REVIEW ARTICLE

Acute leukemia of ambiguous lineage: the known and the uncertain

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Abstract

Acute leukemia of ambiguous lineage (ALAL) is a rare, high-risk form of acute leukemia. It is characterized by the inability to assign a single lineage of differentiation to the leukemia and can manifest with more than one lineage-defining marker, called mixed phenotype acute leukemia (MPAL), or the complete absence of such markers, defined as acute undifferentiated leukemia (AUL). Recent genetic, epigenetic and metabolic insights refine diagnostic frameworks, inform classification and risk-stratification, and expose potential targetable vulnerabilities. However, the rarity and heterogeneous manifestations of ALAL result in ongoing diagnostic and therapeutic uncertainty. The most recent World Health Organization and International Consensus Classification documents provide a pragmatic framework integrating immunophenotypic and genetic criteria for classification, with recognition of specific somatic genetic alterations that define disease biology. These include rearrangements involving *BCR::ABL1*, *KMT2A*, *ZNF384*, and *BCL11B* activation. Current evidence supports the use of acute lymphoblastic leukemia-type induction regimens (with the addition of tyrosine kinase inhibitors for Philadelphia chromosome-positive MPAL) over acute myeloid leukemia or hybrid approaches. For AUL the optimal therapeutic approach is uncertain. Incorporation of targeted therapies in combination with intensive, and lower-intensity chemotherapy backbones based on the specific biological and genetic characteristics of ALAL is an appealing approach and is increasingly reported. The use of lineage-specific targeted approaches may result in therapeutic pressure and lineage switch in patients with acute leukemia with multi-phenotypic potential. The role and optimal platform for minimal residual disease surveillance in ALAL to guide therapy, and inform transplantation is unclear, given the paucity of prospective controlled data.

Introduction

For most patients with acute leukemia a single lineage of differentiation can be assigned based on the expression of lineage-defining markers. Unfrequently, more than one lineage can be assigned to the acute leukemia, termed mixed phenotype acute leukemia (MPAL), or no specific lineage can be assigned to the disease, called acute undifferentiated leukemia (AUL).[1] According to the most recent World Health Organization (WHO) document, MPAL and AUL are collectively referred to as acute leukemia of ambiguous lineage (ALAL). Over the years different terms were coined, and various classification criteria were applied to define these entities, moving from immunophenotypic inclusive criteria to more genetic, and biological-driven stringent criteria that resulted in fewer patients diagnosed with *bona fide* ALAL. With more recent classifications, it is estimated that ALAL is diagnosed in 2-3% of patients with acute leukemia,[2,3] with a Surveillance, Epidemiology and End Results (SEER)-reported incidence of 0.35 per 1,000,000 person-years.[2] The rarity of ALAL along with complex diagnostic and clinical challenges result in much uncertainty about how to diagnose and treat these acute leukemias. Recent insights into the processes driving hematopoiesis and lineage commitment, as well as the role of somatic genetic alterations in driving ALAL further inform classification systems for ALAL and expose potential therapeutic vulnerabilities.

How to diagnose and classify acute leukemia of ambiguous lineage

Historically, the classification systems used to identify

bi-phenotypic leukemias (more than one lineage expressed on the same blast population) and bi-lineal leukemias (two discreet blast populations of divergent lineage in the same patient) relied on the expression of lineage markers assessed by immunophenotype and cytochemistry assays,[3-7] as reflected in the European Group for the Immunological Characterization of Leukemias (EGIL) classification.[8] The major drawback of using a phenotype-based classification system is that many *bona fide* acute myeloid leukemia (AML) syndromes, as defined by founding genetic events, are associated with multi-phenotypic expression. For example, core-binding factor AML can express lymphoid markers including CD19.[9,10]

The most recent WHO and International Consensus Classification (ICC) documents aim to integrate genetic, immunophenotypic and clinical context to provide a practical classification of ALAL (Figure 1).[1,11,12] In these classification systems ≥20% of blasts in the blood or marrow are required for a diagnosis of ALAL. A limited set of lineage-defining markers is utilized. Myeloperoxidase (MPO) or two of five monoblastic markers (CD11c, CD14, CD64, lysozyme or non-specific esterase) define a myeloid lineage, CD3 (membranous or cytoplasmatic) defines T-lymphoid lineage, and CD19 with one or two associated markers (CD79a, cytoCD22 and CD10) define B-lymphoid commitment. In contrast, AUL lacks lineage-defining markers and may express no more than one lineage-associated marker for any given lineage. Most cases show a single myeloid marker alongside stem-cell markers such as CD34, HLA-DR, and TdT.[13]

A key principle is that other WHO-defined AML entities take precedence over ALAL. Thus, ALAL can only be diagnosed after excluding well-defined AML subtypes that may exhibit mixed phenotypes. Once diagnosed, ALAL is further subclassified by genetic drivers including rearrangements in *BCR::ABL1*, *KMT2A*, *ZNF384*, or *BCL11B* activation, with a secondary mention of associate lineage mixture. Remaining cases are categorized by lineage combinations, with B/Myeloid MPAL being most common (~two-thirds of patients), followed by T/Myeloid. Rare forms include B/T, B/T/myeloid, and the more recently defined T/megakaryoblastic subtype, in which megakaryocytic markers (e.g., CD41, CD42, and/or CD61) appear with cCD3 (often as the only T-lineage marker), usually with lineage-associated myeloid, lymphoid and stem-cell markers.[14-16]

While this classification provides a coherent and pragmatic framework for the pathologist and clinician, there are still several potential caveats and challenges in diagnosis and classification.

How to define a positive lineage marker?

The diagnosis of ALAL requires integration of clinical, immunophenotypic and genetic information that can only be achieved through close communication between the clinician, the pathologist, and supporting laboratories. In the most recent WHO document, for CD3 to be regarded as positive its intensity should exceed 50% of mature T-cell level by flow cytometry in the same sample, at least on a portion of the leukemic cells. CD19 intensity should exceed 50% of B-cell progenitor by flow cytometry, and MPO should exceed 50% of mature neutrophils or show a variable pattern reminiscent of that seen on normal CD34-positive myeloid progenitors.[12,17]

MPO is considered a myeloid-defining marker, and no specific clone size or threshold is defined. The interpretation of MPO positivity should always be put in the clinical and pathological context, especially when addressing smaller clones (e.g., <10% by flow cytometry). For example, MPO positivity may be the sole differentiating feature between early T-cell acute lymphoblastic leukemia (ETP-ALL) and T/Myeloid MPAL.[18] The impact of isolated MPO expression in the context of an otherwise *bona fide* B-cell precursor (BCP) ALL may not change the biology and natural history of this disease. Weinberg *et al*. compared adult patients with MPAL B/Myeloid and MPO as their only myeloid-defining marker (MPAL^{IsoMPO}) to patients with other types of MPAL and demonstrated improved overall survival (OS) for patients with MPAL^{IsoMPO} (N=13) as compared to patients with other types of MPAL (N=10; median OS not reached *vs*. 16 months, $P<0.05$), and a similar OS to that of patients with immunophenotypically unremarkable BCP-ALL. In this analysis, MPAL^{IsoMPO} did not differ significantly from other MPAL subtypes in terms of cytogenetics, showing similar rates of abnormal karyotypes, comparable frequencies of *t(9;22)/BCR::ABL1* rearrangements, and absence of *KMT2A* rearrangements (*KMT2Ar*) Results from retrospective pediatric series focusing on MPAL^{IsoMPO} were less consistent and showed mixed results.[19-21]

Bi-phenotypic *versus* bi-lineal leukemia

MPAL can present as a single blast population with multi-lineage expression (bi-phenotypic) or less frequently, as two discrete blast populations of different lineage assignments (bi-lineal). For the latter, a total of ≥20% blasts should be demonstrated in aggregate for the different blast populations. Although there is no clear biological or diagnostic distinction between these two entities in the WHO or ICC documents, retrospective observations suggest that bi-lineal MPAL is associated with inferior outcomes.[5] In one large international multicenter analysis (iBFM-AMBI2012), 20% of 221 pediatric and adolescent patients with MPAL had bi-lineal MPAL. These patients had significantly shorter event-free survival (EFS) and OS as compared to patients with bi-phenotypic MPAL regardless of the induction approach applied, although this did not maintain statistical significance in multivariate analysis.[22]

Many times small lineage-aberrant clones can be identified alongside a dominant clone and may lead to diagnostic uncertainty.[23] Guidance from a recent ICC publication suggests that blast subpopulations of divergent lineage larger than 5% may be sufficient for a diagnosis of bi-lineal MPAL while

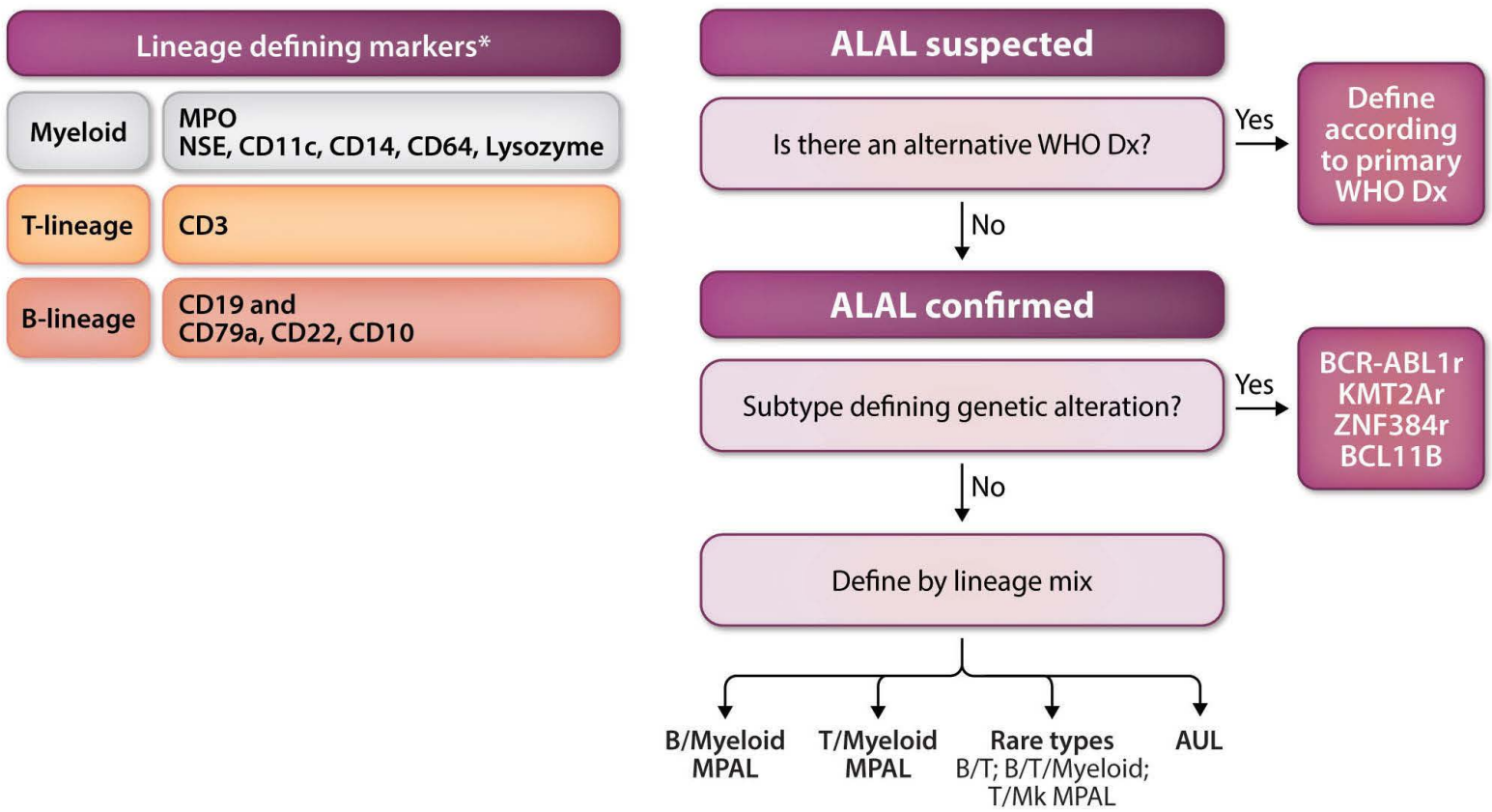

Figure 1. Diagnosis and classification of acute leukemia of ambiguous lineage. A pragmatic approach for the diagnosis and classification of acute leukemia of ambiguous lineage. *Myeloid lineage is defined by cytoplasmic myeloid peroxidase (MPO) expression (>50% of mature neutrophils or variable pattern resembling that of normal CD34⁺ myeloid progenitors). Dim MPO is less specific but gains specificity with high light-scatter or co-expression of CD117/bright CD13/CD33. If MPO is dim/absent, myeloid lineage designation requires ≥2 monocytic markers (CD11c, CD14, CD64, lysozyme, or diffuse nonspecific esterase positivity). B-lineage designation requires CD19 (>50% of normal B progenitors at least in part of the leukemia cells) plus ≥1 additional B-cell marker (CD10, CD22, CD79a); lower CD19 expression requires ≥2 additional markers. CD79a lacks specificity when T-lineage is in the differential. PAX5 is specific but tentative. Rarely, B-lineage can be established without CD19 if PAX5, CD79a, and CD22 are co-expressed. T-lineage requires cytoplasmic/membranous CD3 (expression >50% of mature T cells at least on a portion of the leukemic cells) or by immunohistochemistry, although may not be entirely T-lineage-specific since polyclonal antibodies may react with the CD3 ζ chain (also present in normal NK cells). Cases of acute leukemia of ambiguous lineage (ALAL) that do not satisfy the criteria for a specific ALAL category should be classified as ALAL, not otherwise specified. NSE: nonspecific esterase; WHO: World Health Organization; Dx: diagnosis; MPAL: mixed phenotype acute leukemia; r: rearrangement; Mk: megakaryoblastic; AUL: acute undifferentiated leukemia.

in cases of smaller clones, the diagnosis should be made according to the major clone with addition of a descriptive modifier annotating the small divergent aberrant clone.[12,23] The mention of a minute aberrant clone may prove to be of biological and clinical significance, since these small clones can be the basis for subsequent relapse and lineage switch. Care must be taken to avoid misclassifying residual normal myeloid blasts or hematogones as pathological divergent lineage populations.[23]

Does my patient have mixed phenotype acute leukemia or secondary acute myeloid leukemia with a 'mixed phenotype'?

The current WHO and ICC documents moved towards classification based on somatic genetic aberrations including AML with myelodysplasia-related cytogenetics and AML with myelodysplasia-related mutations.[24] These well-defined AML syndromes can be associated with expression of aberrant lineage markers but should be classified according to their primary WHO diagnostic ascription rather than as ALAL. This presents a specific challenge in the context of ALAL since some of the 'myelodysplasia-related' AML defining cytogenetic aberrations were reported in patients with *bona fide* ALL. For example, in the UKALLXII/ECOG2993 trial, 2-5% of patients harbored 'myelodysplasia-related' cytogenetic aberrations (e.g., complex karyotype, del7, del17p, trisomy 8, and del13q).[25]

Historically, many ALAL cohorts included patients with 'secondary-type' defining genetics that probably affected the epidemiology, prognosis and therapeutic outcomes of these patients.[26] For example, in one pivotal report of 100 patients with MPAL according to the WHO 2008 criteria, the most frequent cytogenetic abnormality was complex karyotype (in 32% of patients).[27] More recent reports utilizing up-to-date WHO criteria for ALAL validate the high frequency of myelodysplasia-related cytogenetics in series of ALAL patients. In an analysis of 28 adult patients with MPAL (per WHO 2016 criteria), complex karyotype was reported in 28% of patients while other myelodysplasia-defining cytogenetics such as del5q/-5, del7q/-7, del17p/-17, trisomy 8, del20q, del9q and del13q were reported in aggregate in 32% of patients.[28]

Galera *et al*. compared the clinical characteristics and outcome of patients with secondary AML with a 'mixed-phenotype' (sAML-MP; N=55; therapy-related AML and AML with myelodysplasia-related changes according to the WHO 2016 criteria) with patients with *bona fide* MPAL (N=45) and AML (N=100). Patients with sAML-MP had worse outcomes than patients with MPAL. Secondary type mutations (STM) as well as myelodysplasia-related cytogenetics were a common finding in the secondary AML group and very uncommon in the MPAL group except for a complex karyotype and mutations in *RUNX1* (identified in 20% and 23% of patients with MPAL, respectively). No *TP53* mutations were found in the MPAL group (Figure 2). As compared to patients with MPAL, patients with sAML-MP had lower remission rates with intensive induction (37.5% *vs*. 90%, *P*<0.001) and inferior survival (median OS, 10.3 *vs*. 42.8 months, *P*<0.0001; hazard ratio [HR]=2.3, 95% confidence interval [95% CI]: 1.4-4.0, *P*=0.002), comparable to the outcome of the 'control' AML cohort. ALL-type induction was very effective in patients with MPAL and was largely ineffective in sAML-MP (complete remission 96.6% *vs*. 14.3%, *P*=0.001). AML-type induction performed better in sAML-MP. Multivariate analyses demonstrated that ALL-directed therapy for sAML-MP was associated with inferior OS (HR=5.68; 95% CI: 1.39 23.4; *P*=0.016), whereas patients with MPAL had significantly improved OS with ALL-directed regimens (*P*=0.0001). Across all ALL-treated patients, age >65 years (HR=9.0; 95% CI 2.28 35.6; *P*=0.001) and sAML-MP subtype (HR=12.5; 95% CI: 2.72 57.8; *P*=0.001) predicted worse OS. With AML-directed intensive therapy, remission was achieved in 12/20 AML-MP cases (60%) *versus* 0/4 MPAL cases (*P*=0.09); here, only age >65 years independently predicted inferior OS (HR=3.0; 95% CI: 1.1 8.0; *P*=0.02). Interestingly, lymphoid lineage switch at progression was much more common in MPAL than in sAML-MP (35.7% *vs*. 2.5%, *P*=0.0003). On the transcriptional level, sAML-MP was enriched for stemness signatures, and demonstrated a relative deficit of transcription factors central for myeloid and lymphoid differentiation (similar to the AML cohort), as compared to MPAL.[29] Kirtek *et al*. investigated the impact of STM (*SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2*, and/or *RUNX1*) on the characteristics and outcome

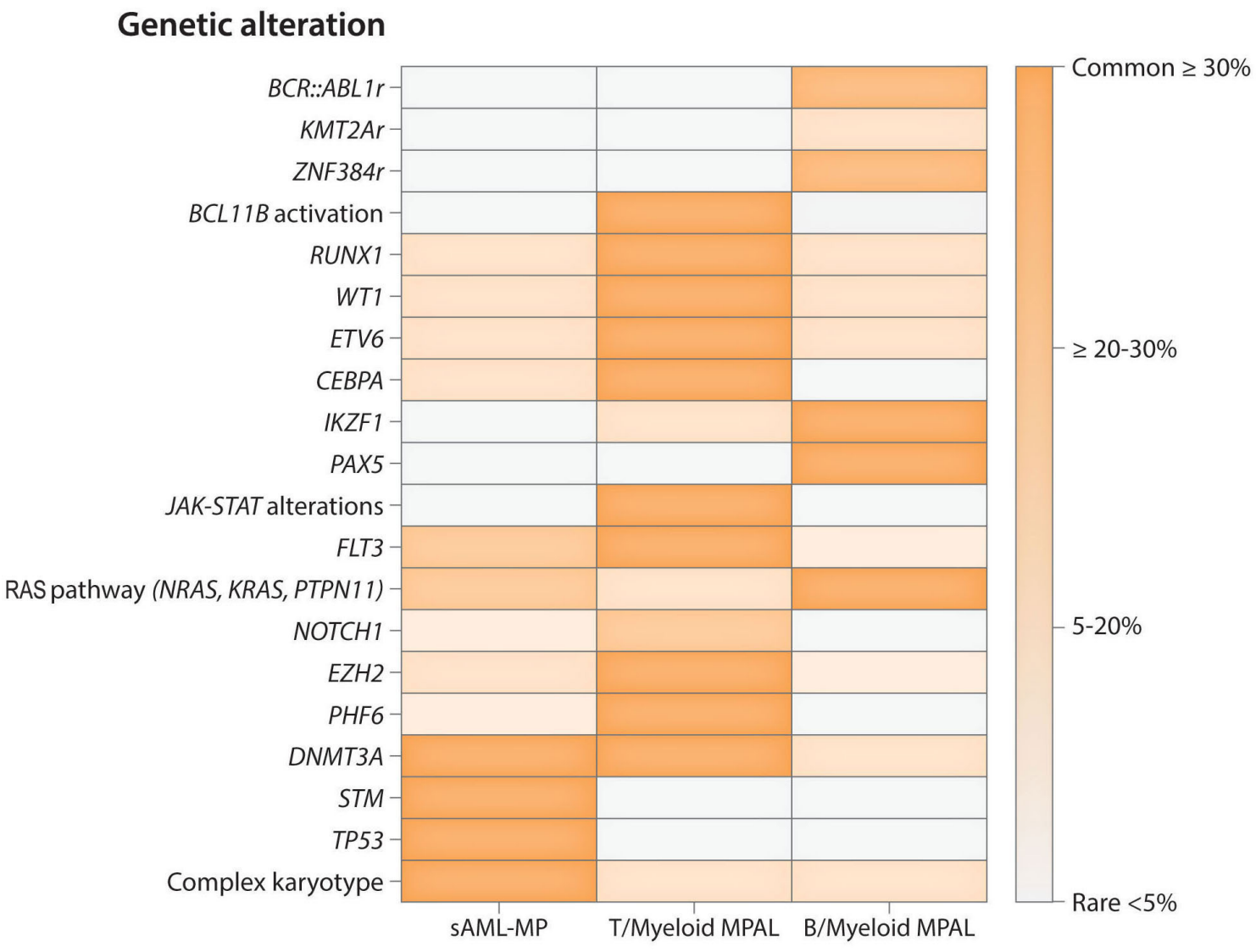

Figure 2. Frequency of somatic genetic alterations in mixed phenotype acute leukemias. Approximate frequency estimations of somatic genetic alterations in B/Myeloid mixed phenotype acute leukemia (MPAL), T/Myeloid MPAL, and secondary acute myeloid leukemia with a mixed phenotype. The estimations are based on data compiled from multiple genomic studies, including small cohorts with notable heterogeneity in age and reported mutation prevalence that may affect frequency (e.g., *ZNF384* rearrangements common in pediatric patients; *BCR::ABL1* rearrangements more common in adults). STM: secondary type mutations (*ASXL1*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRZS2*; per World Health Organization 5th edition). *EZH2* is also depicted by itself, due to reports of high frequency in T/Myeloid MPAL in some studies.

of patients with ALAL (N=23) or AML (N=167). Patients with ALAL and AML with STM were overall comparable in terms of baseline characteristics, other than higher blast counts and rates of abnormal karyotype in patients with ALAL. The clinical course and outcomes were very similar between the two groups suggesting that STM, not immunophenotype, drive the biology and clinical outcome for these patients.[30] A similar study comparing the impact of complex karyotype (defined as ≥3 structural abnormalities) on outcomes of patients with MPAL, AML or ALL confirmed that complex karyotype, not immunophenotype, drives the poor outcome for these patients,[31] although this observation was not confirmed in the study by Galera *et al.*[29]

Taken together, we recommend that patients with myelodysplasia-related defining cytogenetics and/or myelodysplasia-related defining mutations (STM) be defined as such, regardless of their lineage-mix, and treated with myelodysplasia-related AML-directed therapies. One exception is *RUNX1*-mutated cases (regarded as STM by the ICC, but not by the WHO) which are enriched in MPAL cases and seem to share biological and prognostic similarities with other MPAL.

Genetic and epigenetic alterations in acute leukemia of ambiguous lineage

Somatic genetic alterations initiate and drive the biology of acute leukemia. In ALAL, unique patterns of genetic alterations are described with specific associations between genotype and immunophenotype. *BCR::ABL1* rearrangements (*BCR::ABL1r*) and *KMT2Ar* were the first MPAL subgroup-specific alterations. *BCR::ABL1r* account for 15-20% of MPAL cases and are associated with older age and a B/Myeloid immunophenotype. ALAL with *KMT2Ar* can be found in approximately 10% of cases, mostly in infants and children. The most common expected 5' *KMT2A* partners are *AFF1* (*AF4*), *MLLT3* (*AF9*), and *MLLT1* (*ENL*), and most cases will present as B/Myeloid immunophenotype although rare cases of *KMT2Ar* AUL and MPAL B/T have been reported.[1] More recently, two additional ALAL subgroup-defining rearrangements were recognized and incorporated into the formal WHO and ICC classifications.

ZNF384-rearranged (*ZNF384r*) MPAL was shown to occur in up to 50% of pediatric patients with B/Myeloid MPAL,[32] but rarely in adults.[33] Different fusion partners including transcription factors (*TAF15* and *TCF3*) and chromatin modifiers (*CREBBP*, *EP300*, *SMARCA2*, and *ARID1B*) were reported, with *EP300* being the most common. *ZNF384r* MPAL shares genetic and transcriptional similarities with *ZNF384r* BCP-ALL (which is frequently characterized by aberrant expression of myeloid markers).[34] These leukemias were shown to overexpress the *FLT3* gene,[32,35] and the specific type of fusion partner was suggested to impact patients' outcomes (e.g., *EP300-ZNF384* and *TCF3-ZNF384* fusions associated with favorable and poor outcomes, respectively).[32,36]

BCL11B is a master regulator of T-lineage commitment. *BCL11B*-activated ALAL defines a genetic subgroup of ALAL accounting for 10-15% of patients with MPAL and about one third of patients with T/Myeloid MPAL.[1] It can also be found in cases of AUL, ETP-ALL and AML.[37] *BCL11B* activation and overexpression are the result of enhancer hijacking created by repositioning of regulatory sequences (e.g., *ARID1B*, *MYC-BENC*, or *CDK6*) upstream or downstream of the *BCL11B* gene, or from an amplification of a 2.5 kb region downstream of *BCL11B* (*BCL11B* enhancer tandem amplification). These alterations are frequently associated with JAK-STAT pathway activation and *FLT3*-ITD mutations,[37-39] and should not be confused with loss-of-function mutations, deletions, and oncogenic rearrangements of *BCL11B* typically seen in T-ALL.

Philadelphia chromosome (Ph)-like alterations in patients with MPAL are infrequently reported in the literature.[40] For example, in one pivotal analysis of gene expression profiles, only three of 95 patients assessed harbored Ph-like driving alterations (including *EBF1-PDGFRB*, *IGH-CRLF2* and one case lacking an identified kinase lesion).[32]

The advent of comprehensive platforms for detection of translocations and copy number changes such as optical genome mapping and RNA sequencing are instrumental for systematically detecting disease-defining genetic alterations, including additional rare recurrent translocations associated with ALAL such as *PICALM::MLLT10*, *NUP98::NSD1* and *SET::NUP214*.[41]

The landscape of small sequence variants in ALAL encompasses a combination of somatic alterations seen in AML and ALL. Different data sets consisting of different, heterogenous populations report varying patterns of somatic mutations.[28,29,33,42-46] *Bona fide* MPAL (as compared to sAML-MP) rarely exhibit *TP53* mutations or STM[29] with the exception of *RUNX1* mutations, shown to be enriched in patients with MPAL.[28,29,32,33,42,43,47] B/Myeloid and T/Myeloid MPAL display different mutational patterns (Figure 2). In one analysis of 115 pediatric and adolescent patients with MPAL, T/Myeloid MPAL was characterized by high mutational burden involving transcriptional regulators such as *WT1*, *ETV6*, *RUNX1* and *CEBPA* which were mutually exclusive, as well as high rates of JAK-STAT alterations, and mutations in epigenetic regulators (e.g., *EZH2* and *PHF6*) and *FLT3* mutations. B/Myeloid MPAL was associated with lower mutational burden and involved the transcription factors *IKZF1* and *PAX5*, and RAS pathway alterations (most commonly *NRAS* and *PTPN11*). T/Myeloid MPAL and ETP-ALL demonstrated significant overlap in mutational patterns.[32] Other retrospective cohorts of adult or mixed pediatric and adult populations associated T/Myeloid MPAL with higher frequencies of mutations in *CEBPA*,[42] *DNMT3A*,[42,43] *PHF6*,[43] and *NOTCH1*,[33,42] while B/Myeloid MPAL was associated with mutations in *RUNX1*[33] and in the RAS pathway.[42] Data on the genetic makeup of AUL are scarce. In one analysis of 24 adults with AUL, the most common genetic alterations

were trisomy 13 and mutations in *PHF6*, *SRSF2*, *RUNX1*, *ASXL1*, and *BCOR*. Mutations in *PHF6* and *SRSF2* were enriched in AUL as compared to patients with AML and minimal differentiation.[13]

Recent studies demonstrate that epigenetic profiling, including DNA methylation signatures and chromatin accessibility landscapes, are powerful tools to identify lineage identity.[48-50] For example, in *KMT2Ar* MPAL, epigenetic patterns often align with a dominant lineage identity, typically myeloid or lymphoid, despite immunophenotypic ambiguity.[48]

Takahashi *et al*. performed integrated methylome and transcriptome analysis in 31 MPAL patients, revealing distinct epigenetic programs that stratify MPAL by lineage. T/Myeloid MPAL showed hypomethylation patterns supporting T-cell receptor signaling pathways while B/myeloid MPAL demonstrated patterns driving the B-lineage transcriptional axis. Gene set enrichment confirmed NF-κB and B-cell receptor signaling in B/Myeloid MPAL. Methylation-based clustering identified two MPAL subtypes: an 'ALL-like' subtype that clustered with B-ALL or T-ALL, and an 'AML-like' MPAL that aligned with *bona fide* AML. Patients who received an induction approach aligned with their methylome-based lineage assignment (e.g., an ALL-type induction for an 'ALL-like methylome') had significantly higher complete remission rates compared to those receiving mismatched treatments (72% *vs*. 22%, *P*=0.037), although this did not translate into better survival.[33]

The cellular origin of mixed phenotype acute leukemia

The mechanisms underlying multi-phenotypic expression in leukemia have been the focus of investigation. A central unresolved question has been whether phenotypic heterogeneity arises primarily from the stepwise acquisition of somatic mutations ('clonal evolution'), or from intrinsic plasticity of leukemic stem cells with a largely stable genetic make-up.[51-61] Alexander *et al*. presented multiple compelling observations to support the existence of a multipotent leukemic stem cell rather than clonal evolution as the cellular basis for the development of MPAL.[32] The authors demonstrate that leukemia-initiating mutations occur at the stem-cell level. These somatic genomic alterations were shown to have the potential to produce different lineage phenotypes with similar biological implications (such as in the case of *ZNF384r* BCP-ALL or B/Myeloid MPAL) and remain stable across phenotypic subclones. In a key experiment, flow-sorted subpopulations from primary ALAL samples were transplanted into NSG-SGM3 mice and successfully reconstituted the full phenotypic spectrum of the original leukemia, even in the absence of therapeutic pressure.[32] In line with these observations, Xiao *et al*. and Kotrova *et al*. demonstrated that phenotypically diverse blast subpopulations from patients with MPAL harbor similar genetic alterations[43,62] and Galera *et al*. demonstrated similar gene expression patterns in sorted blasts of myeloid and T-cell lineage origin from the same patient.[29] A study of patients with acute leukemia and a CpG island methylator phenotype, an immature form of leukemia associated with a mixed phenotype, demonstrated a similar hybrid epigenetic landscape despite varying somatic initiating mutations suggesting that epigenetic dysregulation rather than genetic lesions drive the mixed phenotype in these ambiguous leukemias.[63] Taken together these observations support the concept that phenotypic diversity results from mutation acquisition in a multipotent progenitor cell rather than from ongoing genomic evolution.

Therapeutic approach

ALAL is considered a high-risk form of leukemia with increased relapse rates and poor long-term survival. A SEER registry analysis demonstrated a 59% and 26% increase in the risk of death for patients with MPAL as compared to patients with ALL and AML, respectively.[2] The high-risk nature of ALAL was further highlighted in a recent retrospective analysis of real-world outcomes of patients with MPAL in the United States (N=4,756 adults; median age 68 years). The median OS was poor at 4.2 months (95% CI: 3.6-4.9) with 30-day mortality of 33%. Subtype analysis revealed markedly improved outcomes for patients with Ph^+ MPAL (median OS 53.6 months, 5-year OS 49%), and poor outcome for AUL (median OS 1.4 months, 5-year OS 14%).[64]

The optimal treatment strategy for ALAL remains undefined. Current approaches are mostly informed by retrospective heterogeneous cohorts, limiting firm conclusions. Consequently, therapy is often individualized, with no clear consensus on induction or long-term management.[65-67] Despite these limitations, a structured approach can guide therapy selection. This includes evaluating patient-specific factors (e.g., age, comorbidities, and fitness) alongside comprehensive analysis of blast morphology, immunophenotype, cytogenetics, and molecular genetics (Figure 3).[67]

What is the optimal induction regimen for acute leukemia of ambiguous lineage?

Over the years, multiple retrospective analyses have compared induction strategies for ALAL (Table 1). A systematic review and meta-analysis examined outcomes in 1,499 patients with MPAL, classified according to WHO 2008 or EGIL criteria, based on the type of induction regimen administered: ALL-type, AML-type, or hybrid. The analysis showed that ALL-based induction was significantly more effective in achieving complete remission than was AML-based therapy (WHO-based, OR=0.33; 95% CI: 0.18-0.58). Multivariable analysis of pooled patient-level data confirmed inferior remission rates with AML induction (OR=0.45; 95%

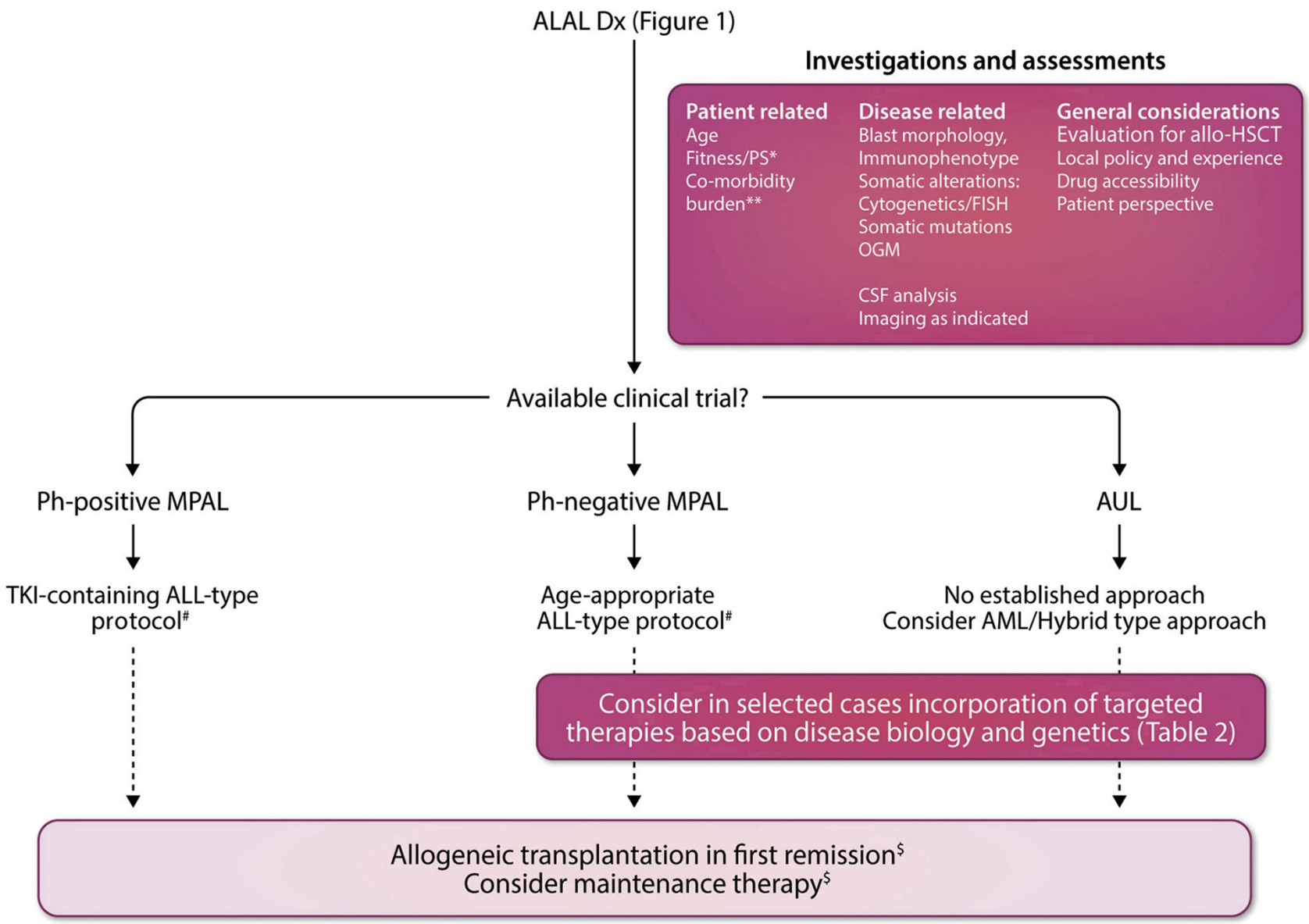

Figure 3. Management of patients with acute leukemia of ambiguous lineage. A pragmatic approach for the workup and management of newly diagnosed adult patients with acute leukemia of ambiguous lineage. *Validated tools for fitness assessment, e.g. comprehensive geriatric assessment. **Comorbidity assessment, e.g. Charlson comorbidity index. #It is important to utilize established age-appropriate acute lymphoblastic leukemia protocols that the medical team are familiar and experienced with. $Tools to aid decision include: measurable residual disease assessment with multiple methods, disease genetic-risk, patient co-morbidity burden and fitness. ALAL: acute leukemia of ambiguous lineage; Dx: diagnosis; PS: Performance Status; FISH: fluorescence *in situ* hybridization; OGM: optical genome mapping; CSF: cerebrospinal fluid; allo-HSCT: allogeneic hematopoietic stem cell transplantation; Ph: Philadelphia chromosome; MPAL: mixed phenotype acute leukemia; TKI: tyrosine kinase inhibitor; ALL: acute lymphoblastic leukemia; AUL: acute undifferentiated leukemia.

CI: 0.27-0.77). OS also favored ALL-type regimens (WHO-based, OR=0.45; 95% CI: 0.26-0.77). While AML induction was not independently associated with worse OS, hybrid regimens were linked to significantly inferior survival (HR=2.11).[68]

The International Berlin-Frankfurt-Münster (iBFM-AMBI2012) study of ALAL reported on a large retrospective multinational cohort of 233 children and adolescents with ALAL. ALL-type primary therapy resulted in superior outcome (5-year event-free survival 80±4%) as compared to AML–type or combined-type approach (36±7.2% and 50±12%, respectively, P<0.0001).[22] Rasekh *et al*. analyzed 102 patients with MPAL (54 pediatric patients and 48 adults) and showed that ALL-like regimens were associated with significantly better response rates as compared to AML-type therapies regardless of age (P=0.001).[69] Conversely, a study by the Children's Oncology Group (COG) retrospectively analyzed 54 centrally reviewed patients with MPAL and demonstrated that both ALL- and AML-based induction regimens resulted in comparable outcomes.[70]

The utility of the hyperCVAD protocol (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) for patients with ALAL was assessed in a retrospective study of 25 patients from five centers. HyperCVAD-based therapy resulted in complete remission or complete remission with incomplete hematologic recovery in 84% of patients. The median OS was not reached (median follow-up of 31.6 months) and two-thirds of responding patients proceeded to allogeneic transplantation (HSCT).[71]

Patients with *BCR::ABL1r* MPAL should receive tyrosine kinase inhibitor-based therapy. The addition of tyrosine kinase inhibitors to the therapeutic protocol of patients with Ph$^+$ MPAL is associated with better OS in comparison to that of other MPAL patients, and comparable to the outcome

Table 1. Comparing induction outcomes in acute leukemia of ambiguous lineage.

First author	Classification system	Context	Outcome with induction approach	Message
Galera *et al.*, 2025[29]	WHO 2022	33 adult patients with MPAL	CR ALL-type 96.6% AML-type 0%**	ALL-type therapy is superior to AML-type in MPAL patients AML-type better in sAML-MP OS advantage for ALL-type confirmed in multivariate analysis*
Rasekh *et al.*, 2021[69]	WHO 2008	102 adult and pediatric patients with MPAL	CR* ALL-type 84.2% AML-type 50% 3-year OS* ALL-type 40.9% AML-type 18.5%	ALL-type therapy is superior to AML-type; age impacts response
Orgel *et al.*, 2020[70]	WHO 2016	54 pediatric/AYA MPAL	CR ALL-type 71.8% AML-type 69.2% Hybrid 100% 5-year EFS ALL-type 73±10% AML-type 62±14% Hybrid NA 5-year OS ALL-type 78±9% AML-type 69±14% Hybrid NA	No significant difference was found between ALL and AML induction regimens
Hrusak *et al.*, 2018[22]	WHO 2008	233 pediatric ALAL	5-year EFS*: ALL-type 80±4.0% AML-type 36±7.2% Hybrid 50±12%	ALL-type therapy is superior to AML-type, especially in CD19⁺ ALAL.
Heesch *et al.*, 2013[46]	WHO 2008	26 adult patients with ALAL	CR ALL-type 40% AML-type 22.2% Median OS ALL-type 21.5 months AML-type 11 months	Outcomes in adult ALAL are poor regardless of treatment protocol type
Matutes *et al.*, 2011[27]	WHO 2008	100 patients with MPAL	CR ALL-type 85% AML-type 41% OS* ALL-type 139 months (range 8-270) AML-type 11 months (range 8-14)	ALL-type therapy is superior to AML-type

*Statistically significant difference reported (P<0.05). **Only four of 33 MPAL patients were treated with AML-type induction in this analysis. WHO: World Health Organization; MPAL: mixed phenotype acute leukemia; CR: complete remission; ALL-type: acute lymphoblastic leukemia-type induction therapy; AML-type: acute myeloid leukemia-type induction therapy; sAML-MP-secondary acute myeloid leukemia with a mixed-phenotype; OS: overall survival; AYA: adolescents and young adults; EFS: event-free survival; ALAL: acute leukemia of ambiguous lineage; NA: not available.

of patients with *bona fide* Ph⁺ ALL.[72,73] For example, a SEER analysis of 241 patients with MPAL defined by WHO 2008 criteria (after the standard incorporation of tyrosine kinase inhibitors) demonstrated that Ph⁺ MPAL patients had a reduced risk of death in comparison to other patients with MPAL (HR=0.28, P=0.002). *KMT2Ar* patients with MPAL had the worst outcome with a 10-fold increased risk of death in comparison to those with Ph⁺ MPAL (HR=10.2, P<0.001). The outcome of patients with Ph⁺ MPAL was comparable to that of patients with Ph⁺ ALL in a one-to-one matched case-control analysis.[73]

The historically poor outcomes of MPAL have prompted the development of hybrid protocols incorporating elements of both AML-like and ALL-like regimens. While several studies reported inferior outcomes with this approach,[27,68] possibly reflecting the increased toxicity associated with such intensive protocols, other reports suggest potential benefit in selected patients.[74,75] A Polish Adult Leukemia Group (PALG) study reported on 16 adult patients with MPAL treated with a CLAG-M hybrid protocol (cladribine,

cytarabine, mitoxantrone and granulocyte colony-stimulating factor). Eight patients received CLAG-M as first-line therapy with an overall response rate of 100% (complete remission, N=6 and partial remission, N=2). Toxicity was acceptable and the median time for recovery of neutropenia and thrombocytopenia was 22 days (range, 16-24) and 17 days (range, 12-24), respectively. Grade 3-4 infections were observed in 12 cases.[76]

The optimal approach to AUL is unknown as systematic data to guide therapy for this extremely rare entity are lacking. Of the 223 patients reported in the IBFM retrospective study, five children fulfilled criteria for AUL. In these few patients ALL-type treatment appeared particularly ineffective.[22]

Regardless of the therapeutic approach chosen, central nervous system assessment, prophylaxis and treatment as indicated should be pursued in a proactive, protocol-driven manner.[67,70,77]

Accordingly, our current approach and recommendation is to treat most patients with MPAL with an ALL-type induction, with the addition of a tyrosine kinase inhibitor for patients with a *BCR::ABL1r*. The optimal induction approach for AUL is not defined and should be individualized (Figure 3).

Novel agents for acute leukemia of ambiguous lineage – promise and pitfalls

The incorporation of targeted novel agents is increasingly utilized in ALAL (Table 2). Preclinical observations demonstrate a BCL2-dependancy in ETP-ALL that is lost in mature forms of T-ALL,[78] prompting interest in the clinical utility of venetoclax in ALAL.[78-81] In one case series, three patients with MPAL were treated with venetoclax in combination with fludarabine, cytarabine, and filgrastim (FLAG), with or without idarubicin or gemtuzumab ozogamicin. Following induction, all patients achieved a sustained complete remission with undetectable minimal residual disease (MRD) by flow cytometry.[82] An additional study of four patients with ALAL who received FLAG-idarubicin-venetoclax demonstrated encouraging responses in the two patients sequenced early with this approach (first-line and first salvage) as compared to poor outcomes in patients treated for advanced disease.[80]

The potential efficacy of FLAG-idarubicin-venetoclax should be balanced against the potential increase in infectious complications and treatment-related mortality that were previously reported for this protocol, especially in the relapsed and refractory setting.[80,83-86]

In older or medically unfit patients, standard high-intensity AML or ALL induction regimens may be inappropriate. Such patients may be candidates for lower-intensity therapeutic approaches such as the combination of venetoclax with azacitidine or low-dose cytarabine, as described in a few case reports.[87-89]

The incorporation of menin-inhibitors for the *KMT2Ar* subset

Table 2. Potential novel agents for acute leukemia of ambiguous lineage.

Drug/agent	Rationale	Target ALAL population	Clinical evidence	Ongoing trials
Venetoclax	ALAL may be *BCL2*-sensitive[78-81]	Nonspecific	Case reports and case series: Ven-low-intensity regimens[87-89,100] Ven-high intensity regimens[80-82]	NCT05901974 NCT03194932 NCT04872790
FLT3 inhibitors	Targeting *FLT3*-mutated ALAL Targeting *FLT3*-mutated and/or overexpressed ALAL	*ZNF384*-rearranged ALAL (overexpression) *BCL11B*-activated (*FLT3*-ITD mutation)	NA	NA
Menin inhibitors	Menin inhibition active in *KMT2A*-rearranged leukemia	*KMT2A*-rearranged ALAL	AUGMENT 101 (revumenib) N=68; ORR 53% (1 pt. with MPAL)[90]	NCT05326516 NCT05761171
JAK inhibitors	Targeting overexpressed *JAK-STAT* pathway	T/Myeloid MPAL *BCL11B*-activated ALAL	Pre-clinical and clinical reports in ALL[92-94]	NCT02723994 NCT02115295
CD123-directed therapies	'Stem-cell' marker	CD123-positive ALAL	Pre-clinical data[95]	NCT06034470
CD38-directed therapies	'Stem-cell' marker	CD38-positive ALAL	Clinical trial in R/R pediatric ALL/LBL (daratumomab)[96]	NA
Blinatumomab	Targets B-lineage defining marker	CD19-positive ALAL	Case series and case reports[97-100]	NCT04827745 NCT06991920 NCT04872790
CD19 CAR T-cell therapy	Targets B-lineage defining marker	CD19-positive ALAL	Not data for ALAL Clinical reports in CD19-positive AML[101,102]	NCT06325748

ALAL: acute leukemia of ambiguous lineage; ITD: internal tandem duplication; NA: not available; ORR: overall response rate; MPAL: mixed phenotype acute leukemia; ALL: acute lymphoblastic leukemia; R/R: relapsed/refractory; LBL: lymphoblastic lymphoma; CAR T-cell: chimeric antigen receptor T-cell; AML: acute myeloid leukemia.

of ALAL is appealing given the activity of these agents in *KMT2Ar* acute leukemia. In the phase II AUGMENT-101 trial that led to the approval of revumenib for *KMT2Ar* relapsed/refractory acute leukemia, only one patient with MPAL was included (and achieved a morphological remission).[90]

In Ph-negative ALL, alterations in the JAK-STAT pathway can be found in approximately 10-20% of patients, most frequently in the context of *JAK1/2*, *IL7R* and *CRLF2* Ph-like mutations and rearrangements.[91] Targeting these high-risk genetic alterations with JAK inhibitors was shown to be effective according to preclinical observations,[92,93] and ongoing clinical studies are assessing the safety and efficacy of incorporating JAK-inhibitors in combination with chemotherapy in JAK-STAT-altered ALL[94] (Table 2). Whether the incorporation of JAK-inhibitors in ALAL subtypes that overexpress the JAK-STAT pathway, such as T/Myeloid MPAL and *BCL11B*-activated ALAL, is effective is unclear to date.

Antibodies directed towards common 'stem-cell' markers that are variably expressed in these leukemias (e.g., CD38 and CD123) may be an attractive therapeutic avenue.[95,96] There are several case reports on the use of blinatumomab, a bispecific T-cell engager, in ALAL,[97] including in combination with venetoclax.[98,99] Lower-Intensity chemo-immunotherapy with cladribine, low-dose cytarabine, venetoclax and sequential blinatumomab was reported in four patients with *BCR::ABL1*-negative B/Myeloid MPAL (median age 71 years [range, 55-77]). Three patients received this regimen as frontline therapy and one as salvage after decitabine-venetoclax. All patients achieved composite complete remission with undetectable MRD by flow cytometry after one cycle. Toxicity was manageable with only low-grade neurotoxicity reported. At last follow-up, three patients remained alive while one patient relapsed with AML.[100]

CD19-directed chimeric antigen receptor (CAR) T-cell therapy in CD19$^+$ ALAL may be a potentially effective treatment strategy as previously reported for patients with CD19$^+$ core-binding factor AML.[101,102]

Lineage-directed targeted therapies and lineage-switch

Lineage switch (LS) is defined as a change in lineage during therapy, or at relapse. Although LS is a well-described event with historically poor outcomes, it has recently emerged as a unique clinical phenomenon and mechanism of disease resistance following lineage-directed targeted immunotherapy,[103,104] with an incidence approaching 8% among patients with B-ALL, following CAR T-cell therapy.[105]

The potential for LS may already exist at the time of diagnosis. In one study of 223 cases of *de novo* BCP-ALL, 31 (13.9%) harbored *CRLF2* rearrangements (*CRLF2r*), and among these, seven (22.6%) exhibited partial monocytic differentiation. These findings suggest that monocytic features in *CRLF2r* B-ALL are relatively common and may predispose to subsequent LS.[106]

Identification and awareness of B-ALL with genotype linked myeloid/monocytic aberrancies is critical to avoid inappropriate deviation from effective ALL-directed therapy. Certain genetically defined B-ALL subtypes, notably *DUX4r*, *PAX5-P80R*-mutated, and *ZNF384r* cases, may develop a pronounced monocytic switch early during therapy, with acquisition of CD14, CD64, or other myeloid/monocytic markers. Novakova *et al*. showed that these populations remained clonally identical to the original B lymphoblasts by immunoglobulin/T-cell receptor rearrangement analysis, retained their defining genetic lesions, and that their emergence was not associated with inferior outcome with ALL-directed therapy.[107]

In one study, 33 patients with LS (defined by cytogenetic/molecular evidence of clonal relatedness between the original leukemia and LS) were analyzed. Risk factors for LS included pediatric patients, the use of CD19 T-cell engaging therapies, recurrent alterations in *EZH2,* and *KMT2A* fusions.[108] In a recent study, single cell transcriptome profiling revealed LS-prone B-ALL subtypes (*BCR::ABL1, KMT2Ar, DUX4r*) that are enriched for multipotent progenitor like states with *CEBPA* activation and myeloid potential. This phenotype underlies leukemic drift and is captured by a 'multi-potency score' associated with inferior survival.[109]

A recent study (EVOLVE project) analyzed 70 cases of LS after exposure to immunotherapies. Most patients (N=53, 75.7%) transitioned from BCP-ALL to AML, while 17 patients (24.3%) had a BCP-ALL to B/Myeloid MPAL or AUL switch. The immunotherapy most proximal to LS included CAR T cells (N=34, 48.6%) and blinatumomab (N=31, 44.3%), and LS emerged within 6 months of the most recent immunotherapy, or during immunotherapy, in 57 patients (81.4%). Only 20 of 65 patients (30.8%) achieved a complete response to first-line LS-directed therapy. Overall, remission rates were <40%, and the median OS following LS diagnosis was 4.8 months. The predominant cause of death was resistant disease (N=52 of 61, 85.2%). Notably, 64% of BCP-ALL to AML LS cases harbored *KMT2Ar*. As compared to other patients, *KMT2Ar* patients were younger and had earlier LS (median 1.1 *vs*. 3 months; *P*=0.16). Complete remission rates after LS were higher in the *KMT2Ar* group (17/40, 42.5%) than in the non-*KMT2Ar* group (6/25, 24%; *P*=0.18), though survival remained poor in both groups (15.6% *vs*. 4% survival, respectively).[103]

These data highlight the need for awareness and proactive surveillance for LS, especially in predisposed genetic subgroups, and after CD19-directed interventions. Combination of lineage-selective targeted therapies with a chemotherapy backbone might offer a potential strategy to reduce LS and remains to be studied.

Can measurable residual disease guide therapy in acute leukemia of ambiguous lineage?

MRD assessment is a powerful predictive tool that is used to make strategic therapeutic decisions for patients with ALL and AML.[110] Since patients with ALAL are poorly represented in large cooperative trials, the use of MRD assessments for

risk stratification and decision analysis are less established. Furthermore, the stability and biological and clinical utility of T-cell receptor or immunoglobulin heavy-chain gene clonal rearrangements for MRD surveillance are uncertain. Several retrospective analyses demonstrated that MRD-negative responses during therapy,[22,111,112] and before HSCT[113] are significantly associated with improved survival as compared to sub-optimal MRD responses. The iBFM-AMBI2012 study demonstrated that patients with >5% leukemic cells at the end of induction had poor 5-year EFS.[70] The predictive utility of flow-based MRD was reported in 112 pediatric patients diagnosed with MPAL. In this analysis, centrally reviewed flow-based MRD was assessed in patients receiving ALL-type regimens. With this approach, end - of - induction MRD-negative (<0.01%) remission was attained in most patients (70%). End-of-induction MRD positivity was predictive of 5-year EFS (HR=6.00, *P*<0.001) and OS (HR=9.57, *P*=0.003). Earlier MRD clearance was associated with better survival.[111] Based on these data, the Children's Oncology Group Acute Leukemia of Ambiguous Lineage Task Force recommended that only patients with end-of-induction blast clearance <5% and end-of-consolidation MRD <0.01% continue ALL therapy. The task force also advised that patients who fail to meet these thresholds be considered for early intensification with AML and/or HSCT consolidation.[70] While we generally support re-evaluating treatment approach in patients with ALAL and MRD-failure, these recommendations should be validated within prospective clinical trials, and in the adult population.

Given limited data on the clinical utility of MRD in MPAL, we recommend it not be used as the sole basis for major clinical decisions such as HSCT or therapy de-escalation outside of clinical trials. MRD should be utilized according to the therapeutic protocol applied and MRD-failure should prompt the clinician to re-assess and re-consider the therapeutic plan including consideration of HSCT. Combining different MRD platforms (e.g., flow cytometry with molecular or next-generation sequencing assays) may improve predictive accuracy.[110,111]

Allogeneic transplantation in first remission

Since ALAL is regarded as a high-risk leukemia with increased relapse rates, HSCT in first remission should be considered in eligible patients. Total body irradiation-based conditioning may be preferred, when feasible, based on ALL guidelines.[114] A retrospective registry study evaluated 519 adult patients with MPAL who underwent HSCT in first remission. Since the study spanned over several years (2000-2014), patients were classified by different classification systems. At 3 years after transplantation, the cumulative incidence of relapse was 31.4% (95% CI: 26.9-35.9), and non-relapse mortality was 22.1% (95% CI: 18.4-26.1). Leukemia-free survival and OS rates were reported to be 46.5% (95% CI: 41.7-51.4) and 56.3% (95% CI: 51.5-61.2), respectively. In a multivariate analysis, age and year of transplantation had a strong impact on outcome. Myeloablative conditioning using total body irradiation correlated with a better leukemia-free survival.[115] Another study reported outcomes in 77 adult patients diagnosed with MPAL over 10 years (median age 49 years; ALL-type induction in 61%) and reported median OS for the whole cohort of 41.9 months. Fifty patients (65%) were transplanted and the 5-year OS for this group was 54% with better outcomes reported for patients who were MRD-negative prior to transplantation (75.8% *vs*. 45.2%, *P*=0.06).[113]

In pediatric MPAL, HSCT offers no clear survival benefit. Most patients achieve durable remissions with ALL-based therapy alone, and HSCT is typically reserved for select high-risk genetic or clinical features.[70,115-117] The decision regarding transplantation for adult patients in first remission is complex and should be guided by disease genetic-risk, MRD response (as assessed by multiple methods), the patient's co-morbidity burden, and fitness. A specific group of interest is formed of patients with *BCR::ABL1* MPAL in whom the transplantation decision can be informed by the criteria applied for *BCR::ABL1* B-ALL.

Uncertainties and future challenges for acute leukemia of ambiguous lineage

ALAL is a rare disease with several diagnostic and therapeutic uncertainties. Genetic, epigenetic and metabolic translational insights improve the ability to better classify and risk-stratify ALAL as reflected in the most recent WHO and ICC documents. From the diagnostic perspective, close cooperation between the clinician, pathologist and laboratory services is needed to yield optimal diagnostic and therapeutic results.

Still, several diagnostic dilemmas exist. The reproducibility of diagnostic criteria for lineage commitment in the clinical setting across different laboratory services, is uncertain, and prospective validation of the most recent diagnostic schemes is needed. The clinical relevance of morphological correlations (e.g., Auer-Rod bodies in the context of ALAL) and the diagnostic impact of small, minute divergent clones is uncertain. Current classification systems for AML are rapidly moving towards genetically based classification of disease ontogeny. The diagnostic, prognostic and therapeutic impacts of myelodysplasia-related genetics including STM which may overlap between ALAL and secondary AML need further clarification. The clinical utility of transcriptomic and epigenomic profiles to aid classification and guide therapy requires further investigation.

Although cumulative evidence on the optimal treatment approach for patients with ALAL largely supports an ALL-type induction for most patients, prospective controlled

data are lacking. Novel, innovative approaches for specific and rare subtypes of ALAL with extremely poor outcomes such as AUL and LS are needed. Incorporation of novel, targeted therapies in combination with intensive, and lower-intensity chemotherapy backbones based on the specific biological and genetic characteristic of ALAL is an appealing approach and is increasingly reported. While the use of lineage-specific targeted approaches in acute leukemia with multi-phenotypic potential is promising, one must consider the potential for driving LS. Lastly, the role and optimal platform for MRD surveillance in ALAL to guide therapy and transplantation are unclear given the paucity of prospective controlled data.

Disclosures

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Contributions

AS and OW conceived and designed the manuscript, reviewed the literature, wrote the manuscript and revised it.

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