Pediatric-inspired protocols in adult acute lymphoblastic leukemia: are the results bearing fruit?

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Observational findings demonstrating improved survival for younger adults following pediatric, as opposed to adult, acute lymphoblastic leukemia (ALL) regimens have been translated into international, prospective multicenter clinical trials testing the pediatric regimen in young adult ALL. The results of these studies confirm the feasibility of delivering the pediatric regimen in the adult oncology setting and establish the superiority of this approach relative to historical adult cooperative group regimen results. Specific toxicities, including thrombosis, hepatotoxicity, and osteonecrosis, are more prevalent in adults receiving the pediatric regimen relative to young children. Persistent minimal residual disease (MRD) is a strong prognostic indicator in adults receiving the pediatric regimen; sensitive, high-quality MRD evaluation should be performed in all patients receiving these therapies. Incorporation of targeted agents, particularly in the frontline and MRD$^+$ setting, will usher in the next era of the pediatric regimen in adult ALL.

Learning Objectives

- Understand the role of the pediatric regimen in adult acute lymphoblastic leukemia through analysis of recently reported results of multicenter prospective clinical trials
- Review the clinical management and toxicities associated with delivering the pediatric regimen in adults

Clinical case, part 1: diagnosis

The patient is a 34-year-old attorney who presented with progressive fatigue, weight loss, and flu-like symptoms. He was found to have cervical lymphadenopathy and a white blood cell (WBC) count of 25 000/μL with 80% circulating blasts; hemoglobin, 8.9 g/dL; and platelets, 28 000/μL. Flow cytometry performed on the peripheral blood demonstrated an abnormal T-cell population expressing CD45 (dim), CD2, cCD3, CD5, CD7, CD8, CD1a, and terminal deoxynucleotidyl transferase, and lacking expression of CD10, CD13, CD19, CD20, CD22, CD33, CD34, and myeloperoxidase. Bone marrow examination confirmed a diagnosis of T-cell acute lymphoblastic leukemia (T-ALL), cortical subtype. Cytogenetic studies demonstrated a normal male karyotype and a targeted next-generation sequencing (NGS) panel detected an activating mutation in *NOTCH1*. Analysis of the cerebral spinal fluid (CSF) revealed 1 WBC, 5 red blood cells, and no atypical cells. Prior to initiation of therapy, he underwent sperm cryopreservation.

Initial diagnosis and workup

The patient presented in this clinical case received a diagnosis of T-ALL based upon the immunophenotypic analysis of the blasts in the peripheral blood and bone marrow. In addition to distinguishing B-cell ALL (B-ALL) from T-ALL, a detailed phenotypic analysis is increasingly important at diagnosis and at relapse or progression in order to determine whether targeted antibody-based therapies may be appropriate (eg, rituximab for CD20$^+$ B-ALL). In T-ALL, careful determination of the immunophenotype aids in identifying patients with early T-cell precursor ALL (a biologic subtype of T-ALL defined by lack of CD1a and CD8 expression), dim or absent CD5 expression, and expression of 1 or more myeloid- or stem cell–associated antigens.[1] The patient in this clinical case does not have the characteristic phenotype of early T-cell precursor ALL; this is an important clinical determination as this subtype of T-ALL in adults appears to have inferior prognosis and may benefit from intensified consolidation therapy.[2,3]

Routine cytogenetic analysis remains an essential component of the workup of newly diagnosed ALL in adults. In particular, fluorescent in situ hybridization (FISH) analysis for t(9;22) identifies Philadelphia chromosome–positive (Ph$^+$) ALL, and conventional cytogenetics/FISH may demonstrate additional abnormalities of prognostic importance. In addition, NGS approaches are increasingly being used in the clinic to identify genetic alterations with prognostic and/or predictive significance. For instance, mutations activating NOTCH1 signaling, as in this patient's case, occur in approximately three-quarters of pediatric and young adult T-ALL and are generally associated with a more favorable prognosis.[4] Although not applicable to this case, a combination of flow cytometry, specialized FISH panels, and RNA-sequencing approaches can be useful in diagnosing the characteristic gene fusions and alterations associated with Ph-like B-ALL, another high-risk biologic subtype.

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Table 1. Comparison of "pediatric" and "adult" chemotherapy regimens

Feature	Typical pediatric ALL regimen	Typical adult ALL regimen
Asparaginase	Higher cumulative dose	Lower cumulative dose or no use through therapy
Vincristine	Higher cumulative dose	Lower cumulative dose
Intrathecal therapy	Higher cumulative dose	Lower cumulative dose
Steroid	Higher or similar cumulative dose	Lower or similar cumulative dose
Anthracycline	Lower cumulative dose	Higher cumulative dose
Cyclophosphamide	Lower cumulative dose	Higher cumulative dose
Cranial radiation	Variable/not commonly recommended	Variable
Hospitalization	Induction only	Often with each cycle
Adverse effects	More asparaginase-related toxicities	More myelosuppression-related toxicities

Evaluation of the central nervous system (CNS) with diagnostic lumbar puncture, including cytologic analysis of the CSF, should be routinely performed in patients with ALL. In many treatment protocols, CNS status at time of diagnosis informs specific CNS-directed treatment. The Steinherz/Bleyer algorithm,[5] as used in the Children's Oncology Group (COG) protocols, can be used to determine CNS involvement should there be peripheral blood contamination of the CSF. Fertility preservation should also be discussed with all younger adults at the time of diagnosis, ideally prior to treatment with cytotoxic chemotherapy.

Clinical case, part 2: frontline therapy

Induction therapy was then initiated following the US Intergroup Cancer and Leukemia Group B (CALGB) 10403 protocol,[6] a pediatric-inspired regimen with multiagent chemotherapy consisting of multiple doses of vincristine, daunorubicin, pegylated asparaginase (peg-asparaginase), and prednisone, in addition to intrathecal cytarabine and methotrexate. The induction was complicated by a significant elevation in liver function studies, including hyperbilirubinemia, which resolved without intervention.

The pediatric regimen as frontline therapy in younger adults

Pediatric and medical oncologists have traditionally approached the treatment of ALL using markedly different therapeutic regimens (Table 1). The mainstay of the "pediatric" approach is to use high cumulative doses of nonmyelosuppressive agents such as vincristine, glucocorticoids, and asparaginase, as well as more intensive and prolonged CNS prophylaxis.[7-11] Most pediatric treatment protocols are based upon regimens pioneered by the Berlin-Frankfurt-Münster (BFM) study group, which consist of 6 to 9 months of intensive induction/consolidation/delayed intensification therapy, followed by prolonged maintenance. Some pediatric groups in the United States use strategies that differ from BFM-based therapy, but continue to rely on nonmyelosuppressive chemotherapy as a backbone of treatment.[9,10] In contrast, "adult" regimens for ALL have historically consisted of intensive use of myelosuppressive agents including daunorubicin, cytarabine, and cyclophosphamide, as well as allogeneic stem cell transplant in first remission (complete remission 1 [CR1]).[12-14]

It has been over a decade since the first observational retrospective studies demonstrated that older adolescents and young adults (AYAs; currently considered to be patients aged 15-39 years old at diagnosis) with ALL fare significantly better following the "pediatric" approach compared with the "adult" approach.[15,16] This finding, reproduced worldwide, ushered in a novel field of oncology (AYA oncology), and catalyzed a number of prospective clinical trials testing the feasibility and outcome of delivering the pediatric ALL regimen to adults (predominantly younger adults) in the adult oncology setting. In the United States, the adult cancer cooperative groups conducted CALGB 10403, a prospective phase 2 trial evaluating a pediatric ALL regimen previously used by the COG in high-risk children.[6,17] From 2007 to 2012, 318 young adults (aged 17-39 years; median, 24 years) with newly diagnosed Ph^- B- or T-ALL were enrolled in the clinical trial across 70 adult cancer sites. Compared with the historical 3-year overall survival (OS) of 58% (95% confidence interval [CI], 52%-64%) for young adults treated on previous CALGB ALL clinical trials, the 3-year OS of 73% (95% CI, 68%-78%) for young adults treated on CALGB 10403 was a striking improvement. Similarly, the 3-year disease-free survival (DFS) was significantly higher than the historical rate (66% [95% CI, 60%-72%] vs 48% [95% CI, 41%-55%]). Patients with B- and T-ALL fared equally well and no significant differences in outcomes were observed by decade of age. Interestingly, of the pretreatment variables examined, only obesity (hazard ratio, 1.82; $P = .04$) and aberrant *CRLF2* (hazard ratio, 2.84; $P < .001$), a commonly involved gene in Ph-like ALL, were independently associated with inferior DFS.

In addition to the US report, several cooperative groups around the world have published results of pediatric regimens administered to adults with ALL in the adult oncology setting (Table 2). The European Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) conducted 2 consecutive trials incorporating the pediatric approach to therapy for adults with ALL up to the age of 55 to 60 years.[18,19] In the larger of the 2 studies, GRAALL-2005, the estimated 2-year event-free survival (EFS) rate of 65.1% (95% CI, 60.5%-69.3%) and the 2-year OS rate of 74.3% (95% CI, 70.0%-78.1%) for patients ≤39 years were similar to the US 10403 results.[18] However, the GRAALL trials also found that toxicity increased and survival dropped in adults over 45 to 55 years, potentially limiting the applicability of this approach to older adults. However, the Dana-Farber Cancer Institute (DFCI) conducted a prospective, multicenter study of a DFCI pediatric consortium regimen with dose-adjusted asparaginase intensification in adults up to age 50 years and found this approach to be tolerable, with similar outcomes in patients across the age spectrum.[20] The Nordic and Baltic groups (NOPHO) took a slightly different approach and treated all newly diagnosed ALL patients aged 1 to 45 years on the same pediatric protocol (NOPHO ALL2008), with pediatric and adult oncologists working together to apply this universal protocol.[21] Although the adolescent and adult groups did not fare quite as well as young children on this protocol, the estimated 5-year EFS (74% ± 4%) and DFS (78% ± 3%) for the adult cohort were nonetheless impressive.

It is important to note that none of the prospective cooperative group studies were designed to test the pediatric regimen directly against adult ALL regimens in a randomized fashion, and comparisons currently rely on historical control data. However, it is striking that these multicenter studies have all reported superior outcomes with the pediatric regimen relative to similar, although not identical,

Table 2. Summary of prospective trial results of the pediatric regimen in adolescent and adult ALL

Trial	Description	No. evaluable	Participant age, y	EFS, % (95% CI)	OS, % (95% CI)
CALGB 10403[6]	Phase 2 single-arm multicenter trial conducted by the US adult cooperative groups using a pediatric regimen based on COG AALL0232	295	17-39	3 y, 59 (54%-65%)	3 y, 73 (68%-78%)
DFCI 01-175[20]	Multicenter trial conducted in the United States and Canada utilizing a pediatric-inspired regimen	92	18-50	4 y, 58 (47%-68%)	4 y, 67 (56%-76%)
GRAALL-2003[19]	Phase 2 multicenter trial conducted by the GRAALL adult cooperative group across France, Belgium, Switzerland evaluating a pediatric-inspired regimen	225	15-60	3.5 y, 55 (48%-62%)	3.5 y, 60 (53%-66%)
GRAALL-2005[18]	Multicenter successor trial of GRAALL-2003; included a randomization to standard or hyperfractionated cyclophosphamide	787	18-59	5 y, 52.2 (48.5%-55.7%)	5 y, 58.5 (54.8%-61.9%)
PETHEMA ALL-96[55]	Multicenter trial conducted by the Spanish adult cooperative group utilizing a common pediatric regimen in adolescents and young adults with SR ALL	81	15-30	6 y, 61 (51%-72%)	6 y, 69 (59%-79%)
MDACC[24]	Single-center trial conducted by MDACC evaluating an augmented BFM pediatric regimen	106	13-39	Not provided	5 y, 60%
NOPHO ALL2008[21]	Multicenter protocol conducted by the Nordic cooperative group evaluating a common pediatric regimen across children, adolescents, and adults	221*	18-45	5 y, 74% ± 4%†	5 y, 78% ± 3%†

GRALL, Group for Research on Adult Acute Lymphoblastic Leukemia; MDACC, MD Anderson Cancer Center; No., number; NOPHO, Nordic Society of Pediatric Hematology and Oncology; PETHEMA, Programa Español de Tratamiento en Hematología; SR, standard risk.
*A total of 1509 participants were reported, including children and adolescents; the table describes results for the 221 young adults.
†95% CI provided in a different format (as reported in the referenced article).

historical patient populations treated on adult cooperative group protocols. It is hypothesized that the improved results of these modern multicenter adult ALL trials are due to the pediatric regimen itself. It is possible that additional etiologies may also contribute, such as improvements in clinician/investigator compliance with the study regimen, a greater focus on AYAs in oncology and their unique characteristics and needs, and greater patient protocol and medication adherence, although these theories are currently untested. There are also data to suggest that the pediatric regimen may offer additional benefits, such as fewer late occurring health complications, including retained fertility, and less cost to the health care system, although additional investigation and reporting are required on these topics.[22,23]

In contrast to the study results detailed in the previous sections, in a single-center prospective study, the MD Anderson Cancer Center (MDACC) reported outcomes of a cohort of AYAs treated with an augmented BFM pediatric regimen at their center, and found that outcomes were not significantly different between this approach and their previous hyperfractionated cyclophosphamide, vincristine, Adriamycin, dexamethasone (hyper-CVAD) experience.[24] In this report, the 5-year OS for AYAs was 60% with BFM and 60% with hyper-CVAD, and the 5-year continuous complete remission rates were 53% and 55%, respectively. Toxicity profiles differed by approach, with asparaginase-related adverse events (hepatotoxicity, pancreatitis, thrombosis) in the BFM group and significantly greater myelosuppression-associated complications, including grade 3 infections, in the hyper-CVAD group (45% vs 22%; $P < .001$). Although results with hyper-CVAD in young adults at MDACC are very encouraging, other groups have not consistently replicated these outcomes and there is concern that this regimen alone, which typically does not incorporate asparaginase, may be insufficient for subtypes of T-ALL.[25,26] Given that there is unlikely to be a randomized comparison of these approaches in adult ALL, it is advised that adult ALL patients receive frontline therapy at centers experienced with ALL therapies and that the therapeutic regimen reflect the center's expertise. Furthermore, as clinical trial results and real-world outcomes are not always aligned, it is important that population-based studies are conducted in this population to ensure that the clinical trial results are truly translating into improvements in ALL outcomes.

Toxicities associated with the pediatric regimen in adult ALL

Although the pediatric regimen is generally well tolerated in adults with a treatment-related mortality of <5% reported in patients under 45 years of age,[6,20,21] select regimen-related toxicities are more prevalent in adults relative to young children. The most direct comparison of toxicities across the age spectrum comes from the NOPHO ALL2008 protocol, in which patients between the ages of 1 and 45 years received an identical risk-adapted pediatric ALL regimen.[21] Although the incidence of asparaginase-related anaphylactic reactions was significantly lower in adults than young children (5.2% vs 14.5%; $P < .001$), thrombosis was much more common in adults than children (17.5% vs 3.6%; $P < .001$), as were pancreatitis (11.3% vs 5.9%; $P < .001$) and osteonecrosis (8.5% vs 2.3%; $P < .001$). Both thrombosis and hepatotoxicity were also noted to be more common toxicities in the CALGB 10403 young adult population than in the COG AALL0232 pediatric population, despite the

use of a similar pediatric regimen.[6] It was also striking that 30% of the young adults enrolled in CALGB 10403 were obese based upon body mass index, and not only did these patients have inferior DFS, but obesity may have exacerbated the excess hepatic, hyperglycemic, and thrombotic toxicities seen in these patients. As mentioned previously, treatment-related morbidity and mortality also appear to increase when the pediatric regimen is applied to patients over 50 years of age; this approach should therefore be limited to adults younger than 45 to 50 years or in the context of a clinical trial in older adults.[18,19]

Many of the toxicities observed in the pediatric-based regimens, such as hepatotoxicity, thrombosis, and pancreatitis, have been associated with asparaginase. However, it is well established that asparaginase is an integral component of pediatric-based treatment and several approaches have been incorporated to attempt to mitigate asparaginase-related toxicities and allow for continued use of asparaginase throughout therapy. Importantly, a peg-asparaginase dose of 2500 IU/m^2 is used most commonly in pediatric regimens, but pharmacodynamic studies have shown that doses of 1000 to 2000 IU/m^2 may be sufficient to achieve adequate asparaginase depletion.[21,27] Therefore, several groups are using lower doses of peg-asparaginase (1000 IU/m^2)[21] and/or capping the dose of peg-asparaginase at 3750 IU (1 vial) and following asparagine depletion or activity levels, which is the strategy in the currently enrolling US AYA ALL adult cooperative group trial A041501 (NCT03150693). Whether these dose adjustments will lead to increased tolerability and decreased toxicity in adult ALL has not yet been established.

Additional strategies to prevent asparaginase-related complications have been described. Although some clinicians may attempt to prevent thrombosis through prophylactic anticoagulation and repletion of hypofibrinogenemia, data are limited to support the efficacy of these approaches.[28] Recent reports suggest monitoring and repletion of antithrombin III may decrease the risk of thrombosis in adults treated with asparaginase,[29,30] but further study is needed. Interest in L-carnitine, an amino acid derivative compound that promotes mitochondrial β-oxidation of long-chain fatty acids, has grown, following case reports of rapid reversal of hepatotoxicity following administration of this compound[31]; a randomized trial of L-carnitine to prevent asparaginase-induced hepatotoxicity is being planned (W. Stock, University of Chicago, oral communication, 30 June 2019). Finally, although hypersensitivity reactions to asparaginase are not as common in adults as in children, hypersensitivity may be associated with the development of neutralizing antibodies rendering asparaginase ineffective. A premedication strategy of diphenhydramine, hydrocortisone, and acetaminophen prior to each peg-asparaginase dose was introduced into CALGB 10403 after hypersensitivity reactions were seen early on in the study; this intervention reduced the incidence of grade 3/4 hypersensitivity to 4% in subsequent patients.[6] Therapeutic monitoring of asparaginase activity levels should be strongly considered in patients receiving premedications to ensure adequate asparagine depletion, as the development of silent inactivation due to neutralizing antibodies may not be clinically evident. Patients who experience anaphylaxis following peg-asparaginase should not be rechallenged and should be switched to an *Erwinia* asparaginase formulation. In contrast, as described in the clinical case in this article, many of the asparaginase-associated toxicities, including hepatotoxicity, are most commonly self-limiting and should not preclude additional use of this agent.

Clinical case, part 3: response assessment

Following induction and hematopoietic recovery, a bone marrow examination was performed that demonstrated a normocellular marrow with trilineage hematopoiesis and no morphologic evidence of leukemia. Flow cytometry performed at the treating university's hematopoathology laboratory demonstrated no evidence of leukemia (sensitivity of 0.01%) and minimal residual disease (MRD) by NGS demonstrated zero cells remaining of the original leukemia's T-cell receptor (TCR) clonal sequence (sensitivity of 0.0001%). The patient was evaluated by a hematopoietic cell transplantation (HCT) specialist, and a decision was made to pursue consolidation and maintenance therapy following CALGB 10403 rather than HCT in first remission (CR1); he and his 1 full biological sibling did undergo HLA typing and his sibling was haploidentical.

MRD assessment in adults receiving the pediatric regimen

Assessment of MRD response following frontline therapy should be performed in all ALL patients, regardless of patient age or the frontline regimen used. It has been shown repeatedly that the presence of MRD following pediatric induction therapy and persistent MRD following pediatric consolidation is an incredibly important prognostic feature in both children and adults receiving the pediatric regimen.[32] The options for MRD evaluation include multiparameter flow cytometry, NGS, and quantitative polymerase chain reaction; expert consensus recommendations conclude that regardless of methodology, a sensitivity of at least 10^{-4} is required for adequate MRD assessment in ALL.[33] Relative to multiparameter flow cytometry, detection of ALL MRD by NGS evaluating clonal immunoglobulin heavy chain and/or TCR gene rearrangements provides a higher analytic sensitivity (10^{-6}) and a lower false-negative rate in childhood ALL[34]; additional investigation is needed to ascertain whether MRD of $<10^{-4}$ offers enhanced prognostic discrimination in adult ALL.

MRD quantification by polymerase chain reaction for clonal immunoglobulin H/TCR rearrangements was performed in 80 young adult patients on the CALGB 10403 study.[6] Thirty-five (44%) had undetectable MRD at the end of induction; this MRD$^-$ group had an excellent 3-year DFS of 85% (95% CI, 74%-98%). Forty-two (53%) had detectable MRD at $>10^{-4}$ and their 3-year DFS of 54% (95% CI, 41%-71%) was significantly worse. Although persistent MRD retained prognostic utility in young adults treated with the pediatric regimen, the rate of end-induction MRD detection was higher in this young adult population than is typically seen in childhood ALL. This suggests that adults with persistent MRD detection may benefit from targeted consolidation therapies to abolish MRD, such as blinatumomab, which was recently approved by the US Food and Drug Administration for MRD$^+$ B-ALL in adults.[35,36] Additional intensification with allogeneic HCT has shown benefit for adults with persistent MRD following pediatric-inspired induction, and should be offered to appropriate adult patients with persistent MRD following pediatric or adult ALL regimens.[37] Outcomes following HCT are also superior if patients enter HCT with low or absent MRD[38-40]; therefore, if feasible, MRD clearance prior to HCT is preferred. Additional investigations are required to determine whether HCT is necessary for all adult patients with CR1, MRD$^+$ ALL after clearance of MRD with novel therapies. In the absence of very high-risk features or persistent MRD, allogeneic HCT in CR1 should not routinely be offered to adults receiving the pediatric regimen; therefore, our case patient with T-ALL without high-risk features and in MRD$^-$ CR1 was appropriately guided to continue the pediatric regimen through completion of maintenance therapy.

Clinical case, part 4: completion of the pediatric regimen

The patient tolerated the consolidation, interim maintenance, and delayed intensification courses of the pediatric regimen well and was hospitalized only once, briefly, for neutropenic fever; the remainder of his care was delivered in the outpatient setting. He received all scheduled intrathecal therapies and his treatment team recommended against prophylactic cranial irradiation therapy (CRT). He returned to his legal practice at the beginning of maintenance therapy and subsequently completed 3 years of 6-MP, vincristine, methotrexate, prednisone maintenance. Following completion of maintenance, he was referred to a cancer survivorship specialist and received a comprehensive survivorship care plan.

Prophylactic cranial irradiation and the pediatric regimen

Prevention of CNS relapse is an extremely important component of all pediatric ALL regimens, and typically includes aggressive and prolonged delivery of intrathecal as well as systemic therapeutics that cross the blood-brain barrier. Relative to B-ALL, patients with T-ALL have a higher frequency of CNS involvement, are more likely to experience relapse in the CNS, and are more difficult to salvage upon relapse. Therefore, some protocols additionally require prophylactic CRT for patients with T-ALL, but there is no consistent practice across clinical trials. For example, CALGB 10403 included prophylactic CRT for T-ALL to be delivered during the first cycle of maintenance therapy (as well as CRT for patients with CNS involvement at diagnosis); the NOPHO ALL2008 trial omitted CRT altogether.[6,21] The investigators at St. Jude's Children's Research Hospital have successfully omitted CRT in all children with newly diagnosed ALL, including those with T-ALL and other high-risk features.[41] The CALGB 10403 regimen also included an interim maintenance course with Capizzi-style methotrexate (MTX), which includes escalating IV MTX plus peg-asparaginase. In recent COG studies, Capizzi-style MTX was shown to be potentially superior to high-dose MTX in children and younger adults with T-ALL[42] but inferior to high-dose MTX in patients with B-ALL.[17] In the absence of randomized data, systematic reviews and meta-analyses evaluating CRT in T-ALL may be informative,[43] and decision-making should be personalized and informed by interpretation of available data.

Optimal delivery of pediatric maintenance therapy in adult ALL

The final phase of treatment in the pediatric regimen consists of a prolonged maintenance course, typically 2 to 3 years in duration. During this time, ensuring adherence to therapy and achieving sufficient myelosuppression are critical. It has been shown that <90% adherence to the daily oral mercaptopurine (6MP) that is required throughout maintenance therapy is associated with a significantly increased risk of relapse in children.[44] Furthermore, an analysis of children and adolescents treated with methotrexate and 6MP maintenance therapy showed that mean WBC count, a surrogate for adherence and lack of adequate myelosuppression, was significantly correlated with risk of relapse.[45] Adherence to maintenance among young adults treated in adult cancer centers is unknown. As patient-reported compliance has been shown to be a poor surrogate for adherence to maintenance therapy, current efforts are under way to assess adherence in AYA ALL using MEMS TrackCap technology (NCT 03150693).

Patients should receive comprehensive survivorship care following completion of therapy. Although analyses of late complications and survivorship issues are beyond the scope of this article, a thorough review of these topics pertinent to young adult leukemia survivors is available.[46] Given the lower cumulative cyclophosphamide and doxorubicin dose equivalents with the pediatric regimen as opposed to a traditional adult ALL regimen, it is hypothesized that the incidence of infertility, cardiac complications, and therapy-related myeloid neoplasms may be lower in young adults treated with pediatric-based ALL therapy. Longer follow-up and careful study are required to determine whether the pediatric approach will in fact result in fewer late effects in adult ALL survivors.

The pediatric regimen in adult ALL: future directions

Based upon the data generated from observational studies and the more recent prospective clinical trials outlined in this review, the pediatric regimen has become an international standard of care in newly diagnosed younger adults with Ph^- ALL. The management of adult ALL has become increasingly complex, and there appears to be a learning curve associated with delivering the pediatric regimen in adult oncology clinics. Several population-based studies have demonstrated that outcomes for ALL patients are superior following treatment in comprehensive cancer centers.[47-49] Although this is not always feasible, efforts should be made to treat ALL patients in centers with disease expertise.

The use of the pediatric regimen in younger adult ALL has been a significant advancement for the field, but the currently reported survival rates are not good enough. The next frontier of ALL therapy includes a personalized approach intended to abolish MRD through the incorporation of novel targeted therapies into the frontline and/or MRD^+ settings (see Advani and Copelan[50] for a comprehensive review on novel agents and MRD-driven approaches in B-ALL). In brief, the US adult Intergroup is currently conducting Alliance 041501 (NCT 03150693), the successor trial to CALGB 10403, which is testing the incorporation of inotuzumab ozogamicin into the frontline setting for young adults with Ph^- B-ALL. This trial uses a similar therapeutic backbone to CALGB 10403 and also allows for the incorporation of rituximab in patients with $CD20^+$ ALL. Similarly, the ongoing Eastern Cooperative Oncology Group (ECOG) 1910 trial is evaluating blinatumomab in combination with frontline therapy combination chemotherapy in adult ALL (NCT 02003222). The ECOG 1910 trial incorporates components of the AYA regimen but with dose modifications of asparaginase and steroids in patients aged 55 years and older. The pediatric cooperative groups are developing studies of targeted immune and cellular therapies to eradicate MRD, and studies incorporating targeted kinase inhibitors into the pediatric regimen for Ph-like ALL are ongoing (NCT 03571321).

In T-ALL, the COG incorporated nelarabine into frontline pediatric ALL therapy in children and younger adults up to 30 years of age (COG AALL0434) and have shown that this strategy is safe and effective.[51,52] It is important to note that the dosing and schedule of nelarabine in AALL0434 followed pediatric dosing (650 mg/m^2 for 5 consecutive days), whereas adult dosing is typically 1.5 mg/m^2 on days 1, 3, and 5.[53] The MDACC also evaluated incorporating nelarabine into hyper-CVAD and found that this was feasible but did not lead to significant improvement in survival relative to historical controls.[54] Although nelarabine can be incorporated into the pediatric regimen when administered to adults, it has not been proven to improve outcomes in patients over the age of 30 years and the potential toxicities associated with this combination in adults have not been clearly defined. Additional approaches, such as small molecule inhibitors, antibody-based therapies such as daratumumab,

and cellular therapies are being studied for relapsed T-ALL and may ultimately be incorporated into frontline therapy.

Conclusion

The promise of pediatric-inspired regimens in adult ALL has been realized through concerted efforts among multiple international groups to conduct well-designed, prospective trials evaluating the feasibility and outcomes of this approach. The toxicity profile and survival benefits associated with the pediatric regimen demonstrate that this approach can be safely and effectively offered to adults up to the age of 50 years. There is still much room for improvement, but it is clear that incorporation of the pediatric regimen in adult ALL is bearing fruit for numerous adults with ALL around the world.

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