Overview of High-Risk Treatment
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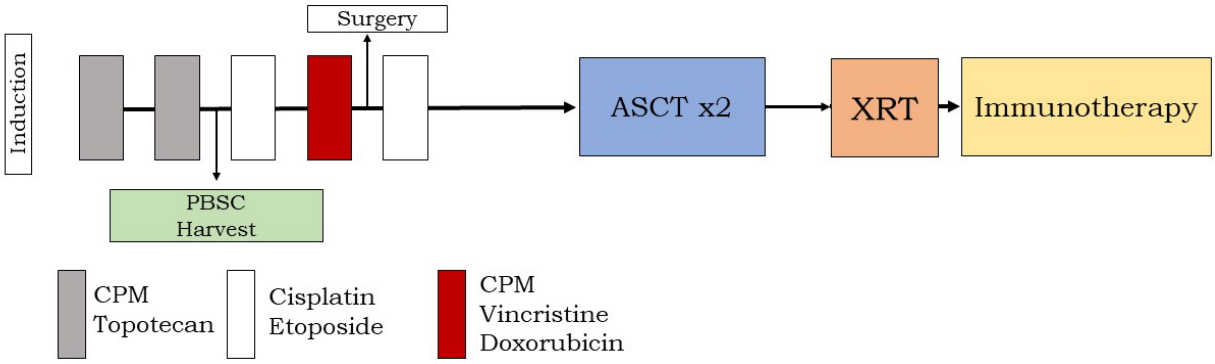
High-risk neuroblastoma (NB) requires intensive treatment with a combination of chemotherapy, surgery, radiation, stem cell transplant, and immunotherapy. The treatments for newly diagnosed high-risk NB are similar around the world, but there are some differences in approaches depending on your institution or currently available national and international clinical trials. These differences can include the types and administration of chemotherapy agents, timing of surgery, type of radiation therapy (or not), timing and type of transplant, and type of immunotherapy after transplant. Subtle changes in the treatment of high-risk NB are often a result of new scientific discoveries or experience of the treatment center, with the goal of improving survival rates for children.

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 ways to cope with them, are discussed in Chapter 3, "**Coping with Treatment: Side Effects, Comfort Measures and Safety Precautions**." Treatments for refractory and relapsed NB are discussed in the respective chapters Chapter 7, **"Treating Refractory NB"** and Chapter 8, **"Dealing with Relapse."** Information about clinical trials, contacting NB specialists for second opinions, and other matters that arise at diagnosis may be found in Chapter 1, **"Confronting the Diagnosis."**

The following summary has been prepared by a team of NB parents and pediatric oncologists with expertise in NB. This guide can be used to help you have informed and meaningful discussions with your team, with the understanding that some of this information may not directly apply to your child's specific case. You should always bring questions to your NB team, who can help you determine what is relevant to your child.

Example of high-risk NB treatment plan



PBSC = peripheral blood stem cell; ASCT = autologous stem cell transplant; XRT = radiation; CPM = cyclophosphamide

Central venous line (CVL)

CVLs are semi-permanent catheters usually placed prior to beginning chemotherapy. Most CVLs are placed by a surgeon under anesthesia. Some type of central (in a large vessel) venous access is necessary for chemotherapy treatments and eventual stem cell harvest and transplant. Additionally, CVLs are helpful for blood and platelet transfusions, IV medications, and fluids for hydration. And throughout treatment, blood samples are needed quite frequently, and these can be easily obtained through a central line with minimal trauma to the child. The type of CVL may vary -- usually a double lumen Broviac™ or Hickman™ central line will be placed, although some children receive a single or double "port"—a device implanted under the skin that is accessed by a special needle.

Induction Phase

The initial phase of treatment is called **"induction"**, and the goal is to eliminate as much detectable NB from the body as possible. Induction consists of multiple rounds of chemotherapy as well as surgery to remove the tumor and any affected lymph nodes. Typically, at the end of induction there are tests (which can include scans, blood work, and bone marrow biopsies) to monitor response to treatment. If the child is showing a response to induction treatment, they will move on to next phase of treatment called "consolidation." Often, a "complete response" (CR) is not required to move on to the next phase of treatment, but this should be discussed with your NB team.

Chemotherapy

There are various combinations and schedules of induction chemotherapy for high-risk NB. In general, a "cycle" of chemotherapy is approximately 21 days (in the US), with the chemotherapy medications administered intravenously over the first few days of the cycle, followed by a recovery time. During this recovery time, the team will check labs frequently, and the child may require blood transfusions or IV fluids. This induction chemotherapy usually consists of 5-8 cycles, and the chemotherapy is most often given while admitted to the hospital.

Chemotherapy Agents used in Selected High-Risk Induction Protocols

Study group	COG[1]	SIOP[2]	GPOH[3]	MSK[4,5]
phase	III	III	III	pilot N7
date open	2024	2002	2005	1994-99
accrual	478	1000	360	31
cycles	5	8	6/8*	5
length of cycle, days	21	10	21	21
cisplatin	x	x	x	x
carboplatin		x		
cyclophosphamide/Cytoxan	x	x	x	x
doxorubicin/Adriamycin	x		x	x
etoposide/VP-16	x	x	x	x
vincristine	x	x	x	x
topotecan	x		x*	
vindesine			x	
dacarbazine			x	
ifosfamide			x	

**GPOH randomizes half enrolled to extra two cycles containing topotecan.*
***MSK began using N7 in 1990, reduced number of cycles from 7 to 5 in 1994, accrued 31 patients on N7 from 1994-1999*

COG Children's Oncology Group; SIOP International Society of Pediatric Oncology; GPOH German Pediatric Hematology Oncology Group; MSK Memorial Sloan-Kettering Cancer Center, New York

Growth Factor. One side effect of chemotherapy is decreasing the number of neutrophils in the blood (neutropenia). Neutrophils are important for protecting the body against infection, and so a growth factor is administered after each cycle of chemotherapy to boost neutrophil count recovery. Granulocyte colony stimulating factor (G-CSF) can be given as a one-time subcutaneous injection (pegfilgrastim or Neulasta®) or a daily injection until the neutrophil count reaches a prescribed level (filgrastim or Neupogen®).

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

Stem Cell Harvest

All high-risk NB treatment protocols currently include a collection of peripheral blood stem cells, which are stored for later use during high intensity treatments (such as stem cell transplant or ^{131}MIBG therapy). This collection is commonly done after Cycle 2 of chemotherapy, but the timing may vary. Relatively early collection reduces the stem cell exposure to chemotherapy while still treating NB cells that may be in the bone marrow. It is not necessary to give extra treatment to children who had NB cells in their bone marrow at diagnosis before collecting stem cells. In general, there are extremely low levels of NB cells in the marrow after starting treatment, and even less neuroblastoma cells circulating in the blood. Additionally, a large, randomized trial (COG A3973) found that "purging" stem cells (i.e., removing NB cells from the stem cell collection bag) did not increase survival rates.[6] The advantage to *not* purging is that some of the stem cells could be damaged or lost in the purging process.

The collection process starts with boosting the number of stem cells in the body. This is done by administering daily G-CSF shots after a cycle of chemotherapy, which stimulates the bone marrow to push stem cells out into the peripheral blood, where they can be collected. These shots are typically given for a week or more until the white blood count reaches a high enough level. The collection is performed through a process known as **"apheresis."** Blood is drawn from the child's existing central line or a specially placed temporary apheresis central line and passed into a machine that spins the blood to remove stem cells (those identified as "CD34+"), and then the blood is returned to the child. Apheresis may be scheduled as an outpatient or your child may be admitted to the hospital, depending on the institution's practice. The apheresis process is usually done over 4-6 hours, but may also require repeated consecutive days to collect enough stem cells. The stem cells are divided into "rescue" doses and frozen with a preservative called DMSO (dimethyl sulfoxide; this causes the distinct smell of "creamed corn" when thawed and reinfused in the child during "rescue"). The cells will be tested for viability before use and have been used successfully as long as 8 to 10 years after collection.[7]

The most common use for the collected stem cells is in the setting of autologous stem cell transplant (ASCT) in the consolidation phase of treatment. However, even children who do not undergo ASCT may have need for stem cells later, as some NB treatments may be damaging to the bone marrow and a stem cell "rescue" may be given to help the bone marrow recover. For example, treatment with ^{131}MIBG is often followed by a stem cell rescue. Having additional frozen stem cells available could also be helpful for potential future treatments, should the NB not respond to initial treatment or recur.

Surgery

Most children will first have a biopsy in order to diagnose the NB. It is then usually after receiving some chemotherapy that high-risk NB patients undergo resection of their primary tumor. The timing varies according to different protocols. NB tumors are notorious for growing tightly around important blood vessels and organs, and so although some tumors are removed upfront, this is rare. Chemotherapy helps shrink the tumor and makes removal less difficult, although resection of a high-risk NB is still a difficult and major surgery. The surgical team carefully plans the surgery to remove the primary tumor as well as all suspicious nearby lymph nodes while aiming to spare organs (such as the kidney). Parents should expect their children to be in the operating room at least five hours and sometimes 12 hours or longer.

The overall goal for surgery in high-risk patients with NB is the most complete tumor resection with as much preservation of organ function as possible. This balances the short- and long-term risks of the surgery with the goal of curing the disease. The importance of full removal (gross total resection, GTR) in high-risk cases remains somewhat unclear. There are no large randomized clinical trials comparing GTR to not having a GTR, as this is heavily dependent on the individual child's tumor and surgical experience (and would not be ethical to offer GTR to some children and not others). Some older retrospective studies suggest that a GTR might be related to increased survival.[8,9,10] Whereas, some newer data implies that survival is not affected by achieving a GTR, although it is likely that the more tumor that can be removed, the better.[11] You should have thorough discussions with your child's team about surgical plans, risks and benefits of different approaches, and expectations for recovery.

Consolidation Phase

Consolidation therapy is anti-cancer treatment given when a child is in complete remission (CR) or partial remission (PR), aimed at killing any remaining cancer cells. Consolidation therapy varies according to different protocols.

Stem Cell Transplant

Stem cell transplant is currently the most frequently used form of consolidation. Terminology surrounding stem cell transplant can be confusing, as many terms used are synonymous. *Autologous* means the stem cells are one's *own,* and *allogeneic* means the source of stem cells is a *donor*. Most NB treatments use autologous stem cells collected from the patient's peripheral blood. Peripheral blood stem cells engraft much faster than stem cells taken from the bone marrow, so "bone marrow transplants" are much less common in NB treatment today.[12] 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.

Stem cell transplant is high-dose chemotherapy or other treatment so severely suppressing the bone marrow that a subsequent "transplant" or "rescue" infusion of stem cells is required. A rationale for this procedure is that the stem cells collected after a couple cycles of chemotherapy have been exposed to *less* chemotherapy than the rest of the child's bone marrow by the end of induction. The harvested stem cells then repopulate the bone marrow at the time of transplant, and incidence of secondary leukemia after stem cell transplant has been reported to be very low.[13] [14]

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 children to transplant versus no treatment, consolidation chemotherapy, or oral "maintenance" chemotherapy respectively, and all three showed improved

survival with transplant. [15,16,17] A follow-up study of the Phase III study CCG-3891 was published in March 2009 confirming long-term survival benefit to transplant.[18]

Subsequently, autologous stem cell transplant has been widely adopted for treatment of high-risk NB. Double[19] and triple[20] autologous tandem transplants have also been tested in pilot studies, as well as allogeneic transplants.[21]

The phase III study COG-A3973, as noted above, showed no need for purging stem cells used for rescue at transplant, and other important changes in treatment adopted for that study included 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 most recent COG phase III transplant study, ANBL0532, began accruing patients in December 2007 and randomized them to either a single or double (tandem) autologous stem cell transplant with local radiation. This study showed a significant benefit for children receiving tandem transplant and has been adopted as the standard of care at most centers in North America.

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, or using triple tandem transplants, and some institutions use protocols from closed trials. Most conditioning regimens use mega-doses of chemotherapeutic agents—usually drugs not used in the induction phase—while less common regimens use chemo with total body irradiation (TBI) or MIBG radiation therapy. Until recently the current European SIOP trial randomized children to one of two different chemo combinations: CEM (carboplatin, etoposide, melphalan) or BulMel (busulphan, melphalan) and early results showed survival advantage to BulMel so randomization was stopped and all children on that trial received BuMel conditioning.[22] (*See* "Appendix" below).

See Chapter 3**, "Coping with Treatment: Side Effects, Comfort Measures and Safety Precautions – Special Issues of 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 MSK, whose frontline protocols have not included stem cell transplant since 2004 and instead use antibody treatment for consolidation. After successful response to induction chemotherapy and surgery, patients on MSK's current protocol move on to local radiation, anti-GD2 antibodies, and isotretinoin (Accutane).

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 following stem cell 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 places radiate only the spots still showing before transplant. At least one protocol includes MIBG radiation therapy if remaining disease is detected by MIBG scan before transplant.[23]

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, so children undergo a planning session with three-dimensional CT scan simulation before treatment starts. They may receive tiny pinpoint tattoos that are used to align the radiation beams. For children receiving radiation to the head or orbits, a mask is made that can be fastened to the

radiation table, so the child does not move during the treatments. Similar "forms" may be made to hold a child's arm or leg in position, if treatment to those areas is necessary.

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.

Post-Consolidation

One of the things that makes NB so difficult to cure is the fact that even when it cannot be found through scans, lab tests, or bone marrow biopsies, the disease can still be present in very small amounts in the body. Doctors believe that this undetectable disease can sometimes smolder and grow, eventually coming back as relapsed NB, which is much harder to cure. The last phase of standard therapy for high-risk NB is called "post-consolidation." This phase of treatment uses monoclonal antibodies and isotretinoin. Isotretinoin and antibodies are two strategies that have been developed to help eradicate undetectable disease, but the two work in very different ways.

Isotretinoin

Isotretinoin (Accutane or 13-*cis* retinoic acid) is a synthetic vitamin A derivative that has been shown to stop the growth of NB cells. Isotretinoin can cause some NB cells to mature (differentiate) into non-cancerous cells. A five-year (1991-1996) randomized study (CCG-3891) concluded that high doses of isotretinoin improved the event-free survival for children in remission.[24] Since those findings were published in 1999, the use of isotretinoin has become widely accepted for high-risk NB.

Isotretinoin is given by mouth in capsule form in two-week on/off cycles—the medicine is taken twice a day for two weeks, then children take no medication for two weeks. Typically, children receive Isotretinoin over six months. 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. Because some of isotretinoin's side effects can be more serious, children are monitored during their isotretinoin treatment with regular check-ups and blood draws (particularly for calcium levels, liver enzymes and triglycerides).

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

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."**

Immunotherapy

Our bodies manufacture antibodies that create an immune response to bacteria, viruses, and other foreign substances to help keep us healthy. Ordinarily, a child's immune system will not attack NB because the cancer is a part of the child's body. Monoclonal antibody therapy (*monoclonal* refers to development from *one clone*) uses mouse antibodies produced in the laboratory from plasma (myeloma) cells. The antibodies used in NB treatment attach to a ganglioside (a glycolipid or "fat-sugar" complex molecule) on the NB cell called GD2. Because the antibody alerts the child's own

immune system to attack the NB cell the antibody is attached to, the cancer cell is destroyed. Long-term immune response may be initiated by antibody treatments in some cases.

A randomized Phase III COG study (COG-ANBL0032) showed that giving the monoclonal antibody dinutuximab (also referred to as ch14.18 or Unituxin), administered with "cytokines" to augment the immune response to the antibody, to patients following completion of induction chemotherapy, surgery, autologous stem cell transplant and radiation. After an early review of 226 children enrolled determined significantly higher survival with antibodies, the study was amended in April 2009 to stop randomization and allow all patients subsequently enrolled to receive the antibody.[25] [26] The *ch* prefix indicates the antibody is "chimeric" or part human (75%) and part mouse (25%) in its formulation. In 2015, dinutuximab received FDA approval for the treatment of high-risk neuroblastoma, the first FDA-approved drug for this disease. Dinutuximab is the current standard of care for remission maintenance at most centers in North America, Australia and New Zealand, and is currently being studied as an addition to induction chemotherapy (*See* **"Induction"** above*)* in the COG Phase 3 randomized trial, ANBL2131. Another type of ch14.18 antibody, dinutuximab-beta (also referred to as Qarziba), has been approved for use in Europe by the European Medicines Agency.

MSK has developed their own GD2 antibody, hu3F8 (Naxitamab), that has been used to treat some patients with relapsed neuroblastoma and has conditional approval from the FDA for use in patients with relapsed high-risk disease in the bone and/or bone marrow spaces only. MSK is required to conduct further research to confirm its clinical benefit in children fitting these criteria. 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 – "What to expect with Naxitamab"**

Remission Maintenance Studies

High-risk neuroblastoma can still relapse after patients achieve a remission, and so many centers are researching therapies that could be given as maintenance to prevent relapse. Some examples of these strategies are outlined below.

Vaccines

Various vaccines against NB have been created and tried in relapsed and refractory children, with the goal of creating the body's own GD2 and/or GD3 antibodies in patients in order to prevent neuroblastoma relapse. MSK is currently evaluating a GD2/GD3 vaccine in patients with high-risk neuroblastoma who are in remission either after upfront treatment or after a relapse.

DFMO

DFMO (difluoromethylornithine) is an orally administered drug that can be given to patients in remission. This drug is thought to inhibit an enzyme critical for neuroblastoma cell growth and is capable of killing neuroblastoma cells at very high doses. Lower doses of this drug were studied in a non-randomized trial of post-remission DFMO through the Beat Childhood Cancer consortium. In December 2023, the FDA granted approval for DFMO in patients with high-risk NB who have had at least a partial response to multiagent therapy, including anti-GD2 immunotherapy.

Summary

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

Please contact info@cncfhope.org with any comments

APPENDIX

A brief history of *phase III* studies for high-risk neuroblastoma

Treatment randomized in bold.

1982-1985: European Neuroblastoma Study Group (ENSG1) enrolled 167 children and randomized to melphalan autologous **bone marrow transplant or no further therapy** (no radiation therapy given to any). Transplant and no-transplant arms each had 65 patients, and recent long-term follow-up report revealed better 5-year event-free survival for stage 4 over 1 year old in melphalan-transplant group versus no further treatment.[27]

1990-1999: European study (EU-20592 or CCLGNB-1990-11) randomized 262 high-risk children over 1 year old and revealed higher survival rate for **rapid sequence induction** (10-day cycle) versus **standard induction** (21-day cycle) with same total dose. Ten-year event free survival was 27% and 18% respectively with non-aggressive surgical approach, no radiotherapy, and melphalan-only autologous bone marrow or stem cell transplant for both groups.[28]

1991-1996: Phase III trial with two sequential randomizations for 379 high-risk NB patients was carried out by the Children's Cancer Group (CCG-3891) which demonstrated improved survival with **myeloablative therapy** (with total body irradiation) and **13-*cis*-retinoic acid** (Accutane) with 50 patients in each of the four arms of the study.[29]

1996-2003: The German (GPOH) study NB97 compared outcomes of 295 high-risk NB patients randomized for **stem cell transplant** or **consolidation chemotherapy**. Results showed increased survival with transplant.[30]

2000-2006: The recent study (COG-A3973)[31] questioned the need for **purged stem cells** for CEM-LI (carboplatin, etoposide, melphalan, with local irradiation)[32] transplant, and accrued 486 patients. Purging stem cells was not found to improve survival.[33]

2000-2012: An additional study (COG-ANBL0032)[34] determined that the **antibody ch14.18** with interleukin 2 and GM-CSF improved survival when given after stem cell transplant (early analysis prompted the end of the randomization portion in April 2009) and will accrue a total of 423 patients.[35]

2002-2008: SIOP (International Society of Paediatric Oncology) formed the European SIOP Neuroblastoma Group (ESIOP NB) in 1994[36] and activated a phase III high-risk NB protocol in 2002 (SIOP-EUROPE-HR-NBL-1)[37] using "rapid" COJEC (8 cycles of chemotherapy given at 10-day intervals) followed by transplant randomization to CEM (carboplatin, etoposide, melphalan) or BuMel (busulfan, melphalan) and then randomization to with or without **ch14.18/CHO antibody** treatment. This study will also evaluate the use of **growth factors** as well as compare **transplant regimens**, and all patients receive *cis*-retinoic acid. This trial will accrue 1000 patients (175 per year). There are eight arms to this study. As of 2011, G-CSF, transplant regimen, and ch14.18/CHO are no longer randomized. All receive G-CSF between chemotherapy cycles, busulfan/melphalan for transplant conditioning, and all receive ch14.18/CHO with randomization for **subcutaneous IL2** or no IL2.

2005-2010: The current German NB2004 **randomizes topotecan** use in up-front therapy, includes MIBG therapy for positive lesions before transplant, and will accrue a total of 340. After transplant, the high-risk protocol includes six months of *cis*-retinoic acid, a three-month break, and another three months of retinoic acid. [38,39]

2007-2015: The COG phase III ANBL0532[40] trial opened December 2007 for accrual of 495 and compared **single versus tandem transplants**,and showed that patients who received tandem transplants had a lower likelihood of experiencing a relapse at 5 years.[41]

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