Leukemia Supplements (2012) **1**, S1 – S2
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PROCEEDINGS ARTICLE

Change in prognostic factors

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The purpose of evaluating prognostic factors in acute lymphoblastic leukemia is, first, to stratify patients into adverse- or good-risk groups, second, to determine different treatment options accordingly and, third, to evaluate their potential outcome. Prognostic factors are particularly relevant for disease-free survival and overall survival.

Leukemia Supplements (2012) **1,** S1–S2; doi:10.1038/leusup.2012.4

Keywords: acute lymphoblastic leukemia; prognostic factors; minimal residual disease; risk stratification; targeted therapies

PROGNOSTIC FACTORS

Historically, the survival rate for acute lymphoblastic leukemia (ALL) in the 1970s was only about 10%,[1] and a variety of single parameters had been found to have an influence on treatment outcome. However, prognostic factors as such became relevant only when larger prospective trials with uniform therapy and reasonable improved outcome were conducted. The German Multicenter Study Group for Adult ALL (GMALL) described first in 1984 (ref. 2) and 1987 (ref. 3) the following prognostic factors for remission duration and overall survival.

B-precursor ALL	
WBC	$\langle / \rangle$ 30 000/μl
Age	$\langle / \rangle$ 35 years
Time to CR	$\langle / \rangle$ 4 weeks
T-precursor ALL	
WBC	$\langle / \rangle$ 100 000/μl

These prognostic factors were later extended to the immunophenotypes 'pro-B-ALL' and 'early' and 'mature T-ALL,' which have an adverse outcome. In addition, the cytogenetic aberrations t(4;11) in pro-B-ALL and t(9;22) in Ph+ ALL were continuously found to be adverse prognostic factors.

STRATIFICATION INTO RISK GROUPS

Standard-risk (SR) patients were defined as those without any of the above adverse risk factors, whereas high-risk (HR) groups were defined as those with one or more of the risk factors.

Similar risk stratifications were reported by several study groups including the Memorial Sloan-Kettering Cancer Center,[4] the MD Anderson Hospital[5] and the Cancer and Leukemia Group B,[6] which are summarized in detail.[7]

The aim of those prognostic models is usually to define a SR patient group with a 50% or higher probability to survive at 5 years and a HR patient group with an overall survival in the range of 25%.[8]

The purpose of stratification into several risk groups is to provide an optimal treatment approach for each. The major impact for adult ALL patients is to decide whether or not they should have a hematopoietic stem cell transplantation (HSCT) in first CR (CR1). HR patients are generally candidates for an immediate HSCT, whereas SR patients in most studies continue with consolidation cycles, ± reinduction and maintenance therapy. An intermediate-risk group preferentially used in pediatric ALL risk stratification was not well defined in adult studies. The reason might be that the only therapeutic implication is to either have a HSCT in CR1 or not.

CHANGE IN PROGNOSTIC FACTORS

In addition, a variety of other parameters can be of prognostic relevance, such as clinical manifestations including CNS involvement or mediastinal tumors, biochemistry, for example, LDH, prednisone response, drug resistance, pharmacokinetics, cytogenetics, new molecular markers and gene expression profiles. If these parameters were all taken into consideration, one would end up with a large number of subcategories leading to very small ALL cohorts. Practically, it would be impossible to handle those in larger multicenter trials. However, the therapeutic options are very limited and could not be adapted to specific subgroups with the exception of a few targeted therapies. Thus, it is not surprising that most pediatric and adult treatment groups stratify their patients according to few and similar prognostic parameters.[9]

The relevance of prognostic factors is continuously changing with improvements in therapy. Best examples are CNS involvement or mediastinal tumor in T-ALL having no more an adverse impact.

In the recent decades, substantial progress has been made in adult ALL, particularly by targeted therapies such as tyrosine kinase inhibitors in Ph/bcr-abl-pos. ALL or antibody therapies, for example, with anti-CD20 in Burkitt-leukemia/lymphoma and in B-precursor ALL, anti-CD22 antibodies or with the new bispecific CD19/CD3 antibody. In addition, new chemotherapeutic drugs such as nelarabine for T-ALL or intensification by conventional drugs such as PEG-asparaginase can improve the outcome. Thus, Ph/bcr-abl-pos. ALL, so far the poorest adult ALL subtype with an overall survival of less than 10% at 5 years in all studies and only limited improvement by SCT in CR1 to 30–35%, has changed to a 'good' subtype with an overall survival of 70% when adequately treated with a combination of chemotherapy, tyrosine kinase inhibitors and stem cell transplantation.

Among the most changing prognostic factors is age. Historically, $\langle / \rangle$ 35 years was the best cutoff in a continuous decline of survival. It was in addition a practical cutoff point at that time for a HSCT in CR1. Currently, the age limit has increased to 55 years for full myeloablative SCT with an allo/SIB/MUD donor, and the age

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limit for reduced intensity conditioning is even approaching up to 70 years. This leads to a continuous change in prognostic factors and the definition of risk groups in adult ALL.

MINIMAL RESIDUAL DISEASE (MRD)

The evaluation of MRD in the past decade brought undoubtedly the greatest progress in risk stratification in ALL and for the decision of treatment strategies. ALL is so far a model disease for MRD, as it can be evaluated in 95% of the cases. The value of MRD is extensively elicited in Campana (this issue).

The following risk model is proposed to bring the conventional prognostic factors and MRD into a decision algorithm. At diagnosis, patients are stratified into SR and HR by the conventional risk factors. The consequence for HR patients is that they are candidates for stem cell transplantation in CR1 after induction and consolidation therapy. The donor search has to start immediately after diagnosis to guarantee the SCT realization, which means finding a suitable HLA-matched donor within this period of $\sim$3 months. Initial diagnosis also identifies the patients who are candidates for a targeted therapy; for example, Ph/bcr-abl-pos. patients for tyrosine kinase inhibitors or, for example, CD20 + B-precursor/Burkitt Leukemia/lymphoma patients for anti-CD20 rituximab.

MRD pattern is followed during induction and consolidation therapy in most studies. The treatment decision based on MRD positivity or negativity is usually after this period, at weeks 12–20 after start of therapy in most protocols.

SR patients who remain MRD negative will follow consolidation cycles and maintenance therapy. There is, however, a small proportion (5–7%) of SR patients defined by the conventional risk factors who remain MRD positive. They have to be considered as HR patients for MRD with the therapeutic consequence of a HSCT or an experimental therapy.

HR patients are to a larger extent MRD positive after consolidation/induction. As a consequence, they should receive a HSCT in CR1 as soon as possible. There is, however, a smaller fraction of HR patients who become MRD negative at this time point. Nevertheless, in most risk-adapted treatment procedures, these are candidates for a HSCT in CR1. However, this procedure has to be questioned, and randomized trials for MRD-negative HR patients evaluating the benefit of a HSCT are now planned.

In conclusion, prognostic factors defined at diagnosis change considerably over time particularly because of new targeted therapies. MRD, available in most patients, is a decision criteria after the first part of therapy (induction/consolidation).

Thus, the balance between the initially determined prognostic factors leading to the conventional stratification into SR and HR patients and the second treatment stratification based on MRD has to be continuously refined. In addition, it is not known whether these MRD-based decisions overcome all prognostic factors defined at diagnosis, for example, specific molecular genetic aberrations.

CONFLICT OF INTEREST

NG has received consulting fees from Micromet Inc., Gilead, ERYtech Pharma and Mundipharma, and received lecture fees from Medac Inc., GlaxoSmithKline and Mundipharma. DH declares no conflict of interest.

ACKNOWLEDGEMENTS

NG has also received grant support from GlaxoSmithKline, Mundipharma, Genzyme Corporation, EUSA Pharma, Micromet Inc., Medac Inc. and the Jose Carreras Foundation.

This article was published as part of a supplement that was supported by Novartis, MSD Italia, Roche, Celgene, GlaxoSmithKline, Sanofi, Gilead, Adienne, Italfarmaco, Pierre Fabre Pharmaceuticals with an unrestricted educational contribution to AREO—Associazione Ricerche Emato-Oncologiche (Genoa) and AMS—Associazione Malattie del Sangue (Milan) for the purpose of advancing research in acute and chronic leukemia.

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