Outcome of Stem Cell Transplantation in HTLV-1-associated North American Adult T-cell Leukemia/Lymphoma

Narvel H[1], Bazarbachi A[1], Reef D[2] , Patel R[1], Thakkar A[2], Zareef S[2],Castro A[2], Mustafa J[2], Khatun F[2], Lombardo A[2], Gritsman A[2], Goldfinger M[2], Wang Y[2], Kornblum N[2], Shastri A[2], Mantzaris I[2], Shah N[2], Braunschweig I[2], Verma A[2], Ye H[2], Sica A[2]

1Jacobi Medical Center, Albert Einstein College Of Medicine., New York, USA. 2. Montefiore Medical Center, Albert Einstein College of Medicine, New York, USA.

Background

- Adult T-cell leukemia/lymphoma (ATLL) is a rare mature T cells malignancy driven by the human T-cell lymphotropic virus type I (HTLV-1) and associated with a grim prognosis.
- This is the **largest experience studying the feasibility of stem cell haploidentical donors,** which will greatly improve donor **transplantation in ATLL outside Japan or Europe**, it is additionally **the first one in studying the effect of alternative access to this patient population**
- NA ATLL differs from Japanese ATLL due to higher relapse rates and chemo refractoriness, where allo SCT with either myeloablative (MAC) or reduced-intensity (RIC)conditioning is associated with favorable long-term outcomes.
- **Limitations to the use of allo – SCT** :
  Lack of suitable donors given the ethnic minorities and poor performance status.
- **Drawbacks of auto SCT**
  higher relapse rates likely due to graft-vs-leukemia (GVL) effect.

Methods

- Electronic health records of ATLL patients were reviewed. Overall survival (OS) and progression free survival (PFS) probabilities were estimated using the Kaplan-Meier method.
- Cumulative incidence functions were used to estimate RI and NRM in a competing risk setting. A Cox proportional hazards model was used for multivariate regression. When there was an interval between last date known alive and first date known to have died, death was assumed at the end of the interval.

Figures/ Tables

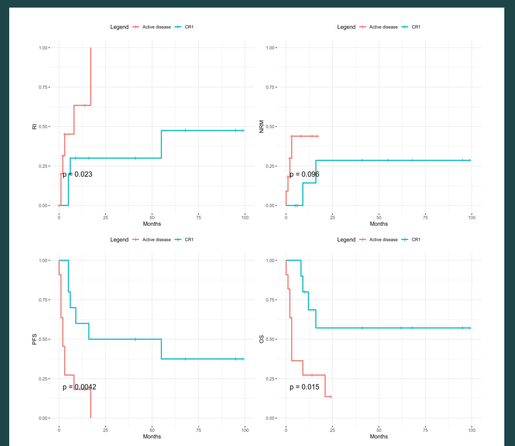


Figure 1: Post-transplant outcomes of ATLL patients in first complete remission (CR1) vs advanced disease

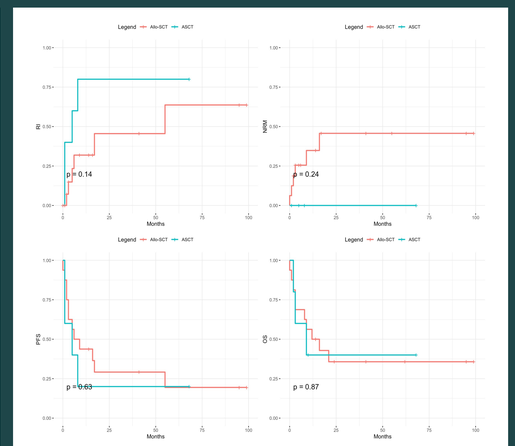


Figure 2: Post-transplant outcomes of ATLL patients in allo-SCT vs ASCT

Patient Characteristics	n=21 N (%)/ Median (Range) [IQR]
Age (years)	56 (39-74) [45-65]
Year of Transplant	2016 (2005-2020) [2013-2018]
Lines of Therapy before transpl.	2 (1-4) [1-3]
Diagnosis to Transplant (month	7 (4-41) [6-11]
Follow-up (months)	41 (9-99) [14-68]
Gender	
Male	12 (57%)
Female	9 (43%)
Ethnicity	
Black	14 (67%)
Hispanic	6 (29%)
ATLL Subtype	
Acute	10 (48%)
Lymphomatous	11 (52%)
Status at transplant	
CR1	9 (43%)
PR	4 (19%)
PD/Relapsed	7 (33%)
Karnofsky score	
≥90	14 (67%)
<90	5 (24%)
missing	2 (10%)
Patient CMV serology	
CMV+	17 (81%)
CMV-	2 (10%)
missing	2 (10%)

Transplant characteristics	n=21 N (%)
Transplant Type	
Allo	16 (76%)
Auto	5 (24%)
Donor	n=16
Matched sibling	7 (44%)
10/10 Matched unrelated	1 (6%)
9/10 Matched unrelated	2 (13%)
Haploidentical	6 (38%)
Source of stem cells	n=16
Bone marrow	3 (19%)
Peripheral blood	10 (63%)
Bone marrow + Peripheral blood	1 (6%)
missing	2 (13%)
Donor HTLV serology	n=16
HTLV+	3 (19%)
HTLV-	2 (13%)
missing	11 (69%)
In vivo T-Cell Depletion	n=16
No	14 (88%)
Yes	1 (6%)
missing	1 (6%)
Donor CMV serology	n=16
CMV+	4 (25%)
CMV-	1 (6%)
missing	11 (69%)

Table 1 : Baseline characteristics. A) Patient Characteristics B) Transplant characteristics

Table 2 : Univariate Analysis

Whole Population		1 year RI	1 year NRM	1 year PFS	1 year OS	4 years RI	4 years NRM	4 years PFS	4 years OS
Ethnicity	Black	35% [0-57]	22% [0-41]	50% [30-84]	57% [36-90]	48% [4-72]	35% [0-59]	33% [15-72]	41% [21-78]
	Hispanic	60% [0-86]	58% [0-90]	17% [3-100]	17% [3-100]	60% [0-86]	58% [0-90]	17% [3-100]	17% [3-100]
	P value	0.19	0.39	0.11	0.07	0.27	0.51	0.2	0.12
Karnofsky	<90	62% [0-92]	40% [0-71]	20% [3-100]	40% [14-100]	62% [0-92]	100% [NA-NA	0% [NA-NA]	0% [NA-NA]
	≥90	31% [0-53]	27% [0-49]	50% [30-84]	57% [36-90]	43% [4-66]	27% [0-49]	42% [22-79]	49% [28-84]
	P value	0.26	0.19	0.08	0.24	0.26	0.03	0.02	0.06
Status at transplant	Advanced	70% [9-90]	39% [0-64]	17% [5-59]	33% [15-74]	100% [NA-NA]	39% [0-64]	0% [NA-NA]	17% [3-83]
	CR1	22% [0-45]	14% [0-37]	67% [42-100]	67% [42-100]	22% [0-45]	29% [0-55]	56% [31-100]	56% [31-100]
	P value	0.03	0.1	0.01	0.06	0.01	0.15	0.002	0.04
Transplant type	Allo	32% [0-54]	35% [4-56]	44% [25-76]	50% [31-82]	46% [3-70]	46% [8-68]	29% [13-64]	36% [18-70]
	Auto	80% [0-97]	0% [0-0]	20% [3-100]	40% [14-100]	80% [0-97]	0% [0-0]	20% [3-100]	40% [14-100]
	P value	0.045	0.27	0.35	0.71	0.08	0.24	0.51	0.87

Table 3 : Multivariate Analysis

Outcome	Variables	HR (95% CI)	p value
RI	Karnosky >90	0.7 (0.05-10)	0.8
	CR1 vs other	0.1 (0.01-0.8)	0.03
	Hispanic vs Black	5 (0.7-30)	0.1
	Auto vs Allo	3 (0.3-20)	0.4
NRM	Karnosky >90	5e-10 (4e-11-5e-09)	<0.001
	CR1 vs other	5e-10 (7e-11-4e-09)	<0.001
	Hispanic vs Black	1e+09 (1e+08-1e+10)	<0.001
	Auto vs Allo	3e-18 (0-Inf)	1
PFS	Karnosky >90	0.1 (0.02-0.7)	0.02
	CR1 vs other	0.09 (0.02-0.4)	0.003
	Hispanic vs Black	5 (1-20)	0.04
	Auto vs Allo	0.5 (0.05-5)	0.5
OS	Karnosky >90	0.1 (0.02-0.9)	0.03
	CR1 vs other	0.1 (0.02-0.8)	0.03
	Hispanic vs Black	7 (1-50)	0.04
	Auto vs Allo	0.1 (0.005-3)	0.2
GRFS	Karnosky >90	0.1 (0.02-0.7)	0.01
	CR1 vs other	0.4 (0.1-1)	0.1
	Hispanic vs Black	1 (0.3-7)	0.6

. HR : Hazard Ratio,
CI : Confidence interval.
CR1 : First complete remission
NRM : Non – Relapse mortality,
PFS : Progression Free Survival,
OS : Overall Survival,
GFRS : GVHD and relapse free survival
RI = Relapse Incidence

Results

- We follow one of the **largest ATLL cohorts in the USA with 116 patients, of which 21 were transplanted.** 39-74 years old including 10 acute and 11 lymphomatous, 16 of which underwent allo-SCT and 5 autologous SCT (ASCT) between 2005-2020 with a median follow-up of 41 months.
- **3-year relapse incidence (RI) - 54%**
- **non-relapse mortality (NRM) - 39%,**
- **3-year progression-free survival (PFS) - 27%**
- **overall survival (OS) - 35%**
- Four of five patients who received ASCT rapidly relapsed with 3 dying from disease progression and one lost to follow-up, with 1-year RI of 80% vs 32% in allo-SCT (p=0.045). In exploratory multivariate analysis, patients achieving first complete response (CR1) and with good baseline performance scores had significantly better outcomes compared to their counterparts regardless of transplant type, and surprisingly, **race was a significant predictor of outcomes including NRM, PFS and OS with OS HR of 7; p=0.04**. Thirteen patients died within 2 years 3 of which were ASCT recipients, eight from relapse/progression including the 3 ASCT patients, and 4 from transplant-related toxicities

Conclusions

OUTCOMES

ALLO SCT > ASCT

Blacks > Hispanics

NO SUITABLE DONOR → Haploidentical donor or HTLV1 positive donor is an option

- The treatment of ATLL and particularly NA-ATLL remains challenging, with most patients relapsing and succumbing to the disease
- Our data are in line with the reported literature, whereby **ASCT is associated with increased short-term relapse compared to allo-SCT leading to poor outcomes overall.** Good performance status and having achieved CR prior to transplant are known positive outcome predictors, and our findings were not surprising.
- Interestingly, **Hispanic patients appear to have worse outcome compared to Black patients regardless of performance status, disease response, or transplant type as evident in MVA**. To our knowledge this has not been previously described and could be possibly attributed to epidemiologic genetic variations in HTLV-1 subtypes between the 2 groups. Further investigation is required including genomic profiling of these patients.