Modern Therapy of Acute Lymphoblastic Leukemia

Renato Bassan and Dieter Hoelzer

ABSTRACT

Although acute lymphoblastic leukemia is curable in one third of adult patients, results vary greatly on account of different clinical, immunologic, and cytogenetic/genetic characteristics. These data, along with the kinetics of response to early treatment, help establish the individual risk class with considerable accuracy, and support risk-specific treatments that should warrant optimal results with as little as possible nonrelapse mortality. Modern first-line therapy consists of standard- and high-dose chemotherapy (increasingly inspired to pediatric principles), hematopoietic stem-cell transplantation, and new targeted therapy, all integrated with the analysis of prognostic factors and the study of subclinical residual disease for key therapeutic decisions. These changes are improving long-term outcome, which in ongoing studies is expected close to 50% or greater.

J Clin Oncol 29:532-543. © 2011 by American Society of Clinical Oncology

INTRODUCTION

The estimated annual incidence of adult acute lymphoblastic leukemia (ALL) is about one in 100,000. Contrary to childhood ALL, in which overall survival is more than 80% at 5 years, therapeutic progress has been slow, with an average survival of 35% in patients age 18 to 60 years. A recent survey indicates a positive trend with an age-dependent increase of 14% to 20% in the years 2000 to 2004 compared with 1980 to 1984.2 ALL requires a survival increase of 14% to 20% in the years 2000 to 2004.

The objective of newer clinical trials is to bring survival close to 50% and pave the way to further improvement. To this end, it is essential to develop fully the concepts of risk-oriented and targeted therapy.

PROGNOSTIC FACTORS

Age and WBC

Age and WBC are the two most important risk factors. Older adults (older than 55 years) are regarded as a prognostically unfavorable group, with a probability of survival of 20% at 3 years; while adolescents and young adults (younger than 25 years) do extremely well if treated according to pediatric protocols.3-10

Immunophenotype

In BCP ALL, a CD10-negative pro-B phenotype is HR especially when associated with t(4;11)/abn q23. Ph-negative common ALL (CD10+/abn q23) with WBC lower than 30 × 10^9/L is standard risk (SR). The pre-B subtype expressing cytoplasmic μ heavy chains has a bad outlook when harboring MLL rearrangements. Mature B-type ALL (monotypic surface immunoglobulin positive [S Ig+] ) is described separately. CD20 antigen is expressed in nearly half of BCP ALL, and may be prognostically adverse.14 In TCP ALL, the prognosis is worse for pro- and mature-T subtypes (CD1a-, CD3-/CD3+) compared with the CD1a+ cortical/thymic phenotype,19,20 and usually for CD56+ and probably CD13+ cases.

Cytogenetics

Karyotype is another important prognostic factor.21,22 Most patients fall within an intermediate-risk (IR) group comprising the normal diploid subset plus hyperdiploidy and several random chromosomal abnormalities. Those with isolated +21, +8, and perhaps del(6q) and t(1;19) may constitute...
an IR/high-risk (HR) group. Patients with t(9;22)/Ph chromosome or BCR-ABL rearrangements, t(4;11) or MLL rearrangements at 11q23, −7, low hypodiploidy/near triploidy fall into the HR cytogenetic category, with a disease-free survival (DFS) rate lower than 25%.

Molecular Genetics, Genomics, and Pharmacodynamics

Molecular genetics identifies specific gene translocations (eg, BCR-ABL1 in Ph+ ALL, MLL rearrangements in t[4;11]+ ALL) and integrates the cytogenetic analysis when it fails or documents a normal karyotype. Mutation analysis can reveal gene silencing or amplifications that could bear prognostic significance, but is seldom performed. In t(4;11)+ ALL, FLT3 mutation is frequently detected. In TCP ALL, overexpression of HOX11L2 and ERG would impart a bad outlook, whereas overexpression of TLX1, combined low ERG and BAALC expression, and mutations of NOTCH1 and FBXW7 would be favorable markers. An early T/myeloid stem cell variant with mutant CEBPA expression and other distinct gene lesions may represent a new adverse subset. Genome-wide analysis identifies specific gene signatures which may be prognostically relevant when associated with drug resistance. The polymorphism of genes metabolizing thiopurines, methotrexate, and cytarabine has been associated with variable treatment response.1

KINETICS OF EARLY RESPONSE

Time to Complete Remission

The primary determinant of outcome remains the disease response to chemotherapy. Patients achieving complete remission (CR) within the first chemotherapy course (ie, 3 to 5 weeks), and showing a rapid peripheral blood (day 7) or bone marrow (day 14) blast cell clearing or a positive prednisone response (prephase), exhibit an improved outcome. The best assay for response kinetics evaluation is however the study of minimal residual disease (MRD).

MRD

This term defines submicroscopic ALL present in remission patients, whose bone marrow may still harbor up to 10^5 leukemic cells. Persistence of MRD after induction/early consolidation, between weeks 4 to 22 and with a level ≥10−4, reflects intrinsic drug resistance and heralds overt hematologic relapse. MRD-positive patients are at higher risk of relapse, whether clinically SR or HR, to constitute a true HR group. This distinction is crucial and has therapeutic consequences. A major challenge of current trials is to determine whether MRD could replace the traditional risk factors in the individual risk definition. While this has not been conclusively proven for HR subsets, SR patients should be routinely treated with MRD-based programs.

MISCELLANEOUS

P-glycoprotein–encoding multidrug resistance gene (MDR1) is detectable in up to 38% of patients with ALL, more frequently in HR CD7+ pro-T ALL, and carries a great risk of treatment failure. MDR-associated protein and lung-related protein are occasionally overexpressed. Resistance to single chemotherapeutic agents is reported for methotrexate and glucocorticoids. Also, a delayed administration or undue reduction of early treatment blocks is an underestimated risk factor. Adherence to treatment plan is a fundamental of ALL therapy.

RISK STRATIFICATION

The prognostic factors and the way how the different ALL study groups define risk groups is detailed in Table 1.

Patients with no or exceptionally one risk feature constitute the standard-risk (SR) subset. Ph+ ALL and sometimes t(4;11)+ ALL constitute the VHR group. In the IR/HR groups, an inverse relationship exists between cumulative incidence of risk factors and survival, from 25% to 35% with 1 to 2 to lower than 10% with 3 to 4. The variable incidence of risk subsets mirrors the heterogeneous definitions adopted by different study groups: 20% to 45% for SR, 30% to 70% for IR/HR, and 20% to 40% for VHR. In SR ALL, the survival probability at 5 years was 50% or higher with chemotherapy only and without hematopoietic stem-cell transplantation (HSCT), as opposed to worse results in IR (not recognized in all studies), HR, and VHR groups (survival 40% to <10%), depending on the cumulative incidence of risk factors. Of note, clinical risk models are being prospectively integrated with MRD study. In this way, SR patients are confirmed as such when MRD negative (55% to 80% of patients). This is applicable to a proportion of HR patients as well (40% to 50%). On the contrary, MRD-positive patients are at higher risk of relapse, whether clinically SR or HR, to constitute a true HR group. This distinction is crucial and has therapeutic consequences. A major challenge of current trials is to determine whether MRD could replace the traditional risk factors in the individual risk definition. While this has not been conclusively proven for HR subsets, SR patients should be routinely treated with MRD-based programs.

CHANGE IN PROGNOSTIC FACTORS AND RISK STRATIFICATION

Apart from the conventional ease to determine prognostic factors, such as age, WBC, immunophenotype, and cytogenetics, an increasing number of new molecular (or better genetic markers) are emerging. In addition, we have the important evaluation of MRD. How to deal with it in a practical life? It seems advisable to use at diagnosis all available prognostic markers, and conventional, as well as molecular markers, for risk stratification. This is of practical relevance (eg, to search for a stem cell donor for HR patients immediately). After induction and consolidation, MRD becomes of much higher prognostic value and treatment decisions should be based more on MRD.

However, in reality, it is also true that for a certain proportion of patients, no clear MRD pattern is available (approximately 20%)
Table 1. Clinical Significance of Risk Factors and Associated Risk Models (as identified retrospectively or prospectively applied), With or Without Integrated MRD Analysis, for OS and/or DFS in Adult ALL

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No.</th>
<th>Median</th>
<th>Range</th>
<th>Age</th>
<th>WBC (×10³/L)</th>
<th>IM</th>
<th>Cytog</th>
<th>Other#</th>
<th>Definition of Risk Group*</th>
<th>OS/DFS by Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMALL</td>
<td>1988</td>
<td>388</td>
<td>25</td>
<td>15-65</td>
<td>&gt; 35</td>
<td>&gt; 30</td>
<td>BCP CD10-</td>
<td>—</td>
<td>CR &gt; 4w</td>
<td>—</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
</tr>
<tr>
<td>MIKCC</td>
<td>1988</td>
<td>199</td>
<td>≥ 15</td>
<td>&gt; 60</td>
<td>&gt; 20</td>
<td>BCP</td>
<td>—</td>
<td>—</td>
<td>CR &gt; 5w</td>
<td>—</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
</tr>
<tr>
<td>CALGB</td>
<td>1995</td>
<td>197</td>
<td>32</td>
<td>16-80</td>
<td>&gt; 60</td>
<td>&gt; 30</td>
<td>Ph+</td>
<td>L3, Med</td>
<td>—</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
<td>P = .0001, 3-year OS: 58%-100% in SR v 0%-26% in HR</td>
</tr>
<tr>
<td>GIMEMA</td>
<td>2002</td>
<td>794</td>
<td>27</td>
<td>12-60</td>
<td>&gt; 30</td>
<td>&gt; 50</td>
<td>Ph+</td>
<td>—</td>
<td>—</td>
<td>PH 1 c</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
</tr>
<tr>
<td>JALSO</td>
<td>2002</td>
<td>263</td>
<td>31</td>
<td>15-59</td>
<td>&gt; 30</td>
<td>&gt; 30</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
</tr>
<tr>
<td>MDACC</td>
<td>2004</td>
<td>288</td>
<td>40</td>
<td>15-92</td>
<td>—</td>
<td>—</td>
<td>Ph+</td>
<td>—</td>
<td>ECOG 3-4, L2, ≤ 14</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
<td>P = .0001, 5-year DFS: 52% in SR v 37% in IR v 10% in HR</td>
</tr>
<tr>
<td>GOELAMS</td>
<td>2004</td>
<td>215</td>
<td>33</td>
<td>15-59</td>
<td>&gt; 35</td>
<td>&gt; 30</td>
<td>Ph+</td>
<td>—</td>
<td>L1,119</td>
<td>PH 1 c</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
</tr>
<tr>
<td>LALA</td>
<td>2004</td>
<td>922</td>
<td>33</td>
<td>15-55</td>
<td>—</td>
<td>—</td>
<td>Ph+</td>
<td>L1,11</td>
<td>FAB 1 c</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
<td>P = .0001, 5-year DFS: 35% in SR v 30% in IR v 20% in IR v 41% in CN S+; in multivariate analysis age &gt; 35 (P = .01), and lack of day 8 response (P = .02) were significant risk factors</td>
</tr>
<tr>
<td>PETHMA</td>
<td>2006</td>
<td>222</td>
<td>27</td>
<td>15-50</td>
<td>30-50</td>
<td>&gt; 25</td>
<td>Ph+</td>
<td>L1,113</td>
<td>—</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
<td>P = .0001, 5-year OS: 53% in SR v 30% in IR v 20% in IR v 41% in CN S+; in multivariate analysis age &gt; 35 (P = .01), and lack of day 8 response (P = .02) were significant risk factors</td>
</tr>
<tr>
<td>MRC-ECOG</td>
<td>2008</td>
<td>1,913</td>
<td>NR</td>
<td>15-64</td>
<td>&gt; 35</td>
<td>&gt; 30</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
<td>P = 10,75, SR, not reported</td>
</tr>
<tr>
<td>GRAALL</td>
<td>2008</td>
<td>225</td>
<td>31</td>
<td>15-60</td>
<td>—</td>
<td>—</td>
<td>Ph+</td>
<td>L1,11</td>
<td>—</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
<td>P = .0001, 5-year DFS: 66% in SR v 52% in HR</td>
</tr>
<tr>
<td>HOVON</td>
<td>2009</td>
<td>433</td>
<td>NR</td>
<td>&gt; 30</td>
<td>&gt; 30</td>
<td>&gt; 25</td>
<td>Ph+</td>
<td>L1,11</td>
<td>—</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
<td>P = 0.001, 5-year OS: 56% in SR v 31% in IR</td>
</tr>
<tr>
<td>GMALL</td>
<td>2006,</td>
<td>713</td>
<td>34</td>
<td>15-55</td>
<td>—</td>
<td>&gt; 30</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
<td>P = .0001, 5-year DFS in IR patients: 58% in SR v 55% in HR v 49% in VR; 3-year DFS in SR by MDR: 100%; in MDR+ 53% in MDR v 6% in MDR (HR &gt; 0.001)</td>
</tr>
<tr>
<td>NILG</td>
<td>2009</td>
<td>280</td>
<td>36</td>
<td>16-66</td>
<td>—</td>
<td>&gt; 30</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Low: 0; Intermediate: 1; High: 2</td>
<td>P = .0001, 5-year DFS: 49% in SR v 27% in IR v 24% in VR (HR &gt; .0005); 5-year DFS by MDR: 72% in MDR v 14% in MDR+ (HR &gt; .001)</td>
</tr>
</tbody>
</table>

Abbreviations: MRD, minimal residual disease; OS, overall survival; DFS, disease-free survival; ALL, acute lymphoblastic leukemia; IM, immunophenotype; Cytog, cytogenetics/genetics; GMALL, German Multicenter Study Group for Adult ALL; BCP, B-cell precursor ALL; CR, complete response; w, week; SR, standard risk; HR, high risk; MIKCC, Memorial Sloan-Kettering Cancer Center; Ph, Philadelphia chromosome; CALGB, Cancer and Leukemia Group B; Med-, no mediastinal mass; GIMEMA, Gruppo Italiano Malattie Ematologiche dell’Adula; Pharm, prednisone poor response; NR, not reported; JALSO, Japan Adult Leukemia Study Group; IR, intermediate risk; MDACC, MD Anderson Cancer Center; d14 BM+; bone marrow blasts > 5% on day 14; ECOG, Eastern Cooperative Oncology Group; GOELAMS, Groupe Ouest-Est des Léucémies Aigus et Maladies du Sang; c, cycle; LALA, Leucémie Aigües Lymphoblastiques de l’Adula; CNS+, CNS involvement; PETHMA, Programa Espanol de Tratamiento en Hematologia; MRC-ECOG, Medical Research Council-Eastern Cooperative Oncology Group; TCP, T-cell precursor ALL; GRAALL, Group for Research in Adult ALL (plus ongoing trial GRAALL-05, ClinicalTrials.gov Identifier NCT00327678); d8 BM+; bone marrow blasts > 5% on day 8; HOVON, Dutch-Belgian Cooperative Trial Group for Hematology/Oncology; VHR, very high risk; NILG, Northern Italy Leukemia Group (plus ongoing trial NILG-10, ClinicalTrials.gov Identifier NCT00795756). ^According to cumulative incidence of risk factors (indicated in each category): SR, IR, HR, and VHR. 1Cytog: lo-hypo, low hypodiploid; near-trip, near triploid; adverse: ah 1q23 = 8, = 7, del(6q), low-hypo/near-trip, complex ≥ 3 abnormalities). 2CR after w or c; L3/L2, ALL morphological subtypes according to FAB classification; Med-, no mediastinal mass; Pharm, (prephase); ECOG 3-4, performance score according to ECOG scale; d14/BM; CNS+. 

for a variety of reasons, mostly technical. Also, not all institutions may have the opportunity to follow MRD. In this situation, the clinical decision making should be based on the risk stratification at diagnosis.

TREATMENT: REMISSION INDUCTION AND CONSOLIDATION

Induction of CR

The goal of induction therapy is the eradication of ALL cells in as many patients, as early, and with as few toxic adverse effects as possible. This process can involve prephase, induction I, and induction II, a widespread schema patterned after the pediatric protocols of the Berlin–Frankfurt–Munster group, adapted to adults by Hoelzer et al.3 CR should be attained in 90% or more and 75% or more of SR and HR patients, respectively. During prephase, all relevant diagnostic and prognostic information are collected, and corticosteroids used to identify prednisone good responders. Induction I is the most critical phase, carrying the highest risk of serious toxicity and requiring a high level of supportive care. Most programs are centered on a vincristine, prednisone, and
The general consensus is that intensive postremission consolidation is most often followed by long-term maintenance with daily oral mercaptopurine and weekly methotrexate for 2 years or longer, sometimes with periodic reinforcements (eg, vincristine, prednisone, other drugs). Omission of maintenance worsens outcome significantly in BCP ALL, but less so in TCP ALL, and not at all in mature B-ALL.

**Postremission Consolidation**

The general consensus is that intensive postremission consolidation will improve outcome especially in HR groups. The programs developed over the past 25 years yielded an average cure rate of 35% in unselected series from multicentric trials (Table 2).1-11,15 Pegylated asparaginase, with superior activity due to longer periods of asparagine depletion, may be preferable. Induction II consists of cyclophosphamide, mercaptopurine, and cytarabine, regardless of CR status, but a more intensive regimen can be used in patients refractory to induction I.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Age (years)</th>
<th>CR Rate</th>
<th>HSCT Realization</th>
<th>HSCT Outcome by intention</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9114</td>
<td>1996</td>
<td>198</td>
<td>35-168</td>
<td>167</td>
<td>46%</td>
<td>—</td>
</tr>
<tr>
<td>NWOG 8714</td>
<td>2001</td>
<td>353</td>
<td>32-158</td>
<td>218</td>
<td>65%</td>
<td>—</td>
</tr>
<tr>
<td>NILS 09/89</td>
<td>2001</td>
<td>121</td>
<td>35-157</td>
<td>102</td>
<td>48%</td>
<td>—</td>
</tr>
<tr>
<td>JALSG 937</td>
<td>2002</td>
<td>263</td>
<td>31-155</td>
<td>206</td>
<td>30%</td>
<td>—</td>
</tr>
<tr>
<td>Sweden 78/83</td>
<td>2002</td>
<td>153</td>
<td>42-168</td>
<td>131</td>
<td>30%</td>
<td>—</td>
</tr>
<tr>
<td>GIMEMA 02/90</td>
<td>2002</td>
<td>767</td>
<td>28-12-60</td>
<td>627</td>
<td>33%</td>
<td>—</td>
</tr>
<tr>
<td>MDACC 11</td>
<td>2004</td>
<td>288</td>
<td>408-159</td>
<td>269</td>
<td>38%</td>
<td>—</td>
</tr>
<tr>
<td>EORTC ALL39</td>
<td>2004</td>
<td>340</td>
<td>33-14-79</td>
<td>253</td>
<td>36%</td>
<td>—</td>
</tr>
<tr>
<td>LALA 9412</td>
<td>2004</td>
<td>922</td>
<td>33-15-55</td>
<td>771</td>
<td>30%</td>
<td>—</td>
</tr>
<tr>
<td>GOELAL 92/9</td>
<td>2004</td>
<td>198</td>
<td>33-15-59</td>
<td>170</td>
<td>41%</td>
<td>—</td>
</tr>
<tr>
<td>PETHEMA ALL-939</td>
<td>2005</td>
<td>222</td>
<td>27-15-50</td>
<td>183</td>
<td>34%</td>
<td>—</td>
</tr>
<tr>
<td>GMALL 07/15</td>
<td>2007</td>
<td>713</td>
<td>34-15-65</td>
<td>635</td>
<td>54%</td>
<td>—</td>
</tr>
<tr>
<td>MRC/ECCO-10</td>
<td>2008</td>
<td>1,646 (Ph+)</td>
<td>15-64</td>
<td>1,484</td>
<td>39%</td>
<td>—</td>
</tr>
<tr>
<td>HOVON 11</td>
<td>2009</td>
<td>433</td>
<td>33-15-55</td>
<td>288</td>
<td>37%</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic leukemia; HSCT, hematopoietic stem-cell transplantation; CR, complete response; DFS, disease-free survival; OS, overall survival; CALGB, Cancer and Leukemia Group B; SWOG, Southwest Oncology Group; NILG, Northern Italy Leukemia Group (plus ongoing trial NILG-10, ClinicalTrials.gov Identifier NCT00795765); HR, high risk; SCT, stem cell transplantation; CHT, chemotherapy; NS, not significant; JALSG, Japan Adult Leukemia Study Group; GIMEMA, Gruppo Italiano Malattie Ematologiche dell’Adulti; MDACC, MD Anderson Cancer Center; EORTC, European Organisation for the Research and Treatment of Cancer; LALA, Leucémie Aiguës Lymphoblastiques de l’Adulte; GOELAMS, Groupe Ouest-Est des Léucémies Aigus et Maladies du Sang; NR, not reported; PETHREEA, Programa Espanol de Tratamiento en Hematologia; GMALL, German Multicenter Study Group for Adult ALL; NRC, Medical Research Council; ECOG, Eastern Cooperative Oncology Group; HOVON, Dutch-Belgian Cooperative Trial Group for Hematology/Oncology.

*All patients: allogeneic SCT applicable to all patients with potential compatible donor (genetic randomization); or to selected risk groups as indicated (risk stratification criteria vary among studies); CHT (randomization V autologous SCT arm).

**Long-Term Maintenance**

Postremission consolidation is most often followed by long-term maintenance with daily oral mercaptopurine and weekly methotrexate for 2 years or longer, sometimes with periodic reinforcements (eg, vincristine, prednisone, other drugs). Omission of maintenance worsens outcome significantly in BCP ALL, but less so in TCP ALL, and not at all in mature B-ALL.

**Allogeneic HSCT**

HSCT from peripheral blood (or bone marrow) is an important postremission strategy. The curative potential of HSCT must be balanced against the disadvantages (mortality of 20% to 30%, morbidity, late complications, reduced quality of life) and assessed in relation to the improved outcome by chemotherapy regimens. Overall results would be pharmacologically justified in BCP and TCP ALL up to 2.5 and 5 g/m², respectively.1
with different types of HSCT and current recommendations by disease status are given in Table 3. Relapse rate and transplantation-related mortality (TRM) both range between 25% and 30%. Although TRM is increasing with age, the upper age limit has continuously extended to 50 to 55 years.

**Risk-Adapted HSCT**

Owing to good results obtained with chemotherapy in SR subsets, one sensible option is to reserve allogeneic HSCT for HR/VHR patients only, as those with Ph+ ALL, t(4;11) ALL, adverse immunophenotype or cytogenetics, and higher leukocyte count. This policy aims to reduce TRM by identifying patients who have a real chance of cure without HSCT. The evaluation of MRD improves significantly the definition of risk class (Table 4). In a modern, optimized treatment design, SR patients who are confirmed MRD negative are treated with chemotherapy, with excellent results, while the HSCT option is mandatory for the MRD-positive group.

**Unrestricted HSCT Policy**

A radical view implies that allogeneic HSCT be performed in all patients with HLA-identical donor, owing to the higher antileukemic activity provided by the allogeneic graft. The reduction of the relapse risk is unquestionably superior to chemotherapy alone or autologous HSCT. Several such studies were published and updated, including the largest prospective Medical Research Council-Eastern Cooperative Oncology Group (MRC-ECOG) trial, which incidentally showed a benefit from HSCT in SR but not HR patients. Overall survival rates were eventually similar to studies adopting a risk-adapted HSCT strategy, partly because of TRM (Table 3). In trials fully open to allogeneic HSCT, survival was more than 60% in SR patients, with transplantation-related mortality of 16% to 20%. In HR patients, 5-year survival ranged from 33% to 75%, but again not all studies including the MRC-ECOG trial reported a better outcome than in controls, and TRM was as high as 36%.

**Unrelated Donor, Reduced Intensity, Haploidentical, and Cord Blood HSCT**

Because HLA-identical siblings are available in 24% to 40% of eligible patients, with proportional rates of HSCT realization (Table 2), family-unrelated volunteer donors are frequently used as stem cell source, particularly in VHR patients. This allows, together with autologous HSCT, to bring more than 50% and up to 70% the feasibility of HSCT. Survival in first CR is around 42% to 45%, with lower relapse rate and higher TRM compared with siblings donor HSCT. The MRC-ECOG study reported an overall survival of 55% for siblings donor and 46% for matched unrelated donor HSCT (in Ph+ ALL). In GMALL study 06/99, survival was 53% for sibling donor and 44% for unrelated donor HSCT. Compared with family donors, unrelated donors are, in general, of younger age, show less morbidity, and can be selected by high-resolution HLA typing and negative cytomegalovirus status. If all of these criteria are fulfilled, the results may be superior to sibling donor HSCT.

**Table 3. Overall Results of HSCT in Adult ALL and Current Recommendations**

<table>
<thead>
<tr>
<th>Sibling donor</th>
<th>DFS/OS*</th>
<th>Relapse*</th>
<th>TRM*</th>
<th>Decision</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1</td>
<td>1,100</td>
<td>50</td>
<td>21-71</td>
<td>24</td>
<td>10-50</td>
</tr>
<tr>
<td>CR2</td>
<td>1,019</td>
<td>31</td>
<td>16-60</td>
<td>48</td>
<td>62-71</td>
</tr>
<tr>
<td>Relapsed/refractory</td>
<td>216</td>
<td>18</td>
<td>8-33</td>
<td>75</td>
<td>60-77</td>
</tr>
<tr>
<td>Matched unrelated donor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>318</td>
<td>39</td>
<td>32-51</td>
<td>10</td>
<td>6-19</td>
</tr>
<tr>
<td>CR2</td>
<td>231</td>
<td>27</td>
<td>17-28</td>
<td>8†</td>
<td>75†</td>
</tr>
<tr>
<td>Autologous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>1,369</td>
<td>42</td>
<td>15-65</td>
<td>51</td>
<td>27-68</td>
</tr>
<tr>
<td>CR2</td>
<td>258</td>
<td>21</td>
<td>20-27</td>
<td>70</td>
<td>59-75</td>
</tr>
<tr>
<td>Non-myeloablative, all stages</td>
<td>132</td>
<td>23</td>
<td>0-50</td>
<td>47</td>
<td>30-56</td>
</tr>
</tbody>
</table>

NOTE. Adapted from Hahn et al.41

Abbreviations: HSCT, hematopoietic stem-cell transplantation; ALL, acute lymphoblastic leukemia; DFS, disease-free survival; OS, overall survival; TRM, transplantation-related mortality; CR1, first complete response; CHT, chemotherapy; HR, high risk; CR2, second complete response; RIC, reduced intensity conditioning; TBI, total body irradiation.

†One study.
Haploidentical HSCT is an experimental therapy whose usefulness is to be explored in VHR conditions and late-stage disease.\(^\text{47}\) With a new nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide, haploidentical SCT seems to be improvable.\(^\text{48}\) Cord blood HSCT is another option for the patients lacking a related/unrelated donor. To obtain more information on these modalities, European Group for Blood and Marrow Transplantation registers prospectively cord blood versus haploidentical HSCT.

### Autologous HSCT

When allogeneic HSCT is precluded, high-dose therapy followed by autologous HSCT can be a suitable alternative. The graft is obtained through bone marrow harvest or apheresis of CD34+ blood stem cells primed by myeloid growth factors. In some trials, patients excluded from allogeneic HSCT were randomly assigned between chemotherapy and autologous HSCT. In one study, chemotherapy proved superior (not in TCP ALL),\(^\text{10,13}\) while a marginal superiority of autologous HSCT was ascertained in HR patients in another.\(^\text{12}\) Postgraft maintenance was attempted, with some suggested benefit,\(^\text{17,49}\) but was occasionally difficult to administer\(^\text{14}\) and therefore remains investigational. In a recent European retrospective analysis on autologous HSCT,\(^\text{30}\) patients who were MRD negative (which meant MRD negativity of the patient as well as of the graft) at the end of induction/1st consolidation had a significantly better survival.\(^\text{50}\)

### PEDIATRIC-TYPE REGIMENS

Pedicatric-type regimens like the L series from Memorial Hospital\(^\text{4}\) and Berlin-Frankfurt-Munster–type protocols\(^\text{5}\) have been used in adults since the late 1970s. Recent reports renewed interest, which is important because the majority of patients still depend on chemotherapy for survival (Table 2). Pediatric-inspired therapy provides an increased drug intensity at several treatment steps, which should be strictly adhered to, with a reduced role for HSCT. Retrospective...
Table 5. Recent Applications of Pediatric-Like Therapy in Adolescents (15 to 18 years), Young Adults (19 to 30 years), and Adults (30+ years) With ALL

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Age</th>
<th>CR</th>
<th>Risk Groups</th>
<th>HSCT</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFCI</td>
<td>2007</td>
<td>51</td>
<td>NR</td>
<td>15-18</td>
<td>48</td>
<td>94</td>
<td>Event-free survival 78% at 5 years</td>
</tr>
<tr>
<td>PETHEMA</td>
<td>2008</td>
<td>81</td>
<td>20</td>
<td>15-30</td>
<td>79</td>
<td>98</td>
<td>Overall survival 81% at 5 years</td>
</tr>
<tr>
<td>CCG</td>
<td>2008</td>
<td>197 v 124</td>
<td>16 v 19</td>
<td>16-20</td>
<td>177 v 112</td>
<td>90 v 90</td>
<td>Event-free survival CCG 63% v CALGB 34% at 7 years (P &lt; .001)</td>
</tr>
<tr>
<td>GRAALL-2003</td>
<td>2009</td>
<td>225</td>
<td>31</td>
<td>15-60</td>
<td>210</td>
<td>93.5</td>
<td>Overall survival 60% at 3.5 years (same when censoring HSCT)</td>
</tr>
<tr>
<td>Toronto</td>
<td>2009</td>
<td>85</td>
<td>37</td>
<td>18-60</td>
<td>76</td>
<td>89</td>
<td>DFS 59% at 3.5 years (same when censoring HSCT)</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>2009</td>
<td>46</td>
<td>33</td>
<td>18-57</td>
<td>44</td>
<td>96</td>
<td>8HR 71% at 5 years</td>
</tr>
</tbody>
</table>

**T-Cell ALL**

The outcome of TCP ALL in adults is generally considered superior to BCP ALL. Recent studies from Gruppo Italiano Malattie Ematologiche dell’Adulito, GMALL, and MRC with a large data set and consequent immunophenotyping, have found a correlation between maturation stage and outcome. In GMALL studies 06/99 and 07/03 in more than 700 patients, the distribution of TCP ALL was thymic 56%, early-T 23%, and mature-T 21%. The highest CR rate (92%) was obtained in thymic phenotype versus early-T 84% and mature-T 77%. Induction failure was 13% to 17% in early- and mature-T compared to only 5% in thymic. Thus cortical/thymic TCP ALL has the best outcome with a survival of 60% to 70%, compared to 33% and 22% in early- and mature-T phenotypes, respectively. These poor prognosis patients are candidates for HSCT in first CR (CR1), resulting in survival rates of 44% and 59%, respectively. The additional evaluation of MRD may be most important for the decision to transplant in CR1.

**Mature B-ALL**

Mature B-ALL is grouped together with Burkitt lymphoma and is treated according to protocols mostly based on childhood studies. The drugs responsible for the improvement were high-doses of fractionated cyclophosphamide, ifosfamide, and methotrexate (0.5 to 8 g/m²) and cytarabine, in conjunction with conventional drugs for remission induction, given in short cycles at frequent intervals over a period of 6 months. These protocols, in original or modified form, brought the CR rate to approximately 75% (range, 62% to 83%) and DFS to 55%.
vent discriminating TKI with few selected cytostatic agents to pre-monotherapy; the so called nongenotoxic therapy, a new concept combining TKI together with current multiagent chemotherapy; TKI monotherapy with induction chemotherapy. This increased CR rate compared with chemotherapy alone. Imatinib with/without corticosteroids resulted in astonishing high CR rates of 90% to 100%, whereby results after allogeneic HSCT in mature B-ALL occurred almost always within the first 1.5 years. There are no clear prognostic factors to predict an early relapse, which might be due to the small patient cohorts. Evaluation of MRD could help to select prognostically unfavorable patients for HSCT in CR1. Maintenance therapy is not given since relapse occurs early and most patients are cured after approximately 1.5 years. B-ALL has higher incidence of CNS involvement at diagnosis and CNS relapse. Effective prophylactic measures are important components of treatment.

**Ph+ ALL**

Translocation t(9;22) and the respective fusion gene BCR-ABL until recently marked the most unfavorable subgroup of adult ALL (Ph+ ALL). Although CR rate was 75%, overall survival with chemotherapy was 10% to 19%, improved by allogeneic HSCT in CR1 to approximately 30%. Tyrosine kinase inhibitors (TKI) changed the outcome of Ph+ ALL substantially (Table 6).63-69 There are three different approaches to use TKI in Ph+ ALL: TKI together with current multiagent chemotherapy; TKI monotherapy; the so called nongenotoxic therapy, a new concept combining TKI with few selected cytostatic agents to prevent BCR-ABL mutations.

**TKI plus combination therapy.** The first approach was to combine imatinib with induction chemotherapy. This increased CR rate to 90%, and molecular remissions from lower than 5% with chemotherapy to more than 50%.63-70 It seems that overall survival has improved to more than 50% at 1 to 4 years, however, this was not conclusively proven. The proportion of patients transferred to HSCT in CR1 has increased. The combination of imatinib and multiagent chemotherapy did not result in increased toxicity and did not unfavorably affect HSCT. The latter is still considered the best curative option in adult Ph+ ALL, but the extent of improvement in this area is as yet unclear.63,64,70 Results after allogeneic HSCT may be improved by the use of imatinib as maintenance. A GMALL study showed that patients remaining BCR-ABL positive after HSCT achieved molecular remission with imatinib and survived long-term. Thus, post-transplantation imatinib, either first-line, independent of MRD or after MRD detection, can reduce the relapse rate. Imatinib should not be given before 6 to 8 weeks after HSCT to avoid cumulative toxicity. Duration of TKI maintenance remains open, either for 2 years as in BCP ALL or stopped after repeated MRD negativity.

**TKI monotherapy.** Monotherapy with imatinib was explored in elderly patients, who had an extremely poor outcome with chemotherapy alone. Imatinib with/without corticosteroids resulted in astonishing high CR rates of 90% to 100%,71-73 whereby in one randomized trial the CR rate for imatinib alone was 93% compared with 54% for chemotherapy. The high CR rates were also due to the avoidance of toxic deaths in induction, compared to 20% to 30% with earlier chemotherapy regimens. There was a substantial improvement of life quality by this all oral treatment, given partly as outpatients. Unfortunately, most patients eventually relapsed. One reason was probably the development of resistance caused by kinase domain mutations. Dasatinib, a second generation TKI, has been explored in combination74 and as a monotherapy in a Gruppo Italiano Malattie Ematologiche dell’Adulto trial, where all patients irrespective of age received a short corticosteroid course plus dasatinib for 84 days, resulting in 100% CR rate.75 How to continue in CR patients remains open. Use of TKI only could be an option in molecularly negative patients, but a more rigorous approach with HSCT is needed in BCR-ABL-positive patients. That HSCT in CR1 might not be necessary was demonstrated in a recent pediatric study, where children receiving intensive multidrug chemotherapy with imatinib had a survival higher than 80% compared to 35% in historical controls, and even better than related or unrelated HSCT (> 60%).76

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MDACC93 (n = 20)</th>
<th>Korea94 (n = 20)</th>
<th>GMALL95 (n = 92)</th>
<th>JALSG96 (n = 80)</th>
<th>GRAALL97 (n = 45)</th>
<th>PETHEMA98 (n = 32)</th>
<th>NILG99 (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction regimen</td>
<td>Hyper-CVAD</td>
<td>DNR, VCR, PDN, ASP</td>
<td>DEX, CY, VCR, DNR, ASP, Ara-C, MP</td>
<td>CY, DNR, VCR, PDN</td>
<td>DNR, CY, VCR, PDN, MT, Ara-C, DEX</td>
<td>VCR, DNR, PDN</td>
<td>VCR, IDR, ASP, PDN</td>
</tr>
<tr>
<td>Imatinib, mg/d</td>
<td>600</td>
<td>600</td>
<td>400</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>CR</td>
<td>93</td>
<td>95</td>
<td>95</td>
<td>96</td>
<td>96</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>HSCT</td>
<td>50</td>
<td>75</td>
<td>77</td>
<td>71</td>
<td>48</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td>Induction mortality</td>
<td>NR</td>
<td>5</td>
<td>7</td>
<td>2.5</td>
<td>5</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Death in CR</td>
<td>16</td>
<td>10 (by HSCT)</td>
<td>5</td>
<td>27 (by HSCT)</td>
<td>11 (9 by HSCT)</td>
<td>35 (by HSCT)</td>
<td>22 (15 by HSCT)</td>
</tr>
<tr>
<td>OS</td>
<td>75, at 20 months</td>
<td>60, at 2.5 years</td>
<td>36-43, at 2 years</td>
<td>61, at 1 year</td>
<td>65, at 1.5 years</td>
<td>30, at 4 years</td>
<td>38, at 5 years</td>
</tr>
<tr>
<td>PCR negative</td>
<td>59</td>
<td>72</td>
<td>52</td>
<td>52</td>
<td>71</td>
<td>38</td>
<td>86</td>
</tr>
</tbody>
</table>

Abbreviations: MDACC, MD Anderson Cancer Center; GMALL, German Multicenter Study Group for Adult ALL; JALSG, Japan Adult Leukemia Study Group; GRAALL, Group for Research in Adult ALL (plus ongoing trial GRAALL-05, ClinicalTrials.gov Identifier NCT00327678); PETHEMA, Programa Espanol de Tratamiento en Hematologia; NILG, Northern Italy Leukemia Group (plus ongoing trial NILG-10, ClinicalTrials.gov Identifier NCT00795756); Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone plus methotrexate, high-dose cytarabine; DNR, daunorubicin; VCR, vincristine; PDN, prednisone; ASP, asparaginase; DEX, dexamethasone; CY, cyclophosphamide; IDR, idarubicin; Ara-C, cytarabine; MP, mercaptopurine; MT, mitoxantrone; CR, complete remission; HSCT, hematopoietic stem-cell transplantation; OS, overall survival.
Nongenotoxic therapy. The appearance of mutations which are most probably but not exclusively related to resistance led to avoid induction drugs, such as antracyclines or alkylating agents, which can cause mutational resistance, and to prefer intermediate-dose methotrexate, cytarabine, and asparaginase in elderly patients with Ph+ ALL. Such a trial in patients with median age of 71 years led to high CR rate (> 80%) and improved DFS and overall survival, however, the dropout rate due to toxicity remained high.77

Future options for therapeutic improvement are TKI monotherapy or nongenotoxic therapy in induction, HSCT in MRD-positive patients only, maintenance after HSCT, and evaluation of second generation TKI dasatinib or nilotinib, or third generation TKI which may overcome resistant mutations, such as T315I. A further approach could be the addition of antibody therapy, such as rituximab, since Ph+ ALL can be CD20+ (40%). Ph+ ALL, so far the poorest ALL subtype, may rapidly turn into one with a good prognosis.

ELDERLY PATIENTS

In elderly patients, specifically designed reduced-dosage regimens are more successful than unmodified protocols for younger patients. New strategies for subtype specific treatment as mentioned for Ph+ ALL or mature B-ALL are currently explored. Also, the use of drugs such as asparaginase or intermediate/high-dose methotrexate, previously not given, seems promising. HSCT is also a curative approach, and considerable interest emerged to use non-myeloablative HSCT.76 In an elderly ALL cohort with a median age of 62 years, the survival rate with allogeneic HSCT was 40%. The conditioning regimen included or not total-body irradiation (8 or 2 Gy only), and most patients received transplants from unrelated donors.

CNS INVOLVEMENT

CNS leukemia occurs in 6% (range, 1% to 10%) of patients at diagnosis,78 and is confirmed by the detection of ALL cells in the CSF, cranial nerve palsies, significant neurologic dysfunction, or combinations thereof. Treatment and prophylaxis of CNS involvement may consist of intrathecal methotrexate alone or together with cytarabine or prednonsone (triple intrathecal therapy), systemic high-dose cytarabine and methotrexate, and cranial irradiation. CNS+ patients may have a slightly inferior outcome and are sometimes considered HR and eligible to allogeneic HSCT (Table 1).12,13 They receive triple intrathecal bi-weekly until clearing of CSF, early cranial irradiation (18 to 30 Gy), and high-dose chemotherapy. Concurrent spinal irradiation (12 Gy) can be administered without prejudice of subsequent total-body irradiation (13, 2 Gy) for allogeneic HSCT, but its exact role remains undefined.78 In protocols with intensive intrathecal therapy and systemic high-dose therapy, the rate of CNS relapse is below 5% compared to approximately 30% without prophylaxis. The risk is higher with an elevated lactate dehydrogenase and WBC, in B-ALL and TCP ALL, but varying the intensity of CNS prophylaxis according to risk factors is seldom considered.79©80 In TCP ALL, a NOTCH1-related upregulation of the CCR7 gene appears essential to target ALL cells into CNS.81 This observation may herald therapeutic innovations. Several trials have omitted prophylactic irradiation. However, an intensive prophylaxis consisting of triple intrathecal therapy (methotrexate, cytarabine, and dexamethasone), cranial irradiation (24 Gy), and systemic high-dose methotrexate and cytarabine reduced incidence of CNS relapses to 2% in a GMALL study. Treatment of CNS relapse is largely unsuccessful because followed by systemic relapse, whereas highly intensive CNS-directed therapy such as craniospinal irradiation plus high-dose systemic and intrathecal therapy can cause acute leukoencephalopathy. Thus, other approaches, such as intrathecal liposomal cytarabine (that needs to be carefully used in association with high-dose regimens)82 or even antibody therapy, are under evaluation. Allogeneic HSCT is indicated in patients with isolated CNS relapse and is probably the only curative approach for some patients, because of the HR of occult marrow contamination at time of CNS progression.

RELAPSE AND RESISTANCE

Patients who fail to achieve CR or those who relapse subsequently have been treated with a variety of protocols. In recent studies with more than 2,000 patients and published between 2007 and 2010, the CR rate was 42% to 44% and the overall survival was 5% to 8% (22% in one study). HSCT is the best curative chance in patients achieving a second CR (Table 3).83 Therefore, the goal is to achieve a CR or partial remission, to search immediately for a donor, and proceed to HSCT. In the rare patients with testicular relapse, local boost irradiation is added. The survival after sibling or unrelated donor HSCT is approximately 25%, and 18% for subsequent CRs or refractory disease, but patients with HR features who have a short duration of CR before relapse (< 12 to 18 months) are unlikely to survive long-term and are the best candidates to experimental treatments with new agents. New drugs for refractory or relapsed ALL are nelarabine (TCP ALL), and clofarabine in combination with etoposide and cyclophosphamide. Targeted therapies are integrated in relapse protocols. Phase I to II studies with investigational agents should focus primarily on CR and CR with incomplete hematologic recovery, and evaluate surrogate endpoints like MRD, the bridge to transplantation effect, and quality of life, after a joint Federal Drug Administration and American Society of Hematology workshop.84 Perhaps the best approach is to treat molecular relapse (ie, to follow MRD during CR1 and detect conversion in MRD positive status before full blown relapse). In this situation with lower tumoral mass, the anti-CD19 antibody blinatumomab was successfully applied and HSCT results seem to be improved.57

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure

540 © 2011 by American Society of Clinical Oncology

Downloaded from jco.ascopubs.org by BERNIE FITZHARRIS on February 27, 2011 from 159.117.1.11
Copyright © 2011 American Society of Clinical Oncology. All rights reserved.
REFERENCES


Manuscript writing: Renato Bassan, Dieter Hoelzer
Final approval of manuscript: Renato Bassan, Dieter Hoelzer
Bassan and Hoelzer


42. Ribera J-M, Oriol A, Morgades M, et al: Treatment of high-risk (HR) Philadelphia chromosome-negative (Ph-) adult acute lymphoblastic leukemia (ALL) according to baseline risk factors and minimal residual disease (MRD): Results of the PETHEMA ALL-AR-03 trial including the use of propensity score (PS) method to reduce assignment bias. Blood 114:136, 2009 (abstr 322)


60. Ferrando AA: The role of NOTCH1 signaling in T-ALL. Hematology Am Soc Hematol Educ Program 353-361, 2009


By signing up for JCO’s Early Release Notification, you will be alerted and have access to new articles posted online every Monday, weeks before they appear in print. All Early Release articles are searchable and citable, and are posted on JCO.org in advance of print publication. Simply go to jco.org/earlyrelease, sign in, select “Early Release Notification,” and click the SUBMIT button. Stay informed—sign up today!