Causes of Inferior Outcome in Adolescents and Young Adults with Acute Lymphoblastic Leukemia: Across Oncology Services and Regardless of Clinical Trial Enrollment

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Abstract

Background: Adolescents and young adults (AYA: 15–39y) with acute lymphoblastic leukemia (ALL) have inferior survival when compared with children (1–14y). An approach is lacking that includes both patients enrolled, and not enrolled on clinical trials, and includes the contribution of health care delivery, treatment and clinical prognosticators.

Methods: We assembled a retrospective cohort of ALL patients diagnosed between 1–39y (AYA: n=93; Child: n=91) and treated at a single institution between 1990 and 2010, irrespective of clinical trial enrollment. We modeled relapse risk i) during therapy and ii) after completing therapy.

On-therapy relapse: AYA experienced an increased risk of on-therapy relapse vs. children (HR=10.5, p=0.004). In multivariable analysis restricted to AYA, independent predictors of relapse included lack of clinical trial enrollment (HR=2.6, p=0.04) and non-white race/ethnicity (HR=2.2, p=0.05).

Relapse after completing therapy: When compared with children, AYA experienced an increased risk of relapse after completing therapy (HR=7.7, p<0.001). In multivariable analysis restricted to AYA, longer therapy (months of maintenance: HR=0.7, p<0.001; months of consolidation: HR=0.8, p=0.03) protected against relapse.

Conclusions: Among AYA, aspects of healthcare delivery (clinical trial enrollment, non-white race/ethnicity) are associated with relapse during therapy, and aspects of treatment (shorter duration of maintenance and consolidation) are associated with relapse after completing therapy.

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Impact: These findings highlight the importance of clinical trial enrollment, and therapy duration (maintenance, consolidation) in ensuring durable remissions in AYA ALL. Future studies encompassing healthcare delivery, treatment and biology are needed.

Keywords

AYA; outcome; leukemia; clinical trial; maintenance

INTRODUCTION

Adolescents and young adults (AYA: 15–39 years) diagnosed with acute lymphoblastic leukemia (ALL) have seen modest improvements in outcome over time, and continue to experience inferior survival when compared with children (<15 years).(1–4) This phenomenon in ALL and several other malignancies(5) has resulted in the coinage of the term *AYA Gap*, and led the National Cancer Institute (NCI) to provide AYA with a special designation.(6) Therapeutic approach has been implicated in these differences in outcome; young AYA (15–21 years at diagnosis) with ALL treated on pediatric clinical trials experience superior survival when compared with AYA treated on adult clinical trials.(7–11) However, these observations were made as secondary analyses of patients enrolled on therapeutic clinical trials; it is well known that only a small fraction of AYA are treated on clinical trials and the causes of inferior outcome in those between 22 and 39 years at diagnosis remain unexplored.(12, 13) Furthermore, a number of factors could possibly influence ALL outcomes, but remain unexplored in both patients placed on clinical trials and treated without enrollment on trials. There is a critical need for a broad approach that considers factors related to healthcare delivery (insurance, socioeconomic status [SES], race/ ethnicity) and treatment (enrollment on clinical trials, duration of therapy, therapeutic approach, treating oncology service) while adjusting for clinical prognosticators across the entire age spectrum of AYA with ALL (i.e., 15 to 39 years at diagnosis. These factors have not been examined together across both pediatric and adult oncology services in patients both enrolled, and not enrolled, on clinical trials; rather, many of these factors have been examined in isolation, often as secondary analyses of therapeutic clinical trials. We addressed these knowledge gaps in AYA with ALL treated on both adult and pediatric oncology services, and both enrolled and not enrolled on clinical trials; we evaluated the association between risk of relapse and factors related to both healthcare delivery and treatment.

MATERIALS AND METHODS

We assembled a retrospective cohort of patients newly diagnosed with ALL between 1990 and 2010 when they were between the ages of 1 and 39 years. All patients were diagnosed and/or treated at City of Hope, irrespective of enrollment on clinical trial. Due to a companion study with focus on host biology, the cohort included consecutive children and AYA with ALL who [1] had available bone marrow specimens in the institutional biospecimen repository; and [2] had not received a hematopoietic cell transplant in first clinical remission (CR1). Of the 196 patients who met these criteria, 12 patients were excluded because of incomplete medical records, leaving an evaluable cohort of n=184.

[Supplemental Figure 1] Medical records were used to abstract data on clinical prognosticators, variables related to healthcare delivery and treatment, as well as response to therapy; a combination of documents was used to construct these variables including therapy roadmaps, clinician documentation (physician, practitioner or nursing notes), medication orders and medication administration records. This study was approved by the Institutional Review Boards of the University of Alabama at Birmingham and City of Hope.

Variables related to Healthcare Delivery

The following characteristics were abstracted from the medical records: [1] *Demographics* [gender, age at diagnosis, and race/ ethnicity]; [2] *Insurance status* [private, public, uninsured]; [3] *SES* [patients' residential address was used to assign zip-code level median household income and median education level to determine SES; using these levels, patients were ranked into quintiles by education and income]. Due to a correlation between SES and insurance, a composite variable was created: high SES + private insurance, low SES + non-private insurance, and mixed profile [i.e. low SES + private insurance and high SES + non-private insurance].

Variables related to Treatment

The following characteristics were abstracted from the medical records: [1] *Clinical trial enrollment* [yes/no]; [2] *Duration of treatment*; [3] *Treatment approach; and* [4] *Oncology service*.

Duration of treatment: We recorded the start and end dates of consolidation and maintenance. Due to significant variability between treatment regimens, consolidation was defined as all phases between induction and maintenance. For purposes of standardization across regimens, a second planned induction phase was considered to be part of consolidation. Maintenance was defined as a phase where patients received oral corticosteroids, vincristine and oral antimetabolite chemotherapy and/or was specifically termed 'maintenance'.

Treatment approach: We abstracted information regarding treatment regimens received by patients and classified them according to NCCN Guidelines(14) as either pediatric-inspired or adult-inspired. Pediatric-inspired regimens included those sponsored by the Pediatric Oncology Group, Children's Cancer Group, and Children's Oncology Group as well as the pediatric-inspired approach used by adult oncology services (modified BFM protocol). Adult-inspired regimens included those sponsored by adult cooperative groups (SWOG, CALGB) as well as institutional and consortial regimens.

Oncology service: We classified primary oncologists based on their treatment of patients on either pediatric or medical oncology services. 'International' patients were those initially treated at international institutions, and transferring care to City of Hope after initial therapy; these patients were included if the availability of complete medical records met eligibility criteria.

Due to the correlation between type of therapeutic approach and oncology service [pediatric vs. medical oncology], we created a composite variable: pediatric oncology + pediatric-inspired therapy; medical oncology + adult-inspired therapy; mixed profile [international institutions or other combinations of oncology service and therapy].

Clinical Prognosticators

These included [1] *white blood cell count (WBC) at diagnosis* [>50K vs. <50K]; [2] *immunophenotype* [T-cell vs. precursor B-cell]; [3] *CNS disease status* [positive vs. negative/ not documented]; [4] *Disease response* (details below) and [5] *Cytogenetic profile* (details below). The wide temporal span of the study precluded use of contemporary prognosticators (e.g., minimal residual disease) across the entire cohort.

Disease response: Response to therapy was assessed at the end of induction; this was dichotomized into patients with an M1 marrow [<5% blasts in bone marrow] vs. an M2 or M3 marrow [M2: 5%−25% blasts; M3: >25% blasts]. All patients with an M2-M3 marrow eventually achieved an M1 marrow; the date of this first clinical remission (CR1) was captured. In adult-inspired regimens in which two induction phases are given, only the first induction phase was used to determine end-induction remission status.

Cytogenetic profile: If leukemic blasts harbored either a Philadelphia chromosome (Ph+) or MLL rearrangement, or exhibited hypodiploidy (<44 chromosomes) the patient was considered to have a high-risk cytogenetic profile.

Outcome of interest

First relapse (irrespective of site) served as the dependent variable of interest. Dates of relapse, death and last contact were abstracted from medical records. We conducted separate analyses to evaluate the risk of relapse for patients who relapsed on therapy or who relapsed after completion of therapy.

Statistical Analysis

Kaplan-Meier survival analysis was used to calculate relapse-free survival from diagnosis through relapse, death or date of last contact (whichever came first). For patients who relapsed on therapy, we calculated time from CR1 to on-therapy relapse. For patients who relapsed after completion of planned therapy, we calculated time from completion of therapy to off-therapy relapse. We divided follow-up time into 'months' of 30.4 days. We then constructed a discrete-time dataset that allowed for updating covariates monthly including duration of treatment received (consolidation and maintenance), and time from CR1 (for on-therapy relapse) or end of treatment (for off-therapy relapse). Logistic regression with a complementary log-log link was used to model recurrence; patients were censored at relapse, death from non-relapse causes or date of last follow-up, whichever occurred first. In this context, the underlying hazard was modeled directly over time and model coefficients were transformed into hazard ratios. Initial analyses used generalized additive models to consider potential non-linear relationships. Multivariable models included variables related to *healthcare delivery* [gender, race/ ethnicity (non-Hispanic white [referent group] vs. other), SES and insurance status (high SES + private insurance [referent group] vs. low SES

+ non-private insurance vs. mixed profile)], and *treatment* [clinical trial enrollment (yes/no), duration of therapy (consolidation, maintenance), and oncology service and type of therapy (pediatric oncology + pediatric-inspired therapy [referent group] vs. medical oncology + adult protocols vs. other)]. Models were adjusted for *clinical prognosticators* [WBC at diagnosis (<50K vs. 50K), immunophenotype (T-cell vs. precursor B-cell), disease response (M2-M3 marrow vs. M1 at end-induction), CNS disease status at diagnosis (positive vs. negative/ not documented) and high-risk cytogenetic profile (yes/no)]. Hazard ratios (HR) of relapse with associated 95% confidence intervals (CI) were calculated. Two-sided tests with p<0.05 were considered statistically significant. SAS 9.3 (SAS Institute, Cary, NC) and R version 3.3.2 (R Core Team, Vienna, Austria; https://www.R-project.org) were used for all analyses. These analyses addressed two major questions: [1] Magnitude of difference in relapse risk between AYA and children with ALL (adjusting for healthcare delivery, treatment and clinical prognosticators); [2] Predictors of relapse risk (healthcare delivery, treatment and clinical prognosticators) among AYA with ALL. In evaluating predictors of relapse among AYA, age was included as a covariate in order to minimize any age-related differences over the age span of 15 to 39 years. Univariable analyses are presented in Supplemental Table 1.

RESULTS

Patient Characteristics

Table 1 summarizes the patient characteristics for both AYA and children. The cohort included 91 children (median age: 4y; interquartile range [IQR] 3–10y) and 93 AYA (median age: 23y; IQR 19–30y). The distribution of children and AYA was comparable with respect to gender (p=0.4), insurance (p=0.2), race/ ethnicity (p=0.1) and SES (p=0.2). The majority of children received pediatric-inspired therapy and were treated by a pediatric oncology service (n=84; 92%). Among AYA, 18% (n=17) received treatment with pediatric-inspired therapy on a pediatric oncology service; these included 19 (46%) 15–21 year-olds and 1 (2%) 22–39 year-old. A larger proportion of AYA had T-cell disease (25% vs. 13%, p=0.04), a high-risk cytogenetic profile (14% vs. 6%, p=0.05), and an M2-M3 marrow at the end of induction (15% vs. 4%, p<0.01). Among patients without high risk features in their cytogenetic profile (n=166; 90%), 10 patients (5% of the cohort) had either no documentation of cytogenetics being performed, or insufficient samples to perform cytogenetics. When considering patients who completed therapy (n=119), there was no difference in duration of either phase of therapy (consolidation p=0.5; maintenance p=0.9). However, when considering all patients (irrespective of whether they did or did not complete therapy), AYA had a shorter duration of both consolidation and maintenance phases of therapy than children (p<0.01). Of note, both pediatric and adult oncology regimens in ALL call for a specific duration of maintenance, independent of the duration of consolidation received. Although the number of new patients in the cohort varied throughout the diagnostic eras, with a larger proportion of patients diagnosed prior to 2000, there was a comparable proportion of AYA and children in the cohort through time (p=0.9) [Supplemental Figure 2].

Comparison of ALL Outcomes between AYA and Children

Overall, children with ALL had superior relapse-free survival (5y: 74%, 95% CI, 65%−83%) as compared to both young AYA (15−21 years: 29%, 95% CI, 15−43%) and older AYA with ALL (22−39 years: 32%, 95%CI, 19−45%, p<0.0001). There was no statistically significant difference in relapse-free survival between the younger and older AYA with ALL (p=0.6) [Figure 1].

Relapse On Therapy—The proportion of AYA vs. children suffering a relapse while on therapy was 48% vs. 17% (p<0.001). In multivariable analysis (adjusting for clinical prognosticators, healthcare delivery and treatment), this resulted in a 10.5-fold higher risk of relapse for AYA on therapy (HR=10.5, 95%CI, 2.1−52.5, p=0.004) as compared to children [Table 2]. AYA relapses tended to occur earlier than did relapses among children [Figure 2].

Relapse After Completion of Therapy—The proportion of AYA vs. children suffering a relapse after completion of therapy was 47% vs. 13% (p<0.0001). In multivariable analysis (adjusting for clinical prognosticators, healthcare delivery and treatment), this resulted in a 7.7-fold increased risk of relapse after completion of therapy for AYA (HR=7.7, 95%CI, 2.5−23.9, p<0.001) as compared to children [Table 2]. Again, AYA relapsed earlier than children [Figure 2]. Among AYA who completed therapy, the duration of maintenance was shorter in patients who relapsed (median 23.5 mos.) than in patients who did not relapse (median 29.0 mos.; p<0.01); in children there were no differences in maintenance duration by relapse status (p=0.7). There was no difference amongst these groups with respect to duration of consolidation therapy (p=0.5).

Predictors of relapse risk among AYA with ALL

Relapse On Therapy—In a multivariable model restricted to AYA, after taking clinical prognosticators into account, independent predictors of relapse included race/ ethnicity (non-white race/ ethnicity: HR=2.2, 95%CI, 1.0−4.8, p=0.05) and enrollment on clinical trials (not enrolled on trial: HR=2.6, 95%CI, 1.0−6.3, p=0.04) [Table 3].

Relapse After Completion of Therapy—In a multivariable model restricted to AYA, after taking into account clinical prognosticators, independent predictors of relapse included duration of consolidation (months of consolidation: HR=0.8, 95%CI, 0.6−1.0) and duration of maintenance (months of maintenance: HR=0.7, 95%CI, 0.6−0.8, p<0.001). There was a trend towards an association between relapse and SES/payor (low SES + public: HR=6.8, 95%CI, 0.8−60.8, p=0.09) [Table 3].

DISCUSSION

In patients both enrolled and not enrolled on clinical trials, and cared for across medical and pediatric oncology, we show that patients diagnosed with ALL between the ages of 15 and 39 years have 7.7-fold to 10.5-fold higher risk of relapse as compared to children between 1 and 14 years of age. Among AYA, predictors of relapse varied by time of relapse. Relapse while on therapy was associated with non-white race/ ethnicity and lack of enrollment on a clinical trial. Relapse after completion of therapy was associated with a shorter duration of

consolidation and maintenance. We found a trend towards an association between relapse and low SES + public insurance.

Lack of clinical trial enrollment was associated with a 2.6-fold increased risk of relapse among AYA relapsing on-therapy. The benefit provided by clinical trial enrollment is likely multi-factorial. Treatment on a clinical trial is characterized by a highly protocolized approach to therapy and stringent guidelines for supportive care, likely resulting in minimal 'breaks' in therapy. Our results suggest that, considering clinical trial enrollment as a surrogate for treatment intensity in this way, that it would be important in the early phases of therapy. Variability in exposure to 6-mercaptopurine has been associated with relapse in pediatric ALL; this includes both a lack of medication adherence and physician-directed time off from therapy.(15) Our previous work has shown a benefit for AYA ALL being treated at an NCI-designated Comprehensive Cancer Center (NCICCC);(16) the current findings at an NCICCC suggest that one aspect of this designation that provides benefit to the patients is the potential to enroll on a clinical trial. In addition to enrollment on clinical trials, non-white race/ ethnicity remained an independent predictor of on-therapy relapse among AYA, despite adjustment for clinical prognosticators including WBC at diagnosis, response to therapy, immunophenotype, high-risk cytogenetic profile and CNS disease. It is conceivable that racial/ ethnic differences are a surrogate for host genetics (as have been associated with poor prognosis in childhood ALL(17)) or disease biology; these domains could be contributing in this way to differences in on-therapy relapse among AYA, as our analyses are adjusted for other factors associated with racial/ethnic disparities in outcome such as insurance and SES. However, this construct could not be completely evaluated in the current study, since this retrospective study spanned two decades of laboratory techniques, therefore, a prospective comprehensive approach is necessary that includes ALL biology, germline genetic determinants of disease prognosis, healthcare delivery as well as treatment.

Among AYA who completed therapy, we found that both a shorter duration of consolidation and maintenance were associated with relapse. Of note, both adult and pediatric ALL regimens prescribe a duration of maintenance that is independent from the duration of consolidation received. Specifically, each additional month of consolidation was associated with a 20% decreased risk of relapse and each additional month of maintenance was associated with a 30% decreased risk of relapse. These findings are consistent with what has been shown in clinical trials, i.e., systemic exposure to 6MP and methotrexate for ~2 years of maintenance therapy is critical for durable remissions in ALL.(18) The trend towards an association between relapse and SES/ insurance status is consistent with the notion that these components are important for adherence to all aspects of therapy. In our study, SES has components of both income and education, which have been typically associated with a patient's access to insurance, especially during the study period (data collection ended before implementation of the Affordable Care Act and Medicaid expansion in California). Tangible aspects of poverty have been associated with outcome in child health(19) and ALL relapse;(20) our findings could imply that resource deprivation at a community level and/or a personal level have a potential link to outcome. Insurance may play a role in securing medications, and/or regular and timely follow up. Finally, in childhood ALL, low SES is a predictor of non-adherence to oral 6-mercaptopurine during maintenance, and non-adherence is associated with relapse.(15, 21, 22) It is also plausible that either insurance-

level and/or transportation-associated barriers get in the way of patients following up in clinic on time and as prescribed, to keep to their prescribed therapy plan both in terms of how long the therapy continues and how intense the therapy is delivered. Thus both SES and insurance status deserve prospective examination at a granular level in children and AYA as it appears vital to provide adequate social support to ensure completion of treatment and/or adherence to therapy.

This study is limited by the retrospective nature of data collection. As an example, a therapy roadmap documenting treatment delivered was available in the medical records for 76% of children, 34% of 15–21 year-olds and only 2% of 22–39 year-olds (p<0.001). These differences may serve as a clinician-directed target for intervention, and are the focus of an ongoing multi-site study. Additional limitations include the evolution over time in terms of standard laboratory tests to evaluate somatic mutations and disease response (such as minimal residual disease); however we were able to abstract several key clinical prognosticators including immunophenotype, morphologic disease response, WBC at diagnosis (NCI "high-risk" criterion[23]), CNS disease at diagnosis, and cytogenetic profile. The proportion of pediatric patients in this cohort enrolled on a clinical trial is lower than those previously reported, while the proportion of AYA enrolled is higher. This institutional enrollment pattern is consistent with the notion that City of Hope is a Cancer Center, with pediatric patients presenting via referral rather than through an emergency department; therefore, pediatric patients may have started treatment before arrival thus making them ineligible to enroll on a trial. On the other hand, many adult community oncologists refer ALL patients to a subset of centers (such as City of Hope) which treat ALL; therefore, it is conceivable that the institution saw a larger proportion of AYA ALL than other adult oncology practices and was more often enrolling on trials. Data suggest the most common reason for AYA not enrolling on a clinical trial is the lack of availability of a clinical trial, [24] and the adult hematology service consistently had open clinical trials in ALL. Similarly, it is challenging for national estimates of enrollment to account for institutional, regional or consortial trials (also open at City of Hope). While this study is limited in its single institution approach and limited sample size, its strength lies in its span of two decades and inclusion of patients treated both on and off clinical trials by both pediatric and adult oncology services. An additional strength is the representation of robust ethnic and socioeconomic diversity in the cohort. This hypothesis-generating study confirms the need for further work in areas discussed above.

The importance of factors related to both *healthcare delivery* and *treatment* suggests the significance of further evaluation of this aspect of care. In terms of treatment approach, pediatric-style approaches to ALL therapy include earlier and more frequent CNS-directed therapy, higher cumulative doses of both glucocorticoids (prednisone or dexamethasone) and asparaginase, and a longer maintenance therapy with less myelosuppressive agents; on the other hand, adult-style therapeutic approaches rely on more myelosuppressive agents.[25] From a healthcare delivery perspective, there are well-documented differences in a pediatric-oriented practice model and an internal medicine practice model;[26] the therapeutic approach used for an AYA patient depends on the 'door' through which an AYA patient enters oncology care. Such structural differences in care include a disease-focused approach in the adult model that is oriented towards an autonomous individual, and a family-centered

pediatric model which incorporates biopsychosocial aspects in a multidisciplinary and comprehensive manner.(26, 27) A prospective study is necessary to evaluate these concepts in an all-encompassing fashion.

In summary, AYA with ALL experience a higher risk of relapse when compared with children. Among AYA, predictors of relapse vary with time of relapse. Factors related to healthcare delivery are associated with relapse during therapy, and include race/ ethnicity and clinical trial enrollment. Factors related to treatment are associated with relapse after completion of therapy and include duration of both consolidation and maintenance; there is also a trend towards an association with SES and insurance status. Among AYA with ALL, predictors of relapse include factors related to both healthcare delivery and treatment. These findings highlight the importance of providing adequate social support to ensure completion of treatment, as well as the role for clinical trial enrollment and duration of both consolidation and maintenance therapy in ensuring durable remissions in AYA with ALL. Future studies are necessary which encompass all aspects that could potentially contribute to outcome in AYA ALL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

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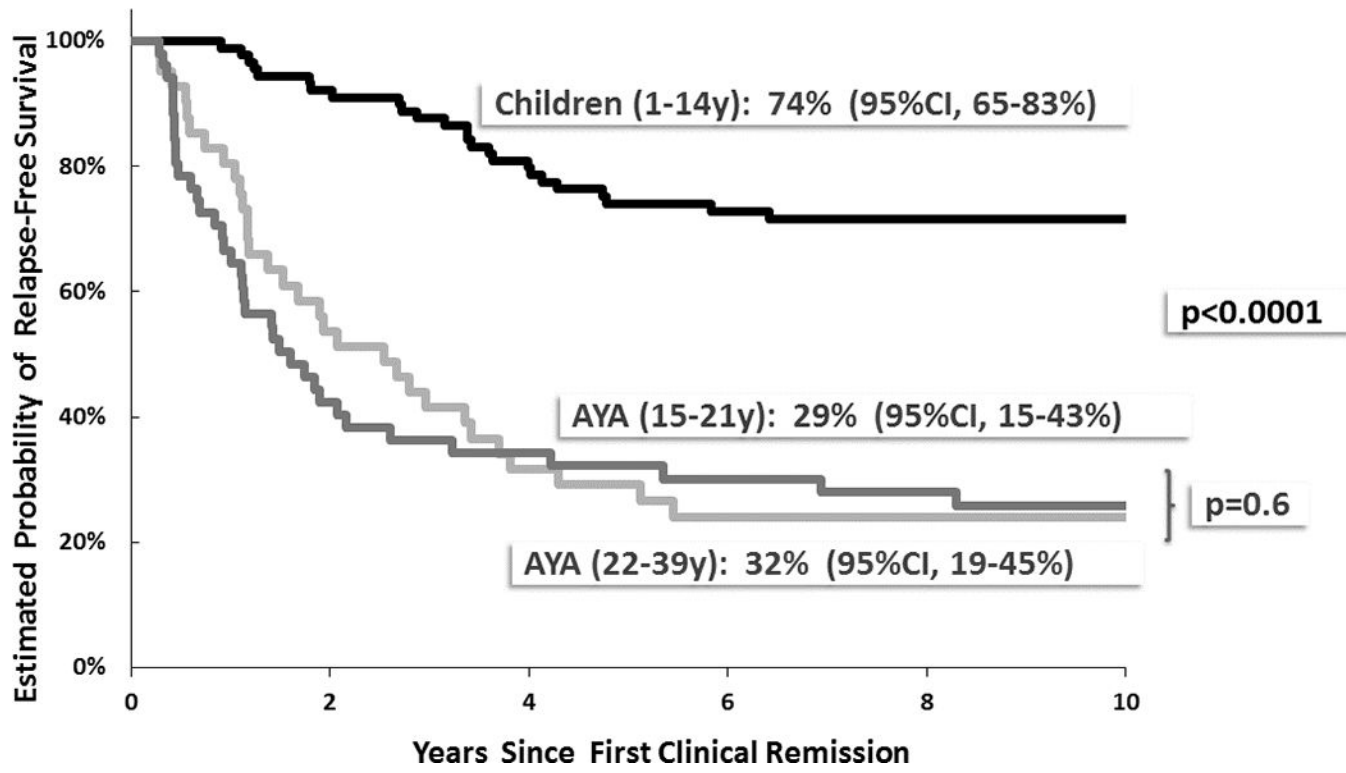
Figure 1.
AYA and children with ALL: 5-year relapse-free survival by age group.
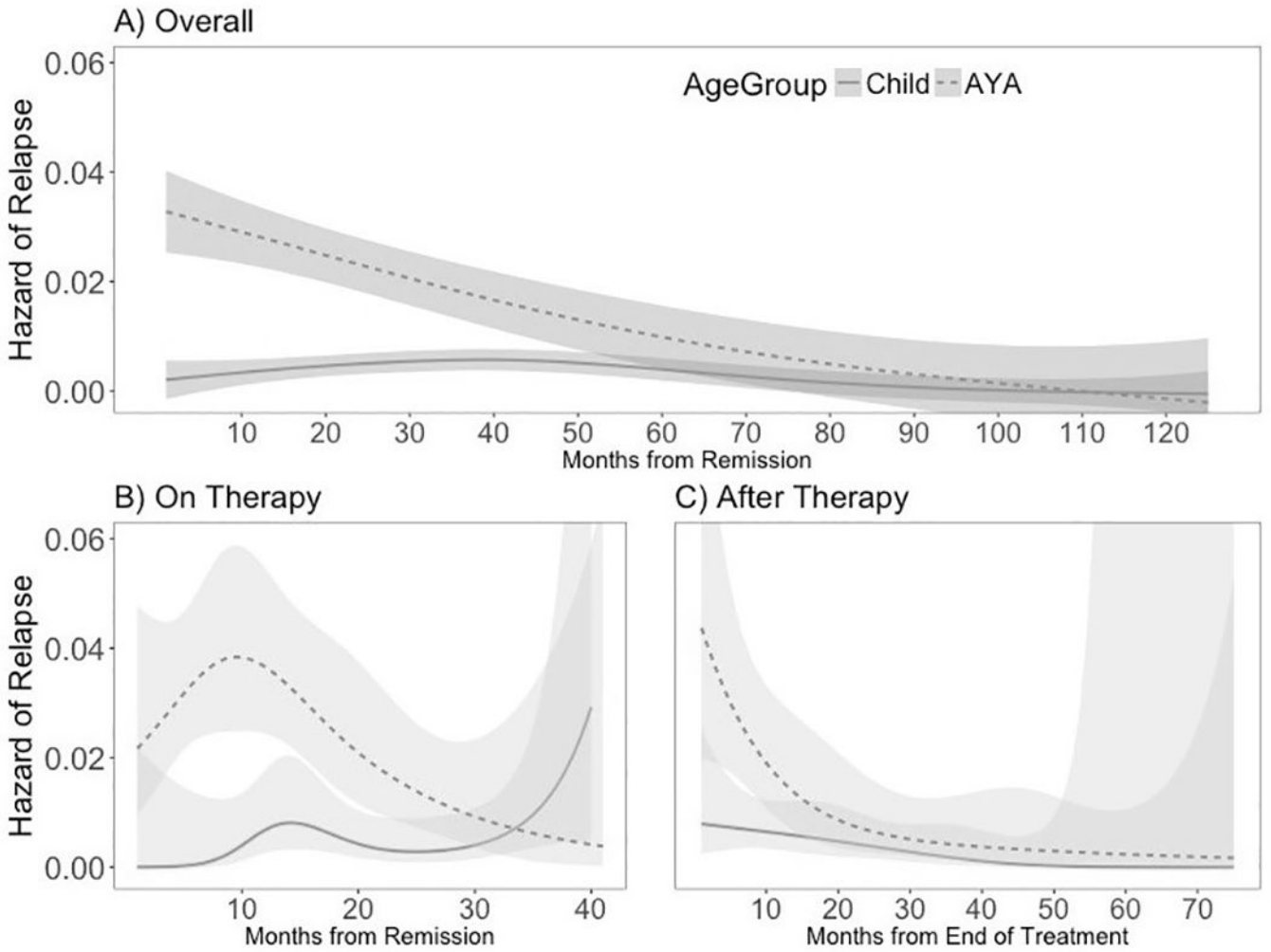
Figure 2.
Hazard of relapse in AYA and children with ALL. Smoothed plot of risk of relapse per month, stratified by age (AYA vs. child) for the following groups: **A,** Overall hazard of relapse from first CR1 to 10 years. **B,** Hazard of relapse during treatment from CR1. **C,** Hazard of relapse after completion of treatment (from date of last treatment). Shaded areas indicate confidence regions.

Table 1.

Characteristics of Children and AYA (Adolescents and Young Adults) with Acute Lymphoblastic Leukemia

	Total (n=184)	Child: 1–14y (n=91)	AYA: 15–39y (n=93)	p-value
Sociodemographics				
Age				
Median (Interquartile Range)	15y (4.75–34y)	4y (3–10y)	23y (19–30y)	
Gender				
Male	119 (64.7%)	56 (61.5%)	63 (67.7%)	0.4
Female	65 (35.3%)	35 (38.5%)	30 (32.3%)	
Race/ Ethnicity				
Non-Hispanic White	63 (34.2%)	30 (33.0%)	33 (35.5%)	0.1
African-American	1 (0.5%)	0 (0%)	1 (1.1%)	
Hispanic	99 (53.8%)	46 (50.6%)	53 (57.0%)	
Asian-Pacific Islander	21 (11.4%)	15 (16.5%)	6 (6.5%)	
Insurance				
Private	85 (46.2%)	48 (52.8%)	37 (39.8%)	0.2
Public	66 (35.9%)	30 (33.0%)	36(38.7%)	
No Insurance / Unknown	33 (17.9%)	13 (14.3%)	20 (21.5%)	
SES				
Low	32 (17.4%)	10 (11.0%)	22 (23.7%)	0.2
Mid-Low	36 (19.6%)	18 (19.8%)	18 (19.4%)	
Mid	39 (21.2%)	23 (25.3%)	16 (17.2%)	
Mid-High	39 (21.2%)	20 (22.0%)	19 (20.4%)	
High	38 (20.7%)	20 (22.0%)	18 (19.4%)	
Insurance + SES Combined				
Private Insurance + High SES	47 (25.5%)	26 (28.6%)	21 (22.6%)	0.3
Public/None + Mid/Low SES	69 (37.5%)	29 (31.9%)	40 (43.0%)	
Mixed Profile[1]	68 (37.0%)	34 (31.9%)	32 (34.4%)	
Treatment Variables				
Therapy				
Pediatric	102 (55.4%)	84 (92.3%)	18 (19.4%)	<0.0001
Adult	65 (35.3%)	0 (0%)	65 (69.9%)	
Mixed	7 (3.8%)	0 (0%)	7 (7.5%)	
International	10 (5.4%)	7 (7.7%)	3 (3.2%)	
Oncology Service				
Pediatric	101 (54.9%)	84 (92.3%)	17 (18.3%)	<0.0001
Adult	71 (38.6%)	0 (0%)	71 (76.3%)	
Mixed	2 (1.1%)	0 (0%)	2 (2.2%)	
International	10 (5.4%)	7 (7.7%)	3 (3.2%)	

	Total (n=184)	Child: 1–14y (n=91)	AYA: 15–39y (n=93)	p-value
Oncology Service + Therapy				
Pediatric Oncology / Pediatric Therapy	101 (54.9%)	84 (92.3%)	17 (18.3%)	
Adult Oncology / Adult Therapy	65 (35.3%)	0 (0%)	65 (69.9%)	<0.0001
Mixed Oncology / Mixed Therapy	18 (9.8%)	7 (7.7%)	11 (11.8%)	
Duration of Maintenance Mean (SD) in Months				
All patients	19 (11.2)	23.5 (8.5)	14.9 (12)	<0.01
Patients who completed therapy	25.4 (6.8)	25.3 (6.5)	25.4 (7.3)	0.9
Duration of Consolidation Mean (SD) in Months				
All patients	7.2 (3.6)	8.0 (3.6)	6.5 (3.5)	<0.01
Patients who completed therapy	8.0 (3.5)	8.2 (3.6)	7.7 (3.4)	0.5
Clinical Trial Enrollment				
Enrolled on Clinical Trial	60 (32.6%)	39 (42.9%)	21 (22.6%)	0.003
Not Enrolled on Clinical Trial	124 (67.4%)	52 (57.1%)	72 (77.4%)	
Clinical Prognosticators				
White Blood Cell Count At Diagnosis				
WBC <50K	129 (70.1%)	67 (73.6%)	62 (66.7%)	0.3
WBC >50K	55 (29.9%)	24 (26.4%)	31 (33.3%)	
Response to Therapy at the End of Induction[2]				
M1 marrow at End of Induction	139 (75.5%)	78 (85.7%)	61 (65.6%)	
M2-M3 marrow at End of Induction	18 (9.8%)	4 (4.4%)	14 (15.1%)	<0.01
Other	27 (14.7%)	9 (9.9%)	18 (19.4%)	
Immunophenotype				
Precursor B-cell	149 (81%)	79 (86.8%)	70 (75.3%)	0.04
T-cell	35 (19%)	12 (13.2%)	23 (24.7%)	
High Risk Cytogenetic Profile[3]				
High Risk Cytogenetic Profile	18 (9.8%)	5 (5.5%)	13 (14.0%)	0.05
No presence of high risk features	166 (90.2%)	86 (94.5%)	80 (86%)	
CNS Disease				
Positive	6 (3.3%)	2 (2.2%)	4 (4.3%)	
Negative	168 (91.3%)	86 (94.5%)	82 (88.2%)	0.3
Unknown	10 (5.4%)	3 (3.3%)	7 (7.5%)	

[1] *Mixed Profile* in this situation reflects a combination of either Public or No Insurance + High SES or Private Insurance + Low SES.

[2] Response to therapy at the end of induction was grouped as follows: (a) patients with an M1 marrow (<5% blasts) at the end of induction; (b) patients with an M2-M3 marrow (5% blasts) at the end of induction, but with M1 marrow on follow-up evaluation after additional therapy; (c) patients who did not have a documented end of induction marrow, but the first marrow documented after initiation of treatment (>36 days) was M1 ("Other").

[3] High-risk cytogenetic profile indicates presence of either: Philadelphia chromosome, MLL rearrangement and/or hypodiploidy.

Table 2.

Multivariable Hazard of Relapse in AYA (Adolescents and Young Adults) and Children

	Relapse During Therapy[1] (All Patients: n=184)			Relapse After Completion of Therapy[1] (Patients Completed Therapy: n=119)		
	HR	95%CI	p-value	HR	95%CI	p-value
Age Group						
Child	1.0	--	--	1.0	--	--
AYA	**10.5**	**2.1–52.5**	**0.004**	**7.7**	**2.5–23.9**	**<0.001**
Duration of Therapy						
Duration of Maintenance[2]	1.0	0.8–1.3	0.9	**0.9**	**0.8–0.9**	**<0.001**
Duration of Consolidation[2]	1.0	0.8–1.3	0.9	0.9	0.8–1.0	0.2
Oncology Service and Therapy Types						
Pediatric Oncology + Pediatric Therapy	1.0	--	--	1.0	--	--
Adult Oncology + Adult Therapy	**2.5**	**1.1–5.7**	**0.03**	0.6	0.2–1.8	0.3
Mixed Oncology + Mixed Therapy	0.5	0.2–1.8	0.3	**0.23**	**0.04–1.0**	**0.04**
Insurance and Socioeconomic Status (SES)						
Private Insurance + High SES	1.0	--	--	1.0	--	--
Public Insurance + Low SES	0.7	0.3–1.5	0.3	**6.2**	**1.8–21.9**	**0.004**
Mixed Profile	0.9	0.4–0.8	0.7	2.1	0.5–8.3	0.3
Race / Ethnicity						
Non-Hispanic White	1.0	--	--	1.0	--	--
Non-White Race/ Ethnicity	**2.1**	**1.1–4.0**	**0.03**	0.6	0.2–1.5	0.2
Clinical Trial Enrollment						
Enrolled on Clinical Trial	1.0	--	--	1.0	--	--
Not Enrolled on Clinical Trial	1.8	0.9–3.5	0.09	0.6	0.3–1.5	0.3
Gender						
Female	1.0	--	--	1.0	--	--
Male	0.7	0.4–1.3	0.3	**3.3**	**1.3–8.5**	**0.01**
Time						
Time in Months[2]	1.0	0.8–1.3	0.8	**1.0**	**0.9–1.0**	**<0.001**
Clinical Prognosticators						
WBC at Diagnosis <50K	1.0	--	--	1.0	--	--
WBC at Diagnosis >50K	**1.6**	**1.0–3.0**	**0.07**	**3.5**	**1.4–8.8**	**0.007**
Precursor B-cell	1.0	--	--	1.0	--	--
T-cell	1.1	0.6–2.1	0.8	**0.2**	**0.07–0.7**	**0.007**
No high-risk cytogenetics identified	1.0	--	--	1.0	--	--
High risk cytogenetic profile	1.1	0.5–2.3	0.8	0.5	0.1–2.0	0.3
M1 marrow at End of Induction[3]	1.0	--	--	1.0	--	--

	Relapse During Therapy[1] (All Patients: n=184)			Relapse After Completion of Therapy[1] (Patients Completed Therapy: n=119)		
	HR	95%CI	p-value	HR	95%CI	p-value
M2-M3 marrow at End of Induction[3]	1.8	0.9–4.0	0.1	2.0	0.5–7.5	0.3
CNS Negative	1.0	--	--			
CNS Positive	**4.9**	**1.6–15.3**	**0.006**			

[1] Adjusted discrete time survival analysis, modeling hazard of relapse with death due to non-relapse causes and date of last contact as censoring events. Bolded values represent statistically significant findings. On-therapy model adjusted for AYA*time interaction.

[2] These variables were modeled as time-varying covariates. Months represents: (a) months from remission in the model calculating hazard of relapse on therapy; (b) months from completion of therapy in the model calculating hazard of relapse after completing therapy. HRs represent each additional month of time from remission/ completion of therapy, or each additional month of therapy.

[3] Patients with M2-M3 marrows (5% blasts) at the end of induction were compared to patients who either (a) had M1 marrows (<5% blasts) at the end of induction or (b) did not have a documented end of induction marrow, but the first marrow documented after initiation of treatment (>36 days) was M1.

Table 3.

Multivariable Hazard of Relapse in AYA (Adolescents and Young Adults) by Time of Relapse

	Relapse During Therapy[1] (All AYA: n=93)			Relapse After Completion of Therapy[1] (AYA Who Completed Therapy: n=42)		
	HR	95%CI	p-value	HR	95%CI	p-value
Duration of Therapy						
Duration of Maintenance[2]	0.9	0.7–1.2	0.6	**0.7**	**0.6–0.8**	**<0.001**
Duration of Consolidation[2]	0.9	0.7–1.2	0.6	**0.8**	**0.6–1.0**	**0.03**
Oncology Service and Therapy Types						
Pediatric Oncology + Pediatric Therapy	1.0	--	--	1.0	--	--
Adult Oncology + Adult Therapy	1.9	0.7–5.2	0.2	0.8	0.1–4.7	0.8
Mixed Oncology + Mixed Therapy	0.3	0.1–1.5	0.2	0.3	0.04–1.9	0.2
Insurance and Socioeconomic Status (SES)						
Private Insurance + High SES	1.0	--	--	1.0	--	--
Public Insurance + Low SES	0.5	0.2–1.4	0.2	6.8	0.8–60.8	0.09
Mixed Profile	0.6	0.2–1.7	0.4	1.2	0.1–12.5	0.9
Race and Ethnicity						
Non-Hispanic White	1.0	--	--	1.0	--	--
Non-White Race/ Ethnicity	**2.2**	**1.0–4.8**	**0.05**	0.2	0.03–1.9	0.2
Clinical Trial Enrollment						
Enrolled on Clinical Trial	1.0	--	--	1.0	--	--
Not Enrolled on Clinical Trial	**2.6**	**1.0–6.3**	**0.04**	1.1	0.2–6.0	0.9
Gender						
Female	1.0	--	--	1.0	--	--
Male	0.8	0.4–1.7	0.6	1.3	0.3–5.1	0.7
Age						
Age in Years	1.00	1.0–1.1	0.5	1.0	0.9–1.1	1.0
Time						
Time in Months[2]	1.1	0.8–1.4	0.7	**0.98**	**0.96–1.0**	**0.03**
Clinical Prognosticators						
WBC <50K	1.0	--	--	1.0	--	--
WBC >50K	1.6	0.8–3.1	0.2	**7.9**	**1.6–38.8**	**0.01**
Precursor B-Cell	1.0	--	--	1.0	--	--
T-Cell	1.3	0.6–2.6	0.5	0.3	0.04–1.6	0.2
No high-risk cytogenetics identified	1.0	--	--	1.0	--	--
High risk cytogenetic profile	1.2	0.6–2.6	0.7			
M1 marrow at End of Induction[3]	1.0	--	--	1.0	--	--
M2-M3 marrow at End of Induction[3]	2.0	0.9–4.9	0.1	1.2	0.2–6.6	0.9

	Relapse During Therapy[1] (All AYA: n=93)			Relapse After Completion of Therapy[1] (AYA Who Completed Therapy: n=42)		
	HR	95%CI	p-value	HR	95%CI	p-value
CNS Negative	1.0	--	--			
CNS Positive	**8.6**	**2.1–35.0**	**0.003**			

[1] Adjusted discrete time survival analysis, modeling hazard of relapse with death due to non-relapse causes and date of last contact as censoring events. Bolded values represent statistically significant findings. On-therapy model adjusted for AYA*time interaction.

[2] These variables were modeled as time-varying covariates. Time at risk represents: (a) months from CR1 in the model calculating hazard of relapse on therapy; (b) months from completion of therapy in the model calculating hazard of relapse after completing therapy. HRs represent each additional month of time from remission/ completion of therapy, or each additional month of therapy.

[3] Patients with M2-M3 marrows at the end of induction were compared to patients who either (a) had M1 marrows at the end of induction or (b) did not have a documented end of induction marrow, but the first marrow documented after initiation of treatment (>36 days) was M1.