



Superior Outcomes in Hispanic Patients compared to Non-Hispanic Patients with Ph-negative Acute Lymphoblastic Leukemia (USC ALL) Regimen for Newly Diagnosed ALL Patients in the Era of Novel Agents; A Retrospective Study



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Introduction

- Hispanic patients with acute lymphoblastic leukemia (ALL) are historically known to have poor outcomes compared to non-Hispanic patients even though outcomes in the general ALL population have since the 1990s (1)
- Per SEER and WHO data, the Hispanic population has higher incidence rates, but lower 5-year over-all survival compared to non-Hispanic counterparts (2-4)
- Our institution, LAC-USC (LA County Hospital/ University of Southern California) has shown a complete remission rate of 96% with use of peg-asparaginase at 2000 IU/m2 using the USC ALL regimen (based on CCG-1882) for patients aged 17-55 years with a 7-year OS of 51% reported in 2014 (5-6)
- The modified USC ALL regimen now uses a single dose of cytarabine rather than fractionated doses and uses a single dose 3g/m² methotrexate compared to 1g/m² (2.5g/m² if T-cell) D1, 15 in original USC ALL regimen to improve compliance, while consolidation was increased to six cycles allowing for PEG holidays to improve toxicity (Table 1)

Objectives

- Since our institution takes care of a large population of Hispanic patients with ALL we report outcomes in Hispanic and Non-Hispanic patients using the modified USC ALL regimen in the era of novel agents like blinatumomab and inotuzumab
- Primary Outcomes:**
 - Over-all survival (OS) and event-free survival (EFS) at 3 years for Ph-negative ALL patients (any ALL (B, T cell), except Ph-Positive type)
- Secondary Outcomes:**
 - Complete remission/complete remission w/ incomplete recovery (CR/CRi) and minimal residual disease (MRD) flow status [≥0.01%= positive] rates

Materials & Methods

- Distribution of time-to-event end points/outcomes were calculated with Kaplan-Meier (KM) method and OS and EFS reported through KM curves. Two-sided p value ≤0.05 was considered significant.
- This is a retrospective, single institution chart review study
- Included adults >18 years old with newly diagnosed Ph-negative ALL (2016-2020) treated at our institution
- Demographics presented using descriptive statistics, and patients were stratified into Hispanic and non-Hispanic cohorts and evaluated using Fisher's exact test
- OS and EFS were reported through Kaplan Meier curves and Log-rank tests. Two-sided p-value ≤0.05 was significant

USC ALL	Modified USC ALL
Induction phase 1 Daunorubicin 60 mg/m ² intravenously (IV) on days 1, 2, 3; Vincristine 1.4 mg/m ² IV (maximum, 2 mg) on days 1, 8, 15, and 22 Pegaspargase 2,000 IU/m ² IV on day 15 Prednisone 60 mg/m ² orally on days 1 to 28; Methotrexate 12 mg intrathecally (IT) on days 8 and 15.	Induction phase 1 Daunorubicin 60 mg/m ² IV day 1, 2,3 Vincristine 1.4 mg/m ² IV day 1,8,15,22 Peg-asparaginase 2000 IU/m ² IV day 15 Prednisone 60 mg/m ² orally on days 1 to 28; Methotrexate 12 mg intrathecally (IT) on days 15 and 22.
Induction phase 2 Cyclophosphamide 1 g/m ² IV on days 1 and 29 Cytarabine 75 mg/m ² IV on days 1 to 4, 8 to 11, 29 to 32, and 36 to 39 Vincristine 1.4 mg/m ² IV (maximum, 2 mg) on days 15, 22, 43, and 50 Pegaspargase 2,000 IU/m ² IV on day 15 Prednisone 20 mg/m ² orally on days 15 to 29 Mercaptopurine 60 mg/m ² orally on days 1 to 14 and 29 to 43; Methotrexate 12 mg IT on days 1, 8, 15, and 22.	Induction Phase 2 Cyclophosphamide 1 g/m ² IV on days 1 Cytarabine 1.4 mg/m ² IV (maximum, 2 mg) on days 1 and 15 Methotrexate 3 g/m ² IV day 15 Leucovorin 50 mg every 8 hours IV starting 24 hours from start of methotrexate Pegaspargase 2,000 IU/m ² IV on day 16 Prednisone 20 mg/m ² orally on days 15 to 29 Mercaptopurine 60 mg/m ² orally on days 1 to 14 and 29 to 43; Methotrexate 12 mg/hydrocortisone 25 mg IT on days 1
Intensification Methotrexate 1 g/m ² (T-cell acute lymphoblastic leukemia, 2.5 g/m ²) IV on days 1 and 15; leucovorin 15 mg every 6 hours IV starting 36 hours from start of methotrexate Pegaspargase 2,000 IU/m ² IV on day 16; Prednisone 20 mg/m ² orally on days 16 to 30.	Methotrexate 3 g/m ² IV day 1 Leucovorin 50 mg every 8 hours IV starting 24 hours from start of methotrexate Pegaspargase 2,000 IU/m ² IV on day 15 Prednisone 20 mg/m ² orally on days 15-22 Methotrexate 12 mg/hydrocortisone 25 mg/cytarabine 30 mg triple chemo) IT on days 15
Consolidation Cytarabine 75 mg/m ² IV on days 1 to 5 Mercaptopurine 60 mg/m ² IV on days 1 to 5.	Consolidation I Cytarabine 500 mg/m ² IV day 1 Cytoxin 1g/m ² IV day 1 Vincristine 1.4 mg/m ² IV day 1 Mercaptopurine 60 mg/m ² orally on days 15-28 Methotrexate 12 mg/hydrocortisone 25 mg/cytarabine 30 mg triple chemo) IT on days 1
Delayed reinduction Daunorubicin 25 mg/m ² IV on days 1, 8, and 15 Vincristine 1.4 mg/m ² IV (maximum, 2 mg) on days 1, 8, 15, 43, and 50 Dexamethasone 10 mg/m ² orally on days 15 to 22 and 43 to 50. Pegaspargase 2,000 IU/m ² IV on day 15 Cyclophosphamide 1 g/m ² on day 29; Cytarabine 75 mg/m ² IV on days 29 to 32 and 36 to 39 Thioguanine 60 mg/m ² orally on days 26 to 42 Methotrexate 12 mg IT on days 1, 29, and 36.	Consolidation II Cytarabine 1000 mg/m ² IV day 1 Cytoxin 1000 mg/m ² IV day 1 Vincristine 1.4 mg/m ² IV (maximum, 2 mg) on days 15-22 Pegaspargase 2,000 IU/m ² IV on day 15 Prednisone 20 mg/m ² orally on days 15-22 Methotrexate 12 mg/hydrocortisone 25 mg/cytarabine 30 mg triple chemo) IT on days 1, 15
Intensification 2 Methotrexate 1 g/m ² (T-cell acute lymphoblastic leukemia, 2.5 g/m ²) IV on days 1 and 15; leucovorin 15 mg every 6 hours IV starting 36 hours from start of methotrexate Pegaspargase 2,000 IU/m ² IV on day 16; Prednisone 20 mg/m ² orally on days 16 to 30.	Consolidation III Daunorubicin 25 mg/m ² IV day 1,8,15 Cytoxin 1000 mg/m ² IV day 1 Vincristine 1.4 mg/m ² (max 2) IV day 1,8,15 Dexamethasone 10 mg/m ² PO day 15-22 Pegaspargase 2,000 IU/m ² IV on day 15 Prednisone 20 mg/m ² orally on days 15-22 Methotrexate 12 mg/hydrocortisone 25 mg/cytarabine 30 mg triple chemo) IT on days 1, 15
Consolidation 2 Cytarabine 75 mg/m ² IV on days 1 to 5 Mercaptopurine 60 mg/m ² IV on days 1 to 5.	Consolidation IV Cytarabine 3 g/m ² IV day 1, 15 Leucovorin 50 mg every 8 hours IV starting 24 hours from start of methotrexate Vincristine 1.4 mg/m ² IV (maximum, 2 mg) on days 1 and 15 Pegaspargase 2,000 IU/m ² IV on day 16 Prednisone 20 mg/m ² orally on days 16-23
Delayed reinduction 2 Daunorubicin 25 mg/m ² IV on days 1, 8, and 15 Vincristine 1.4 mg/m ² IV (maximum, 2 mg) on days 1, 8, 15, 43, and 50 Dexamethasone 10 mg/m ² orally on days 15 to 22 and 43 to 50. Pegaspargase 2,000 IU/m ² IV on day 15 Cyclophosphamide 1 g/m ² on day 29; Cytarabine 75 mg/m ² IV on days 29 to 32 and 36 to 39 Thioguanine 60 mg/m ² orally on days 26 to 42 Methotrexate 12 mg IT on days 1, 29, and 36.	Consolidation V Cytarabine 500 mg/m ² IV day 1 Cytoxin 1g/m ² IV day 1 Vincristine 1.4 mg/m ² (max 2) IV day 1 Mercaptopurine 60 mg/m ² orally on days 15-28 Methotrexate 12 mg/hydrocortisone 25 mg/cytarabine 30 mg triple chemo) IT on days 1, 15
Maintenance (monthly x 24 mos) prednisone 60 mg/m ² orally on days 1 to 5 (year 1, monthly; year 2, every 2 months) Vincristine 1.4 mg/m ² IV (maximum, 2 mg) on day 1 (year 1, monthly; year 2, every 2 months) Mercaptopurine 60 mg/m ² orally on days 1 to 28 Methotrexate 20 mg/m ² orally on days 1, 8, 15, and 22 and 12 mg IT	Maintenance prednisone 60 mg/m ² orally on days 1 to 5 (year 1, monthly; year 2, every 2 months) Vincristine 1.4 mg/m ² IV (maximum, 2 mg) on day 1 (year 1, monthly; year 2, every 2 months) Methotrexate 10mg/m ² po weekly x 2 years IT AAH-C 30mg, HCT2 25mg, MTX 12mg every 3 months in first year

Table 1. Original USC ALL vs modified USC ALL regimen

Variable	All Ph-Negative Patients (n=121)	Patient Ethnicity		p-value
		Non-Hispanic (NHP) (n=34)	Hispanic (HP) (n=87)	
Age at diagnosis (years)	38.5 (24.3)	35 (28) (19.68)	39 (22) (18.73)	0.510
Age Groups				0.669
<25	18 (15.0%)	7 (21.2%)	11 (12.6%)	
25 – 34	35 (29.2%)	9 (27.3%)	26 (29.9%)	
35 – 44	25 (20.8%)	5 (15.3%)	20 (23.2%)	
45 – 54	21 (17.5%)	7 (21.2%)	14 (16.1%)	
55+	21 (17.5%)	5 (15.2%)	16 (18.4%)	
BMI (kg/m ²)	28.9 (9.5)	26.9 (10.0) (16.6, 37.1)	29.0 (9.1) (16.5, 50.5)	0.421
BMI Categories				0.867
<30	67 (55.4%)	20 (58.8%)	47 (54.0%)	
30 – 40	45 (35.5%)	12 (35.3%)	31 (35.6%)	
40+	11 (9.1%)	2 (5.9%)	9 (10.3%)	
Gender				0.076
Male	70 (57.9%)	24 (70.6%)	46 (52.9%)	
Female	51 (42.1%)	10 (29.4%)	41 (47.1%)	
Race				
White		19 (55.9%)	9 (10.3%)	
African American		12 (35.3%)	3 (3.5%)	
Asian		0	0	
Other		0	0	
Karyotype				0.999
Unfavorable	65 (54.6%)	19 (55.9%)	46 (54.1%)	
Intermediate	5 (4.2%)	1 (2.9%)	4 (4.7%)	
Favorable	45 (37.3%)	12 (35.3%)	32 (37.7%)	
Uninform				
Hepatic Steatosis				0.239
Yes	62 (52.5%)	15 (44.1%)	47 (56.0%)	
No	54 (45.3%)	19 (55.9%)	31 (35.6%)	
Cirrhosis only	2 (1.7%)	0	2 (2.4%)	
Hep. Steatosis & Cirr.	0	0	0	
CNS Disease				0.652
No	112 (94.9%)	29 (93.5%)	83 (95.4%)	
Yes	6 (5.1%)	2 (6.5%)	4 (4.6%)	
Allogeneic SCT				0.397
No	82 (67.8%)	25 (73.5%)	57 (65.5%)	
Yes	39 (32.2%)	9 (26.5%)	30 (34.5%)	
Number of Peg-Asp doses	2 (3)	2 (4) (0.6)	2 (3) (0.8)	0.496
Ph-Negative Subtypes				0.684
Ph-Neg B ALL	60 (49.6%)	16 (47.1%)	44 (50.6%)	
Ph-Like ALL	29 (24.0%)	7 (20.6%)	22 (25.4%)	
B cell LBL	1 (0.8%)	0	1 (1.2%)	
T cell ALL	11 (9.1%)	5 (14.7%)	6 (6.9%)	
T cell LBL	5 (4.1%)	2 (5.9%)	3 (3.5%)	
Early T cell ALL	5 (4.1%)	1 (2.9%)	4 (4.6%)	
NPA/L/ALL	7 (5.8%)	2 (5.9%)	5 (5.8%)	
Others	3 (2.5%)	1 (1.9%)	2 (2.3%)	

Table 2. Demographic and clinical characteristics by patient ethnicity

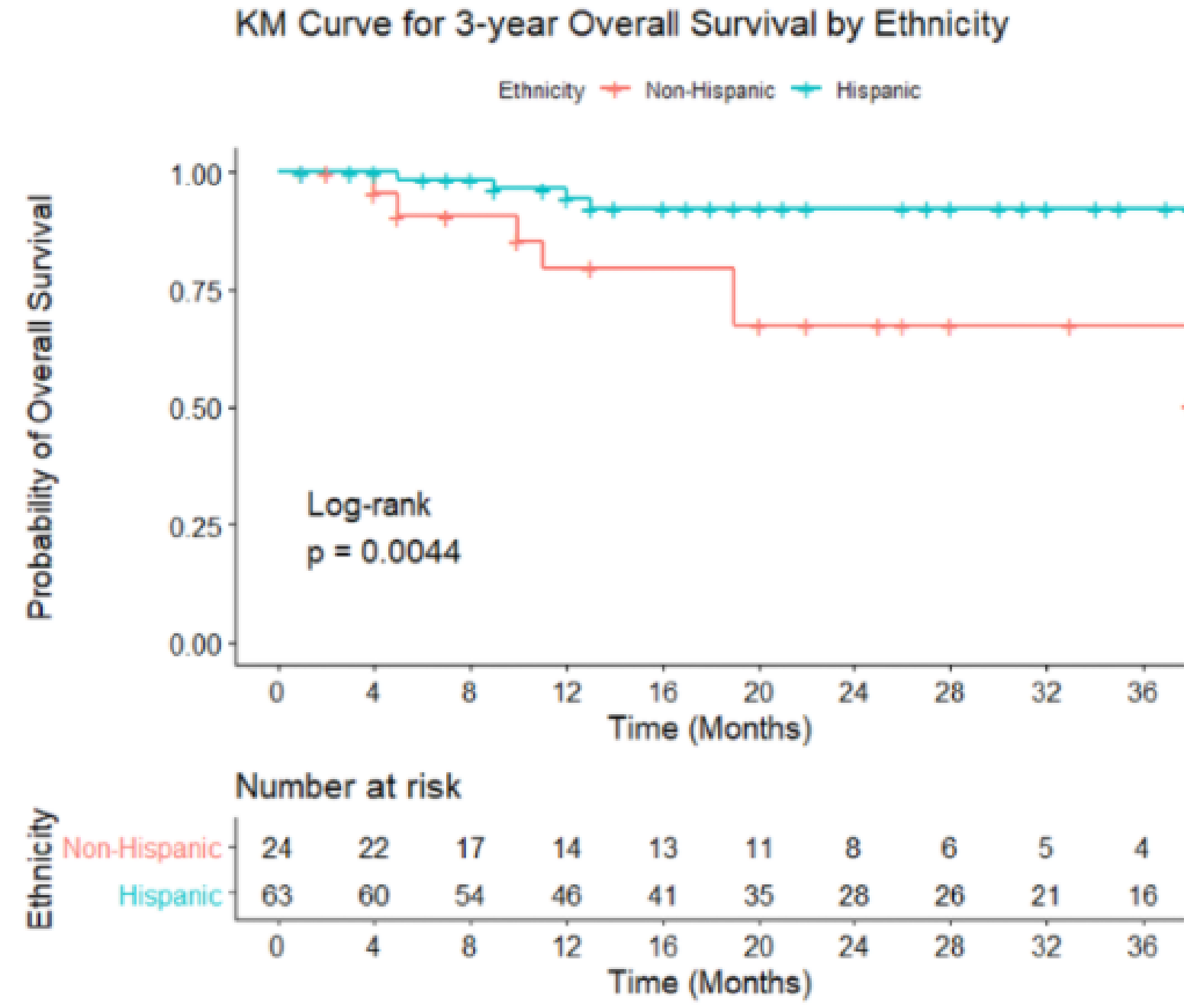
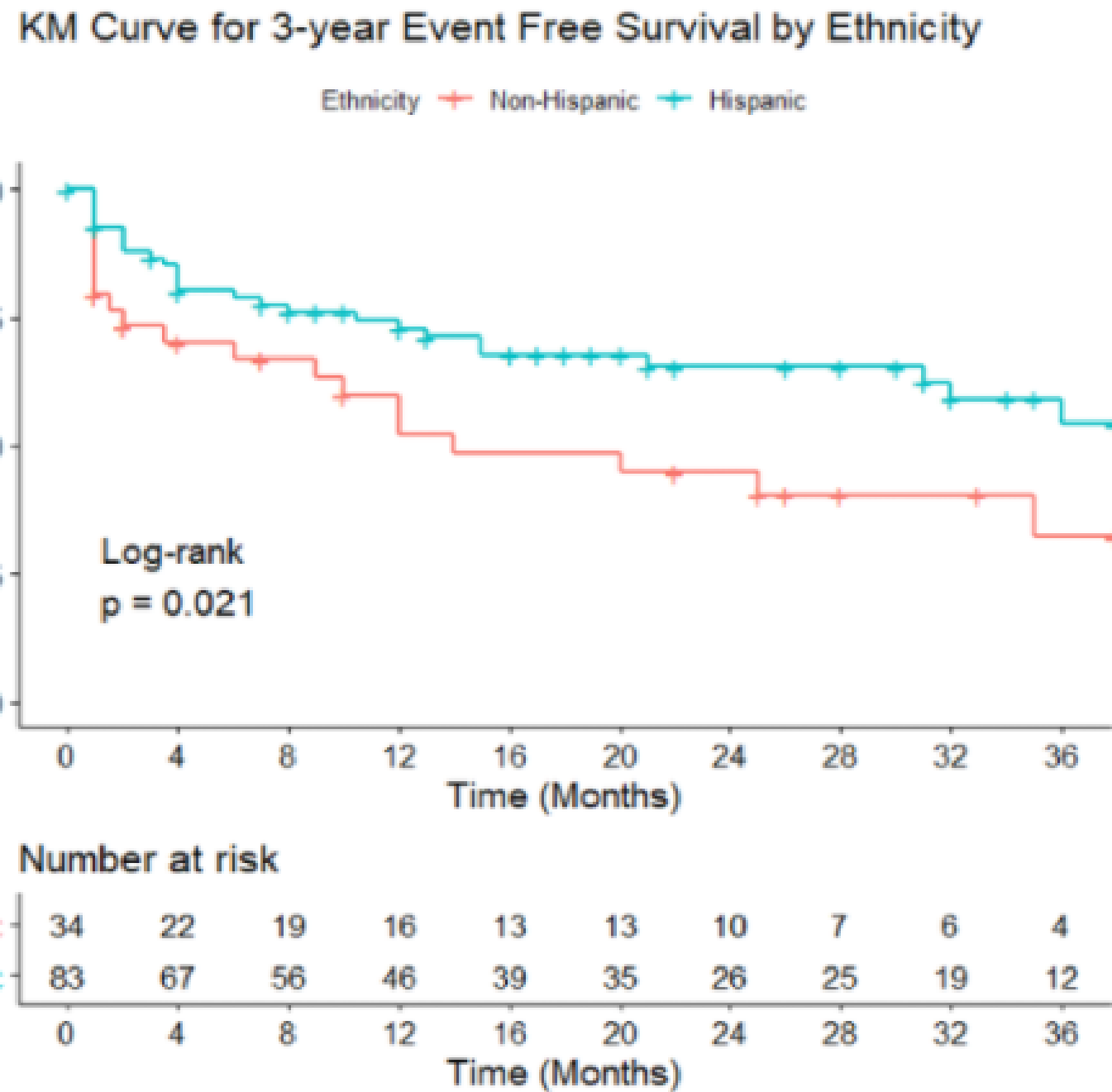


Table 5. KM curves showing 3-year OS and EFS in Hispanic vs Non-Hispanic patients after receiving the modified USC ALL regimen

Variable	N	Patient Ethnicity		p-value
		Non-Hispanic (NHP) (n=34)	Hispanic (HP) (n=87)	
Died				0.015*
No	80	18 (72.0%)	62 (92.5%)	
Yes	12	7 (28.0%)	5 (7.5%)	
Missing	29			
Relapsed				0.741
No	88	24 (70.6%)	64 (73.6%)	
Yes	33	10 (29.4%)	23 (26.4%)	
Induction 1 Response				0.092
CR	56	17 (56.7%)	39 (50.0%)	
CRi	33	5 (16.7%)	28 (35.9%)	
Refractory	19	8 (26.6%)	11 (14.1%)	
Missing	13			
Induction 2 Response				0.999
CR	48	13 (65.0%)	35 (66.0%)	
CRi	12	3 (15.0%)	9 (17.0%)	
Refractory	13	4 (20.0%)	9 (17.0%)	
Missing	48			
MRD Negative after Induction 1				0.127
No	76	25 (73.6%)	51 (58.6%)	
Yes	45	9 (26.4%)	36 (41.4%)	
MRD Negative after Induction 2				0.733
No	79	23 (67.6%)	56 (64.4%)	
Yes	42	11 (32.4%)	31 (35.6%)	
MRD Flow after Consolidation 1				0.574
Positive	5	0	5 (11.6%)	
Negative	50	12 (100%)	38 (88.4%)	
Missing	66			
Given Blinatumomab				0.918
No	81	23 (67.7%)	58 (66.7%)	
Yes	40	11 (32.3%)	29 (33.3%)	
Given Inotuzumab				0.999
No	115	33 (97.1%)	82 (94.3%)	
Yes	6	1 (2.9%)	5 (5.7%)	

Table 3. Outcomes and Responses in Hispanic vs. Non-Hispanic Patients (Ph Negative only)



Results

- 121 Ph-negative patients were reviewed: 87 were Hispanic patients (HP) and 34 non-Hispanic patients (NHP); Median ages were 39 and 35 years (p=0.51) and median BMI were 29 and 26.9 kg/m² (p=0.42), respectively. Both HP and NHP were mainly of the Ph-negative ALL subtype, 50.6% vs 47.1 % (p=0.884) (**Table 2**)
- Majority of the population were unfavorable risk by NCCN karyotypic risk stratification, 55.9% in HP compared to 56.0% in NHP (p=0.99) (**Table 2**)
- After induction 1:** CR/CRi was 85.9% in HP and 73.4% in NHP (p=0.09). MRD negativity by flow cytometry in HP was 41.4% compared to 26.4% in NHP (p=0.13); **After induction 2:** 83% of HP were in CR/CRi compared to 80% in NHP (p=0.99) and MRD negativity by flow was 35.6% in HP compared to 32.4% in NHP (p=0.73) (**Table 3**)
- Blinatumomab was given in 33.3% of HP and 32.3% of NHP (p=0.92) while only 5.7% of HP and 2.9% of NHP received inotuzumab (p=0.99) and 34.5% of HP underwent allogeneic hematopoietic stem cell transplant (allo-HSCT) versus 26.5% in NHP (p=0.40). Rate of relapse for HP and NHP were 23.4% vs 29.4% (p=0.74) while rate of mortality for HP and NHP were 7.5% vs 28% (p=0.015), respectively (**Table 3**)
- 3-year OS was 92.2% in HP versus 67.4% in NHP (p=0.004) and 3-year EFS was 54.1% in HP versus 32.3% in NHP (p=0.02) (Table 5)**
- About the same % of Grade 3/4 PEG toxicities noted in HP and NHP except more hypertriglyceridemia in HP (p=0.019) (**Table 4**)

Discussion & Conclusion

- Over-all, no significant difference between baseline characteristics in both cohorts; however, our data shows significantly better outcomes in Hispanic patients compared to non-Hispanic patients [OS (92.2% vs 67.4%, p=0.004) and EFS (54.1% vs 32.3%, p=0.02)]
- No clear difference in grade 3/4 PEG toxicities were found in HP and NHP except more hypertriglyceridemia in HP (p=0.019)
- This study demonstrates that given equal access to care (eg.receiving blinatumomab, allo-HSCT), outcomes in HP with Ph-negative ALL are not worse, but rather superior to those in NHP. Utilization of novel immunotherapy like blinatumomab in the salvage setting to achieve deeper molecular response and increased utilization of haploidentical allo-HSCT have likely contributed to reducing ethnic disparities in Hispanic ALL patients

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