Diagnosis, Prognostic Factors and Assessment of ALL in Adults: 2023 ELN Recommendations from a European Expert Panel

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Abstract:
Working groups of the European Leukemia Net (ELN) have published several important consensus guidelines. Acute lymphoblastic leukemia (ALL) has many different clinical and biological subgroups and the knowledge on disease biology and therapeutic options is increasing exponentially. The European Working Group for Adult ALL has therefore summarized the current state of the art and provided comprehensive consensus recommendations for diagnostic approaches, biologic and clinical characterization, prognostic factors and risk stratification as well as definitions of endpoints and outcomes. Aspects of treatment, management of subgroups and specific situations, aftercare and supportive care are covered in a separate publication. The present recommendation intends to provide guidance for the initial management of adult ALL patients and to define principles as a basis for future collaborative research.

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Data Sharing Statement
The manuscript does not include any original data or protocols. Therefore, no data are available to be shared.

Abstract

Working groups of the European Leukemia Net (ELN) have published several important consensus guidelines. Acute lymphoblastic leukemia (ALL) has many different clinical and biological subgroups and the knowledge on disease biology and therapeutic options is increasing exponentially. The European Working Group for Adult ALL has therefore summarized the current state of the art and provided comprehensive consensus recommendations for diagnostic approaches, biologic and clinical characterization, prognostic factors and risk stratification as well as definitions of endpoints and outcomes. Aspects of treatment, management of subgroups and specific situations, aftercare and supportive care are covered in a separate publication. The present recommendation intends to provide guidance for the initial management of adult ALL patients and to define principles as a basis for future collaborative research.
Introduction

Scientific progress in acute lymphoblastic leukemia (ALL) has been driven by the activities of national academic multicenter study groups in Europe and US in the past decades. The European national study groups have founded a collaboration within the European Leukemia Net (ELN) named European Working Group for Adult ALL (EWALL). The group has published a Consensus Recommendation for the Management of Adult ALL which was broadly distributed among the participating centers.

ALL is rare compared to other cancers of adulthood. It has many different clinical and biological subgroups and the knowledge on disease biology and therapeutic options is increasing exponentially. There is an unmet need for guidance for clinicians, regulatory agencies, and health care systems. Available guidelines from the National Comprehensive Cancer Center (NCCN) or European Society of Medical Oncology are relevant but need to be complemented by a broad and comprehensive expert consensus considering the different regulatory and socio-economic framework for ALL management in Europe. Therefore, the group decided to develop ELN Recommendations as published for other entities. The focus of this article is on diagnostic approaches, biological and clinical characterization, risk stratification, definitions of endpoints and outcomes. Aspects of treatment, management of subgroups and specific situations, aftercare and supportive care are covered in a separate publication (cross-reference).

Methods

The panel includes 17 members representing national study groups. Members met in person and defined topics, tables, and responsibilities of co-authors (Table S1). Coauthors performed literature searches of PubMed database and considered relevant abstracts. The manuscript was reviewed by all co-authors. Formal corrections were performed by the corresponding author. Disagreements were summarized and discussed in the whole group. The whole group agreed on the final version of the manuscript. Due to rapid innovation and availability of new data together with a lack of randomized trials for many essential questions, most of the statements have an evidence level of ‘expert recommendation’ for clinical practice.

Diagnostic Procedures and Classification

The work-up should be comprehensive to allow a precise diagnostic work-up and an accurate stratification, as well as to set the basis for minimal residual disease (MRD) monitoring. Morphology, multicolor flow cytometry (MFC) and molecular genetics are obligatory (Table 1A). Additional genomic analyses are used to better define molecular subgroups. Diagnosis is usually based on a bone marrow (BM) aspirate which should be attempted even in cases with high peripheral blast (PB) counts. A BM biopsy is recommended in patients with a dry aspirate; in these cases, BM aspiration can be repeated after the pre-phase to obtain further material. Biobanking is recommended. It should include nucleic acid (DNA, RNA), viable cells and possibly germline material. Further work-up includes a lumbar puncture (LP) with classification and imaging procedures as needed to define potential extramedullary involvement (Table S2).

Morphology/Cytochemistry

BM morphology is necessary to evaluate the degree of infiltration and to differentiate ALL from mainly from acute myeloid leukemia (AML) and ALL from lymphoblastic lymphoma (LBL). There are no specific cytochemistry reactions to classify ALL. Myeloperoxidase is always negative with the exception of mixed-phenotype leukemia (MPAL), where low/dim/strong levels of expression have been described particularly in B-myeloid cases where isolated MPO expression (isoMPO) may occur.

Immunophenotyping

MFC (at least eight colors) is central. It allows to: i) make a differential diagnosis with AML, ii) to establish lineage affiliation and differentiation, iii) define an aberrant phenotype for MRD monitoring and iv) to detect target antigens for immunotherapy. The EuroFlow consortium has
standardized MFC. TdT is expressed by all B- and T-cell progenitors, except for mature B-ALL (Burkitt's Leukemia), while being negative in AML.

B-lineage ALL (B-LIN) accounts for 75-80% of cases. The crucial markers are CD19, CD22 and cytoplasmic (cy) CD79a. The EGIL classification defines four differentiation stages: pro-B, common, pre-B ALL and mature B-ALL (Table 1A). An aberrant coexpression of myeloid markers can be detected in about 40% of cases. Pro-B ALL is CD10-negative and often associated with t(4;11)/KMT2A while pre-B ALL often carries t(1;19)/TCF3::PBX1 aberration. The identification of surface markers as potential targets for immunotherapy is essential for therapeutic approaches (cross-reference).

T-lineage ALL (T-LIN) represents 20-25% of adult ALL. Crucial markers are cyCD3 and sCD7. Furthermore, CD1a, CD2, sCD3, CD4, CD5 and CD8, as well as TCRα/β or γ/δ, may be variably expressed. T-ALL can also be classified into four subtypes: pro-T ALL, pre-T ALL, cortical (thymic) and mature T-ALL. Pro-T ALL cases express only cyCD3 and CD7, cortical T ALL is CD1a positive, while mature T-ALL express sCD4 and/or CD8, and usually CD3. The so-called ETP-ALL (Early-T Precursor), represents an entity within pro-T/pre-T ALL with weak CD5 expression which shows at least one myeloid and/or stem cell marker. CD34 and myeloid markers are expressed in a proportion of T-ALL. The maturation stage correlates with molecular aberrations such as LMO2/HOXA in immature, TLX1/TLX3 in cortical, TAL1 in mature T-ALL. Beside EGIL there is no uniform international classification of immunophenotypes. To achieve comparability, it is recommended to report results including this classification.

Mixed-phenotype acute leukemia (MPAL) represents 1-5% of acute leukemias and is characterized by blasts coexpressing antigens of more than one lineage on the same cells or that have separate populations of blasts of different lineages. The definition of MPAL has been refined in the WHO 2008 and 2016 classification, the latter discriminating B-myeloid from the other MPAL. The combination of antigens used for MPAL recognition is summarized in Table 1A. Furthermore, the WHO 2016 classification takes into account also the presence of specific genetic aberrations, particularly the BCR::ABL1 and KMT2A rearrangements.

Cytogenetics/Molecular Genetics

Karyotyping, fluorescence-in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR) techniques are used for the genetic characterization.

B-LIN: t(9;22)/BCR::ABL1 is the most frequent aberration. Its detection in the shortest possible time is essential. Other subtypes include KMT2A rearrangements, monosomy 7, hypodiploidy/low hypodiploidy (and the related near-triploid), t(1;19)/TCF3::PBX1 and t(17;19)/TCF3::HLF. t(8;14)/MYC/IGH is rarely detected; also t(12;21)/ETV6::RUNX1 and high hyperdiploidy (51-65 chromosomes) are rare in adults.

T-LIN: Genetic aberrations often comprise the 14q11 and 7q34 breakpoints, leading to the juxtaposition of the TCR loci to transcription factors, namely TAL1, TAL2, LYL1, LMO1, LMO2, TLX1 (HOX11), TLX3 (HOX11L2), HOXA, MYC and MYB. In addition, cryptic ABL-1 rearrangements with different partner genes such as NUP214, EML1 and ETV6 have been identified.

MPAL: The list of genomic lesions detected in MPAL is rather large, and is likely to increase, given its heterogeneity. As mentioned, the most frequent rearrangements as already mentioned, are BCR::ABL1 detected in about 15% of cases and KMT2A found in roughly 10% of patients; ZNF384 rearrangements have also been reported in about 49% of B/MPAL.

Extended Genomics

Gene expression profiling (GEP), copy number alteration analysis (CNA), genome-wide and next generation sequencing (NGS) techniques have identified new subgroups. These techniques are not part of the standard work-up but may be carried out for a refined classification in research laboratories. The Philadelphia (Ph)-like subgroup is discussed separately (cross-reference). ETP-ALL is genetically heterogeneous, with mutations of multiple pathways including hematopoietic and lymphoid development, Ras, cytokine receptor, and kinase signaling, and loss-of-function mutations targeting epigenetic regulators.
CNA allows to identify aberrations that affect cell cycle (CDKN2A/B and RB1), as well as lymphoid development (IKZF1, PAX5, VPREB1 and LEF1). Among those, IKZF1 deletion (ΔIKZF1)\(^{19,20}\) can be found in about 80% of Ph+ and Ph-like cases\(^ {21}\). The IKZF1-plus genotype (i.e. iKZF1 plus CDKN2A/B and/or PAX5 deletions) is considered in some trials. Recently, further subtypes have been identified in B-LIN. The DUX4- and ERG-rearrangement leads to the formation of an ERG isofrom, which - in mice models - induces leukemic transformation. MEF2D rearrangements have transforming capability in vitro. Finally, ZNF384 deregulation, which can rearrange with several partners (EP300, CREBBP, TAF15, SYNRG, EWSR1, TCF3 and ARID1B) often displays a weak CD10 and CD13/CD33 expression\(^ {15}\).

NGS has identified novel mutations and rearrangements; the most frequent involve the RAS pathway (N/K RAS, FLT3, PTPN11, NF1 and BRAF mutations) and can be detected in more than 40% of cases, are prevalent in the hyperdiploid and KMT2A-rearranged cases and tend to increase at relapse. More rare mutations affect the Janus kinase (JAK)/STAT pathway (JAK1/2, JAK3, IL7R, rarely CRLF2, SH2B3 and IL2RB). RAS and JAK/STAT mutations are detected in both B- and T-LIN\(^ {22}\). In T-ALL, NOTCH1/FBXW7 lesions represent the most frequent event (60%) (Table 1B).

WHO (World Health Organization) and International Consensus Classification (ICC)

The updated classifications are largely overlapping; the ICC identifies more distinct molecular categories\(^ {15,23}\) (Table S3). A variety of methods would be required to establish the respective categories. This is not standard in most countries and beside the most relevant diagnostic characterizations summarized in Table 1A the new subcategories to date have limited clinical consequences. Nevertheless, their identification is of interest in a research context. Further WHO and ICC classifications with more detailed guidance on recommended and standardized methods for identification of subgroups are warranted.

MRD Testing

MRD testing aims at detecting and quantifying residual blasts beyond the sensitivity of cytomorphology which is around 5\(^ {24,25}\). It is important to establish the target structures for MRD testing based on primary diagnostic material. The panel strongly advises to perform MRD evaluation in reference laboratories participating in standardization approaches. The most common methods for MRD monitoring are MFC and real-time quantitative PCR (RQ-PCR). MFC can be applied to most cases (>90%), can reach a sensitivity of 0.1-0.01% (10\(^ {−3}\)-10\(^ {−4}\)) and results are promptly available. Disadvantages are: i) samples must be rapidly analyzed; ii) small number of evaluable cells due to BM hypocellularity; iii) misleading results due to phenotypic shift; iv) interpretation to some extent operator dependent; v) suboptimal sensitivity. The EuroFlow Consortium has standardized the procedures\(^ {26}\). Further efforts are ongoing to implement the use of next generation flow mainly for better interoperability and sensitivity.

Molecular MRD monitoring of fusion genes (e.g. BCR::ABL1) has a sensitivity around 0.01%, is possible in about 40% of cases, is not patient-specific, relatively easy to perform and inexpensive. However, its accuracy is hampered by the variability in the number of RNA transcripts per leukemic cell. The EuroMRD Consortium has standardized MRD detection based on the BCR::ABL1\(^ {27}\).

In most patients, a clonal Immunoglobulin/T-cell receptor (IG/TR) rearrangement can be identified for MRD evaluation. The technology is applicable to over 90% of cases\(^ {28}\) and has been extensively standardized within the EuroMRD Consortium. Technical issues are: i) in the most immature forms, IG/TR gene rearrangements may not be found; ii) the designed probes may not be sufficiently sensitive; iii) clonal evolution may lead to false negative results; iv) the amount of diagnostic DNA may be too low.

Any RQ-PCR may fail to precisely define the amount of residual disease in cases with a very low burden, i.e. "positive-not-quantifiable" (PNQ); their identification is an unmet need in clinical practice. These cases are being investigated with novel techniques e.g. digital droplet PCR (ddPCR) and NGS. For NGS neither methodology nor reporting is standardized. In part similar technical issues apply as for IG/TR PCR and particularly the claimed higher sensitivity...
depends on the amount of DNA. MRD-testing by NGS is so far not incorporated in the clinical practice\textsuperscript{29}. The various techniques are summarized in Table S4 and therapeutic application of MRD is discussed separately (cross-reference).

**Prognostic Factors (PF)**

Different risk subsets according to disease- and host-related factors can be identified\textsuperscript{30}. The individual prognosis must be refined by assessing MRD response\textsuperscript{24,25} and its integration with other PFs. Patients without poor PF and/or with a favorable post-induction MRD course may represent 50-60\% of all cases and are defined as standard-risk (SR, 5-year overall survival >50-60\% and up to 70-80\% in selected good-risk subsets) while those with any poor PF and/or poor MRD response are classified as high-risk (HR, 5-year overall survival <40\%) (Table 2A). This distinction is crucial to develop an effective risk-oriented treatment strategy.

One approach is to select HR patients for an allogeneic stem cell transplantation (SCT) and/or other novel therapies, while SR patients are treated with chemotherapy with good to very good results and low risk of therapy-related mortality (TRM). Risk models depend on treatment protocol, differ among clinical studies and are periodically updated (Table 2B).

**Clinical Risk Factors: Age, White Blood Cell Count (WBC) and Immunophenotype**

Older age and high WBC counts are universally recognized as predicting poorer outcome\textsuperscript{30}. WBC is still a relevant and easily assessable PF. Cut-offs for HR B-ALL are often set >30 x10\(^9\)/L. A WBC based stratification in T-ALL (>100 x10\(^9\)/L) is not generally adopted. Other clinical PF are poor performance score (ECOG >1), CNS-positive ALL in some trials, and undue reductions or delay of post-induction therapy\textsuperscript{31,32}. Pro-B-ALL is sometimes defined as HR. Some trials report a poorer prognosis in CD20-positive cases\textsuperscript{33}, unless associated with good MRD response\textsuperscript{34} or treated with rituximab. In T-ALL the prognosis is worse for the pro/pre-T (or ETP as subentity of immature T-ALL) and mature T subsets whereas the cortical phenotype has a good prognosis\textsuperscript{35}. Outcome of HR T-ALL may be improved using pediatric-based (p-b) chemotherapy in conjunction with SCT\textsuperscript{36}. In newly diagnosed ALL, the bone marrow blast count differentiating ALL from LBL is not considered as a prognostic feature but as a feature identifying a clinically relevant subtype which has an impact on practical management as outlined below. In relapsed ALL bone marrow blast count can be predictive for response rates (cross-reference).

**Cytogenetics**

Recent cytogenetic classifications suffer from lack of information in up to 50\% of the patients, low incidence of some aberrations and interactions with other PFs\textsuperscript{37-39}. ‘Good risk’ karyotypes such as t(12;21) are rare in adults. Most adults fall within an intermediate-risk (IMR) group. According to one of the published classifications, IMR includes the normal diploid subset, hyperdiploidy and some other abnormalities. Monosomy 7, low hypodiploidy/near triploidy and complex karyotype with 3-5 simultaneous abnormalities are allocated to a HR cytogenetic category as the t(4;11)/KMT2A rearranged ALL by several groups\textsuperscript{39,40}. For complex karyotype a uniform definition is recommended (Table 2A). There is no generally accepted cytogenetic classification for adult ALL and it remains open whether the prognostic impact of rare aberrations as outlined above is still valid in modern protocols.

**Molecular Genetics and Genomics**

Further genetic aberrations can exert significant prognostic effects (Table 1B). Cases with iAMP21, Ph-like ALL\textsuperscript{21,41,42}, and an altered CNA profile can be associated with a higher relapse risk (RR) in both Ph- ALL\textsuperscript{43,44} and Ph/BCR::ABL-positive (Ph+) ALL\textsuperscript{45,46}. An 8-gene CNA profile was validated in pediatric B-ALL\textsuperscript{47}. The good-risk CNA classifier consisted of no deletion of IKZF1, CDKN2A/B, PAR1, EBF1, RB1; by an isolated deletion of ETV6, PAX5, BTG1; or by a deletion of ETV6 with single additional deletion of either BTG1, PAX5, or CDK2A/B. Any other CNA combination exerted a negative prognostic effect. Adult studies identified KMT2A-AFF1, Ph-like, low hypodiploid/near haploid, BCL-2/MYC-rearranged, PAX5alt, ZNF384-like and MEF2D-rearranged as HR or IMR-HR genotypes\textsuperscript{48,49}. CDX2 de-
regulated ALL with UBTF::ATXN7L3 has been described as a new unfavorable subtype which may benefit from targeted therapies. In T-ALL, overexpression of HOX11L2 and ERG, lack of NOTCH1 and FBXW7 mutations, and presence of RAS or PTEN abnormalities yielded unfavorable outcomes. Mutations/alterations of TP53, JAK/STAT, BCL-2, MYC are unrestricted to cell lineage and may confer poor prognosis. As for cytogenetics it is important to note that prognostic annotations are often based on small patient numbers and not always based on outcomes with current protocols.

Early Response Dynamics
Patients with poor blast cell clearance and late responders requiring more than one chemotherapy course to complete remission (CR) have an inferior outcome. The most useful prognostic information for RR and overall survival (OS) and individual risk stratification comes from MRD testing. As a general rule, with RQ-PCR (sensitivity of 0.01%) good prognosis patients reach MRD levels <0.1% to <0.01% (better if negative) at end of induction (weeks 4-6) and <0.01% (better if negative) following 1-3 early consolidation courses around weeks 10-16. Therapeutic consequences are discussed separately (cross-reference).

Integrated Risk Models
In children, an independent genotype-specific effect on MRD-related outcomes improved the risk stratification. In adults, one study demonstrated the usefulness of a mixed MRD and genetic risk classification, showing the independent prognostic effect of a 4-gene classifier (favorable: lack of KMT2A rearrangements and ΔIKZF1 in B-ALL; mutated NOTCH1/FBXW7 without RAS/PTEN abnormalities in T-ALL). In addition a comprehensive risk model combined WBC, cytogenetics and MRD results. Both models have not been uniformly adopted.

Recommendations for Analysis of PFs and Risk Stratification
MRD testing is recommended in all cases to optimize risk stratification. In a European survey, MRD was the only PF shared by 11 national study groups to define HR ALL and to decide about SCT indication. No other PF achieved the same level of consensus, although adverse genetics rank high in HR definitions (8/11 groups). Altogether, it is strongly recommended to perform MRD analysis in all ALL patients. New evidence may prove the independent prognostic power of several genetic abnormalities that in different combinations concur to define novel HR subsets. Appropriate diagnostic identification and clinical data in relevant patient numbers with modern protocols are a pre-requisite. New combined risk models are therefore recommended for research purposes to improve the diagnostic and prognostic platforms.

Response Criteria and Definition of Outcomes
Formal criteria for BM response assessment in ALL are based on AML and those for extramedullary response on Non-Hodgkin's Lymphoma (NHL). Recently new standards for remission, treatment failure and relapse have been defined for pediatric ALL, which should be adopted for adult ALL.

Cytologic Response in BM
Whereas criteria for CR are uniformly used, CR with incomplete recovery (CRI) can be an endpoint in clinical trials. Failure or partial remission (PR) can be differentiated or combined. For PR cases a correlation with MRD testing is recommended. If technical criteria for MRD testing are met, PR or CRI with negative MRD status can be considered as CR. On the other hand, patients with MRD of 1% or higher can be considered as failure. For future clinical trials a standardized terminology is requested. Publications should also define time-point (TP) of response assessment and avoid reporting of cumulative response rates.

MRD Response

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Response criteria are redefined by integrating MRD assessment. Usually, MRD assessment is only considered in patients with hematologic CR or CRi. In any case the reference population should be clearly stated and evaluable and non-evaluable MRD results should be named. Complete MRD response is defined as no detection of MRD with a minimum sensitivity of 0.01% at the respective TP. MRD persistence is defined as quantifiable MRD, usually 0.01% or greater. Some groups consider any MRD positivity as prognostically relevant; others consider thresholds like 0.1% or 0.01% for different TP or different treatment consequences. Beyond these categories additional MRD results may be reported, including non-quantifiable MRD at different levels of sensitivity or negative MRD with insufficient sensitivity. For TP with non-quantifiable MRD additional ddPCR or NGS testing may be used to separate true negative from false positive results. Of note - any negative MRD result without the corresponding sensitivity level at a distinct TP does not fulfill technical requirements. The latter are different for MFC, PCR of IG/TR, PCR of fusion genes and often not reported for NGS based methods. MRD results should include information on the material tested and specifics: PB versus BM, level, and status of MRD i.e. positive vs negative or non-evaluable. Two variants of MRD based response assessment are given in Table 3. The panel is in favor or variant 1 since the exact MRD level (not considered in variant 2) is relevant for any treatment decisions and for comparability of reported results.

Extramedullary Response
Between 20-90% of ALL patients show extramedullary involvement at diagnosis. Type and extent of involvement should be documented. These localizations should have regressed in size at the TP of CR confirmation. Standard criteria for NHL are recommended for classification. In case of persistent extramedullary involvement after induction and early consolidation, Positron Emission Tomography (PET) analysis can be considered. This approach raises challenges in dose dense treatment protocols for ALL due to the recommended treatment-free interval. For the purposes of clinical trials, patients with CRi or PR, PET negative may be considered as CR. Therapeutic consequences from positive PET remain to be defined.

Summary and Outlook
The management of ALL is often organized by national study groups and international consortia. Their reference laboratories and/or associated biobanks together with clinical data bases are essential for research on disease biology and prognostication and are
sources of reliable real-world data. Reference laboratories are crucial to establish and maintain high standards for diagnostic procedures and biologic characterization as basis for risk stratification and optimal management. Cytomorphology, immunophenotyping and the identification of prognostically relevant molecular markers together with measurement of MRD are the basis for diagnosis and risk adapted therapy.

Further genetic characterization of samples from biobanks has identified many new subtypes of ALL. The prognostic and therapeutic impact however often remains open for current treatment regimens and diagnostic identification is not part of SoC in many countries. It will be essential to define reliable and cost-effective diagnostic procedures to improve classification of ALL. On this basis, future risk stratification may integrate molecular markers, potential treatment targets, risks for relapse and toxicities as well as the dynamics of MRD. Furthermore, improved understanding of disease biology can contribute to the development of new, targeted precision medicine approaches.

For comparability of data on an international level it will be essential to use uniform and standardized criteria for reporting of results. This applies particularly for the use of MRD as endpoint of clinical trials and for any MRD-based treatment decisions.

Whereas there is no standard risk model for adult ALL, all experts agree that depending on treatment protocols and clinical subgroup risk-adapted approaches for management are standard (cross-reference). Future risk models may also integrate pharmacogenomics in order to predict and potentially avoid toxicities and in-vitro-sensitivity testing for identification of potentially active drugs for later-line approaches in relapsed/refractory ALL.

Author Contribution Statement
All coauthors reviewed literature, wrote parts of the manuscript, reviewed the manuscript and approved the final manuscript.

Conflict of Interest Statement
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References


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Table 1A: Specific Diagnostic Work-up in Adult ALL

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<th>Recommendation</th>
<th>Outputs</th>
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| Morphology     | Mandatory | • Defines infiltration (>25% required for a diagnosis of ALL versus LBL)  
                 |          | • Allows a differential diagnosis with AML (MPO- vs +)  
                 |          | • Recognizes L3 (Burkitt-type) subsets |
| Flow cytometry | Mandatory | • Allows a differential diagnosis with AML  
                 |          | • Permits to define the cell of origin  
                 |          | • Permits to define the stage of differentiation |
| MPO*           | Mandatory | • Allows a differential diagnosis with AML |
| B-lineage ALL*:| Mandatory | • Pro-B: CD19/CD79a/cCD22+/CD10- (B-I), NG2  
                 |          | • Common: CD10+/clgM- (B-II)  
                 |          | • Pre-B: clgM+/slg- (B-III)  
                 |          | • Mature: slg+ (B-IV), CD20+ |
| T-lineage ALL*:| Mandatory | • Pro-T: cCD3/CD7+ (T-I)  
                 |          | • Pre-T: CD2/CD5+ (T-II)  
                 |          | • Cortical-T: CD1a+ (T-III)  
                 |          | • Mature-T: sCD3+/CD1a- (T-IV) |
| Molecular genetics | Mandatory | • t(9;22)/ Ph+/ BCR::ABL1  
                 |          | • t(4;11)+ / KMT2Ar  
                 |          | • t(1;19)+ / TCF3::PBX1  
                 |          | • Other high-risk cytogenetics |
| MRD (Molecular or MFC) | Mandatory | • Individual MRD assay for further follow-up |
| Extended genomics (GEP, CNA, WES, WGS, NGS) | In clinical trials and for research purposes | • Identification of novel subgroups with prognostic/biologic significance  
                 |          | • Identification of molecular targets for targeted therapies |

Abbreviations: MPO: myeloperoxidase; c: cytoplasmic; s: surface; GEP: gene expression profiling; WES: whole exome sequencing, WGS: whole genome sequencing, NGS: next generation sequencing

* MPAL: Myeloid: Myeloperoxidase or at least 2 of the following antigens: nonspecific esterase, CD11c, CD14, CD64, lysozyme; B-lineage: Strong CD19 expression plus at least 1 of the following strongly expressed antigens : CD79a, cyCD22, CD10 or weak CD19 with at least 2 of the following strongly expressed antigens: CD79a, cytoplasmic CD22, CD10 ; T-lineage: cCD3or rarely sCD3
<table>
<thead>
<tr>
<th><strong>ALL subset</strong></th>
<th><strong>Prevalence and prognosis</strong></th>
<th><strong>Related aberration(s)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-lineage ALL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCR::ABL1+/(9;22)(q34;q11.2) (Ph+)</td>
<td>20-50%, increasing with age; improved by TKI therapy</td>
<td>BCR::ABL1 rearrangement</td>
</tr>
<tr>
<td>Ph-like</td>
<td>25-27%; Unfavorable/Controversial for current regimens</td>
<td>Gene expression profile like BCR::ABL1+ ALL except for lack of BCR::ABL1 rearrangement</td>
</tr>
<tr>
<td>TCF3::PBX1+/t(1;19)(q23;p13)</td>
<td>10-15% Favorable with intensive therapy</td>
<td>TCF3::PBX1 rearrangement</td>
</tr>
<tr>
<td>KMT2A(MLL)-AFF1+/t(4;11)(q21;q23.3), KMT2A-rearranged/t(v;11q23.3)</td>
<td>~5% (KMT2A-AF4+) Unfavorable</td>
<td>KMT2A::AFF1 or KMT2A-other partner gene rearrangement</td>
</tr>
<tr>
<td>IGH::MYC+/t(8;14)(q24;q32)</td>
<td>1-5% Unfavorable</td>
<td>IGH-MYC rearrangement</td>
</tr>
<tr>
<td>TCF3::HLF/t(17;19)(q22;p13.3)</td>
<td>&lt;1% Unfavorable</td>
<td>TCF3-HLF rearrangement</td>
</tr>
<tr>
<td>iAMP21</td>
<td>~2% Intermediate/unfavorable</td>
<td>-</td>
</tr>
<tr>
<td>14q32 translocations</td>
<td>&lt;5%, higher in adolescents Intermediate/unfavorable</td>
<td>IGH fusion with partner genes CRLF2, ID4, CEBP, BCL2, EPOR, LHX4 and IL-3</td>
</tr>
<tr>
<td>9p13 deletions/translocations</td>
<td>~25% No impact on outcome</td>
<td>PAX5 fusion with partner genes ETV6, ELN, POM121, PML, FOXP1, MLLT3, JAK2, C20orf112, AUTS2, CHFR, SOX5, POM121C</td>
</tr>
<tr>
<td>7p12.2 focal deletions/ mutations</td>
<td>50%; 80% in Ph+ and Ph-like Controversial prognosis</td>
<td>Deletions of IKZF1</td>
</tr>
<tr>
<td>DUX4-rearranged and ERG-deregulated</td>
<td>3-7% Favorable</td>
<td>ERG and IKZF1 deletions</td>
</tr>
<tr>
<td>MEF2D-rearranged ALL</td>
<td>3-4% Poor</td>
<td></td>
</tr>
<tr>
<td>Type of ALL</td>
<td>Subtype</td>
<td>%</td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>---</td>
</tr>
<tr>
<td>ZNF384-rearranged ALL</td>
<td>6-7%</td>
<td>Intermediate</td>
</tr>
<tr>
<td>CDX2/UBTF</td>
<td>2.7-4%</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>T-lineage ALL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAL and LMO rearrangements/del(1)(p32), t(1;14)(p32;q11), t(1;7)(p32;q34), t(7;9)(q34;q32), t(11;14)(p15;q1), t(11;14)(p13;q1), t(7;11)(q35;p13)</td>
<td>30-40%</td>
<td>Favorable, partly depending on additional lesions</td>
</tr>
<tr>
<td><strong>HOXA aberrations/inv(7)(p15q34), t(7;7)(p15;q34), t(10;11)(p13;q14), t(v;11q23), del(9)(q34).</strong></td>
<td>20-25%</td>
<td>Outcome depending on additional lesions</td>
</tr>
<tr>
<td>TLX1-10q24 rearrangements/t(7;10)(q34;q24), t(10;14)(q24;q11)</td>
<td>20-30%</td>
<td>No impact on prognosis</td>
</tr>
<tr>
<td><strong>ETP ALL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLX3-5q35 rearrangement/t(5;14)(q35;q32)</td>
<td>10%</td>
<td>No impact on prognosis</td>
</tr>
<tr>
<td>t(8;14)(q24;q11)</td>
<td>1%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>ABL1 rearrangements</td>
<td>~3%</td>
<td>Potentially targetable by TKIs</td>
</tr>
<tr>
<td>LYL/MEF2C rearrangement and immature cluster/t(7;19)(q34;p13), del(5)(q14)</td>
<td>3-17%</td>
<td>Unfavorable; improved by intensive treatment</td>
</tr>
<tr>
<td>NKKX2-1/NKKX2-2 rearrangements/inv(14)(q11.2;q13), t(7;14)(q34;q13), inv(14)(q13q32.33), t(14;20)(q11;p11)</td>
<td>6%</td>
<td>No impact on prognosis</td>
</tr>
</tbody>
</table>
Any prognostic statements should be considered carefully, since they depend on protocol, presence of other prognostic features and are often based on small patient numbers.
Table 2A: Potential Prognostic and Predictive Factors in Adult ALL

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Annotations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-related</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>&gt;30-60 years (continuous variable)</td>
</tr>
<tr>
<td></td>
<td>&gt;55 years (older adults and elderly)</td>
</tr>
<tr>
<td>Performance (ECOG)</td>
<td>&gt;1</td>
</tr>
<tr>
<td></td>
<td>Retrospective data; relevance in older patients</td>
</tr>
<tr>
<td><strong>Disease-related</strong></td>
<td></td>
</tr>
<tr>
<td>WBC (x10⁹/l)</td>
<td>&gt;30 (B), &gt;100 (T)</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Pro-B, CD20+ (B), Pro/Pre-T, ETP, mature-T (T)</td>
</tr>
<tr>
<td>Cytogenetics and FISH</td>
<td>Ph+, t(4;11), hypodiploidy, complex*</td>
</tr>
<tr>
<td>Genetics</td>
<td>BCR::ABL1+, KMT2Ar</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Ph-like, mutated CLRF2/TP53/JAK-STAT, adverse CNA profile (B), unmutated NOTCH1/FBWX7 and abnormal RAS/PTEN (T)</td>
</tr>
<tr>
<td>Genetics</td>
<td>Ph-like, mutated CLRF2/TP53/JAK-STAT, adverse CNA profile (B), unmutated NOTCH1/FBWX7 and abnormal RAS/PTEN (T)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>CNS involvement</td>
</tr>
<tr>
<td></td>
<td>Poor treatment compliance, undue treatment reductions and delay</td>
</tr>
<tr>
<td></td>
<td>Pharmacogenomics (affecting antimetabolite disposition)</td>
</tr>
<tr>
<td></td>
<td>Immune marrow microenvironment</td>
</tr>
<tr>
<td></td>
<td>Drug response profiling</td>
</tr>
<tr>
<td><strong>Treatment response dynamics</strong></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid sensitivity (pre-phase)</td>
<td>Poor prednisone response (peripheral blast ≥1x10⁹/L at the end of prephase)</td>
</tr>
<tr>
<td>Early/incomplete blast cell clearance (BM morphology)</td>
<td>Day 8-15 or end of induction BM blasts ≥ 5%</td>
</tr>
<tr>
<td>Time to CR (no. of courses)</td>
<td>&gt;1 cycle (late CR)</td>
</tr>
<tr>
<td>MRD (molecular/flow cytometry)</td>
<td>MRD positivity (from end of induction onwards):</td>
</tr>
<tr>
<td></td>
<td>≥ 0.1% / 0.01% after induction</td>
</tr>
<tr>
<td></td>
<td>≥ 0.01% / positive after/during consolidation and pre/post-allogeneic SCT</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ETP, early thymic precursor; CNS, central nervous system; CR, complete remission
Definition of complex karyotype: 5 or more chromosomal abnormalities excluding those patients with an established translocation.
Table 2B: Risk Stratification Models for Allogeneic SCT in Adult Ph/BCR::ABL1-negative (Ph-) ALL (European Study Groups)

<table>
<thead>
<tr>
<th>National Study Group</th>
<th>Patient age (years)</th>
<th>Post-induction MRD</th>
<th>Cytogenetics/Genetics§</th>
<th>WBC (x10⁹/L)</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMALL (Germany)</td>
<td>&lt;55</td>
<td>≥0.01% after consolidation I (week 16 onward)</td>
<td>KMT2A+</td>
<td>&gt;30 (B)</td>
<td>Late CR, Pro-B, early/mature-T</td>
</tr>
<tr>
<td>GIMEMA (Italy)</td>
<td>&lt;65</td>
<td>≥0.01% after early consolidation (week 10-16), any positivity (week 22)</td>
<td>Adverse, KMT2A+</td>
<td>&gt;100</td>
<td>Early/mature-T</td>
</tr>
<tr>
<td>HOVON (The Netherlands)</td>
<td>&lt;40</td>
<td>≥0.01% after consolidation (wk 14-16)</td>
<td>Adverse KMT2A, hypodiploidy, complex karyotype</td>
<td>&gt;30 (B), &gt;100 (T)</td>
<td>Late CR</td>
</tr>
<tr>
<td>PALG (Poland)</td>
<td>&lt;55</td>
<td>≥0.1% after induction, ≥0.01% during/after consolidation</td>
<td>KMT2A+</td>
<td>&gt;30 (B), &gt;100 (T)</td>
<td>CNS+</td>
</tr>
<tr>
<td>UK NCRI ALL Group</td>
<td>&lt;40</td>
<td>≥0.1% after induction and consolidation (mathematical risk model integrating MRD, cytogenetics and WBC)</td>
<td>Adverse</td>
<td>High count</td>
<td>-</td>
</tr>
<tr>
<td>FALL (Finland)</td>
<td>&lt;45</td>
<td>≥0.1% after consolidation block B</td>
<td>Abn11q23, hypodiploidy</td>
<td>&gt;100</td>
<td>Late CR, d15 BM blasts &gt;25%</td>
</tr>
<tr>
<td>RALL (Russia)</td>
<td>&lt;55</td>
<td>Positive during/after consolidation</td>
<td>t(4;11), t(1;19), KMT2A+</td>
<td>-</td>
<td>Age &gt;30</td>
</tr>
<tr>
<td>SVALL (Sweden)</td>
<td>&lt;65</td>
<td>≥0.1% after consolidation</td>
<td>Hypodiploidy, KMT2A+</td>
<td>-</td>
<td>EOI BM blasts &gt;5%</td>
</tr>
<tr>
<td>PETHEMA (Spain)</td>
<td>&lt;55 (60 fit)</td>
<td>≥0.1% after induction, ≥0.01% during/after consolidation</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GRAALL (France/Belgium/Switzerland)</td>
<td>&lt;60</td>
<td>≥0.1% after induction at week 6 or ≥0.01% after consolidation at week 12</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CELL (Czech Republic)</td>
<td>&lt;65</td>
<td>≥0.1% after induction, ≥0.01% after consolidation</td>
<td>KMT2Ar</td>
<td>&gt;30 (B)</td>
<td>Early/mature-T</td>
</tr>
</tbody>
</table>

*Independent risk factors adopted in clinical trials for the definition of HR ALL and the consequent allocation to SCT; adapted from

§Adverse cytogenetics/genetics (details to be found in single study protocols)

Abbreviations: CNS, central nervous system; CR, complete remission; EOI, end of induction
Table 3: Response Criteria for ALL (modified from\textsuperscript{70})

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic response criteria</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Complete remission (CR)\textsuperscript{a}                   | BM blasts < 5%  
Absence of extramedullary disease  
Absolute neutrophil count > 1x10\textsuperscript{9}/L  
Platelet count > 100x10\textsuperscript{9}/L  
(Independence of red cell transfusions)  
*If available: MRD <1%\textsuperscript{65}                                                                 |
| CR with incomplete recovery (CRi)\textsuperscript{a}          | All CR criteria except for residual thrombocytopenia  
<100x10\textsuperscript{9}/L or neutropenia <1x10\textsuperscript{9}/L  
*If available: MRD <1%\textsuperscript{65}                                                                 |
| Morphologic leukemia-free state\textsuperscript{b}           | BM blasts < 5%;  
Absence of extramedullary disease;  
No hematologic recovery required  
*If available: MRD <1%\textsuperscript{65}                                                                 |
| Partial remission (PR)\textsuperscript{e}                    | Relevant in the setting of phase 1 and 2 clinical trials only;  
all hematologic criteria of CR; decrease of BM blast percentage to 5% to 25%; and decrease of pretreatment BM blast percentage by at least 50%  
*If available: CR if MRD <1%\textsuperscript{65}                                                                 |
| Failure (F)                                                   | None of the above  
*If available: MRD ≥1%\textsuperscript{65}                                                                 |
| **MRD response criteria (Variant 1)\textsuperscript{c}**       |                                                                                                                                                                |
| Complete MRD response                                         | No detectable MRD\textsuperscript{d}                                                                                                                                 |
| MRD Failure                                                   | MRD above 0.01% (i.e. 10\textsuperscript{-4})                                                                                                                                 |
| MRD Other Negative                                           | MRD negative with insufficient sensitivity                                                                                                                                 |
| Positive/Intermediate                                         | MRD positive below 0.01%, quantifiable  
MRD positive below 0.01%, non-quantifiable  
MRD positive, non-quantifiable                                                                                                                                 |
| **MRD response criteria (Variant 2)\textsuperscript{c}**       |                                                                                                                                                                |
| MRD complete response                                         | No detectable MRD\textsuperscript{d}                                                                                                                                 |
| MRD persistence                                               | Any quantifiable MRD                                                                                                                                                                      |
| **Criteria for extramedullary response assessment**           |                                                                                                                                                                |
| Published criteria for NHL\textsuperscript{64}                |                                                                                                                                                                |
| PET in case of CRu/PR according to published criteria for NHL\textsuperscript{68} |                                                                                                                                                                |

1 All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.  
2 CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved during the entire treatment plan. In these instances, the overall remission rate should include CR and CRi patients.  
3 This category may be useful in the clinical development of novel agents within phase 1 clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.  
4 Marrow should not merely be “aplastic”; at least 200 cells should be enumerated, or cellularity should be at least 10%\textsuperscript{70}  
5 Confirmation of any MRD response requires the application of standardized methods with minimum technical requirements\textsuperscript{28} in reference laboratories  
6 Confirmation of negative MRD requires that technical requirements for establishment of sensitivity of each individual TP are fulfilled  
7 Any PR should be confirmed or falsified by parallel MRD assessment.
Conclusions: • Basic diagnostic work-up should be performed in patients of all age groups in experienced reference laboratories • MRD assays should be established at diagnosis and followed in all patients • Risk stratification depends on protocols and should be pre-defined.

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