The Impact of Age-Related Clonal Hematopoiesis on Outcomes of Adults With Acute Lymphoblastic Leukemia

Caner Saygin[1], Ibrahim Aldoss[2], Todd C Knepper[3], Alexandra Rojek[1], Peng Wang[1], Angela Lager[1], Jeremy Segal[1], Sandeep Gurbuxani[1], Girish Venkataraman[1], Jason Cheng[1], Bijal Shah[3], Wendy Stock[1]

[1] Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL; [2] City of Hope Cancer Center, Duarte, CA; [3] Moffitt Cancer Center, Tampa, FL

Introduction

- Acute lymphoblastic leukemia (ALL) represents 20% of adult leukemias. Recent technologic advances have enabled detailed characterization of the genetic basis of leukemogenesis in ALL, including somatic structural DNA rearrangements and sequence mutations that disrupt lymphoid development, signaling, tumor suppression, and epigenetic modification.
- Adult ALL patients, especially older adults (≥40 years), were underrepresented in these large series.
- Clinical outcomes of older ALL patients are inferior to young ALL patients (<40 years) and the molecular basis for these differences is not completely understood.
- Hematopoietic stem cells accumulate DNA mutations with aging, and age-related clonal hematopoiesis (ARCH) has been linked to increased incidence of myeloid malignancies. The prevalence of ARCH increases logarithmically as the population ages, but its role in lymphoid leukemogenesis has not been fully established.

Hypothesis

- We hypothesize that ARCH is a common precursor lesion for the development of ALL in older adults, and patients with ARCH-associated ALL have different clinical outcomes compared to patients whose disease do not harbor these mutations.

Methods

- We retrospectively studied adult ALL patients treated at the University of Chicago and Moffitt Cancer Center between July 2014 and April 2021.
- Genetic profiling of tumor samples was performed by using Miseq Illumina next-generation sequencing (NGS) platform with a comprehensive sequencing panel covering commonly mutated myeloid and lymphoid genes.
- We classified pathogenicity using American College of Medical Genetics and Genomics guidelines.

Results

Table 1. Baseline characteristics of study cohort (n= 353)

	B-ALL (n= 290)	T-ALL (n= 50)	ETP-ALL (n= 13)	p value
Age at diagnosis, median (range)	49 (18-84)	38.5 (19-88)	30 (18-72)	**0.012**
Age group, n (%)				
<40 yrs	106 (37%)	26 (52%)	8 (62%)	**0.03**
≥40 yrs	184 (63%)	24 (48%)	5 (38%)	
Female, n (%)	139 (48%)	13 (26%)	5 (38%)	**0.014**
CH mutations, n (%)				
Present	80 (28%)	19 (38%)	6 (46%)	0.13
Absent	210 (72%)	31 (62%)	7 (54%)	
Median OS, months (range)	48 (1-123)	NR (4-78)	32 (2-76)	0.90
Median RFS, months (range)	32 (1-97)	NR (1-77)	13 (1-54)	0.78

OS, overall survival; RFS, relapse-free survival

Figure 1. Variant allelic frequencies (VAFs) of most frequently mutated genes in adult ALL

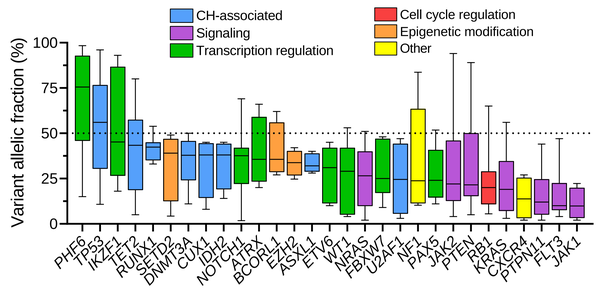


Figure 2. Oncoprint of mutations in B-ALL cohort

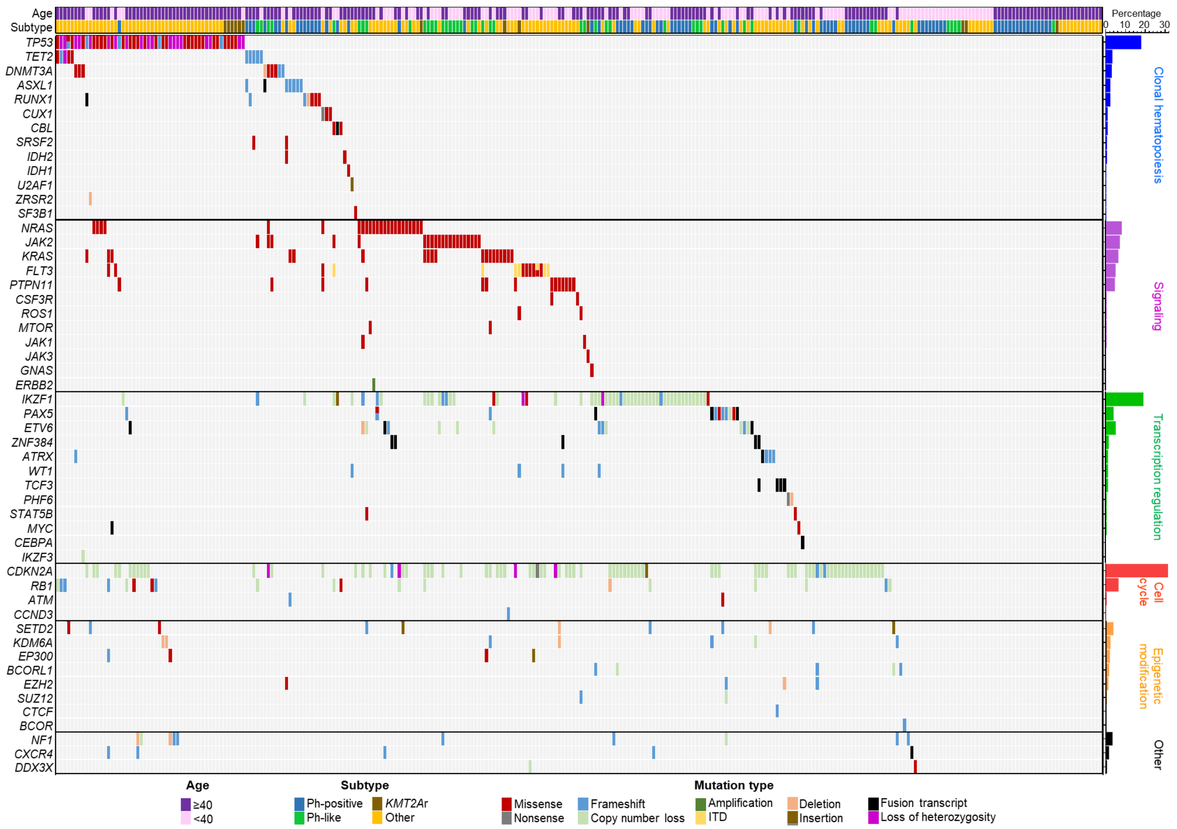


Figure 3. CH-associated ALL has inferior outcomes

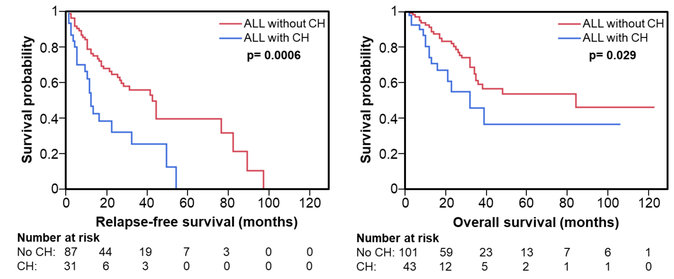


Figure 4. Association between mutations and clinical variables

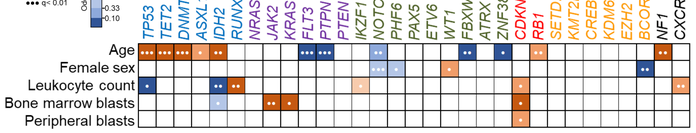
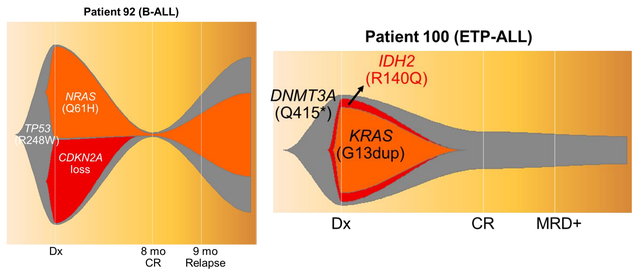


Figure 5. Clonal evolution of CH-associated ALL



Conclusion

- ARCH is commonly identified as an ancestral event in older adults with ALL, with *TP53* mutations being the most prevalent.
- ALL patients harboring CH-associated mutations have inferior survival compared to patients without CH mutations.
- ARCH may constitute a fertile soil for acute lymphoblastic leukemogenesis and further studies are warranted to interrogate the dynamic interplay between myeloid and lymphoid compartments of these patients.