Management of Acute Lymphoblastic Leukemia in Young Adults

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Abstract: Substantial interest in acute lymphoblastic leukemia (ALL) in young adults (YAs) and investigations focused on this patient population have resulted in therapeutic advancements that are changing the management paradigm and improving outcomes. The pediatric ALL approach is feasible and effective when administered by medical oncologists. Advanced diagnostics and minimal residual disease measurements aid in prognostication and have resulted in shifting recommendations regarding allogeneic hematopoietic cell transplant in first remission. Blinatumomab, inotuzumab, and chimeric antigen receptor T-cell therapies are transforming the treatment of relapsed/refractory ALL. This comprehensive review of the current management of ALL in YAs summarizes recent scientific developments and clinical trial findings related to ALL biology, frontline management approaches, novel therapies, and supportive care specific to this patient population. Finally, a practical guide to modern YA management for practicing clinicians is provided.

Introduction

Acute lymphoblastic leukemia (ALL), the most prevalent hematologic malignancy in children, also affects both younger and older adults. Increased attention has been devoted to young adults (YAs) with ALL in recent years, after population-level reports and clinical trial results revealed a survival disadvantage for patients in whom ALL was diagnosed between the ages of 18 and 40 years compared with both younger and older patients. A considerable amount of work has been undertaken to elucidate the biological underpinnings and therapeutic strategies associated with improving survival in this age group. Novel and exciting therapies are changing the landscape of residual and relapsed YA ALL. Increased awareness of supportive care and survivorship issues unique to YA ALL patients has resulted in the ability to provide comprehensive care to this population.

Acute Lymphoblastic Leukemia Risk Stratification in Young Adults

Adult ALL traditionally has been characterized as standard risk or adverse risk according to the age of the patient (with age <30-35 years

typically used as the cutoff for standard risk), leukocyte count at diagnosis, and the presence of certain unfavorable cytogenetic abnormalities, such as *BCR-ABL1*, *MLL* rearrangements, hypodiploidy, and complex karyotype.[1,2] Although these traditional prognostic features remain of value, ALL risk stratification has been greatly enhanced in recent years through an improved understanding of recurrent molecular alterations in B-cell and T-cell ALL, and the incorporation of sensitive measures of residual disease throughout the treatment course.

Relative to children, adults with B-cell ALL have a higher frequency of poor-risk genetic abnormalities. For example, the presence of *BCR-ABL1* increases with age, such that the prevalence of Philadelphia chromosome–positive (Ph-positive) ALL is less than 5% in children younger than 10 years, 10% to 20% in YAs, and as high as 50% in adults older than 60 years with B-cell ALL.[3-5] A newly recognized adverse risk entity, *BCR-ABL1*–like (Ph-like) ALL, describes a category of B-cell ALL characterized by gene expression profiles similar to those of *BCR-ABL1* ALL but lacking the *BCR-ABL1* translocation.[6] Ph-like ALL commonly involves rearrangements, mutations, and copy number alterations affecting tyrosine kinases or cytokine receptor signaling genes such as cytokine receptor-like factor 2 (*CRLF2*) and is frequently associated with loss of IKAROS family zinc finger protein 1 (IKZF1).[7] The frequency of Ph-like ALL appears to peak in YAs, with a prevalence of nearly 30% (vs 10% in children and 20%-25% in older adults), and Ph-like ALL is associated with a poor prognosis across the age spectrum.[3,8-11] In clinical practice, a 15-gene low-density array (LDA) gene expression card has been developed[12] to identify ALL patients with the Ph-like gene signature in clinical practice, and is currently incorporated into pediatric and YA cooperative group clinical trials (NCT02883049 and NCT03150693). In addition to or in lieu of gene expression analyses, *CRLF2* translocations, which are found in 50% to 60% of cases of Ph-like ALL in YAs,[3] can be uncovered by fluorescence in situ hybridization or by flow cytometric detection of the thymocyte stromal lymphopoietin receptor (TSLPR) gene product of *CRLF2* on leukemia cells.[6]

Outcomes for adult patients with T-cell ALL are similar to, if not better than, outcomes of adult patients with B-cell ALL.[1] A subgroup of T-cell ALL with inferior response to standard chemotherapy is early T-cell precursor (ETP) ALL, a population of malignant lymphoblasts derived from thymic cells at the early T-cell precursor differentiation stage that have retained some myeloid and stem cell properties.[13] By definition, ETP ALL lymphoblasts express CD7, lack CD1a and CD8, and are positive for at least one of the myeloid or stem cell markers, including CD34, CD117, HLADR, CD13, CD33, CD11b, or CD65.[6] ETP ALL is characterized by genomic instability; by a lower frequency of common T-cell ALL molecular alterations, such as those in *NOTCH1*; and by a higher proportion of myeloid-associated genetic mutations, such as *FLT3, DNMT3A*, *IDH1/2*, and *WT1*.[14-16] Evidence suggests that in YAs, ETP ALL is associated with a survival significantly inferior to that of non-ETP ALL.[11]

The incorporation of minimal residual disease (MRD) monitoring into ALL risk stratification has been pioneered by the pediatric oncologists, where MRD-guided prognostication and therapy is standard of care.[17] MRD is increasingly recognized as a critical component of ALL care in YAs, where MRD has proven to be among the most significant prognostic tools following induction and hematopoietic cell transplant (HCT).[18-22] Methodologies for MRD monitoring include flow cytometry, allele-specific oligonucleotide (ASO) polymerase chain reaction (PCR), and next-generation sequencing (NGS) of immunoglobulin and T-cell receptors (recently reviewed by Petit and colleagues[23]). Assessment of MRD following induction therapy aids YA ALL risk stratification and has been incorporated into the most recent National Comprehensive Cancer Network (NCCN) guidelines.[24]

Pediatric-Inspired Protocols as Induction and Consolidation Therapy

More than a decade ago, retrospective reports from around the world demonstrated that the survival of YAs treated according to pediatric ALL chemotherapy protocols administered by pediatric oncologists was superior to the survival of YAs treated with adult ALL regimens delivered by medical oncologists.[25-30] Pediatric ALL protocols include more asparaginase, glucocorticoids, vincristine, and intrathecal therapies than traditional adult ALL regimens or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD). This seminal finding translated into the development of prospective clinical trials of pediatric-inspired ALL regimens delivered by adult oncologists to YAs with ALL, which demonstrated that this approach is feasible and appears to result in outcomes superior to those of historical controls treated with adult cooperative group ALL regimens.[18,31-34] Between 2008 and 2012, the prospective US Intergroup Trial C10403 (Combination Chemotherapy in Treating Young Patients With Newly Diagnosed Acute Lymphoblastic Leukemia) enrolled 318 YAs aged 17 to 39 years in a single-arm phase 2 trial evaluating delivery of the augmented Berlin-Frankfurt-Münster[35] protocol to YAs with newly diagnosed Ph-negative ALL.[18] Toxicities included hepatotoxicity in approximately 50% of patients, hyperglycemia in 30%, and neuropathy in 15%; the rate of pegylated asparaginase hypersensitivity

reactions was lower (10%) than that reported in children with ALL (20%).[18,36] At the time of initial outcomes reporting, with 32 months of follow-up, the 2-year event-free survival rate was 66% (95% CI, 61%-72%) and the 2-year overall survival (OS) rate was 79% (95% CI, 74%-84%).[18] Outcomes for B-cell and T-cell ALL were equivalent, and no significant differences in survival were seen by age group.[18] Body mass index above 40 (hazard ratio [HR], 3.8; 95% CI, 1.91-7.35) and a high level of *CRLF2* expression (HR, 2.57; 95% CI, 1.08-6.16) were significantly associated with inferior OS.[18] In a subset of patients with postinduction MRD evaluated by ASO PCR, the 42% of the patients with undetectable MRD had an excellent disease-free survival rate of greater than 80%, whereas the patients with detectable postinduction MRD fared significantly worse (P=.01).[18]

The successor study to US Intergroup Trial C10403 for YA ALL, A041501 (Inotuzumab Ozogamicin and Frontline Chemotherapy in Treating Young Adults With Newly Diagnosed B Acute Lymphoblastic Leukemia; NCT0315069), opened for accrual in the summer of 2017. This trial includes the C10403 pediatric backbone but has added rituximab (Rituxan, Genentech/Biogen) for CD20-positive patients on the basis of the GRAALL (Group for Research on Adult Acute Lymphoblastic Leukemia) trial results, which demonstrated a statistically significant improvement in event-free survival when rituximab was added to chemotherapy for adults with CD20-positive B-cell ALL.[37] The primary objectives of this randomized phase 3 trial are to test whether the addition of 2 post-remission courses of inotuzumab ozogamicin (Besponsa, Pfizer), an anti-CD22 conjugate that produces an 81% response rate in patients with relapsed disease (see section below), can eradicate MRD when incorporated early into frontline treatment, and improve disease-free survival and OS for YAs with B-cell ALL.

Although national guidelines recommend the use of pediatric-inspired ALL protocols for YAs with ALL up to the age of 40 years,[24,38] it is not clear that medical oncologists caring for such patients are routinely administering these regimens.[39,40] For example, population-level analyses demonstrate that as recently as 2014, only one-third of YAs with newly diagnosed ALL were being treated according to pediatric-inspired ALL protocols. Additional investigations are required to understand the barriers that medical oncologists perceive in delivering pediatric-inspired ALL regimens to YAs with ALL, and to expand this approach to more YAs with newly diagnosed ALL.

Management of Ph-Positive and Ph-Like ALL

Patients who have ALL with *BCR-ABL1* have benefited substantially from the advent of tyrosine kinase inhibitors (TKIs) such as imatinib and dasatinib (Sprycel, Bristol-Myers Squibb), which often result in deep remissions when combined with multiagent chemotherapy. Imatinib has been combined with multiagent chemotherapy in both children and adults. In a study from the MD Anderson Cancer Center, the combination of imatinib and hyperCVAD in 54 adults with Ph-positive ALL resulted in a 5-year OS rate of 43%.[41] US Intergroup Trial S0805 (Combination Chemotherapy With or Without Donor Stem Cell Transplant in Treating Patients With Acute Lymphoblastic Leukemia) was a phase 2 prospective study of dasatinib with hyperCVAD that enrolled 97 adults up to age 60 years with Ph-positive ALL. Relative to historical controls who did not receive TKIs, this cohort had significantly superior response rates and survival rates, with a complete response (CR) rate of 85% and 1-year OS and relapse-free survival (RFS) rates of 88% and 85%, respectively.[42] At the time of reporting, a statistically significant advantage in RFS was seen with HCT for patients in first complete response (CR1), but OS was similar in the patients who underwent transplant and those who did not.[42] In a multicenter prospective phase 2 trial of multiagent chemotherapy plus nilotinib (Tasigna, Novartis) conducted in Korea, among 90 adult patients (61% of them <45 years), this combination was feasible and resulted in a deep MRD-negative response rate of 95% and 2-year RFS and OS rates of 72% for patients achieving a complete hematologic response.[43] Multivariable analysis revealed that allogeneic HCT (HR, 3.3; P=.048) and achievement of major molecular remission (MMR; HR, 12.3; P=.038) were associated with superior 2-year RFS.[43]

The group at MD Anderson Cancer Center recently reported updated results of their frontline trial of hyperCVAD plus ponatinib (Iclusig, Ariad) in adults with newly diagnosed Ph-positive ALL.[44,45] At the time of reporting, 64 patients have been treated, with the protocol amended midway to reduce the ponatinib dosing in patients in CR following induction owing to an increased risk for cardiac and vascular events.[44] Following 8 cycles of hyperCVAD plus ponatinib, patients received ponatinib, vincristine, and prednisone maintenance for 2 years followed by ponatinib indefinitely. A complete cytogenetic response, MMR, and complete molecular response were achieved in 98%, 97%, and 77% of the patients, respectively.[44] Pancreatitis (19%), thrombotic events (6%), and myocardial infarction (5%) were among the side effects of ponatinib.[44] The 3-year RFS and OS rates were 79% and 76%, respectively; 38 patients continued to receive treatment at the time of reporting.[44]

The optimal management of Ph-like ALL in YA patients is not yet clear. Because approximately 70% of patients in this subgroup harbor genetic alterations

such as *CRLF2* rearrangements with or without *JAK1/2* mutations, as well as other gene mutations and rearrangements that may be responsive to JAK inhibitors,[3] this strategy is of great interest. The Children's Oncology Group (COG) is conducting a phase 2 multicenter study evaluating the addition of the JAK inhibitor ruxolitinib (Jakafi, Incyte) to chemotherapy for children with de novo high-risk *CRLF2*-rearranged and/or JAK pathway–mutant ALL (AALL1521; NCT02723994). Another attractive approach to Ph-like ALL with kinase alterations including *ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, and *PDGFRB* abnormalities is with kinase-targeting agents such as dasatinib. The COG has amended its frontline high-risk B-cell ALL protocol to include dasatinib for patients who have Ph-like ALL with a predicted TKI-sensitive mutation (AALL1131; NCT02883049). MD Anderson is conducting a phase 2 trial of chemotherapy with either ruxolitinib or dasatinib in patients aged 10 years and older who have Ph-like ALL (NCT02420717). Additional prospective studies are planned in children and adults to evaluate these and other novel agents in Ph-like ALL (recently reviewed by Wells and colleagues[46]).

Hematopoietic Cell Transplant in Young Adult Acute Lymphoblastic Leukemia

Allogeneic HCT remains an important modality in ALL management, but optimal patient selection for this intensive procedure is shifting and continues to evolve as more sensitive diagnostics (eg, MRD) and newer therapies become available in clinical practice. The largest study of HCT in adults with newly diagnosed ALL was the international Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) E2993 trial, which enrolled 1929 patients with newly diagnosed B-cell or T-cell ALL between 1993 and 2006.[1,47] Patients received a standard adult ALL induction protocol, and patients younger than 50 to 55 years who achieved remission were biologically randomized to receive a matched sibling allogeneic HCT with high-dose total-body irradiation and etoposide conditioning vs a second randomization to consolidation/maintenance chemotherapy or high-dose therapy and autologous stem cell rescue.[1,47] ALL risk in this study followed standard adult categories, with age older than 35 years, high white blood cell count at diagnosis, and Ph positivity denoting high risk. Among the high-risk Ph-negative patients, no statistically significant improvement occurred in the donor group (the relapse rates were 37% in the donor group and 63% in the no-donor group, but this was offset by the strikingly high rate of nonrelapse mortality of 36% in the donor group at 2 years).[47] However, 5-year OS rates for standard-risk Ph-negative patients were 62% in the donor group vs 52% in the no-donor group (P=.02).[47] The study report concluded that allogeneic HCT in first remission should be the treatment of choice for standard-risk patients with Ph-negative B- or T-cell ALL—in other words, the majority of YAs without a high WBC count or Ph-positive disease at diagnosis.

Although the MRC/ECOG study remains the largest phase 3 study to evaluate the role of HCT in adult ALL, advancements in ALL since the conclusion of this trial have aided the formulation of recommendations for HCT patient selection in adult ALL. First, it has now been shown repeatedly and in a large meta-analysis that MRD status following induction or consolidation therapy is one of the most—if not the most—important prognostic marker in adult ALL.[48] Thus, YA patients who have persistent MRD following induction or consolidation are often considered for allogeneic HCT, whereas patients who achieve MRD-negative status appear in general to fare as well without consolidative HCT. For example, in a retrospective analysis of the GRAALL 2003 and 2005 trials, in which YAs received pediatric-inspired regimens and high-risk patients with an available donor were assigned to allogeneic HCT in CR1, survival outcomes in MRD-negative patients ($<10^{-3}$ by ASO PCR following induction therapy) receiving HCT and outcomes in those receiving chemotherapy consolidation were not statistically significantly different; however, a statistically significant interaction was observed in favor of allogeneic HCT for patients who were MRD-positive following induction.[49] Furthermore, with the transition to pediatric ALL regimens for YAs with ALL, it is anticipated that non-HCT outcomes will improve relative to those previously reported for adult regimens, as in the MRC/ECOG trial. It is unlikely that another prospective trial of this magnitude will be conducted to answer definitively the question of who are the optimal adult patients with ALL to undergo allogeneic HCT in CR1. However, on the basis of data showing excellent outcomes for YAs treated on pediatric protocols who achieve early MRD negativity,[18,31,32] many ALL experts now recommend that allogeneic HCT in CR1 be reserved for YAs with persistent MRD and those with disease characterized by high-risk molecular genetic features, such as *BCR-ABL1* ALL and Ph-like ALL.

Allogeneic HCT in CR1 for Ph-positive ALL has been regarded as the standard of care owing to the historically dismal outcomes of these patients when treated with chemotherapy. With the advent of TKIs and subsequently deeper pre-HCT remissions, survival outcomes following HCT in patients who have Ph-positive ALL have improved dramatically, with recent reports demonstrating 3-year RFS and OS rates of 75% to 80%.[50] The achievement of molecular remissions with TKI-based

induction therapies in patients who have Ph-positive ALL has led investigators to reconsider the role of allogeneic HCT in this population. The COG reported outcomes of 50 children who had Ph-positive ALL treated with high-dose imatinib plus intensive chemotherapy in AALL0031 (A Phase III Randomized Trial for Newly Diagnosed High Risk B-precursor Acute Lymphoblastic Leukemia Testing Clofarabine in the Very High Risk Stratum) and found no statistically significant survival advantage for HCT relative to imatinib plus consolidation and maintenance therapy.[51] Retrospective outcomes of 85 adults treated at MD Anderson for Ph-positive ALL with hyperCVAD plus TKI therapy who did not undergo HCT in CR1 were recently reported.[52] Patients who achieved a complete molecular response following 3 months of therapy had median 4-year RFS and OS rates of 63% and 66%, respectively, whereas patients who did not achieve MMR had median 4-year RFS and OS rates of 26% and 32%, respectively.[52] However, the trial mentioned above, S0805, a prospective phase 2 trial of dasatinib plus hyperCVAD followed by allogeneic HCT in younger adults with newly diagnosed Ph-positive ALL, found a statistically significant advantage in both RFS and OS in favor of patients who underwent HCT vs those who did not.[50] This study did not, however, report MRD rates or on the impact of MRD on outcomes. It is hoped that ongoing multicenter prospective studies will further clarify the optimal role of HCT for Ph-positive ALL in the TKI era.

Patients who have ETP ALL, as mentioned earlier, are another high-risk ALL subgroup for whom allogeneic HCT is often considered in CR1. Recent reports of T-cell ALL outcomes from the GRAALL demonstrate that the majority of adults with ETP ALL are MRD-positive following induction (70%), but that early allogeneic HCT appears to offset chemotherapy resistance and provide a significant survival benefit in this group.[53] In their analysis of 47 adults with ETP ALL (median age, 35 years) treated according to the GRAALL 2003 and 2005 protocols, the investigators found a trend toward superior OS with allogeneic HCT in ETP ALL and a significant interaction between ETP ALL and HCT in T-cell ALL multivariable survival analysis, suggesting benefit with early HCT for this specific subgroup of YAs with ALL.[53]

Novel Therapies for Residual or Relapsed Acute Lymphoblastic Leukemia

Blinatumomab

A bispecific T-cell–engaging antibody therapy targeting CD19, blinatumomab (Blincyto, Amgen), received accelerated approval by the US Food and Drug Administration (FDA) in 2014 for the treatment of relapsed/refractory Ph-negative B-cell ALL. Blinatumomab received full FDA approval for the treatment of relapsed/refractory Ph-negative and Ph-positive B-cell ALL in July 2017. In the international phase 3 TOWER study (Blinatumomab Versus Standard of Care Chemotherapy in Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia) of 405 adults with relapsed or refractory Ph-negative B-cell ALL randomly assigned to blinatumomab vs standard salvage chemotherapy, remission was achieved in 45% of patients treated with blinatumomab vs 25% of those treated with chemotherapy (P <.001); 76% of the patients with blinatumomab remissions were MRD-negative.[54] OS was 7.7 months (CI, 5.6 to 9.6 months) following blinatumomab vs 4.0 months (95% CI, 2.9 to 5.3 months) with chemotherapy (P=.01).[54] Patients with 50% or more bone marrow blasts at the time of receipt of blinatumomab had inferior remission rates (34.4%) relative to those with less than 50% marrow blasts (65.5%).[54] Blinatumomab was used to treat 45 patients with Ph-positive ALL who had resistance or relapse following second-generation TKI-based therapy.[55] CRs were achieved in 36% (95% CI, 22%-51%); 88% of these were MRD-negative responses.[55] Ongoing clinical trials in adults with ALL are evaluating blinatumomab therapy in a variety of treatment settings, including the MRD-positive setting (NCT03109093 and NCT02458014) and the up-front setting in combination with chemotherapy (NCT02877303, NCT02003222, and NCT02143414).

Inotuzumab Ozogamicin

Inotuzumab ozogamicin, a humanized anti-CD22 antibody conjugated to calicheamicin, received FDA approval in August 2017 for the treatment of relapsed/refractory B-cell ALL in adults. The phase 3 INOVATE trial (A Study Of Inotuzumab Ozogamicin Versus Investigator's Choice Of Chemotherapy In Patients With Relapsed Or Refractory Acute Lymphoblastic Leukemia) randomly assigned 279 adults with relapsed/refractory CD22-positive ALL to receive either inotuzumab or standard ALL salvage therapy.[56] Remission (CR or CR with incomplete hematologic recovery) was achieved in 80.7% (95% CI, 72.1%-87.7%) of patients treated with inotuzumab and in 29.4% (95% CI, 21.0%-38.8%) of patients treated with standard therapy (P <.001).[56] Of those achieving CR with inotuzumab, 78.4% were MRD-negative. Both progression-free survival (HR, 0.45; P<.001) and OS (HR, 0.77; P=.04) favored inotuzumab.[56] Hepatotoxicity, in particular sinusoidal obstructive syndrome, is a particular concern following inotuzumab. Hepatotoxicity occurred in 13% of the study participants, including the 22% of patients receiving inotuzumab who proceeded to allogeneic HCT.[57] As mentioned earlier, inotuzumab will be tested in the frontline setting for YAs with newly diagnosed ALL in a recently launched trial sponsored by the Alliance for Clinical Trials in Oncology (NCT03150693).

Chimeric Antigen Receptor T-Cell Therapy

Among the most exciting advances in the treatment of B-cell malignancies is the incorporation of chimeric antigen receptor T-cell (CAR T-cell) therapy into clinical practice. A complete review of CAR T-cell therapy in ALL is beyond the scope of this article (see reviews by Davis and Mackall[58] and Maude and colleagues[59]). Tisagenlecleucel (Kymriah, Novartis), the CAR agent targeting CD19, recently received FDA approval for the treatment of relapsed/refractory B-cell ALL in children and YAs up to 25 years. Updated results of the phase 2 ELIANA trial (Determine Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-cell ALL) of CTL019 administered to children and adults up to age 21 years were recently reported. Of 63 evaluable patients, 83% achieved MRD-negative CR (95% CI, 71%-91%) within 3 months of infusion, and the estimated probability of RFS 6 months following CR was 75% (95% CI, 57%-87%).[60] Cytokine release syndrome occurred in 78% of patients and grade 3 neurologic adverse events in 15%; no patients died of cytokine release syndrome, and no grade 4 neurologic adverse events or neurologic deaths occurred.[60] Results of CD19-targeting CAR T-cell therapy in adult ALL have also been reported, with highly promising response rates.[61,62] Additional CAR-T targets of interest in ALL, such as CD22, are currently under development and will be necessary in order to deal with CD19-negative relapses seen following CD19 CAR T-cell therapy.[63-65]

Agents for T-Cell Acute Lymphoblastic Leukemia

Nelarabine (Arranon, Novartis), a synthetic purine nucleotide antimetabolite with preferential activity in T lymphoblasts, is the only agent to be approved specifically for relapsed/refractory T-cell ALL/lymphoblastic lymphoma in both adults and children in recent years. Given the high frequency of activating mutations in *NOTCH1* in T-cell ALL, efforts to target the NOTCH1 signaling pathway through γ-secretase inhibitors are underway (NCT02518113).[66] Preclinical work would suggest a possible role for combination therapy with γ-secretase inhibitors and agents that target the mTOR pathway,[67] as well as the potential for targeting the NOTCH1 pathway with anti-NOTCH1 antibodies.[68] Additional strategies, such as inhibition of BCL2 and of the JAK/STAT pathway, appear potentially promising in ETP ALL, and clinical trials with these agents are underway (NCT03181126 and NCT03117751).

Supportive Care Issues for Young Adults With ALL

YAs with ALL struggle with unique psychosocial issues that result from receiving a cancer diagnosis during the transition to adulthood and independence, a time of critical development. For example, the diagnosis of ALL and its treatment often disrupt normal life, which may reduce self-esteem and result in poor social skills and isolation from peers, as well as a farsighted view of the future. Additionally, YA patients with cancer are exposed to complex issues, such as early confrontation with mortality, preservation and/or loss of fertility, financial and insurance problems, and concerns regarding the attainment of further education, career development, and return to normal life.[69-71] These numerous stressors likely contribute to the higher rates of substance abuse, depression, adherence issues, and overall decreased quality of life reported in adolescent and YA patients with cancer.[72-74] Furthermore, a pilot study demonstrated that nearly one-third of YA patients with leukemia may meet the criteria for depression, anxiety, or traumatic stress disorder—both while undergoing therapy and during early survivorship.[75]

Given the host of unique psychosocial and supportive care issues facing the YA population with ALL, the optimal care of these patients should rely on a multidisciplinary approach focused on understanding and addressing unique YA qualities and needs. YA patients with ALL benefit when additional disciplines, such as social work, pharmacy, physical therapy, and psychology, are included in the creation of specialized multidisciplinary adolescent and YA teams.[76,77] Additionally, systematic and early integration of palliative care into the standard oncology practice of YA cancer management is another potential approach to improve the overall cancer experience. Patient involvement in support groups and shared group activities, specifically those dedicated to YA patients with cancer, has been shown to develop connections and improve self-esteem.[78,79] Online resources, such as those from the Leukemia and Lymphoma Society (www.lls.org), the Dear Jack Foundation (www.dearjackfoundation.org), and the Young Adult Cancer Alliance (criticalmass.org), which offer support groups and psychosocial, financial, and educational resources, may assist YA patients, caregivers, and providers.

Psychosocial concerns are compounded by the fact that even the successful treatment of ALL is unfortunately associated with potential short- and long-term toxicities.[80-82] Long-term follow-up guidelines for YAs with cancer, extrapolated largely from guidelines developed for pediatric cancer survivors,[83] recommend providing fertility counseling as well as routine screening for possible complications, including vincristine-associated neuropathy, glucocorticoid-associated osteonecrosis, cardiac toxicity, metabolic abnormalities, and secondary malignancies.[38] Additional research focused specifically on the effect of the administration of pediatric ALL therapies to YAs is needed to tease apart specific YA toxicities and generate evidence-based guidelines specific to this population.

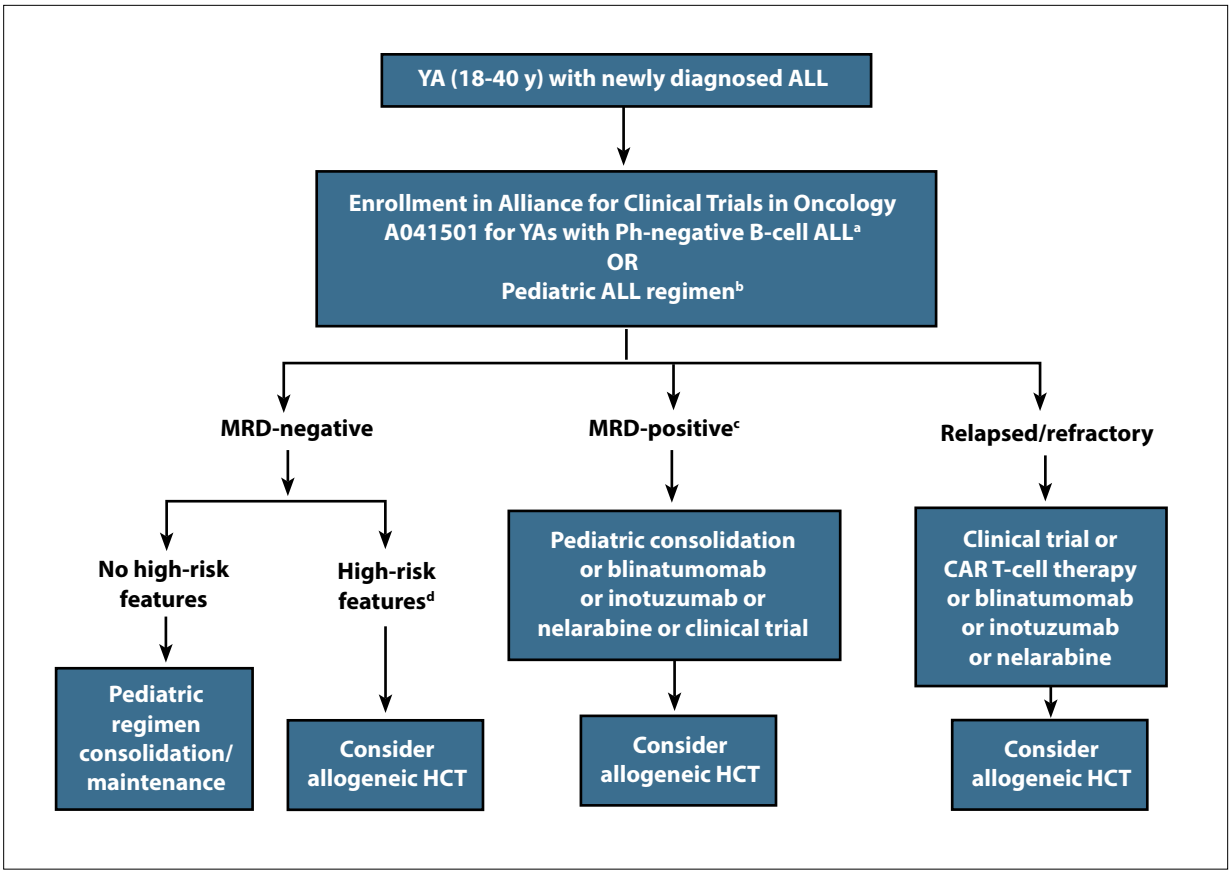

Figure. Treatment algorithm for acute lymphocytic leukemia in young adults.

[a] Clinicaltrials.gov identifier: NCT03150693.

[b] Consider adding rituximab for CD20-positive ALL and add TKI for Ph-positive ALL; may consider multiagent chemotherapy +/- rituximab based on single-center reports.[84]

[c] MRD assessment by multiparameter flow cytometry, next-generation sequencing, or PCR.

[d] High-risk features include high-risk cytogenetics, Ph-like ALL, and ETP ALL.

ALL, acute lymphocytic leukemia; CAR, chimeric antigen receptor; ETP, early T-cell precursor; HCT, hematopoietic cell transplant; MRD, minimal residual disease; PCR, polymerase chain reaction; Ph, Philadelphia chromosome; TKI, tyrosine kinase inhibitor, y, years; YA, young adult.

Conclusion

The past decade has witnessed dramatic advancement in the management of YAs with ALL. The application of pediatric ALL protocols by medical oncologists, a more sophisticated understanding of the molecular underpinnings of ALL, the incorporation of sensitive measures of MRD, and new and exciting therapeutic agents are changing the landscape of ALL for this population. A practical guideline to the modern treatment of YA ALL, based on the opinion of the authors, appears in the Figure. Additional research focused specifically on the impact of pediatric ALL therapies administered to YAs is needed in order to tease apart specific YA toxicities and generate evidence-based guidelines specific to this population.

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