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Novel Adaptive T-Cell Oncological Treatments Lead to New Challenges for Medical Emergency Teams: A 2-Year Experience From a Tertiary-Care Hospital in Switzerland

Anna Sarah Messmer, MD[1]
Yok-Ai Que, MD, PhD[1]
Christoph Schankin, MD, PhD[2]
Yara Banz, MD, PhD[3]
Ulrike Bacher, MD[4]
Urban Novak, MD[5]
Thomas Pabst, MD[5]

To the Editor:

Cancer remains a major public health problem and a leading cause of death (1). However, recent progress in cancer treatment has led to an increasing number of patients currently living with (and surviving) cancer (2, 3) and, subsequently, an increasing number of ICU admissions of patients with oncological diseases (4). Recently, chimeric antigen receptor (CAR) T-cell therapy, a paradigmatic example of a novel adaptive T-cell therapy, revolutionized the treatment of relapsed or refractory B-cell malignancies (5). CAR T-cells are "living drugs," genetically engineered to give T-cells the ability to attack specific cancer cells (6). Yet, this therapy can be associated with life-threatening side effects, mainly due to immune-related toxicities. Such specific toxicities involve cytokine release syndrome (CRS) characterized by otherwise unexplained fever, hypotension, hypoxia, or multiple organ failure, and immune effector cell-associated neurotoxicity syndrome (ICANS) with altered mental state, aphasia, and/or raised intracranial pressure that require immediate treatment. Besides supportive management of organ dysfunction or failure, which follows respective standard intensive care guidelines, there are specific therapies against immune-related toxicities. IV corticosteroids are the first-line therapy for patients with ICANS greater than or equal to grade 2, whereas, in CRS, they are used for second line in the case of refractory symptoms (7, 8). The first-line immunosuppressive therapy of CRS is tocilizumab, an interleukin (IL)-6 receptor antagonist, which is effective for severe or life-threatening CRS and usually symptoms resolve within hours after application (7, 8). For patients with isolated ICANS, tocilizumab has been shown to be ineffective and should only be administered in patients with concurrent CRS (7, 8). Siltuximab, a direct IL-6 antagonist, has similar effects as tocilizumab and might have a more favorable outcome in ICANS. However, data comparing tocilizumab with siltuximab are largely lacking, and the latter is still off-label use.

Both the changes in the epidemiology of oncological disease and the introduction of novel therapies profoundly modified the clinical situations that medical emergency teams (METs) are confronted with (2, 3). Yet, only few studies evaluated MET interventions in the population of cancer patients. Current data suggest that cancer patients requiring MET activation, particularly when the patient needs ICU admission, have higher inhospital mortality and use up more MET resources than noncancer patients (9, 10). It has been reported that up to 40% of patients undergoing CAR T-cell therapy require ICU admission (8, 11). Azoulay et al (11) recently reported that more than a quarter of patients receiving CAR T-cell therapy require ICU admission and all for CRS, ICANS or sepsis. However,

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the proportion of patients requiring MET involvement, the reason for MET activation, as well as requiring subsequent ICU admission has not yet been reported. Here, we report our MET experience after introduction of CAR T-cell therapy for aggressive B-cell malignancies at our institution back in 2019. This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the competent ethical committee (Comission cantonale d'éthique de la recherche sur l'être humain No. 2021-00021). Statistical analysis was performed in R (Version 4.1.0, 2021-05-18; RStudio, PBC, Boston, MA).

Our 900-bed institution (Inselspital, University Hospital Bern, Bern, Switzerland) serves as a tertiary hospital for 1.2 million inhabitants. It introduced the MET system in 2009. All healthcare staff can call for a board-certified intensive care medicine physician 24 hr/7 d to request immediate patient evaluation in the case of acute deterioration as assessed by changes in blood pressure, respiratory rate, oxygen saturation, body temperature, as well as threatened airway or altered mental state. Over the last decade, there were about 500 documented MET interventions per year (approximately 8.6 documented calls per 1,000

TABLE 1.
Baseline Characteristics

Characteristics	Overall ($n = 53$)[a]	MET Call		p[b]
		No ($n = 38$)[a]	Yes ($n = 15$)[a]	
Age	69 (59–74)	68 (58–74)	69 (62–72)	0.8
Sex (male)	28 (54%)	19 (51%)	9 (60%)	0.6
Hospital length of stay[c]	21 (20–25)	21 (20–22)	28 (24–51)	< 0.001
Toxicity				
None	11 (22%)	11 (31%)	0 (0%)	< 0.001
CRS	24 (49%)	20 (56%)	4 (31%)	
ICANS	2 (4%)	1 (3%)	1 (8%)	
Both	12 (24%)	4 (11%)	8 (62%)	
Grade of CRS				
1	27 (69%)	17 (68%)	10 (71%)	0.15
2	8 (21%)	7 (28%)	1 (7%)	
3	3 (8%)	1 (4.0%)	2 (14%)	
4	1 (2.6%)	0 (0%)	1 (7%)	
Grade ICANS				
1	5 (31%)	4 (80%)	1 (9%)	0.038
2	3 (19%)	1 (20%)	2 (18%)	
3	5 (31%)	0 (0%)	5 (45%)	
4	3 (19%)	0 (0%)	3 (27%)	
Therapy				
Tocilizumab	29 (55%)	16 (42%)	13 (87%)	0.003
Siltuximab	7 (13%)	1 (3%)	6 (40%)	0.001
Steroids	9 (17%)	5 (13%)	4 (27%)	0.3
ICU_admission	13 (25%)	1 (3%)	12 (80%)	< 0.001
90-d mortality	9 (17%)	1 (3%)	8 (53%)	< 0.001
Time to death[c]	46 (29–194)	194 (153–208)	29 (29–46)	0.057

[a]Median (interquartile range); *n* (%).
[b]Wilcoxon rank-sum test; Pearson χ^2; Fisher exact test.
[c]In days.

hospitalization admissions). Prior to the start of CAR T-cell therapy in Bern, we introduced an interdisciplinary treatment algorithm, and intensive care physicians who are part of the MET were trained in the most common CAR T-related toxicities (12).

During the period between January 1, 2019, and December 31, 2020, 53 patients received CAR T-cell therapy for relapsed/refractory aggressive B-cell malignancies (mostly diffuse large B-cell lymphoma). Among them, 15 patients (28%) required from one up to three MET evaluations, and 18 patients required ICU admission. We observed no difference in age or gender in those who required MET compared with the patients without MET intervention (Table 1). However,

TABLE 2.

Case Series of Medical Emergency Team Calls in Patients Undergoing Chimeric Antigen Receptor T-Cell Therapy at the University Hospital Bern, Switzerland

Patient No.	Medical Emergency Team Call	Reason for Call	Disposition	Diagnosis	After/Before Chimeric Antigen Receptor-T Transfusion (d)
1	1	Altered mental state	ICU	ICANS	7
2	2	Altered mental state	ICU	ICANS	7
3	3	Oxygen desaturation and refractory hypotension	ICU	Septic shock[a]	27
4	4	Postoperative situation after emergency laparotomy	ICU	Bowel obstruction	–3
5	5	Oxygen desaturation	ICU	Transfusion reaction or early CRS	0
6	6	Oxygen desaturation and altered mental state	ICU	ICANS and possible CRS	3
	7	Refractory hypotension due to intestinal bleeding	ICU	Hemorrhagic shock	1
7	8	Refractory hypotension	Ward	Sepsis Clostridium difficile toxin positive	–2
	9	Oxygen desaturation	ICU	Transfusion reaction	0
	10	Refractory hypotension	ICU	Bowel perforation	19
8	11	Altered mental state	ICU	ICANS	5
9	12	Refractory hypotension	Ward	Sepsis[a]	–1
	13	Altered mental state	ICU	ICANS	5
	14	Oxygen desaturation	ICU	Cardiac failure and possible transfusion-associated circulatory overload	16
10	15	Altered mental state	ICU	ICANS	4
11	16	Possible airway obstruction	Ward	Mild angioedema	2
12	17	Seizure	ICU	ICANS	21
	18	Refractory hypotension	ICU	Hemorrhagic shock after chest drain insertion for spontaneous pneumothorax	28
13	19	Fever, refractory hypotension	ICU	Septic shock[b]	–7
14	20	Seizure	ICU	ICANS	10
15	21	Seizure	ICU	Late-ICANS	37

CRS = cytokine release syndrome, ICANS = immune effector cell-associated neurotoxicity syndrome.

[a]Culture positive.

[b]Culture negative.

the length of hospital stay was longer (28 d [interquartile range {IQR}, 24–51] vs 21 d [IQR, 20–22]), and the 90-day mortality was significantly higher in those who needed MET involvement (8 [53%] vs 1 [2.6%]). None of the deaths were related to toxicities, but all were due to progression of the underlying malignancy. CAR T-cell–related toxicities were more frequent in patients requiring MET evaluation, who received significantly more tocilizumab (13 [87%] vs 16 [42%]) and siltuximab (6 [40%] vs 1 [3%]).

The median interval between CAR T-cell infusion and MET call was 5 days [IQR, 0–19]. Four patients required MET assessment prior to the CAR T-cell administration, namely, during the time of lymphodepleting chemotherapy. Approximately half of the 21 documented MET assessments were due to specific immune-related toxicities (10 calls [47.6%]), whereas the other half (11 calls [52.4%]) were due to other treatment- or malignancy-related complications, such as sepsis or septic shock, bowel obstruction or perforation, or hemorrhagic shock (Table 2). Half of the resulting ICU admissions were due to ICANs, and all patients made a full neurologic recovery.

In summary, MET teams will likely be increasingly involved in the management of oncological patients treated with novel immune therapies and will thus be confronted with new clinical presentations related to therapy-associated toxicities. In our cohort, the majority of CAR T-cell recipients developed one or more CAR T-related toxicities. However, half of the MET interventions and about 40% of the resulting ICU admissions were not due to CAR T-cell therapy, but rather due to the underlying malignancy. Although patients might experience severe immune-related toxicities leading to life-threatening neurotoxicities, full recovery is expected to occur in most cases. Improved knowledge of these toxicities and development of new pharmacological options, especially for prevention and therapy of ICANS, will hopefully further increase safety and practicability of CAR T-cell application in the near future.

1 *Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland*

2 *Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland*

3 *Institute of Pathology, University of Bern, Bern, Switzerland*

4 *Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland*

5 *Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland*

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