacting institutions of interest and principal investigators, you will learn pertinent information not only about current clinical trials, but may also learn about trials that are expected to open soon or treatments available “off-trial.”

It is common for children to see one or more of the following treatment categories during the battle against relapse:

- **Enrollment on phase I or II clinical trials.** These may be specific to NB or for unspecified solid tumors. Phase III studies are rare for relapsed pediatric tumors including NB.
- **Treatment “per” a clinical trial protocol although not enrolled,** if not eligible and drugs are already FDA approved.
- **Treatment with “off the shelf” agents** that are FDA approved.
- **Treatment on a “compassionate use” basis** with drugs not yet FDA approved.

You will find on-line information about clinical trials organized in different ways, but key items to note are:

- whether trial is active/enrolling;
- any age limit;
- rationale for treatment on such trial;
- any requirement for disease sites/measurable disease;
- any organ function criteria; and
- any prior treatment limitations.

Becoming familiar with eligibility criteria of trials is a good idea, so you know what items are generally listed. Often the “consent forms” for the protocols can be read or downloaded from the internet. (See “**Managing Emotions: Informed Consent**” for personal perspective on consent forms from an NB dad.)

**Phase I and Phase II distinctions.** There is an important difference between phase I and phase II clinical trials. Drugs being administered in phase II studies have *possible* response results in children in a prior phase I study, and toxicities and maximum tolerated dose are known. Drugs in phase I studies do not have such information available—the purpose of a phase I study is to *determine* toxicities and maximum tolerated dose of a drug based on promising laboratory data from cell lines in glass dishes (*in vitro*) or activity in mice. Some agents look promising *in vitro* or in mice,

but responses in children may be disappointing.

For further discussion of the distinctions between phase I, II, and III clinical trials, and background information about enrolling in a clinical trial, see **“Clinical Trials.”**

**Timing of entry.** Another issue in considering enrollment in phase I studies has to do with timing. Many phase I studies enroll a small number of children (usually 3-6, called a *cohort*) at a certain dose level, observe for toxicities, and then the next cohort is enrolled at a higher dosage. Speaking with your child’s oncologist and the principal investigator about the timing of enrollment is important, to determine if your child would be one of the first to receive the drug, or would be enrolling at a higher dose level. Trials also sometimes open and close and then open again, depending on drug availability, toxicities and other factors. The principal investigator will be able to give you the up-to-date status of enrollment and may give an indication of how the earlier cohorts have fared.

**Interpreting “response” from study reports.** As parents investigate available trials and try to discern what is most promising, they should be aware of the range of possibilities when studies report a “response” rate. Let’s say you are considering a phase II study of drug X. You uncover the phase I drug X results reporting a “30% response rate.” What does this mean? Does it mean 30% of the children on the study were cured? Unfortunately no, it does not. The 30% response rate may indicate that 30% of the children in the trial had some shrinkage or reduction in their NB, but often the duration of the response is unclear. Did some of the children have a complete response -- i.e., reach NED again? How long did the children respond before the disease progressed again? Did some of the children have shrinkage or reduction in their disease, and then experience stable disease for a while? How long? Asking such questions and getting all relevant information is advisable before committing to a trial. Unfortunately, some promising drugs that have a “high response rates” actually produce responses that are very short-lived, and you are entitled to know that. Answers to these questions are usually not available until a phase I study ends.

It helps to know the terminology used to report “response” in studies. Clinical trial protocols include a plan for closely monitoring the disease response so that if the treatment is not working, the child can quickly move onto something else. The International Neuroblastoma Response Criteria (INRC) was established in 1993 and uses the following terms:<sup>27</sup>

- “complete response” (CR) is no evidence of disease;
- “very good partial response” (VGPR) is primary mass reduced by 90–99%, no evidence of distant disease except for skeletal residua, and catecholamines normal;
- “partial response” (PR) is greater than 50% decrease in measurable disease and 1 or no positive BM site;
- “mixed response” is greater than 50% decrease of any lesion with less than 50% decrease in any other;
- “no response” is less than 50% decrease but less than 25% increase in any lesion; and
- “progressive disease” (PD) is new lesion or greater than 25% increase in an existing lesion.

**Risks and benefits of treatment.** In evaluating any treatment, you must ask whether the potential for beneficial results outweighs the potential for further harm, either from progressive disease or side-effects. Your child’s prior 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. See discussion on “maximizing your options,” above.

***It is advisable to contact the principal investigator or those most experienced with the treatment strategy in order to get answers to your specific questions about any clinical trial or new treatment.***

## **SUMMARY**

The rigors of relapse treatment cannot be minimized. You may be consulting with new and different doctors, traveling far from home for your child's treatment on various clinical trials, weighing difficult quality of life issues for your family, and at times making treatment decisions based on a leap of faith. An oncologist with experience in treating relapsed NB, and equally importantly, someone you feel comfortable with and can communicate with effectively, is the key resource in making your treatment decisions. However, the more informed you are, the more comfortable you will feel that you have made the best possible choices for your child.

There *are* successes in relapse situations. Unfortunately, because the relapse population involves such variation in relapse sites, in amount of disease, types of treatments tried, multiple treatment centers, and many other variables, it is virtually impossible to report long-term survival statistics. Even so, the reports of long-term survivors in some studies, the increasing numbers and approaches of available treatments, and the anecdotal evidence -- all suggest that the prospect for long survivorship after relapse is improving. There is increasing hope for relapsed children, and having an NB team who expresses and shares your hopes is also essential to this stage of the battle.<sup>28</sup>

*Please contact [editors@nbhope.org](mailto:editors@nbhope.org) with any comments*

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