UCI Chao Family Comprehensive Cancer Center
2024 Scientific Retreat

Pegaspargase Therapy in Acute Lymphoblastic Leukemia (ALL): Therapeutic Drug Monitoring and Toxicity

Van Huynh, MD

Director, Leukemia Program

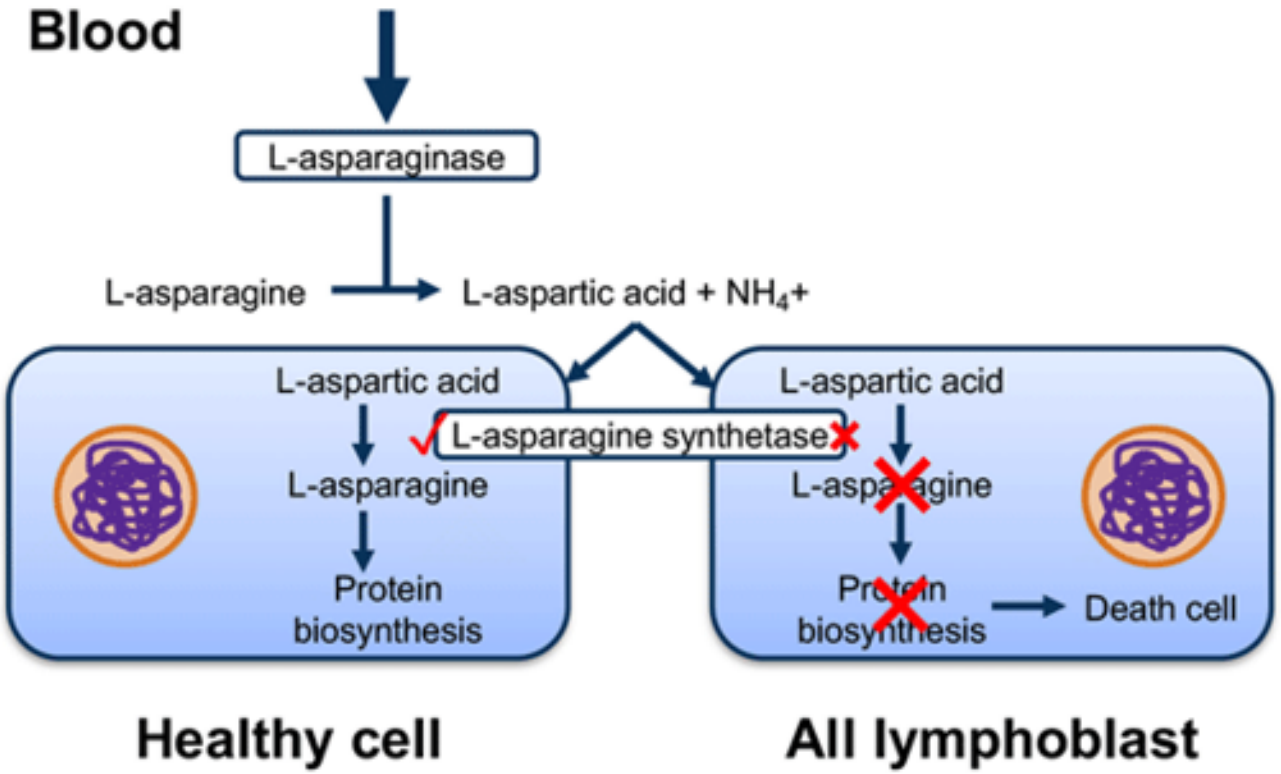
Section Director, CAR T-Cell Program

CHOC Children's Hospital

11/8/2024

Anti-leukemic Affects of Asparaginase

- Children with ALL have overall survival rates >90% versus ~50% in adults
- Asparaginase is key component of pediatric/adolescent ALL therapy
  - 2 to 7 doses given over 2.5 years
  - Levels ≥ 0.1 IU/mL are therapeutic
- Asparaginase high incidence of toxicities and allergic reactions



Multicenter Study to Assess Asparaginase-related Hypersensitivity and Toxicity in Multi-Ethnic Population

- Evaluate pharmacokinetic profile of asparaginase levels at 7 and 14 days after Pegaspargase (PEG)
- Determine if PEG levels vary with obesity, sex, age, race/ethnicity, leukemia type
- Evaluate the incidence of hypersensitivity reactions (HSR) and toxicities related to PEG
- Genome-wide association study (GWAS) to identify pharmacogenomic markers associated with hypersensitivity and Grade ≥3 toxicities

CHOC

Results - Demographics

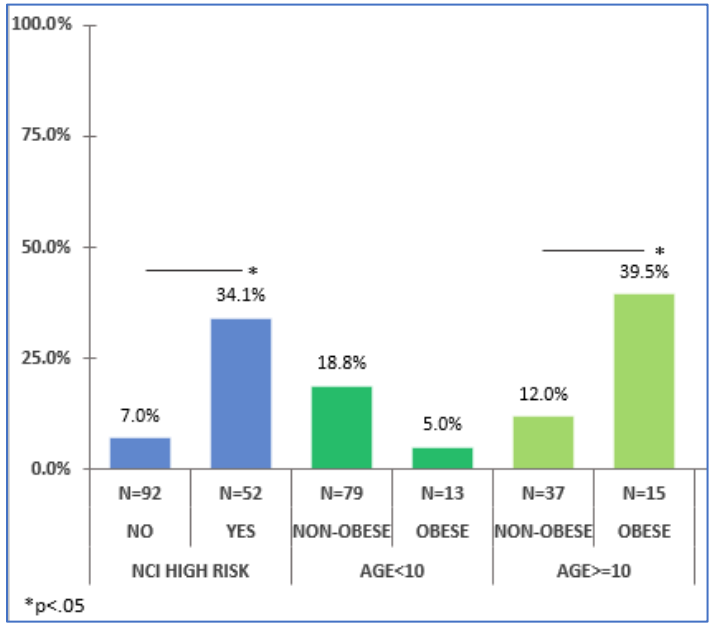
- 358 doses of PEG were administered to 144 patients
- Mean was 8.6 yrs (range 1.1-23.9)
- 61.8% males
- 52.5% Hispanic
- 32.6% obese/overweight
- Hispanic patients more likely to be obese 24.7% vs 10.6% Non-Hispanics

Characteristic	*participants N=144*
Demographics	
Age at diagnosis, years	*7.4 [3.6, 12.1]*
Age at diagnosis ≥ 10 years	*52 (36.1%)*
Gender, male	*89 (61.8%)*
Race/Ethnicity, Hispanic	*73 (52.5%)*
BMI (kg/m^2)	*19.3 (5.6)*
BMI percentile	
Underweight	*10 (6.9%)*
Normal	*87 (60.4%)*
Overweight	*19 (13.2%)*
Obese	*28 (19.4%)*
Clinical status	
B-cell ALL	*125 (86.8%)*
CNS Involvement, CNS1	*118 (82.5%)*
NCI Risk Group, high risk	*52 (36.1%)*
Down Syndrome	*9 (6.3%)*
MRD (day 29) <0.01%	*112 (78.9%)*

CHOC

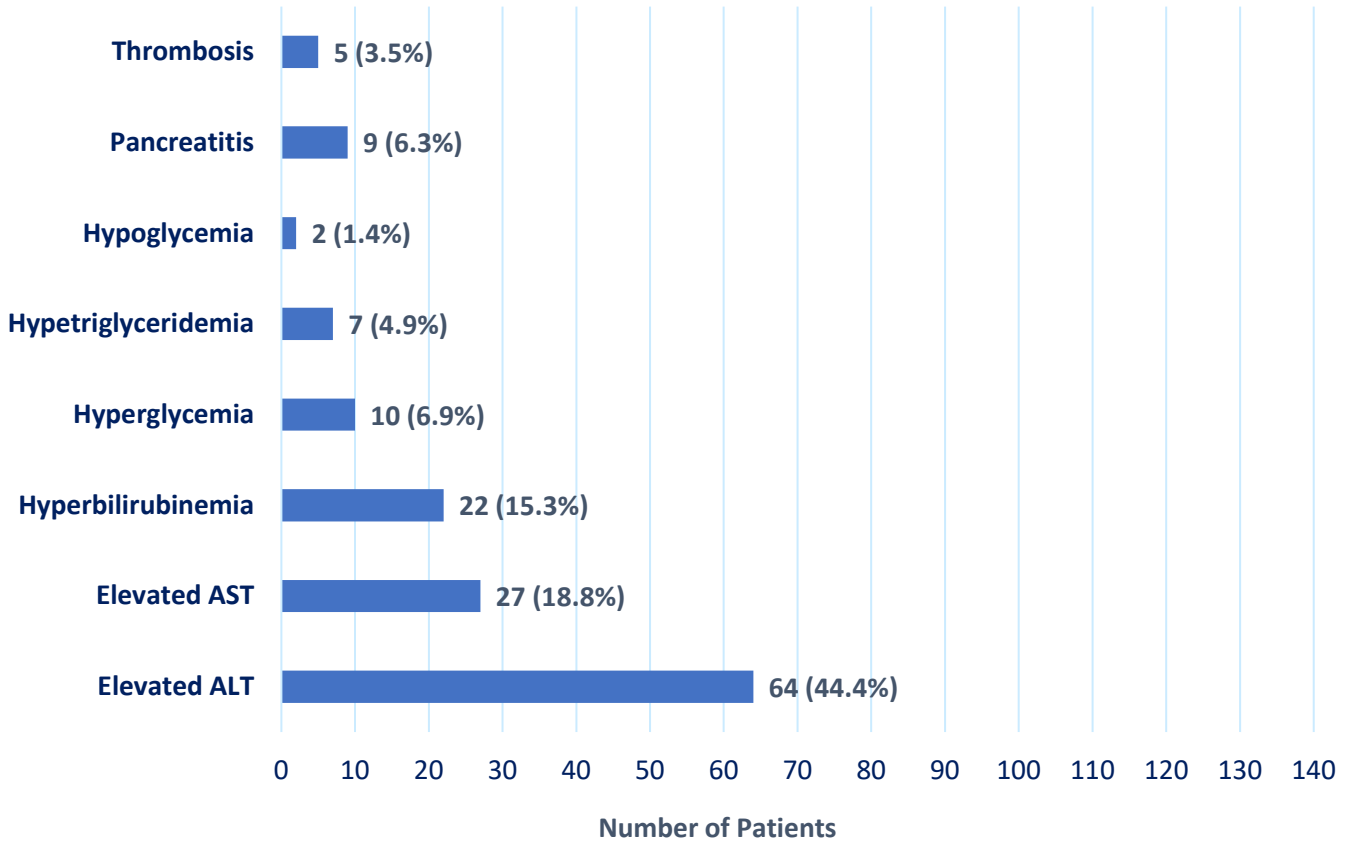
Characteristics associated with increased odds of hypersensitivity reaction (HSR) to PEG

- Incidents of HSR was 19.4% (28 of 144 patients)
- Mean age with HSR 10.5 years
- Fifteen (53.6%) were Hispanic and 10 (35.7%) were obese
- In the bivariate analysis: the likelihood of HSR was increased with obesity (p=0.020), older age ≥10 years (p= 0.036), NCI HR (p=0.013) and non B-ALL



Characteristics	Bivariate	Multivariable
	OR (95% CI), p-value	OR (95% CI), p-value
Sex (Female vs. Male)	1.06 (0.45, 2.49), p=.894	----
Ethnicity (Hispanic vs. Non-Hispanic)	1.30 (0.54, 3.09), p=.556	----
Age at diagnosis (≥10 vs. <10 yrs)	2.47 (1.06, 5.75), **p=.036**	0.41 (0.10, 1.59), p=.195
Obesity (Obese vs. Non-obese)	3.03 (1.20, 7.68), **p=.020**	1.78 (0.40, 7.83), p=.446
CNS status at diagnosis (1 vs. 2 or 3)	0.56 (0.20, 1.51), p=.246	----
NCI risk stratification at diagnosis (High vs. Standard Risk)	2.96 (1.26, 6.95), **p=.013**	6.89 (1.82, 26.13), **p=.005**
B-cell ALL (Y vs. N)	0.35 (0.12, 0.99), **p=.048**	0.29 (0.06, 1.50), p=.139
Time after pre-medication to start PEG infusion (<60 vs. >=60 minutes)	1.51 (0.64, 3.56), p=.344	2.53 (0.87, 7.41), p=.088

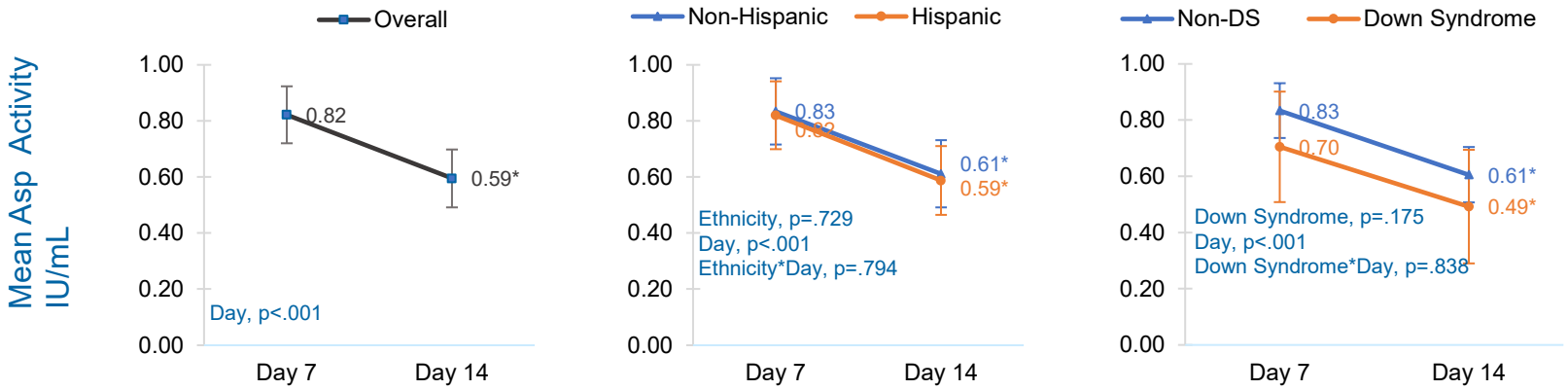
Grade 3-4 (severe) PEG-Associated Toxicities

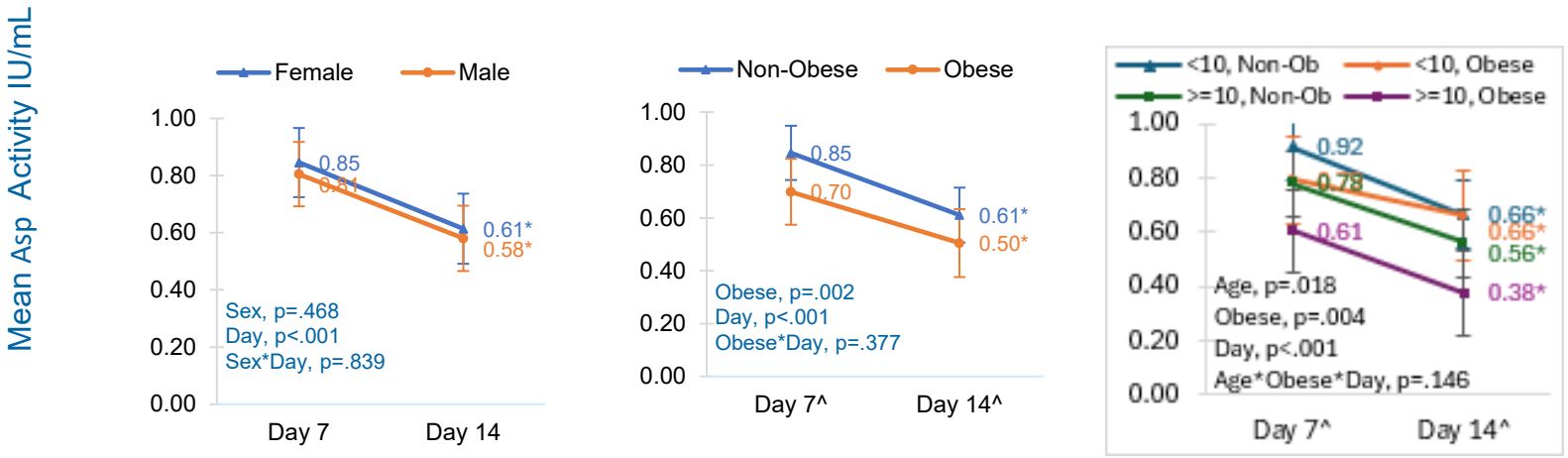


- Toxicities were observed in 41% of patients (59 of 144 pts)
- Most common was liver toxicity (elevated ALT)
- Pancreatitis occurred in 9 patients (6.3%) and all were Hispanics
- The risk factor for PEG-associated toxicity was older age $\geq$ 10 years (OR=2.75 (95% CI 1.31, 5.77), p=.008

CHOC

Mean asparaginase activity (AA) levels at Day 7 and 14 after PEG administration by demographic characteristics





- The mean AA levels:
  - Day 7 = 0.82 IU/mL
  - Day 14 = 0.59 IU/mL
- In general – levels are supratherapeutic (need AA >0.1 IU/ml to be effective)

GWAS to identify Pharmacogenetic Markers associated with PEG-related Hypersensitivity and Toxicities

- Abstract: 208260 – 66th ASH meeting in San Diego (Dec 2024)
- Collaboration with Drs. Jatinda Lamba and Vivek Shastri at Univ of Florida
- Infinium GSA-24 v3.0 was used to genotype 650,000 single nucleotide polymorphisms (SNPs) and post standard QC, 233,798 SNPs were tested
- Confirmed SNPS reported in literature

- **Identified novel, unique markers not previously reported**
- 72 SNPs in 59 genes associated with PEG-related hypersensitivity
  - PRKCE, ALX4, STAG1, DAB1, MPK10
- 75 SNPs in 64 genes were associated with PEG-toxicities
  - SPRY4, PALM2-AKAP2 fusion gene, and ALK

CHOC

GWAS in Hispanic Population

Hypersensitivity: Adjusted for Hispanic race/ethnicity

- 34 SNPs in 30 genes were associated with hypersensitivity ($p < 0.001$)
- SNPS included: ITPR2, ABHD6, ST6GAL2, RORA, and PAPSS1

Toxicities: Adjusted for Hispanic race/ethnicity

- 25 SNPs in 24 genes were associated with any grade >3 toxicity ($p < 0.001$)
- SNPs included: KCNN2, KCNH5, CLASP1, PON2, WWOX, STIM1, IQCE, and FUT10

CHOC

Summary

- 19.4% of patients experienced HSR to PEG therapy
- Risk factors for HSR include age ≥ 10, obesity, NCI HR and non B-ALL. In patients ≥ 10, obesity amplified their risk for HSR.
- A high number of patients (41%) experienced severe PEG-associated toxicity; older age increased the risk for toxicity
- Mean AA levels exceeded the level needed to be therapeutic
- We identified novel, unique SNPs not previously reported that are associated with HSR and toxicities
- Additional studies are warranted to determine whether sequencing can identify populations at risk for HSR and toxicities and can benefit from dose reductions of PEG to minimize toxicity

CHOC

Thank You

- CHOC Children's Hospital
  - Sonia Morales, MD
  - Keri Zabokrtsky, MS
  - Carol Lin, MD
  - Tricia Morphew
- Cincinnati Children's Hospital
  - Christine Phillips, MD
- UCSF Benioff Children's Hospital
  - Beth Winger, MD
- UCSF – Oakland Children's
  - Anu Agrawal, MD
- Lucille Packard – Stanford Children's
  - Catherine Aftandilian, MD
- Kansas - Mercy Children's
  - Keith August, MD
  - Erin Guest, MD
- Lamba Lab – University of Florida
  - Jatinder Lamba, PhD
  - Vivek Shastri, PhD
- Funding
  - CHOC PSF Tithe Grant, CHOC Hyundai Cancer Institute Research Grant, Servier Pharmaceuticals

Thank you to our patients and families

Contact: Van Huynh / vahuynh@choc.org