

COG-ANBL0532: Phase III Randomized Trial of Single vs. Tandem Myeloablative as Consolidation Therapy for High-Risk Neuroblastoma

PATIENT ELIGIBILITY:

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

- ___ 1. Patients must be enrolled on ANBL00B1 prior to the time of enrollment on ANBL0532. In emergency situations (or if in the opinion of the treating physician, it is in the patient's best interest) consent can be obtained and patient enrolled on ANBL00B1 and subsequently enrolled on ANBL0532 as soon as the assignment of "High-Risk" has been made in the eRDE system. When ANBL0532 enrollment is done prior to start of beginning protocol therapy, the date protocol therapy is projected to start must be no later than *five (5)* calendar days after enrollment. In a case of a need for emergency therapy, protocol therapy may start before enrollment on ANBL0532; however, ANBL0532 consent part 1 must be obtained prior to start of therapy AND enrollment must take place within **fourteen (14)** calendar days of beginning protocol therapy. Study enrollment must occur within 4 weeks of diagnosis or after only one cycle of chemotherapy on the low/intermediate risk neuroblastoma studies, or within 4 weeks of progression to stage 4 for INSS stage 1, 2, 4S.
- ___ 2. Randomization will take place at **completion of Induction phase of therapy** via RDE. Patients will be assigned to either single myeloablative therapy or tandem myeloablative therapy. Randomization will be stratified by initial stage of disease, biologic characteristics and response to induction chemotherapy.
- ___ 3. **Non-Randomized Consolidation therapy: Patients 365 to 547 days of age (12 – 18 months) with Stage 4, MYCN nonamplified tumor with unfavorable histopathology or diploid DNA content or with indeterminant histology or ploidy and patients who are greater than 547 days of age with Stage 3, MYCN nonamplified tumor AND unfavorable histopathology or indeterminant histology** will be nonrandomly assigned to single myeloablative transplant arm.
- ___ 4. Patients must be ≤ 30 years of age at the time of initial diagnosis.
- ___ 5. **Diagnosis** - Patients must have a diagnosis of neuroblastoma (ICD-O morphology 9500/3) or ganglioneuroblastoma verified by histology or demonstration of clumps of tumor cells in bone marrow with elevated urinary catecholamine metabolites. Patients with the following disease stages at diagnosis are eligible, if they meet the other specified criteria. See Appendix VII.
 - Patients with newly diagnosed neuroblastoma with INSS Stage 4 are eligible with the following:
 - MYCN amplification (greater than four-fold increase in MYCN signals as compared to reference signals), regardless of age or additional biologic features.
 - Age > 18 months (>547 days) regardless of biologic features.
 - Age 12 – 18 months (365-547 days) with any of the following three unfavorable biologic features (MYCN amplification, unfavorable pathology and/or DNA index = 1) or any biologic feature that is indeterminant/unsatisfactory/unknown.
 - Patients with newly diagnosed neuroblastoma with INSS Stage 3 are eligible with the following:
 - MYCN amplification (greater than four-fold increase in MYCN signals as compared to reference signals), regardless of age or additional biologic features
 - Age > 18 months (> 547 days) with unfavorable pathology, regardless of MYCN status.
 - Patients with newly diagnosed INSS Stage 2a/2b with MYCN amplification (greater than four-fold increase in MYCN signals as compared to reference signals), regardless of age or additional biologic features.
 - Patients with newly diagnosed INSS Stage 4s with MYCN amplification (greater than four-fold increase in MYCN signals as compared to reference signals), regardless of additional biologic features.
 - Patients ≥ 365 days initially diagnosed with: INSS stage 1, 2, 4S who progressed to a stage 4 without interval chemotherapy. These patients must have been enrolled on ANBL00B1. It is to be noted that study enrollment must occur within 4 weeks of progression to Stage 4 for INSS Stage 1, 2, 4S.
- ___ 6. **Prior Therapy** - Patients must have had no prior systemic therapy except for localized emergency radiation to sites of life threatening or function-threatening disease and/or no more than one cycle of chemotherapy per low or intermediate risk neuroblastoma therapy (P9641, A3961, ANBL0531) prior to determination of MYCN amplification and histology.

___7. Organ Function Requirements:

- Patients must have adequate renal function defined as:
 - Creatinine clearance (CrCl) or radioisotope GFR $\geq 70\text{mL}/\text{min}/1.73\text{ m}^2$ or
 - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

- Patients must have adequate liver function defined as:
 - Total bilirubin $< 1.5 \times$ upper limit of normal (ULN) for age, and
 - SGOT (AST) or SGPT (ALT) $< 10 \times$ upper limit of normal (ULN) for age.
- Patients must have adequate cardiac function defined as:
 - Shortening fraction of $\geq 27\%$ by echocardiogram, or
 - Ejection fraction of $\geq 50\%$ by radionuclide angiogram.
- Patients must have the ability to Tolerate PBSC Collection:

No known contraindication to PBSC collection. Examples of contraindications might be a weight or size less than the collecting institution finds feasible, or a physical condition that would limit the ability of the child to undergo apheresis catheter placement (if necessary) and/or the apheresis procedure.

EXCLUSION CRITERIA:

- ___1. Females of childbearing potential must have a negative pregnancy test. Patients of childbearing potential must agree to use an effective birth control method.
- ___2. Female patients who are lactating must agree to stop breast-feeding.
- ___3. Patients that are 12-18 months of age with INSS Stage 4 and **all 3** favorable biologic features (i.e., non-amplified *MYCN*, favorable pathology, and DNA index > 1) are not eligible.

REQUIRED OBSERVATIONS:

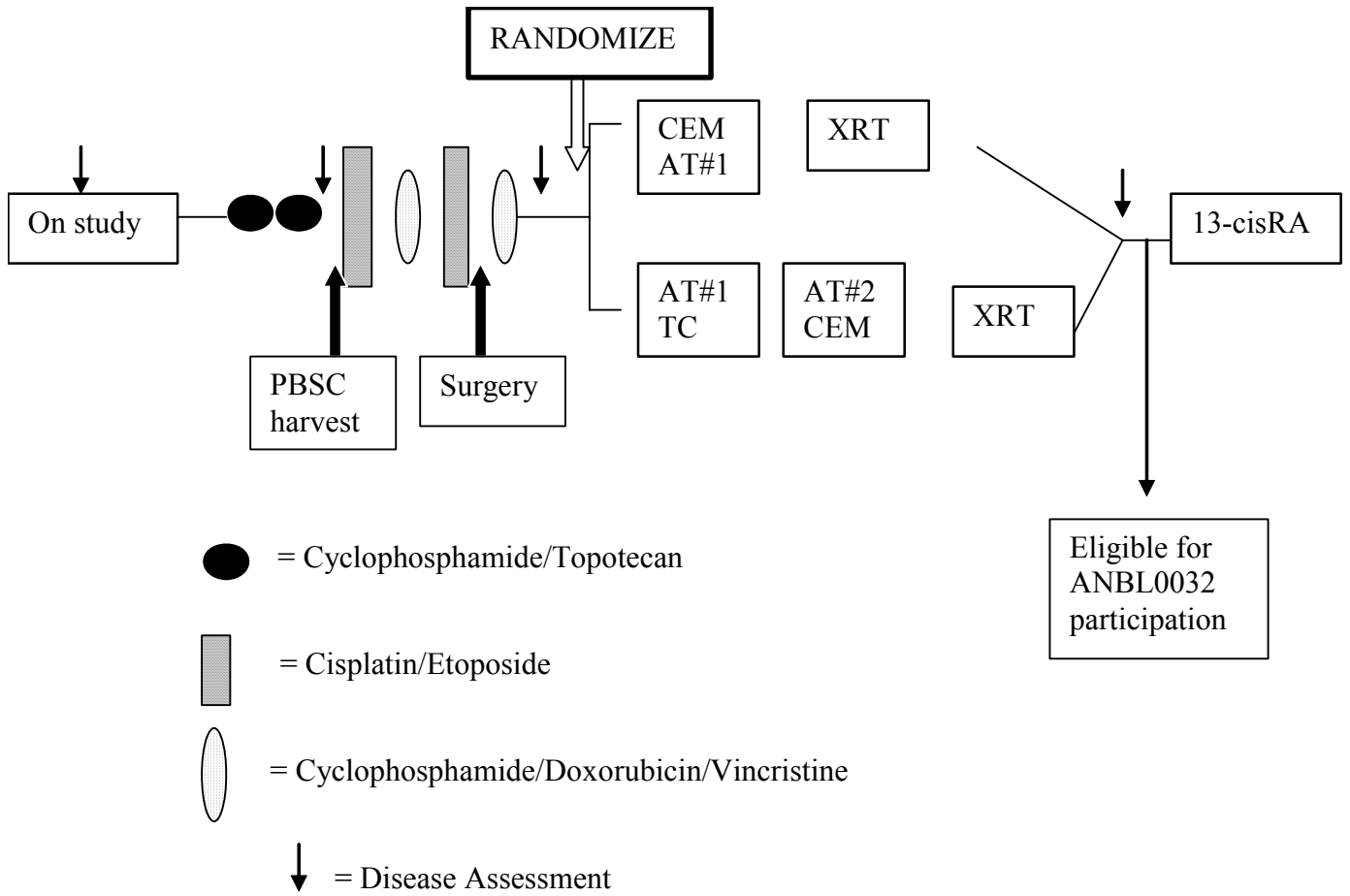
Required Observations Pre-Treatment and During Induction

- Physical Exam
- Height, Weight
- CBC
- Electrolytes, BUN, Cr., Ca, Phos, Mg
- ALT, AST, Bilirubin, Urinalysis, albumin ¹
- ECG and MUGA or ECHO
- GFR or Creatinine Clearance ²
- Audiogram or BAERs
- Bilateral BM Asp/Bx
- BM ICC and PCR ³
- Peripheral Blood PCR ⁴
- Peripheral blood for immune assessments ⁵
- Topotecan pharmacokinetics ⁶
- Pharmacogenetics ⁷
- PBSC immuno ⁸
- PBSC PCR ⁹
- Tumor Imaging ¹⁰
- MRI Spine and Neurologic Evaluation ¹¹
- Bone Scan ¹²
- MIBG ¹³
- Catecholamines (VMA, HVA)
- Pregnancy Test ¹⁴

1. Obtain serum albumin pre-treatment only and then as clinically indicated.
2. GFR required prior to cycle 5 and at end of induction/prior to consolidation. No restriction on method for GFR calculation prior to cycle 5. GFR prior to consolidation must be obtained by blood sampling method. Camera method IS NOT allowed as measure of GFR prior to or during Consolidation therapy.
3. Obtain 10 cc of bone marrow (5 cc from each side) in sodium heparin tube. See section 15.4 for details regarding bone marrow immunohistochemistry and PCR analyses.
4. Obtain 2 ml peripheral blood in sodium heparin tube. See section 15.6 for details.
5. Obtain 20 cc peripheral blood in sodium heparin tubes prior to initiation of chemotherapy. See section 15.8 for details
6. Collect 2 cc in green top tube 15 minutes after completion of topotecan infusion on day 1 of cycles 1 and 2. See Section 15.3 for details and ordering of sample collection kit.
7. Collect one time sample of 10 cc in purple top tube (ETDA tube) prior to start of therapy (preferable) or when patient is not leukopenic (WBC > 2000). See section 15. 2 for details.
8. At time of harvest for PBSC, send 1 x 10⁸ nucleated cells in sodium heparin tube (local stem cell lab will need to determine cell count of PBSC product and aliquot 1 x 10⁸ cells for sample submission) of the FIRST DAY OF COLLECTION for determination of tumor cell content by immunochemistry to Dr. Seeger's Lab. An adequate sample **MUST** be received by Dr. Seeger's Lab for patient to receive this PBSC product for transplant. See Section 15.5 for shipping details.
9. Collect 1 cc of PBSC into sodium heparin tube and then transfer to PAX gene tubes. See Section 15.5 for details.
10. Tumor imaging = CT/MRI as needed for optimum visualization of all areas of bulk tumor (primary and tastases). **CT/MRI required prior to surgical resection.** Repeat imaging of surgical sites within 4-6 weeks post-operatively (can be the same as end of induction scans if this is within 4-6 weeks of surgical resection).
11. Obtain for paraspinal tumors only. See section 13.4 and Appendix III for details.
12. Obtain if positive at diagnosis and results discordant with MIBG scan or tumor MIBG non-avid
13. MIBG scan can be performed within 2 weeks of starting chemotherapy if it is not possible to obtain scan prior to starting chemotherapy. Repeat MIBG later in therapy only if positive at diagnosis. I123 MIBG scan preferred, see section 16.4 for details.
14. Perform for all females of childbearing age.

TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA



TC = Thiotepa/Cyclophosphamide

CEM = Carboplatin/Etoposide/Melphalan

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

SPECIMEN REQUIREMENTS:

See Section 15.

BIOLOGY REQUIREMENTS:

Patients must be enrolled on ANBL00P1 prior to the time of enrollment on ABL0532.