INCIDENCE AND RISK FACTORS ASSOCIATED WITH BLEEDING FOLLOWING ANTI-B CELL MATURATION ANTIGEN CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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BACKGROUND

Bleeding and thrombotic events are an emerging toxicity associated with chimeric antigen receptor (CAR) T-cell therapies. In lymphoma patients treated with axicabtagene ciloleucel, bleeding occurred in 9% and was associated with low pretreatment platelet count and grade ≥ 3 neurotoxicity 1.

AIM

The impact of anti-B cell maturation antigen (BCMA) CAR T on hemostasis in patients with relapsed/refractory multiple myeloma (RRMM) has not been reported. Here, we describe the incidence of bleeding and associated factors in RRMM patients receiving anti-BCMA CAR T.

METHODS

We retrospectively analyzed 83 consecutive RRMM patients with > 30 days follow up after receipt of commercially available anti-BCMA CAR T. 77 patients received Idecabtagene Vicleucel and 6 received Ciltacabtagene Autoleucel. Chi-square and Kruskal Wallis rank sum tests were used to examine differences in baseline patient characteristics and outcomes including overall response rate (ORR), cytokine release syndrome (CRS), and neurotoxicity (NT) by bleeding complications. We did not conduct these analyses by thrombosis due to a small number of events. The 'cmprsk' R package was used to estimate cumulative incidence of bleeding and thrombosis events.

RESULTS

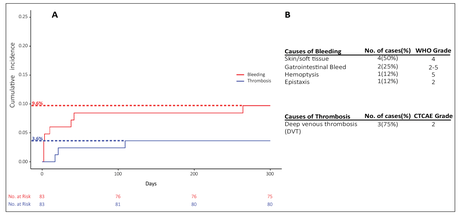
Eight patients (9.6%) had a bleeding complication and three patients (3.6%) had a thrombotic event. Bleeding occurred at a median of 6.5 days (range, 2-264 days) and thrombosis at a median of 21 days (range,17-109 days). Table 1 demonstrates the study population characteristics by bleeding event. Bleeding sites included gastrointestinal, soft tissue and respiratory tract, while all thrombotic events manifested as deep vein thromboses (Figure 1). Patients who experienced bleeding had a higher disease stage (Revised - International Staging System - 3: 50% vs. 16%, p=0.04), baseline ferritin (935 vs. 260, p=0.04), and peak ferritin post CAR T (7937 vs. 989, p=0.002) compared to patients who did not have a bleeding event. Patients with bleeding were more likely to have a prior history of bleeding compared to those who did not experience bleeding event post CAR T (25% vs. 0%, p=0.008). Both baseline platelet count (58.5 x 103 vs. 150 x 103, p=0.01) and platelet nadir (7 x 103 vs. 49 x 103, p=0.01) were significantly lower among those with versus without bleeding complication, respectively.

Baseline coagulation parameters were not significantly different except for slightly higher prothrombin time in those with a bleeding versus no bleeding event (13.8s vs. 11.7s, p=0.03). Prior receipt of anticoagulant was not associated with significant risk of bleeding (25% vs. 16%, p=0.6). Higher grade NT (grade ≥2) was associated with increased risk of bleeding (38% vs. 8%, p=0.03), however, CRS was not. Day 30 ORR was higher among patients who did not experience a bleeding event (73% vs. 38%, p=0.05). However, no difference in response rates were observed at day 90 (67% vs. 38%, p=0.1). Seventy five percent (6/8) of patients required platelet transfusions and 12% (1/8) required fresh frozen plasma during bleeding events. Three of these patients had WHO grade 4 bleeding requiring admission to an intensive care unit.

Table 1. Characteristics in patients with bleeding treated with anti- BCMA CAR T-cell therapy

Baseline characteristics, Coagulation parameters, safety, and efficacy	BLEEDING EVENT			*P*-Value
	Overall, N = 83	No, N = 75	Yes, N = 8	
Age, Median (Range)	65.0 (38.0, 81.0)	65.0 (38.0, 81.0)	63.0 (43.0, 75.0)	>0.9
Male Sex, n (%)	36 (43%)	32 (43%)	4 (50%)	0.7
ECOG ≥ 2, n (%)	3 (4%)	2 (3%)	1 (12%)	0.2
Revised – ISS, n (%)				**0.038**
R-ISS I	18 (22%)	18 (24%)	0 (0%)	
R-ISS II	49 (59%)	45 (60%)	4 (50%)	
R-ISS III	16 (19%)	12 (16%)	4 (50%)	
High risk cytogenetics, n (%)	24 (30%)	21 (29%)	3 (38%)	0.7
Penta-refractory ds, n (%)	33 (40%)	30 (40%)	3 (38%)	0.06
Baseline LDH (U/L)	207.5 (135.0, 1,108.0)	205.0 (138.0, 1,108.0)	398.5 (135.0, 538.0)	**0.027**
Baseline Ferritin, ng/mL, median (range)	344.0 (15.0, 4,960.0)	260.0 (15.0, 4,960.0)	935.0 (116.0, 4,862.0)	**0.043**
Baseline CRP, mg/dL, median (range)	0.4 (0.0, 12.1)	0.4 (0.0, 10.6)	0.9 (0.0, 12.1)	0.1
History of bleeding, n (%)	2 (2.4%)	0 (0%)	2 (25%)	**0.008**
History of prior anticoagulant use, n (%)	14 (17%)	12 (16%)	2 (25%)	0.6
Prothrombin Time (PT), median (range) secs	11.7 (9.8, 19.5)	11.7 (9.9, 15.1)	13.8 (9.8, 19.5)	**0.031**
Activated Partial Thromboplastin Time (PTT), median (range) secs	30.3 (21.8, 77.3)	30.3 (21.8, 77.3)	33.0 (25.6, 43.9)	0.5
INR median (range)	1.0 (0.8, 1.6)	1.0 (0.8, 1.3)	1.2 (0.8, 1.6)	0.058
Baseline platelets (x 10^9/µL)	142.0 (32.0, 414.0)	150.0 (32.0, 414.0)	58.5 (35.0, 199.0)	**0.013**
Platelets Nadir (x 10^9/µL)	36.0 (3.0, 194.0)	49.0 (5.0, 194.0)	7.0 (3.0, 22.0)	**0.013**
Cytokine release syndrome (CRS), n (%)				**0.4**
CRS gr.0-1	66 (80%)	61 (81%)	5 (62%)	
CRS gr.≥2	17 (20%)	14 (19%)	3 (38%)	
Neurotoxicity (NT), n (%)				**0.038**
NT gr.0-1	74 (89%)	69 (92%)	5 (62%)	
NT gr.≥2	9 (11%)	6 (8.0%)	3 (38%)	
30-day ORR, n (%)	58 (70%)	55 (73%)	3 (38%)	**0.05**
90-day ORR, n (%)	53 (64%)	50 (67%)	3 (38%)	0.1

R – ISS; Revised international staging system, LDH; lactate dehydrogenase, CRP; C- reactive protein, INR; International normalized ratio. High risk cytogenetics include del(17p), t(4;14) and t(14:16). Penta-refractory was defined as disease refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab/isatuximab, ORR; Overall response rate.



Cumulative Incidence of bleeding and thrombotic events after anti - BCMA CAR T (A) Cumulative incidence of bleeding and thrombosis. (B) Tables characterizing the bleeding and thrombosis events and their respective clinical grades according to World Health Organization (bleeding) and Common Terminology Criteria for Adverse Events criteria (thrombosis). Events were included if the grade was ≥ 2 or if a clinical intervention was necessary.

CONCLUSION

Patients with more aggressive disease features including higher R-ISS, baseline thrombocytopenia, and grade ≥ 2 NT are at increased risk of bleeding, particularly in the first month post CAR T. Further investigation in a larger cohort is needed to assess risk factors for systemic coagulopathies in patients receiving anti-BCMA CAR T including association with NT and efficacy.

LIMITATIONS

Retrospective nature of the study, issues with missing data, selection bias, unmeasured variables.

REFERENCES

1. Johnsrud A, Craig J, Baird J, Spiegel J, Muffly L, Zehnder J et al. Incidence and risk factors associated with bleeding and thrombosis following chimeric antigen receptor T-cell therapy. Blood Adv 2021; 5 (21): 4465–4475. doi: https://doi.org/10.1182/bloodadvances.2021004716