Review

Treating the younger adult with acute lymphoblastic leukemia

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Practice Points

- Older adolescents and young adults (AYAs) with acute lymphoblastic leukemia (ALL) have historically had worse outcomes when compared with younger children with ALL.
- Inferior outcomes of AYAs may be due to more high-risk, less favorable leukemia features as well as psychosocial complexities specific to this age group.
- Relative to traditional adult ALL protocols, pediatric ALL regimens employ higher cumulative doses of nonmyelosuppressive agents (e.g., asparaginase, vincristine and corticosteroids), earlier and more frequent CNS prophylaxis, and extended maintenance therapy.
- Multiple retrospective comparative studies have demonstrated a significant survival advantage for AYAs aged 15–21 years treated on pediatric compared with adult protocols.
- Prospective studies utilizing a true pediatric approach in young adult patients are demonstrating feasibility and encouraging improvements in disease-free survival.
- The role of allogeneic stem cell transplantation in first remission for young adults with standard-risk ALL remains unclear; however, with the improving outcomes using modern pediatric-inspired chemotherapy approaches, transplantation in first remission is not generally advised and should be reserved for patients with very-high-risk features who are transplanted in prospective studies.
- Awareness of treatment-related toxicities, treatment compliance, psychosocial and survivorship issues is of great importance when caring for the AYA patient.
- AYA patients with ALL, as well as treating physicians, should be strongly encouraged to enroll all ALL AYA patients in clinical trials.

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SUMMARY The past decade has witnessed an increasing awareness of older adolescents and young adults (AYAs) with acute lymphoblastic leukemia as a distinct group of patients, with outcomes historically inferior to those of younger children. Retrospective comparison studies of AYAs treated on pediatric or adult clinical trials have demonstrated significantly improved outcomes for AYAs treated in pediatric trials. These findings have spurred international interest in prospectively evaluating pediatric regimens in young adults, and early results from several of these trials are encouraging. Additional study dedicated to the leukemia biology and psychosocial factors unique to the AYA patient will add further insight and hopefully improve outcomes for AYAs with acute lymphoblastic leukemia.

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood, but is less common in adults. Success in the treatment of children aged 1–10 years with ALL has increased steadily, with long-term survival estimates of nearly 90% [1]. While the majority of children diagnosed with ALL can be cured, the prognosis of adults with ALL remains unsatisfactory: approximately 60% will ultimately die of the disease. At a crossroads between these groups is the adolescent and young adult (AYA) population, whose outcomes fall between those of younger children and older adults [2,3]. Recent data extracted from the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) database show that survival rates for AYAs with ALL have improved; however, they remain inferior to the excellent outcomes seen in children. From 2000 to 2004, the 5-year survival rate for children aged 10–14 years was >80%, whereas adolescents aged 15–19 years had a 5-year survival rate of 60%, which fell even further to 45% in young adults aged 20–29 years [2].

Definition of the age range that constitutes the AYA patient varies greatly. The NCI SEER database considers an AYA patient to be one who is diagnosed between 15 and 29 years of age [4], while the NCI's AYA Oncology Progress Review Group extends the AYA age range to 15–39 years. The retrospective comparison studies of AYAs with ALL described below mainly include patients diagnosed between 16 and 21 years of age, while prospective studies that utilize high-risk pediatric ALL regimens are testing this approach in adults up to the age of 40 years, and in some trials those up to 60 years of age.

It is likely that differing disease biology, therapeutic tolerance, clinical trial enrolment and psychosocial complexity all contribute to the observed outcomes of the AYA patient with ALL. This review highlights known biological and clinical features that may influence prognosis, advances in treatment strategies, potential complications, as well as promising new approaches to the treatment of ALL in the younger adult.

Prognostic features of ALL

ALL is a heterogeneous disease, with outcomes differing depending on various clinical and biological features. Of the many variables that influence prognosis, older age, elevated white blood cell count at diagnosis, failure to respond to initial induction therapy, early T-cell precursor immunophenotype and specific genetic abnormalities (including t[4;11][q21;q23] resulting in the *MLL–AF4* fusion gene, other *MLL* gene rearrangements and hypodiploid karyotype with <46 chromosomes) appear to be most important in characterizing disease risk. The presence of t(9;22)(q34;q11; Philadelphia chromosome [Ph+]) resulting in the *BCR–ABL1* fusion gene was previously associated with very poor outcomes; however, the recent addition of molecularly targeted therapy has improved the prognosis for Ph+ ALL [5]. The presence of minimal residual disease (MRD) determined by leukemia clone-specific quantitative PCR and/or flow cytometry during and following remission induction and consolidation therapy has important prognostic significance in both childhood and adult ALL. MRD assessment is now used in several clinical trials to define patients at increased risk for relapse who may benefit from treatment intensification and/or novel therapeutic approaches [6–8].

The impact of age on prognosis is due in part to the varying prevalence of genetic abnormalities present amongst different age groups.

Relative to children aged 1–9 years, AYAs tend to present with lower rates of favorable genetic abnormalities. Hyperdiploidy (defined by the presence of >50 chromosomes) is present in 25% of childhood and 4–5% of adult ALL. The t(12;21)(p13;q22)(*ETV6–RUNX1*) is frequent in younger children, and extremely rare in adults [9]. Conversely, the incidence of Ph+ ALL is lower in children (2–4%) than in adults (20–25%) [10].

More recently, the application of microarray-based gene expression profiling has yielded new insights into the pathogenesis and biology of ALL. For example, genome-wide studies in precursor B-cell ALL have identified deletions or sequence mutation of the *IKZF1* gene, encoding the early lymphoid transcription factor IKAROS, to be associated with very poor outcomes [11]. Deregulated expression of the *CRLF2* gene has been identified in high-risk ALL, and *CRLF2* overexpression is frequently associated with activating mutations of *JAK1* or *JAK2* and deletion or mutations of *IKZF1* [12,13]. Similar to B-cell ALL, translocations involving transcription factors are common in T-cell ALL; the most commonly involved genes include *HOX11* and *HOX11L2*. Activating mutations of the *NOTCH1* gene are detected in nearly half of T-cell ALL cases, and may be associated with a favorable prognosis [14].

Treatment of ALL in children & adults

In order to understand the following sections describing the treatment of the AYA patient with ALL, it is instructive to review the treatment strategies for ALL in children and adults. Pediatric ALL regimens were designed decades ago to include combinations of available antileukemic agents delivered over multiple extended phases of therapy. Similar approaches were adapted for adult ALL; however, the empiric drug combinations and schedules in multistep ALL regimens used for children and adults have evolved in different ways.

The treatment of ALL begins with remission induction, which consists of multidrug induction regimens that typically utilize three to four agents (glucocorticoids, vincristine, anthracycline and L-asparaginase). With these agents, complete remission (CR) can be achieved in >98% of children, and 90% of adults [15]. The addition of L-asparaginase clearly has improved outcomes in pediatric ALL trials; however, L-asparaginase has been under-used in adult ALL due to its unique toxicities (see below) and concerns regarding tolerance in adults [16,17]. PEG-asparaginase, a modified form of *Escherichia coli* asparaginase with a longer serum half-life and a reduced risk of hypersensitivity, has replaced native asparaginase in several protocols. In hopes of further improving disease-free survival (DFS), adult protocols have attempted to further intensify induction regimens with additional myelosuppressive agents, such as cyclophosphamide, cytarabine and high-dose anthracyline; however, these strategies have not clearly shown a survival benefit and are associated with greater toxicity [18,19].

Once normal hematopoeisis has been restored, patients in remission proceed to risk-adapted postremission therapy. This typically includes consolidation/intensification therapy followed by long-term maintenance and CNS prophylaxis. The Berlin–Frankford–Muenster (BFM) group initially demonstrated that the use of an intensive induction, consolidation and delayed intensification phase for children with ALL produced a cure rate of approximately 70% [20]. Subsequent pediatric cooperative group trials have successfully refined the BFM backbone with augmentation of the delayed intensification phase, addition of an interim maintenance phase and a reduction in the number of children receiving cranial irradiation. These strategies, which are focused on intensive and extended use of glucocorticoids, vincristine and L-asparaginase (or PEG-asparaginase) – the 'core' drugs – have resulted in curing the vast majority of children with ALL [21–23]. Although intensification is favored in adults as well, there have been doubts regarding the feasibility of prolonged intensified consolidation in adults because of greater toxicity and poorer compliance [23]. In general, the cumulative dose of glucocorticoids, L-asparaginase and vincristine is lower in adult protocols, and overall survival (OS) in adults remains at only 35–40%.

Therapy aimed at preventing CNS relapse is a crucial component of treatment. Intrathecal therapy begins during induction and continues throughout the therapeutic course. Systemic agents with CNS penetration are not as crucial for CNS prophylaxis. The COG 0232 trial randomized children and young adults up to the age of 30 years with high-risk ALL to receive high-dose methotrexate versus Capizzi

escalating methotrexate plus PEG-asparaginase during interim maintenance, and demonstrated an improved 5-year event-free survival (EFS) in favor of high-dose methotrexate (82 vs 75.4%; p = 0.006), with fewer marrow and CNS relapses [24]. It has not yet been reported whether the benefit was seen in the subset of young adults included in this study. Finally, 2–3 years of maintenance therapy with low-dose antineoplastic agents (daily mercaptopurine and methotrexate, sometimes with pulses of steroids and vincristine, adjusted to achieve optimal yet safe myelosuppression), is administered to eradicate MRD. The incorporation of long-term maintenance therapy for adults derives from the benefit seen in pediatrics, and has not been prospectively evaluated in adults. However, two different adult cooperative group studies that omitted maintenance therapy reported clinically inferior outcomes [25,26].

Several novel agents show considerable promise in relapsed or refractory Ph^- ALL, and are now being evaluated in the upfront setting in both children and adults. The purine nucleoside analog clofarabine showed 30% response rates in relapsed/refractory ALL in children, and is now US FDA approved for this indication, with data emerging regarding the use of clofarabine in adult ALL [27,28]. Nelarabine, a synthetic purine analog, was FDA approved for relapsed T-cell ALL in 2006 after both COG and Cancer and Leukemia Group B (CALGB) trials demonstrated single-agent CR rates of approximately 30% [29,30], and it is now being included in front-line cooperative group trials of T-cell ALL. The CD22 antibody–drug conjugate inotuzumab ozogamicin and the bi-specific T-cell engager blinatumomab have demonstrated remarkable single-agent activity in relapsed or refractory ALL [31–33].

Outcomes for Ph^+ ALL have improved substantially with the introduction of the tyrosine kinase inhibitor (TKI) imatinib [34]. Owing to the emergence of imatinib resistance, second-generation TKIs such as dasatinib are being studied as single-agent therapy, as well as in combination with chemotherapeutics, with very promising early results [5,35]. Allogeneic stem cell transplantation in first remission had been the standard of care for Ph^+ ALL in adults, as well as children. This approach is being challenged by recent studies suggesting that transplant may not offer additional benefit over TKIs and intensive chemotherapy [36].

AYAs with ALL

Because an AYA patient may be viewed as either an older child or a younger adult, AYAs have historically been treated on either pediatric or adult ALL protocols. The type of treatment was typically determined by the population most often seen by the treating pediatric or adult oncologist. Additionally, AYAs are not enroling on clinical trials at the same high rates as children in the USA; it has been estimated that only 10% of patients aged 15–19 years and 1–2% of patients aged 20–39 years are enrolled on clinical trials [37]. A number of comparisons of the clinical outcomes of AYAs enrolled on adult and pediatric ALL clinical trials have resulted in interesting observations regarding the most effective treatment regimens for this population and, for the first time, have guided the development of prospective clinical trials designed specifically for AYAs with ALL.

■ Evidence supporting improved outcomes for AYAs treated on pediatric versus adult cooperative group trials

Table 1 summarizes the results of retrospective studies performed by various cooperative groups around the world, describing the outcomes of AYA patients treated on contemporaneous pediatric or adult cooperative group trials. In the USA, the CALGB and the Children's Cancer Group (CCG) evaluated 321 AYA patients aged 16–20 years treated on consecutive pediatric and adult trials between 1988 and 2001 [38]. Although the age range was the same for both groups examined, the median age of the patients in the CALGB studies was 19 years compared with 16 years in the CCG studies. The groups were well matched for biological features, including cytogenetics and immunophenotype. Although CR rates were 90% for both groups, 7-year EFS and OS rates favored AYAs treated on the CCG protocols (EFS: CCG 63 vs CALGB 34%; p < 0.001; OS: CCG 67 vs CALGB 46%; p < 0.001). CNS relapse was also significantly lower in the AYAs treated on CCG protocols (1.4%) compared with CCG (11%; p < 0.001). In comparing the treatment regimens, CCG patients received more treatment with nonmyelosuppressive agents (glucocorticoids, vincristine and L-asparaginase), had earlier and more intensive administration of CNS prophylaxis and continued maintenance (with adjustments to achieve continued

Table 1. Retrospective comparison studies of adolescents and young adults treated on pediatric and adult cooperative group trials.

Study	Protocol type	Subjects evaluated (n)	CR rate (%)	EFS† (%)	OS† (%)	Ref.
Stock *et al.* (USA) (2008)						[38]
CALGB	Adult	124	90	34	46	
COG	Pediatric	197	90	63	67	
Boissel *et al.* (France) (2003)						[39]
LALA-94	Adult	100	83	41	45	
LALA-93	Pediatric	77	94	67	78	
De Bont *et al.* (The Netherlands) (2005)						[40]
HOVON	Adult	73	91	34	38	
DCOG	Pediatric	47	98	69	79	
Ramanujachar *et al.* (UK) (2007)						[41]
UKALLXII/E2993	Adult	67	94	49	56	
ALL97	Pediatric	61	98	65	71	
Usvasalo *et al.* (Finland) (2008)						[43]
Finnish Leukemia Group	Adult	97	97	60	70	
NOPHO	Pediatric	128	96	67	77	

†EFS and OS are 5-year estimates except in the US study in which EFS and OS are 7 years.
CR: Complete remission; EFS: Event-free survival; OS: Overall survival.

myelosuppression) for a longer duration. Each of these differences likely contributes in part to the favorable outcomes seen in the AYAs treated on the pediatric protocols.

Subsequent to the initial report from the CALGB/CCG, similar results were also reported by several European groups [39–43]. Despite considerable differences in the treatment schedules and regimens, the outcome data are remarkably similar to those in the above study, showing improved outcomes for AYAs treated on pediatric as compared with adult protocols. Similar to the CALGB–CCG comparison, the pediatric protocols evaluated in these studies utilized higher cumulative doses of nonmyelosuppressive agents, in addition to intensive CNS prophylaxis. A retrospective comparison study reported from Finland contrasted with these results [43]. This study found no difference in 5-year EFS (67% for those treated on pediatric protocols vs 60% for those treated on adult protocols; p = not significant) or in OS (77% for the pediatric group vs 70% for the adult group; p = not significant). However, the doses of nonmyelosuppressive agents did not appear to differ between the pediatric and adult protocols that were compared in this study, which may explain the lack of difference in outcomes observed. Additional potential explanations for the differing outcomes of the above pediatric and adult trials have been proposed [44,45]. ALL is the most common malignancy of childhood, yet a rare disease in adults. Therefore, children with ALL are almost always referred to highly experienced pediatric centers and treated on clinical trials, whereas adults are less frequently treated on trials, and adult oncologists and their staff are often less familiar with the complex regimens used to treat ALL. Patient-specific factors may also be important, such as protocol compliance and follow-up, stable insurance and prescription drug coverage, and psychosocial complexities experienced by young adults as they transition away from living with their family to a more independent lifestyle. In addition to the retrospective comparison studies discussed above, two recent retrospective reports from pediatric cooperative groups have demonstrated that older AYAs up to 21 years of age have favorable outcomes when treated on contemporary pediatric protocols. In a subset analysis, the Dana–Farber Cancer Institute (DFCI) ALL Consortium compared the outcomes of older adolescents aged 15–18 years, with younger children treated on two consecutive DFCI-ALL Consortium protocols between 1991 and 2000, and found that the older adolescents had a 5-year EFS of 78%, which was not significantly inferior to the 5-year EFS of 85% seen in younger

children (p = 0.09) [46]. However, numbers of patients were small; the Children's Oncology Group also performed a subset analysis of 262 young adults aged 16–21 years, enrolled on the CCG 1961 study between 1996 and 2002 [47]. This trial randomly assigned therapies to evaluate the impact of postinduction treatment intensification on outcome. The 5-year EFS and OS for the AYA patients were 71.5 and 77.5%, respectively, which was favorable in comparison to the 5-year EFS seen in their previous young adult cohort [48]. Young adults appeared to have better outcomes with augmented intensity therapy, although the trial was not powered to adequately assess survival differences in young adults by treatment regimen.

Prospective trials examining pediatric regimens in young adults with ALL

The recognition of superior outcomes for AYAs treated on pediatric protocols has led to cooperative group clinical trials designed to prospectively evaluate the use of pediatric-inspired protocols in adults. The results of several of these studies have been recently reported, and are summarized in **Table 2**.

The Program Español de Tratamiento en Hematología (PETHEMA) protocol ALL-96 evaluated the use of a pediatric-based protocol in 35 adolescents aged 15–18 years and 46 young adults aged 19–30 years with standard-risk ALL [49]. This protocol included a five-agent induction, early consolidation and maintenance that included monthly reinforcement cycles for 1 year followed by standard maintenance for up to 2 years following CR. At a median 4.2 years of follow-up, the 6-year EFS and OS for the entire group were 61 and 69%, respectively, with no differences in outcomes seen between the two age groups. The only parameter that demonstrated prognostic significance was rapid versus slow response to therapy (>10% blasts on day 14 induction of bone marrow aspirate).

In the French GRAAL-2003 study, 225 adults aged 15–60 years old with Ph^- ALL were treated with a pediatric-inspired regimen, with the option for stem cell transplant for high-risk patients [50]. After censoring the 71 patients who received a transplant in first CR, 42-month EFS and OS were 55 and 60%, respectively, which compared favorably to Ph^- patients treated on their previous ALL adult trial, LALA-94, in which EFS and OS were 33 and 41%, respectively [50]. Patients over the age of 45 years had increased morbidity and mortality, with a cumulative incidence of treatment-related death of 23%, prompting the authors to conclude that pediatric-inspired therapy markedly improves outcomes of adult ALL up until the age of 45 years. However, the protocol differed in several ways from typical pediatric regimens, as it did not include the same dose intensity of steroids, asparaginase and vincristine that are routinely used in current pediatric regimens, prophylactic cranial irradiation was routinely administered and allogeneic stem cell transplantation (allo-SCT) in first CR was frequently utilized. These important differences from true pediatric regimens make it difficult to interpret the contribution of the actual chemotherapy intensification to survival.

The Dutch recently published the results of their HOVON 70 prospective study, evaluating the use of the childhood FRALLE-93 regimen in younger adults [39,51]. Allo-SCT was offered in first remission for those with sibling donors or high-risk patients with HLA-matched unrelated donors. Fifty four patients were enrolled, with a median age of 26 years (range: 17–39 years). Grade 3–4 infections were frequent (40% in induction and consolidation), with three deaths attributed to toxicity. With a median follow-up of 32 months, the estimated 2-year EFS and OS for the entire group were 66 and 72%, respectively. After censoring the 19 patients who underwent allo-SCT, the 2-year EFS and OS of the chemotherapy-treated only patients were 73 and 80%, respectively. The authors concluded that the pediatric approach appeared feasible and encouraging in adults up to age 40 years, and have initiated a Phase III trial.

The DFCI Consortium has also conducted an exploratory Phase II study, extending their successful high-risk pediatric ALL regimen to older patients without the routine recommendation for allo-SCT in first CR [52]. Early results for 75 patients with a median age of 28 years (range: 18–50 years) have been reported. The induction CR rate was 84%. At the median 15.3-month follow-up, the estimated 2-year EFS versus 2-year OS was 72.5 and 77.1%, respectively.

The largest prospective trial evaluating the use of an intensive pediatric regimen in young adults with ALL treated by adult hematologists/oncologists is ongoing in the USA (CALGB 10403). This is a prospective Phase II trial that is currently enrolling young adults between the ages

Table 2. Results of published prospective trials using pediatric-inspired acute lymphoblastic leukemia regimens in young adults.

Group/study	Age range (years)	Subjects evaluated (n)	Protocol elements	Reported outcomes	Ref.
PETHEMA ALL-96 (2008)	15–30	81	Five-drug induction followed by two cycles of early consolidation, maintenance with monthly reinforcement cycles for 1 year following remission and standard maintenance chemotherapy for up to 2 years following CR	2-year EFS: 72.5% 2-year OS: 77.1%	[49]
GRAAL-2003 (2009)	15–60	225	Five-drug induction, dose-intense consolidation, delayed intensification and 2-year maintenance therapy. Allo-SCT for patients <55 years was recommended	42-month EFS: 55% 42-month OS: 60%	[50]
HOVON 70 (2011)	17–39	54	7-day prednisone pre-phase followed by multiagent induction, consolidation, two intensification courses, and 2 years of maintenance. Allo-SCT in first remission recommended	2-year EFS: 66% 2-year OS: 72%	[51]
DFCI (2007)	18–50	75	Multiagent induction, intensification of nonmyeloablative agents (especially asparaginase), early and frequent intrathecal therapy, 2 years of maintenance following CR	2-year EFS: 72.5% 2-year OS: 77.1%	[52]

Allo-SCT: Allogeneic hematopoietic stem cell transplantation; CR: Complete remission; EFS: Event-free survival; OS: Overall survival.

of 16 and 39 years, utilizing one treatment arm of a Children's Oncology Group protocol previously used in adolescents and high-risk children. The study has now accrued more than 250 of the anticipated 300 patients [Stock W, Pers. Comm.]. In addition to examining the safety and the ability to administer intensive therapy in a timely manner, this study is prospectively evaluating several issues such as molecular genetics, MRD, psychosocial and socioeconomic disparities, and treatment adherence, which may be of particular relevance to the young adult population. The results of this large multicenter trial should provide key insights into the feasibility of adopting a pediatric treatment approach to AYAs with ALL, as well as into various biological and psychosocial factors that may be linked to outcomes of AYA patients.

Role of allogeneic stem cell transplantation

The optimal role of allo-SCT for the AYA is an area of ongoing controversy. The option for allo-SCT in first remission has been used more frequently in prospective adult trials than in pediatric protocols, where excellent outcomes are achieved for most patients with chemotherapy alone. The use of stem cell transplantation in pediatric centers is frequently dictated by the presence of MRD [47,48]. The largest prospective study to evaluate the role of allo-SCT in first remission was the International Medical Research Council UKALL XII/Eastern Cooperative Oncology Group (ECOG) E2993 trial, in which all patients aged 15–55 years with an HLA-matched sibling donor were assigned to receive a myeloablative allo-SCT in first complete remission, whereas those without a compatible sibling donor were randomized to receive either autologous stem cell transplantation or prolonged chemotherapy [53]. This trial enrolled 234 patients under the age of 20 years, and 301 patients between the ages of 20–29 years. A significant OS benefit in favor of allo-SCT was seen only in those with standard-risk disease (5-year OS: 62% for allo-SCT vs 52% in those lacking a donor; $p = 0.02$), defined as <35 years of age with no adverse biological features. The 5-year OS for the overall group of patients aged 15–29 years was 45%. Although these results suggest that allo-SCT in first remission may be superior in young adults without adverse biological risk factors, the survival rates seen with all postremission therapy arms in this study appear inferior to outcomes currently reported for AYAs receiving pediatric-inspired regimens. Further study will be necessary to determine the evolving role of allo-SCT for the AYA patient, including which subset of patients appear to gain the most benefit in the context of increasing utilization of pediatric approaches for young adults.

Treatment-related complications & survivorship care

The improved disease control seen with pediatric regimens may come at a cost for young adults, namely increased treatment-related toxicities. The key component that contributes to the success of the pediatric regimen is the intensified use of asparaginase/PEG-asparaginase, glucocorticoids and vincristine, with each presenting a unique set of potential toxicities.

Asparagine depletion has been associated with multiple serious toxicities, including pancreatitis, hepatic dysfunction, thrombosis, hyperglycemia and hypersensitivity reactions. Although the asparaginase-associated toxicity profile seen in adults appears to be qualitatively similar to children, adults suffer from more grade 3–4 toxicities than children [54,55]. The incidence of asparaginase-associated thombotic complications is clearly age dependent [56]. A comprehensive set of recommendations regarding the prevention and treatment of asparaginase/PEG-asparaginase-associated toxicities in adults and older adolescents was recently published [55].

The intensive use of glucocorticoids in pediatric ALL regimens has been associated with significant rates of symptomatic osteonecrosis, particularly in adolescent females [57]. It has been suggested that rates of osteonecrosis are higher with dexamethasone as compared with prednisone-containing regimens, although this remains controversial [58]. Corticosteroid use is also associated with hyperglycemia, myopathies, and changes in body habitus and mood, all of which may have significant relevance to the daily functioning of the AYA patient.

Vincristine-related neuropathy is common, and may necessitate dose adjustment. Most studies cap individual vincristine doses at 2 mg but this may not be optimal for individual patients.

The diagnosis and treatment of ALL during adolescence or young adulthood may have a significant impact on the psychological and social functioning of the AYA patient. Loss of independence, treatment-related toxicities and effects on body habitus, financial issues and fear about the future can all negatively impact quality of life. Nonadherence to treatment regimens, as well as other components of treatment (e.g., keeping appointments, as well as refusing examinations and studies) is a particularly significant problem in AYA patients undergoing lengthy, complicated ALL therapies. Evidence from clinical trials including AYA patients with leukemia and lymphoma suggests that up to 63% of AYAs have difficulties adhering to oral treatment regimens [59,60]. Additionally, the successful treatment of ALL is associated with potential long-term complications, such as secondary neoplasms, chronic physical and mental health conditions, endocrine dysfunction and fertility issues, as well as late mortality [61]. Much of the understanding of late effects in AYA cancer survivors comes from the Childhood Cancer Survivor Study (CCSS), which included survivors diagnosed with cancer prior to age 21 years; however, no large cohorts have yet specifically addressed survivorship issues related to cancer diagnosed in young adults between the ages of 22 and 39 years. Given the paucity of literature on survivorship issues related to cancer diagnosed in young adulthood, the National Comprehensive Cancer Network (NCCN) has recommended that the findings of the CCSS focusing on survivors of childhood and adolescent cancer may be extrapolated to the survivors of AYA cancers, with some caution, and has documented recommended survivorship guidelines in the NCCN Guidelines for Adolescent and Young Adult Oncology [101].

Conclusion & future perspective

In summary, the past decade has witnessed significant advancements in the treatment of children with ALL, which are only beginning to be realized in the AYA population. The recognition that AYA patients have superior outcomes when treated on multiagent, intensive pediatric ALL regimens has prompted the development of prospective trials evaluating the safety, tolerability and outcomes of AYAs treated by adult oncologists on pediatric-inspired protocols. The role of allo-SCT continues to evolve and will likely be influenced by the results of these ongoing clinical trials. Further refinement of biological risk classification and MRD-based treatment intensification is under study. Promotion of clinical trial participation is recommended for all AYAs with ALL. It is likely that increased awareness and attention to patient compliance, treatment-related toxicities, psychosocial concerns and survivorship care will further improve outcomes. New insights into the biology of the disease will allow for improved prognostication of the AYA with ALL, and ultimately more effective novel therapies.

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References

Papers of special note have been highlighted as:

- ▪ of interest

1 Smith MA, Seibel NL, Altekruse SF *et al.* Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J. Clin. Oncol.* 28(15), 2625–2634 (2010).

2 Pulte D, Gondos A, Brenner H. Improvement in survival in younger patients with acute lymphoblastic leukemia from the 1980s to the early 21st century. *Blood* 113(7), 1408–1411 (2009).

- ▪ **Uses the Surveillance, Epidemiology and End Results database to assess trends in acute lymphoblastic leukemia (ALL) survival comparing 2000–2004 with 1980–1984, and found that survival for young adults has improved; however, to a lesser degree than the remarkable improvements in survival seen in young children over the same period of time.**

3 Pulte D, Gondos A, Brenner H. Trends in survival after diagnosis with hematologic malignancy in adolescence or young adulthood in the United States, 1981–2005. *Cancer* 115(21), 4973–4979 (2009).

4 Bleyer A, Viny A, Barr R. Cancer in 15- to 29-year-olds by primary site. *Oncologist* 11(6), 590–601 (2006).

5 Ravandi F, O'Brien S, Thomas D *et al.* First report of Phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. *Blood* 116(12), 2070–2077 (2010).

6 Coustan-Smith E, Sancho J, Hancock ML *et al.* Clinical importance of minimal residual disease in childhood acute lymphoblastic leukemia. *Blood* 96(8), 2691–2696 (2000).

7 Campana D, Coustan-Smith E. Minimal residual disease studies by flow cytometry in acute leukemia. *Acta Haematol.* 112(1–2), 8–15 (2004).

8 Raff T, Gokbuget N, Luschen S *et al.* Molecular relapse in adult standard-risk ALL patients detected by prospective MRD monitoring during and after maintenance treatment. Data from the GMALL 06/99 and 07/03 trials. *Blood* 109(3), 910–915 (2007).

9 Armstrong SA, Look AT. Molecular genetics of acute lymphoblastic leukemia. *J. Clin. Oncol.* 23(26), 6306–6315 (2005).

10 Advani AS, Hunger SP, Burnett AK. Acute leukemia in adolescents and young adults. *Semin. Oncol.* 36(3), 213–226 (2009).

11 Mullighan CG, Su X, Zhang J *et al.* Deletion of *IKZF1* and prognosis in acute lymphoblastic leukemia. *N. Engl. J. Med.* 360(5), 470–480 (2009).

12 Harvey RC, Mullighan CG, Chen IM *et al.* Rearrangement of *CRLF2* is associated with mutation of JAK kinases, alteration of *IKZF1*, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. *Blood* 115(26), 5312–5321 (2010).

13 Mullighan CG, Collins-Underwood JR, Phillips LA *et al.* Rearrangement of *CRLF2* in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia. *Nat. Genet.* 41(11), 1243–1246 (2009).

14 Ben Abdelali R, Asnafi V, Leguay T *et al.* Pediatric-inspired intensified therapy of adult T-ALL reveals the favorable outcome of *NOTCH1*/*FBXW7* mutations, but not of low *ERG*/*BAALC* expression. A GRAALL study. *Blood* 118(19), 5099–5107 (2011).

15 Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N. Engl. J. Med.* 354(2), 166–178 (2006).

16 Pession A, Valsecchi MG, Masera G *et al.* Long-term results of a randomized trial on extended use of high dose L-asparaginase for standard risk childhood acute lymphoblastic leukemia. *J. Clin. Oncol.* 23(28), 7161–7167 (2005).

17 Wetzler M, Sanford BL, Kurtzberg J *et al.* Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia. Cancer and Leukemia Group B Study 9511. *Blood* 109(10), 4164–4167 (2007).

18 Larson RA, Dodge RK, Burns CP *et al.* A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia. Cancer and Leukemia Group B Study 8811. *Blood* 85(8), 2025–2037 (1995).

19 Faderl S, O'Brien S, Pui CH *et al.* Adult acute lymphoblastic leukemia. Concepts and strategies. *Cancer* 116(5), 1165–1176 (2010).

20 Schrappe M, Reiter A, Zimmermann M *et al.* Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. Berlin–Frankfurt–Munster. *Leukemia* 14(12), 2205–2222 (2000).

21 Nachman JB, Sather HN, Sensel MG *et al.* Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. *N. Engl. J. Med.* 338(23), 1663–1671 (1998).

22 Seibel NL, Steinherz PG, Sather HN *et al.* Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood* 111(5), 2548–2555 (2008).

- ▪ **CCG-1961 study demonstrating that more intensive postinduction intensification improves outcomes for children and adolescents with high-risk ALL.**

23 Annino L, Vegna ML, Camera A *et al.* Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. *Blood* 99(3), 863–871 (2002).

24 Larsen EC, Salzer WL, Devidas M *et al.* Comparison of high-dose methotrexate (HD-MTX) with Capizzi methotrexate plus asparaginase (C-MTX/ASNase) in children and young adults with high-risk acute lymphoblastic leukemia (HR-ALL): a report from the Children's Oncology Group Study AALL0232. *J. Clin. Oncol.* 29(Suppl.), Abstract 3 (2011).

25 Cuttner J, Mick R, Budman DR *et al.* Phase III trial of brief intensive treatment of adult acute lymphocytic leukemia comparing daunorubicin and mitoxantrone. A CALGB Study. *Leukemia* 5(5), 425–431 (1991).

26 Dekker AW, Van't Veer MB, Sizoo W *et al.* Intensive postremission chemotherapy without maintenance therapy in adults with acute lymphoblastic leukemia. Dutch Hemato-Oncology Research Group. *J. Clin. Oncol.* 15(2), 476–482 (1997).

27 Advani AS, Gundacker HM, Sala-Torra O *et al.* Southwest Oncology Group Study S0530. A Phase 2 trial of clofarabine and cytarabine for relapsed or refractory acute lymphocytic leukaemia. *Br. J. Haematol.* 151(5), 430–434 (2010).

28 Kantarjian H, Gandhi V, Cortes J *et al.* Phase 2 clinical and pharmacologic study of clofarabine in patients with refractory or relapsed acute leukemia. *Blood* 102(7), 2379–2386 (2003).

29 Deangelo DJ, Yu D, Johnson JL *et al.* Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma. Cancer and Leukemia Group B Study 19801. *Blood* 109(12), 5136–5142 (2007).

30 Berg SL, Blaney SM, Devidas M *et al.* Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. *J. Clin. Oncol.* 23(15), 3376–3382 (2005).

31 Wayne A, Bhojwani D, Silverman LB *et al.* A novel anti-CD22 immunotoxin, moxetumomab pasudotox: Phase I study in pediatric acute lymphoblastic leukemia (ALL). *ASH Annual Meeting Abstracts* 118, 248 (2011).

32 Topp MS, Kufer P, Gokbuget N *et al.* Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *J. Clin. Oncol.* 29(18), 2493–2498 (2011).

33 O'Brien SEA. Inotuzumab ozogamycin (I0), a CD22 monoclonal antibody conjugated to calecheamicin, is active in refractory-relapse acute lymphocytic leukemia (R-R ALL). *ASH Annual Meeting Abstracts* 118, 875 (2011).

34 Lee HJ, Thompson JE, Wang ES, Wetzler M. Philadelphia chromosome-positive acute lymphoblastic leukemia: current treatment and future perspectives. *Cancer* 117(8), 1583–1594 (2011).

35 Foa R, Vitale A, Vignetti M *et al.* Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 118(25), 6521–6528 (2011).

36 Schultz KR, Bowman WP, Aledo A *et al.* Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a Children's Oncology Group Study. *J. Clin. Oncol.* 27(31), 5175–5181 (2009).

37 Bleyer A, Budd T, Montello M. Adolescents and young adults with cancer: the scope of the problem and criticality of clinical trials. *Cancer* 107(Suppl. 7), 1645–1655 (2006).

38 Stock W, La M, Sanford B *et al.* What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. *Blood* 112(5), 1646–1654 (2008).

■ **Large retrospective study of adolescents and young adults with ALL treated on contemporaneous Children's Oncology Group and Cancer and Leukemia Group B trials that demonstrated a significant survival advantage in favor of treatment on pediatric protocols.**

39 Boissel N, Auclerc MF, Lheritier V *et al.* Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. *J. Clin. Oncol.* 21(5), 774–780 (2003).

40 De Bont JM, Van Der Holt B, Dekker AW, van der Does-van den Berg A, Sonneveld P, Pieters R. Adolescents with acute lymphatic leukaemia achieve significantly better results when treated following Dutch paediatric oncology protocols than with adult protocols. *Ned. Tijdschr. Geneeskd.* 149(8), 400–406 (2005).

41 Ramanujachar R, Richards S, Hann I *et al.* Adolescents with acute lymphoblastic leukaemia: outcome on UK national paediatric (ALL97) and adult (UKALLXII/E2993) trials. *Pediatr. Blood Cancer* 48(3), 254–261 (2007).

42 Hallbook H, Gustafsson G, Smedmyr B, Soderhall S, Heyman M. Treatment outcome in young adults and children >10 years of age with acute lymphoblastic leukemia in Sweden: a comparison between a pediatric protocol and an adult protocol. *Cancer* 107(7), 1551–1561 (2006).

43 Usvasalo A, Raty R, Knuutila S *et al.* Acute lymphoblastic leukemia in adolescents and young adults in Finland. *Haematologica* 93(8), 1161–1168 (2008).

44 Schiffer CA. Differences in outcome in adolescents with acute lymphoblastic leukemia: a consequence of better regimens? Better doctors? Both? *J. Clin. Oncol.* 21(5), 760–761 (2003).

45 Parsons HM, Harlan LC, Seibel NL, Stevens JL, Keegan TH. Clinical trial participation and time to treatment among adolescents and young adults with cancer: does age at diagnosis or insurance make a difference? *J. Clin. Oncol.* 29(30), 4045–4053 (2011).

46 Barry E, Deangelo DJ, Neuberg D *et al.* Favorable outcome for adolescents with acute lymphoblastic leukemia treated on Dana–Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium Protocols. *J. Clin. Oncol.* 25(7), 813–819 (2007).

47 Nachman JB, La MK, Hunger SP *et al.* Young adults with acute lymphoblastic leukemia have an excellent outcome with chemotherapy alone and benefit from intensive postinduction treatment. A report from the Children's Oncology Group. *J. Clin. Oncol.* 27(31), 5189–5194 (2009).

■ **Subset analysis of young adults treated in the Children's Oncology Group 1961 study demonstrating improved outcomes with early intensification.**

48 Nachman J, Sather HN, Buckley JD *et al.* Young adults 16–21 years of age at diagnosis entered on Childrens Cancer Group acute lymphoblastic leukemia and acute myeloblastic leukemia protocols. Results of treatment. *Cancer* 71(Suppl. 10), 3377–3385 (1993).

49 Ribera JM, Oriol A, Sanz MA *et al.* Comparison of the results of the treatment of adolescents and young adults with standard-risk acute lymphoblastic leukemia with the Programa Español de Tratamiento en Hematologia pediatric-based protocol ALL-96. *J. Clin. Oncol.* 26(11), 1843–1849 (2008).

50 Huguet F, Leguay T, Raffoux E *et al.* Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J. Clin. Oncol.* 27(6), 911–918 (2009).

51 Rijneveld AW, Van Der Holt B, Daenen SM *et al.* Intensified chemotherapy inspired by a pediatric regimen combined with allogeneic transplantation in adult patients with acute lymphoblastic leukemia up to the age of 40. *Leukemia* 25(11), 1697–1703 (2011).

52 Deangelo DJ, Dahlberg S, Silverman S *et al.* A multicenter Phase II study using a dose intensified pediatric regimen in adults with untreated acute lymphoblastic leukemia. *ASH Annual Meeting Abstracts* 110, 587 (2007).

■ **Prospective Phase II study from the Dana–Farber Cancer Institute demonstrates that use of true pediatric regimen in adults with ALL is feasible, with encouraging early results.**

53 Goldstone AH, Richards SM, Lazarus HM *et al.* In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients. Final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood* 111(4), 1827–1833 (2008).

■ **International prospective study evaluating allogeneic stem cell transplantation versus autologous transplantation or continued chemotherapy for ALL in first remission found in 5-year overall survival advantage in favor of allogeneic stem cell transplantation for younger patients with standard-risk disease (53 vs 45%; p = 0.01).**

54 Earl M. Incidence and management of asparaginase-associated adverse events in

patients with acute lymphoblastic leukemia. *Clin. Adv. Hematol. Oncol.* 7(9), 600–606 (2009).

55 Stock W, Douer D, Deangelo DJ *et al.* Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents. Recommendations of an expert panel. *Leuk. Lymphoma* 52(12), 2237–2253 (2011).

56 Caruso V, Iacoviello L, Di Castelnuovo A, Storti S, Donati MB. Venous thrombotic complications in adults undergoing induction treatment for acute lymphoblastic leukemia: results from a meta-analysis. *J. Thromb. Haemost.* 5(3), 621–623 (2007).

57 Te Winkel ML, Pieters R, Hop WC *et al.* Prospective study on incidence, risk factors, and long-term outcome of osteonecrosis in pediatric acute lymphoblastic leukemia. *J. Clin. Oncol.* 29(31), 4143–4150 (2011).

58 Sala A, Mattano LA Jr, Barr RD. Osteonecrosis in children and adolescents with cancer – an adverse effect of systemic therapy. *Eur. J. Cancer* 43(4), 683–689 (2007).

59 Butow P, Palmer S, Pai A, Goodenough B, Luckett T, King M. Review of adherence-related issues in adolescents and young adults with cancer. *J. Clin. Oncol.* 28(32), 4800–4809 (2010).

60 Kondryn HJ, Edmondson CL, Hill J, Eden TO. Treatment non-adherence in teenage and young adult patients with cancer. *Lancet Oncol.* 12(1), 100–108 (2011).

61 Robison LL. Late effects of acute lymphoblastic leukemia therapy in patients diagnosed at 0–20 years of age. *Hematol. Am. Soc. Hematol. Educ. Program* 2011, 238–242 (2011).

■ **Comprehensive review of late effects of ALL therapy in patients diagnosed up to age 20 years.**

■ Website

101 NCCN Guidelines Version 1.2012 Adolescent and Young Adult Oncology. www.nccn.org