Incorporation of machine learning tools to predict global outcomes for patients with relapsed and refractory peripheral T and NK/T-cell lymphomas in the contemporary era

L.S. BOUSSI[1], M. KOH[2], X. HAN[3], L. PENG[4], M. KOH[5], I. ECHE[1,6], S. SINGH[5], M. SORIAL[5], J. GABLER[5], J. FORD[5], R. STUVER[7], S. HORWITZ[7], E. MIRANDA[8], C. CHIATTONE[8], Y. KIM[9], J. CHO[9], C. VAN DER WEYDEN[10], M. PRINCE[10], M. MANNI[11], M. FEDERICO[11], N. YOSHIDA[12,13], T. OKATANI[12,13], S. YOON[14], W. KIM[14], R. HAMOUCHE[15], F. FOSS[15], G. PANCHOO[16], E. VERBURGH[16], M.J. FERNANDEZ TURIZO[1], E.D. JACOBSEN[6], M.H. MERRILL[6], J. CUENCA ALTURAS[17], M. AL-MANSOUR[17], B. CASADEI[18], P.L. ZINZANI[18], M.E. CABRERA[19], O.A. O'CONNOR[20], E. MARCHI[20], S. JAIN[5,21]

1. Beth Israel Deaconess Medical Center, Boston, MA; 2. Georgetown University School of Medicine, Washington, DC; 3. Massachusetts Institute of Technology, Cambridge, MA; 4. College of Science, Northeastern University, Boston, MA; 5. Division of Hematology and Oncology, Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, MA; 6. Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA; 7. Medical Oncology & Hematology, Memorial Sloan Kettering Cancer Center, New York, NY; 8. Department of Medicine, Santa Casa Medicine School, Sao Paulo, Brazil; 9. Department of Medicine, Gangnam Severance Hospital, Yonsei University School of Medicine, Seoul, Korea, Republic of (South); 10. Department of Hematology, Peter MacCallum Cancer Center, Melbourne, Australia; 11. Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy; 12. Radiation Effects Research Foundation, Hiroshima, Japan; 13. Department of Hematology, Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, Hiroshima, Japan; 14. Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South); 15. Hematology, Yale Cancer Center, New Haven, CT; 16. University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa; 17. Department of Medicine, King Abdulaziz Medical City, Jeddah, Saudi Arabia; 18. Institute of Hematology L. e A. Seràgnoli, University of Bologna, Bologna, Italy; 19. Hematology Department, Hospital del Salvador, Santiago, Chile; 20. Program for T-Cell Lymphoma Research, University of Virginia, Charlottesville, VA; 21. Harvard Medical School, Boston, MA

BACKGROUND

Comparative efficacy of single agents (SA) to combination chemotherapy (CC) for patients with relapsed and refractory (R/R) T-cell lymphomas (TCLs) remains poorly defined. Here, we present preliminary results of an international collaborative study spanning multiple centers across 6 continents with diverse histological epidemiology, demographics, treatment patterns and drug access.

OBJECTIVES

Primary objectives:

- Define global overall survival (OS) of R/R patients receiving 1st retreatment and beyond
- Compare OS by country, histological subtype, 1st retreatment (CC vs. SA), diagnosis period, PIT scores, relapsed vs. refractory
- Contrast ability to bridge to stem cell transplant for SA relative to CC

Exploratory objective:

- Incorporate novel machine learning tools such as synthetic interventions to build predictive models of response to SA and CC

METHOD

This is an ongoing retrospective study estimated to cumulate exhaustive treatment characteristics for 2000 patients with R/R TCLs treated with SA or CC from centers in USA (COMPLETE, MSKCC, MGH, DFCI, Yale), Brazil, South Korea (Samsung, Yonsei), Australia, Saudi Arabia, South Africa, Italy, and Japan. Except for T-LGLL and CTCL, all patients are eligible if they have a diagnosis of histologically confirmed PTCL between 2010 and 2021. Existing clinical records of participating institutions are utilized for eligibility. Patients are followed from lymphoma diagnosis to death or lost to follow-up. Survival was estimated and compared by Cox regression models. Random forest and regularized synthetic intervention analysis was applied to build predictive modeling.

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CONTACT

Salvia Jain, MD, salvia_jain@dfci.harvard.edu
Jon and Jo Ann Hagler Center for Lymphoma
Massachusetts General Hospital Cancer Center

RESULTS

Table 1. Baseline demographic and clinical characteristics

Characteristic	All (n = 698)	USA (n = 311)	Australia (n = 69)	Brazil (n = 120)	South Korea (n = 123)	South Africa (n = 24)	Saudi Arabia (n = 13)	Japan (n = 38)	P[a]
Age at lymphoma diagnosis (years), Median (IQR)	58 (47-67)	60 (51-68)	63 (53-71)	51 (40-60)	57 (48-65)	49 (37-56)	45 (31-57)	69 (65-78)	<0.001
Biological Sex, No. (%)									
Male	433 (62)	198 (64)	45 (65)	68 (57)	70 (57)	18 (75)	10 (77)	24 (63)	0.4[b]
Race, No. (%)									
White	323 (52)	237 (79)	24 (89)	59 (61)	0	3 (14)	0	0	<0.001[b]
Black	49 (8)	33 (11)	1 (4)	10 (10)	1 (<1)	4 (19)	0	0	
Asian	192 (31)	19 (6)	2 (7)	2 (2)	122 (99)	0	9 (69)	38 (100)	
Other	55 (9)	12 (4)	0	25 (26)	0	14 (67)	4 (31)	0	
Unknown	73	4	42	24	0	3	0	0	
Histological subtypes, No. (%)									
AITL	158 (23)	98 (32)	13 (19)	11 (9)	20 (16)	4 (17)	0	12 (32)	<0.001[b]
ALCL (ALK-)	81 (12)	25 (8)	11 (16)	20 (17)	6 (5)	6 (25)	6 (46)	7 (18)	<0.001[b]
ALCL (ALK+)	32 (5)	15 (5)	3 (4)	6 (5)	3 (2)	2 (8)	2 (15)	1 (3)	0.4[b]
ATLL	31 (4)	5 (2)	0	25 (21)	0	0	0	1 (3)	-
EATL	19 (3)	8 (3)	0	1 (<1)	8 (7)	0	0	2 (5)	-
ENKTL	70 (10)	15 (5)	3 (4)	10 (8)	40 (33)	0	2 (15)	0	<0.001[b]
HSTCL	14 (2)	4 (1)	5 (7)	2 (2)	2 (2)	1 (4)	0	0	0.1[b]
PTCL-NOS	279 (40)	127 (41)	34 (49)	45 (38)	44 (36)	11 (46)	3 (23)	15 (39)	0.5
TPLL	9 (1)	9 (3)	0	0	0	0	0	0	-
Other	5 (1)	5 (2)	0	0	0	0	0	0	-
Ann Arbor Stages at diagnosis, No. (%)									
I	60/686 (9)	23/309 (7)	4/61 (7)	13 (11)	13 (11)	6 (25)	0	1 (3)	0.003[b]
II	75/686 (11)	26/309 (8)	3/61 (5)	16 (13)	21 (17)	4 (17)	3/11 (27)	2 (5)	
III	154/686 (22)	83/309 (27)	8/61 (13)	22 (18)	26 (21)	1 (4)	3/11 (27)	11 (29)	
IV	397/686 (58)	177/309 (57)	46/61 (75)	69 (58)	63 (51)	13 (54)	5/11 (45)	24 (63)	
IPI scores at diagnosis, No. (%)									
0	27/597 (5)	9/269 (3)	2/40 (5)	1/101 (<1)	8 (7)	6/21 (29)	0	1 (3)	<0.001[b]
1	73/597 (12)	30/269 (11)	2/40 (5)	12/101 (12)	24 (20)	3/21 (14)	0	2 (5)	
2	170/597 (28)	79/269 (29)	7/40 (18)	32/101 (32)	38 (31)	6/21 (29)	3/5 (60)	5 (13)	
3	203/597 (34)	86/269 (32)	21/40 (53)	43/101 (43)	36 (29)	4/21 (19)	1/5 (20)	12 (32)	
4	100/597 (17)	49/269 (18)	6/40 (15)	12/101 (12)	16 (13)	2/21 (10)	1/5 (20)	14 (37)	
5	24/597 (4)	16/269 (6)	2/40 (5)	1/101 (<1)	1 (1)	0	0	4 (11)	
PIT scores at diagnosis, No. (%)									
0	81/580 (14)	35/267 (13)	3/43 (7)	12/102 (12)	28 (23)	0	0	3 (8)	<0.001[b]
1	206/580 (36)	103/267 (39)	8/43 (19)	41/102 (40)	46 (37)	0	4/6 (67)	4 (11)	
2	183/580 (32)	75/267 (28)	21/43 (49)	40/102 (39)	32 (26)	1/1	1/6 (17)	13 (34)	
3	88/580 (15)	41/267 (15)	8/43 (19)	9/102 (9)	15 (12)	0	1/6 (17)	14 (37)	
4	22/580 (4)	13/267 (5)	3/43 (7)	0	2 (2)	0	0	4 (11)	
B symptoms at diagnosis, No. (%)	340/668 (51)	137/300 (46)	27/60 (45)	75 (62)	59 (48)	7/18 (39)	5/9 (56)	30 (79)	<0.001[b]
Extra nodal involvement, No. (%)	464/687 (68)	195/304 (64)	55/66 (83)	86 (72)	82 (67)	13 (54)	8/12 (67)	25 (66)	0.04[b]
> 1 site, No. (%)	293/644 (45)	81/279 (29)	28/61 (46)	73 (61)	69 (56)	21 (88)	6/11 (55)	15/26 (58)	<0.001[b]
Bone marrow involvement, No. (%)	202/606 (33)	92/266 (35)	26/63 (41)	34/82 (41)	32 (26)	8/22 (36)	2/12 (17)	8 (21)	0.06[b]
Performance status, No. (%)									
0	256/647 (41)	103/278 (37)	28/58 (48)	44 (37)	70 (57)	8/21 (38)	1/9 (11)	2 (5)	<0.001[b]
1	284/647 (42)	134/278 (48)	24/58 (41)	51 (43)	44 (36)	9/21 (43)	5/9 (56)	17 (45)	
2	79/647 (12)	33/278 (12)	4/58 (7)	17 (14)	9 (7)	4/21 (19)	3/9 (33)	9 (24)	
3	24/647 (4)	7/278 (3)	2/58 (3)	6 (5)	0	0	0	9 (24)	
4	4/647 (1)	1/278 (<1)	0	2 (2)	0	0	0	1 (3)	
Time to follow up since diagnosis (years), Median (IQR)	1.81 (0.90-3.86)	2.58 (1.29-5.02)	1.08 (0.73-3.32)	1.14 (0.79-2.14)	1.80 (0.98-3.87)	1.70 (0.63-4.18)	1.25 (0.68-2.57)	1.35 (0.60-2.51)	<0.001
Current Status, No. (%)									
Alive	236 (34)	118 (38)	21 (30)	39 (32)	43 (35)	7 (29)	7 (54)	1 (3)	<0.001[b]
Dead	428 (61)	185 (59)	36 (52)	75 (62)	77 (63)	16 (67)	5 (38)	34 (89)	
Lost to Follow up	34 (5)	8 (3)	12 (17)	6 (5)	3 (2)	1 (4)	1 (8)	3 (8)	

[a]P values for the comparison between patients in different national cohorts were calculated using Kruskal-Wallis and chi-square tests for non-normally distributed continuous variables and categorical variables, respectively
[b]P values based on Fisher's exact test due to some small cell counts
Abbreviation: ATLL-Adult T-cell leukemia/lymphoma, AITL-Angioimmunoblastic T-cell lymphoma, ALCL-Anaplastic large cell lymphoma, ALK-Anaplastic lymphoma kinase, EATL-Enteropathy-associated T-cell lymphoma, ENKTL-Extra nodal NK/T-cell lymphoma, HSTCL-Hepatosplenic T-cell lymphoma, IPI-International Prognostic Index, IQR-Inter Quartile range, TPLL-T cell prolymphocytic leukemia, PIT-Prognostic Index for T-cell lymphoma, PTCL-NOS-Peripheral T-cell lymphoma-not otherwise specified

Fig 1. OS of TCL by country

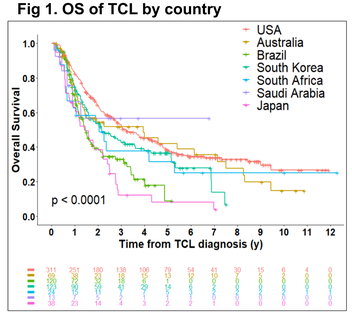


Fig 2. OS of TCL by histological subtype

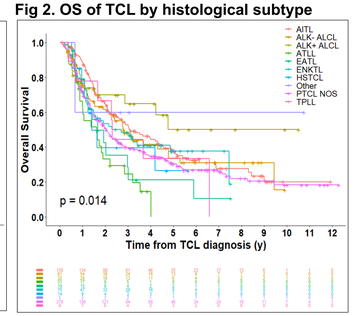


Fig 3. OS of TCL SA vs. CC

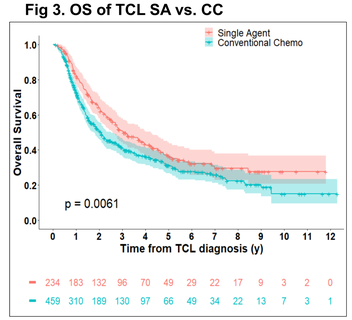


Fig 4. OS of TCL Relapse vs. Refractory

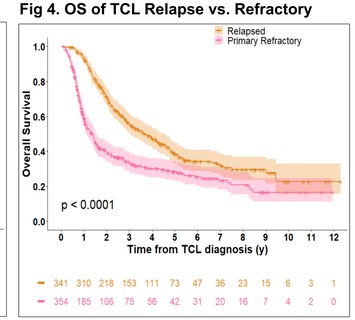
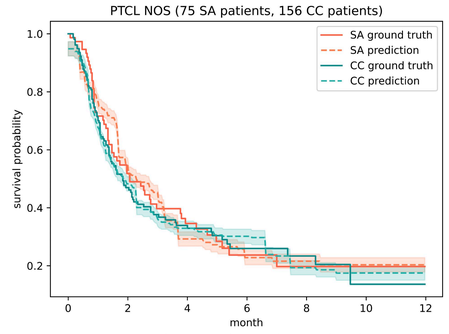


Table 2. Treatment characteristics

Characteristic	All (n = 698)	USA (n = 311)	Australia (n = 69)	Brazil (n = 120)	South Korea (n = 123)	South Africa (n = 24)	Saudi Arabia (n = 13)	Japan (n = 38)	P[a]
Relapsed	341/695 (49)	195 (63)	26/67 (39)	33 (28)	63 (51)	7 (29)	2/12 (17)	15 (39)	<0.001
Primary Refractory	354/695 (51)	116 (37)	41/67 (61)	87 (72)	60 (49)	17 (71)	10/12 (83)	23 (61)	
Initial Chemotherapy									
Treatment, No. (%)									
CHOP-based	255/693 (37)	108 (35)	31/65 (48)	24/119 (20)	76 (62)	6 (25)	3 (23)	7 (18)	<0.001[b]
CHOEP-based	196/693 (28)	95 (31)	17/65 (26)	60/119 (50)	4 (3)	17 (71)	3 (23)	0	<0.001[b]
EPOCH-based	36/693 (5)	30 (10)	1/65 (2)	1/119 (<1)	3 (2)	0	0	1 (3)	-
CHP+BV	15/693 (2)	11 (4)	0	1/119 (<1)	0	0	3 (23)	0	-
Alemtuzumab	7/693 (1)	6 (2)	0	0	0	0	1 (8)	0	-
Other	184/693 (27)	61 (20)	16/65 (25)	33/119 (28)	40 (33)	1 (4)	3 (23)	30 (79)	<0.001[b]
Treatment Response, No. (%)									
Complete response	297/685 (43)	169/302 (56)	22/67 (33)	33 (28)	49/122 (40)	7 (29)	2/12 (17)	15 (39)	<0.001[b]
Partial response	130/685 (19)	24/302 (8)	18/67 (27)	29 (24)	29/122 (24)	10 (42)	10/12 (83)	10 (26)	
No Response/Stable	31/685 (5)	13/302 (4)	7/67 (10)	1 (<1)	4/122 (3)	4 (17)	0	2 (5)	
Progressive Disease	227/685 (33)	96/302 (32)	20/67 (30)	57 (48)	40/122 (33)	3 (12)	0	11 (29)	
Underwent auto SCT consolidation, No. (%)	147/657 (22)	95/310 (31)	6/32 (19)	7 (6)	32 (41)	2 (8)	5/10 (50)	0	-
Received radiation, No. (%)	85/642 (13)	22/259 (8)	6 (9)	17 (14)	32 (26)	1 (4)	5/9 (56)	2 (5)	<0.001[b]
Second line therapy									
Commonly used therapy, No. (%)									
SA	234 (34)	163 (52)	24 (35)	7 (6)	18 (15)	7 (29)	2 (15)	13 (34)	<0.001[b]
CC	459 (66)	148 (48)	44 (64)	110 (92)	104 (85)	17 (71)	11 (85)	25 (66)	
Both	5 (1)	0	1 (1)	3 (3)	1 (1)	0	0	0	
Achieved complete remission, No. (%)	200/563 (36)	108/268 (40)	18/52 (35)	23/70 (33)	31/110 (28)	10/16 (62)	4/9 (44)	6 (16)	<0.001[b]
Underwent SCT consolidation, No. (%)	150/631 (24)	71/302 (24)	14/35 (40)	19 (16)	32/102 (31)	7 (29)	4/10 (40)	3 (8)	0.003[b]
Auto transplant	82/146 (56)	19/67 (28)	12/14 (86)	15/19 (79)	27/32 (84)	4/7 (57)	3/4 (75)	2/3 (67)	<0.001[b]
Allotransplant	66/146 (45)	50/67 (75)	2/14 (14)	4/19 (21)	5/32 (16)	3/7 (43)	1/4 (25)	1/3 (33)	

[a]P values for the comparison between patients in different national cohorts were calculated using chi-square tests for categorical variables
[b]P values based on Fisher's exact test due to some small cell counts
Abbreviation: CHOP-Cyclophosphamide +Hydroxydaunorubicin +Oncovin +Prednisone, CHOEP- Cyclophosphamide +Hydroxydaunorubicin +Oncovin +Etoposide +Prednisone, EPOCH- Etoposide phosphate +Prednisone +Oncovin +Cyclophosphamide +Hydroxydaunorubicin, CHP+BV- Cyclophosphamide +Doxorubicin +Prednisone +Brentuximab

Fig 5. Prediction of survival probability with regularized synthetic intervention



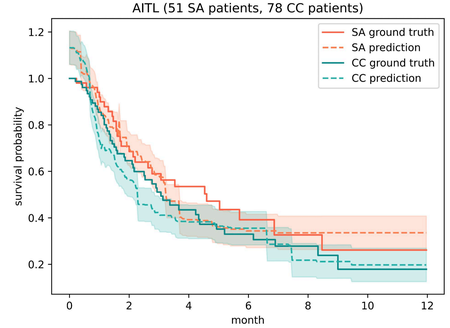


Table 3. Cox regression / Random forest analysis/ Synthetic intervention

HR (P value)	Univariate	Multivariate			
Treatment type (ref: single agent)					
Conventional chemotherapy	1.24 (0.06) Concordance: 0.53		1.21 (0.09)	1.20 (0.11)	1.18 (0.16)	1.03 (0.84)
Histological subtype						
(Ord: ALCL, ENKTL, AITL, PTCL-NOS, EATL, HSTCL, ATLL)[a]	1.15 (<0.005) Concordance: 0.55	1.12 (<0.005)	1.13 (<0.005)		1.11 (<0.005)	1.10 (0.01)
PIT score at diagnosis	1.38 (<0.005)	1.37 (<0.005)	1.37 (<0.005)	1.38 (<0.005)	1.40 (<0.005)	1.39 (<0.005)
(Ord: 0, 1,2, ≥3)[a]	Concordance: 0.60					
Country (ref: Australia)						
USA (Complete)	0.55 (0.01)					0.69 (0.10)
Brazil	1.04 (0.88)					1.15 (0.59)
South Korea	0.73 (0.19)					1.01 (0.97)
South Africa	2.79 (0.32)					3.46 (0.23)
Saudi Arabia	0.37 (0.17)					0.44 (0.27)
Japan	1.39 (0.23)					1.61 (0.09)
	Concordance: 0.58					
Diagnosed period (ref: 2010-2015)	1.23 (0.06)					
2016-2020	Concordance: 0.53				1.28 (0.03)	1.14 (0.29)
Response to 1st treatment						
(Ord: Complete response, partial response, stable disease, progressive disease)[a]	1.27 (<0.005) Concordance: 0.63	1.26 (<0.005)		1.27 (<0.005)	1.24 (<0.005)	1.25 (<0.005)
AIC		3857.57	3885.92	3865.04	3855.03	3842.80
Concordance index		0.67	0.62	0.67	0.67	0.68
RANDOM SURVIVAL FOREST ANALYSIS						
Concordance index		0.69	0.65	0.68	0.70	0.70

CONCLUSIONS

This global study represents the first analysis of this type in R/R PTCL contrasting SA to CC and demonstrates that both strategies are comparable. Results confirm dismal prognosis for patients with primary refractory disease but also highlight improvements in OS in ALCL and ENKTCL in the last 5 years. We continue to enroll patients in our study and build better prediction models using state of the art synthetic intervention approaches to inform future clinical trials.

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