Transplant in Pediatric Hematology Oncology (TiP-HO)
Tumor Board Meeting Minutes (Thursday, December 1st, 2022)

Discussion board during the last meeting (Alphabetical):

Name	Affiliation
Prof. Dr. Alaa Elhaddad	Clinical Director of Pediatric Oncology and Stem cell transplant program Children's Cancer Hospital (CCHE-57357) National Cancer Institute, Cairo University, Egypt
Prof. Dr. Amr Abdullah	Consultant of pediatric Hematology/Oncology & stem cell transplant. Sultan Qaboos University Hospital, Muscat, Oman
Prof. Dr. Hanafy Hafez	Consultant of Pediatric Hematology/Oncology & Stem cell transplant Children's Cancer Hospital (CCHE-57357) National Cancer Institute, Cairo University, Egypt
Prof. Dr. Ibrahim Abdelkader	Consultant of pediatric Hematology/Oncology & stem cell transplant Children's Mercy Hospital, Kansas City. University of Missouri-Kansas City School of Medicine. USA
Prof. Dr. Iman Ragab	Consultant of Pediatric Hematology / Oncology, Ain Shams University , Egypt
Prof. Dr. Leslie Lehmann	Clinical director of the Stem Cell Transplantation Program Dana-Farber/Boston Children's Cancer and Blood Disorders Center
Prof. Dr. Mahmoud Hammad	Consultant of Pediatric Hematology/Oncology & Stem cell transplant Children's Cancer Hospital (CCHE-57357) National Cancer Institute, Cairo University, Egypt
Prof. Dr. Maneh Gizhlaryan	Pediatric Hematologist and Oncologist Department of Pediatric Hematology Pediatric Cancer and Blood Disorders Center of Armenia
Prof. Dr. Paiman Ali Ihsan	Consultant of Pediatric Hematology / Oncology, Nanakali Hospital, Iraq
Prof. Dr. Sadaf Altaf	Consultant of Pediatric Hematology Oncology Agha Khan University Hospital, Pakistan
Prof. Dr. Sajad Khazal	Professor, Department of Pediatrics Patient Care, Division of Pediatrics, The University of Texas MD Anderson Cancer Center, USA
Prof. Dr. Sondus Alsharidah	Head of Pediatric Hematology oncology department Head of Pediatric SCT unit NBK children's hospital, Kuwait
Prof. Dr. Yossef Madney	Consultant of Pediatric Hematology/Oncology & Stem cell transplant Children's Cancer Hospital (CCHE-57357) National Cancer Institute, Cairo University, Egypt

List of participating Centers

1. Children's Cancer Hospital (CCHE-57357), Egypt
2. National Cancer Institute, Cairo University, Egypt
3. Faculty of Medicine Ain Shams University, Egypt
4. Air Force Specialized Hospital , Egypt
5. South Egypt Cancer Institute, Assiut university, Egypt
6. Shefaa El Orman Oncology Hospital (SOH), Luxor, Egypt
7. Dar el Salam Cancer Hospital (Harmal Hospital), Cairo, Egypt
8. Borg Alarab Hospital, Alexandria, Egypt
9. Dana-Farber/Boston Children's Cancer and Blood Disorders Center, United States
10. Sultan Qaboos University Hospital, Muscat, Oman
11. Prince Sultan Military Medical City (PSMMC), Saudi Arabia
12. King Saud Medical City, Riyadh, Saudi Arabia
13. King Faisal Specialist Hospital, Jeddah, Saudi Arabia
14. Newcastle Upontyne Hospitals NHS Foundation Trust, United Kingdom
15. NBK children's hospital, Kuwait
16. Children Hospital, Pakistan
17. Agha Khan University Hospital, Pakistan
18. Apollo hospitals Chennai, India
19. Meenakshi Mission hospital, India
20. Royal Hospital, Oman
21. MD Anderson cancer Center, USA

Case 1— Indication of HSCT in AML with t(6;9)

- 16y old female patient
- Diagnosis: ***AML with t(6;9)(p23;q34.1), DEK-NUP214, high-risk group***
- Complains: weaknesses, fatigue and tailbone (coccyx) pain
- **CBC**: WBC-12.59 ×109/L, NEUT- 3.38×109/L (26.9%), LYMPH- 4.42×109/L (35.1%), MONO-4.79x109/L (38%), Hgb- 39g/dl, PLT- 17.000/L
- **Blast cells**: PB: 44% blast cells BM: 83.0% blast cells
- **CSF** (07.09.2022): negative
- **Blast cella abs.**
  - WBS-BF- 0.001x103/uL
  - RBS-BF-0.000x106/uL
  - MN - 0.001x106/uL
  - PMN - 0.000x106/uL
- **Immunophenotyping in HC** (05.09.2022-08.09.2022):
  72% of blast cells of the population are myeloid lineage

CD13	70%	CD38	87%
CD33	88%	CD64	37%
CD34	50%	HLA_DR	56%
CD117	48%	CD3	Negative
CD11c	28%	CD79a	Negative
CD15	22%	MPO	30%

- **Immunophenotyping in RF** (08.09.2022):
  75% of blast cells of the population are myeloid lineage, with lymphoid B cells and T cell makers, CD123(66.0%) expression

CD19	**37.0%**	**CD11b**	**95.0%**
CD2	**40.0%**	CD11c	39%
CD34	51.0%	CD13	96%
CD45	100.0%	CD33	100%
HLA-DR	68.0%	CD117	77%
CD11a	93.0%	***CD123***	66%

- **Cytogenetic** examinations by FISH method (08.09.2022)‘ t(6,9)(p22;q34)
- **Treatment:** OML-MRD-2018 protocol, Induction therapy with AM42E
- **Complications:** Tailbone cyst (pilonidal cyst), anal fissure and Sepsis
- **Post chemotherapy period:**
  - After induction therapy CBC was recovered up to 4 weeks, and due to long recovery performed BM aspiration. BM was hypoplastic and Blast cells were negative
  - On 42 days BM: 1% blast cells
  - MRD: negative by FISH and PCR (t (6,9)DEK::NUP214
- The available donor for the patient is a haplo-identical donor

Questions raised by presenter (Dr. Maneh Gizhlaryan, Armenia)

- Does the patient need HSCT in any case (due to t(6;9) and CD123), or it should be based on MRD?
- What conditioning regimen is preferable?
- Is it essential to do DSA in a haplo-identical transplant?

Tumor board recommendations:

- t(6,9) is a high risk AML and should go to transplant preferably on a negative MRD with the best available donor
- FlT3-ITD mutation status should be checked before transplant as it might need FLT3 inhibitors
- A Bu/Cy/post Cy conditioning is a valid option for the patient
- It's essential to check on donor specific antibodies (DSA) before haplo-identical transplant

Scientific materials:

- Marina Dıaz-Beya, Myriam Labopin, et al, **Allogeneic stem cell transplantation in AML with t(6;9)(p23; q34);DEK-NUP214 shows a favorable outcome when performed in first complete remission,** British Journal of Haematology, 2020, doi: 10.1111/bjh.16433

Case 2: DOCK 8 Deficiency for Haplo Transplant

- 6 yo girl
- History of recurrent infections required hospital admissions since age of 1 year
- At 2 yo admitted to the local hospital with pseudomonas skin infection required PICU for 1 week (depressed nasal bridge and deformed finger tips)
- Continued repeated hospital admissions with similar episodes of skin and sino-pulmonary infections
- No family History of similar conditions
- At age of 4 years patient started to develop generalized skin eczema with multiple skin lesions
- Picture of ***Mollascum Contagiosum***, with progressive course, started 1st on the face then progressed to involve about 60-70% of skin; bilateral ear pinnae, bilateral eye lids, both upper and lower limbs, genitalia and lower abdomen
- **Diagnosis:** Genetic molecular study at age of 6yo: ***DOCK8 deficiency***
- Patient referred to SCT on July, 2022:
  - Skin condition shown in figure 1, thriving, well, active, voice hoarseness
  - MDT with dermatology: advised for Cidofovir
- **Work up:**
  - CBC, LFT, RFT, immunoglobulin levels: Normal
  - TFT and virology PCRs: Normal
  - Skin swab: MRSA +ve form axilla, groin and nose (treated)
  - **Best selected haplo donor is dad:** referred for donor pre-transplant workup
  - Patient pretransplant assessment (dental/cardio/pulmo/ ophthalmology) are normal
  - Audiology: B/L conductive hearing defect

- **Plan of management:**
  - Proper hygienic instructions were given to the parents.
  - Patient started:
    - MRSA protocol guidelines
    - Cidofovir, cyotherapy stopped
- After 9 doses of Cidofovir: improvement shown in figure 2
- **Laryngoscope** done (hoarseness of voice): chronic upper airway edema with mobile vocal cords
- **Progress**:
  - Started budesonide nebulization and oral antihistamine
  - Clinically stable, still with hoarseness
  - Father PBSC harvest done
- **Planned conditioning:**
  - Treo/Flu, ATG, PTCy
  - Anti GvHD: MMF + Tacrolimus
  -

Questions raised by presenter (Prof. Dr. Sondus Alsharidah, Kuwait)

- Can we proceed for transplant with this chronic upper airway vocal cords edema?
- Best conditioning?

Tumor board recommendations:

- The chronic upper airway edema is mostly caused by repeated infections so the patient needs a transplant as early as possible and the patients seems to be fit for transplant
- Bone marrow stem cell source is preferred for pediatric patients especially in Immunodeficiency cases transplant
- Thiotepa/Treo/Flu/ATG + PTCy conditioning is a valid option
- Screening the donor for DOK 8 deficiency is recommended but in the absence of other donors you can settle for a heterozygous status (Autosomal recessive)

Scientific materials:

- A. C. Lankester, M. H. Albert, et al, **EBMT/ESID inborn errors working party guidelines for hematopoietic stem cell transplantation for inborn errors of immunity,** Bone Marrow Transplantation (2021), https://doi.org/10.1038/s41409-021-01378-8
- Nirali N. Shah, Alexandra F. Freeman, et al, **Haploidentical Related Donor Hematopoietic Stem Cell Transplantation for Dedicator-of-Cytokinesis 8 Deficiency Using Post-Transplantation Cyclophosphamide,** Biol Blood Marrow Transplant. 2017, doi:10.1016/j.bbmt.2017.03.016

Case 3: Autoimmune Hemolytic Anemia in Acute Lymphoblastic Leukemia

- 8 years old male patient presented on june 2021
- **Diagnosis:** ***B-ALL, standard risk group***, confirmed by BMA and flowcytometry
- No cytogenetics test done initially
- He was good responder to steroid, received induction on group A ,UKALL protocol
- Achieved CR1 on day 14, confirmed on day 28
- He completed his consolidation and CNS prophylaxis and delayed intensification uneventful
- Confirmation of remission done by BMA morphology
- He reached maintenance on March 2022
- **On 3rd month of maintenance:**
  - Evidence of progressive anemia with reticulocytosis reaching 15%
  - Hb down to 6g/dl
  - Coombs test negative
  - Normal G6PD level
  - Repeated blood transfusion was given
- **Examination**:
  - His condition progressed to pancytopenia with splenomegaly 4cm BCM
  - No significant LAP
  - No jaundice
  - Active with occasional low grade fever
  - Chest ,and CVS normal, no mediastinal enlargement
  - Liver 2cm BCM
  - Spleen 4cm soft
- **Work up:**
  - CBC, pancytopenia, no blasts
  - Hb 6.2 gl/dl (normochromic normocytic)
  - WBC 2.3 N 0.4 L 1.8 M 0.3
  - Plat. 25000
  - Retics count 10_15%
  - LFT, RFT ,TSP: normal
  - Parvovirus by PCR negative
  - CMV and EBV virus negative
  - BMA: hypercelluar, active hematopoiesis, erythropoiesis, leukopoeisis and megakaryocytes active, blast 3%
  - BMB: active hematopoeisis, no excess blast, no fibrosis
  - Immunoglobulin assay within normal
  - Liver doppler: no portal hypertension
- **Management:**
  - We tried tapering of mercaptopurine to 25% of required dose and stopped for more than 2weeks without improvement
  - Metheprim stopped replaced by Amoxil
  - Trial of prednisolone given then methylprednisolone for more than 6 weeks given with partial improvement
  - IV Immunoglobulin G given every 2week
  - Rituximab was given to control the hemolysis every 3 weeks for 3 doses without response
  - He is at week 50 of maintenance therapy
- **Morbidities/complications:**
  - More than 15 times blood transfusion given till now
  - Tapering the doses of mercaptopurine and methotrexate because of pancytopenia holds the risk of relapse
  - There is clear evidence of hypersplenisim but possibility of auoimmune lymphoproliferative disorders cannot be excluded
  - Option of splenectomy is risky

Questions raised by presenter (Prof. Dr. Paiman Ali Ihsan , Iraq)

- Suggestions for reaching the underlying cause of this condition?
- What is the option for its management?

Tumor board recommendations:

- Excluding disease relapse and repeating MRD is important to exclude a hidden disease behind pancytopenia
- Repeating the viral screening by PCRs as well as complement assay and ADAMST13 activity is recommended
- Splenectomy is not a preferable option for the patient at this time point
- Sirolimus, Bortezomib and Daratumumab are treatment options for the patient to treat an underlying autoimmune cytopenia in addition to proper antibacterial and antifungal prophylaxis

Scientific materials:

- Markus G. Seidel, **Treatment of immune-mediated cytopenias in patients with primary immunodeficiencies and immune regulatory disorders (PIRDs),** Hematology Am Soc Hematol Educ Program. 2020, doi: 10.1182/hematology.2020000153
- David T Teachey and Carolyn A Felix, **Development of cold agglutinin autoimmune hemolytic anemia during treatment for pediatric acute lymphoblastic leukemia,** J Pediatr Hematol Oncol 2005, DOI: 10.1097/01.mph.0000174031.63108.eb
- Wilma Barcellini, Juri Alessandro Giannotta and Bruno Fattizzo, **Autoimmune Complications in Hematologic Neoplasms,** Cancers 2021, https://doi.org/10.3390/cancers13071532

Case 4: Indication of HSCT in AML intermediate risk (2 Cases)

- **Case 1:**
  - 4 year, 6-month-old male AML intermediate risk negative for favorable and unfavorable markers
  - 1st Induction had to be (ADE) truncated, given without Etoposide, due to significant respiratory distress
  - MRD at the end of induction 3% myeloblasts
  - Induction 2 with 2% myeloblasts
  - MRD after intensification 1%
  - HLA: haploidentical with older sibling
- **Case 2:**
  - 15-year-old female intermediate risk AML
  - Induction 1 and 2 with ADE
  - MRD post 1st induction 3%
  - MRD post 2nd induction 0.5%

- Current institutional standard for AML transplant in CR1 is limited to HR group
- Flowcytometry based MRD recently started

Questions raised by presenter (Prof. Dr. Sadaf Altaf, India)

- Are both patients candidates for transplant?
- Growing evidence supportive of use of MRD after induction 1 regarding transplant decision
- Diversity in practice with MRD before intensification being used for transplant decision

Tumor board recommendations:

- Transplant is recommended for AML without favorable cytogenetics and with high MRD at end of 1st induction as per recent COG protocol AAML 1831
- The board recommends HSCT if a matched sibling donor is available, however, in case that the accuracy of results for measurable residual disease is doubtful and not reliable in a center then it is recommended to postpone HSCT for CR2

Scientific materials:

- Katherine Tarlock, Maria Luisa Sulis, et al, **Hematopoietic Cell Transplantation in the Treatment of Pediatric Acute Myelogenous Leukemia and Myelodysplastic Syndromes: Guidelines from the American Society of Transplantation and Cellular Therapy,** Transplantation and Cellular Therapy (2022), https://doi.org/10.1016/j.jtct.2022.06.005

Our next TiP-HO meeting will be on Thursday January 5, 2023 (3-4 PM Cairo local time, GMT+2)
Whenever possible, please send your cases one week before the due date of our next meeting.
For further inquiries please do not hesitate to contact us

Best Regards
TiP-HO meeting coordinators

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