

The Safety of Stem Cell Collection in a Patient with Neuroblastoma Complicated by a Thrombus

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Clinical History

- The patient is a 27 month old girl who presented with fever, diarrhea and weight loss, admitted in September, 2010
- PMH:
 - Uncomplicated birth history
 - At 17 months old, removal of a right external ear mass (Dx: ganglioneuroma)
 - At 22 months old, h/o diarrhea and malnutrition
- PE: Pertinent findings were a tired looking child, somewhat emaciated with fullness in the RUQ, visible veins along the abdominal wall secondary to the prominent RUQ mass

Clinical History

- Pertinent Laboratory findings:
 - Low H/H
 - Platelet count: normal
 - Vasointestinal Peptide (VIP): increased
 - Blood levels of catecholamines: not elevated
 - 90% of neuroblastomas have elevated catecholamines
 - 24 hour urine VMA (vanillymandelic acid) and HVA (homovanillic acid): problems with urine collection
 - Metabolites of catecholamines

Clinical History

- CT scan abdomen: Right large adrenal mass with variable density pushing the right kidney caudally measuring 9.8 x 10.3 x 9.7 cm. with mass effect showing anterior displacement of the liver, IVC and portal vein; presence of paraaortic lymphadenopathy

LightSpeed VCT
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ABDOMEN
Se: 2/8
Im: 23/51
Ax: 192.5

A

Anonymous Hospital
PATIENT45594
2008 May 29 F ID45594
Acc: ACC304733
2010 Sep 27
Acq Tm: 02:13:33

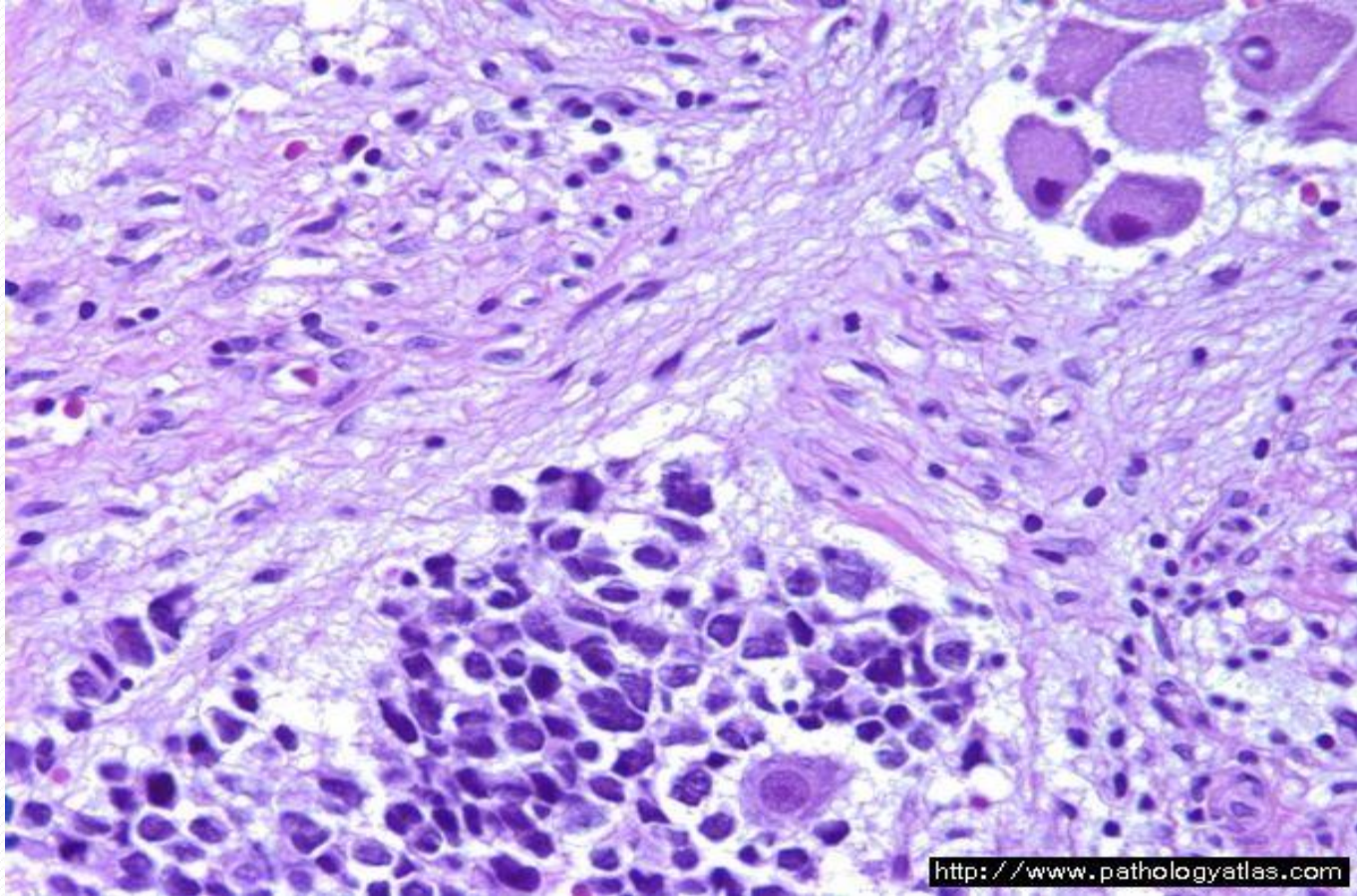


Clinical History

- CT guided FNA and biopsy: Neuroblastoma, stroma poor with some ganglionic differentiation
- IHC: positive stain for nerve tissue (e.g. synaptophysin)
- FISH: gain of N-MYC but no amplification
 - Amplification is an unfavorable prognosis
- Cytogenetics: Loss of 4p and 16q; Gain of 17q c/w high grade tumor and unfavorable prognosis
- Bone marrow biopsy: no tumor seen

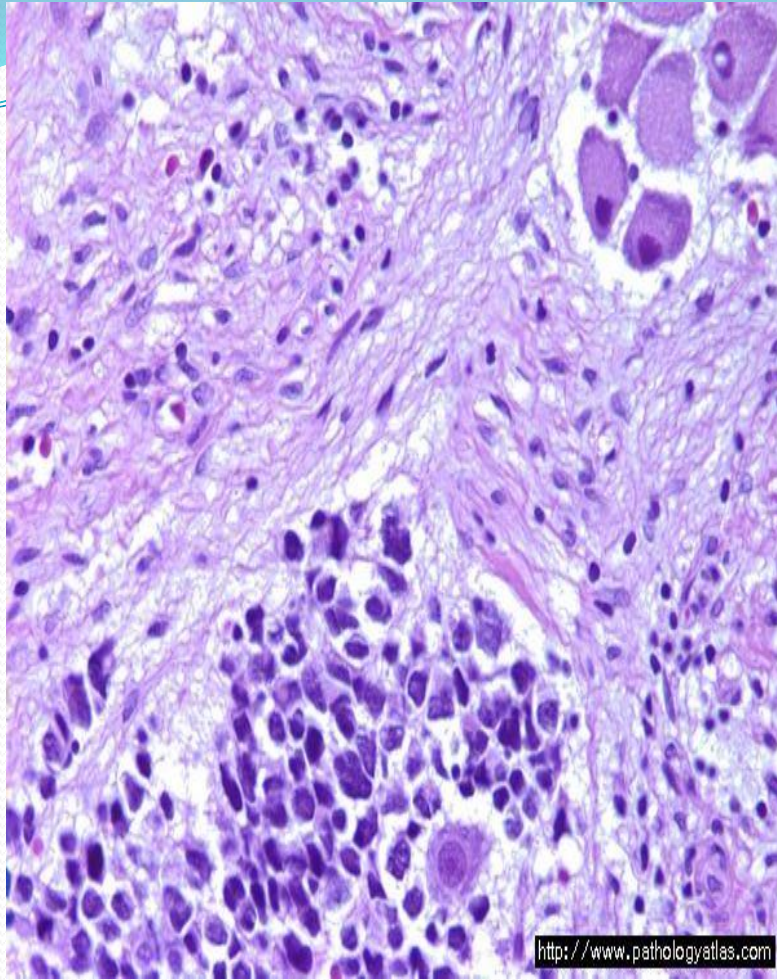
Diagnosis

- Ganglioneuroblastoma, stage III with extensive involvement
 - Stage 3: unilateral tumor infiltrating across the midline with regional lymph node involvement
 - Stage 1, 2A and 2B: excellent prognosis with low to intermediate risk
 - Stage 3 and 4: higher stage tumors with unfavorable prognostic markers are “high risk”

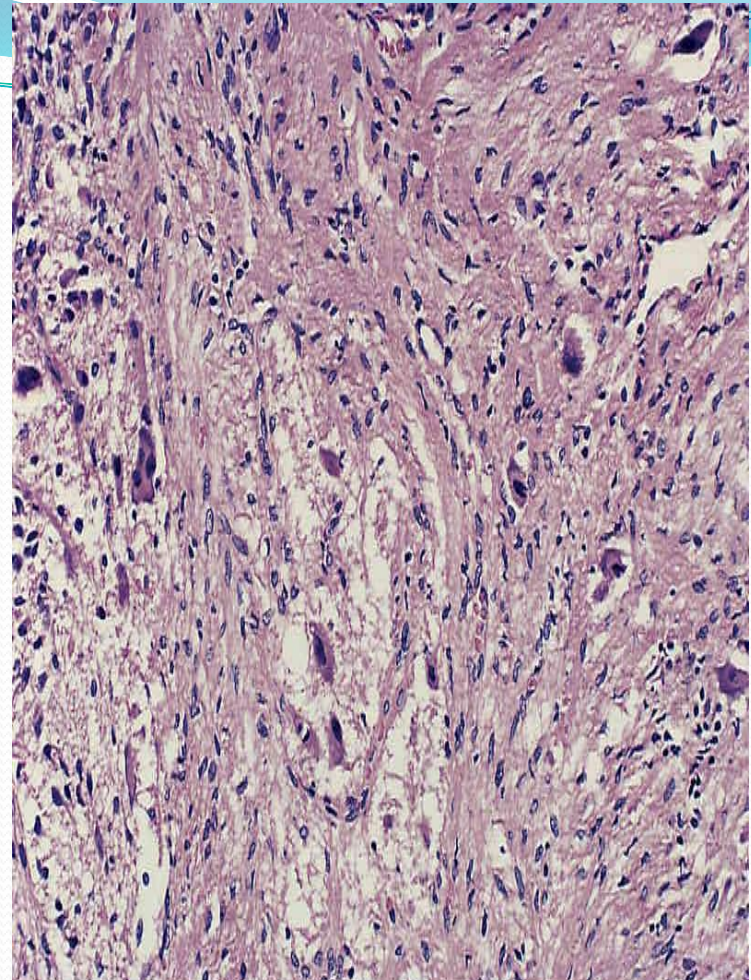


Review of Neuroblastic or Neurogenic Tumors

- Tumors of the sympathetic nervous system which are completely undifferentiated cells of the sympathetic nervous system (neural crest cells)
- Three classic histopathologic patterns of neuroblastic tumors which reflects a spectrum of maturation, differentiation and clinical outcome
 - Neuroblastoma- most poorly differentiated; malignant
 - Ganglioneuroblastoma- malignant
 - Ganglioneuroma- most differentiated (benign)



Ganglioneuroblastoma



Ganglioneuroma

Review

- Most common extracranial malignant solid tumor of childhood
- Patients mostly present with abdominal disease
- More than 50% have advanced stage 3 or 4
- Median age: 18 months (>18 carries an unfavorable prognosis)
- Mostly sporadic, 1-2% familial

Treatment

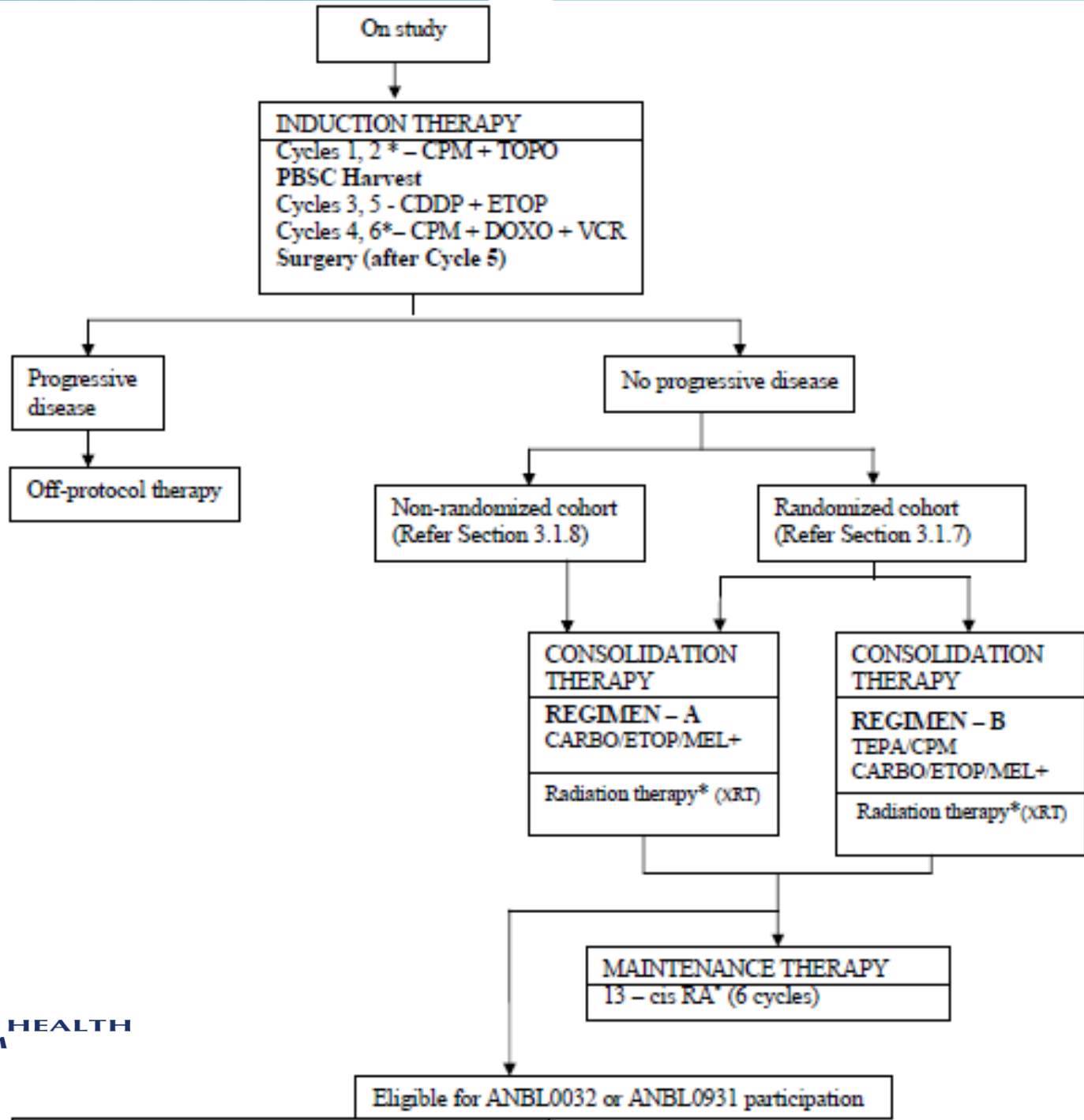
- High-dose chemotherapy with stem cell rescue (SCR) has been shown to improve survival for children with high-risk neuroblastoma (NB)
 - It has become the standard of care for such patients
- Autologous peripheral blood stem cells (PBSCs) are the preferred source of rescue over autologous bone marrow grafts as stem cell collection (SCC) is easier
- Tumor cell contamination is lower with a higher stem cell yield

Treatment

- Our patient was enrolled under the Children's Oncology Group Protocol ANBL0532
- Primary goal: to find out if further intensification of myeloablative therapy will improve the cure rate for high risk neuroblastoma
- Eligibility: Neuroblastoma or ganglioneuroblastoma by pathology
- Randomization to either one myeloablative consolidation or 2 myeloablative consolidation
 - Randomization stratified by stage, N-MYC status and response to induction therapy

Treatment

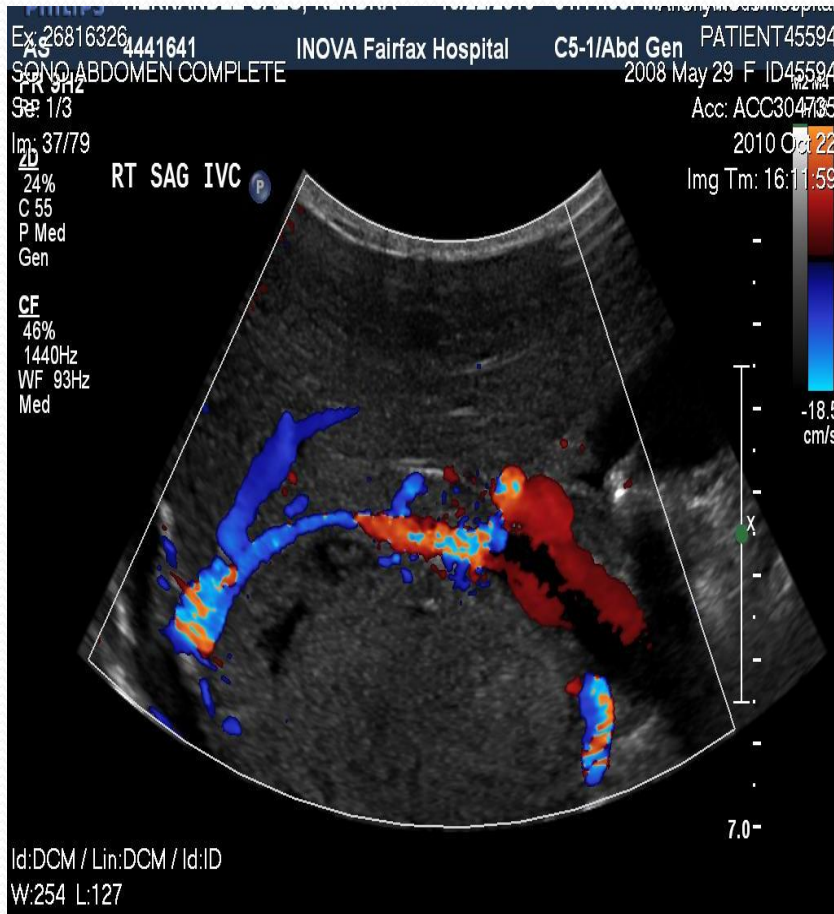
- The treatment protocol includes 6 cycles of induction therapy with peripheral blood stem cell (PBSC) harvest after 2 cycles
- Our patient qualified, she was >18 months old with unfavorable neuroblastic tumor pathology, high risk with ganglioneuroblastoma stage 3



Treatment

- The patient began the initial phase of induction therapy with 2 cycles of topotecan and cyclophosphamide
- Follow-up abdominal CT scan and ultrasound in October 2010 showed a thrombus, > 1 cm in size, located in the inferior vena cava (IVC) between the tumor and the liver
 - Blood clot vs tumor thrombus
 - Radiologist convinced it was likely a blood clot

Ultrasound



10/22/2010

Definitions

- Hemostasis is a tightly regulated process that maintains blood flow in the fluid state in a normal vessel
- Thrombosis (blood clot) is a disturbance of this normal hemostasis
 - Triad of stasis, vessel injury and hypercoagulability
- Tumor thrombus is an extension of the tumor into the vessel

PBSC Harvest

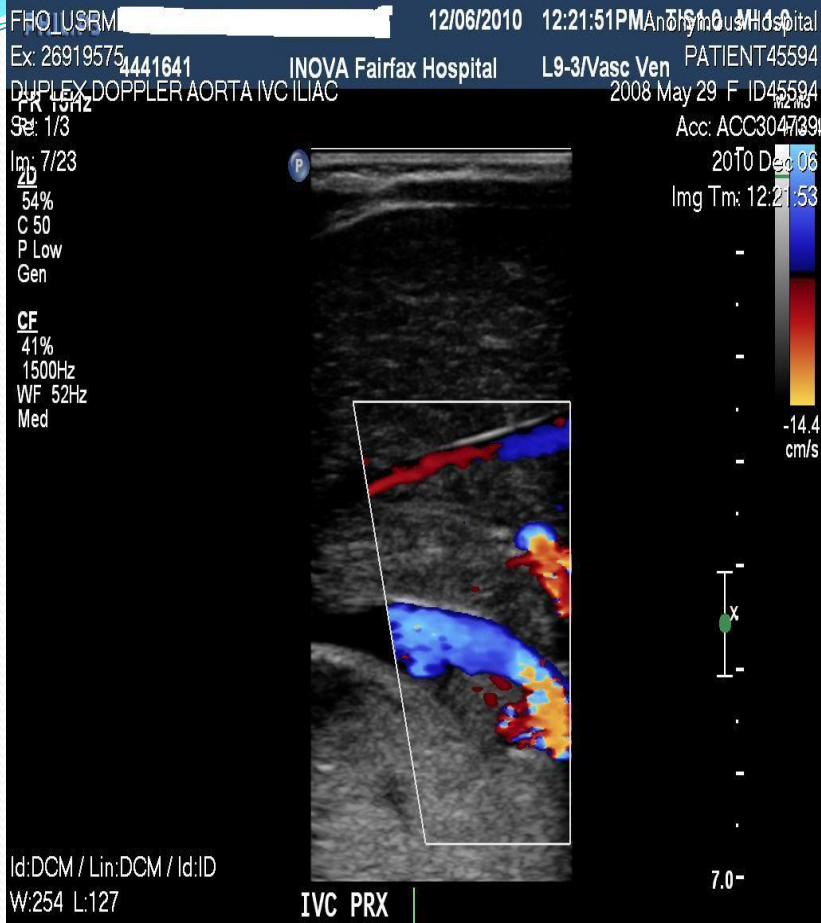
- The PBSC harvest after 2 cycles of chemotherapy (ANBL0532) was cancelled
- Concerns about break-up of the thrombus and possible embolism during PBSC collection
- Large volume PBSC harvest was required with goals to collect high numbers CD34+ cells with blood volumes (BV) processed of ~6 BV and a lengthy procedure
- Proceeded with caution and anticoagulation started
- Lovenox (LMWH) was began along with 3rd cycle of chemotherapy
- Monitor thrombus size with repeat abdominal ultrasound



Res 1/1
Z: 17
Im: 13/14
2d
72%
C 50
P Low
Res

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2010 Nov 14
Img Tm: 13:28:10

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W:254 L:127



PBSC Harvest

- Follow-up abdominal ultrasound showed a stable thrombus without progression in size
 - A consensus was made to proceed with the PBSC harvest after discussions with the radiologist, hematology-oncologist, PICU intensivist and apheresis physician
 - Mobilization with G-CSF 5 mcg/kg daily for 3 days prior to PBSC harvest
 - LMWH temporarily discontinued
 - PBSC harvest successfully completed on 12/09/10 and 12/10/10
- Setting: PICU after placement of a double lumen central venous catheter (femoral line)
- MNC program on Cobe Spectra (Caridian BCT, Lakewood, CO), auto PBSC

PBSC Harvest

- The circuit was primed with PRBC (ECBV >10% of BV) and for patients <25 kg per study guidelines
 - Patient weight: 10.8 kg
- Citrate was used for anticoagulation (inlet to ACD-A ratio 14)
- Calcium gluconate drip prophylaxis to reduce citrate toxicity and titrated to keep a normal serum ionized calcium (worked closely with pediatric intensivist)

PBSC Harvest and ANBL0532

- Collection Goals:
 - large volume apheresis for each collection
 - the target volume of whole blood processed approximately 480 mL/kg (~6 blood volumes)
- Optimal collection goal (total for all collections) of 10×10^6 CD 34+ cells/kg for PBSC
 - May be obtained in 1-3 collection days
 - Our patient underwent a PBSC harvest collected in 2 days with blood volume processed on 1st day, 4.7 BV and 2nd day 4.1 BV

PBSC Harvest and Stem Cell Processing

- Protocol: collection be stored in at least 3 aliquots of cells:
 - $2-4 \times 10^6$ CD34+ cells/kg for the first HSCT procedure
 - $2-4 \times 10^6$ CD34+ cells/kg for the second HSCT procedure
 - $2-3 \times 10^6$ CD34+ cells/kg as a backup for delayed engraftment, or for potential subsequent use.

DOB: 5/29/2008 Wt (actual): _____ kg Wt used for CD34 collection 10.8 kg (weight circled on the Apheresis order)

Summary of Collections Available for Infusion

Unit # of Product	Date of Collection	# bags frozen	Volume frozen	Total CD 34 $\times 10^8/\text{kg}$	CD 34 $\times 10^8/\text{kg}/\text{bag}$	Grams of DMSO/Kg/day	Cellular Composition $\times 10^8$	Viability cryopreserved CD34+ cells
1. W089810007547	12/9/2010	2	66	3.59	1.79	0.67	0.17	89.1
2. W089810007548	12/10/2010	3	75	10.4	3.46	0.76	0.37	84.8
3.								
4.								

PBSC Harvest

- The patient tolerated the 2 consecutive PBSC collections without any adverse reactions with stable BP and increased PR (mild agitation/crying)
- Except for a low ionized calcium on I-Stat, there were no acute problems such as respiratory distress from a possible embolism during the PBSC collection

PR 2812
Res 1/2 P
7.20
Im 6/10
2D
72%
C 50
P Low
Res

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2011 Jan 20
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IVC PRX

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Neuroblastoma & Thrombosis

- Bagatelle et al (2002) reported two cases of pediatric neuroblastoma diagnosed with tumor thrombus in the IVC before the initiation of chemotherapy
 - Anticoagulation therapy was followed by successful autologous PBSC harvest
- Our patient developed a thrombus after 2 cycles of chemotherapy: blood clot secondary to clotting pathway activation or a tumor extension?
- Schiavetti et al (2010) reported elevated procoagulant factors (e.g. tissue factor) in high risk neuroblastoma
 - Risk of venous thrombosis in neuroblastoma 2.33% (other pediatric solid organ tumors 0.5-13%)

Neuroblastoma & Thrombosis

- In patients with high risk neuroblastoma (NB), plasma levels of tissue factor (TF) are increased
- Chemotherapy potentiates the prothrombotic state of cancer patients by increasing the release of circulating TF from tumor cells

FHO_USRM [REDACTED] 04/15/2011 11:29:12AM Tisona M, MD

Ex: 27235684 4441641 INOVA Fairfax Hospital C8-5/Vasc Ven PATIENT 45594

DUPLEX DOPPLER ABDOMEN PELVIS 2008 May 29 F ID 45594

PR 55Hz

Ss 1/2

Im: 1/24

2D

71%

C 55

P Off

Gen

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2011 Apr 15

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IVC SAG

7.0-

Conclusions

- The presence of venous thrombosis should not be a deterrent to PBSC harvest since high dose chemotherapy along with PBSC rescue has been shown to increase survival of children with high risk neuroblastoma: “standard of care”
- The risk of a thrombus dislodging and causing a PE is a valid concern during PBSC harvest and it is important to be aware of this risk
- However, it is also possible that apheresis procedures may not be a contributory factor and PBSC collection is safe
- Differentiating a “blood clot” from a tumor extension may not be easy, it is prudent to start anticoagulation therapy immediately prior to PBSC harvest
- Suggest a “huddle” prior to each procedure to discuss with the PICU staff nurses and apheresis nurses the potential complications during the collection and helps in immediate recognition of an adverse event such as PE, just in case it happens

Follow-up of Patient

- Unfortunately the patient relapsed with progression of the disease and she was taken off the protocol and awaits transfer to CHOP

Thank you