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REVIEW ARTICLE

Understanding the Etiology of Pancytopenias in the CAR T-Cell Therapy Setting: What We Know and What We Don't?

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Abstract

Chimeric antigen receptor T-cell (CAR T-cell) therapy represents an innovative and transformative therapy for patients with relapsed and/or refractory (R/R) hematological malignancies. CAR T-cell therapy was first approved in R/R diffuse large B-cell lymphoma (DLBCL) and acute lymphoblastic leukemia, today the use of CAR T-cell therapy has expanded to multiple myeloma and other lymphoma subtypes such as follicular and mantle cell lymphoma. It is also being explored in earlier lines of therapy in DLBCL. CAR T-cell therapy is associated with a unique toxicity profile and development of cytopenias post CAR T-cell therapy has been reported in all pivotal clinical trials and is now considered a related side effect. Here, we provide an in-depth evaluation of etiologies, consequences, and current management strategies for cytopenias following CAR T-cell therapy.

Keywords: Chimeric antigen receptor T-cell therapy (CAR T-cell), Cytopenias, Lymphomas

1. Introduction

The development of chimeric antigen receptor T-cell (CAR T-cell) therapy represents a major advancement in the treatment algorithm of relapsed or refractory (R/R) B-cell lymphomas, namely diffuse large B-cell (DLBCL), follicular and mantle cell, in addition to acute lymphoblastic leukemias (ALL) and multiple myeloma (MM) [1–9]; however, CAR T-cell therapy is associated with a unique toxicity profile. The most serious adverse events are cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS). These adverse events, albeit unique to these therapies, are better understood than other adverse events like cytopenias [1,3]. In the ZUMA-1 trial, which evaluated axicabtagene ciloleucel (axi-cel) in patients with R/R large B-cell lymphoma, (LBCL) all-grade neutropenia, anemia, and thrombocytopenia were reported at 84%, 66% and 58% respectively. Grade≥3 neutropenia, anemia, and thrombocytopenia were reported at 78%, 43% and 38%, respectively [1]. Grade≥3 cytopenias were the most common adverse event in the ZUMA-5 trial which evaluated the safety and efficacy of axi-cel in R/R follicular or marginal zone lymphoma and were reported at 70% [4]. Cytopenias were also reported in patients with ALL who received CAR T-cell therapy, with all-grade neutropenia, anemia and thrombocytopenia observed in 27%, 53% and 33%, respectively [7]. These data highlight that cytopenias post CAR T-cell therapy represent an adverse event that appears to be unique to CAR T-cell and occur regardless of the primary disease type.

The duration of cytopenias observed post CAR T-cell therapy is variable, ranging from 14 to 180 days and at times even longer [10]. While most patients recover blood counts by 30 days, a notable percentage of patients experience persistent cytopenias lasting beyond 30 days [11,12]. Additionally, the

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etiology and pathophysiology of these cytopenias is not fully understood. Delayed hematopoietic recovery post-CAR T-cell predicts for increased infections, transfusions requirements, prolonged hospitalization, and increased medical costs [13–15]. It is important to understand the mechanisms responsible for post-CAR T-cell cytopenia and develop innovative management strategies.

Here, we provide a comprehensive review of the available evidence pertaining to the etiology(ies) of cytopenias post CAR T-cell, their impact on post CAR T-cell therapy outcomes, and available management strategies.

2. Factors associated with cytopenias

The proposed etiologies behind the occurrence of CAR T-cell related cytopenias are best understood in relation to the timing of cytopenias post CAR T-cell therapy. Cytopenia can be described as early, defined as those occurring within the first 30 days; prolonged defined as those occurring between 30 and 90 days and persistent or late, defined as those persisting after 90 days and beyond [16].

The inflammatory milieu that accompanies initial CAR T-cell expansion has been associated with early cytopenia. In one study, increasing grade of CRS and ICANS were associated with lower likelihood of count recovery at 30 days. For patients who experienced grade $\geq$3 CRS or ICANS, only 6% were able to recover counts by 30 days [17]. Additionally, presence of baseline cytopenia and design of CAR construct were also associated with absence of early count recovery in univariate models, but this association was not significant after adjustment, whereas the association of increased inflammatory markers and high-grade CRS/ICANS with lack of count recovery remained significant [17]. Hemophagocytic lymphohistiocytosis is a hyperinflammatory syndrome and falls within the spectrum of severe CRS [18]. It is reported to occur in 1–3.5% of patients receiving CAR T-cell therapy and also occurs typically in the first 30 days and can be an important factor in development of early cytopenias [18,19]. Lymphodepleting (LD) chemotherapy is an important part of the CAR T-cell treatment as it is crucial to facilitating T-cell expansion and activation but the myelosuppressive effect on the bone marrow (BM) can contribute adversely towards early count recovery [20].

Cytopenias that are prolonged and persist beyond 30 days require evaluation to rule out reversible causes like infection and autoimmune etiologies [16]. Nearly one-third of patients who receive CAR T-cell experience persistent or late cytopenias lasting 90 days and beyond [11,21]. There is limited understanding of factors that impact late cytopenias, but various studies have suggested that greater number of previous lines of therapy and a prior autologous or allogeneic hematopoietic cell transplant (HCT) can decrease bone marrow reserve and potentially lead to late cytopenias [17,22]. Markers of impaired hematopoietic reserve, including low baseline platelet count, hemoglobin, absolute neutrophil count (ANC), inflammatory state as evidenced by hyperferritinemia, and tumor microenvironment have been shown to be predictive of prolonged and severe neutropenia [23]. These have now been validated as predictive of profound and prolonged hematotoxicity in the CAR-HEMATOTOX model [24]. Secondary malignancies of the BM have been reported anecdotally in recipients of CAR T-cell, in one study, 5% (n = 4) of patients who received CAR T-cell developed myelodysplastic syndrome on long term follow up [25]. Of note, half of these patients (n = 2) had cytogenetic abnormalities before receipt of CAR T-cell [25]. It remains unclear at the present if secondary hematological malignancies are related to CAR T-cell or is the result of prior lines of therapies. But this highlights the importance of a BM biopsy to rule out underlying marrow disease for patients who experience late cytopenia (Fig. 1).

3. Postulated mechanisms associated with cytopenias

The above-mentioned highlight various factors that are associated with the development of cytopenias post CAR T-cell therapy but there is limited understanding of the pathophysiology behind the development of cytopenias. Current literature indicates that macrophage activation during CRS lead to secretion of interleukin (IL)-1, IL-6 and interferon gamma (IFN-γ), these cytokines exert myelosuppressive effects on the marrow resulting in the

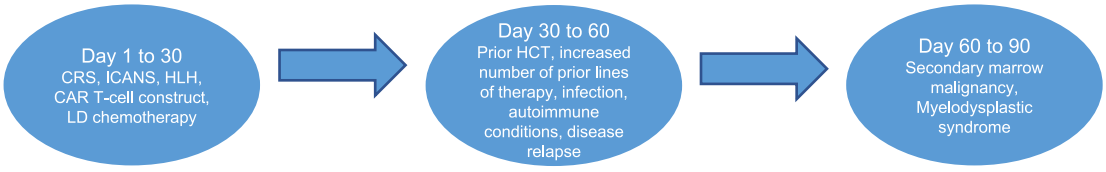

Fig. 1. Factors contributing to cytopenias post CAR T-cell therapy. Abbreviations: CRS, cytokine release syndrome; ICANS, immune effector cell associated neurotoxicity; HLH, Hemophagocytic lymphohistiocytosis; LD, lymphodepleting; HCT, hematopoetic cell transplant.

development of cytopenias [26]. A higher peak level of IL-6 has been associated with greater likelihood of cytopenias at day 30 while higher levels of transforming growth factor-β1 has been shown to be associated with increased blood counts [27]. Clonal hematopoiesis of indeterminate potential (CHIP) has been shown to have inferior outcomes in patients with non-Hodgkin lymphoma and MM [28,29]. The impact of CHIP in patients receiving CAR T-cell therapy was also investigated but was not shown to negatively impact long-term outcomes [30].Whether the presence of CHIP leads to development of cytopenias remains an important question, that is yet to be answered. The presence of CHIP can theoretically contribute to cytopenias via alteration in inflammatory pathways [31]. In one study, delayed cytopenia was associated with decreased levels of stromal-derived factor, a chemokine which is central to early B-cell development [32]. This mechanism is similar to that described for rituximab associated late onset neutropenia [33].

4. Impact of cytopenias on post CAR T-cell outcomes

With increased utilization of CAR T-cell therapy and longer follow up of CAR T-cell recipients, the impact of CAR T-cell associated cytopenias on patient outcomes is continually being examined.

One important outcome is the incidence of infection in patients with prolonged cytopenias, including neutropenia. Several studies have described risk of infections in patients with cytopenias. Severe infections occurring 30 days or later following CAR T-cell therapy have been reported in 10–60% of patients with prolonged cytopenias [34]. Other studies have conversely evaluated the incidence of prolonged cytopenia in those with late (30 day or later) infections. One large study by Hill and colleagues of 119 CAR T-cell therapy recipients found late infections occurring in 14% of patients, with 22% of those occurring in those with prolonged neutropenia [35]. Another report by Thakkar et al. reported median ANC of 800 cells/μL in CAR T-cell therapy recipients who developed late infections, compared to having an ANC of 1550 cells/μL in those who did not develop late infections [36]. Wang and colleagues also reported a large series of patients who received CAR T-cell therapy for ALL but found no correlation between the presence of prolonged cytopenias and rates of infection, in contrast with the aforementioned studies [10].

Other adverse effects of prolonged CAR T-cell therapy associated cytopenias are less reported, but are important to consider. The risk of bleeding has been described in patients with prolonged cytopenias and in patients with baseline thrombocytopenia, while another study reported no major bleeding events associated with prolonged thrombocytopenia [10,32,37]. The effect of prolonged cytopenias on survival is also unclear. One study found that presence of prolonged cytopenia was associated with a shorter 1-year overall survival compared to those without cytopenias. Another study by Schafer et al. found that prolonged cytopenias have a favorable impact on progression free survival, with prolonged anemia associated with improved overall survival [11,13].

Healthcare utilization is an important outcome in CAR T-cell therapy, especially in those with long-term CAR T-cell therapy associated toxicities such as prolonged cytopenias. While one study demonstrated severe cytopenias being associated with longer hospital length of stay and hospital expenses, there is a need for more studies to confirm the impact of CAR T-cell related cytopenias on healthcare utilization [10]. Larger registry studies and long term follow up from CAR T-cell therapy survivorship clinics in large CAR T-cell referral centers are needed to further elucidate the impact of cytopenias on post-CAR T-cell therapy outcomes.

5. Proposed management strategies for cytopenias

How to best manage cytopenias secondary to CAR T-cell is an area of ongoing investigation. Currently, the management of CAR T-cell therapy associated cytopenias rests on supportive care with the use of growth factors and transfusion support as clinically indicated. Granulocyte colony-stimulating factor (G-CSF) has been used for management of CAR T-cell associated neutropenia. Initially there was a heightened concern for CRS exacerbation, but subsequent studies have shown no increase in incidence of CRS with G-CSF and a lower risk of infection was reported when the initiation of G-CSF was based on the ANC instead of the measured risk of the infection [38–40]. The European Society of Blood and Marrow Transplantation practice guidelines recommend waiting at least 14 days post CAR T-cell infusion prior to considering G-CSF for the management of neutropenia [41]. Routine anti-bacterial and anti-fungal prophylaxis is not recommended but anti-viral and anti-pneumocystis pneumonia prophylaxis is recommended to be initiated from the start of LD to one year post CAR T-cell infusion or until CD4+ is greater than 0.2×10^9/L(41). The use of thrombopoietin receptor

agonists for management of thrombocytopenia post CAR T-cell represents another logical approach but has only been reported anecdotally and still requires further investigation in larger studies [42]. Similarly, use of erythropoietin stimulating agents has been described in the management of persistent anemia [43]. Sirolimus has been reported in one case report to reverse persistent grade 4 thrombocytopenia and severe platelet transfusion in a patient who received CAR T-cell therapy for DLBCL, and did not appear to affect the efficacy of CAR T-cells [44]. This suggests that immune modulation may represent another attractive approach in the future for management of CAR T-cell associated hemotoxicity. Infusion of autologous peripheral blood hematopoietic stem cells (PBSC) for the management of persistent pancytopenia post CAR T-cell has been shown to lead to complete resolution of cytopenias with transfusion independence as a result [45,46]. There is lack of available guidance on the timing of autologous PBSC rescue post CAR T-cell infusion but patients who continue to require transfusion support at 100 days post infusion should be considered for an autologous PBSC rescue. This strategy is limited by the availability of cryopreserved autologous PBSC. For patients who do not have cryopreserved autologous PBSC and continue to be transfusion dependent, a BM biopsy should be considered to evaluate for underlying dysplasia, cytogenetic abnormalities, and pathogenic mutations. In patients where signs of underlying BM damage are discovered, search for an appropriate allogeneic donor can be considered. These strategies merit further investigation in larger controlled studies.

6. Conclusions and future directions

Currently available studies provide a limited understanding of the mechanisms underlying hematopoietic recovery post CAR T-cell therapy. Cytopenias do not seem to be strictly limited to anti-CD19 CAR T-cell therapy but are rather a class effect as they are frequently observed when other disease specific antigens are targeted. For instance, the most common adverse events observed with anti-BCMA CAR T-cell for R/R MM were cytopenias of grade≥3 including anemia (45%), leukopenia (58%), neutropenia (85%) and thrombocytopenia (45%) [47]. A notable difference however was the time to count recovery. Most patients who received anti-BCMA CAR T-cell therapy recovered counts within 1 month after the infusion while only 3% and 35% of patients had persistent grade≥3 neutropenia and thrombocytopenia at 30 days [47]. This contrasts with studies of anti-CD19 CAR T-cell therapy where 17–34% of patients continued to experience grade≥3 cytopenia lasting up to 3 months post CAR T-cell infusion [3,21]. Table 1 provides a summary of cytopenias reported in selected pivotal CAR T-cell clinical trials.

Cytopenias are more likely to occur in patients experiencing higher grades of ICANS and CRS [17]. Inflammatory state prior to infusion of CAR T-cells, as measured by an elevated ferritin level and C-reactive protein, have also been associated with an increased likelihood of cytopenia, especially when occurring after 21 days [24]. Other identifiable risk factors include the CAR construct itself, the extent of BM involvement pre-treatment, baseline cytopenia at the time of CAR T-cell infusion and having received a prior HCT [48,49].

Long-term follow-up of some of the early CAR T-cell clinical trials is now being reported and a significant percentage of patients have cytopenias that are lasting beyond 30 days [21]. At the 2-year follow-up of ZUMA-1, 17% of patients had grade ≥3 at 3 months [21]. Other studies have described a biphasic nature of CAR T-cell cytopenia with an initial phase that develops soon after CAR T-cell infusion and is associated with the myelosuppressive effect of the LD chemotherapy or CRS and other inflammatory states such as macrophage activation syndrome. The second phase is described as cytopenia that develops beyond 21–30 days [32]. This phase may or may not be preceded by count recovery and is less likely to be related to factors associated with early cytopenia.

CAR T-cell therapy within the context of clinical trials is expanding to other diseases including solid organ malignancies and autoimmune disorders [50]. Also, CAR T-cell therapy showed promising results in earlier lines of therapy for patients with LBCL in 2 studies while did not appear to be beneficial in 1 study [51–53]. Based on the results of these studies, two of the CAR T-cell constructs, namely axi-cel and lisocabtagene maraleucel are now approved by the food and drug administration for patients with LBCL who have refractory disease after front line chemoimmunotherapy (CIT) or relapse within one year of first line CIT. Long-term follow-up from these studies will shed further light on the patterns of cytopenias in the future, as patients will be expected to have received fewer lines of therapy prior to CAR T-cell infusion. Corticosteroids are now incorporated as a prophylaxis to reduce the rates of high-grade CRS and ICANS based on the results of cohort 6 of ZUMA-1 [54]. Increased use of

Table 1. Incidence of cytopenias in selected pivotal CAR T-cell clinical trials.

Disease	Study [ref]	CAR T-cell product	N patients evaluable for safety	Cytopenias, N (%)			Infections	Hypogammaglobulinemia
					All-grade	Grade≥3		
LBCL	ZUMA-1 [1]	Axi-cel	101	Anemia	67 (66%)	43 (43%)	All-grade: 8 (8%)	NR
				Leukopenia	31 (31%)	29 (29%)		
				Neutropenia	85 (84%)	79 (78%)		
				Thrombocytopenia	59 (58%)	38 (38%)		
	TRANSCEND [2]	Liso-cel	269	Anemia	129 (48%)	101 (37%)	Grade≥3: 33(12%)	All-grade: 37(14%)
				Leukopenia	44 (16%)	39 (14%)		
				Neutropenia	169 (63%)	161 (60%)		
				Thrombocytopenia	84 (31%)	72 (27%)		
	JULIET [3]	Tisa-cel	115	Anemia	55 (49%)	45 (40%)	All-grade: 43 (37%)	All-grade: 10 (9%)
				Leukopenia	41 (35%)	37 (32%)	Grade≥3: 22 (19%)	
				Neutropenia	23 (20%)	23 (20%)		
				Thrombocytopenia	15 (14%)	14 (13%)		
NHL (FL and MZL)	ZUMA-5 [4]	Axi-cel		Anemia	56 (39%)	36 (25%)	Grade≥3: 26 (18%)	All-grade: 26 (18%)
				Leukopenia	23 (15%)	20 (13%)		
				Neutropenia	53 (36%)	49 (33%)		
				Thrombocytopenia	29 (20%)	22 (15%)		
MCL	ZUMA-2 [5]	Brexu-cel	68	Anemia	46 (68%)	34 (50%)	Grade≥3: 22 (32%)	Grade≥3: 1 (1%)
				Leukopenia	NR	NR		
				Neutropenia	59 (87%)	58 (85%)		
				Thrombocytopenia	50 (74%)	35 (51%)		
B-ALL	ELIANA [6]	Tisa-cel	75 (children and young adults)	Anemia	NR	NR	All-grade: 32 (43%)	NR
				Leukopenia	NR	7 (9%)	Grade≥3: 18 (24%)	
				Neutropenia	NR	7 (9%)		
				Thrombocytopenia	NR	5 (6%)		
	ZUMA-3 [7]	Brexu-cel	55	Anemia	29 (53%)	27 (49%)	Grade≥3: 14 (25%)	Grade≥3: 0
				Leukopenia	14 (25%)	13 (23%)		
				Neutropenia	15 (27%)	15 (27%)		
				Thrombocytopenia	18 (33%)	17 (30%)		
MM	KarMMA [8]	Ide-cel	128	Anemia	89 (70%)	77 (60%)	All-grade: 88 (69%)	All-grade: 6 (5%)
				Leukopenia	54 (42%)	50 (39%)	Grade≥3: 28 (22%)	
				Neutropenia	117 (91%)	114 (89%)		
				Thrombocytopenia	81 (63%)	67 (52%)		
	CARTITUDE [9]	Cilta-cel	97	Anemia	79 (81%)	66 (68%)	All-grade: 56 (58%)	NR
				Leukopenia	60 (62%)	59 (61%)	Grade≥3: 19 (20%)	
				Neutropenia	93 (96%)	92 (95%)		
				Thrombocytopenia	77 (79%)	58 (60%)		

Abbreviations: **N:** number; **LBCL**: large B-cell lymphoma; **NHL**: non-Hodgkin lymphoma; **FL**: follicular lymphoma; **MZL**: marginal zone lymphoma; **MCL**: mantle cell lymphoma; **B-ALL**: B-cell acute lymphoblastic leukemia; **MM**: multiple myeloma; **Axi-cel**: axicabtagene ciloleucel; **Liso-cel**: lisocabtagene maraleucel; **Tisa-cel:** tisagenlecleucel; **Brexu-cel:** brexucabtagene ciloleucel; **Ide-cel:** idecabtagene vicleucel; **Cilta-cel:** ciltacabtagene autoleucel; **NR**: not reported.

prophylactic strategies may also change the current pattern observed for cytopenias post CAR T-cell therapy in the future.

Cytopenias currently pose a notable challenge after CAR T-cell infusion. Cytopenias also appear to correlate with B-cell aplasia, which has been reported in recent studies in up to 47% of patients at 6 months and 36% at one year later, necessitating long-term immunoglobulin replacement [51,56]. Monthly monitoring of quantitative immunoglobulins and T-cell subsets is recommended in the first three months to assess for immune reconstitution and recovery [41]. Continued efforts are needed to better understand and manage cytopenias post CAR T-cell treatments. These include longitudinal monitoring of blood counts post CAR T-cell therapy at multiple defined time points in future prospective studies. Identifying clinical biomarkers that can help predict the occurrence of cytopenia represent another important area for future research efforts. Additionally, management and supportive strategies for CAR T-cell therapy associated cytopenia are extrapolated from chemotherapy-induced cytopenia. Better understanding of mechanism(s) driving CAR T-cell cytopenia will likely assist in the future development of management strategies that are specifically tailored to CAR T-cell related cytopenias.

Conflict of interest

The authors have no relevant conflict of interest to disclose.

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