Transplant in Pediatric Hematology Oncology (TiP-HO)
Tumor Board Meeting Minutes (Thursday, November 3, 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. Hanafy Hafez	Consultant of Pediatric Hematology/Oncology & Stem cell transplant Children's Cancer Hospital (CCHE-57357) National Cancer Institute, Cairo University, Egypt
Prof. Dr. Hisham Eissa	Consultant of pediatric Hematology/Oncology & stem cell transplant Children Hospital Colorado, United States
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. Mansoor Ahmed Mazari	Consultant of Pediatric Hematology/Oncology, Children Hospital, Pakistan
Prof. Dr. Ramya Uppuluri	Pediatric hemato/oncologist and BMT physician Apollo hospitals Chennai, India
Prof. Dr. Revathi Raj	Senior consultant and head of BMT unit Apollo hospitals Chennai, India
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 Stem cell transplant program NBK Children's hospital, Kuwait
Prof. Dr. Zohreh Nademi	Consultant of Immunology and Stem Cell Transplant. Children's BMT, Great North Children Hospital, Newcastle upon Tyne, England

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 upon Tyne Hospitals NHS Foundation Trust, United Kingdom
15. NBK Children 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— Challenges in Managing mixed Chimerism with GVHD in a Child with CGD post MUD-SCT

- 4 months old, only child in a non-consanguineous marriage
- Complaining of loose stools with blood streaks and many episodes of otitis media
- Diagnosed as probable cow's milk protein allergy
- Required steroids with flare up of symptoms on steroid tapering
- Evaluation for possible inborn error of immunity was done:
    - Whole exam sequencing: **CYBB** mutation, X-linked recessive
- Diagnosed as ***chronic granulomatous disease*** and referred for transplantation at 8 months of age
- On presentation:
    - Recent flare up of colitis - steroid dependent
    - Otitis media on/off
- **Pet CT** revealed: ill-defined multiple nodules in the lungs bilaterally
- Infectious disease specialist opinion was to give antibiotics for 10 days
- **HSCT data:**
    - No compatible family donor
    - No unrelated donor in DATRI-indian registry
    - 10/10 donor in DKMS-german registry (**54 years old male)**
    - Reduced intensity conditioning (**TT / TREO / FLU / ATG**)
    - PBSCS
    - CD34: 7 x 10^6
    - GVHD prophylaxis: MTX and Tacrolimus
- **Stormy course post stem cell infusion:**
    - Persistent fever
    - Combination of cytokine release syndrome and with culture positive candida sepsis
    - Persistent loose stools
    - TTT: low dose adrenaline, low dose steroids, Amphotercin B, PPN, continuous nasogastric feeds as tolerated
- Engrafted on D+14 with 100% chimerism on several occasions
- Continued to have loose stools
- **Rectal biopsy** done twice and revealed **acute grade 2-3 GVHD**
- Patient was on steroids and Ruxolitinib and Cyclosporin was added
- Fecal microbial transplant done on several occasions
- Transient improvement with each intervention with flare up again later on
- **5 months post-transplant:**
    - Features of skin and gut GVHD
    - Chimerism started to drop to 77%
    - Split chimerism revealed: 100% lymphoid chimerism with 5.9% myeloid chimerism
- **Recurrence of inflammatory bowel disease**:
    - Loose stools with blood streaks
    - Abdominal pain with progressive loss of weight
    - Invasive pulmonary aspergillosis
    - On tube feeding and Morphia infusion
- Succumbed to the above, 8 months post-transplant

Questions raised by presenter (Dr. Ramya Uppuluri, India)

- In the event of mixed chimerism with features of GVHD, what should be the course for immunosuppression?
- Experience in managing IBD in CGD children?

Tumor board recommendations:

- For patients with CGD and IBD like symptoms, obtaining a pathology prior to transplant would be helpful to compare with the pathology post-transplant in case of symptoms recurrence
- In regards to the patient's transplant history, most probably the patient had manifestations of GVHD that needed to be treated appropriately
- ECP could have been used to manage the steroid refractory GVHD with less side effects than other drugs
- It is challenging to find the balance between treating GVHD with the appropriate immunosuppression, protecting the graft and preventing severe infections, and this decision should be personalized according to each patient's condition
- Granulocyte infusion can help treating severe infections in patients receiving immunosuppressive drugs
- If the patient was alive, his only option would have been treating the infection and going for a second HSCT

Scientific materials:

1. Sima T. Bhatt, Megha Malhotra and Jeffrey J. Bednarski, **Narrative review of contemporary strategies in stem cell transplantation for chronic granulomatous disease,** pediatric medicine, 2021, http://dx.doi.org/10.21037/pm-20-10
2. Sarah E. Henrickson, Artemio M. Jongco, et al, **Noninfectious Manifestations and Complications of Chronic Granulomatous Disease**, Journal of the Pediatric Infectious Diseases Society, 2018, DOI: 10.1093/jpids/piy014
3. Natasha Kamal1, Beatriz Marciano, et al, **The response to vedolizumab in chronic granulomatous disease-related inflammatory bowel disease**, Gastroenterology Report, 2020, https://doi.org/10.1093/gastro/goaa005

Case 2: Transplant Associated Thrombotic Microangiopathy

- A 9 yeras old girl
- **Date of Transplant**: 30/06/2022
- **HSCT Indication**: Severe SCD. ACS, Splenectomized (2016)
- **CMV Risk status**: high risk
- **HSCT Source**: Haplo-identical from her father, PBSC, CD34 dose 8.2 x 10^6/ kg
- **Blood group**: (O) positive, Donor blood group: (A) positive
- **Conditioning**: FTT ATG, PTCy
- **GVHD Prophylaxis**: MMF, Tacrolimus
- **Date of Neutrophil Engraftment**: (D+14)
- **Date of Platelet Engraftment:** (D+18)
- **Chimerism:**
    - D+28: peripheral blood: 99.2% Lymphocyte: 99.6 %
    - D+60: peripheral blood: 98.5% Lymphocyte: 98.3 %
    - D+90: peripheral whole blood>99%
- **TRANSPLANT RELATED MORBIDITY:**
    - Skin GVHD D+38: Grade II ,improved with local creams.
    - Gut GvHD D+40: Methylprednislone and Budesonide
    - UTI D+ 42: Kleibsella pneumoniae treated and discharged home
- **Presented (D+84)**: absence seizure, unresponsive then GTC convulsions for about 45 minutes
    - Stopped after Midazolam, Diazepam, keppra, then Phenytoin
    - Antinfective agents: Meropenem, Vancomycin, Aciclovir
- Admitted to PICU:
    - Unconscious unwell, tachycardic 160-170/mint,
    - PLT 24X109/L, Mg 0.48 mmol/L, Tacrolimus level was 11 ng/ml
    - CT brain showed post-ictal changes. (?PRES/encephalitis)
- Remain unwell:
    - Deteriorating in her mental status and behavior
    - (delirium, visual hallucinations, aggressive, insomnia)
- Psychiatric evaluation: start risperidone, melatonin
- Neurologist opinion: EEG showing focal slowness, to be repeated
- Progress: Still unwell, febrile, deteriorating mentally, hypertensive, tachycardic, maculopapular rash
- Cardiac echo: vegetation at catheter edge
- Blood film: **fragmented RBCs**
- **Other investigations done:**
    - LYMPHOCYTE subset: CD4 absolute 237 cells/ ml
    - Virology: Negative PCR for CMV, EBV, BKV/JCV
    - **Hapotglobin: 2.39 g/L normal**
    - **LDH: high**
    - **No proteinuria**
    - Galactomnnan: negative
    - COVID swab: negative
    - G6PD: normal
    - Brain MRI, MRA/V: normal study
    - CT chest: normal
    - Patient refused to do LP
    - Complement assay was not available

Diagnosis:

- **Infective endocarditis:**
  - Continue on antibiotics for 6 weeks
  - Repeated Echo: disappeared previously seen shadow
- **TA-TMA:**
  - Methylprednisolone 2 mg/Kg/D (Tachycardia, hypertension and rash improved)
  - Eculizumab 600 mg IV once a week
- **In summary:** D +130, post-SCT PBSC haploidentical transplantation, with resolved line related IEC and with TA-TMA/PRES (full chimerism all through)
- **Current medications**: Prednisolone 10 mg PO BD/ MMF 500mg BD/ Acyclovir 400 mg po bd/ Eculizumab 600 mg IV once a week/ Keppra/ Melatonin/ Risperidone/ Amlodipine/ Folic acid
- Symptoms relapsed on tapering steroids so she was kept on 1mg/kg/day

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

- Proper Duration of steroids and Eculizumab therapy?

Tumor board recommendations:

- TA-TMA can mimic many other conditions so a diagnosis should be made carefully going through the diagnostic criteria and excluding other etiologies (LP to exclude infectious etiology would be helpful)
- Although it is an atypical presentation, isolated CNS TA-TMA can occur
- A complement assay (C5b9 – CH50) & 24-hour protein in urine are recommended to help confirming the diagnosis of TMA as well as guide regarding the frequency and dosing of Eculizumab
- Keeping the patient on adequate meningococcal coverage while on Eculizumab is recommended
- TA-TMA can be initiated by infection or GVHD and in absence of an infectious etiology, the patient needs to be kept on proper GVHD prophylaxis for a longer period
- Appropriate GVHD prophylaxis for this pt should not include calcineurin inhibitors nor mTOR inhibitors, so it would be appropriate to use steroids +/- MMF with a clear plan of slow tapering of steroids to avoid side effects
- Other treatment options for TA-TMA includes lectin inhibitors and defibrotide

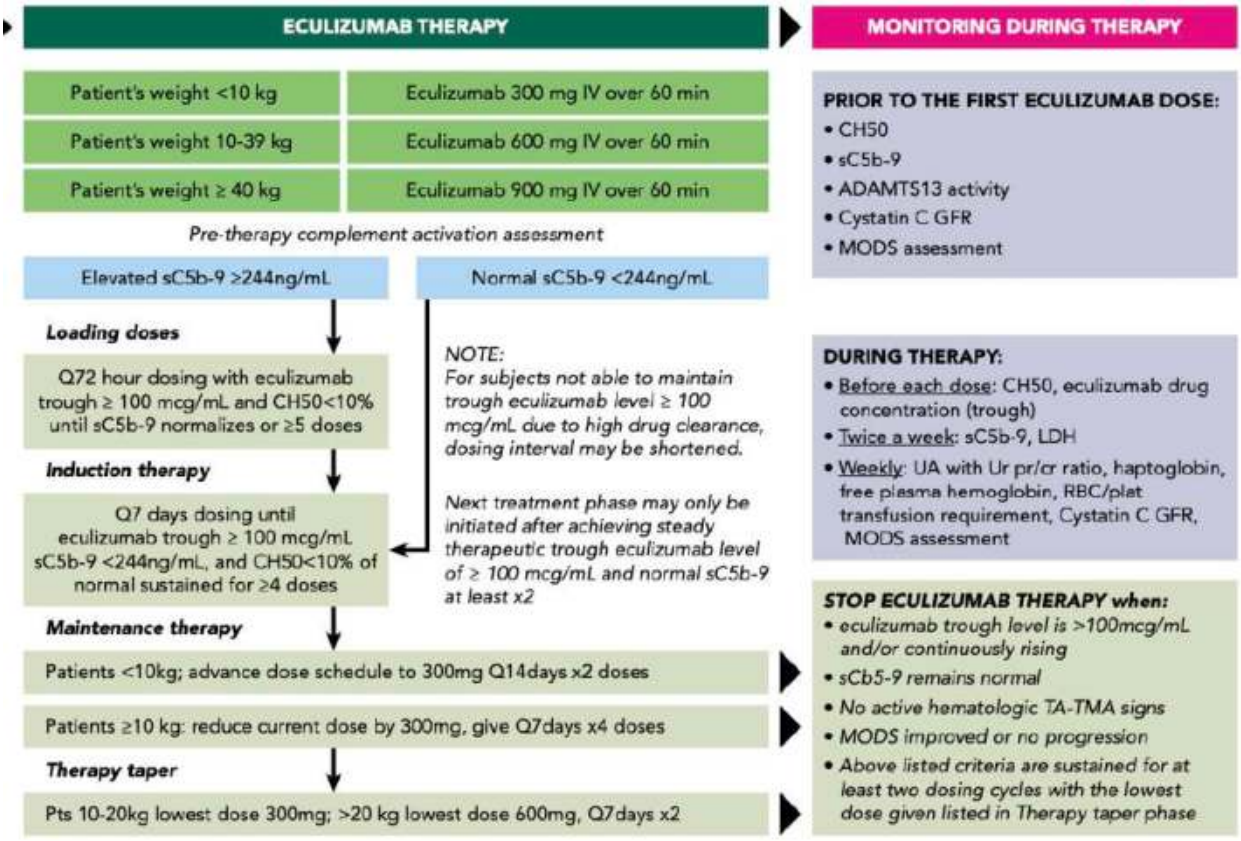
Scientific materials:

Table 1. TA-TMA diagnostic criteria and supportive biomarkers by for children and young adults.

Diagnostic TA-TMA criteria for children and young adults by Jodele et al.[1]	
A. Microangiopathy diagnosed on tissue biopsy or B. Laboratory and clinical markers indicating TA-TMA	
Biomarker	Description
1. Lactate dehydrogenase	Elevated above the upper limit of normal for age
2. Proteinuria	A random urinalysis protein concentration of ≥30 mg/dL x2 or random urine protein/creatinine ratio (rUPCR) ≥2 mg/mg
3. Hypertension	<18 y of age: a blood pressure at the 95th percentile for age, sex and height. ≥18 y of age: a blood pressure ≥140/90 mm Hg.
4. De novo thrombocytopenia	Thrombocytopenia with a platelet count <50 × 10^9/L or a ≥ 50% decrease in the platelet count or thrombocytopenia requiring transfusion support
5. De novo anemia	A hemoglobin below the lower limit of normal for age or anemia requiring transfusion support
6. Evidence of microangiopathy	The presence of schistocytes in the peripheral blood or histologic evidence of microangiopathy on a tissue specimen
7. Terminal complement activation	Elevated plasma concentration of sC5b-9 above upper normal laboratory limit

Need to meet >4 of 7 biomarkers for diagnosis of TA-TMA
Biomarker 2 and 7 present indicate high risk TA-TMA associated with poor outcome

Jodele et al, EXPERT REVIEW OF HEMATOLOGY, 2021



Jodele et al, Blood, 2020

- S. JODELE AND A. SABULSKI, **Transplant-associated thrombotic microangiopathy: elucidating prevention strategies and identifying high-risk patients**, EXPERT REVIEW OF HEMATOLOGY, 2021, DOI: 10.1080/17474086.2021.1960816
- S. Jodele, Christopher E. Dandoy et al, **Complement blockade for TA-TMA: lessons learned from a large pediatric cohort treated with eculizumab,** Blood, 2020, DOI 10.1182/blood. 2019004218
- Joanna A. Young, Christopher R. Pallas, Mary Ann Knovich, **Transplant-associated thrombotic microangiopathy: theoretical considerations and a practical approach to an unrefined diagnosis,** Bone Marrow Transplantation, 2021, https://doi.org/10.1038/s41409-021-01283-0

Our next TiP-HO meeting will be on Thursday, December 1, 2022 (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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