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CASE REPORT

Severe anaphylaxis after chimeric antigen receptor T-cell injection: a case report

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Abstract

Anaphylactic reactions at the time of chimeric antigen receptor T (CAR-T) cell infusion are adverse events that have not been reported in pivotal clinical trials or in real-world series. We report the case of patient with severe anaphylaxis with cardiac arrest after tisagenlecleucel injection for Diffuse Large B cell Lymphoma, who recovered after resuscitation and intensive care treatment; we also conducted a Food and Drug Administration Adverse Event Reporting System database analysis and found several cases of severe anaphlyaxis after CAR-T cell injection. Although not reported in pivotal CAR-T cell studies, anaphylaxis can occur after CAR-T cell injection, highlighting the need to include anaphylaxis as a possible side effect in future studies.

KEYWORDS
anaphylaxis, cardiac arrest, CAR-T cells, tisagenlecleucel

Chimeric antigen receptor T (CAR-T) cells have revolutionized the treatment of relapsed/refractory B-cell malignancies and multiple myeloma. Risks related to CAR-T cell administration have been extensively described and mainly include cytokine release syndrome (CRS) and immune effector-cell-associated neurotoxicity syndrome (ICANS), two frequent and potentially severe adverse events [1]. Anaphylactic reactions at the time of CAR-T cell infusion are adverse events that have not been reported in pivotal clinical trials or in real-world series. Here, we describe the case of a patient developing grade V anaphylaxis with cardiac arrest during the administration of tisagenlecleucel and we provide a summary of the relevant literature and of the cases reported to date in the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

A 77-year-old patient with no history of allergy was admitted for administration of tisagenlecleucel for grade IV refractory activated B-cell-like diffuse large B-cell lymphoma. He had been treated with two lines of treatment with eight cycles of rituximab, vincristine, adriamycin, cyclophosphamide (R-CHOP) followed by three cycles of rituximab, gemcitabine, oxaliplatin (R-GemOx) and bridging to CAR-T with rituximab, lenalidomide, with progressive disease at the time of lymphodepletion. He received fludarabine/cyclophosphamide lymphodepletion, with a good clinical and biological tolerance. He received a premedication with intravenous (IV) paracetamol and clemastin one hour prior to CAR-T cell infusion. Approximately 2 min after the beginning of the intravenous administration of tisagenlecleucel, he developed an extensive urticarial rash and shortly became unresponsive with no detectable carotid pulse. The infusion was stopped, and cardiopulmonary resuscitation (CPR) maneuvers were started. The first monitored rhythm was pulseless electrical activity. After 7 min of CPR and intravenous administration of adrenalin (1 mg) and methylprednisolone (125 mg), he recovered a pulse and regained consciousness. Hyperlactatemia (6.7 mmol/L, normal <2 mmol/L) was

TABLE 1 Cases of allergic reactions and cardiac arrests declared on the Food and Drug Administration Adverse Event Reporting System (FAERS) database in patients who received tisa-cel, axi-cel, brexu-cel, liso-cel, cilta-cel, and ide-cel. The total number of cases is the total number of cases that were declared for each product to the FAERS database as of March 31, 2023. Each column indicates the number of cases found when searching for the terms indicated in the first column. The last line indicates a number of cases that matched both anaphylaxis and cardiac arrest queries.

Queries	Tisa-cel	Axi-cel	Brexu-cel	Liso-cel	Cilta-cel	Ide-cel
Total number of cases	2753	4319	875	342	305	468
Search 1: "anaphylaxis"/"anaphylactic shock"/"anaphylactoid reaction"	7	3	1	0	0	1
Search 2: "cardiac arrest"/"cardio-respiratory arrest"/"pulseless electrical activity" (*n*: number of cases)	37	53	9	7	2	2
Search 1 and 2 (allergy AND cardiac event) (*n*: number of cases)	2	2	0	0	0	0

found at arterial gas analysis post-return of spontaneous circulation. He then required a short course of norepinephrine (maximum dose of 0.1 μg/kg/min). Blood tryptase levels measured within 30 min of the cardiac arrest were strongly increased in the blood (96.4 μg/L, normal <11 μg/L) and normalized (7.3 μg/L) at 3 weeks after the event. Collectively, these elements pointed to an allergic cause of the cardiac arrest, with other causes, being ruled out by bedside ultrasound and laboratory analyses.

On day 4 after administration, the patient developed grade II CRS for which he received tocilizumab, with immediate resolution of CRS symptoms and signs. Unfortunately, his lymphoma progressed rapidly over the first weeks following treatment. The patient was transitioned into palliative care and died on day 38 after a CAR-T cell injection.

Based on the remaining non-infused volume and the product information provided by the manufacturer, we estimated that approximately 0.84×10^8 CAR-positive viable cells were administered, a dose still within the recommended dose range ($0.6–6.0\times10^8$). CAR-T cells were detectable by flow cytometry in the peripheral blood starting from day 3 after injection (0.3 cells/μL), reached a peak of expansion at day 10 (165 cells/μL), and contracted thereafter (11 cells/μL at day 21).

To look for additional post-marketing evidence of anaphylaxis, we searched the FAERS, for reports made before March 31, 2023, for the six commercially available CAR-T cell products ("tisagenlecleucel", "Kymriah", "axicabtagene ciloleucel", "Yescarta", "brexucabtagene ciloleucel", "Tecartus", "lisocabtagene maraleucel", "Breyanzi", "Ciltacabtagene Autoleucel", "Carvykti", "Idecabtagene vicleucel", and "Abecma"), using keywords associated with anaphylaxis ("anaphylaxis", "anaphylactic shock", and "anaphylactoid reaction") and with cardiac arrest ("cardiac arrest", "cardio-respiratory arrest", and "pulseless electrical activity").

Detailed results of separate FAERS queries are summarized in Table 1. Based on queries related to anaphylaxis, we found a total of 12 cases having received tisagenlecleucel (tisa-cel) ($n = 7$), axicabtagene ciloleucel (axi-cel) ($n = 3$), brexucabtagene ciloleucel (brexu-cel) ($n = 1$) or idecabtagene vicleucel (ide-cel) ($n = 1$) (Table 2). Among them, four patients (tisa-cel $n = 2$, axi-cel $n = 2$)) had a cardiac arrest. Two other patients (brexu-cel $n = 1$, ida-cel $n = 1$) experienced anaphylactic shock with no reported cardiac arrest. Death was reported in 2/12 patients, but this number may be underestimated because death is not systematically reported in the FAERS database and, when reported, the cause of death is not specified.

Anaphylactic reactions occurring during or immediately after infusion were not reported in the pivotal trials for CAR-T cells, namely tisa-cel [2–4], axi-cel [5, 6], brexu-cel [7, 8], liso-cel [9], cilta-cel [10] and ide-cel [11]. Similarly, we did not find reports of anaphylactic reactions in more recent real-world series involving these products.

The four main potentially allergenic components of CAR-T cells are genetically engineered CAR-T cells, Dextran 40, DMSO (Dimethyl sulfoxide), and human albumin. The CAR construct itself may cause anaphylactic reactions through the generation of new immunogenic epitopes. This mechanism requires preceding sensitization. However, our patient developed anaphylactic shock after the first infusion of CAR-T cells. Therefore, an IgE-mediated mechanism toward the chimeric receptor appears unlikely. Grade V anaphylaxis has been reported in a phase I clinical study using mRNA-based mesothelin CAR-T cells in patients with mesothelioma and pancreatic cancer where authors tested multiple, sequential infusions of T cells electroporated with mesothelin CAR mRNA containing a scFv derived from the murine monoclonal antibody SS1 [12]. Among the four patients included in this study, one patient developed anaphylaxis and cardiac arrest within minutes after the third administration of the product. Like in our case, the authors detected a significant increase in serum tryptase levels compared to basal value, demonstrating strong mast cell degranulation. High levels of human anti-mouse (HAMA) antibodies were found in patient serum after the event, pointing to hypersensitization toward murine antigens part of the CAR construct. A similar analysis conducted in plasma samples collected from our patient before and after tisagenlecleucel infusion did not reveal any HAMA (data not shown) suggesting an alternative cause for anaphylaxis. Dextran 40 is a polysaccharide previously found in intravenous iron preparations plasma expanders and has been described as a potential trigger of anaphylaxis. The underlying mechanism seems to be immunoglobulin G (IgG)- but not IgE-mediated [13]. In particular, it has been incriminated in anaphylactic reactions to cryopreserved cord blood stem cells [14]. Dimethyl sulfoxide (DMSO) is a widely employed

TABLE 2 Individual cases of anaphylactic reaction reported in the Food and Drug Administration Adverse Event Reporting System (FAERS) database in patients who received commercially available CAR T cells. Queries in the database were made with the following keywords: "anaphylaxis", "anaphylactic shock", and "anaphylactoid" reaction. Cases that matched both anaphylaxis and cardiac arrest queries (made with the following keywords: "cardiac arrest", "cardio-respiratory arrest", and "pulseless electrical activity") are indicated in bold. NS: not specified.

Case	Country	Age (years)	Sex	Indication	CAR-T used	Symptoms
1	**IT**	**10**	**Female**	**Acute lymphoblastic leukaemia**	**Tisa-cel**	**Cardiac arrest Death**
2	**CH**	**NS**	**Male**	**Diffuse large B-cell lymphoma**	**Tisa-cel**	**Cardiac arrest**
3	US	NS	Female	Acute lymphoblastic leukemia	Tisa-cel	NS
4	US	20	Female	Acute lymphoblastic leukemia	Tisa-cel	Death
5	CA	70	Male	NS	Tisa-cel	NS
6	US	18	Female	Acute lymphoblastic leukemia	Tisa-cel	NS
7	US	5	Female	Acute lympho lymphoblastic cystic leukemia	Tisa-cel	Hospital admission
8	**US**	**69**	**Female**	**Diffuse Large B-cell lymphoma**	**Axi-cel**	**Pulseless electrical activity**
9	**FR**	**NS**	**Female**	**NS**	**Axi-cel**	**Cardiac arrest**
10	JP	70	Male	B cell lymphoma	Axi-cel	NS
11	FR	63	Male	Mantle cell lymphoma	Brexu-cel	Anaphylactic shock
12	US	56	Female	Multiple myeloma	Ide-cel	Anaphylactic shock

cryopreservation and penetration enhancer agent whose administration can induce histamine release through an incompletely understood mechanism, potentially leading to anaphylaxis. The occurrence of adverse events after DMSO-containing stem cell product administration has been reported with varying degrees of frequency and severity. Efforts were made in the last decades to reduce risks associated with DMSO-cryopreserved cellular products such as antihistamine premedication, slow infusion, concentration decrease, or removal prior to infusion [15]. Finally, although also extremely rare, anaphylaxis to human albumin has been reported by several authors and may be due to several mechanisms (contaminants, preservatives, and genetic albumin variants) [16].

To our knowledge, this is the first published report of severe anaphylaxis with cardiac arrest during CAR-T cell infusion. It highlights that, besides CRS and ICANS, other serious adverse events directly related to the CAR-T cell product contents can occur. Future studies should include anaphylaxis as a possible side effect that needs to be specifically reported.

AUTHOR CONTRIBUTIONS

Sarah Morin wrote the manuscript, contributed to patient care, and conducted the FAERS analysis; Filippo Boroli, Sophie Vandenberghe-Durr, Daniele Allali, Stavroula Masouridi-Levrat, and Yves Chalandon contributed to patient care and edited the manuscript; Federico Simonetta provided overall guidance, contributed to patient care, and edited the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

The patient provided written informed consent authorizing the use of his clinical data for research proposes.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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