Authors: Ishan Roy MD, PhD[1,2,3], Gordon Smilnak BS[2], Madelyn Burkart MD[2,3], Elizabeth Hamilton NP[4], Katherine Thorp NP[4], Sarah Miyata NP[4], Shuo Ma MD, PhD[2,3], Jane Winter MD[2,3], Leo Gordon MD[2,3], Reem Karmali MD[2,3]

Affiliations:

1. Shirley Ryan AbilityLab
2. Feinberg School of Medicine, Northwestern University
3. Robert H. Lurie Comprehensive Cancer Center, Northwestern University
4. Northwestern Memorial Hospital

Title: Impact of cachexia at apheresis and infusion on post-CAR-T cell therapy outcomes in aggressive lymphoma

Abstract:

Introduction: Chimeric antigen T-cell (CAR-T) cell therapy is an emerging curative treatment option for patients with aggressive B-cell non-Hodgkin's lymphoma (B-NHL). Since approximately 40% of lymphoma patients receiving CAR-T cell therapy achieve complete remission, further investigation into relapse and morbidity post-CAR-T cell therapy is needed (Byrne et al., 2019). Cachexia is an inflammatory muscle wasting syndrome that affects the morbidity and mortality of 50% of all cancer patients (Baracos et al., 2018). Cachexia is an independent factor in cancer treatment response, but also leads to decreased quality of life and increased disability (Naito, 2019). We have previously shown that patients with B-NHL are at high risk of cachexia, and within this population, cachexia is linked to poor response to chemotherapy, treatment toxicity, and decreased survival (Burkart et al., 2019). While prior studies have established that cachexia is a predictor of poor response to immune-checkpoint inhibitors (Miyawaki et al., 2020), the relationship between CAR-T cell therapy and cachexia has not been previously investigated. Herein, our objective was to determine the relationship between cachexia and post-CAR-T cell therapy clinical and functional outcomes in patients with B-NHL.

Methods: Retrospective cohort study of 70 patients with Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma who received CAR-T cell therapy between 2016 and 2021. Inclusion criteria were age ≥18 years old and prior treatment with ≥ 1 line of chemotherapy. Exclusion criteria were patients with primary central nervous system lymphoma. Cachexia was identified at time of apheresis and therapy infusion using the following markers: consensus weight-loss criteria for pre-cachexia (0.1–5.0% body weight loss) and cachexia (>5% body weight loss), neutrophil-to-lymphocyte ratio (NLR), weight-loss grading scale (WLGS), serum albumin, and prognostic nutritional index (PNI). Primary outcomes included progression-free survival (PFS), overall survival (OS), and disability-free survival (DFS) – defined as the need for inpatient rehabilitation (IPR) at any point in follow up after CAR-T cell therapy. Secondary outcomes included 90-day relapse, cytokine release syndrome (CRS), neurotoxicity (NT), infection, or need for rehabilitation services immediately after hospital discharge for infusion.

Results:
In our cohort of aggressive B-NHL patients receiving CAR-T, the median age was 62 years old, and 36% were female. 16% had IPI =1, 31% had IPI=2, 42% IPI=3, and 11% had IPI=4. The median follow-up time for surviving patients was 16 months. Amongst non-surviving patients (n=12), the median time to death was 32.5 days. 90-day rate of complete response was 47%.

Rate of need for rehabilitation services immediately after infusion was 30% and rate for need for IPR any time after CAR-T was 20%.

Amongst clinical outcomes, increased WLGS at time of CAR-T was associated with increased odds of relapse at 90 days (Table 1). PNI < 44 at CAR-T infusion was associated with decreased PFS, and NLR > 3 at apheresis trended towards decreased PFS (Table 2). Weight loss between diagnosis and apheresis, weight loss between diagnosis and infusion, albumin < 3.5 at apheresis and infusion, and PNI < 44 at apheresis and infusion were each associated with decreased OS. To determine the influence of key co-variates, in a limited multivariate model including age, PNI and IPI, PNI at infusion was significantly associated with OS (HR=1.11, p-value=0.01, R^2=0.20). No cachexia markers were significantly associated with CRS or infection, though both albumin and PNI trended towards increased odds of NT (Table 1).

Amongst functional outcomes, using logistic regression, there was a trend towards post-infusion rehabilitation services with both low albumin and low PNI (Table 1) and using AUC analysis, albumin < 3.5 had OR of 5.2 for rehabilitation (p=0.004). Notably, patients with NT had significantly higher odds of requiring rehabilitation services post-infusion, (OR=14.7, 95% CI = 4.208 to 44.59, p<0.0001). While weight loss trended towards lower DFS, both albumin and PNI were significantly associated with lower DFS.

Conclusions: Cachexia is associated with several negative clinical and functional outcomes post-CAR-T cell therapy in lymphoma patients. Amongst emerging cachexia markers, prognostic nutritional index was associated with all three primary outcomes, including PS, OS, and DFS. Further study is needed into directly addressing cachexia in patients receiving CAR-T cell therapy in order to improve response rates and post treatment morbidity.

Table 1. Odds ratio for select clinical and functional outcomes after logistic regression with cachexia markers obtained at apheresis or infusion. CRS = cytokine release syndrome. NT = neurotoxicity. Significant (p-value < 0.05) denoted by "*". Trending or significant findings annotated in bold.

		Apheresis			Infusion		
Variable	Outcome	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Body weight change	D90 relapse	0.99	0.94 to 1.04	0.74	0.96	0.89 to 1.01	0.15
	CRS	1.00	0.95 to 1.05	0.92	1.02	0.96 to 1.07	0.55
	Infection	0.98	0.92 to 1.02	0.35	0.96	0.90 to 1.01	0.17
	NT	0.99	0.94 to 1.04	0.73	1.00	0.94 to 1.05	0.91
	Rehab services	0.99	0.94 to 1.04	0.74	1.00	0.94 to 1.05	0.97
Weight loss grading scale	**D90 relapse**	1.32	0.92 to 1.93	0.14	**1.62**	**1.09 to 2.47**	**0.02***
	CRS	0.92	0.64 to 1.31	0.66	0.93	0.63 to 1.34	0.70
	Infection	1.30	0.91 to 1.86	0.15	1.15	0.80 to 1.66	0.45
	NT	1.04	0.73 to 1.48	0.82	1.06	0.73 to 1.53	0.75
	Rehab services	1.05	0.73 to 1.50	0.78	1.04	0.72 to 1.50	0.82
Neutrophil to lymphocyte ratio	D90 relapse	1.01	0.96 to 1.05	0.61	1.04	0.97 to 1.12	0.27
	CRS	0.99	0.94 to 1.03	0.53	0.95	0.87 to 1.01	0.19
	Infection	1.00	0.95 to 1.03	0.81	1.02	0.96 to 1.09	0.55
	NT	1.01	0.96 to 1.05	0.59	1.03	0.97 to 1.11	0.35
	Rehab services	1.01	0.96 to 1.05	0.61	1.03	0.97 to 1.10	0.37
Albumin	D90 relapse	1.01	0.43 to 2.45	0.98	0.53	0.20 to 1.30	0.17
	CRS	0.86	0.35 to 1.99	0.73	0.66	0.24 to 1.62	0.39
	Infection	0.85	0.36 to 1.92	0.69	0.68	0.27 to 1.61	0.39
	NT	0.90	0.39 to 2.10	0.81	**0.40**	**0.14 to 0.98**	**0.05**
	Rehab services	0.96	0.41 to 2.21	0.91	**0.40**	**0.14 to 0.97**	**0.05**
Prognostic Nutritional Index	D90 relapse	1.00	0.92 to 1.07	0.95	0.94	0.86 to 1.02	0.16
	CRS	1.01	0.93 to 1.09	0.75	0.99	0.91 to 1.07	0.87
	Infection	0.99	0.92 to 1.07	0.89	0.97	0.90 to 1.04	0.47
	NT	0.99	0.91 to 1.06	0.79	**0.94**	**0.86 to 1.01**	**0.10**
	Rehab services	0.99	0.91 to 1.06	0.77	**0.93**	**0.85 to 1.01**	**0.09**

Table 2. Progression free survival (PFS), overall survival (OS) and disability free survival (DFS) based on cachexia markers collected at apheresis and infusion. Significant univariate results (p-value < 0.05) denoted by "*". "-" indicates no calculated median value in the current follow up period. NLR = neutrophil to lymphocyte ratio. PNI = prognostic nutritional index. Significant multivariate results (p-value < 0.05) denoted by "#". Trending or significant findings annotated in bold.

		Apheresis					Infusion				
Variable	Outcome	Median survival		HR	95% CI	p-value	Median survival		HR	95% CI	p-value
Body weight change		Weight loss	No weight loss				Weight loss	No weight loss			
	PFS	11.3	-	1.50	0.67 to 3.32	0.34	7.37	-	1.87	0.83 to 4.2	0.17
	OS	**16.1**	-	**2.88**	**1.18 to 7.00**	**0.05**	**16.1**	-	**3.50**	**1.41 to 8.61**	**0.03***
	DFS			2.32	0.60 to 8.79	0.28			**5.46**	**1.44 to 20.6**	**0.07**
Weight loss grading scale		WLGS >2	WLGS ≤2				WLGS >2	WLGS ≤2			
	PFS	11.5	11.3	1.05	0.47 to 2.33	0.90	11.5	11.3	1.13	0.49 to 2.57	0.77
	OS	21	-	1.54	0.63 to 3.73	0.32	20.83	29	1.55	0.64 to 3.70	0.27
	DFS	-	-	1.48	0.41 to 5.23	0.53	-	-	1.65	0.49 to 5.51	0.36
NLR		NLR>3	NLR≤3				NLR>3	NLR≤3			
	PFS	**6.3**	-	**2.15**	**1.06 to 4.34**	**0.05**	11.3	11.5	1.18	0.57 to 2.41	0.65
	OS	20.8	-	1.50	0.71 to 3.15	0.30	-	12.8	0.62	0.29 to 1.32	0.19
	DFS			1.01	0.35 to 2.91	0.98	-	-	1.04	0.35 to 3.08	0.94
Albumin		Alb <3.5	Alb ≥3.5				Alb <3.5	Alb ≥3.5			
	PFS	11.3	11.7	1.14	0.49 to 2.62	0.74	4.2	-	1.74	0.80 to 3.74	0.11
	OS	**12.7**	-	**2.29**	**0.97 to 5.39**	**0.02***	**12.7**	-	**3.14**	**1.36 to 7.24**	**0.001***
	DFS	-	-	1.86	0.53 to 6.44	0.26	**18.3**	-	**3.27**	**0.94 to 11.2**	**0.02***
PNI		PNI <44	PNI ≥44				PNI <44	PNI ≥44			
	PFS	7.6	-	1.37	0.68 to 2.72	0.36	**7.4**	-	**2.48**	**1.23 to 4.98**	**0.03***
	OS	**12.9**	-	**2.83**	**1.36 to 5.89**	**0.01***	**20.8**	-	**2.72**	**1.29 to 5.68**	**0.02*#**
	DFS	-	-	1.77	0.61 to 5.08	0.28	-	-	**3.23**	**1.13 to 9.23**	**0.05**