MultipleMyelomaHub

General MM, Relapsed/refractory patients

Cytopenia associated with CAR T-cell therapy

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CAR T-cell therapies have shown efficacy across a range of hematologic and solid tumors, are standard of care for certain types of lymphoma. As with other therapies, patients may report CAR T-cell treatment-related adverse events (AE). Cytopenia has been reported following lymphodepletion and CAR T-cell infusion with axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tis-cel).[1-3] During the 2nd European CAR T Meeting, Sitges, ES session dedicated to the management of the side effects, Marion Subklewe, from the Ludwig Maximilian University of Munich, DE, discussed cytopenia in patients who received CAR T- cell therapy.[4] This article summarizes the key messages from the presentation.

Marion Subklewe started the presentation by describing the grading of cytopenia by Common Terminology Criteria for Adverse Events (CTCAE) presented in **Table 1**.

Table 1. Grading of cytopenia according to the CTCAE version 3.0 (values per mm^3 unless otherwise stated)[4]

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	> 10 g/dL	> 8 g/dL	< 8 g/dL*	Life-threatening	Death
Neutropenia	> 1500	> 1000	> 500	< 500	N/A
Thrombocytopenia	> 75000	> 50000	> 25000	< 25000	N/A
Lymphocytes	> 800	> 500	> 200	< 200	N/A
CD4 lymphocytes	> 500	> 200	> 50	< 50	
N/A, not available *transfusion indicated					

She then followed with an overview of the CAR-T clinical trials in lymphoma and multiple myeloma (MM) **(Table 2).**

Table 2. Overview of clinical trials evaluating CAR T-cell therapies in lymphoma and MM[1,4-7]

	JULIET[1,4] (N = 111)	**ZUMA**[4] (N = 108)	**TRANSCEND**[4-6] (N = 269)	**EVOLVE**[4,7,8] (N = 44)
CAR T-cell therapy	tis-cel	axi-cel	liso-cel	JCARH125
NCT number	NCT02445248	NCT02348216	NCT02631044	NCT03430011
Disease area	R/R DLBCL	R/R DLBCL PMBCL tFL HGBCL	DLBCL PBMCL tFL tCLL tMZL MCL FL3B HGBCL	R/R MM
Median age, years	56 (22–76)	58 (23–76)	63 (18–86)	62 (36–79)
HGBCL, %	27	NR	13	100
Refractory to last therapy, %	55	74	67	100
≥ 3 prior therapies, %				
Prior HSCT, %	52 49	76 NR	26 35	100 NR

Blood count threshold	ANC < 1000/ul PLT < 50000 g/L	ANC < 1000/ul PTL < 75000 g/L ALC < 1000/ul	No threshold for blood count	No threshold for blood count
Lymphodepletion	Flu 25 mg/m^2 + Cy 250 mg/m^2 for 3 days or benda 90 mg/m^2 for 2 days	Flu 30 mg/m^2 + Cy 500 mg/m^2 for 3 days	Flu 30 mg/m^2 + Cy 300 mg/m^2 for 3 days	Flu 30 mg/m^2 + Cy 300 mg/m^2 for 3 days
ALC, absolute lymphocyte count; ANC, absolute neutrophil count; axi-cel, axicabtagene ciloleucel; benda, bendamustine; cy, cyclophosphamide; DLBCL, diffuse large B-cell lymphoma; HGBCL, high grade B-cell lymphoma (double/triple hit lymphomas); FL3B, follicular lymphoma Grade 3B; flu, fludarabine; HSCT, hematopoietic stem cell transplant; MM, multiple myeloma; liso-cel, lisocabtagene maraleucel; NR, Not reported; PMBCL, primary mediastinal B-cell lymphoma; PTL, platelet count; R/R relapsed or refractory; tCLL, transformed chronic lymphocytic leukemia, tis-cel, tisagenlecleucel; tFL, transformed follicular lymphoma; tMZL, marginal zone lymphoma *pediatric and young adult patients				

Cytopenia (most frequently neutropenia) is the most common AE, seen in patients across different hematological tumors who underwent lymphodepletion and infusion with any CAR T-cell therapy

- Early cytopenia (> 10 days) occurred in < 80% of patients
- Late cytopenia (> 21–28 days) Grade 3/4 occurred in 30–40% of patients
- Prolonged cytopenia (> 90 days) occurred in 8–18% of patients

In the ZUMA-1 trial, cytopenia was the most frequent AE, reported in 93% of patients:

- Neutropenia was the most common form of any-grade cytopenia, experienced by 86% of patients *vs* thrombocytopenia 62% of patients, and anemia 68% of patients
- Neutropenia was also the most common Grade ≥ 3 cytopenia, 80% *vs*40% and 45%, respectively
- There were no significant differences in the incidence of cytopenia between patients older and younger than 65 years

Early and late cytopenia[4]

- In the JULIET trial, 44% of patients had any-grade cytopenia on Day 28, including 32% with Grade ≥ 3
- The incidence of late cytopenia in ZUMA-1, TRANSCEND and EVOLVE is presented in **Table 3**

Table 3. Incidence of late cytopenia with axi-cel, liso-cel, and JCARH125*,[4]

	ZUMA-1 (N = 108)	**TRANSCEND** (N = 269)	**EVOLVE** (N = 44)
Neutropenia, n (%)			
All Grade	39 (36)	169 (63)	NA
Grade ≥ 3	28 (26)	161 (60)	38 (86)
Anemia, n (%)			
All Grade	31 (29)	129 (48)	NA
Grade ≥ 3	11 (10)	101 (38)	22 (50)
Thrombocytopenia, n (%)			
All Grade	44 (41)	84 (31)	NA
Grade ≥ 3	26 (24)	72 (27)	19 (43)
*cytopenia present on Day 30			

Prolonged cytopenia[4]

In JULIET trial, prolonged cytopenia, defined as Grade 3/4 cytopenia not resolved to Grade ≤ 2 by Day 28, was reported in

- 8% of patients (16.7% of patients responding to treatment) had neutropenia at 6 months; all cases resolved by 9 months
- 7% of all patients (26.2% of responding patients) had thrombocytopenia at 6 months; 7.2% of cases remained unresolved at 9 months; all cases resolved by 12 months
- 1% of all patients (36.4% of responding patients) had lymphocytopenia at 6 and 9 months, with 31.6% of cases unresolved at 12 months

- There were no cases of unresolved anemia reported between 6 and 12 months

In the ZUMA trial

- On Day > 90, 34% of patients experienced cytopenia of any grade, including 17% with Grade ≥ 3
  - Neutropenia in 19% and 11% of patients, respectively
  - Thrombocytopenia in 18% and 7% of patients, respectively
  - Anemia in 18% and 3% of patients, respectively
- Incidence of cytopenia at 1- and 2-years after infusion are described in Table 4

Table 4. Prolonged cytopenia at 1 and 2 years[4]

Treatment-emergent cytopenia	At 1 year	At 2 years
ANC/HGB/PLT < Grade 3, %	75	85
ALC (> 1x 10^9/L), %	80	100
CD4 (> 200 cells/mm^3), %	63	86
CD8 (> 82 cells/mm^3), %	100	100
CD56 (> 0 cells/mm^3), %	100	100
ALC, absolute lymphocyte count; ANC, absolute neutrophil count; HGB, hemoglobulin count; PLT, platelet count		

Infectious complications after CAR T-cell therapy[4]

Patients on CAR T-cell therapies are at risk of infections and the presence of cytopenia can further increase susceptibility and reduce the ability to fight pathogens.

ZUMA-1

- Infections of any grade occurred in 38% of patients, including 23% Grade ≥ 3

- Viral in 16% and 4% of patients, respectively
- Bacterial in 13% and 9% of patients, respectively
- Fungal in 5% and 0%, respectively
- Unspecified pathogen 26% and 16% of patients, respectively
- Grade ≥ 3 lung infections occurred in 12/108 (11%) patients

TRANSCEND

- Infections Grade ≥ 3 occurred in 12% of patients
  - Viral in 1% of cases
  - Bacterial in 4% of cases
  - Fungal in 1% of cases
  - Unspecified pathogen in 8% of cases

Infectious complications after anti-CD19 CAR T-cell therapy at Fred Hutchinson Cancer Research Center, Seattle, US

In total 133 patients were analyzed for the incidence of infection in the first 100 days post CAR-T (n = 62 with lymphoma, n = 24 with CLL, and n = 47 with acute lymphoblastic leukemia).

- Patients received antimicrobial prophylaxis
  - Levofloxacin 750 mg/day
  - Fluconazole 400 mg/day while the ANC was < 500 G/L
  - Acyclovir 800 g/day or valacyclovir 500 mg twice a day (until > 3 months after CAR T-cell infusion)
  - Trimethoprim 160 mg or sulfamethoxazole 800 mg twice a day for 2 days a week starting after neutrophil recovery till > 3 months after infusion
  - Granulocyte-colony stimulating factor (G-CSF) after lymphodepletion if the neutrophil count was < 500 cells
- Within 28 days after CAR T-cell infusion, 43 infections were recorded in 30 patients (23%), including:
  - Bacterial infections 17%
  - Viral infections 9%
  - Fungal infections 4%
  - Fatal or life-threatening infection in 4%
- Median time of the first infection was six days after infusion

Causes of cytopenia and role of prophylaxis[4]

- Early cytopenia was an AE after lymphodepleting chemotherapy with fludarabine, cyclophosphamide and mitoxantrone (FCM) and rituximab-FCM

- Late cytopenia was associated with inflammation and was more frequent in patients with Grade ≥ 3 cytokine release syndrome (CRS) and within one year after HSCT

Infectious prophylaxis at Ludwig Maximilian University of Munich Hospital

- Recommend influenza vaccination of patients and family members
- Acyclovir 400 mg 3x daily and cotrimoxazol 160 mg/trimethoprim 800 mg twice a day, two days a week, for 6 months following CAR T-cell infusion and until CD4 cell count is > 200 cells/ul
- Antifungal agents should be considered for high-risk patients
- G-CSF should be considered in patients after CRS with > 7 days of neutropenia
- Empiric antibiotics should be considered upon the onset of fever
- Patients, family, and physicians should be educated about late cytopenia and risk of infection

Conclusion

CART-cell therapies are becoming established in clinical practice, increasing the treatment options available to patients with refractory or relapsed disease. As with many treatment regiments, CAR-Ts are associated with an increased risk of cytopenia and higher susceptibility to infections. However, clinical benefits outweigh the risks, which can be reduced with appropriate prophylaxis.

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