Acute lymphoblastic leukemia in adults

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Abstract

Acute lymphoblastic leukemia (ALL) is the most frequent neoplastic disease in children, being a rare disease in adults. Many of the advances in pediatric ALL have been through modifications in the doses and schedules of available agents as opposed to the introduction of new compounds. In recent years some improvements in the outcome of ALL in adults have occurred. Application of pediatric regimens to young and middle-aged adults shows promise to improve outcome. Advances in the supportive care of patients undergoing allogeneic stem cell transplantation (SCT), the use of alternative sources of hematopoietic stem cells and the use of reduced-intensity conditioning regimens will expand the number of patients who can benefit from this therapeutic modality. The evaluation of minimal residual disease will further stratify risk classification and redefine the role of therapeutic modalities such as SCT or biologic agents. New drugs such as tyrosin kinase inhibitors or monoclonal antibodies have led to incremental improvements in outcome. Advances in the genetic and epigenetic mechanisms of the disease provide hope that targeted therapies can more effectively treat the disease with less toxicity.

Introduction

Acute lymphoblastic leukemia (ALL) is a clonal proliferation of progenitors of B or T lymphocyte origin that arise in the bone marrow. The disease has a bimodal age distribution, being most commonly seen in children with a subsequent decline in incidence in middle age and a subsequent increase in older individuals. With modern chemotherapy the cure rate in children now exceeds 80% to 90%. On the contrary, cure rates in adults are within the 30-40% range, despite complete remission (CR) exceeding 90% in contemporary treatment series. However, on comparison of patients treated in the early 1980s with those

treated in the early 2000s, overall survival (OS) has improved in all age groups except those over the age of 60. The reasons for the poorer outcome in adults are multiple, but mainly relate to the higher incidence of poor risk cytogenetic and molecular features and the decreased ability to tolerate intensive chemotherapy regimens.

Significant advances in the treatment of adult ALL

In recent years, new studies and new drugs have raised the level of optimism in improving the rate of cure in adult ALL. These advances can be summarized as follows: a. Improvement in the results in young adults (YA) as a result of treatment with pediatric-inspired regimens, b. Improvement in the outcomes of stem cell transplantation (SCT), c. Use of minimal residual disease (MRD) assessment to stratify risk, and d. Incorporation of new chemotherapy agents associated with conventional chemotherapy.

Advances in the treatment of young adults

Several retrospective comparative studies from the United States and Europe have demonstrated that survival outcomes are improved in adolescent and young adults (AYA) treated with pediatric as opposed to adult regimens. The main reason for these differences is the use of much higher doses of non-myelo-suppressive drugs such as corticosteroids, vincristine and L-asparaginase and more intense CNS prophylaxis in AYAs treated on pediatric regimens. Whether this improvement is also related to other factors such as the greater experience of pediatric hematologists in caring AYA with ALL compared with adult hematologists-oncologists or to stricter adherence to scheduled treatment regimens, among other reasons, is unclear.

Several prospective studies utilizing pediatric-inspired regimens in young and middle-aged adults have been developed. All have shown improvement in the outcomes, with EFS probabilities ranging from 55% to 70%. However, in these protocols toxicity rose with increasing age, the upper age limit being 40-45 years. No randomized trials comparing pediatric-based protocols with standard adult protocols have been reported, but the Cancer and Acute Leukemia Group B (CALGB 10403 protocol) is currently treating adults with Philadelphia chromosome-negative ALL up to the age of 40 years with a regimen taken from one arm of a Children's Cancer Group (CCG) protocol. Although this is a phase II study, the results will be compared to the outcomes of patients treated in the designated arm of the CCG protocol, allowing a prospective comparison. In addition, other important aspects such as patient and physician adherence to the dosing and scheduling requirements of the protocol,

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or psychosocial and socioeconomic issues in AYA population will be evaluated.

Improvement in the outcomes of stem cell transplantation

From the results of randomized trials and meta-analyses an evidence-based review has been performed on the role of SCT in the treatment of adult ALL recommended allogeneic SCT for ALL in first remission for patients with high-risk but not standard-risk disease. However, a randomized trial from the Medical Research Council (MRC) and the Eastern Cooperative Oncology Group (ECOG) demonstrated significant improvement with allogeneic SCT compared to the non pediatric-inspired chemotherapy arm for standard-risk patients. No comparative study of the results of allogeneic SCT with those from pediatric-based regimens currently given to standard-risk adult ALL patients is available at present.

In recent years the results of allogeneic SCT have improved, being those from HLA-identical siblings identical to those from well matched unrelated donors. In addition, there is an increasing use of alternative sources of hematopoietic progenitors, such as those from umbilical cord blood (UCB), with the results of unrelated UCB transplants being similar to those from unrelated blood in recent studies. On the other hand, reduced-intensity conditioning (RIC) regimens in the setting of allogeneic SCT have been developed to reduce the transplant-related mortality (TRM) associated with the procedure while preserving the graft-versus-leukemia effect. Retrospective comparative studies based on registry data from either the European Group of Blood and Marrow Transplantation (EBMT) or the Center for In-

ternational Blood and Marrow Transplant Research (CIBMTR) have shown equivalent results in terms of OS between myeloablative conditioning (MAC) and RIC allogeneic SCT. The slightly greater number of relapses in the RIC SCT was counterbalanced by the increased TRM observed in MAC SCT. These results suggest that RIC in first CR could be a suitable therapeutic option for older adults with ALL or for patients with comorbidity.

Minimal residual disease testing

For more than one decade it has been demonstrated that the presence of MRD at the end of chemotherapy or at later time points in pediatric ALL was a significant independent predictor of relapse, and is currently considered as the main prognostic factor in childhood ALL, independent of baseline prognostic factors. More recent studies in adults using polymerase chain reaction (PCR) for immunoglobulin or T-cell receptor gene rearrangements or cytofluorometry to identify aberrant phenotypes have also demonstrated the prognostic value of the pattern of MRD clearance. Several published or ongoing trials use the pattern of MRD reduction for risk assessment and therapeutic decisions, i.e.: sparing those patients with good MRD clearance from allogeneic SCT, irrespective of their risk factors at baseline.

New chemotherapy agents

Many new drugs are being actively investigated in adult ALL but a comprehensive review of all of them is outside the scope of this article. One of the most important compounds is the *ABL* tyrosin kinase inhibitors (TKI), such as imatinib and the second generation TKIs, dasatinib and nilotinib. Several trials have demonstrated the feasibility of their combination with chemotherapy in newly diagnosed patients with Ph-positive ALL, resulting in an

increase in the CR rate and allowing allogeneic SCT to be performed in a high proportion of patients in molecular remission status. As a result of this, the survival of young and middle-aged patients with Ph-positive ALL has significantly improved compared with historical controls. Promising results have also been observed in elderly patients combining TKIs with moderate intensity chemotherapy.

The second group of drugs is the monoclonal antibodies. CD20 is expressed on B-lineage ALL in 40% to 50% of cases with levels of expression rising to 80% to 90% in mature B ALL or Burkitt-type leukemia or lymphoma. CD20 expression at a level $\geq 20\%$ is associated with poor prognosis especially in patients under the age of 60 years. Recent studies have shown that the inclusion of rituximab into chemotherapeutic regimens has improved the prognosis of CD20-positive adults with ALL, but randomized trials are lacking. In addition, on comparison with historical controls, a marked improvement has been observed with the addition of rituximab to the specific chemotherapy schedules in patients with Burkitt's leukemia or lymphoma. Anti-CD22 monoclonal antibodies such as epratuzumab and others are being actively investigated in childhood ALL but results in adults are lacking. Anti CD52 (alemtuzumab) is under investigation for eradication of MRD after induction treatment in a phase II study from the CALGB. The bispecific anti-CD19 and anti-CD3 monoclonal antibody blinatumomab is a promising agent that has been investigated in a phase II study in patients in complete hematologic remission with either persistent or recurrent MRD at any time after initial consolidation of frontline therapy, with very promising results. Further trials with larger patient samples are in progress to better understand its benefit and efficacy.

Nelarabine, a pro-drug of guanine arabinoside, has shown good activity in children and

adults with relapsed or refractory T-ALL and is currently incorporated in frontline combination chemotherapy regimens for newly diagnosed T-ALL. Clofarabine has been approved by the FDA for relapsed or refractory pediatric ALL and is now being used in combination studies with other chemotherapy agents such as cyclophosphamide and etoposide with promising results in pediatric ALL, but data are scarce in adults.

Liposomal encapsulated drugs are promising agents to enhance the efficacy and reduce toxicity. Among them vincristine sulfate liposomes injection is being investigated in combination with dexamethasone in relapsed or refractory ALL, with a good tolerability profile. Cytarabine liposome has shown good activity in the treatment of CNS relapse in ALL and is currently being investigated as CNS prophylaxis with the aim of reducing the number of intrathecal administrations. On the contrary, liposomal anthracyclins do not seem to be of benefit according to the recent results of a randomized trial. Pegylated asparaginase led to more effective asparagine depletion, but the dose and schedule remain to be defined in adults.

Other emerging therapies are under active investigation in ALL. They include NOTCH inhibitors, DNA methylase inhibitors, other BCR-ABL inhibitors, proteasome inhibitors, mammalian target of rapamycin (mTOR) inhibitors, or other kinase inhibitors (MDM2, MEK, PIM, JAK, PI3K...) among others. Many of these compounds are the results of the molecular revolution in genomics that has provided an increasing understanding of malignant diseases and this clearly holds true for ALL. Advances in genetic and epigenetic understanding of the mechanisms of ALL provide the hope that targeted therapies can more effectively treat the disease with less toxicity. Although the task ahead is great, the future looks bright.