Treatment of Acute Lymphoblastic Leukemia

Sima Jeha, MD[1]

(1) Director of the Leukemia / Lymphoma Developmental Therapeutics, Saint-Jude Children's Research Hospital Memphis - USA

✉ *Corresponding Author: Sima Jeha, Director of the Leukemia / Lymphoma Developmental Therapeutics, Saint-Jude Children's Research Hospital, Memphis - USA, Email: sima.Jeha@stjude.org*

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Abstract

Acute lymphoblastic leukemia (ALL) affects both children and adults, with prevalence between the ages of 2 and 5 years. Serial clinical trials have resulted in steady improvement in the outcome of patients with ALL. Most children and over a third of adult patients are cured with widely available treatment approaches based on the use of risk-directed multiagent chemotherapy regimens and diligent supportive care. Ongoing research is now aiming at reducing long term treatment sequelaes in children and younger adults, and at improving the outcome of adults and some subgroups of children with poor prognosis. This review tracks six decades of progress in the therapy of ALL, summarizes the rational of contemporary ALL therapy, and addresses remaining challenges.

Introduction

Steady progress in the development of treatment strategies for acute lymphoblastic leukemia (ALL) started in the 1950s, when complete remissions were achieved using single chemotherapeutic agents.1,2 Significant improvement in remission duration was achieved in pediatric trials combining and cycling these agents, with the addition of central nervous system (CNS) prophylaxis.3 Further progress was accomplished with serial clinical trials using outcome predictors to stratify therapy.4-12 Drugs developed over 30 years ago, such as mercaptopurine, methotrexate, vincristine, corticosteroids, anthracyclines, and asparaginase, still constitute the backbone of contemporary ALL protocols resulting in long-term, event-free survival rates exceeding 80% in children, but seldom exceeding 40% in adult patients.4 With improved understanding of the immunology and molecular pathways involved in ALL, current risk classification typically include age, leukocyte count at diagnosis, blast cell immunophenotype and genotype, as well as early treatment response. The favorable hyperdiploidy >50 (more than 50 chromosomes) and TEL-AML1 gene fusion (with expression of ETV6-CBFA2) are present in about 50% of childhood ALL, and rarely seen in adults. On the other hand, the unfavorable Philadelphia chromosome (BCR-ABL) is present in about 25% of adults, but is not common in children.13-14 Early response to therapy, as measured by minimal residual disease (MRD) evaluation, has played an increasingly important role in risk stratification of ALL. Early and vigorous assessment of the risk of relapse in individual patients help improve outcome of patients with high-risk leukemia while minimizing long term sequelaes and enhancing the quality of life in patients at low risk of relapse.4 Historically, adult ALL trials included more intensive alkylating agents based chemotherapy. Recently, adult investigators are exploring pediatric protocols in the young adult population, and innovative approaches in high risk subgroups.

Principles of treatment

Accurate assessment of relapse hazard is an integral part of ALL therapy. The prognostic impact of age, and to a lesser extent, leukocyte count can be explained partly by their association with specific genetic abnormalities. For example, the poor prognosis of infants is associated with MLL rearrangement (detected in 70% to 80% of patients in this age group), and the overall favorable outcome of patients aged 1 to 9 years is related to the preponderance of cases with hyperdiploidy >50 or TEL-AML1 fusion.4,14 However, primary genetic features do not entirely account for treatment outcome. While up to 15% of patients with hyperdiploidy >50 or TEL-AML1 fusion suffer recurrences of their leukemia, a substantial proportion of the patients with the t(9;22) and BCR-ABL fusion who are 1 to 9 years old and have low leukocyte counts at diagnosis may be cured with intensive chemotherapy alone.15 Among patients with MLL-AF4 fusion, infants and adults have a worse prognosis than children.16-18 Interindividual variability in the pharmacokinetics and pharmacodynamics of many antileukemic agents might partially explain the heterogeneity in treatment response among patients with specific genetic abnormalities and the difference in outcome by age group. Multiple genetic polymorphisms have been associated with relapse risk, acute toxicity, and late effects.19-24 The prime example of optimizing therapy based on germline genetic status is the use of polymorphisms of thiopurine methyltransferase (TPMT), an enzyme that catalyzes the methylation of thiopurines such as mercaptopurine and thioguanine, to guide treatment.23 Some drugs affect outcome when administered concomitantly with ALL therapy. Drugs that induce cytochrome P450 enzymes (e.g. phenobarbital and phenytoin), significantly increase the systemic clearance of several antileukemic agents and may adversely affect treatment outcome. On the other hand, drugs that inhibit cytochrome P450 enzymes (e.g. azole antifungal and macrolide antibiotics), potentiate the effects of vincristine, anthracyclines and etoposide resulting in increased toxicity.

Response to therapy is determined by several factors including the leukemic cell biologic features, the pharmacogenetics of the patient, the treatment regimens administered, and compliance to therapy. The degree of reduction of the leukemic cell clone early during remission induction therapy has greater prognostic strength than any other individual biological or host related feature.25 Assessing MRD by flow-cytometric detection of aberrant immunophenotypes or analysis by polymerase chain reaction (PCR) of clonal antigen-receptor gene rearrangements, provides a level of sensitivity and specificity that cannot be attained by traditional morphological assessment of treatment response.25 There is strong concordance between the assessment of MRD by flow cytometry and by PCR methods. Over 95% of patients can be followed by flow cytometry which is a simple and rapid method. PCR method could be reserved for the few patients whose leukemic cells lack a suitable immunophenotype.

Phases of therapy

With the exception of mature B-cell ALL cases, which are treated with short-term intensive chemotherapy (including high-dose methotrexate, cytarabine, and cyclophosphamide), therapy for ALL typically consists of a brief remission-induction phase followed by intensification (or consolidation) therapy to eliminate residual disease, and then prolonged continuation treatment to maintain remission.

All patients also require treatment directed to the CNS early in the clinical course to prevent relapse due to leukemic cells sequestered in this site.4
Contemporary pediatric protocols stratify therapy based on risk groups defined by age, leukocyte count, immunophenotype, leukemic genotype, and response to early remission induction therapy.5-12 The standard or lower risk category includes patients between 1 and 10 years of age with an initial leukocyte count less than 50 x 109/L, and the remaining patients are considered higher risk. Additional features used by some investigators to stratify patients as lower risk include hyperdiploidy > 50 (DNA index > 1.16) and trisomy of chromosomes 4 and 10. Conversely, other characteristics, such as T-cell phenotype, adverse cytogenetic translocations [t(9;22) and t(4;11)], overt CNS leukemia at diagnosis, and slow early response to induction chemotherapy, have been used to stratify patients as high risk.

Remission induction

Remission induction therapy aims at eradicating leukemic cell burden and restoring normal hematopoiesis. This treatment phase typically lasts 4 to 6 weeks, and includes the administration of a glucocorticoid (prednisone or dexamethasone), vincristine, and at least a third drug (asparaginase or anthracycline, or both). A two-drug remission induction regimen of weekly vincristine and daily prednisone results in remission in 80% to 90% of children with ALL.26,27 Addition of a third agent, such as asparaginase or an anthracycline, increases the remission rate to approximately 95%.28,29 In addition to improving remission rates, intensified induction regimen also prolong remission duration.29,30 A three-drug induction regimen appears sufficient for most standard-risk cases, provided they receive intensified postremission therapy.31 The benefit in long-term survival of using 4 or more drugs during induction is widely accepted in higher risk patients but less clear in lower risk patients.32 Addition of a tyrosine kinase inhibitor has greatly improved the remission induction rate, duration of disease-free survival and quality of life of patients with Philadelphia positive (Ph+) ALL.33-35
Based on reports of more potent in-vitro antileukemic activity and better CNS penetration,36-39 dexamethasone has replaced prednisone in some induction and many continuation regimens.12,40-42 However, the biologically equivalent doses between dexamethasone and prednisone are not known, and one study suggested that prednisone can yield results comparable to dexamethasone, provided higher dose is used (i.e. 60 mg/m2/day).43 Dexamethasone given at higher dose was associated with increased incidence of hyperglycemia, hypertension, myopathy, bony morbidity, severe behavioral changes and infectious complications.44 As with glucocorticoids, the pharmacodynamics of asparaginase differ by formulation.45 The native E. coli asparaginase has been the most commonly used preparation. Polyethylene glycol-conjugated asparaginase, a long-acting and less allergenic form, is progressively replacing the native product and is being increasingly administered intravenously instead of intramuscularly.46 Asparaginase derived from
Erwinia chrysanthemi, has a short half-life and its use is currently limited to patients who are allergic to the E-coli formulations. The dose schedule for asparaginase should take into account the variability in the pharmacokinetic profile and potency among the different preparations.
The rapidity of response to induction therapy, as measured by clearance of peripheral and bone marrow blasts, is an important predictor of outcome,4,5 although intensification of postinduction therapy can improve the adverse prognosis of slow early responders.47 With modern chemotherapy and supportive care, 97% to 99% of children can be expected to attain complete morphological remission (i.e. < 5% blasts in bone marrow) at the end of remission induction; those who do not have poor outcome.48,49 Hence, most investigators offer these patients the option of allogeneic hematopoietic stem cell transplantation at the end of extended induction treatment.50 We and others have found that patients with 1% blasts identified by MRD studies had an outcome as poor as those with induction failure and the patients may also be candidates for allogeneic transplantation following intensification therapy to reduce MRD prior to transplant.51,52

Consolidation (Intensification)

Following remission induction, consolidation (or intensification) is given to eradicate drug-resistant residual leukemic cells. Therapy is tailored to the leukemia subtype and risk-group. Intensifying asparaginase therapy during the early phase of treatment improved results of Dana Farber Cancer Institute (DFCI) studies,53 adding doxorubicin to asparaginase favorably influenced the outcome of high-risk patients, particularly those with T-cell disease.54,55 Significant improvement was also reported in the outcome of patients receiving early intensification consisting of intermediate-dose or high-dose antimetabolite therapy.55-58
Delayed intensification, pioneered by the Berlin-Frankfurt-Münster (BFM) consortium, consists of using drugs similar to those used in remission induction therapy after a three months period of a less intensive, interim maintenance chemotherapy.5 The Children's Cancer Group (CCG) confirmed the efficacy of delayed re-induction therapy in low-risk cases,59 and showed that double-delayed intensification with a second re-induction at week 32 of treatment, improved outcome in patients with intermediate-risk disease.60 An augmented intensification regimen consisting of the administration of additional doses of vincristine and asparaginase during the myelosuppression period following delayed intensification, and sequential escalating-dose parental methotrexate followed by asparaginase (Capizzi methotrexate), improved the outcome of high-risk patients whose disease had responded slowly to initial multiagent induction therapy.47

Continuation (Maintenance)

Continuation or maintenance phase consists of 2 to 2.5 years of low intensity metronomic chemotherapy designed to eradicate any residual leukemic cell burden. Weekly low-dose methotrexate and daily oral mercaptopurine form the backbone of most continuation regimens. Adjusting chemotherapy doses to maintain neutrophil counts between 0.5 and 1.5x109/L has been associated with a better clinical outcome.4,61 Overzealous use of mercaptopurine, to the extent that neutropenia necessitates chemotherapy interruption, reduces overall dose intensity and is counterproductive.62 It is generally recommended to give mercaptopurine at bedtime to patients with an empty stomach,63 and to avoid taken it together with milk or milk products which contain xanthine oxidase, an enzyme that can degrade the drug.64 About 10% of the population inherit one wild-type gene encoding TMPT and one nonfunctional variant allele, resulting in intermediate enzyme activity, while 1 in 300 people inherits two nonfunctional variant alleles and are completely deficient of this inactivating enzyme.65,66 Patients with heterozygous and especially homozygous deficiency of TPMT are at high risk of severe myelosuppression. Identification of these patients allows to selectively guide reductions in mercaptopurine dosage without modifying the dose of methotrexate.23,67 Patients with TPMT deficiency are also at greater risk of developing therapy-related acute myeloid leukemia and radiation-induced brain tumors, in the context of intensive thiopurine therapy.23,68-70 Substituting thioguanine for mercaptopurine during continuation therapy was associated with a high incidence of profound thrombocytopenia and hepatic veno-occlusive disease.71-73 Thioguanine use has therefore been limited to short pulses administered during consolidation therapy in some trials, while mercaptopurine is selected for prolonged administration.
Many groups add regular pulses of vincristine and corticosteroids to this regimen although the benefit of these pulses in the context of contemporary therapy has not been established.74 The optimal duration of therapy remains unknown. Attempts to shorten therapy duration from 24 months to 12 or 18 months have resulted in a significant increase in relapses.75 Many studies extend treatment for boys to 3 years because of their generally poorer outcome compared with girls,76,77 although the benefit of this approach remains to be demonstrated. Several studies showed no advantage to prolonging treatment beyond 3 years.78,79

CNS directed therapy

The importance of therapy directed to the CNS was first demonstrated by investigators at St. Jude Children's Research Hospital in the 1960s, when the incidence of CNS leukemia as an initial site of relapse became progressively more common as more effective chemotherapeutic regimens resulted in longer duration of hematologic remissions. This was attributed to the CNS acting as a pharmacologic sanctuary, poorly penetrated by conventional doses of systematically administered chemotherapeutic agents.3,80,81 Radiation therapy was the first modality successfully used to prevent CNS relapse.82 The effectiveness of 2400 cGy cranial radiation as preventive therapy was offset by substantial late effects in long-term survivors, including learning disabilities, multiple endocrinopathy, and an increased risk of second malignancies. Subsequent trials demonstrated that, in the context of intensive systemic and intrathecal therapy, cranial irradiation can

be reduced 5,83 or even omitted altogether. 5,8,83,84

Because cranial irradiation can cause many acute and late complications (eg, second cancers, neurocognitive deficits, endocrine disorders and growth impairment), it has been largely replaced by intensive intrathecal treatment and systemic chemotherapy. Prophylactic cranial irradiation (12-18 Gy) given to patients with ALL who have an increased risk of CNS relapse restricts CNS relapse to 3-8% of patients. Patients with high-risk genetic features, T-cell immunophenotype, large leukemic burden, poor response to remission induction treatment, and leukemic cells in the cerebrospinal fluid (CSF) even from iatrogenic introduction from a traumatic lumbar puncture at diagnosis, are at increased risk of CNS relapse and require more intense CNS-directed therapy.85,86 Special care should be taken to minimize traumatic lumbar punctures, to deliver intrathecal therapy optimally, and to intensify systemic and intrathecal therapy in high-risk cases.87 Studies have successfully used triple intrathecal therapy or intrathecal methotrexate alone.72 Systematically administered agents including high dose methotrexate,88-90 dexamethasone,36 and asparaginase91 may contribute to prevention of CNS relapse.

Allogeneic hematopoietic stem-cell transplantation

Comparisons between allogeneic hematopoietic stem-cell transplantation and intensive chemotherapy have yielded inconsistent results due to the small numbers of patients studied and differences in case selection criteria.92,93 Allogeneic transplantation during initial complete remission may improve outcome of patients with poor response to initial induction chemotherapy, t(9;22), early hematologic relapse, or T-cell ALL with poor early response or hematologic relapse.15,35,94 The benefit of allogeneic hematopoietic stem-cell transplantation in infants with t(4;11) ALL remains controversial.17,95-97 Matched unrelated-donor or cord blood transplantation has yielded outcomes comparable to those obtained with matched related-donor transplantation, and should be considered reasonable alternatives if a matched donor is not available.98,99 Autologous transplantation has failed to improve outcome in ALL.92 With improving prospects for effective targeted therapy, the need for allogeneic transplantation should be continuously re-evaluated.

Challenging age groups

As cure rates approach 90% in children aged 1 to 9 year old, the following age groups still present challenges that need to be addressed with more innovative approaches.
Infants

> Infant
ALL comprises about 2% of total ALL cases (4% of childhood ALL). Whereas the outcome of the 15-20% infants with MLL germline ALL is comparable to that of older children with ALL, those with very young age (< 6 months), high initial leukocyte count (WBC > 300 x 109/L), MLL rearrangement, and a poor early response to therapy have a dismal prognosis with less than 20% survival rates.17,95,100,101 The use of hematopoietic stem-cell transplantation in infants is controversial. Studies suggesting that the use of hematopoietic stem-cell transplantation contributed to a favorable outcome in infant ALL did not have a control arm in which patients only received chemotherapy and the data were not corrected for waiting time to hematopoietic stem-cell transplantation.97,98 Moreover, in one of these studies total body irradiation was used and led to substantial late effects in infants.98 Data from a large retrospective intergroup analysis did not show differences between infant MLL rearranged cases who did or did not receive hematopoietic stem-cell transplantation.17

> Adolescents and young adults
Older adolescents and young adults (AYA) 16-21 years receive treatment from either pediatric or adult oncologists depending on referral pattern. Overall, the number of patients in this age range comprise a relatively small percentage of either pediatric or adult ALL trial populations, and they are often analyzed together with patients 10-15 years old in pediatric series, or those patients 20-30 years and older in adult clinical trials. Several retrospective analyses have demonstrated significantly better survival for AYA patients treated on pediatric cooperative group studies (event free survival 60-65%) compared with survival of patients from the same age group who were treated on adult cooperative group trials (event free survival 30-40%). Pediatric protocols generally include more intensive use of nonmyelosuppressive agents (glucocorticoids, asparaginase, and vincristine), earlier and more intense CNS directed therapy, and more prolonged maintenance. Differences in adherence to protocol therapy among pediatric or adult medical oncologists and the patients they treat may also contribute to the discrepancy in survival. To understand the actual basis for this difference in outcome, several investigators and consortia are using common regimens to treat patients aged 1-50 years.

> Older adults
Despite improvements in the achievement of complete remission and progress in the supportive care of adults with ALL, the majority of patients eventually relapse, and the overall survival is only 30-40%. The Philadelphia chromosome (Ph+) resulting in the BCR-ABL fusion gene is the most common cytogenetic abnormality in adults with ALL, and is detected in approximately 50% of patients with B-precursor cell ALL who are over 60 years old. Elderly patients cannot tolerate intensive treatment, and trials including older adults have provisions for dose reductions in this age group. The incorporation of molecularly targeted therapy using the ABL tyrosine kinase inhibitor, imatinib mesylate, has begun to change the therapeutic landscape and outcome.33 Ongoing trials are incorporating newer kinase inhibitors to overcome resistance. Addition of rituximab to the hyper-CVAD regimen appear to improve outcome in CD20+ patients, compared to CD20+ ALL on hyper-CVAD alone.102

Relapse

Therapeutic options for refractory ALL are limited. Most relapses occur during treatment or within the first 2 years after its completion, although relapses have been reported as late as 10 years after initial ALL diagnosis.103 The most common site of relapse is the bone marrow. Relapse in extramedullary sites, such as the CNS and testes, has decreased to less than 5% and 2% respectively.104 Leukemia relapse occasionally occurs at other sites. Patients presenting with an isolated extramedullary relapse often have MRD in the bone marrow.105 Patients with isolated bone marrow relapse generally fare worse than those with combined bone marrow and extramedullary relapse.105 Factors indicating an especially poor prognosis are short initial remission and T-cell immunophenotype. Other adverse factors include t(9;22). The presence of minimal residual disease at the end of second remission induction is also a strong adverse prognostic indicator.106,107 Salvage regimens are mostly based on different combinations of the same agents used in frontline therapy, and are associated with significant morbidity and dismal long term survival rates in most cases. Patients with early or multiple relapses and heavy prior chemotherapy exposure, have an expected median survival of 9 to 10 weeks even when multiagent chemotherapy is used. While chemotherapy may secure a prolonged second remission in children with ALL who experience late relapse (defined as more than 6 months after cessation of therapy), allogeneic hematopoietic stem cell transplantation is the treatment of choice for patients who experience hematologic relapse during therapy or shortly thereafter and for those with T-cell ALL. Patients with late-onset isolated CNS relapse who had not received cranial irradiation as initial CNS-directed therapy have a very high remission retrieval rate, with long-term prognosis approaching that of newly diagnosed patients in those who had a long initial remission before the CNS event.92,108,109

Future directions

Current therapy for patients with ALL has become increasingly dependent upon patient and disease-specific characteristics. Expanding the application of pharmacogenomics, a science which aims to define the genetic determinants of drug effects, will allow further individualized therapy in the future. While optimizing the use of old drugs continues through serial studies, new formulations of existing agents are being tested to improve the efficacy and reduce the toxicity of the parent compounds. Such modifications include improving drug transport and delivery, or altering the molecular structure to improve the therapeutic index. Ongoing trials are studying the benefit of the two novel nucleoside analogs, clofarabine and nelarabine, in high risk ALL and T-cell ALL respectively. In addition to refining leukemia classification, studies of global gene expression help identify potential molecular targets for therapy. It remains to be determined whether the success in targeting BCR-ABL with tyrosine kinase inhibitors will translate to other

pathways including NOTCH and FLT3. The challenge is to combine our current knowledge with technology to design effective risk-targeted therapies based on biological features of leukemic cells, host genetics, and early response to therapy. The dramatic increase that has occurred in the cure rate for children with ALL will be difficult to replicate in older patients without considerable additional research. In order to raise the survival rate of adolescents and adults with ALL, researchers will need a more thorough understanding of the biology of this form of leukemia, including the role that genes play in therapies.

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