In the name of God

Indication of Hematopoietic Stem Cell Transplantation (HSCT) in Pediatric Acute Myeloid Leukemia

Bibi Shahin Shamsian (MD) .

Mofid Children Hospital

CASE Presentation

Acute Megacaryoblastic Leukemia (AMKL, AML M7)

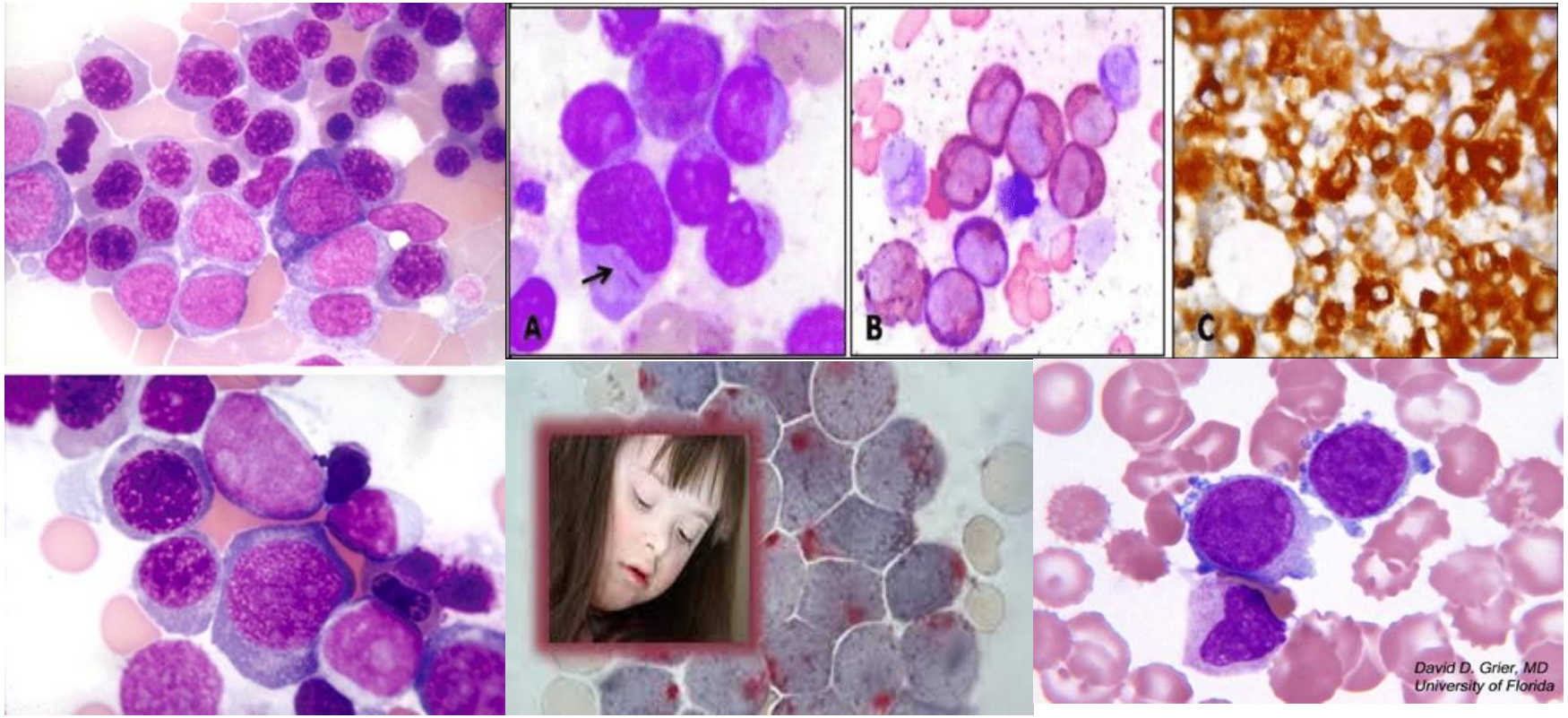
- A 3.5 Y old Boy, Single child, History of Neonatal Trombocytopenia & improving
- **CC: at 2.5 y old;** Weakness , Splenomegaly & Bicytopenia WBC ; 8800 Hb:7 plate: 53000
- BMA & CD &BMB : **AML M7 (CD61;44 CD41;44 Cd71:66 Cd117; 73, Cd33;55 Cd235; 71)**
- No Translocation, FLT3 neg
- Cytogenetic : **47XY Extra ch of + 21 /**, Der 5 t(1,5) (q15;p15.1),**Del(7)**(p11 p15) Deletion
- **Chemotherapy ;** MRC protocol & 1 course/DAT and 1course Flag Duo to MRD pos **CSF : NL**

CASE Presentation

Acute Megacaryocytic Leukemia (AMKL, AML M7)

- **HAPLOIDENTICAL HSCT**; Father, (D&R BG: O neg , CMV+)
- Time of HSCT (BMA) : CR1 MRD : 0.003 CSF: NL
- Condition Regimen : Bus ,Flu ,Mel
- SC infusion : CD34: 20x106/kg ,CD3: 800 x106/kg
- GVHD : CPM post HSCT days+3 and+ 4 ,and MMF +Cyclospurine Day+ 5
- Engraftment : Day + 15
- Complications : Engraftment syndrome,CMV infection day +21, Skin GVHD stage 2 that is under control.
- Chimerism : 100%
- BMA post HSCT ; Remission MRD : <0.003
- Now; 4 mo post HSCT : Chimerism : 100%

HSCT in ACUTE MYELOIED LEUKEMIA IN CHILDREN



Pediatric Acute Myeloid (AML)

- Pediatric Acute Myeloid Leukemia (AML) , constitutes ¼ **of cases of pediatric acute leukemia,** is a heterogeneous disease .
- **Children with AML in comparison with Adults have <u>superior outcomes</u> due to:**
- **Fewer adverse Genetic Mutations**
- **The ability to tolerate the high-intensity chemotherapy currently necessary for cure**
- **But pediatric AMl remains a therapeutic Challenge**
- **The rate of event-free (EFS) and overall survival (OS) rates are commonly around 50% and 70% & the relapse rate is high, 30%.**

HSCT In pediatric AML

- During last years remarkable achievements obtained with **Frontline Chemotherapy** in the treatment of children with acute leukemia (Acute leukemia: ALL & AML)

- **Allogeneic Hematopoietic Stem Cell Transplantation** (HSCT) ,in significant proportion of patients still are used with either in **first complete remission (CR1) or beyond,** to achieve definitive disease eradication .

HSCT In Pediatric AML

- **HSCT is an Treatment option for improving outcomes in pediatric AML:**
- Discovery and application of clinically relevant **HR features (Genetic risk Stratification**
  - Use of **highly Sensitive methods of Minimal Residual Disease(MRD) detection**

  - **Changes in HSCT Strategy including:**

✓Human leukocyte antigen (HLA) (High resolusion Method)

✓Expansion of the Donor pool(MSD, MRD , **MURD, Haploidentical,..**)

✓Conditioning regimen

✓Graft-versus-host disease (GVHD) prophylaxis

✓Toxicity Management & Better Supportive Care

✓**Integration of Targeted Therapies & Novel Agent**

RISK STARTIFICATION & Treatment Plan IN AML

- **Cytogenetic Markers & Treatment Response** are strongly associated with **Survival in pediatric AML.**
- **Challenge: is t**he **variability in the Classification of HR patients**, which leads to the **inconsistent use of HSCT in Clinical trials**

- **Risk stratification for pediatric AML : 2001 , then 2008 WHO Classification; Cytogenetic Markers & Disease Response (Morphologic Evaluation)**
- Advancement of Technology - MRD assay ;**Multidimensional Flow Cytometry, Cytogenetics, & Next-Generation Sequencing(NGS),**

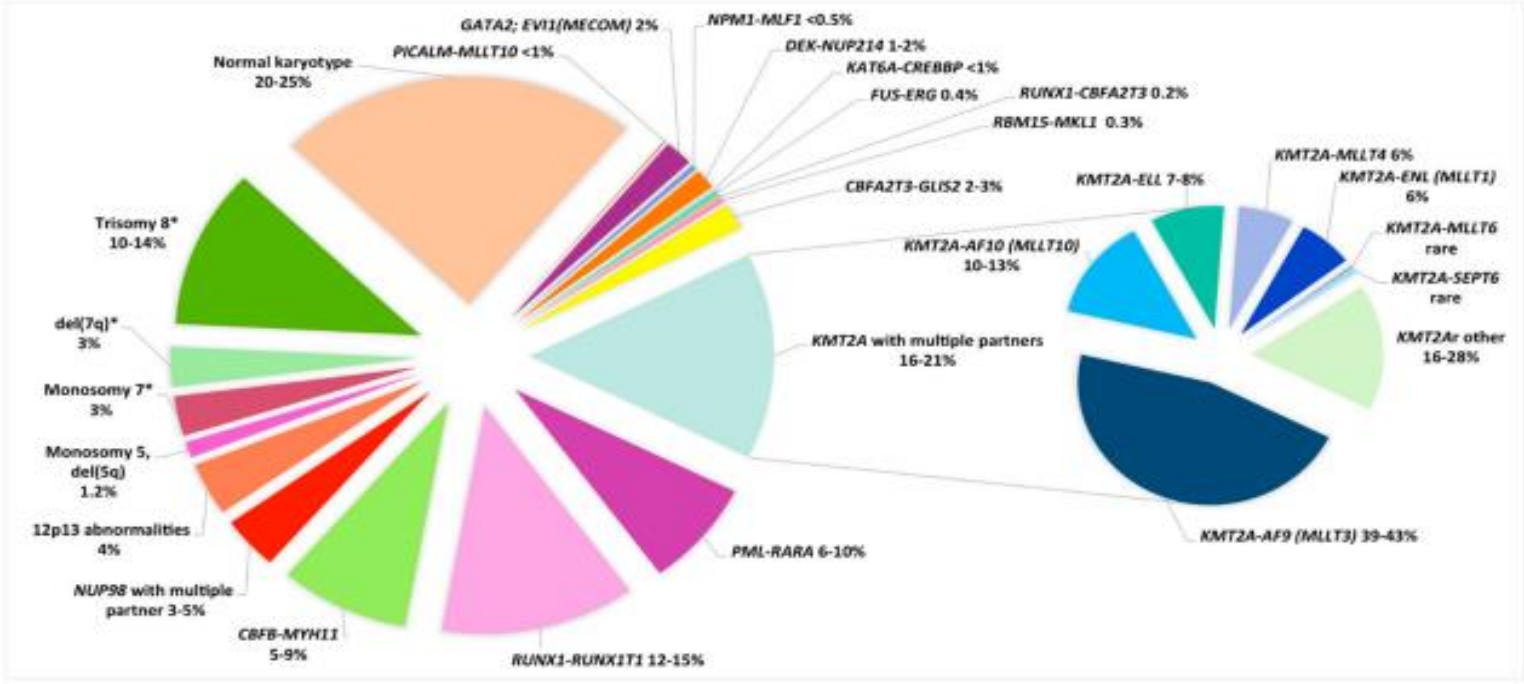
MRD is a major area of focus for the determination of prognostic significance.

Risk Classification in pediatric AML
Genetic Risk Classification

- Treatment decisions, for HSCT, in pediatric AML are primarily driven by **Genetic risk classification which is quickly evolving.**

- The identification of **recurrent and New** mutations has provided an opportunity to develop New treatment approaches.
- **These strategies are now being employed in children with the aim of improving cure rates and providing more options in the relapse setting.**

Distribution of cytogenetic subgroups in pediatric AML. * As a sole abnormality .Risk-adapted therapy:
. Cytogenetics of Pediatric Acute Myeloid Leukemia: A Review of the Current Knowledge. Julie Quessada. Genes 2021, 12, 924



AML in Children: Emerging Paradigms in Genetics and New Approaches to Therapy .Shannon E. Conneely. Curr Oncol Rep (2021) 23: 16. Texas Children's Hospital

Category	Mutation	Reference	Prevalence	Estimated EFS	Estimated OS	Special considerations
Tyrosine kinase	FLT3/ITD AR > 0.1	13, 20	15%	25–35%	60%	Co-occur with *WT1*, *DEK-NUP214*, and *NUP98* fusions
	FLT3-TKD	13	8–10%			
	RAS	13, 21	35–40%	65%	81%	*NRAS* mutations more common than *KRAS*
	KIT	13, 21	12%	60%	90%	Enriched in inv(16) and t(8;21) AML
Epigenetic modifiers	KMT2A fusions	9, 27	15–20%	44%	56%	Prognosis dependent on fusion partner
	t(9;11)		39–43%[a]	50%	63%	
	t(4;11)		1–2%[a]	29%	27%	
	t(6;11)		5–8%[a]	11%	22%	
	t(10;11)(p11.2q23)		1–2%[a]	17%	27%	
	t(10;11)(p12q23)		13%[a]	31%	45%	*MLL-MLLT10* fusion
	t(11;19)		12–14%[a]	46-49%	47-61%	
	MLLT10 fusion (non-KMT2A)	29, 30	< 1%		36%	EMD common
	DEK-NUP214	13, 17, 32	1–2%	32% 68%[b]	53%	High rates of induction failure More common in > 10 years of age
	KAT6A fusion	35	< 0.5%	57%	59%	Common in c-AML and may have spontaneous remission 66% with EMD
Transcription factors	WT1 mutation	10, 13	10–15%	30%	45%	Often co-occurs with *NUP98* fusion or *FLT3*/ITD

New therapeutics in pediatric AML.Drug Mechanism of action Current stage of development in pediatric AML.

Shannon E. Conneely. Curr Oncol Rep (2021) 23: 16

Drug	Mechanism of action	Current stage of development in pediatric AML
Drug-antibody conjugates		
Gemtuzumab ozogamicin [14]	Anti-CD33 antibody with calicheamicin payload	FDA-approved for newly diagnosed AML > 1 month of age Standard of care as single dose in induction 1
Flotetuzumab [58]	CD123/CD3 bispecific dual-affinity retargeting antibody	Phase I trials for r/r AML
Nivolumab [61]	Anti-PD-1 antibody/checkpoint inhibitor	Phase I/II trial for r/r AML combined with azacitidine
Epigenetic modifiers		
Decitabine [67]	Hypomethylating agent: inhibits DNA methyltransferases	Completed phase I trial for r/r AML Phase II trial with standard chemotherapy in newly diagnosed AML

New therapeutics in pediatric AML.Drug Mechanism of action Current stage of development in pediatric AML.

Curr Oncol Rep (2021) 23: 16

Azacitidine [68]	Hypomethylating agent: inhibits DNA methyltransferases	Phase I/II trials for r/r AML Phase II trial with standard chemotherapy in newly diagnosed AML
Vorinostat [72]	Inhibits histone deacetylase	Phase I trial for r/r AML
Panobinostat [71]	Inhibits histone deacetylase	Phase I trial for r/r AML
Tyrosine kinase/*FLT3* inhibitors		
Sorafenib [80]	1st-generation type II TKI: active against *FLT3*-ITD and *FLT3*-TKD mutations	Completed phase III trials for high AR *FLT3*-ITD AML
Midostaurin [83]	1st-generation type I TKI: active against *FLT3* and *KIT* mutations	USA: phase I/II trials terminated for low enrollment International: ongoing phase II trial
Gilteritinib [87]	2nd-generation type I TKI: active against *FLT3* and *AXL*	Phase III trials combined with standard chemo in newly diagnosed AML Phase I/II trial combined with FLAG for r/r AML
Quizartinib [75]	Type II TKI	Phase I/II trials in r/r AML
Crenolanib [75]	Type I TKI	Completed phase I trial in r/r leukemias
Others		
Venetoclax [99]	Inhibits BCL-2	Phase I/II trials for r/r AML
CPX-351 [99]	Liposomal formulation of daunorubicin and cytarabine—enhances synergy between drugs and extends half-life	Completed phase I/II trials for r/r AML Current phase III trial for newly diagnosed AML
Atovaquone [99]	Inhibits oxidative phosphorylation and STAT3 activation	Phase I trial with standard chemotherapy
Chimeric antigen receptor T cells		
CD123-targeting CAR-T [62]	T cells genetically modified to target/kill CD123-expressing AML cells	Phase I trials for r/r AML
CD33-targeting CAR-T [46]	T cells genetically modified to target/kill CD33-expressing AML cells	Phase I trials for r/r AML

Current Treatment Approach & New Therapy in Pediatric AML Shannon E. Conneely. Curr Oncol Rep (2021) 23: 16. Curr Oncol Rep (2021) 23: 16. Texas Children's Hospital.

- **Novel Agents :**

- Immune-Based Therapy ,Drug-Antibody Conjugates: Gemtuzumab Ozogamicin (GO-Anti Cd33, Mylotarge)
- FLT3 Inhibitors: Sorafenib, Giltrinib
- Checkpoint Inhibitors: NIVILUMAB
- Epigenetic Modifiers: Hypomethylating Agent: Decitabine & Azacitidine
- BCL-2 Inhibition : Venetoclax (wwith or without cytozar)
- Liposomal Chemotherapy (Cytarabine & Daunorubicin) :CPX-351
- Chimeric Antigen Receptor T Cell(CAR Tcell) : AgCD33 & CD123

Bridge to: HSCT in Pediatric AML

Indications of HSCT In PEDIATRIC AML

Risk Criteria

- Cytogenetic Markers
- Treatment Response (MRD?...)

Strongly are associated with **Survival** in pediatric AML.

HSCT Indications in AML

- Considering recent improvements in **Chemotherapy and the potential Risk of Acute & Late toxicities** after **HSCT**

The current practice restricts the use of HSCT in CR1 only to:

- **AML patients with high-risk (HR) features.**
- **However, there is no universal agreement on the definition of HR disease and different criteria have been, and continue to be, used by different cooperative groups**
- **There is general consensus that standard-risk patients (Favorable& Intermediate?) should not be transplanted in CR1 but only after the First relapse and achievement of a second complete remission**

HSCT indications in Childhood AML.

J. Mattia Algeri & Franco Locatelli . Jurnal Clin Med. 2021, 10, 3790.Italy

	GENETIC RISK CRITERIA
CR1	Complex karyotype (≥3 aberrations including at least one structural aberration)
	Monosomal karyotype (−7, −5, del 5q)
	11q23/KMT2A rearrangements, involving: - t(10;11)(p12;q23)/*KMT2A-AF10* - t(10;11)(p11.2;q23)/*KMT2A-ABI1* - t(6;11)(q27;q23)/*KMT2A-MLLT4* - t(4;11)(q21;q23.3)/*KMT2A-MLLT2*
	t(11;12)(p15;p13)/*NUP98-KDM5A*
	t(7;11)(p15.4;p15)/*NUP98-HOXA9*
	t(5;11)(q35;p15)/*NUP98-NSD1*
	t(6;9)(p23;q34)/*DEK-NUP214*
	t(16;21)(q24;q22)/*RUNX1-CBFA2T3*
	t(7;12)(q36;p13)/*MNX1-ETV6*
	t(3;21)(26.2;q22)/*RUNX1-MECOM*
	t(16;21)(p11.2;q22.2)/*FUS-ERG*
	FLT3-ITD with AR ≥0.5 without NPM1 mutations
	inv(3)(q21.3q26.2)/t(3;3)(q21.3q26.2)/*RPN1-MECOM*
	inv(16)(p13.3q24.3)/*CBFA2T3-GLIS2*
	12p abnormalities

HSCT indications in Childhood AML.

J. Mattia Algeri & Franco Locatelli . Jurnal Clin Med. 2021, 10, 3790.Italy

	RESPONSE RISK CRITERIA
	MRD ≥ 1% after the first induction course
	MRD ≥ 0.1% after the second induction course
	Primary Induction Failure [i.e. patients with ≥25% blasts after the first induction course and ≥5% blasts after the second induction course]
	SECONDARY AML
	Therapy-related AML
	AML evolving from myelodysplastic syndrome (MDS)
CR2 Al	All patients

Favorable Group in Pediatric AML.

Mattia Algeri .Clin. Med. 2021, 10, 3790.Italy

- **Patients with Acute promyelocytic leukemia (AML- M3 ,APL) & t(15;17), owing to the advent of ATRA and Arsenic trioxide, ;Extremely favorable prognosis**
- Core-binding factor (CBF) transcription factors, **Inversion16(p13;1q22), t(16;16)(p13;q22) & t(8;21)(q22;q22),** By all study groups as favorable risk group markers
- **Core binding factor mutations t(8;21) and inv(16) with OS > 90%**

Favorable Group in Pediatric AML.

Mattia Algeri .Clin. Med. 2021, 10, 3790.Italy

- **Recently, CBF, t(16;21)(q24;q22),** resulting in RUNX1-CBFA2T3 fusion: **Good prognosis**
- Different translocation of ch **16 and 21,** **t(16;21)(p11;q22) (FUS-ERG),** a rare subgroup of AML /Eextremely poor prognosis, **/needs HSCT in CR1**
- **Biallelic Mutations of CEBPA**
- **Mutations in Nucleophosmin1 (NPM1) with a normal karyotype**
- **wild-type FLT3**

Medical Research Council (MRC)-AML group

Adverse cytogenetic features

Mattia Algeri Clin. Med. 2021, 10, 3790.Italy & Julie Quessada. Genes 2021, 12, 924

- −7; (Monosomy 7): **OS rate of 30% ,** -5 Monosomy , Del(5q)
- Abnormal 3q or **Complex karyotype**
- t(6;9)(p22;q34), < 1% cases of AML Cases associated with FLT3 ITD in approximately 40% & **Treatment failure**
- t(9;22)(q34;q11): BCR-ABL1 in **< 0.6% , Adverse**

➢ **Tyrosine Kinase; FLT3 internal tandem duplication (FLT3/ITD) : 10% to 20% of p- AML cases with high Allelic ratio**

➢ **There is a report by** COG trial for Using of **Bortezomib and Sorafenib in** De Novo AML Patients / High Allelic Ratio FLT3/ITD) (AAML1031- A Phase III Randomized Trial)

Medical Research Council (MRC)-AML group, Adverse cytogenetic features

Mattia Algeri Clin. Med. 2021, 10, 3790.Italy

- **Epigenetic Modifiers:**
- **KMT2A (MLL) rearrangements** (20% - 24% childhood AML) ; different prognostic value depending on the specific fusion partner.
  - In a large study / 756 p the result was with dismal outcome
  - **t(4;11)(q21;q23.3)/KMT2A-MLLT2**
  - **t(6;11)(q27;q23)/KMT2A-MLLT4**
  - **t(10;11)(p12;q23)/KMT2A-AF10**
  - **t(10;11)(p11.2;q23)/ KMT2A-ABI1.**
  - **Patients with such abnormalities are almost candidates for Allo-HSCT in CR1**

HSCT Indications in Childhood AML

Mattia Algeri Clin. Med. 2021, 10, 3790.Italy

Allyson Flower. Clinical Advances in Hematology & Oncology Volume 15, Issue 1 January 2017. NY . USA

- **Secondry AML:**
  - Therapy Related
  - AML evolving from Myelodysplastic syndrome(MDS)

&

- **ALL Pediatric patients of AML in CR2**

HSCT Indications in Childhood AML

Mattia Algeri Clin. Med. 2021, 10, 3790.Italy

Allyson Flower. Clinical Advances in Hematology & Oncology Volume 15, Issue 1 January 2017. NY . USA

- (MFC-MRD) : is a strong & independent prognostic marker of Relapse in pediatric AML as a risk criteria .
- Response> 1% MRD after first induction
- > 0.1% MRD after second induction
- MRD can be used to identify HR patients among those without prognostically significant cytogenetic markers.

- Risk criteria : (BM Morphology)
- Patients > 25% blast after 1th induction course , or > 5% blast after 2th induction course

The Role of Pre-Transplant Minimal Residual Disease: Better Remission for Better HSCT Outcome? J. Clin. Med. 2021, 10, 3790

- pre-transplant MRD status correlates with the risk of relapse and OS after HSCT.
- Target Therapy :Several immunotherapies are in various stages of pre clinical and clinical development for AML, including Antibody-drug conjugates, Bispecific antibodies, cellular therapies and checkpoint inhibitors may be used.
- Currently, Early-phase cellular immunotherapy studies for children with AML are used as a **bridge to transplant.**

- It is too early to speculate whether such approaches will also be able decrease the need for subsequent HSCT???

MRD Evaluation in pediatric AML /Pre HSCT.
Allyson Flower. Clinical Advances in Hematology & Oncology Volume 15, Issue 1 January 2017.
NY . USA

- **Immunotherapy, in the settings of AML:**
- Where the availability of immunotherapy approaches outside clinical trials is still limited, the benefit of repeated efforts aimed at achieving MRD-negativity before transplant should be carefully *weighed against the risks* of inducing additional toxicities affecting post-transplant outcome.

MRD Evaluation in pediatric AML /Pre HSCT.

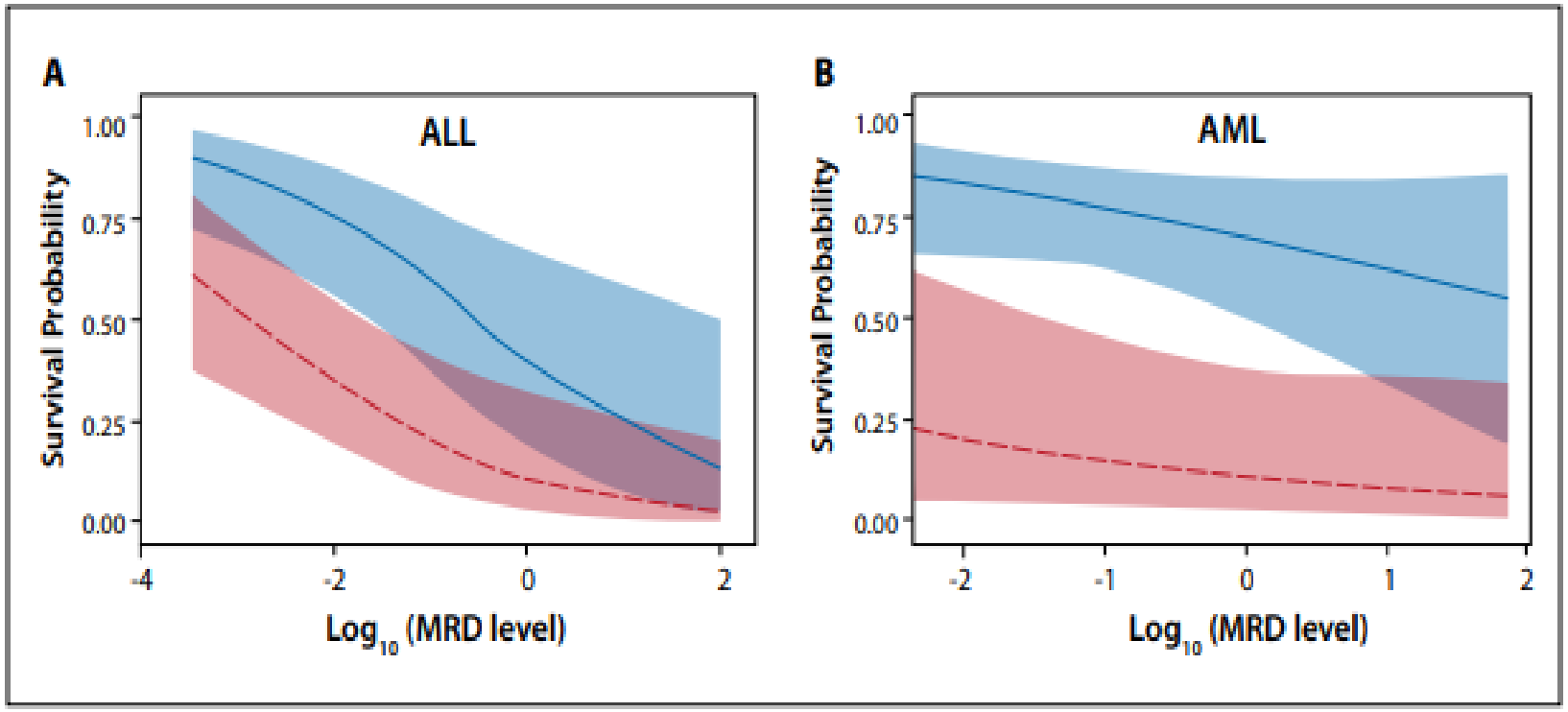
Allyson Flower. Clinical Advances in Hematology & Oncology Volume 15, Issue 1 January 2017.
NY . USA

- **Prospective study related to MRD : 232 children /AML**
- MRD Assay as risk-stratification criteria together with Genetic features:
- **High-level MRD positivity** (≥1% leukemic cells) after **first induction** was associated with a greater **incidence of relapse** compared to low-level of MRD (< 0.0001).
- Subsequent studies by different cooperative groups have confirmed the strong prognostic relevance of MRD after the first and the second induction course

Graphs show probability of survival according to level of MRD, stratified by leukemia type and treatment era. After HSCT

The effect of MRD level on survival was significant for ALL (P=.002) but not for AML (P=.18).

Allyson Flower. Clinical Advances in Hematology & Oncology Volume 15, Issue 1 January 2017 5. USA



Maintenance therapy in AML: The past, the present and the future

Matteo Molica. **Am J Hematol. 2019;94:1254–1265. Texas MD Anderson Cancer Center, Houston,Texas**

- **Maintenance treatments might play a crucial role in specific subsets of AML patients in CR after consolidation or SCT**
- **Effective maintenance therapy could play an important role in prolonging the remission interval in the post-consolidation setting, especially in high risk AML patients.**
- Maintenance treatment approaches based on conventional chemotherapy, immunotherapy, hypomethylating agents, and targeted small molecules have been explored in this setting
- **No data so far have been convincing enough to establish this approach as the standard of care.**

Post-Transplant MRD in AML : Is There Room for Intervention?

- **The role of MRD after transplant in pediatric AML is less defined**
- There is evidence that **post-HCT positivity of MFC-MRD** can predict of **Relapse**

- **Chimerism :**Finally, although less sensitive than MRD, **close chimerism monitoring** on peripheral blood has proven useful for the early detection of impending **Relapse in both ALL and AML**

MRD positivity in post HSCT in AML

Intervention

- Rapid Discontinuation /or abrupt cessationof immune suppression
- Infusion of Donor-derived lymphocytes(DLI)
- Administration of Cytokines ;NK cell infusion
- Combination of **Azacytidine & DLI** :prevent overt disease recurrence in MRD-positive patients of AML
- AML - FLT3/ITD-positive; post-transplant TKI (Imatinib and Sorafenib or Midostaurin) especially for patients showing **Molecular MRD recurrence after-HSCT**

HSCT in RELAPSE & REFRACTORY P- AML

- **30% -40% of all pediatric patients / AML relapse.**
- Allogeneic HSCT offers the best chance of cure, ideally after the achievement of second CR (CR2)
- **Independent Key Factors in Survival:**
- **Age Younger than 10 years, Favorable Cytogenetics, Duration of CR1,No of HSCT**
- **OS :Relapse > 12 months after diagnosis (48%) Vs relapse during the first 12 mo (21%).**
- **AML - P with low Leukemia burden or in CR at the time transplant have the highest chance of cure**

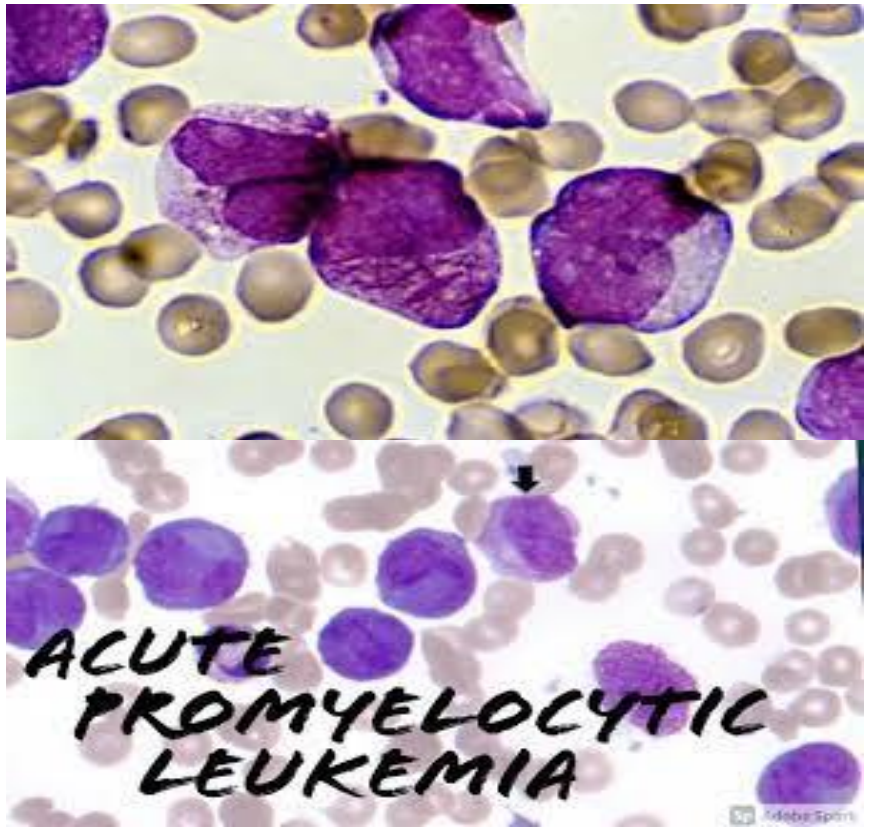
HSCT in RELAPSE & REFRACTORY AML

- Refractory AML, defined as: Failure to achieve a morphological remission after two courses of chemotherapy, is estimated to be as high as 10%
-
- Allogeneic HSCT is currently considered as the only curative strategy in these subjects, being capable of producing long-term DFS in up to 50% of cases .

HSCT for children with AML in Second Remission: report from the Australasian BMT Recipient Registry and the Australian and New Zealand Children's Haematology Oncology Group . Adrian Selim. Pediatr Blood Cancer. 2019;66

- **Achieving (CR2) prior to HSCT is desirable in Relapse AML**
- DATA Analyze/ pediatric HSCT centers in **Australia** & New Zealand /**Relapsed childhood** AML /**1998 - 2013.**
- **Results:**
- **Improved (OS) in children receiving 2 chemotherapy cycles, compared to one cycle or three or more cycles pre-HSCT.**
- **Conclusions: These data suggest that a second chemotherapy cycle pre-HSCT may improve survival by lowering disease burden.**

HSCT IN Sub Groups of AML



Subgroups of Pediatric AML.

- AML with Down Syndrome
- AML post Myelodysplastic syndrome (MDS)
- AML M6, or AML M7
- Reports : Acute Erythroid Leukemia (FAB M6 – FAB M6)& Acute Megakaryoblastic Leukemia (AMKL; FAB M7) are Different from FAB M0-M5.

- More frequency Mono 7
- EFS and OS significantly inferior to that of other AML subtypes.

Allyson Flower.

Clinical Advances in Hematology & Oncology Volume 15, Issue 1 January 2017

AML M7: HSCT in AMKL/ AML M7 of Children

1-Allyson Flower.Clinical Advances in Hematology & Oncology Volume 15, Issue 1 January 2017.2- Jana Schweitzer. *Annals of Hematology* volume 94, pages1327–1336 (2015). Genes 2021, 12, 924.

- Incidence: up to 15% of ped AML .The **most common subtype of AML in children with T21**
- **DS-AMKL blasts harbor Megakaryoblastic and Erythoid markers; that it is reported in the WHO classification as "myeloid leukemia associated with (Down syndrome**") with excellent response & cure with reduced doses of chemotherapy
- **Acquired cytogenetic abnormalities** (mainly trisomy 8, and 1q gain), did not impact on the outcome in one study, whereas in another, trisomy 8 indicated a poor prognosis
- **2-year EFS** IN M7 AML-p without T21 (14%) vs (83%) in M7 AML with T21
- **Translocation *t*(1;22)(p13;q13) :an inferior 5-year EFS (38 ± 17 %)**
- **2-year EFS: Allo HSCT in CR : (46%) Vs (0%) in paitients who are were not in CR**
- **AMKL (Non DS) remains an AML subgroup with inferior outcome .**
  (Constitutional mosaicism for trisomy 21may be seen in 1/10 of cases)
  - **Relapse rate: 48%**

HSCT IN DOWN SYNDROME.

Hitzler etal. Biol Blood Marrow Transplant. 2014 June 01.

- Data on outcomes of Allogeneic HSCT in children with Down syndrome and (DS-AML) are scarce and conflicting.
- Early reports stress, **treatment-related mortality** as the main barrier
- AML in DS (DS-AML) ; Young age of onset, somatic mutations GATA1
- Excellent outcomes with chemotherapy (DFS 80% due to the **increased drug sensitivity of DS-AML blasts** especially in the younger patients . **Most of whom have M7 disease**
- SO: **HSCT is not typically** considered for **DS AML in first remission.**
- For patients beyond first remission, Allo HSCT may be offered but data are scarce and the pattern of treatment failure is unclear.

OUTCOME OF TRANSPLANTATION FOR ACUTE MYELOGENOUS LEUKEMIA IN CHILDREN WITH DOWN SYNDROME. Johann K. Hitzler. Biol Blood Marrow Transplant. 2013 June ; 19(6): 893–897.

- **STUDY:** Outcome data for 28 patients with DS-AML reported to the Center for (CIBMTR) between 2000 - 2009
- A first matched-pair analysis of 21 patients with DS-AML & 80 non-DS AML controls.
- Median age at transplantation for DS-AML was 3 Y . (P< 18 Y)
- Almost 50% of the cohort was in Second Remission.
- Donors: HLA-matched siblings, and matched or mismatched unrelated adult donors or umbilical cord blood
- All but one patient received **MAC regimens.**

1-OUTCOME OF TRANSPLANTATION FOR AML IN CHILDREN WITH DOWN SYNDROME. Johann K. Hitzler. Biol Blood Marrow Transplant. 2013 June ; 19(6): 893–897.
2-AML in children: Current status and future directions. Takashi Taga. Pediatrics International (2016) 58, 71–80. Japan

- 3-year OS: only 19%.
- Only 4 / 28 patients are alive and disease-free.
- The most important reason for Death : Relapse (70%)
- Conclusion:
- Both transplant-related mortality and relapse contribute to higher mortality.
- Chemotherapy approaches are now well defined for DS-AML

Subgroups in Pediatric AML .

Allyson Flower. Clinical Advances in Hematology & Oncology Volume 15, Issue 1 January 2017

- **AML M3/APL:**
- **HSCT should be considered only for patients with Relapse.**
- In a comparison of **Allogeneic vs Autologous HSCT** in relapsed or refractory APL:
- 5-year EFS and OS were not significantly different
- In ALLO HSCT ;Lower rates of relapse but treatment-related **Mortality was significantly higher.**

Secondary AML. Allyson Flower. Clinical Advances in Hematology & Oncology Volume 15, Issue 1 January 2017

- **Therapy-related secondary pediatric AML**
- **2-year OS for therapy-related secondary AML** in pediatric patients undergoing **HSCT while in CR** after reinduction chemotherapy ; **40%.**
- **There are few reported cases of familial cancer syndrome-associated pediatric AML; therefore, the role of HSCT in this population is unclear**

Autologous HSCT in Pediatric AML

- An Evaluation of Autologous HSCT for **pediatric patients with AML demonstrated an OS equivalent to that achieved with chemotherapy alone.**
- Although relapse rates were lower in the autologous HSCT group, the rate of treatment-related toxicity was significantly higher for these patients.
- A clinical trial of pediatric patients with AML that compared Chemotherapy, Autologous HSCT,& Allogeneic HSCT demonstrated superior long-term OS for Allogeneic HSCT (60%) vs Autologous HSCT (48%) and Chemotherapy (53%) for patients in first complete response (CR1) after 2 induction cycles
- **Studies: Autologous HSCT is not currently indicated for pediatric AML consolidation therapy.**

  - Allyson Flower.Clinical Advances in Hematology & Oncology Volume 15, Issue 1 January 2017

1-Maintenance therapy in AML after HSCT

Li Xuan. *Journal of Hematology & Oncology* volume 14, Article number: 4 (2021

2- Low-dose Azacitidine maintenance therapy after Allogeneic HSCT for high-risk pediatric AMl . Akihiro Tamura.*Pediatric Blood & Cancer* (IF3.167), Pub Date : 2018-06-13.

- **Relapse** : the main cause of treatment failure in (AML) undergoing Allo-HSCT
- The dismal prognosis of pediatric (AML) relapsing after (HSCT) requires exploration of novel strategies to prevent relapse.

- **Targeted drugs** such as hypomethylating agents(Azacitidine), FLT3 inhibitorsas as maintenance therapy in AML patients may be useful especially for high-risk AML patients.

CONCLUSION

- **In Pediatric AML for further improve outcomes:**

❑ **Accurate risk stratification strategies using Molecular Genetic analysis**

❑ **Assessment of minimum residual disease(MRD)**

❑ **Introduction of New drugs in international collaborative clinical trials could be effective**

4- Also ,for reduction of TRM in pediatric -AML all factors should be considered :

- Timing of HSCT ,Improving Conditioning Regimen (MAC) or Reduced-intensity(RIC),GVHD prophylaxis,Management of Different Toxicity , Supportive Care ,**Monitoing for Relapse**

Thank You

Mofid Children Hospital (HSCT WARD)