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ACUTE LYMPHOCYTIC LEUKEMIAS (K BALLEN, SECTION EDITOR)

# Treatment of Childhood Acute Lymphoblastic Leukemia: Prognostic Factors and Clinical Advances

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**Abstract** While the majority of children and adolescents with newly diagnosed childhood acute lymphoblastic leukemia (ALL) will be cured, as many as 20 % of patients will experience relapse. On current treatment regimens, the intensity of upfront treatment is stratified based upon prognostic factors with the aim of improving cure rates (for those at the highest risk of relapse) and minimizing treatment-related morbidity (for lower-risk patients). Here we review advances in the understanding of prognostic factors and their application. We also highlight novel treatment approaches aimed at improving outcomes in childhood ALL.

**Keywords** Acute lymphoblastic leukemia · Relapse · Treatment

## Introduction

Over the last several decades, there have been substantial advances in the treatment of children and adolescents with acute lymphoblastic leukemia (ALL). With current risk-stratified regimens, more than 80 % of those diagnosed between 1 and 18 years of age are expected to be long-term, event-free survivors and approximately 90 % are ultimately cured of their disease [1–4]. However, for those patients who relapse or who experience significant toxicities of therapy, it is clear that further advances are needed. Indeed, relapsed ALL is a leading cause of cancer-related mortality in children, and survivors of intensive regimens for newly diagnosed and relapsed ALL are faced with long-term treatment-related sequelae [5–7].

Efforts to improve therapy for newly diagnosed ALL and to prevent disease recurrence have included the stratification of the intensity of therapy based upon prognostic factors predictive of outcome. The relevance of an individual risk factor must be considered within the context of the particular treatment regimen, as changes in therapy can alter a factor's prognostic significance. Here we consider advances in the understanding and application of prognostic factors in the context of current treatment regimens for childhood ALL. We also highlight recent treatment approaches designed to improve cure rates and reduce late effects of therapy.

## Prognostic Factors Commonly Used to Stratify Therapy

Several patient and leukemia-related features have been identified as significant predictors of outcome and are used to determine a patient's "risk group" in order to stratify the intensity of delivered therapy (Table 1). These prognostic factors have included the following.

### Age

Age at diagnosis is a long-established predictor of outcome [8, 9]. Infants with ALL (diagnosed at less than 1 year of age) have a significantly worse outcome than older children, with especially poor prognosis seen in younger infants [10]. MLL

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**Table 1** Selected prognostic factors in infant and childhood ALL

| | Favorable | Unfavorable | Application/comments |
|---|---|---|---|
| Age at diagnosis | 1 to <10 years of age | ≥10 years of age | Informs traditional risk group assignment (NCI risk grouping). |
| | | <1 year of age | Treated on separate, more intensive regimens. |
| | | For infants, <6 months of age | Informs risk group assignment in infant ALL. |
| Presenting WBC count | <50,000/mm$^3$ | ≥50,000/mm$^3$ | Informs traditional risk group assignment (NCI risk grouping). |
| | | Within infant group, ≥300,000/mm$^3$ | Informs risk group assignment in infant ALL. |
| Immunophenotype | B ALL | T ALL | Informs treatment selection. With current regimens, outcome of B ALL and T ALL appears to be similar. |
| | | ETP | Associated with inferior prognosis in initial assessments. May be associated with poorer early response and higher rates of induction failure but overall similar long-term outcomes within contemporary treatment regimens. |
| Cytogenetic and genomic features | Hyperdiploidy, (favorable trisomies), ETV6-RUNX1 | | "Low-risk" feature on some treatment protocols, treated on low-intensity regimens. |
| | | BCR-ABL1 | Designates use of higher intensity treatment regimens with use of TKI. |
| | | MLL rearrangements, hypodiploidy | Inform very high-risk status and intensification of therapy within some treatment protocols. |
| | | iAMP21 | Associated with inferior outcome in some reports. Informs the use of non-standard risk therapy within some treatment protocols. |
| | | IKZF1 deletions | Application under active investigation. |
| | | Philadelphia chromosome-like ALL | Application under active investigation. |
| End-induction MRD Response | Undetectable or low[a] | High[a] end-induction MRD | Incorporated into risk group assignment in modern treatment protocols. |

[a] Thresholds defined differently based on MRD assessment methodology, on different protocols, and at different time-points

gene rearrangements are observed in approximately 80 % of infants with ALL; infants with MLL-rearranged ALL (regardless of the fusion partner) fare much worse than those whose leukemia lacks this abnormality, with long-term event-free survival (EFS) rates of 50 % or less [10, 11•]. Because of their poor outcome, infants with MLL-rearranged ALL are typically treated with different, more intensive cytotoxic regimens than children over 1 year of age at diagnosis [10,11•].

The outcome of older children and adolescents (age over 10 years at diagnosis) is, in general, reported to be inferior to that of younger children (1–10 years) but not as poor as infants. This difference in outcome may be due, in part, to differences in underlying biology, as older children and adolescents are less likely to present with more favorable cytogenetic features (such as ETV6-RUNX1 fusion and high hyperdiploidy with favorable trisomies) and more likely to present with "higher-risk" disease (T cell immunophenotype, BCR-ABL fusion) [9,12]. Retrospective studies have indicated that adolescents and young adults have more favorable outcome when treated on pediatric rather than adult protocols [13,14]. A recent report of long-term outcomes in patients with ALL aged 18–50 years treated with a pediatric-inspired chemotherapy regimen demonstrated the safety and efficacy of this approach in the younger adult population [15]. Older children and adolescents tend to experience more treatment-related complications than younger children, including osteonecrosis and asparaginase-associated pancreatitis and thrombotic complications [4,16,17].

## High Presenting Leukocyte Count

High presenting leukocyte count (defined in NCI category criteria as white blood cell count over 50,000 cells/mm$^3$) has been associated with a higher risk of relapse, particularly in B ALL, and, along with age, is a key component of the NCI risk group assignment [8]. The prognostic significance of presenting leukocyte count in T ALL is less clear.

## Immunophenotype

Historically, patients with T ALL (approximately 10–15 % of childhood ALL), have fared worse than those with B ALL. However, with contemporary treatment regimens, T ALL outcomes have improved and are now similar to outcomes in B ALL [18].

## Cytogenetics

Certain cytogenetic abnormalities have established prognostic significance, particularly in B ALL. For example, a more favorable prognosis has been associated with high hyperdiploidy,

defined as 51–65 chromosomes or DNA index greater than or equal to 1.16, noted in approximately 30 % of cases of childhood B ALL [19]. Several studies have indicated that trisomies of chromosomes 4 and 10 are associated with a particularly favorable outcome in patients with high hyperdiploidy [19, 20]. Similarly, the ETV6-RUNX1 (TEL-AML1) fusion, observed in approximately 20–25 % of cases of childhood B ALL has been associated with favorable outcome [21•].

Other cytogenetic features have been associated with poor prognosis. Rearrangements of the MLL gene, located at chromosome 11q23, which occur in up to 5 % of childhood ALL cases (1–18 years of age) and approximately 80 % of infant ALL are associated with poor prognosis [10, 21•,22]. Historically, patients with Philadelphia chromosome-positive (Ph+) ALL have fared poorly with standard chemotherapy and have received alternative therapy including allogeneic hematopoietic stem cell transplant (HSCT); more recently, such patients appear to have a much better prognosis with kinase-targeted therapy (see below) [23].

## Update on Prognostic Factors of Emerging Significance

Recent reports have furthered our understanding of other factors with prognostic significance.

### Hypodiploidy

Hypodiploidy is observed in approximately 5 % of childhood ALL cases and is associated with inferior outcome, with one large retrospective series of patients treated by ten different cooperative groups reporting EFS of approximately 40 % [24]. End-induction minimal residual disease levels appear to impact the prognosis of patients with hypodiploid ALL [25].

Hypodiploid ALL is characterized by distinctive biology. In a recent genomic profiling study of 124 cases of hypodiploid ALL, near haploid ALL (24–31 chromosomes) was characterized by alterations targeting receptor tyrosine kinase signaling, Ras signaling, and IKZF3 (IKAROS family zinc finger 3, the lymphoid transcription factor gene). Low-hypodiploid ALL (32–39 chromosomes) was characterized by alterations of IKZF2, RB1, and TP53 genes. TP53 alterations were noted in 91.2 % of pediatric low-hypodiploid ALL (compared with fewer than 5 % in non-low-hypodiploid ALL), and interestingly, were also present in non-tumor cells in 43.3 % of cases, suggesting a possible link between low-hypodiploidy and Li-Fraumeni syndrome [26]. Other investigators have also reported a high frequency of TP53 mutations within hypodiploid ALL [27, 28].

### Intrachromosomal AML1 Amplification

Intrachromosomal amplification of the AML1 gene on chromosome 21 (iAMP21) occurs in approximately 2 % of childhood ALL and has been associated with older age at diagnosis (median age approximately 10 years) and with lower presenting leukocyte count (less than 50,000 cells/mm$^3$) [21•,29, 30]. Therefore, many patients with iAMP21 fall into the NCI standard risk group. In an initial retrospective analysis from the UK ALL group (UKALL), children with iAMP21 had very poor 5-year EFS of 29 % [31]. Low EFS (37 %) for this group of patients was also reported by the Berlin-Frankfurt-Munster (BFM) group [32].

Subsequent reports have indicated that, with more intensive treatment, patients with iAMP21 may not have as high a risk of relapse as these initial studies indicated [33•]. On the UKALL 2003 trial, patients with iAMP21 were treated as high risk, regardless of other presenting features, resulting in EFS of 78 %. Similarly, the Children's Oncology Group reported that iAMP21 was associated with inferior EFS and OS in standard risk patients (treated with less intensive therapy), but for high-risk patients (treated with more intensive therapy), iAMP21 was not associated with statistically significant differences in EFS or OS [34•]. Thus, high-risk therapy appears to abrogate the adverse prognostic significance of this abnormality. A recent report from the Ponte di Legno International Workshop in Childhood Acute Lymphoblastic Leukemia of 530 iAMP21 patients provided additional evidence; in that analysis, patients with iAMP21 treated with high-risk ALL regimens had superior EFS compared with those treated with less intensive regimens [30].

### IKZF1 Deletions

Deletions in the IKZF1 gene, which encodes the Ikaros transcription factor, are identified in approximately 15 % of childhood B ALL, with higher frequency in Ph + ALL. IKZF1 deletions are more frequent in older children and adolescents and in patients with high presenting leukocyte counts. In multiple studies IKZF1 deletions have been shown to be an independent predictor of adverse outcomes [35, 36, 37•].

In a recent report of a large cohort of patients (aged 1–18 years) with Ph-negative B ALL treated on the EORTC-CLG trial 58951, patients with IKZF1-deleted ALL had significantly lower EFS (67.7 %) compared with non-IKZF1 deleted cases (86.5 %; CI 1.75–3.32). IKZF1 deletion was an independent predictor of outcome, retaining its prognostic importance in multivariable analysis [37•]. The presence of deletions identified a subset of patients with high hyperdiploidy (in general associated with a more favorable outcome) with inferior EFS; 8-year EFS was significantly lower for high-hyperdiploid, IKZF1-deleted patients than in high-hyperdiploid patients without IKZF1 deletion (76.2 %

compared with 90.7 %, CI 1.19–5.55). In post hoc analysis, it appeared that the inclusion of vincristine-steroid pulses in maintenance therapy improved outcome in IKZF1-deleted patients, suggesting that intensification of chemotherapy may be warranted for this group of patients. Further investigation will be needed to establish whether prospective incorporation of IKZF1 status into risk stratification will lead to improved clinical outcomes.

### Philadelphia Chromosome-Like ALL

Recent studies have identified a subset of B ALL patients characterized by a gene expression profile similar to Ph + ALL, but without the BCR-ABL1 fusion. This subgroup, termed Philadelphia chromosome-like (Ph-like) ALL, occurs in up to approximately 15 % of pediatric patients with B ALL [35, 38•]. There is a high concordance between Ph-like gene expression and the presence of IKZF1 deletions. Ph-like ALL is more common in older children and adolescents, and like IKZF1 deletion, has been shown to be an independent predictor of adverse outcome [35]. However, one study of 40 patients with Ph-like ALL suggested that the adverse prognostic significance of this subtype may be abrogated when patients are treated with risk-directed therapy based on minimal residual disease (MRD) levels measured early in therapy [39].

Detailed genomic analysis of 154 patients with Ph-like ALL identified kinase activating alterations in over 90 % of patients, involving ABL1, ABL2, CRLF2, EPOR, JAK2, PDGFRB, and other genes. The multiple genetic alterations appear to impact a limited number of signaling pathways, notably ABL-class and JAK-STAT pathways, suggesting the potential for targeted interventions [38•]. For instance, cell lines and human leukemic cells expressing ABL1, ABL2, CSF1R, and PDGRB were sensitive in vitro to dasatinib and those with EPOR and JAK2 rearrangements were sensitive to ruxolitinib.

### Early T cell Precursor ALL

Early T cell Precursor (ETP) ALL is another recently described, biologically distinctive subgroup, observed in approximately 15 % of cases of pediatric T ALL. ETP is characterized by a distinctive immunophenotype (CD1a negative, CD8 negative, CD5 weak, with co-expression of stem cell or myeloid markers) [40]. Whole-genome sequencing studies have indicated that ETP is diverse at the genetic level, with a higher prevalence of mutations involving hematopoietic development, histone modification, and cytokine receptor and RAS signaling, when compared with other T ALL cases [41].

Initial reports suggested that ETP phenotype was associated with inferior outcome [40, 42]. However, more recent reports have suggested that, compared with other cases of T ALL, ETP may be associated with slower early response and higher rates of induction failure, but overall similar long-term rates of EFS and OS [43, 44]. A report from the UKALL 2003 protocol demonstrated that ETP patients had a 5-year EFS of 77 %, which was non-significantly lower than the non-ETP T ALL patients (85 %, $p = 0.2$) [45]. A recent retrospective report from the AIEOP group of 49 ETP patients demonstrated that these patients had high rates of prednisone poor response (55 % of patients) and high rates of induction failure (assessed after phase IA, 15 % of patients). In addition, a high proportion of patients had absence of markers for MRD detection by PCR, but of those with evaluable MRD, the majority had high MRD after phase IA. Despite this, when treated with BFM risk-stratified therapy, 38 of 49 patients (78 %) ultimately remained in continuous complete remission, including 13 of 18 patients who received HSCT based on slow early response [44]. Thus, based on their slow initial response to therapy, patients with ETP might be considered candidates for intensified or novel induction regimens, but currently available evidence suggests that ETP status does not necessarily need to be taken into consideration in stratifying post-induction therapy independent of MRD and other measures of early response.

### Early Response to Treatment: Minimal Residual Disease Assessment

Early response to initial therapy consistently has been demonstrated to be an important predictor of outcome. Patients who do not achieve morphologic remission after the first month of treatment have a poorer prognosis [46, 47]. Other means of assessing the rapidity of response to initial therapy, such as peripheral blood response after a steroid prophase, peripheral blood response early in induction therapy, and bone marrow response at early time-points within induction have been shown to have prognostic significance [48, 49].

MRD assessment is a powerful measure of early treatment response and an independent predictor of long-term outcome in childhood ALL, with risk of relapse strongly correlated with MRD levels at end-induction (weeks 4–5) and end-consolidation (weeks 10–12). Most current treatment regimens stratify the intensity of therapy based on MRD levels at one or both of these time-points [50–52]. The randomized UKALL-2003 study demonstrated that intensification of therapy for non-high-risk patients with high end-induction MRD (greater than 0.01 % by PCR methodology) resulted in a superior event-free survival compared with those receiving standard therapy [53•]. The UKALL-2003 trial also tested de-intensification of therapy for non-high-risk patients with low/favorable MRD (either at end-induction or low at end-induction and undetectable by end-consolidation), randomly assigning patients to receive one or two courses of delayed intensification. No significant difference in EFS was

demonstrated, supporting the feasibility of treatment reduction in patients with favorable end-induction MRD [54•].

### Treatment Adherence

Recently published studies from the Children's Oncology Group (COG) demonstrate that poor adherence to oral 6-mercaptopuine (6-MP), a key component of maintenance therapy in childhood ALL, is an important predictor of relapse [55•]. Using medication event-monitoring system (MEMS) caps to record date and time of 6-MP bottle openings, a progressive increase in relapse was observed with decreasing adherence that remained statistically significant after adjusting for NCI risk classification, chromosomal abnormalities, and other prognostically relevant variables. 6MP adherence lower than 90 % was associated with a 3.9-fold increased risk of relapse. Factors associated with higher risk of non-adherence included older age (≥12 years), non-white race/ethnicity, low annual household income/ low parental education, household structure, and absence of a routine surrounding pill taking [55•,56].

### Race and Socioeconomic Status

Survival rates in childhood ALL have been found to vary by race and ethnicity [57]. Proposed reasons for differences in outcomes may be multi-factorial, potentially reflecting differences in leukemia biology [58], underlying genetic polymorphisms [59], socioeconomic factors, and adherence.

In a retrospective analysis of 575 patients living in the US and treated on DFCI ALL Consortium Protocols 00-001 or 05-001, children living in high-poverty areas had an inferior overall survival compared to those from low-poverty areas [60]. While the cumulative incidence of relapse was similar between groups, a higher proportion of children from high-poverty areas experienced early relapse (<36 months from date of complete remission), with 91 % percent of the relapses observed in children from high-poverty areas noted to be early, compared with 49 % of those in children from low poverty areas ($p = 0.009$). The extent to which race and adherence impact these findings remains to be determined.

## Therapeutic Advances

In addition to identifying novel prognostic factors, recent studies have also addressed new applications of existing treatments, such as allogeneic stem cell transplant, as well as novel therapies, which could ultimately result in better cure rates for high-risk de novo patients and relapsed patients, as well as improvements in quality of cure (by reducing late effects of treatment) in long-term survivors.

### Allogeneic HSCT in First Remission in Very High-Risk ALL

The role of allogeneic HSCT in first complete remission for patients with very high-risk ALL, including infants, those with adverse cytogenetic findings (Ph + ALL, MLL gene rearrangements, low hypodiploidy), and those with slow early response (initial induction failure, high MRD at week 10–12) has been controversial for many years. However, recently published data suggests that allogeneic HSCT may be of benefit for some patient subsets.

On the international Interfant-99 clinical trial, high-risk patients (defined as those with a poor response to a prednisone prophase) were allowed per protocol to undergo HSCT in first complete remission if a suitable donor was available [10]. Adjusting for waiting time to HSCT, DFS was not found to differ significantly for infants who underwent HSCT compared with those treated with chemotherapy alone (without HSCT). However, further analysis suggested that HSCT in first remission was associated with better DFS outcome for "high-risk" infants (defined as those who were less than 6 months of age at diagnosis with MLL rearrangement and presenting leukocyte count of ≥300,000/μL or poor steroid response), while no benefit was observed for other MLL-rearranged infants.

HSCT also appears to have a beneficial role for patients experiencing initial induction failure. In a large retrospective study of 1041 patients with initial induction failure from 14 cooperative groups, the 10-year OS rate was 32 ± 1 %; however, rates were better in some groups of patients if they received allogeneic HSCT once they achieved complete remission rather than continuing treatment with chemotherapy alone [47]. Allogeneic HSCT in first complete remission was associated with superior overall survival in induction failure patients with T ALL, as well as B ALL patients 6 year of age or older (without MLL rearrangement). However, a benefit for HSCT in first complete remission (CR) for younger B ALL patients with initial induction failure was not demonstrated.

The role of HSCT in first CR for patients with slow early response (as assessed by MRD) remains unclear. In a recent report from the AIEOP group, after adjusting for waiting time to HSCT, there was no benefit demonstrated for HSCT in first CR for patients with high end-consolidation (week 10–12) MRD [61•]. Thus, the treatment of this group of patients remains a challenge and illustrates the need for novel and targeted therapies.

### Tyrosine Kinase Inhibitors for Philadelphia Chromosome-Positive ALL

Ph+ ALL occurs in approximately 3–5 % of childhood ALL [21•,62]. Historically, this subset of patients was found to have

especially poor outcomes with standard chemotherapy and so was allocated to HSCT in first CR. The incorporation of tyrosine kinase inhibitors (TKIs), such as imatinib and dasatinib, into frontline therapy for childhood Ph + ALL has changed the approach to treatment for this subgroup of patients. Administration of the TKI, imatinib mesylate, has been shown to be feasible in children with Ph + ALL within the context of an intensive multi-agent chemotherapy regimen, and this combination appears to be as effective as HSCT in first CR for this group of patients [23, 63, 64•].

The COG evaluated the use of imatinib in children with Ph + ALL in combination with intensive multi-agent chemotherapy, enrolling patients between 2002 and 2006, with some patients proceeding to HSCT depending on availability of HLA-matched related donor [63]. With 5.2 years median follow-up, the disease-free survival for those treated without HSCT and with continuous dosing of imatinib was 70 ± 12 % ($n = 28$), which appeared similar to those who underwent HSCT from a related donor (65 ± 11 %, $n = 21$) or unrelated donor (59 ± 15 %, $n = 13$, $p = 0.60$) [64•]. In a European intergroup study which aimed to test the safety and efficacy of post-induction imatinib using a risk-stratified approach (based upon early response at day 7 of therapy and complete remission status), 178 patients were enrolled between 2004 and 2009. All "poor risk" patients received imatinib and "good risk" patients were randomly assigned to receive imatinib (administered in a discontinuous schedule) or not. Almost 80 % of patients underwent allogeneic HSCT in first complete remission. Analyzed by treatment received, the 4-year DFS was 75.2 % for those who received imatinib and 55.9 % for those who did not ($p = 0.06$) [23]. Together, these studies support the feasibility and efficacy of incorporation of TKI therapy into multi-agent therapy for Ph + ALL and suggest no clear benefit to HSCT in first remission. However, further studies are necessary to optimize the therapy of Ph + ALL patients, including investigations of different TKIs and chemotherapy backbones, refinement of prognostic factors to identify high-risk patients who may still benefit from HSCT, and the role of post-HSCT TKI in those who do proceed to HSCT. In addition, whether prolonged TKI-directed therapy in children is associated with long-term sequelae remains to be elucidated.

## Immunotherapy

Promising immunotherapeutic approaches are under active investigation in childhood ALL with the potential to further improve outcomes. For example, blinatumomab is a bispecific antibody that binds to CD19 (expressed in the majority of B ALL) and CD3 (present on T cells), bringing T cells into contact with B lymphoblasts [65]. Blinatumomab has shown efficacy in the treatment of adult patients with relapsed/refractory ALL and received FDA accelerated approval in 2014 for the treatment of adult Ph-negative relapsed or refractory B ALL [66, 67]. In a recently reported multi-center, phase 2 study, 81 of 189 adult patients (43 %, 95 % CI 36-50) with Ph-negative, primary refractory or relapsed ALL who received blinatumomab (by continuous infusion over 4 weeks, every 6 weeks) achieved a complete remission or complete remission with partial hematologic recovery of peripheral blood counts after 2 cycles [66]. Investigation in pediatric B ALL patients is ongoing [68].

Genetically engineered autologous T cell therapy is an emerging immunotherapeutic approach. Initial trials in B ALL have focused on testing chimeric antigen receptor (CAR) T cells that have been engineered to couple an anti-CD19 domain to intracellular T cell signaling domains, thus redirecting cytotoxic T cells to C19-expressing cells (including the vast majority of B ALL cells) [69, 70•]. In a recent report from Maude and colleagues, 30 children and adults with multiply relapsed or refractory ALL were treated with autologous CD19-directed CAR-modified T cells. Notably, 90 % of patients in this heavily pre-treated grouped achieved complete remission, with 6-month EFS reported of 67 % (95 % CI 51–88) and OS of 78 % (95 % CI 65–95) [70•]. In a report from Lee and colleagues of CD 19-directed CAR T cells in patients aged 1–30 years, 70 % of patients with B ALL achieved a complete response, 60 % of whom were MRD-negative [71•]. These promising results highlight the potential of this treatment approach to transform therapy for relapsed and even high-risk de novo patients. However, many questions remain unanswered, including duration of response, mechanisms of resistance, and long-term sequelae of these treatment approaches. Further clinical investigation will be needed in order to determine the optimal integration of CAR T cells and other immunotherapeutic approaches into the care of pediatric ALL patients.

## Reducing Late Effects

For patients cured by currently available therapies, there is an increasingly important need to understand the physical and emotional costs of cure and also to attempt to minimize the long-term impact of treatment. Substitution of cranial radiation with other CNS-directed therapies and the use of dexrazoxane to prevent anthracycline-associated cardiotoxicity are examples of recently tested strategies that aim to reduce late effects without adversely impacting cure rates.

Treatment with cranial radiation results in an increased risk of developing a subsequent malignancy in the radiation field as well as neurocognitive sequelae. Several studies have suggested that the increased risk for development of meningioma does not appear to plateau [72, 73]. Armstrong and colleagues reported that adult survivors of childhood ALL who received 24 Gy of cranial radiation had increased memory impairment [74]. Importantly, survivors treated with 24 Gy cranial

radiation were found to function at a level 1–2 decades older than their chronological age on delayed memory assessments, raising concern for early onset of cognitive impairment. Over the last few decades, the proportion of newly diagnosed patients receiving cranial radiation has dramatically increased, and several published studies have omitted radiation altogether from front-line therapy [1, 2, 75]. Most of these trials have included multiple doses of high-dose methotrexate during post-induction consolidation and an increased frequency of intrathecal chemotherapy as a substitute for radiation in high-risk patients. In general, the overall EFS and OS on these trials appear similar to other trials conducted during the same time period in which some patients received cranial radiation. In a study conducted by the St. Jude Children's Research Hospital, in which all patients were treated without cranial radiation, clinical features associated with a significantly higher risk of isolated CNS relapse included T cell phenotype, the t(1;19) translocation, or the presence of blasts in the CSF at diagnosis [1]. In a meta-analysis of data from more than 16,000 patients treated between 1996 and 2007 by ten cooperative groups, the use of cranial radiation therapy did not appear to impact 5-year OS [76]. In subgroup analyses, the only patients who appeared to benefit from cranial radiation were those with CNS-3 status at diagnosis, in whom a significantly lower rate of CNS relapses were observed with the use of cranial radiation.

Strategies aimed at preventing anthracycline-associated cardiotoxicity have also been implemented in the treatment of childhood ALL. On most treatment regimens, lower risk patients receive a low total cumulative dose of anthracycline, thus minimizing the risk of cardiac late effects. For higher-risk patients (who typically receive higher total cumulative doses of anthracycline), the use of the cardioprotectant agent dexrazoxane has been shown in several trials to prevent heart damage without adversely impacting anti-leukemia outcomes and long-term survival [77, 78, 79•]. In a randomized trial conducted by the DFCI ALL consortium in high-risk ALL patients, the use of dexrazoxane was associated with reduced long-term cardiotoxicity without any adverse impact on longer-term event-free rates [77]. Similarly, in a recent report from the Pediatric Oncology Group Protocol, POG 9404, which included random assignment of patients with T ALL or T lymphoblastic lymphoma to receive therapy with or without dexrazoxane prior to each dose of doxorubicin, dexrazoxane was found to be cardioprotective, based upon echocardiographic measurements of left ventricular function and structure, without any difference in EFS between the two randomized arms. [79•] In both studies, there was no increased risk of second malignancies associated with dexrazoxane. These results support the continued use of dexrazoxane as a cardioprotectant in high-risk ALL patients receiving higher cumulative exposure to anthracycline.

## Conclusion

Significant progress has been made in the understanding of prognostic factors and their clinical application in childhood ALL. The increasingly sophisticated understanding of the biology of ALL will help to refine risk stratification and also inform the development of novel, targeted treatment approaches. Also, the identification of non-biologic prognostic factors, such as medication adherence and socioeconomic status, may lead to non-pharmacologic interventions that could improve cure rates. Novel treatment approaches, such as CAR T cells and other immunotherapeutic approaches, may dramatically alter the prognosis of chemo-resistant patients. For patients who are cured by currently available therapies, careful studies of the long-term impact of therapy and trials to test strategies to decrease late effects are crucial in order to improve the overall quality of cure.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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