Preface

Acute Lymphoblastic Leukemia – Quo Vadis?

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Guest Editors

Acute lymphoblastic leukemia (ALL) is one of the most challenging malignant diseases in adults with respect to the intricacies of clinical presentation, diagnosis, and treatment. This preface previews the articles that follow, touching on current treatment strategies for ALL, presenting the controversies regarding the role of allogeneic stem cell and bone marrow transplantation (BMT) for ALL in first remission, and concluding with a look toward the future and a discussion concerning new data about the leukemia stem cells (LSCs) in this disease and how this knowledge will lead to new therapeutic strategies.

CURRENT ACUTE LYMPHOBLASTIC LEUKEMIA TREATMENT

Table 1 outlines the current treatment approaches for adults with ALL. Many of these approaches have been adapted from the successful treatment regimens developed for children with this disease. The article by Pui and colleagues, elsewhere in this issue reviews in detail the state-of-the-art treatment strategies for children with ALL. The survivorship in pediatric ALL now exceeds 80%. As a result, pediatricians are now turning more of their attention to concerns about sequelae of their treatment, as discussed in the article by Nathan and colleagues, elsewhere in this issue.

Overall, the outcome in adults with either B-cell or T-cell ALL with any of the approaches outlined in Table 1 results in approximately 30% to 40% 5-year survival.1 The main achievements in the last few years have been the inclusion of imatinib mesylate (Gleevec) and other tyrosine kinase inhibitors in Philadelphia-positive ALL (see article by Ravandi and colleagues, elsewhere in this issue), the approval of nelarabine (Arranon) for T-ALL (see article by DeAngelo and colleagues, elsewhere in this issue), the pediatric approach to treat ALL in adolescents and young adults (see article by Ribera and colleagues, elsewhere in this issue), and the inclusion of anti-CD20
### Table 1
Current and future adult ALL treatments

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<th>Characteristics</th>
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<tr>
<td><strong>Treatment</strong></td>
<td>BFM-like regimen:</td>
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<td></td>
<td>Induction with VCR, PRED, daunorubicin, and L-ASP;</td>
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<td></td>
<td>Early intensification with CTX, ARA-C, 6-MP, VCR;</td>
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<td>Central nervous system prophylaxis with intrathecal MTX with either</td>
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<td>cranial irradiation or high-dose MTX and ARA-C;</td>
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<td>Late intensification with doxorubicin, VCR, DEXA, CTX, 6-TG and ARA-C;</td>
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<td>Maintenance with VCR, PRED, 6-MP and MTX to complete 24 months.</td>
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<td>Hyper-CVAD regimen:</td>
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<td>Alternating courses of CTX, VCR, doxorubicin and DEXA with MTX and</td>
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<td>high-dose ARA-C;</td>
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<td>Central nervous system prophylaxis includes intrathecal chemotherapy;</td>
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<td></td>
<td>Maintenance with VCR, PRED, 6-MP and MTX to complete 24 months.</td>
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<td><strong>New aspects</strong></td>
<td>Anti-CD20 Ab(^a); different regimen for AYA(^d)</td>
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<td>Nlarabine(^b); different regimen for AYA(^d)</td>
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<td>New TKIs(^c)</td>
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<td>Anti-CD20 Ab(^a)</td>
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**Abbreviations:** Ab, antibody; ARA-C, cytosine arabinoside; AYA, adolescents and young adults; BFM, Berlin-Frankfurt-Münster; CTX, cyclophosphamide; CVAD, cyclophosphamide, vincristine, doxorubicin and dexamethasone; DEXA, dexamethasone; L-ASP, L-asparaginase; MTX, methotrexate; 6-MP, 6-mercaptopurine; PRED, prednisone; 6-TG, 6-thioguanine; TKI, tyrosine kinase inhibitors; VCR, vincristine; VP-16, etoposide.

\(^a\) See article by Thomas and colleagues, elsewhere in this issue.

\(^b\) See article by DeAngelo and colleagues, elsewhere in this issue.

\(^c\) See article by Ravandi and colleagues, elsewhere in this issue.

\(^d\) See article by Ribera and colleagues, elsewhere in this issue.

antibody into the ALL armamentarium (see article by Thomas and colleagues, elsewhere in this issue).

Two additional drugs are worth mentioning. One is pegylated asparaginase (Onco-spar), which decreases the immunogenicity of the enzyme, thus reducing the risk of hypersensitivity reactions. Another advantage of pegylated asparaginase is its long half-life. Its use in adult ALL has been lagging behind its use in pediatric ALL because of lack of pharmacokinetic and pharmacodynamic data in adults. However, two recent publications may change this trend. Specifically, the demonstration of the safety of intravenous pegylated asparaginase during remission induction in adult ALL with favorable pharmacodynamics and decreased hypersensitivity reactions suggests that this route of administration will replace the intramuscular and subcutaneous routes. Furthermore, the findings that effective asparagine depletion with pegylated asparaginase resulted in improved outcome in adult ALL suggest that monitoring for asparagine depletion will become part of the treatment approach in these patients.

The second drug worth noting is clofarabine (Clolar), a novel deoxyadenosine analog with clinical activity in refractory and relapsed pediatric ALL (see article by Jeha and colleagues, elsewhere in this issue). Its role in combination with other drugs in relapsed/refractory adult ALL is being investigated. If efficacy of clofarabine combination therapy is identified in advanced stage ALL, it might be reasonable to explore the use of clofarabine as a front-line agent in adult ALL.

The concluding article by Abutalib and colleagues, elsewhere in this issue discusses other novel agents.

TO B(MT) OR NOT TO B(MT): A RISK-BASED DECISION

BMT is usually recommended to high-risk ALL patients in first remission and those in second and beyond remission. The recent Medical Research Council (MRC)/Eastern Cooperative Oncology Group (ECOG) trial suggested a benefit for sibling donor transplantation in standard-risk ALL in first remission without any significant benefit for high-risk ALL. Others challenge this recommendation. These data and the current controversies are reviewed elegantly in the article by Forman and colleagues, elsewhere in this issue and in the article by Ribera and colleagues, elsewhere in this issue. To understand the controversies about optimal treatment selection for adults with ALL reviewed in this issue, we highlight below some of the traditional and some of the newer biologic risk factors that prognosticate for treatment outcome in adult ALL.

The traditional ALL risk factors (high-risk factors denoted in parenthesis) are divided between the host and the disease. The host-related factors include age (>60) and performance status (poor), while the disease-related factors include white blood cell count (>30 × 10⁹/L for B-cell ALL and >100,000 × 10⁹/L for T-cell ALL), mediastinal mass (present), immunophenotype (B-cell), karyotype (t[9;22], +8, t[4;11], −7 and hypodiploid karyotypes) and lactate dehydrogenase (high level is associated with poor outcome and central nervous system disease). In addition, time to achieve complete remission (>4 weeks) is also recognized as a significant risk factor. Finally, the treatment team and the patient may also play a role in predicting outcome as it was recently implied that time to postremission treatment was an independent prognostic factor in adult ALL. However, these traditional factors may not be sufficient to predict outcome of standard-risk ALL.

Recently, additional risk factors have been identified. The most important one on the host side is the presence of genetic variability in drug metabolism pathways. Examples include 6-mercaptopurine, methotrexate, steroids, and asparaginase (see article by Abutalib and colleagues, elsewhere in this issue). On the disease side, novel
molecular markers were identified that help determine outcome. In T-cell ALL, high expression of v-ets erythroblastosis virus E26 oncogene homolog (avian) (ERG); brain and acute leukemia, cytoplasmic (BAALC)\textsuperscript{13}; and T-cell leukemia homeobox 3 (TLX3)\textsuperscript{14} were associated with unfavorable outcome. In addition, expression of multidrug resistance proteins in the leukemia blasts is associated with adverse outcome.\textsuperscript{15} Finally, presence of minimal residual disease was shown to adversely affect outcome in both pediatric and adult studies (see article by Campana and colleagues, elsewhere in this issue). These risk factors, however, are currently only available through select and meticulously conducted clinical trials in academic centers. As we begin to study the impact of these factors in prospective trials, we will undoubtedly obtain critical insights that may help to guide the recommendation for a stem cell transplant in first remission.

**ACUTE LYMPHOBLASTIC LEUKEMIA STEM CELLS**

Hematopoiesis is the highly orchestrated process of blood cell production by which the billions of white blood cells, red blood cells, and platelets lost daily are replaced to maintain homeostasis.\textsuperscript{16} Hematopoietic stem cells (HSCs) are the small population of long-lived, quiescent, undifferentiated, pluripotent cells characterized by a capacity of self-renewal, an exceptional proliferation potential, resistance to apoptosis, and the ability of multilineage differentiation into all types of blood cells mediated by the production of several lineage-committed progenitors.\textsuperscript{16–20}

The central role of LSCs in the pathogenesis of leukemias has become well recognized over the last 2 decades. LSCs share many of the basic characteristics with normal HSCs, including quiescence, self-renewal, extensive proliferative capacity, and the ability to give rise to differentiated progeny in a hierarchical pattern.\textsuperscript{21–27} Some scientists even view leukemia as a newly formed, abnormal hematopoietic tissue initiated by a few LSCs that undergo an aberrant and poorly regulated process of organogenesis analogous to that of normal HSCs.\textsuperscript{28} The LSCs from different types of leukemias are likely to exhibit different biologic features, including survival and self-renewal pathways and immunophenotype.\textsuperscript{29}

Many researchers believe that the persistence of LSCs, which are resistant to most of the traditional chemotherapeutic agents that kill the bulk of the leukemic cell populations, is a major cause of leukemia relapse after “successful” induction of remission. Subsequently, designing effective therapeutic modalities that specifically target the LSC is likely to reduce the incidence of relapse, and even possibly lead to cure. The main question that remains unanswered nowadays is: What are the LSCs in ALL?

Due to the clear limitations of conducting controlled experiments on humans, most of our current knowledge about human LSCs was obtained indirectly from in vitro studies, xenotransplantation of human cells into immunodeficient animals, and transplant experiments involving primates and other large animals.\textsuperscript{16} The hypothesis that a subset of leukemia cells has distinct stem cell properties implies that LSCs arise as an inherent property of tumor biology and development.\textsuperscript{30,31} However, the bone marrow surroundings and the immune system offer support and are an intricate part of LSC survival and progression.\textsuperscript{32} One current controversy in the LSC arena concerns the intrinsic characteristic of LSCs in the experimental setting of xenotransplantation, where appropriate microenvironment features are missing because of differences between humans and mice.\textsuperscript{24} This may have significant adverse effects on leukemic initiating capacity when these human LSCs are transplanted into nonobese diabetic (NOD)/severe combined immune-deficient (SCID)
mice.\textsuperscript{33} Thus, LSCs that appeared to have failed transplantation may actually be fully leukemogenic in a microenvironmental setting with appropriate support.\textsuperscript{34,35}

Initially, it was reported that immature ALL stem cells capable of long-term proliferation in vitro and in vivo are $\text{CD34}^+\text{CD10}^-\text{CD19}^-$.\textsuperscript{36} Similar data were reported with Ph$^+$ ALL cells.\textsuperscript{37} However, recent reports demonstrated that more mature $[\text{CD34}^+\text{CD19}^-]$ ALL cells can initiate leukemia by xenotransplantation.\textsuperscript{38,39} These findings were associated with a switch to a more immune-deficient mouse strain, NOD/SCID/IL2r\textsuperscript{null}.\textsuperscript{40} This mouse has a mutation in the interleukin-2 receptor common gamma chain and is therefore devoid of not only T and B cells but also natural killer cells. Most recent twist to the theory of LSCs is the report that B precursor blasts in various stages of differentiation $[\text{CD34}^+\text{CD19}^-]$, $\text{CD34}^-\text{CD19}^+$, $\text{CD34}^-\text{CD19}^+$ displayed self-renewal capability, suggesting that leukemic lymphoid progenitors may not lose their self renewal capability with maturation\textsuperscript{41} or are able to “move backward” in differentiation.

This recent finding brings in the potential malleability or plasticity of LSCs. The term plasticity refers to the ability of organ-specific stem cells to recover their ability to differentiate into cells of other lineages, either in vitro or after transplantation in vivo.\textsuperscript{16,42,43} Here we use this term to describe the ability of more differentiated leukemic cells to reacquire the LSC characteristics. As a proof of concept, it was recently demonstrated that as few as 10 unselected ALL cells can initiate leukemia following xenotransplantation.\textsuperscript{44}

These findings may explain the poor outcome in ALL since any remaining blasts can theoretically “dedifferentiate” and start a progeny after “successful” achievement of remission. If indeed these cells can also regain the other LSC characteristics, such as multidrug resistance and resistance to apoptosis, better treatments targeting these cells are needed.

HSCs reside in the bone marrow, close to the endosteal surfaces of the trabecular bone in what is commonly referred to as the niche.\textsuperscript{45} A stem-cell niche can be defined as a structure in which HSCs are housed for an indefinite period of time and maintained by allowing progeny production through self-renewal in the absence of differentiation.\textsuperscript{45–47} Several cell-surface receptors were implicated in controlling the localization of HSCs to the endosteal niche, among which is the chemokine receptor 4 (CXCR4). Its antagonist, AMD3100 (Mozobil) was recently approved as an HSC mobilizer before stem cell collection.\textsuperscript{48}

Somewhat promising in this regard is the recent demonstration of dependency on the stromal-derived growth factor 1 (SDF-1\textsubscript{a}/CXCR4 axis in Ph$^+$ ALL.\textsuperscript{49} Specifically in this scenario, the Bcr-Abl kinase continued to be inhibited by imatinib, but the cells continued to proliferate in the presence of stromal support. The stromal effect did not require direct cell-cell contact and SDF-1\textsubscript{a} substituted for the presence of the stromal cells. These data imply that the stroma-selected imatinib-resistant Bcr-Abl cells were less dependent on the kinase activity; thus, interrupting the interaction between the lymphoblasts and the stroma may be of benefit in Ph$^+$ ALL and most probably also in Ph$^-$ ALL. Initial studies demonstrating a role for AMD3100 in pediatric ALL\textsuperscript{50} offer promise for the future about our ability to mobilize the remaining lymphoblasts from their niche and eradicate them.

**SUMMARY**

This issue attempts to answer the question: *Quo vadis?* Where are we going with respect to ALL treatment in both children and adults? While health care teams caring for children now focus on tailoring their successful therapies to minimize long-term
toxicities, those caring for adults are still working toward the goal of cure. The focus of therapy is increasingly based on the biologic characteristics of the patients. For one age group, adolescents and young adults, a pediatric approach seems warranted. However, this approach may be difficult to administer to older adults. This issue addresses current treatment strategies based on age and disease biology. The reader should be aware that the definition of “young” and “old” adults is in flux (ranging between 30 to 60 years old) and depends on the group (or the principal investigator) conducting the trial. The concluding article looks toward the future and reviews novel treatments that are moving into the clinic. Furthermore, we anticipate that that recent progress in our understanding LSC biology will shed light on the frequent relapses that occur after “successful” remission induction and will lead to therapeutic innovation and, ultimately, to the improved outcome of all patients with this challenging and heterogeneous disease.

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