

MIXED PHENOTYPIC ACUTE LEUKEMIA, MPAL: REVIEW OF LITERATURE

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ABSTRACT

Mixed-phenotype acute leukemia (MPAL) is a rare disease and comprises 1.5% to 5% of all acute leukemia. The incidence of MPAL was calculated as 0.35/1000000 person-years. A bimodal age distribution was observed with peaks at age 19 and 60 years of age or older. Leukemias with multilineage protein expression often respond poorly to chemotherapy. Two important algorithms have been used to define this entity - EGIL and WHO. In the EGIL and WHO 2001 acute bilineal leukemias were classified as a distinct entity, whereas in the WHO 2008 these are combined with biphenotypic AL as MPAL. The fifth edition of WHO classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms has described two new subtypes of ALAL with defining genetic alterations. (i)MPAL with ZNF384 rearrangement (ii) ALAL with BCL11B rearrangement. WHO Haem5 classification further highlights other genomic findings such as PHF6 mutations and PICALM:: MLLT10 fusions. During the 1980s, 2 leading hypotheses were raised to explain biphenotypic expression in leukemia - The Greaves hypothesis and "lineage infidelity". In the current era of targeted therapies, the molecular basis of Mixed phenotypic Acute Leukemia is being studied intensively. HSC/MPPs give rise to cells of the erythroid/megakaryocytic lineage and to myelo-lymphoid precursor cells (MLP). C/EBPs may trans-differentiate erythro/megakaryocytic precursors, T cells and early B cells into inflammatory macrophages. Loss of Pax5 may generate various types of myeloid cells and loss/reduction of Pax5 in B cells may promote neoplastic transformation. Early B cells may be reprogrammed into induced pluripotent stem cells (iPS) by the four 'Yamanaka transcription factors' (4YF: Oct4, Sox2, Klf4, c-Myc), whereas late B cells require additional C/EBP for iPS reprogramming.

KEYWORDS: Transdermal Drug Delivery, icroneedle, Liposomes, lithosomes, ethosomes, Nanocarrier.

1. INTRODUCTION

Patients diagnosed with acute leukemia (20% blasts in blood or marrow, or fewer in the case of certain chromosomal translocations or an extramedullary presentation) can generally be classified as having either myeloid lineage–derived disease (AML) or lymphoid lineage– derived disease (ALL). Sometimes the immature cells display cyto-chemical and/or immunophenotypic features of both lineages (biphenotypic) or there are different populations of leukemia cells (bilineal). The distinction between bilineal and biphenotypic leukemias is often blurred, especially because 2 “populations” of cells perhaps represent subclones derived from a unique stem cell. Accordingly, this distinction does not generally affect our diagnostic or therapeutic approach.^[1]

Mixed-phenotype acute leukemia (MPAL) is a rare disease and comprises 1.5% to 5% of all acute leukemia.^[2,3] Shi and Munker analyzed data from the Surveillance, Epidemiology and End Results (SEER) registry and identified 313 reported cases of MPAL as compared with 14739 acute lymphoblastic leukemia (ALL) cases and 34326 acute myeloid leukemia (AML) cases of all ages over a period of 10 year.^[3] The incidence of MPAL was calculated as 0.35/1000000 person-years. A bimodal age distribution was observed with peaks at age 19 and 60 years of age or older.^[3]

Leukemias with multilineage protein expression often respond poorly to chemotherapy. The proposed reasons that mixed phenotype may portend a worse prognosis include: primitive multipotent progenitors being chemoresistant owing to slow replication, mixed-phenotype blasts ability to adapt to therapy by switching phenotype and expression of high level of multidrug resistance proteins.^[4]

Given its rarity, there are few actively enrolling clinical trials or randomized controlled trials from which to guide management. Treatments are largely extrapolated from ALL and AML.^[5]

2. REVIEW OF LITERATURE

Catovsky et al were among the first, in 1991, to propose a classification system that defined BAL based on immunophenotyping which was updated to the EGIL classification.^[3,6]

HOW TO DIAGNOSE MIXED PHENOTYPIC ACUTE LEUKEMIA

Definition

EGIL vs WHO

Two important algorithms have been used to define this entity. In the first of these (1995), the European Group for Immunological Characterization of Acute Leukemias (EGIL) presented guidelines for classification of AL with biphenotypic marker expression. EGIL developed a scoring algorithm in which a point system determined whether a patient had enough immunophenotypic variety to qualify as biphenotypic.^[1,7]

According to **EGIL criteria**, biphenotypic leukemia (BAL) is diagnosed when scores >2 for the myeloid and one of the lymphoid lineages. A marker is considered positive if more than 20% of cells stain positive with a monoclonal antibody; a lower threshold of 10% was set for MPO, CD3, CD79a and TdT.^[1]

The **myeloid lineage** defining marker is MPO as detected by flow cytometry, immunohistochemistry, or cytochemistry; and monocytic differentiation is assigned diffuse positivity based on non-specific esterase or expression of at least two of the following: CD11c, CD14, CD36, CD64, and lysozyme.

The **T-lineage** defining markers are cytoplasmic CD3 or surface CD3.

The **B-lineage** defining marker are either **a strong CD19** with at least one of the strongly expressed CD79a (cytoplasmic CD22, CD10, or weak CD19) or **a weak CD19** with at least two of the strongly expressed CD79a (cytoplasmic CD22 and CD10).

AUL include leukemias that express no lineage specific markers.

These criteria were incorporated in the **WHO 2001 guidelines** for classifying AL of ambiguous lineages.^[5] In **2008**, **new WHO criteria** were proposed for classification of acute leukemias of ambiguous lineages.^[5]

In the EGIL and WHO 2001 acute bilineal leukemias were classified as a distinct entity, whereas in the WHO 2008 these are combined with biphenotypic AL as MPAL.

In case of MPAL of bilineal origin (WHO2008) or bilineal AL (EGIL) there should be two or more different populations in which at least one of these meets the immunophenotypic criteria for AML (with the exception that the second population does not need to comprise at least 20%).^[2]

Table 1: Comparison Of Egil And Who Diagnostic Criteria For Multilineal Acute Leukemia.^[1,2,7,8,9]

Characteristics	EGIL	WHO 2001	WHO 2008	WHO 2017	WHO 2022
Scoring	>2 points for each lineage – myeloid; B lymphoid and /or T lymphoid	Must fulfill criteria for any two lineage : myeloid, monocytes, B lymphoid and / or T lymphoid			
Acute Undifferentiated Leukemia	Included	Excluded			
Bilineal and Biphenotypic	Distinct entities		Combined under same category		
No of lineage markers used	Many	Limited	Limited	Limited	Limited
Threshold of blast Percentage with markers	Clearly mentioned	Not mentioned clearly	Not mentioned clearly	Not mentioned clearly	Not mentioned clearly

Although various thresholds for flow based MPO positivity were introduced over the years (eg, 10% of blast population), no specific threshold has been acknowledged in the 2008 WHO monograph.^[1]

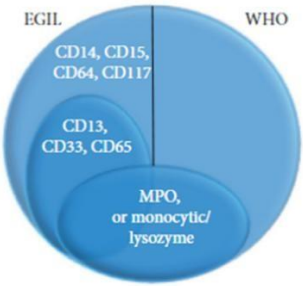
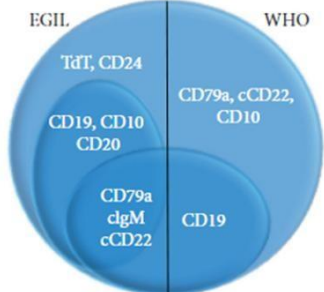
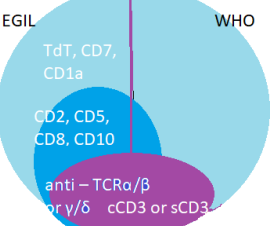
Compared with the EGIL classification, the 2008 WHO classification uses a more limited set of lineage markers that can be more consistently applied. In 2015, the 2008 WHO classification still remained the most practical means to define and subclassify MPAL, but it was hoped that advances in deciphering the molecular pathogenesis of acute leukaemia will soon lead to a more robust approach to the diagnosis of these entities.^[1,2]

The requirements for assigning specific lineages to the blasts are given in the 2008/2017 WHO criteria.

In addition, the 2008 WHO classification includes two distinct categories: MPAL with the t(9;22)(q34;q11) BCR-ABL1 and MPAL with t(v;11q23)/MLL rearrangement.^[8,9]

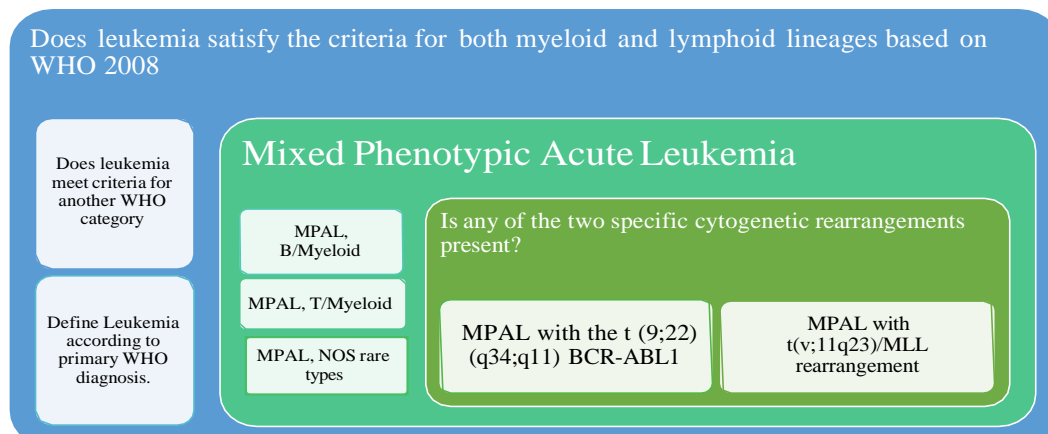
Natural killer (NK) cell lymphoblastic leukemia/ lymphoma was a provisional entity in WHO 2008. It has been removed in WHO 2016 onwards.^[8,9]

Table 2: Lineage Assignment According To Egil And Who.

Lineage	EGIL BAL > 2 points for each lineage	WHO 2008 onwards MPAL must fulfil	Visual comparison between the criteria
Myeloid	0.5 points: CD14, CD15, CD64 1 point: CD13, CD33, CD117, CDw65 2 points: MPO, Lysozyme	MPO or monocytic differentiation (≥ 2 NSE, CD11c, CD14, CD64, Lysozyme)	
B Lymphoid	0.5 points: TdT, CD24 1 point: CD19, CD10, CD20 2 points: cCD79a, cIgM, cCD22	Strong CD19 + ≥ 1 BLM Or Weak CD19 + ≥ 2 BLM	
T Lymphoid	0.5 points: TdT, CD7, CD1a 1 point: CD2, CD5, CD8, CD10 2 points: cCD3 or sCD3, anti-TCR α/β , anti-TCR γ/δ	Strong cCD3 (with antibodies to CD ϵ chain) Or sCD3	

BLM: B lymphoid marker cCD22, CD79a, CD10

2008 Classification of MPAL

**Figure 1 ALGORITHM OF WHO 2008 CLASSIFICATION OF MPAL.**

INCIDENCE

Weinberg and Arber retrospectively reviewed series encompassing 7627 pediatric and adult patients with acute leukemia and determined that 2.8% had BAL and 1.6% had MPAL using the EGIL and WHO 2008 systems, respectively.^[6]

In 517 pediatric and adult **Dutch** patients with acute leukemia, 30 patients (5.8%) would be considered as having BAL based on EGIL criteria, and 8 cases (1.5%) were consistent with MPAL using the WHO 2008 classification; only 6 patients (1.1%) would qualify as both BAL and MPAL, suggesting that these classification systems may select different patients.^[1,3] A more recent **Chinese study** reported MPAL in 2.4% of 4780 patients with acute leukemia (ages 14-81 years).^[1]

MJ. Oberley et al, have evaluated a cohort of 112 cases as to whether they met criteria for WHO2008 MPAL and/or WHO2016 MPAL.^[10,11]

Yan chun Yang, Ya Gao et al have analysed and described eighty-two patients diagnosed with MPAL at Nan fang hospital from 2006 to 2017 using either EGIL or 2008 WHO criteria. They have compared the treatment effect and outcomes between different therapy types. (2) Given the rare occurrence of MPAL and the ability to recognise every possible combination of phenotype, with modern investigation techniques; there are a number of reports of unique forms of MPAL.^[12,13,14]

Mindy P Kresch et al, at the **Memorial Sloan Kettering Cancer Center**, have reviewed 830 patient records since 2015. 54 (6.5%) patients with mixed lineage characteristics were identified. Of these, 26 (48%) carried a formal diagnosis of MPAL while 28 (52%) carried a diagnosis of AML with myelodysplasia related changes (AML-MRC) or therapy related AML (t-AML). They have noted that RUNX1 and SRSF2 predicts a more favorable OS and TP53 is not predictive of worse OS.^[15]

Sukumaran R et al, studied the incidence, clinical features, laboratory findings, and immunophenotype of MPAL at Regional Cancer Centre, Trivandrum, Kerala, India, using flow cytometric analysis during July 2012 to July 2013. In this study among 506 acute leukemia cases a diagnosis of MPAL was made in 15 cases, which accounted for 2.96% of all leukemias. 9 cases were diagnosed as T/myeloid, 5 cases as B/myeloid and 1 case as B/T.^[16]

Hence, we note that several studies have found a difference in the incidence of BAL and MPAL; suggesting that these classification systems may select different patients.^[1,2,3,6]

PATHOGENESIS OF MIXED PHENOTYPIC ACUTE LEUKEMIA^[17,18]

During the 1980s, 2 leading hypotheses were raised to explain biphenotypic expression in leukemia.^[1]

- 1) The **Greaves hypothesis^[1,17]** suggested “**lineage promiscuity**” - hematopoietic progenitor cells possess **multilineage potential** that is **preserved** as a **relic** if leukemic transformation occurs at that stage.
- Immunologic, enzymatic, and molecular investigations of human leukemias and lymphomas support the **notion** of a unicellular (**monoclonal**) origin and an apparent maturation arrest or uncoupling of proliferation and differentiation.
- It has been possible, in the majority of cases, to designate the **predominant lineage** and cell type involved and at least to speculate as to the possible target cell for clonal expansion. Such analyses form the basis of new classification schemes.
- Leukemic phenotypes are **not perfect replicas of normal ones**. In addition to specific chromosomal changes and alteration in the structure and/or control of particular genes, leukemic cells may show **some asynchrony of phenotypic expression** in comparison to their equivalent maturation compartment in normal tissue.^[17]

- **Identity Crisis** for Cells, Monoclonal Antibodies, or Investigators? (17) **McCulloch and colleagues**, have listed about **30 studies** highlighting coexpression on individual cells of markers normally found only on cells belonging to different but related lineages and have **challenged the earlier view of leukemia as monoclonal**.
- In their paper Greaves MF et al argue that several examples of infidelity are suspect on **technical grounds**, whereas others are **bona fide** and require explanation, eg, partial rearrangements and expression of Ig heavy-chain and/or T cell receptor genes in inappropriate cells and terminal deoxynucleotidyl transferase in leukemic myeloblasts.^[17]
- Within the human hematopoietic system, several carbohydrate hapten like the X hapten determinant has been identified using various antibodies on multipotential progenitors and committed progenitors of several lineages and is present in a **cryptic but easily exposable form on acute lymphoblastic leukemia cells**.^[17]
- Similarly **polyclonal antibodies** to molecules like spectrin are **not** erythroid **specific**. T cell differentiation markers may be expressed in several stages of activation by B cells. At the time of writing of the original article of Greaves hypothesis,^[17] **three technical difficulties** were recognised:
 - i. An insufficient recognition of the limited screening and often misleading **nomenclature** of the antibodies. Few antigenic determinants appear to exist that are entirely restricted to a given cell type or lineage. The **exclusive characteristics of cells** may lie more in their **composite mosaic of gene expression**.
 - ii. **Antibodies** whether derived from cloned hybridomas or not, will be potentially able **to cross- react** with a wide variety of related and unrelated structures and, in addition, may **bind via their Fc region** rather than through the antibody-combining sites.
 - iii. **Insufficient knowledge** of the immunophenotypes of normal lymphocyte subsets and the various stem cell/ progenitor cell populations to which leukemias or lymphomas may correspond severely restricts the interpretation of leukemic cell phenotypes.
- 2) The term “**lineage infidelity**” denoted an alternative hypothesis involving **oncogenetically- driven misprogramming** of the leukemic cell, resulting in multilineage-expressing blasts.^[18]

Blast cells from 20 patients with acute leukemia (13 diagnosed myeloblastic and 7 as lymphoblastic using the FAB classification) were studied using antibodies to lineage-specific differentiation markers. The phenotypic findings were usually consistent with the clinical diagnosis. However, examples were encountered where individual blast cells had a cytoplasmic marker of one lineage and a surface marker of a different lineage (lineage infidelity). Six examples of intramyeloid (two different myeloid lineages in the same cell) and three examples of interlineage infidelity (myeloid and lymphoid markers in the same blast cell) were encountered. No doubly marked cells were found in control material consisting of normal marrow cells, marrow regenerating after transplantation, or multilineage colonies derived from marrow in culture. A significant trend was observed relating the presence of lineage infidelity and failure of remission- induction. The data are interpreted as support for **abnormal gene expression in leukemia**.

Infidelity is defined here according to McCulloch's arguments as a **misprogramming of differentiation** in leukemia. McCulloch refers to

- **Intramyeloid** lineage infidelity was considered to exist when individual cells contained markers of more than one of the three myeloid lineages: granulopoiesis, erythropoiesis, and megakaryocytopoiesis.
- **Interlineage** infidelity, that is, individual cells containing markers of both myelopoiesis and lymphopoiesis, was found in samples from three patients with AML.

The authors^[18] have listed the shortcomings of their study as – small study population, strategy to detect the doubly marked cells, the reagents, the numerous controls and perhaps technical difficulties in purification of cell lines.

MOLECULAR BASIS OF BLOOD CELL DIFFERENTIATION^[19,20,21]

In a 2008 review of the stem cell biology of hematopoiesis describes the developmental origins of HSCs and the molecular mechanisms that regulate lineage-specific differentiation. This review has described in detail the role of niches/microenvironment, transcription factors, temporal and stage specific hematopoietic regulators.^[19]

This paper further highlights that the majority of genes encoding these transcription factors were discovered either through analysis of chromosomal translocations found in human leukaemias or study of cooperating leukaemias genes during insertional mutagenesis in the mouse.^[19]

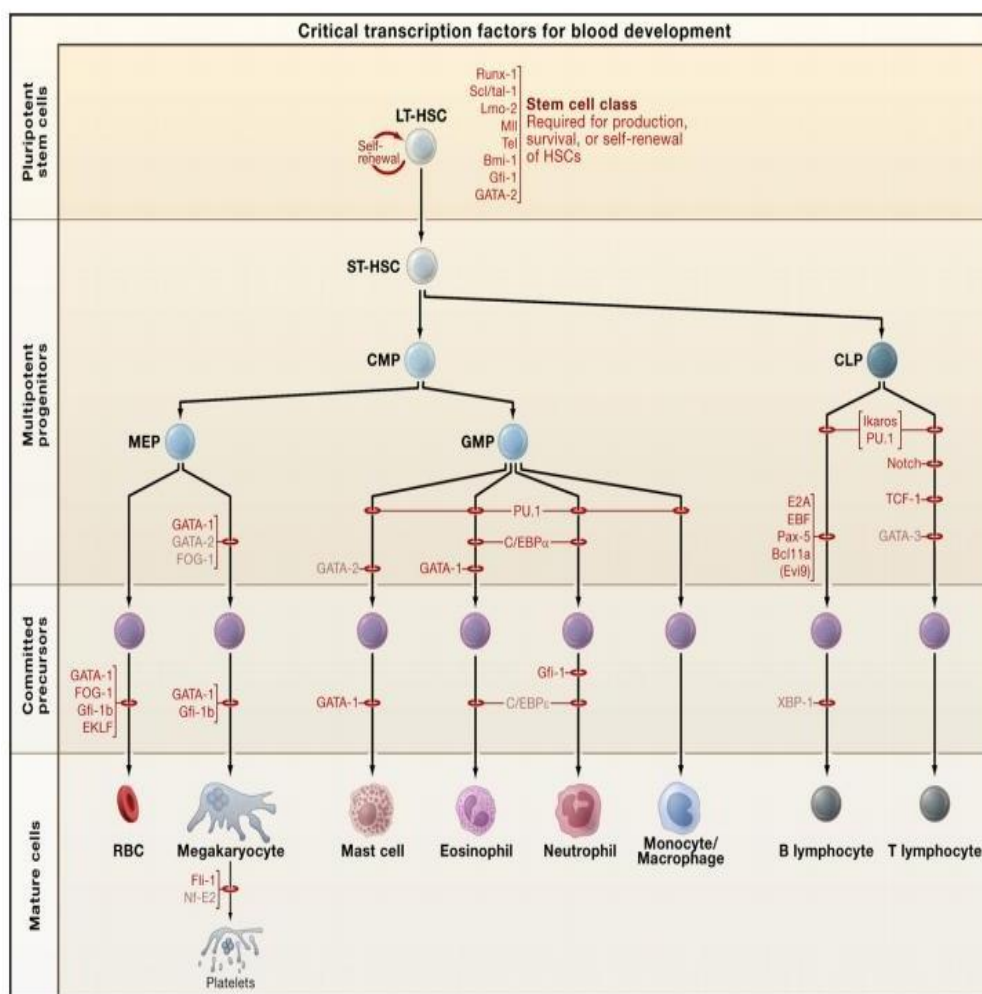


Figure 2: Critical Transcription Factors For Blood Cell Differentiation^[19]

MicroRNAs (miRNAs) provide an additional level of control beyond the transcription factors^[19, 20]

In this cartoon, the current evidence for Lineage Reprogramming of Hematopoietic Cells. (19) or "Lineage priming" has been summarised.^[1]

The orange arrows depict lineage reprogramming upon expression of the transcription factors GATA-1, C/EBP, or GATA-3.

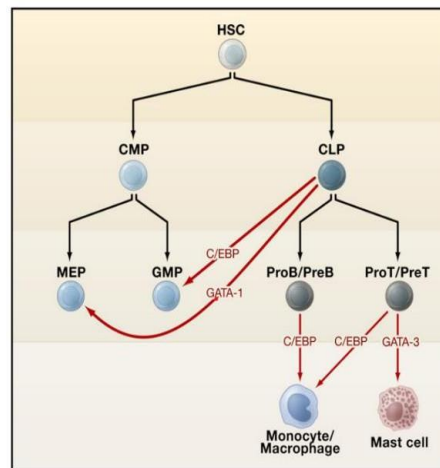


Figure 3: Lineage Reprogramming Of Hematopoietic Cells^[1,19]

Abbreviations: HSC, hematopoietic stem cell; CMP, common myeloid progenitor; CLP, common lymphoid progenitor; MEP, megakaryocyte/erythroid progenitor; GMP, granulocyte/macrophage progenitor.

Regalo et al have reviewed the literature on haematopoietic cell differentiation. They have drawn a similar analogy between the squamous epithelial metaplasia and **transcriptional rerouting** in reprogramming of haematopoietic cells.^[20]

Takahashi K et al have reported data from MD Anderson Cancer Center, Houston, the integrated genomic analysis on 31 MPAL samples and have compared molecular profiling with that from acute myeloid leukemia (AML), B cell acute lymphoblastic leukemia (B-ALL), and T cell acute lymphoblastic leukemia (T-ALL). They have classified the diagnosis, and grouped the mutations by the consensus molecular pathways. In this study they have noted differences in methylation signature between the two phenotypes.^[22]

Huang J et al from Tongji Medical Hospital, China have similarly described the landscape of somatic mutations in the MPAL / ALAL patients presenting to their hospital.^[23]

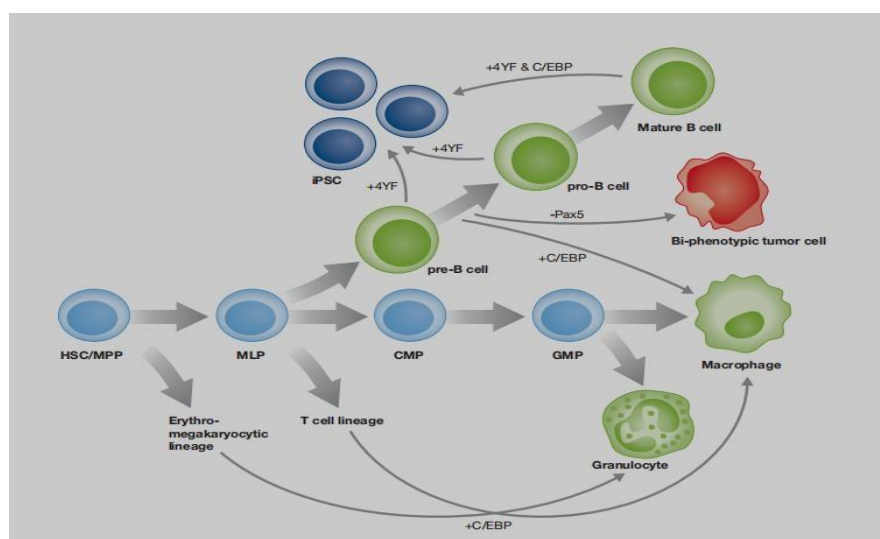


Figure 4: Schematic presentation of haematopoiesis and experimental trans-differentiation. Simplified partial scheme of haematopoiesis, with emphasis on myelo-b lymphoid lineages.

- Haematopoietic stem cells and multipotent progenitors (HSC/MPP) give rise to cells of the erythroid/megakaryocytic lineage and to myelo-lymphoid precursor cells (MLP).
- The adaptive immune B-cell and T-cell lineages emerge and common myeloid progenitors (CMP) give rise to cells of the innate immune system through granulocyte/macrophage progenitors (GMP) that may differentiate into the respective functional end cells (various types of granulocytes, monocytes and dendritic cells; not shown for simplification).
- C/EBPs may trans-differentiate erythro/megakaryocytic precursors, T cells and early B cells into inflammatory macrophages.
- Loss of Pax5 may generate various types of myeloid cells and loss/reduction of Pax5 in B cells may promote neoplastic transformation.
- Early B cells may be reprogrammed into induced pluripotent stem cells (iPS) by the four 'Yamanaka transcription factors' (4YF: Oct4, Sox2, Klf4, c-Myc), whereas late B cells require additional C/EBP for iPS reprogramming.^[20]

The fifth edition of WHO classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms has described two new subtypes of ALAL with defining genetic alterations. (i)MPAL with ZNF384 rearrangement: commonly has a B/myeloid immunophenotype and is identified in ~50% of pediatric B/myeloid MPAL with fusion partners including TCF3, EP300, TAF15, and CREBBP. ZNF384-rearranged B/myeloid MPAL and B-ALL have similar transcriptional profile, suggesting a biological continuum. (ii) ALAL with BCL11B rearrangement, which has a more heterogenous immunophenotype- identified in acute undifferentiated leukaemia (AUL) and ~20-30% of T/myeloid MPAL. BCL11B rearrangement is also identified in AML with minimal differentiation or without maturation and ~20-30% of ETP-ALL. These different types of acute leukaemias with stem cell, myeloid, and T-ALL features having BCL11B rearrangement in common suggests a biological continuum.

WHO Haem5 classification further highlights other genomic findings such as PHF6 mutations and PICALM:: MLLT10 fusions are also enriched in MPAL, which require further study.^[24]

TREATMENT OUTCOMES OF MPAL^[5,11,25,26,27,28]

MJ. Oberley, et al have examined **the predictive value of MRD** for event-free and overall survival (EFS, OS). ALL induction therapy achieved an EOI MRD negative (<0.01%) remission in most patients (70%). EOI MRD positivity was predictive of 5-year EFS (HR=6.00, p<0.001) and OS (HR=9.57, p=0.003). (10) The majority of patients treated with ALL chemotherapy achieved a MRD-negative CR by EOC (~week 12 of therapy); Patients who cleared MRD by EOC had worse survival compared to those EOI MRD negative. Overall survival in this group was excellent. Further prospective validation of MRD is essential to refine risk-stratified therapy for pediatric MPAL. Optimal salvage for those who fail to achieve remission with ALL chemotherapy is unknown and requires further study.^[11]

Hiroaki Shimizu et al, have described **transplant outcomes** in Eighteen MPAL patients (9 men, 9 women) with a median age of 40 years (range, 16–61 years). Among 18 MPAL patients, 5-year OS and RFS rates were 48.1% and 39.7%, respectively, and 5-year CI of relapse and NRM were 43.3% and 17.1%, respectively. Transplant outcomes of adult MPAL patients, in remission at the time of transplant, were comparable to those of both AML and ALL patients, although the statistical power was possibly insufficient due to the relatively small cohort. The existing transplant procedures were not satisfactory for MPAL patients who were not in remission at the time of transplant.^[25]

Rebecca Wetzel et al have analyzed ninety-five cases of T/myeloid MPAL reported from 2010-2016 through the SEER-18 database. The 5-year survival was 50.4%, which was higher than AML (23.3%) and lower than T-ALL (70.6%). Estimated 5-year survival ranged from over 70% for children, adolescents and young adults to only 16% for older adults.^[5]

Claire Andrews, Eshetu G Atenafu, et al have evaluated Seventy-four patients, aged 18 years or older, at the **Princess Margaret Cancer Center** between January 1, 2000 and December 31, 2018. Twenty-five of 36 (80%) achieved a CR using ALL protocols (DFCI Protocol, Hyper-CVAD), while 9 of 23 (39%) achieved a CR using AML protocols (3+7, FLAG-IDA). Consolidation treatment post CR was evenly split, with 24 (51%) receiving chemotherapy followed by an alloHSCT and 23 (49%) receiving chemotherapy only. In the alloHSCT group, RIC was used in 20 (81%) patients while MAC was used in four younger patients with a median age of 51 and 30 respectively.^[26]

Odelia Amit, Yael Bar-On, Irit Avivi, et al, have tested thiotepa based high dose therapy and allogeneic hematopoietic cell transplantation (HCT), in patients with ALL/MPAL who were not eligible for a standard TBI-containing regimen. Thiotepa based regimen has substantial activity in patients with ALL, even in those who are older than 60 years and in patients intelligible to TBI. Reduced doses of thiotepa may have comparable efficacy and a lower toxicity profile when compared to higher doses and should be further investigated in this cohort of patients.^[27]

Table 3: Recent Trials Assessing Allogenic Transplant for patients with MPAL in first remission.^[28]

NCT04904588/ ACCESS	CIBMTR/ NMDP/ Interventional Phase2	Recruiting	CR1: 4 Strata – MAC (FluBu/FluTBI/BuCy/ CyTBI)/ NMA(FluCyTBI)/ RIC(FluBu/FluMeI)
NCT05589896/ PRESERVE I	CIBMTR/ Ossium Health Inc. Interventional Phase1/2	Not yet recruiting	CR1: A First-in-Human Study of HLA- Partially to Fully Matched Allogenic Cryopreserved Deceased Donor Bone Marrow Transplantation for Patients With Hematologic Malignancies
NCT05170828/ PRESERVE	CIBMTR/ Ossium Health Inc. Interventional Phase1	Not yet recruiting	Any CR: Cryopreserved MMUD BM With PTCy for Hematologic Malignancies
NCT04195633 / RG1005742	Fred Hutchinson Cancer Center	Recruiting	Any CR: Donor Stem Cell Transplant With Treosulfan, Fludarabine, and Total-Body Irradiation
NCT05805605/ 2022LS146	Masonic Cancer Center, University of Minnesota	Recruiting	Any CR: Allo HSCT Using RIC and PTCy for Hematological Diseases (Cy/Flu/TBI + Post transplant CY)
NCT03399773/ 9910	Fred Hutchinson Cancer Center Interventional Phase2	Recruiting	Any CR: Infusion of Expanded Cord Blood Cells in Addition to Single Cord Blood Transplant (dilanubicel) (FluCyThiotepaTBI)
Munker, 2016	CIBMTR	95	CR1 – 82%; CR2 – 18%
Tian, 2016	Single Center retrospective	29	CR – 72%; no CR – 28%
Shimizu, 2015	Japanese Transplant registry	18	CR – 72%; no CR – 28%
Liu, 2013	Single – center retrospective	59	CR – 58%; no CR – 42%

Table 4: Recent Clinical Trials with MPAL as one of the inclusion criteria^[28]

NCT04446130/DAC-HAAG-03	Decitabine combined with HAAG Regimen	Interventional Phase 3	Recruiting
NCT05316701/Precision-T (PhIII component)	Biological: Orca-T engineered donor allograft (TregGraft)	Interventional Phase 3	Recruiting
NCT03959085/AALL1732	Inotuzumab Ozogamicin	Interventional Phase 3	Recruiting
NCT05327894/Infant-21 Treatment Protocol	Blinatumomab	Interventional Phase 3	Not Yet Recruiting

3. CONCLUSION

Mixed Phenotypic Acute Leukaemia is a heterogeneous group of disorders. Acute Leukemia of Ambiguous Lineage as defined by European Group of IL includes a more diverse group.

These are difficult diagnostic subsets of Acute Leukemia.

EGIL/WHO help identify this type of leukemia but both are not exclusive.

Identifying this subset, including the cases diagnosed by EGIL criteria exclusively has prognostic value. Correlation with molecular data will add further value.

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