



Overview of High-Risk Neuroblastoma Treatment

Part 1: Background

NB treatment for high-risk cases is generally a long and challenging experience, and many patients and families feel it is empowering to understand as much as possible about the disease and the available treatments. The focus of this chapter is to provide some general background information on the common components of treatment for high-risk disease. Side effects of these treatments and some ways to cope with them are discussed in Chapter 3, **“Coping with Treatment: Side Effects, Comfort Measures and Safety Precautions.”**

Only “frontline” treatments are discussed in this chapter, meaning ones for patients after a first diagnosis (i.e., not for relapsed patients), whose disease is responding to treatment (has not been determined resistant to treatment or “refractory”). Treatments for refractory and relapsed NB are discussed respectively in Chapter 7, **“Treating Refractory NB”** and Chapter 8, **“Dealing with Relapse.”** Information about clinical trials, contacting NB specialists for second opinions, determination of risk assignment, and other matters that arise at first diagnosis can be found in Chapter 1, **“Confronting the Diagnosis.”**

As the title of this chapter indicates, it is an *overview* of standard frontline NB treatments for high-risk disease: it is not a detailed treatise on NB treatment, its underlying science or purposes, or any particular protocol. Much of the information being shared is basic information that most NB parents know all too well by the time the patient has completed NB treatment; however, treatises and research studies used as sources are footnoted in the text for those who wish to read more about the matters summarized. Your medical team is always the ultimate source of information about NB treatments and their relevance to the patient’s specific case, but we hope the following information will help you have a more meaningful dialogue with your NB team.

Part 2: Overview of Treatment Protocols

After a diagnosis of high-risk neuroblastoma (NB), your oncologist will spend time with your family and explain in detail the protocol(s) offered for high-risk disease at your cancer center. It is very likely this treatment will be in the form of a clinical trial, and the parent or adult patient will have to decide whether to consent to a particular trial. A clinical trial is a research study designed to test certain drugs and their impact on the disease. In pediatric cancer, and neuroblastoma in particular, the clinical trial for frontline treatment at a particular cancer center is the standard of care believed by the center to be the best possible therapy at the time.

Information on clinical trials is discussed in Chapter 1, see **“What is a Clinical Trial?”**

Unfortunately, there is no single treatment proven to be effective against all cases of high-risk NB. All treatments for newly diagnosed high-risk NB share many components; however, where significant differences in protocols exist, they are due to continued efforts by research centers to increase survival rates by taking advantage of new discoveries about NB and new types of treatment. Currently, each of the national and international cooperative pediatric oncology groups, such as the Children’s Oncology Group (COG), the International Society of Paediatric Oncology (SIOP), and the German Society for Paediatric Oncology and Haematology (GPOH), have clinical trials specifically for newly diagnosed NB cases. In addition, some research centers, such as Memorial Sloan-Kettering

Cancer Center (MSKCC) and St. Jude Children's Research Hospital,¹ enroll children on their own frontline protocols. The chemotherapy agents (and their administration and dose), number of induction cycles, timing of stem cell collection, timing of surgery, type of radiation therapy, use (or not) of transplant, conditioning regimen for transplant, timing of Accutane, and use (or not) of immunotherapy and cytokines – all of these components differ somewhat in the various frontline protocols.

The summary below sets forth the general treatment approaches, and also highlights key differences.

Children's Oncology Group (COG):

The following is a basic overview of the frontline protocols utilized by COG for high-risk neuroblastoma (as of 2015).

Phase	Treatment	Average Duration*
Induction	Chemotherapy (6 cycles – ANBL0532): <ul style="list-style-type: none"> ▪ Cycles 1 and 2: cyclophosphamide and topotecan with G-CSF. ▪ Cycles 3 and 5: etoposide and cisplatin with G-CSF. ▪ Cycles 4 and 6: vincristine, cyclophosphamide and doxorubicin with G-CSF and mesna. 	7 Months. Stem-cell collection occurs after cycle 2.
	Surgery <ul style="list-style-type: none"> ▪ Typically occurs after the 5th cycle of chemotherapy. 	Day-long surgery with an approximate 1-3 week recovery.
Consolidation	Autologous Stem-Cell Transplant <ul style="list-style-type: none"> ▪ The conditioning chemotherapies are busulphan and melphalan (BuMel) (this regimen was adopted in 2013; carboplatin, etoposide, and melphalan (CEM) were used previously and may still be given in certain circumstances). 	Typically about a month in hospital if a single transplant is done. A tandem (double) transplant increases the time in hospital (2-3 months).
	Radiation Intensity-Modulated Radiation Therapy (IMRT) radiation typically used.	Typically 12 rounds (approximately 2 weeks and often done as out-patient)
Maintenance	Immunotherapy (6 courses – ANBL0032): <ul style="list-style-type: none"> ▪ Courses 1, 3 and 5: one-week hospital admission for infusion of antibody (ch14.18). Two weeks of GM-CSF (includes week in hospital), and two weeks of Accutane post infusion. ▪ Courses 2 and 4: Each often a two week hospital admission. First week IL-2 is infused 24hr/d for 4 days. Second week, IL-2 is infused 24hr/d with the antibody. Two weeks of Accutane post infusion. ▪ Course 6: Accutane at home. 	6 Months (5 in-patient admissions, last course is Accutane at home) Accutane is 13- <i>cis</i> -retinoic acid (13- <i>cis</i> RA).
Approximate treatment time:		15+ Months

* Note: These durations are averages and can be shorter or longer depending on the patient experience.

Memorial Sloan-Kettering Cancer Center (MSKCC):

The following is a basic overview of the frontline protocol(s) utilized by MSKCC for high-risk neuroblastoma (as of 2015).

Phase	Treatment	Average Duration*
Induction	Chemotherapy: <ul style="list-style-type: none"> ▪ Cycles 1, 2 and 4: Cyclophosphamide, doxorubicin and vincristine with G-CSF as needed. ▪ Cycles 3 and 5: Etoposide and cisplatin with G-CSF as needed. ▪ Cycle 6: Cyclophosphamide, vincristine and topotecan. 	5-7 rounds of chemotherapy. Stem cell collection typically occurs after cycle 3.
	Surgery: Surgery is typically done after the third round of chemotherapy but may be done later depending on the patient.	Day-long surgery with an approximate 1-3 week recovery.
Consolidation	Radiation IMRT radiation typically used.	Typically for 7-10 days, twice a day; often as out-patient, and may occur after the first cycle of immunotherapy.
Maintenance	Immunotherapy Involves multiple rounds of antibody therapy (3F8) tailored to the individual case; may be as follows. <ul style="list-style-type: none"> ▪ 2 rounds of high-dose 3F8 with GM-CSF every 4 weeks. ▪ 2 rounds of regular 3F8 with GM-CSF every 4 weeks. ▪ Regular 3F8 every 8 weeks for 2 years. 	Varies by the individual case, but can last up to 2 years.
	Differentiation Therapy Accutane	Approximately 6 cycles (2 weeks of Accutane and then a 2 week break)
Approximate treatment time:		2 1/2+ Years

* Note: These durations are averages and can be shorter or longer depending on the patient experience.

One important difference between the COG² and the MSKCC protocols is that MSKCC does not offer autologous stem-cell transplant during frontline therapy for high-risk neuroblastoma.³

International Society of Pediatric Oncology (SIOP):

The following is an overview of the frontline protocol (NCT01704716) utilized by SIOP in Europe for high-risk neuroblastoma (as of 2015) (<http://clinicaltrials.gov/show/NCT01704716>).

Phase	Treatment
Induction	<p>Patients are randomized into one of two arms for the induction phase of treatment. These are:</p> <p>Arm 1 Chemotherapy (Rapid COJEC):</p> <ul style="list-style-type: none"> ▪ 3 different courses are given every 10 days with G-CSF starting 24 hours after the last dose of chemotherapy in each cycle. These 3 courses are given over 10 weeks. ▪ COJEC refers to: cisplatin (C), vincristine (O), carboplatin (J), etoposide (E), and cyclophosphamide (C). ▪ Course A: Vincristine, carboplatin and etoposide (days 0 and 40). ▪ Course B: Vincristine and cisplatin (days 10, 30, 50, and 70). ▪ Course C: Vincristine, etoposide, and cyclophosphamide (days 20 and 60). <p>Arm 2: Chemotherapy:</p> <ul style="list-style-type: none"> ▪ Course A: Cyclophosphamide, doxorubicin and vincristine. ▪ Course B: Cisplatin and etoposide.
Stem Cell Harvest and Surgery	<ul style="list-style-type: none"> ▪ At the end of induction, the peripheral blood stem cell harvest is performed. ▪ Surgery, with an aim to completely remove the tumor(s).
Additional Chemotherapy Based on Response	<p>More Chemotherapy Possible:</p> <ul style="list-style-type: none"> ▪ If patients do not have an adequate response to induction, they will receive 2 cycles of topotecan, vincristine, and doxorubicin (TVD).
Consolidation	<p>Autologous Stem-Cell Transplant</p> <ul style="list-style-type: none"> ▪ Busulphan and melphalan (BuMel). <p>Radiation</p> <ul style="list-style-type: none"> ▪ Radiotherapy to the site of the primary tumor.
Maintenance	<p>Arm 1 Immunotherapy:</p> <ul style="list-style-type: none"> ▪ ch14.18/CHO (continuous infusion over 10 days^{4,5}) with subcutaneous (half dose) IL-2 and Accutane. <p>Arm 2 Immunotherapy:</p> <ul style="list-style-type: none"> ▪ ch14.18/CHO (continuous infusion over 10 days) without IL-2 and Accutane.

Gesellschaft fur Padiatrische Onkologie und Hamatologie (GPOH):

For more information about clinical trials open through GPOH for high-risk neuroblastoma, please see the National Institute of Health clinical trials website.⁶

Part 3: Induction

The induction phase is the initial or frontline phase of treatment aimed at ridding the body of all detectable NB using chemotherapy and surgery. Before starting treatment the patient will have a complete work-up of scans and tests to establish not only the diagnosis, but to determine the precise location of the primary tumor, the extent of the disease throughout the body, the stage and the risk assignment of the neuroblastoma. It is becoming increasingly standard that a biopsy of the tumor will be done to identify the genetic markers and other prognostic information about the patient's disease. Only then will the induction phase of treatment for high-risk neuroblastoma begin.

Central venous line (CVL)

Patients undergoing chemotherapy will have some type of central venous access device placed before chemotherapy begins. Usually a single or double Broviac™ or Hickman™ central line will be placed. Alternatively, some patients receive a single or double “port”—a device implanted under the skin that is accessed by a special needle. Some type of long-term, efficient and reliable venous access is crucial. In addition to chemotherapy treatments, the patient will need frequent blood and platelet transfusions, medications, fluids for hydration, “contrast” for scanning purposes, and blood samples drawn, all accomplished by IV. In particular, double access lines are required for stem cell transplant and immunotherapy. It wouldn't be possible for so many infusions and blood draws, over so many months and often several occurring simultaneously, to be accomplished by a succession of temporary IVs. However, all these needs can be easily managed through a central line or port with minimal trauma to the patient. The site of the Broviac or Hickman central line will be covered by a special protective dressing; this dressing will be changed and the site cleaned using sterile procedures, once a week or more depending on the patient's needs and the hospital's practice. Your nurse or nurse practitioner will explain this in detail, so that a family member(s) can handle the dressing change when the patient is at home.

Chemotherapy

During the induction phase of treatment, various combinations of chemotherapy are administered intravenously. Although the dosages of the chemotherapies will vary by protocol, induction chemotherapy for high-risk NB is invariably aggressive. At the time of diagnosis, high-risk disease has already spread beyond the primary site in approximately 50-70%⁷ of cases and is life-threatening. The goal is to attack the cancer aggressively and eradicate it as quickly and as completely as possible during frontline treatment.

The chemotherapy kills not only the cancer, but also other fast-growing cells such as the patient's hair, bone marrow, and the lining of the mouth. For this reason, after certain cycles most patients will have a period when the existing platelets and red and white blood cells have been virtually destroyed, usually requiring red blood and platelet transfusions until these cells have repopulated. During this time the patient will have very little immunity from opportunistic infections. The period when a patient has virtually no functioning immune system is known as “neutropenia.” If a patient develops a fever while neutropenic, this typically requires a hospital admission where blood cultures are taken (and possibly other types of cultures and swabs), broad-spectrum IV antibiotics are started, and the patient is closely monitored for possible infections.

After each cycle of chemotherapy, a growth factor known as G-CSF (“granulocyte colony stimulating factor”) is administered in almost all protocols to boost white cell count recovery. G-CSF is usually given as daily injections (subcutaneous) until the white cell count reaches a prescribed level (the exact number varies by institution). Your nurse or nurse practitioner will carefully teach a family member(s) how to administer these shots when the patient is at home.

Your hospital’s protocol will likely provide a schedule for the time between beginning each cycle of chemotherapy; however, in practice this is only an approximate guideline. Although the standard varies by institution, patients will be required to have a certain level of bone marrow function (e.g., platelets of 100,000) to begin a new cycle of chemotherapy. Each patient’s response to chemotherapy, the time required for the bone marrow to recover and the incidence of infections while neutropenic will vary greatly; moreover, the time needed to recover from chemotherapy often becomes longer with each cycle. Some patients may not be able to resume later chemotherapies for several weeks or even months. Although such delays usually cause anxiety, families should be mindful that these variations in experience are not determinative of a patient’s specific prognosis.

Coping with the impact of chemotherapy is discussed in Chapter 3, **“Coping with Treatment: Side Effects, Comfort Measures and Safety Precautions – Getting Through Chemotherapy and Surviving Neutropenia.”**

Stem Cell Harvest

Due to the impact of chemotherapy on a patient’s bone marrow, all high-risk NB treatment protocols currently (2015) include a collection of peripheral blood stem cells. A patient may have his/her stem cells infused back into the blood stream later in the treatment journey to help “rescue” the bone marrow and boost its production of white blood cells. Ideally, the collection is done as soon as the bone marrow is clear of NB. Early collection minimizes the stem cell exposure to chemotherapy and clear bone marrow minimizes the chance for contamination with NB tumor cells.

Whether or not the collected stem cells should be “purged” (i.e., subjected to a laboratory process to remove any NB cells) was answered by a recent randomized study (COG-A3973, 2001-2006), which showed purging stem cells did not increase patient outcomes.^{8,9} The advantage to *not* purging is that some of the stem cells could be damaged or lost in the purging process. It is possible that post-consolidation therapy, such as immunotherapy and Accutane are able to eliminate any cancer cells that may be present in the stem cell product. At this time, most institutions do not manipulate collected stem cells through an additional purging process.

The stem cell harvest may be done as early as after the second round of induction chemotherapy (COG, MSK, and GPOH) or as late as after the last round (SIOP). Stem cells are boosted after a cycle of chemotherapy by administering daily G-CSF shots for a week or more, until white blood count is high enough to begin collection. The G-CSF stimulates the bone marrow to push stem cells into the peripheral blood. For patients who require additional help with stem cell collection, a drug called plerixafor (Mozobil) has had some success in helping to move stem cells into the blood stream.

The stem cell collection is performed through a process known as “apheresis” using a dialysis machine. Blood is drawn and passed into a machine that spins the blood to remove certain stem cells (i.e., undifferentiated stem cells that are identified as “CD34+”), and then the blood is returned to the patient. Apheresis may be scheduled on an out-patient basis in the blood bank, or the patient may be admitted to the hospital, depending on the institution’s practice. The collection typically takes place over 2 days; however, it may be necessary to take more time to collect the desired number of stem cells. The patient is awake during the apheresis process and must stay in bed during that time. The procedure is not painful; however, younger patients may need a number of different activities to help the time pass since they must remain in bed and relatively still during the collection procedure.

The patient may or may not require placement of a special apheresis line or catheter to collect stem cells; this will differ from institution to institution. If an additional line is necessary, generally a temporary line is placed into the femoral vein, in the thigh/groin area (femoral line or femoral venous catheter). The femoral line is placed under general anesthetic and stays in during the collection days. It is typically removed when the procedure is done and removal can usually be accomplished without additional sedation. This process is usually done over a few consecutive days to collect enough stem cells.

The stem cells are tested for the presence of NB cells with very sensitive methods (e.g., “RT-PCR immunocytochemistry” is one method that you may hear described) and are used only if no NB cells are detected (i.e., no NB cells detected per 500,000 stem cells).¹⁰ The stem cells are divided into “rescue” doses (typically 2 million cells per kilogram of the patient’s weight for each rescue dose) and frozen with a preservative called DMSO (dimethyl sulfoxide). This preservative causes the distinct smell of “creamed corn” when thawed and reinfused in the patient during “rescue”. The cells will be tested for viability before use; there are cases of stem cells being used successfully as long as 8 to 10 years after collection.¹¹

Most protocols use the collected stem cells to help the patient recover from autologous stem cell transplant (ASCT) in the consolidation phase of treatment. However, even patients that do not undergo ASCT may have need for stem cells for other treatments (i.e., MIBG Therapy) and/or protocols. For example, some NB treatments, such as those for refractory or relapse cases, may be damaging to the bone marrow and a stem cell “boost” may be given to help rejuvenate bone marrow.

As noted above, generally at least 2 million cells per kilogram (of the patient’s weight) are targeted for one rescue; smaller rescues can still be successful but may result in longer times to engraftment. Most neuroblastoma patients are small at diagnosis (given the average age of 2), so it is also important to consider the potential growth of a child who might double or triple in size, thus requiring a much larger amount of cells for any potential future rescue. In the event a patient’s disease is deemed refractory (resistant to treatment) or relapses (recurs), having stem cells on hand can make the difference between qualifying for a promising new treatment or being ineligible. For this reason, it is advisable to discuss with your doctor the quantity of stem cells that will be collected, with an eye toward preserving options for any necessary long-term treatment.¹²

Surgery

Ideally, all high-risk NB patients undergo tumor resection, usually after receiving at least 3 cycles of chemotherapy. In some cases, a surgeon may be able to remove the primary NB tumor at biopsy, but this is rarely the case, because high-risk NB tumors usually grow invasively around major blood networks and organs. In most cases, chemotherapy helps shrink the tumor and makes removal less difficult, although resection of a high-risk NB tumor is still considered a major surgery and is often a challenging one. Parents can expect their children to be in the operating room at least five hours and sometimes as long as 12 hours or more.

See Chapter 3, “**Coping with Treatment: Side Effects, Comfort Measures and Safety Precautions – Surgery**” for information about caring for your child after surgery.

The scheduling of surgery varies according to different protocols. Surgery may be done after the third (MSKCC), fourth (GPOH), fifth (COG), or eighth cycle (SIOP) of induction chemotherapy.

The necessity of full removal (gross total resection) of the primary NB tumor in high-risk cases remains a subject of disagreement among some NB specialists. Some oncologists believe that total removal of the primary tumor, though desirable, is not a necessity because chemotherapy and radiation given after surgery will destroy any remaining disease, and they cite the possibility of surgical complications as a reason for some partial surgeries¹³. Others have concluded that complete resection is related to increased survival.^{14,15,16} For example, referring to this debate, Dr. Michael

LaQuaglia, author of “The Role of Surgery in the Treatment of Neuroblastoma” in the 2005 pediatric oncology text *Neuroblastoma* (Cheung & Cohn, eds.), says:

*“Despite doubts as to the feasibility, safety, and efficacy of surgical resection in high-risk neuroblastoma, the present consensus in the Children’s Oncology Group (COG), and European and Japanese cooperative groups is that an aggressive resection of loco-regional disease should be attempted. Surgery has an even more important role in low- and intermediate-risk disease.”*¹⁷

Parents with children who have tumors deemed to be unresectable often decide to seek another opinion from an NB surgeon with much experience in removing difficult tumors, such as Dr. Michael LaQuaglia in New York City, Dr. Robert Shamberger in Boston, Dr. Andrew Davidoff in Memphis, or Dr. Jed Nuchtern in Houston, among others. See Chapter 1, **U.S. Neuroblastoma Specialists**.

Additional Induction Treatment

At least one protocol has included “MIBG therapy” if remaining disease is detected by MIBG scan near the end of induction (and before transplant).¹⁸ MIBG therapy involves giving patients high doses of the iodine-131 isotope to target the disease. Work is also being done to understand the benefits of adding MIBG therapy into the induction phase of treatment for newly diagnosed patients, including those with a complete response to induction therapies¹⁹. See Chapter 3, **“Coping with MIBG Treatment”** for more information on this therapy.

Part 4: Consolidation

If the patient responds with a “complete response” (CR) or in some cases a “very good partial response” (VGPR), then he or she moves on to the next phase of treatment, called “consolidation.” The goal of consolidation therapy is the eradication of any cancer cells still remaining after induction chemotherapy and surgery, thus it “consolidates” the impact of the first phase of treatment. Consolidation therapy varies according to different protocols, primarily based on whether and to what extent stem cell transplant is used.

Stem Cell Transplant

Stem cell transplant (also referred to as “myeloablative” therapy) is currently the most frequently used form of treatment in the consolidation phase. Stem cell transplant refers to high-dose chemotherapy or other treatment so severely suppressing the bone marrow that a “transplant” or “rescue” infusion of stem cells is required. A rationale for this procedure is that the stem cells collected after a few cycles of chemotherapy have been treated for cancer, yet have been exposed to far less chemotherapy than the rest of the child’s bone marrow by the end of induction. Thus, the harvested stem cells are able to repopulate the bone marrow at the time of transplant. This enables the patient to receive an aggressive treatment intended to deliver a “consolidating,” deadly blow to any remaining NB cells, one which would be impossible without the “rescue.”

You will hear references to two different types of “transplants”:

1. **Autologous:** The stem cells used are the patient’s *own*.
2. **Allogeneic:** The source of stem cells is from a *donor*.

With very few exceptions, most NB stem cell treatments use autologous stem cells, since use of donor cells involves a significant potential for rejection and other difficult medical issues for the patient. Allogeneic stem cell transplants are more frequently used in Europe, and for relapsed patients.

For autologous stem cell transplants, the stem cells are almost always collected from the patient's peripheral blood, as described above in the section on "Stem Cell Harvest." Peripheral blood stem cells engraft much faster than cells surgically removed from the bone marrow, so "bone marrow transplants" are much less common in NB treatment today.²⁰ Terminology surrounding stem cell transplant can be confusing, as many different terms are used. You will see the synonymous terms "peripheral blood stem cell transplant" (PBSCT), "stem cell transplant" (SCT), "autologous stem cell transplant" (ASCT), "hematopoietic stem cell transplant" (HSCT), and "high-dose chemotherapy with stem cell rescue" (HDC/SCR) all used interchangeably.

Transplant has been frequently used since the 1980s for consolidation for high-risk NB. Three randomized studies totaling 1000 NB patients that accrued during the periods 1982-1985, 1991-1996, and 1996-2003 randomized patients in complete or very good partial remission after induction respectively to transplant versus either no further treatment, consolidation chemotherapy, or oral "maintenance" chemotherapy. All three studies showed that transplant improved event-free survival for this specific group of patients.^{21,22,23} A follow-up analysis of the Phase III study CCG-3891 (run from 1991-1996) was published in March 2009 and confirmed the long-term survival benefit to transplant versus continuing chemotherapy without stem cell transplant.²⁴ (Two statistical errors in this report were found in 2014; however, the corrected data did not change the COG's position on the use of high-dose chemotherapy and stem cell transplant for high-risk neuroblastoma.)^{25,26}

However, in considering these findings, one should be aware that these studies investigated the efficacy of transplant against either no further treatment or low-dose consolidation chemotherapy; were done at a time when induction chemotherapies were lower dose than some protocols now; and most significantly, the trials did not include monoclonal antibodies, now the standard of care in frontline protocols at virtually all institutions.

After these studies, autologous stem cell transplant was widely adopted for treatment of high-risk NB. The treatment regimen was changed to include the use of higher dose induction chemotherapy, using stem cells from peripheral blood rather than bone marrow, and local radiation rather than total body irradiation (TBI). The COG phase III transplant study, ANBL0532 accrued patients from 2007-2012, randomizing patients into either a single autologous stem cell transplant or a tandem (2 smaller transplants), which is followed by local radiation. As of 2015, the standard COG protocol for stem cell transplant is a single autologous stem cell transplant, with local radiation immediately after recovering from transplant.

It should be noted that there are variations in stem cell transplant regimens across institutions. Double²⁷ and triple²⁸ autologous tandem transplants have also been tested, as well as allogeneic transplants.^{29,30} Some institutions offer their own unique regimens for transplant, such as using donor or cord blood for the source of stem cells, or using a new combination of chemotherapy. Some institutions use protocols from closed trials.

Transplant conditioning regimens use "mega-doses" of chemotherapeutic agents—usually drugs not used in the induction phase. Until 2013, COG was using the drug combination of carboplatin, etoposide, and melphalan (CEM). Until recently the current European SIOP trial randomized children to one of two different chemo combinations: CEM (carboplatin, etoposide, melphalan) or BuMel (busulphan, melphalan); early results showed survival advantage to BuMel so randomization has stopped and all children on that trial get BuMel conditioning.³¹ (See "Appendix" below). In April 2013, COG officially changed their standard conditioning regimen from CEM to BuMel. However, even though COG and SIOP utilize BuMel as their standard high-dose chemotherapies, there is still the possibility of using the CEM regimen if there are specific patient concerns about the BuMel chemotherapies.

Stem cell transplant can be the most challenging phase of treatment for many patients and families. The chemotherapies are different from those used in the induction phase, the doses are higher and the side-effects can be more complicated to manage. It can involve an extended time period in

hospital as an inpatient and also under isolation protocols (e.g., often 30+ days in hospital). Patients can be hospitalized for considerably longer if they contract additional infections or experience other difficult side-effects (neither of which is uncommon) during this more prolonged time of neutropenia. There are often many different issues and side-effects that are faced through this phase of treatment. All of this must be carefully managed by an experienced medical team at your institution.

The IV stem cell infusion can be given in an out-patient setting and typically takes under one hour to complete. It is possible that the patient will be given a number of different pre-medications prior to the stem cell rescue such as Tylenol, Demerol (pethidine or meperidine), Benedryl and other drugs to proactively address possible allergic reactions. Pre and post-hydration are also given to help flush the DMSO out of the body (DMSO is the preservative added to the stem cells when they are frozen). The patient is typically asked to remain after the stem cell infusion for observation so that if an allergic reaction develops, that it can be dealt with immediately. With the hydration, medications, and stem cell infusion, this process can take the better part of a day to complete.

Stem cell transplant is a significant phase in the treatment of high-risk neuroblastoma. It is a complicated and multi-stage process that can be very challenging for some patients and require a long hospital stay. However, most patients are able to recover fairly well with few complications.

See Chapter 3, **“Coping with Treatment: Side Effects, Comfort Measures and Safety Precautions – Special Issues with Stem Cell Transplant”** for information to help you get your child through the transplant treatment.

A notable exception to the use of transplant for high-risk NB cases is MSKCC, whose frontline protocols do not include stem cell transplant. Doctors at MSKCC report that stem cell transplant has not improved survival rates of patients in their studies.³² After successful response to induction chemotherapy and surgery, patients on MSKCC’s current protocol move on to local radiation, 3F8 antibodies, and Accutane.

Whether or not to go forward with stem cell transplant is a difficult decision for some patients and families in their treatment journey. Because high-risk patients have been treated in such a wide variety of ways, there is no definitive study that quantifies the exact benefits or failures of stem cell transplant. Moreover, one cannot know in advance how difficult the treatment will be for the particular patient. It is a personal decision to be made in consultation with your medical team.

Radiation

Children diagnosed with high-risk disease routinely undergo radiation therapy after induction chemotherapy and surgery. In protocols that include stem cell transplant, radiation therapy usually begins after the patient is released from the hospital stay that follows transplant.

Even children whose tumors have been completely removed receive radiation to the primary site of disease. Some institutions also radiate bone sites where NB was present at diagnosis, even if those tumors have completely responded to chemotherapy; other treatment centers radiate only the spots still showing before transplant.

NB is generally responsive to radiation, but because intensive radiation treatment poses a significant risk of causing secondary cancers and other health issues, doctors try to use the minimum effective dose. Also, radiation beams must be carefully pinpointed to avoid damaging nearby organs. Patients undergo a thorough planning session with three-dimensional CT scan simulation before treatment starts, and they may be given tiny pinpoint tattoos to align the radiation beams. For patients receiving radiation to the head or orbits, a mask is made that can be fastened to the radiation table, so the patient does not move during the treatments. Similar “forms” may be made to hold a patient’s arm or leg in position, if treatment to those areas is necessary. Young children may have to be under general anesthesia for the planning session as well as for the radiation itself. Even for children old

enough to undergo this process while conscious, the tattooing, the fitting and wearing of a mask, and the experience of being fastened to a table and having to undergo the radiation without a parent present, can be frightening or anxiety-provoking. Many parents recommend seeking the support of the child-life services at the center to introduce the child to the procedure in advance.

Depending on the institution, radiation may be given once a day or possibly twice a day (once in the morning and once in the afternoon). The length of the radiation session will depend on how many areas are being radiated, whether the patient is sedated or not, and other concerns. It is possible that the radiation session could last from as little as twenty minutes in length, to as much as an hour. (However, during this time, the technician and often the parent will be in and out of the room several times, so the patient is not alone in the room the entire time.) The number of sessions will also depend on a number of factors and may range from 7 to 12 days, or possibly longer.

External beam, MIBG radiation therapy, total marrow irradiation (TMI or TomoTherapy), proton beam, radiosurgery (Gamma knife), intraoperative radiation therapy (IORT), and intensity-modulated radiation therapy (IMRT) are various ways radiation can be delivered, depending on the protocol and the patient's circumstances. The two most common types of radiation used for neuroblastoma treatment are external beam and proton beam radiation. A 2013 article³³ examined the differences between these two types and suggests that the decision between external and proton beam radiation must be carefully decided on a case-by-case basis for each patient. At this point in time, external beam radiation is most commonly used for neuroblastoma treatment.

Part 5: Maintenance

Starting in the late 1980s and early 1990s, oncologists began testing new therapies to *add* to existing consolidation treatment, ones hoped to increase survival yet also be less toxic. The rationale was that increasing the intensity and number of traditional therapies had not improved survival rates as desired—and had also come at the price of increased long-term effects for survivors. One of the things that makes NB so difficult to cure is the fact that even when it cannot be detected by scans, lab tests, or bone marrow biopsies, the disease can still be present in very small amounts in the body (called minimal residual disease, MRD). Doctors believe that this undetectable disease can sometimes smolder and grow, eventually coming back as relapsed NB, which is much harder to cure. Accutane and antibodies are two differing strategies that have been developed to help eradicate undetectable disease, and both are now widely used as part of consolidation therapy. Much research on vaccines against NB is also underway, but vaccines are currently being used exclusively for relapsed patients.

Monoclonal Antibodies (Immunotherapy)

Our bodies manufacture antibodies that create an immune response to bacteria, viruses, and other foreign substances to help keep us healthy. However, a patient's immune system generally will not attack NB because the cancer is a part of the patient's body. Monoclonal antibody therapy ("monoclonal" refers to development from *one clone*) uses mouse synthesized antibodies. Some of these antibodies, notable the 3F8 antibody used at MSKCC, are isolated from antibody forming immune cells produced by the spleen of the mouse and are known as "murine" antibodies. Others, such as the ch14.18 antibody used in COG protocols, use a portion of a murine antibody linked with human antibodies to create what is known as a "chimeric" antibody.

The antibodies used in NB treatment attach to a "disialoganglioside" molecule (a glycolipid or "fat-sugar" complex molecule) called GD2, which is found on most NB cells. Because the antibody is a foreign substance in the patient's body, it attracts the patient's own immune system and alerts it to attack the NB cell the antibody is attached to, and the cancer cell can be destroyed.

The monoclonal antibody ch14.18 is a standard treatment for high-risk neuroblastoma in all COG protocols and is currently offered to patients completing frontline treatment that include stem cell transplant.³⁴ Patients will receive the treatment if they meet the protocol's strict criteria on disease status (i.e., no progressive disease and organ/hematologic function). The *ch* prefix indicates the antibody is "chimeric" or part human (75%) and part mouse (25%) in its formulation. It is administered with drugs called "cytokines" that work to stimulate the patient's immune system and help augment the immune response to the antibody. The cytokines used in ch14.18 immunotherapy are GM-CSF and IL-2.

Testing of ch14.18 began in a randomized phase III study (COG-ANBL0032); however, after an early review of 226 patients, it was determined that patients had significantly higher survival rates with antibody therapy. The COG study was amended in April 2009 to stop randomization and allow patients subsequently enrolled to receive the antibody. After the early results of the COG ch14.18 trial were released in 2009, the current European SIOP trial was modified to randomize patients to ch14.18/CHO (ch14.18/CHO, manufactured via hamster cells) with the use of subcutaneous IL2 (half dose), or just ch14.18/CHO. In both arms of the trial, ch14.18/CHO is given by a continuous IV infusion over 10 days. GM-CSF is not used in either arm of the study as it is not available in Europe at this time.

In March 2015, United Therapeutics was issued an initial approval for ch14.18 by the Food and Drug Administration (FDA), the third drug in the history of the FDA to be approved for pediatric cancer. It is the first ever FDA approved immunotherapy drug for children. United Therapeutics produces the drug, which is now called Unituxin or dinutuximab³⁵.

ch14.18 is a very different treatment from chemotherapy and has a number of side-effects that must be carefully managed (such as pain, fluid retention, impacts on blood pressure, allergic reactions, fevers, and others). See Chapter 3, "**Coping with Treatment: Side Effects, Comfort Measures and Safety Precautions – Coping with ch14.18 Antibodies,**" for information about the scheduling, administration and side effects of ch14.18 antibody treatment.

A "third generation" antibody, hu14.18-IL2, given with GM-CSF and Accutane, is currently being used in a COG phase II trial for relapsed or refractory neuroblastoma.³⁶ The *hu* prefix means the antibody is completely humanized, and IL2 is directly fused to the antibody. St. Jude Children's Hospital is experimenting with giving immunotherapy in conjunction with the first cycles of chemotherapy in the induction phase of treatment. They have developed a version of ch14.18 called hu14.18K322A and are testing this in both frontline and relapsed/refractory settings.³⁷

It is important to note that long-term results on the efficacy of ch14.18 have not been published.

In contrast, MSKCC uses a 100% mouse-derived "3F8" antibody treatment for high-risk NB patients who complete induction therapy with a good response. 3F8 has been in use at MSKCC since 1986 and has been a part of all MSKCC's frontline NB protocols since 1990. It acts in a similar way to ch14.18 by attaching itself to the GD2 on the surface of the neuroblastoma cell, and then alerting the immune system to kill the cancer. GM-CSF (granulocyte-macrophage colony-stimulating factor—a "cytokine" that stimulates the immune system) is given with 3F8 as a subcutaneous injection.³⁸ The GM-CSF is started on the Wednesday before treatment and is given for all five days of the 3F8 treatment. 3F8 is typically delivered in an out-patient setting. Prior to the 3F8 infusion, patients are given a number of pre-medications to help manage side-effects. Benedryl, Claritin and famotidine (for allergic reaction), Tylenol (for fever), ondansetron/Zofran (for nausea) and morphine (for pain) are some drugs that may be given before, during, and after treatment. The main side-effects of 3F8 are pain, allergic responses (i.e., hives and rash), and fever. There are other possible side-effects that your care team will also discuss with you if you are pursuing this treatment.

Because 3F8 is 100% mouse derived, the body can develop an immune response that destroys the 3F8 before it can attack the NB. This is known as a HAMA (Human Anti-Mouse Antibody) response. A patient's HAMA level is determined through a blood test and if the level is over 1,000, the patient is considered to be HAMA positive and treatment is suspended. It is often the case that over time the HAMA response will recede and the patient will become HAMA negative again; however, it may also be necessary to use other means to break the HAMA. To achieve a HAMA negative status, additional chemotherapy to suppress the patient's immune system may be used (for example, a combination of rituximab, cyclophosphamide, and/or temozolomide).

MSKCC reports that their studies (which have tracked patients since 1986) have shown improved survival among their patients who successfully complete at least four cycles of 3F8 antibody therapy.³⁹ MSKCC has other formulations of 3F8 such as high-dose 3F8 and humanized 3F8 (hu3F8) that they are currently testing, mostly with relapsed and/or refractory patients.⁴⁰

It is important to note that the 3F8 antibody is proprietary to MSKCC and has not been subject to open, NIH approved Phase III clinical trials.

For more information on the administration and side effects of 3F8 antibodies, see Chapter 3, **“Coping with Treatment: Side Effects, Comfort Measures and Safety Precautions – 3F8 Antibodies.”**

Accutane

Accutane (isotretinoin or 13-*cis* retinoic acid or 13-*cis*RA) is a synthetic retinoid related to vitamin A that is most usually prescribed to treat severe acne. At doses approximately ten times higher, Accutane has been shown to stop the growth of NB cells. In addition, Accutane can cause some NB cells to mature and “differentiate” into non-cancerous cells. A five-year randomized study (CCG-3891, 1991-1996) concluded that high doses of Accutane improved the event-free survival for children in remission.⁴¹ Since those findings were published in 1999, the use of Accutane has become widely accepted for high-risk NB. A follow-up study in 2009⁴² continued to support the use of Accutane. (Two statistical errors in this report were found in 2014; however, the corrected data did not change the COG's position on the use of Accutane for high-risk neuroblastoma.)^{43,44}

Accutane is given by mouth in capsule form generally in two-week on/off cycles—the medicine is taken twice a day for two weeks and then children take no medication for two weeks. Typically, children receive Accutane over six months after completing all other frontline treatment. In the German NB2004 protocol it is given for six months with a three-month break, and then three more months.

Accutane has many side effects, but they are mostly an annoyance, such as dry skin, moodiness, and sun sensitivity. However, because of the high dose used in NB therapy, some of Accutane's side effects can occasionally be serious, patients are monitored during their Accutane treatment with regular check-ups and blood draws (particularly for calcium levels and triglycerides).

It is **extremely** important that pregnant women, and those who may become pregnant, follow strict safety precautions when handling Accutane, because ingestion of the drug (which can be absorbed through the skin) poses a risk of serious birth defects and deformities.

There are also several other important caveats about the proper administration of Accutane; for example, the contents of the capsule should not be exposed to light and not be mixed in liquids, and it's important for the entire dose to be ingested. Insofar as most NB patients are young children who have had significant medical intervention, swallowing Accutane pills can be a challenge requiring patience and creativity. For more information on administering Accutane and coping with its side effects, see Chapter 3, **“Coping with Treatment: Side Effects, Comfort Measures and Safety Precautions – Accutane.”**

Part 6: Summary

The above discussion provides a very general introduction to the common components of frontline treatment for children with high-risk neuroblastoma.

Researchers and oncologists continue to work towards understanding high-risk disease in hopes of further improving survival and tailoring treatment for more refined patient groups (i.e., ultra-high risk patients). The goal is to give patients the therapy that they need to attack the disease in the most effective way possible, while limiting the short- and long-term toxicities of treatment. Researchers are also experimenting with the addition of immunotherapy to the initial rounds of induction chemotherapy in hopes that this will have an expedited impact on disease burden, as well as experimenting with the use of various immunity boosters in tandem with antibodies.

Parents interested in learning more about any of the trials mentioned are advised to contact the doctor or institution in charge of the specific trial. Questions about the rationale, specific components and impact of your child's particular treatment should of course be directed to your child's oncologist. However, we hope that the information provided will make you feel better equipped for these discussions and more informed about what lies ahead in your child's treatment.

Please contact info@cncfhope.org with any comments

- 1 See: <http://www.stjude.org/stjude/v/index.jsp?vnextoid=85e0bfe82e118010VgnVCM1000000e2015acRCRD>
- 2 Matthay, K.K., London, W.B., Maris, J., Adamson, P.C., and Park, J.R. (2014). Reply to N.-K.V. Cheung et al. *Journal of Clinical Oncology*, Vol. 32, No. 6.
<http://jco.ascopubs.org/content/32/36/4174.full?sid=5428826d-ab19-4a0e-9796-2f0e5c526db8>
- 3 Cheung, N-K, Modak, S., Ostrovnaya, I., Roberts, S.S. Basu, E.M., Kramer, K, and Kushner, B.H. (2014). When Overall Survival Fails to Confirm Event-Free Survival, Should the Latter be Used to Set the Standard of Care? *Journal of Clinical Oncology*, Vol. 32, No. 36, pps. 4173-4174.
- 4 <http://www.apeiron-biologics.com/images/news/ASCO%202014%20Poster%20Lode%20et%20al.pdf>
- 5 <http://www.apeiron-biologics.com/images/news/ASCO%202014%20Poster%20Ladenstein%20et%20al.pdf>
- 6 <http://clinicaltrials.gov/ct2/results?term=Gesellschaft+fur+Padiatrische+Onkologie+und+Hamatologie+and+neuroblastoma&Search=Search>
- 7 Maris, J.M. (2007). Neuroblastoma. *The Lancet*, 369, 2106-2120.
- 8 Kreissman, S.G., Seeger, R.C., Matthay, K.K., London, W.B., et al. [Purged versus non-purged peripheral blood stem-cell transplantation for high-risk neuroblastoma \(COG A3973\) a randomized phase 3 trial.](#) *Lancet Oncology* 2013 Sept; 14(10): 999-1008.
- 9 Kreissman, S.G., Villablanca, J.G., Seeger, R.C., et al. [A randomized phase III trial of myeloablative autologous peripheral blood stem cell \(PBSC\) transplant \(ASCT\) for high-risk neuroblastoma \(HR-NB\) employing immunomagnetic purged \(P\) versus unpurged \(UP\) PBSC: A Children's Oncology Group study.](#) *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 10011).
- 10 Reynolds CP (June 2004). [Detection and treatment of minimal residual disease in high-risk neuroblastoma.](#) *Pediatr Transplant* 8 Suppl 5: 56-66.
- 11 Cheung & Cohn (eds), *Neuroblastoma*, Springer (2005), p. 182.
- 12 Grupp S.A., Cohn S.L., Wall D., Reynolds C.P. [Collection, storage, and infusion of stem cells in children with high-risk neuroblastoma: saving for a rainy day,](#) *Pediatr. Blood Cancer*, 46: 719-722, 2006.
- 13 Simon, T., Haberle, B., Hero, B., von Schweinitz, D., and Berthold, F. [Role of surgery in the treatment of patients with stage 4 neuroblastoma age 18 months or older at diagnosis.](#) *Journal of Clinical Oncology*, 2013 Feb 20; 31(6): 752-758.
- 14 LaQuaglia MP, Kushner BH, Su W, Heller G, Kramer K, Abramson S, Rosen N, Wolden S, Cheung NK, ["The impact of gross total resection on local control and survival in high-risk neuroblastoma,"](#) *J Pediatr Surg.*, 2004 Mar; 39(3):412-7; discussion 412-7.
- 15 Cantos MF, Gerstle JT, Irwin MS, Pappo A, Farley S, Cheang T, Kim PC, [Surgical challenges associated with intensive treatment protocols for high-risk neuroblastoma.](#) *J Pediatr Surg.* 2006 May; 41(5):960-5.
- 16 Adkins ES, Sawin R, Gerbing RB, London WB, Matthay KK, Haase GM (June 2004). [Efficacy of complete resection for high-risk neuroblastoma: a Children's Cancer Group study.](#) *J. Pediatr. Surg.* 39 (6): 931-6.
- 17 Cheung & Cohn (eds), *Neuroblastoma*, Springer (2005), p. 151
- 18 National Institutes of Health, Clinical Trials – [NB2004](#)
- 19 <https://clinicaltrials.gov/ct2/show/NCT01175356>
- 20 Cheung & Cohn (eds), *Neuroblastoma*, Springer (2005), p. 174
- 21 Pritchard J, Cotterill SJ, Germond SM, Imeson J, de Kraker J, Jones DR (2005). [High dose melphalan in the treatment of advanced neuroblastoma: results of a randomised trial \(ENSG-1\) by the European Neuroblastoma Study Group.](#) *Pediatr Blood Cancer* 44 (4): 348-57.
- 22 Matthay KK *et al*, [Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid.](#) *N Engl J Med.* 1999 Oct 14; 341(16):1165-73
- 23 Berthold F *et al*. [Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: a randomised controlled trial.](#) *Lancet Oncology* 2005; 6:649-658

-
- 24 Matthay KK, Reynolds CP, Seeger RC, *et al.* (March 2009). "Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study". *J. Clin. Oncol.* 27 (7): 1007–13. PMID 19171716.
- 25 Children's Oncology Group. (2014). CCG-3891 Long Term Outcome for Children with High-Risk Neuroblastoma: Additional Information on Corrected Overall Survival Results. Accessed online August 2014 at <http://www.childrensoncologygroup.org/downloads/CCG-3891%20Q%20and%20A%204-18-14.pdf>
- 26 Children's Oncology Group. (2014). Re. Correction in a Children's Oncology Group Scientific Publication. Accessed online August 2014 at <http://www.childrensoncologygroup.org/downloads/PatientFamilyLetter%20CCG-3891%20April%202014.pdf>.
- 27 George, Rani E., Li, Shuli, Medeiros-Nancarrow, Cheryl, Neuberg, Donna, Marcus, Karen, Shamberger, Robert C., Pulsipher, Michael, Grupp, Stephan A., Diller, Lisa, [High-Risk Neuroblastoma Treated With Tandem Autologous Peripheral-Blood Stem Cell-Supported Transplantation: Long-Term Survival Update](#). *J Clin Oncol* 2006 24: 2891-2896.
- 28 Kletzel M, Katzenstein HM, Haut PR, *et al* (May 2002). [Treatment of high-risk neuroblastoma with triple-tandem high-dose therapy and stem-cell rescue: results of the Chicago Pilot II Study](#). *J. Clin. Oncol.* 20 (9): 2284–92.
- 29 Verneris MR, Wagner JE (June 2007). [Recent developments in cell-based immune therapy for neuroblastoma](#). *J Neuroimmune Pharmacol* 2 (2): 134–9.
- 30 Willems, L., Waer, M., and Billiau, A.D. (2014). The Graft-Versus-Neuroblastoma Effect of Allogeneic Hematopoietic Stem Cell Transplantation, a Review of Clinical and Experimental Evidence and a Perspective on Mechanisms. *Pediatric Blood and Cancer*, Vol. 61, No. 12, pps. 2151-2157.
- 31 Ladenstein RL *et al*, [Busulphan-melphalan as a myeloablative therapy \(MAT\) for high-risk neuroblastoma: Results from the HR-NBL1/SIOPEN trial](#). *J Clin Oncol* 29: 2011 (suppl; abstr 2)
- 32 Cheung NK, [Reducing therapy for low-risk and advancing immunotherapy for high-risk neuroblastoma](#). 2007 ASCO Annual Meeting – Education Session: Embryonal Cancers I: Neuroblastoma--Recent Advances in Biology and Therapy
- 33 Hill-Kayser, C., Tochner, Z., Both, S., *et al*. [Proton versus photon radiation therapy for patients with high-risk neuroblastoma: the need for a customized approach](#). *Pediatric Blood and Cancer*, 2013 Oct; 60(10): 1606-11.
- 34 National Cancer Institute, Cancer Bulletin May 19, 2009 • Volume 6 / Number 10 "An Experimental Treatment Improves Survival for Patients with Neuroblastoma"
<http://www.cancer.gov/ncicancerbulletin/051909/page2>
- 35 <http://www.prnewswire.com/news-releases/neuroblastoma-expert-john-maris-md-available-to-discuss-fda-approval-of-unituxin-the-third-fda-approved-drug-ever-for-children-with-cancer-300049267.html>
- 36 [Biological Therapy, Sargramostim, and Isotretinoin in Treating Patients With Relapsed or Refractory Neuroblastoma](#)
- 37 Navid, F., Sondel, P. M., *et al*. [Phase I Trial of a Novel Anti-GD2 Monoclonal Antibody, Hu14.18K322A, Designed to Decrease Toxicity in Children With Refractory or Recurrent Neuroblastoma](#). *Journal of Clinical Oncology*, May 10, 2014 vol. 32 no. 14 1445-1452.
- 38 Cheung, N-K., Cheung, I.Y., Kushner, B.H., Ostrovnya, I., Chamberlain, E., Kramer, K., and Modak, S. (2012). Murine Anti-GD2 Monoclonal Antibody 3F8 Combined with Granulocyte-Macrophage Colony-Stimulating Factor and 13-Cis-Retinoic Acid in High-Risk Patients with Stage 4 Neuroblastoma in First Remission. *Journal of Clinical Oncology*, Vol. 30, No. 26, pps. 3264-3270.
- 39 Cheung NK, [Reducing therapy for low-risk and advancing immunotherapy for high-risk neuroblastoma](#). 2007 ASCO Annual Meeting – Education Session: Embryonal Cancers I: Neuroblastoma--Recent Advances in Biology and Therapy.
- 40 http://www.mskcc.org/cancer-care/clinical-trials/clinical-trial?keys=3f8&field_trial_diseases_value=Neuroblastoma&phase=All
-

-
- ⁴¹ Matthay KK *et al*, Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid, *N Engl J Med*. 1999 Oct 14; 341(16):1165-73
- ⁴² Matthay, K.K., Reynolds, C.P., Seeger, R.C., Shimada, H., et al. (2009). [Long-Term Results for Children with High-Risk Neuroblastoma Treated on a Randomized Trial of Myeloablative Therapy Followed by 13-cis-Retinoic Acid: A Children's Oncology Group Study](#). *Journal of Clinical Oncology*, Vol 27, No 7, pps. 1007-1013.
- ⁴³ Children's Oncology Group. (2014). CCG-3891 Long Term Outcome for Children with High-Risk Neuroblastoma: Additional Information on Corrected Overall Survival Results. Accessed online August 2014 at <http://www.childrensoncologygroup.org/downloads/CCG-3891%20Q%20and%20A%204-18-14.pdf>
- ⁴⁴ Children's Oncology Group. (2014). Re. Correction in a Children's Oncology Group Scientific Publication. Accessed online August 2014 at <http://www.childrensoncologygroup.org/downloads/PatientFamilyLetter%20CCG-3891%20April%202014.pdf>.