STUDY OF THE EFFECT OF AGE ON TOXICITY DURING TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

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Introduction

- **Background:** Minimizing toxicity to ALL treatment is critical to patient safety and the efficacy of therapy.
- **Existing data:** Published data and clinical experience suggest that adolescents and young adults experience greater toxicity than their younger counterparts during the induction and delayed intensification (DI) phases of therapy due to use of asparaginase and steroids.
- **Limitations of published data:** The data that exist have reflected the use of an older asparaginase preparation, have been based on reviews, or do not address the potential role of BMI, ethnicity, and gender in the expression of toxicities.
- **Objective:** We wanted to determine whether age influences the likelihood of a patient with ALL to experience a higher frequency or maximum grade of grade 3-5 chemotherapy-related toxicities during the induction and DI phases.
- **Other considerations:** We looked at what role BMI, ethnicity, and gender play in the effect of age on toxicity.

Methods

- **Identification of patients:** Patients with ALL aged >1 and < 22 years at diagnosis, classified and treated as having high-risk disease on or as per the Children's Oncology Group protocol AALL0232 over the past 10 years, were identified through the pediatric oncology registry at Children's Health System of Texas.
- **Type of study**: We conducted a retrospective chart review, using electronic medical records to document the toxicities during induction and DI.
- **Data collected:** Type of leukemia, age at diagnosis, ethnicity, BMI, gender, toxicities, WBC count at diagnosis, CNS status, dates of treatment, allergies to chemotherapy, and leukemia cytogenetics.
- **Grading of toxicity severity:** We used the CTCAEv4 system to grade the toxicities listed in an excel spreadsheet.
- **Toxicity exclusions:** We excluded febrile neutropenia in the list of toxicities.
- **Patient characteristics:** Patient characteristics were summarized by quartile of age at diagnosis.
- **Statistical analysis-unadjusted trends:** Unadjusted trends between toxicity outcomes and age were tested using the Jonckheere-Terpstra nonparametric method.
- **Statistical analysis-adjusted trends:** Trends between toxicity outcomes and age adjusted for BMI, ethnicity, and gender were tested using Poisson regression models.

Results

Figure 1. Induction Phase
Age at diagnosis versus maximum grade of toxicity, excluding febrile neutropenia
Unadjusted trends

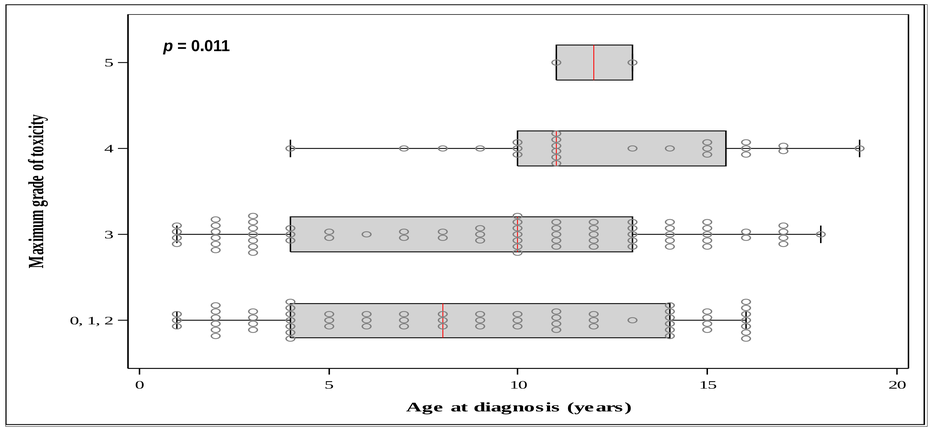

Figure 2. Induction Phase
Age at diagnosis vs. number of grade 3-5 toxicities, excluding febrile neutropenia
Unadjusted trends

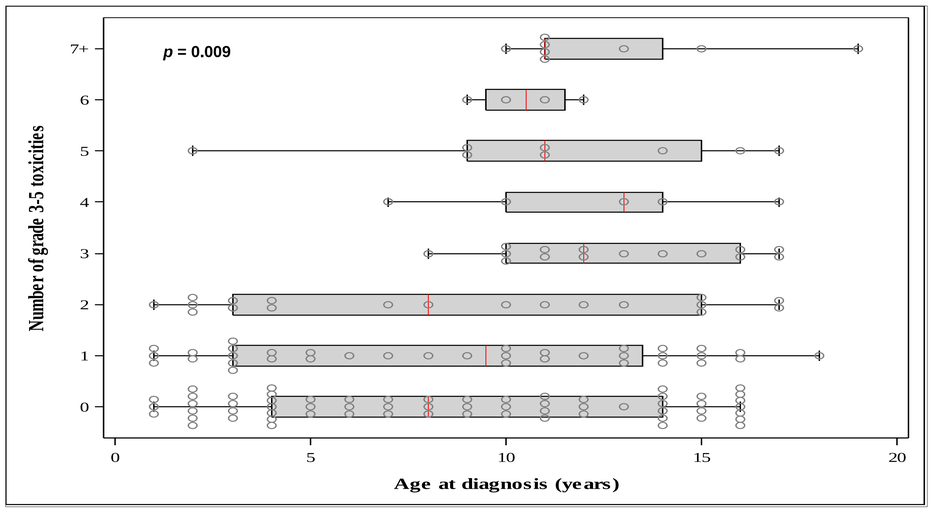

Figure 3. Induction Phase-Toxicity outcomes, excluding febrile neutropenia
Multiple regression models, Adjusted for BMI, ethnicity, and gender

	Maximum grade of toxicity				Number of grade 3-5 toxicities			
	Estimate	Lower 95% CL	Upper 95% CL	P	Estimate	Lower 95% CL	Upper 95% CL	P
Effect								
Multiplier per year of age	1.00	0.98	1.03	0.723	1.01	0.97	1.04	0.747
Multiplier per kg/m² of BMI	1.02	1.00	1.03	0.084	1.05	1.03	1.07	<.001
Multiplier for Mexican, Hispanic, Puerto Rican, or Latin American ethnicity	1.10	0.85	1.35	0.420	1.41	1.09	1.83	0.010
Multiplier for female gender	1.17	0.92	1.43	0.140	1.27	1.00	1.61	0.051

Results

- The two toxicity outcomes are: (1) maximum grade of toxicity, and (2) number of grade 3-5 toxicities.
- All results exclude febrile neutropenia as one of the toxicities.
- In the induction phase of therapy with N=158, the unadjusted trend between age at diagnosis and maximum grade of toxicity is significant (Figure 1).
- In the induction phase of therapy with N=158, the unadjusted trend between age at diagnosis and number of grade 3-5 toxicities is significant (Figure 2).
- The multiple regression results in Figure 3 indicate that when the relationships between age at diagnosis and toxicity are adjusted for BMI, ethnicity, and gender, the relationships between age at diagnosis and both maximum grade and number of grade 3-5 toxicities are no longer significant.
- In Figure 3, BMI and ethnicity seem to significantly influence the number of grade 3-5 toxicities, which may explain age correlates with toxicity in the unadjusted analysis shown in Figure 2.
- The relationships between age at diagnosis and both maximum grade and number of grade 3-5 toxicities during the delayed intensification phase are not significant.

Conclusion

- Conducting a retrospective chart review of the high-risk ALL patients at Children's Health System revealed that age is not a significant risk factor for higher frequency and severity of chemotherapy-related toxicity when adjusted for BMI, ethnicity, and gender.
- BMI and ethnicity significantly influences the number of grade 3-5 toxicities.
- We evaluated the impact of toxicity outcomes using either of two imperfect measures. The maximum grade of toxicity addresses the severity of any particular toxicity but is insensitive to the burden of multiple toxic comorbidities. The number of grade 3-5 toxicities addresses the burden of multiple toxic comorbidities but is insensitive to the severity of any particular toxicity. Further refinements are pending.
- This research will allow for the design of better supportive care measures and will enhance our ability to counsel patients and their parents with respect to the risks associated with ALL therapy.