Overview of High-Risk Treatment

All treatments for newly diagnosed high-risk NB share many components, but differences in protocols do exist, due to continued efforts to increase survival rates using various approaches. 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 for newly diagnosed NB cases. In addition, some hospitals or groups of hospitals 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 isotretinoin (cis-retinoic acid or Accutane), and use (or not) of antibodies and cytokines – all of these components differ somewhat in the various frontline protocols.

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 NB parents in the hope it will help you have a more meaningful dialogue with your NB team – who is always the ultimate source of information about NB treatments and their relevance to your child's specific case.

Induction Phase

The induction phase is the initial phase of treatment aimed at ridding the body of all detectable NB using chemotherapy and surgery. During induction the child will have a central venous line placed, then undergo chemotherapy, surgery to remove the primary tumor and affected lymph nodes, stem cell harvest, and tests, scans, and bone marrow biopsies to monitor response to treatment. If the child responds with a "complete response" (CR) or in some cases a "very good partial response" (VGPR), he or she moves on to next phase called "consolidation."

Central venous line (CVL)

Children undergoing chemotherapy 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, although some children receive a single or double "port"—a device implanted under the skin that is accessed by a special needle. Some type of venous access is necessary because in addition to chemotherapy treatments, the child will need blood and platelet transfusions, IV medications, and fluids for hydration. Double lines are required for stem cell transplant. In addition, blood samples are needed quite frequently, and these can be easily obtained through a central line or port with minimal trauma to the child. For additional information, see Chapter 3, **"Central Venous Lines: Broviacs, Hickmans, & Ports."**

Chemotherapy

Various combinations of high-dose chemotherapy are administered intravenously for a few days out of approximately every 21 days (or 10 days in Europe), for five to eight cycles, usually inpatient. The table below lists the agents used in various protocols, but the dosages are not all the same. (This is *not* an exhaustive list of current protocols.)

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	2007	2002	2005	1994-99
accrual	495	1000	360	31
cycles	6	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/Adriamyacin	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

For example, the COG protocol uses six cycles, the German protocol uses either six or eight cycles (half are randomized to two extra cycles of topotecan), and the European SIOP protocol uses eight 10-day cycles of a rapid chemotherapy administration (termed "Rapid COJEC"). MSK's protocol uses five cycles of induction chemo.

Growth Factor. A growth factor (granulocyte colony stimulating factor or G-CSF) is administered in most protocols after each cycle of chemotherapy to boost white cell count recovery. G-CSF is usually given as daily injections until the white cell count reaches a prescribed level. The use of G-CSF was randomized in the current SIOP protocol in Europe, but after determining children fare better with the use of G-CSF, all children now get G-CSF between cycles of chemotherapy on that trial[6] (*see* appendix below).

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, *ideally* 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 the recent (2000-2006) randomized study COG-

A3973, which showed purging stem cells did not increase survival rates.[7] The advantage to *not* purging is that some of the stem cells could be damaged or lost in the expensive purging process.

The 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. This stimulates the bone marrow to push stem cells out into the peripheral blood.

The collection is performed through a process known as "apheresis." Blood is drawn and passed into a machine that spins the blood to remove certain stem cells (those identified as "CD34+"), and then the blood is returned to the child. Apheresis may be scheduled on an outpatient basis in the blood bank, or your child may be admitted to the hospital, depending on the institution's practice. Your child may or may not require placement of a special apheresis line or catheter to collect stem cells. This process is usually done over a few consecutive days to collect enough stem cells. At least 2 million cells per kilogram (child's weight) are required for one rescue. The stem cells are tested for the presence of NB cells with very sensitive methods (RT-PCR immunocytohistochemistry) and used only if no NB cells are detected (i.e., no NB cells detected per 500,000 stem cells).[8] 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.[9]

Most protocols use the collected stem cells for autologous stem cell transplant (ASCT) in the consolidation phase of treatment. However, even children that 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 "boost" may be given to help rejuvenate bone marrow.

In the event a child'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 any necessary long-term treatment.[10] Most neuroblastoma patients are small at diagnosis (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 a future rescue.

Surgery

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 are invasive and notorious for growing around major blood networks and organs. The surgeon carefully plans the surgery to remove the primary tumor as well as all suspicious lymph nodes while aiming to spare organs. Chemotherapy helps shrink the tumor and makes removal less difficult, although resection of a high-risk NB is still considered a difficult and major surgery. Parents should expect their children to be in the operating room at least five hours and sometimes as long as 12 hours or more.

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

The necessity of full removal (gross total resection) in high-risk cases remains a subject of controversy 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 subsequent to surgery will destroy any remaining disease, and cite complications in difficult surgeries. Others have

concluded that complete resection is related to increased survival.[11,12,13] For example, referring to this controversy, 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."* [14]

Parents with children who have tumors deemed to be unresectable often decide to seek another opinion from an experienced NB surgeon who routinely removes 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**.

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

Consolidation Phase

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

Stem Cell Transplant: 1, 2, 3 or 0?

Stem cell transplant (also referred to as *myeloblative* therapy) 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 cells surgically removed from the bone marrow, so "bone marrow transplants" are much less common in NB treatment today.[15] 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.[16] [17]

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. [18,19,20] A follow-up study of the Phase III study CCG-3891 was published in March 2009 confirming long-term survival benefit to transplant.[21]

Subsequently, autologous stem cell transplant has been widely adopted for treatment of high-risk NB. Double[22] and triple[23] autologous tandem transplants have also been tested in pilot studies, as well as allogeneic transplants.[24]

The recent 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 TBI. The current COG phase III transplant study, ANBL0532, began accruing patients in December 2007 and randomizes them to either a single or double (tandem) autologous stem cell transplant with local radiation (no TBI).

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 has stopped and all children on that trial get BuMel conditioning.[25] (*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. Doctors at MSKCC say they have not observed myeloablative consolidation treatments to have a significant impact on survival rates in their studies over the past 15 years.[26] After successful response to induction chemotherapy and surgery, patients on MSK's current protocol move on to local radiation, 3F8 antibodies, and 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.

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.[27]

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.

For information on helping your child cope with radiation therapy, *see* Chapter 3, **"Coping with Treatment: Side Effects, Comfort, and Safety – Radiation: From Tattoos to Side Effects."**

Treating Minimal Residual Disease

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. Accutane and antibodies are two strategies that have been developed to help eradicate undetectable disease, but the two work in very different ways. Much research on vaccines against NB has been accomplished, but use after frontline therapy is a new development.

Accutane

Accutane (isotretinoin or 13-*cis* retinoic acid) is a synthetic vitamin A derivative that has been shown to stop the growth of NB cells. Accutane 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 Accutane improved the event-free survival for children in remission.[28] Since those findings were published in 1999, the use of Accutane has become widely accepted for high-risk NB.

Accutane 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 Accutane 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 Accutane's side effects can be more serious, children 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.

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."**

Monoclonal Antibodies

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.

COG currently offers a phase III study (COG-ANBL0032) of the monoclonal antibody ch14.18 (administered with "cytokines" to augment the immune response to the antibody) to patients following completion of frontline treatment protocols that include stem cell transplant. 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. The study will continue until final accrual goal of 423 is met, and it is

anticipated that ch14.18 will be part of standard treatment for all COG protocols.[29] [30] The *ch* prefix indicates the antibody is "chimeric" or part human (75%) and part mouse (25%) in its formulation. After the early results of the COG ch14.18 trial were released in 2009, the current European SIOP trial was modified to randomize children to ch14.18/CHO (ch14.18/CHO, manufactured via hamster cells) with the use of subcutaneous IL2, or just ch14.18/CHO, and GM-CSF is not used. A "third generation" antibody, hu14.18-IL2, given with GM-CSF and Accutane is in a COG phase II trial now (only for relapsed or refractory neuroblastoma).[31] The *hu* prefix means the antibody is completely humanized, and IL2 is directly fused to the antibody. *See* Chapter 3, **"Coping with ch14.18 Antibodies**"

MSK uses a 100% mouse-derived 3F8 antibody treatment for high-risk patients who complete induction therapy with a good response. GM-CSF (granulocyte-macrophage colony-stimulating factor—a "cytokine" that stimulates the immune system) is usually given with 3F8. This antibody has been in use for two decades. MSKCC reports that their studies have shown improved survival among their patients who successfully complete at least four cycles of 3F8 antibody therapy.[32] 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."**

Vaccines

Various vaccines against NB have been created and tried in relapsed and refractory children, but recently the CHESAT vaccine became available in a trial In Houston TX for children who have successfully completed frontline therapy with a single transplant.[33]

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.[34]

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.[35]

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.[36]

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.[37]

2000-2006: The recent study (COG-A3973)[38] questioned the need for **purged stem cells** for CEM-LI (carboplatin, etoposide, melphalan, with local irradiation)[39] transplant, and accrued 486 patients. Purging stem cells was not found to improve survival.[40]

2000-2012: An additional study (COG-ANBL0032)[41] 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.[42]

2002-2008: SIOP (International Society of Paediatric Oncology) formed the European SIOP Neuroblastoma Group (ESIOP NB) in 1994[43] and activated a phase III high-risk NB protocol in 2002 (SIOP-EUROPE-HR-NBL-1)[44] 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. [45,46]

2007: The COG phase III ANBL0532[47] trial opened December 2007 for accrual of 495 and will compare **single versus tandem transplants**, and induction begins with two cycles of topotecan.[48]

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1 Clinical Trials (PDQ) - National Cancer Institute. COG-ANBL0532
2 Clinical Trials (PDQ) - National Cancer Institute. SIOP-EUROPE-HR-NBL-1
3 National Institutes of Health, Clinical Trials – NB2004
4 Kushner BH, Kramer K, LaQuaglia MP, Modak S, Yataghene K, Cheung NK, Reduction From Seven to Five Cycles of Intensive Induction Chemotherapy in Children With High-Risk Neuroblastoma, *Journal of Clinical Oncology*, Vol 22, No 24 (December 15), 2004: pp. 4888-4892
5 Kushner BH, Cheung NK, Induction for high-risk neuroblastoma. Pediatr Blood Cancer. 2007 Sep;49(3):221-3.
6 Ladenstein R, Valteau-Couanet D, Brock P et al, Randomized Trial of prophylactic granulocyte colony-stimulating factor during rapid COJEC induction in pediatric patients with high-risk neuroblastoma: the European HR-NBL1/SIOPEN study. J Clin Oncol. 2010 Jul 20;28(21):3516-24. Epub 2010 Jun 21.
7 S. G. Kreissman, J. G. Villablanca, R. C. Seeger, S. A. Grupp, W. B. London, J. M. Maris, J. R. Park, S. L. Cohn, K. K. Matthay, C. P. Reynolds, 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)
8 Reynolds CP (June 2004). Detection and treatment of minimal residual disease in high-risk neuroblastoma. *Pediatr Transplant* 8 Suppl 5: 56–66.
9 Cheung & Cohn (eds), *Neuroblastoma*, Springer (2005), p. 182
10 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.
11 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.
12 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.
13 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.
14 Cheung & Cohn (eds), *Neuroblastoma*, Springer (2005), p. 151
15 Cheung & Cohn (eds), *Neuroblastoma*, Springer (2005), p. 174
16 Kushner BH, Kramer K, Modak S, Qin LX, Yataghena K, Jhanwar SC, Cheung NK. Reduced risk of secondary leukemia with fewer cycles of dose-intensive induction chemotherapy in patients with neuroblastoma. Pediatr Blood Cancer. 2009 Jul;53(1):17-22.
17 Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL; New Malignancies After Blood or Marrow Stem-Cell Transplantation in Children and Adults: Incidence and Risk Factors; *Journal of Clinical Oncology*, Vol 21, Issue 7 (April), 2003: 1352-1358.
18 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.
19 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

[20] 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

[21] 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.

[22] 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.

[23] 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.

[24] Verneris MR, Wagner JE (June 2007). Recent developments in cell-based immune therapy for neuroblastoma. *J Neuroimmune Pharmacol* 2 (2): 134–9.

[25] 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)

[26] 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

[27] National Institutes of Health, Clinical Trials – NB2004

[28] 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

[29] 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

[30] Clinical Trials (PDQ) - National Cancer Institute. COG-ANBL0032

[31] Biological Therapy, Sargramostim, and Isotretinoin in Treating Patients With Relapsed or Refractory Neuroblastoma

[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] http://clinicaltrials.gov/ct2/show/NCT00703222

[34] 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.

[35] Pearson AD, Pinkerton CR, Lewis IJ, Imeson J, Ellershaw C, Machin D (2008). High-dose rapid and standard induction chemotherapy for patients aged over 1 year with stage 4 neuroblastoma: a randomised trial. *Lancet Oncol.* 9 (3): 247–256. .

[36] 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

[37] 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

[38] Clinical Trials (PDQ) - National Cancer Institute. COG-A3973

[39] Villablanca J et al. Autologous Stem Cell Transplantation for High-Risk Neuroblastoma (1999)

[40] Response and toxicity to a dose-intensive multi-agent chemotherapy induction regimen for high risk neuroblastoma (HR-NB): A Children's Oncology Group (COG A3973) study. - ASCO.

[41] Clinical Trials (PDQ) - National Cancer Institute. COG-ANBL0032

[42] 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

[43] SIOP 2005, Neuroblastoma Education Book.

[44] Clinical Trials (PDQ) - National Cancer Institute. SIOP-EUROPE-HR-NBL-1

[45] NB2004 - kinder krebs info . de. GPOH Neuroblastoma trial NB2004

[46] National Institutes of Health, Clinical Trials – NB2004

[47] Clinical Trials (PDQ) - National Cancer Institute. COG-ANBL0532

[48] George RE, Li S, Medeiros-Nancarrow C, *et al* (June 2006). High-risk neuroblastoma treated with tandem autologous peripheral-blood stem cell-supported transplantation: long-term survival update. *J. Clin. Oncol.* 24 (18): 2891–6.

