Current Therapeutic Strategies in Adult Acute Lymphoblastic Leukemia

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- Acute lymphoblastic leukaemia • Adult • Therapy
- Combination chemotherapy

OVERVIEW

Approximately half of all adults with acute lymphoblastic leukemia (ALL) now survive long term. An elegant study of unselected registry data, in which point estimates of survival were made for two 5-year time periods, 20 years apart, demonstrated highly significant 14% to 20% survival improvements for each age group except the over-60 group, in which no significant improvement in outcome had occurred.[1] This article summarizes the current approaches to treating ALL in adults, with a focus on a pragmatic approach to decision making, based on available data. A major problem in treating adults with ALL is that few physicians or institutions have a large personal practice, because the disease is rare. Coupled with a particularly punishing and often complex combination chemotherapy treatment regimen, treatment-related morbidity (TRM) and mortality are frequent and individual patient decisions on how to best balance efficacy with toxicity can be difficult. This article focuses on such situations. As examples, dealing with the toxicity of induction regimens and treating older people with ALL are both scenarios that vex clinicians and areas in which there are few conclusive answers in the literature. In many situations, it can be concluded that there is still "no right answer." Thankfully, there is a vibrant academic interest in ALL, both scientifically and clinically. The field will change significantly over the next few years as many ongoing clinical studies report and molecular insights are translated into providing prognostic information and novel therapeutic targets. Monoclonal antibodies are likely to make a considerable contribution to the treatment of ALL and are discussed in a separate article.

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DIAGNOSIS

ALL is a medical emergency. It should be diagnosed and treated without delay. A bone marrow aspirate should be examined morphologically by an expert hematopathologist. Bone marrow—or peripheral blood, if the blast count is high—should be examined using a panel of monoclonal antibodies to T-cell–associated and B-cell–associated antigens, which identify almost all cases of ALL. Aberrant expression of myeloid antigens is not uncommon and should not deflect from the correct diagnosis.[2] In the differential diagnosis, blastic transformation of chronic myeloid leukemia should be specifically ruled out by morphologic examination. Trephine biopsy examination is sometimes helpful, but the result is not required before starting treatment. Cytogenetic examination of the blast cells is mandatory and should comprise both examination of metaphases and fluorescence in situ hybridization with specific probes (eg, for B*CR*-ABL and MLL-AF4L). Screening by polymerase chain reaction (PCR) for the potential B*CR*-ABL transcripts, p190 and p210, should be performed. MLL-AF4 translocations can also be sought by PCR. Standardized primer sets are specified.[3] It is important that a specimen also be examined by molecular methods for the detection of patient-specific immunoglobulin and T-cell receptor (Ig/TCR) rearrangements[4–8] or by flow cytometry[9,10] to detect a specific immunophenotype, both tests can be used for minimal residual disease (MRD) quantification. If this is not performed at diagnosis, the opportunity to quantify MRD after therapy is lost unless a patient has a specific marker, such as B*CR*-ABL. At present, quantification of Ig/TCR rearrangements is the only standardized method for detection of MRD.[6] If bone marrow transplant is a possible part of a patient's future therapy, tissue typing of any patient siblings who are willing to be typed should also be performed at diagnosis. If there are no HLA-matched siblings, consideration should be given to prompt initiation of an unrelated donor search.

PROGNOSTIC FACTORS

Many factors that can be identified at—or soon after—diagnosis have a bearing on outcome (**Table 1**). These prognostic factors often form the basis for treatment decisions in ALL, although there is little convincing evidence that currently available therapeutic strategies other than allogeneic haematopoietic stem cell transplantation (alloHSCT) are able to overcome the adverse factors. When planning matching a potentially effective—but toxic—therapy, however, such as alloHSCT, a high risk of death as a result of ALL can be balanced against a more risky treatment strategy. Decisions of this nature are used in clinical practice and as tools to stratify patients within clinical trials. In contrast to pediatric practice, examination of prognostic factors cannot yet define a set of adults who have a particularly good prognosis. Hence, there is currently no strategy with which to limit therapy for adults on the basis of an expectation of particularly good outcome.

Minimal Residual Disease

The measurement of MRD deserves a specific discussion due to its pivotal role in the management of ALL. Long accepted as vital for management in pediatric practice, it has been conclusively demonstrated as carrying the same important prognostic information in adult ALL. Its adoption into standard practice, however, has been less quick.

MRD can be quantified by both molecular quantification of patient-specific Ig/TCR rearrangements[6]: by quantification of specific molecular abnormalities, such as B*CR*-ABL or MLL-AF4, or by flow cytometry,[10,31] where leukemia-specific immunophenotypes can be identified and quantified after initial treatment.