Outcomes in patients treated with chimeric antigen receptor T-cell therapy who were admitted to intensive care (CARTTAS): an international, multicentre, observational cohort study

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Summary

Background Chimeric antigen receptor (CAR) T-cell therapy can induce side-effects such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS), which often require intensive care unit admission. The aim of this study was to describe management of critically ill CAR T-cell recipients in intensive care.

Methods This international, multicentre, observational cohort study was done in 21 intensive care units in France, Spain, the USA, the UK, Russia, Canada, Germany, and Austria. Eligible patients were aged 18 years or older; had received CAR T-cell therapy in the past 30 days; and had been admitted to intensive care for any reason. Investigators retrospectively included patients admitted between Feb 1, 2018, and Feb 1, 2019, and prospectively included patients admitted between March 1, 2019, and Feb 1, 2020. Demographic, clinical, laboratory, treatment, and outcome data were extracted from medical records. The primary endpoint was 90-day mortality. Factors associated with mortality were identified using a Cox proportional hazard model.

Findings 942 patients received CAR T-cell therapy, of whom 258 (27%) required admission to intensive care and 241 (26%) were included in the analysis. Admission to intensive care was needed within median 4·5 days (IQR 2·0–7·0) of CAR T-cell infusion. 90-day mortality was 22·4% (95% CI 17·1–27·7; 54 deaths). At initial evaluation on admission, isolated cytokine release syndrome was identified in 101 patients (42%), cytokine release syndrome and ICANS in 93 (39%), and isolated ICANS in seven (3%) patients. Grade 3–4 cytokine release syndrome within 1 day of admission to intensive care was found in 50 (25%) of 200 patients and grade 3–4 ICANS in 38 (35%) of 108 patients. Bacterial infection developed in 30 (12%) patients. Life-saving treatments were used in 75 (31%) patients within 24 h of admission to intensive care, primarily vasoactive drugs in 65 (27%) patients. Factors independently associated with 90-day mortality by multivariable analysis were frailty (hazard ratio 2·51 [95% CI 1·37–4·57]), bacterial infection (2·12 [1·11–4·08]), and lifesaving therapy within 24 h of admission (1·80 [1·05–3·10]).

Interpretation Critical care management is an integral part of CAR T-cell therapy and should be standardised. Studies to improve infection prevention and treatment in these high-risk patients are warranted.

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Introduction

Chimeric antigen receptor (CAR) T-cell therapy has emerged as a promising treatment for refractory haematological malignancies.[1–3] High response rates and durable remissions have led to the approval of CAR T-cell products for B-cell malignancies. Moreover, patients are being recruited for trials to assess the efficacy of CAR T-cell therapy in multiple myeloma.

Once infused, CAR T cells specifically recognise and eliminate tumour cells expressing the target antigen. They rapidly gather around tumour cells and expand locally to kill them via contact-dependent cytotoxicity. Activated CAR T cells release a large number of cytokines, which trigger an inflammatory response that causes potentially fatal adverse events. The most common of these adverse events is cytokine release syndrome,[2,3] the main symptoms of which are fever and capillary leak syndrome with hypotension and lung infiltrates. The second most common potentially life-threatening complication is immune effector cell-associated neurotoxicity syndrome (ICANS), which can occur concurrently with cytokine release syndrome.[2–4] These complications might require intensive care unit admission and can lead to multiorgan failure and death even before patients can be assessed for a clinical response.

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Research in context

Evidence before this study

Chimeric antigen receptor (CAR) T-cell therapy has emerged as a promising treatment for refractory haematological malignancies. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) often require intensive care unit admission and can lead to multiorgan failure and death. We searched MEDLINE, Embase, and Web of Science on Jan 16, 2019, using the search terms "CAR T-cells" OR "cytokine release syndrome" OR "Immune Effector Cell-Associated Neurotoxicity Syndrome" AND ("critical care"), with no date or language restrictions. Publications not including patients (ie, editorials, review articles) were excluded. We found no studies.

Added value of this study

To our knowledge, this study is the first to describe management and outcomes in critically ill CAR T-cell recipients presenting with severe toxicity or sepsis. It extends knowledge obtained from clinical trials and studies in which the rates of cytokine release syndrome and ICANS were reported without in-depth description of critical care management. We found a 90-day mortality of 22·4% (95% CI 17·1–27·7). The results of our multivariable analysis suggest that 90-day mortality is associated with bacterial infection, the need for lifesaving therapy within 24 h of admission to intensive care, and frailty.

Implications of all the available evidence

The finding that mortality is associated with bacterial infection and the need for lifesaving therapy within 24 h of admission to intensive care suggests that there is room for improving outcomes in these critically ill patients. The impact of frailty on mortality also suggests that patients should be comprehensively assessed for eligibility for CAR T-cell therapy, and to detect and treat subclinical organ dysfunction.

In a systematic review of 19 phase 1 trials of anti-CD19 CAR T-cell therapy, the pooled incidence of severe (grade ≥3) cytokine release syndrome was 29·3% in patients with acute lymphocytic leukaemia and 19·8% in patients with non-Hodgkin lymphoma.[5] Neurotoxicity was reported in 40–64% of trials,[1–3] with severe forms (grade ≥3) reported in about half the affected patients.[6] In a single-centre study of 204 patients with lymphoma who received axicabtagene ciloleucel, 73 (58%) patients had neurotoxicity, 51 (25%) of whom had severe forms.[7] Of 275 patients given axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma at 17 US institutions, nine (7%) had grade 3–4 cytokine release syndrome and 85 (31%) had grade 3–5 ICANS.[8] Data are now needed on the outcomes of cytokine release syndrome and ICANS in patients admitted to intensive care units and the relation of these adverse events to CAR T-cell therapies.

In 2018, a consensus panel supported by the American Society for Transplantation and Cellular Therapy (ASTCT) developed recommendations for the definition and grading of cytokine release syndrome and neurotoxicity.[9] Although all studies included in the meta-analysis carefully reported safety and activity data, very little information is available on the real-life use of intensive care unit resources for these patients or on the outcomes associated with organ dysfunctions.[10] Given that intensive care unit admission criteria and practices vary between countries,[11] a large cohort of critically ill recipients of CAR T-cell therapies from different countries would be more likely to detect associations between treatments and outcomes. We therefore aimed to do an international cohort study to describe the characteristics, management, and outcomes for patients who required intensive care unit admission up to 30 days after receiving CAR T-cell therapies.

Methods

Study design and participants

CAR T-cell Toxicity and Sepsis (CARTTAS) is an international, multicentre, observational cohort study established by the Nine-I study group,[12] which is composed of critical care physicians who have extensive experience in the management of critically ill immunocompromised patients. The 21 participating intensive care units in eight countries (France, Spain, the USA, the UK, Russia, Canada, Germany, and Austria; appendix p 1) enrolled patients who received CAR T-cell therapy. Investigators retrospectively included patients admitted between Feb 1, 2018, and Feb 1, 2019, and prospectively included patients admitted between March 1, 2019, and Feb 1, 2020. Both patients who were enrolled in clinical trials and those receiving commercially approved products were included.

Eligible patients were aged 18 years or older; had received CAR T-cell therapy in the past 30 days; and had been admitted to intensive care for any reason. The exclusion criterion was refusal of the patient or family to participate in the study.

Institutional review board approval was obtained from each institution in accordance with local ethics regulations. Written informed consent was waived for the retrospective part of the study and obtained for all participants in the prospective part of the study.

Procedures

A standardised electronic case-report form was used to retrospectively collect the variables listed in the tables and figures from the medical charts of the admitted patients. The Sequential Organ Failure Assessment (SOFA) score was calculated within 24 h after admission to intensive care.[13] Sepsis was either clinically or microbiologically documented.[14] Clinically documented infection included a clinical source of sepsis (such as pneumonia, enterocolitis,

and skin and soft tissue infections). Performance status was evaluated on the basis of the Eastern Cooperative Oncology Group (ECOG) score.[15] Frailty is defined as a clinical state of increased vulnerability before admission to intensive care and was assessed using the Clinical Frailty Score, which is scored from 1 (very fit) to 9 (terminally unwell) as previously reported.[16] The Clinical Frailty Score was assessed by an intensive care physician who directly assessed the patient, or collected information from the hospital record. Cytokine release syndrome was graded on the basis of the ASTCT consensus grading system, which comprises the presence of fever and the severity of hypotension and hypoxaemia.[9] The ICANS grading scale was based on the patient's orientation and ability to name objects, write a standard sentence, and count backwards. For patients enrolled retrospectively in the first year of inclusions, ICANS was graded retrospectively on the basis of the elements that were reported in the medical charts. Neurological symptoms (orientation, naming, following commands, writing, and attention), lethargy, reduced consciousness, motor findings, seizures, and cerebral oedema that were present in the patient's chart were collected. A modified Mini-Mental Status Exam was done for all retrospectively included patients with neurological complications (including orientation, attention span and concentration, naming, and command following, but not writing). The CAR T-cell therapy-associated toxicity (CARTOX) score was prospectively calculated for each patient every day by the intensive care physician and reported in the medical chart.[17]

The management strategy was not uniform across centres. All management decisions were at the discretion of the attending physicians, who followed standard practice and local protocols for managing CAR T-cell therapy toxicities. The following procedures were common to all centres: diagnostic tests to identify sepsis including blood, urine, and sputum cultures for bacteria and fungi; serum and urine antigen assays; PCR for pathogens in blood, serum, and nasopharyngeal aspirates; serological tests; high-resolution CT scans; and echocardiography. Oxygenation methods included the use of non-invasive ventilation or high-flow nasal oxygen and decisions to intubate were at the discretion of the primary care team. Associated organ dysfunctions were managed according to local protocols. Fluid expansion and the timing of vasopressors were also at the discretion of the managing physicians.

In patients with cytokine release syndrome who had low oxygen requirements (<40% fractional concentration of oxygen in inspired air [FiO_2]) and low vasopressor requirements (<20 µg/min norepinephrine), 8 mg/kg tocilizumab (a humanised anti-interleukin [IL]-6R antibody) was given once intravenously. If no clinical improvement in the signs and symptoms of cytokine release syndrome occurred after this initial dose, the tocilizumab dose could be repeated at 8 h intervals up to two times if needed, upon the clinician's decision. In the event of insufficient activity, steroid therapy was considered. In patients with higher oxygen or vasopressor requirements, steroids were given immediately. Steroid therapy was started at a low dose then increased up to 20 mg/m² per day dexamethasone or 10 mg/kg per day methylprednisolone if the symptoms persisted. Once the cytokine release syndrome manifestations improved, the steroid dose was rapidly tapered to nothing. In patients with neurotoxicity, whether isolated or with cytokine release syndrome, tocilizumab was usually not given and steroid therapy was started with 20 mg/m² per day of dexamethasone or high-dose (>2 mg/kg) methylprednisolone.

Outcomes

The primary endpoint was mortality from intensive care unit admission to day 90 and was assessed in all enrolled participants. We selected 90-day mortality as opposed to intensive care unit mortality or hospital mortality to allow comparisons between hospitals, while accounting for possible discharge to step down and post-intensive care unit care in some hospitals, as well as organ dysfunction recovery or functional outcomes. A comparison between patients with bacterial infection and other patients was also preplanned.

Statistical analysis

Continuous variables are described as median (IQR) and compared between groups using the non-parametric Wilcoxon rank-sum test. Categorical variables are described as n (%) and compared between groups using Fisher's exact test. Mortality was assessed by survival analysis. Kaplan-Meier graphs were plotted to express the probability of death from intensive care unit admission to day 90. Comparisons were done using the log-rank test. Proportions of intensive care admissions per disease category (ie, acute lymphocytic leukaemia, B-cell lymphoma, and multiple myeloma) with 95% CI were computed from our sample assuming normal distribution.

Independent risk factors for 90-day mortality were identified using a multivariable Cox model. Conditional stepwise variable selection was done with 0·2 as the p value for entry into the model and 0·1 as the p value for removal. Interactions and correlations between the explanatory variables, the validity of the proportional hazards assumption, the influence of outliers, and the linearity of the relationship between the log hazard and the covariates were checked carefully. For the first step of the variable selection process, age; comorbidities; ECOG performance status; frailty; underlying malignancy with the time since diagnosis; time from CAR T-cell infusion to admission to intensive care; need for lifesaving therapy within 1 day after admission to intensive care; and presence of sepsis, cytokine release syndrome, or ICANS were included in the model. The final model included the centre effect on frailty (hierarchical model).

For the comparison between patients with and without documented bacterial infection, we used the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables.

Imputation of missing data was not done. We assumed that the missing data were missing at random.

Statistical analyses were done with R statistical software, version 3.4.3, using the Survival packages. p values of less than 0·05 were considered significant.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 1, 2018, and Feb 1, 2020, 942 patients received CAR T-cell therapy in the 21 participating centres, including 803 (85%) for diffuse B-cell or follicular lymphoma, 106 (11%) for B-cell acute lymphocytic leukaemia, and 33 (4%) for multiple myeloma. Among them, 258 (27%) required admission to intensive care and 241 (26%) were included in the CARTTAS registry. No patient died in the 30 days following CAR T-cell infusion without having been admitted to intensive care. The patient flow chart is shown in figure 1. Table 1 shows the patient characteristics at admission to intensive care. Among the 241 patients, 89 (37%) were included retrospectively and 152 (63%) were included prospectively. The missing data rate was 2·7% overall and 0% for the primary endpoint.

Median follow-up was 95 days (IQR 93–97). 90-day mortality across all participants was 22·4% (95% CI 17·1–27·7; 54 deaths), intensive care unit mortality was 5·8% (2·9–8·8; 14 deaths), and hospital mortality was 14·9% (10·4–19·4; 36 deaths). The median time from CAR T-cell infusion to death was 25 days (IQR 16–39). All patients who died between day 30 and day 90 died from disease progression. Furthermore, among the 701 patients who did not require admission to an intensive care unit within 30 days of CAR T-cell infusion, 127 (18%) died between day 30 and day 90 from disease progression.

Admission to intensive care was required in 27·2% (95% CI 24·2–30·3) of patients with B-cell or follicular lymphoma, 32·1% (23·2–40·9) of patients with acute lymphocytic leukaemia, and 15·2% (2·9–27·4) of patients with multiple myeloma. Admission to intensive care occurred within median 4·5 days (IQR 2·0–7·0) after the CAR T-cell infusion (appendix p 5). Reasons for admission to intensive care were hypotension (168 patients [70%]), sepsis (39 [16%]), acute kidney injury (37 [15%]), acute respiratory failure (25 [10%]), coma (22 [9%]), arrhythmia (12 [5%]), haemophagocytic lymphohistiocytosis (11 [5%]), tumour lysis syndrome (eight [3%]), and miscellaneous reasons (haemorrhagic shock in two patients, pulmonary oedema in two patients, pancreatitis in one patient [2%]). Reasons for admission to intensive care did not differ across centres (data not shown).

Within 24 h after admission to intensive care, 100 (41·5% [95% CI 35·3–47·7]) patients had isolated cytokine release syndrome, 100 (41·5% [35·3–47·7]) had cytokine release syndrome and ICANS, and seven (2·9% [0·8–5·0]) had isolated ICANS. At initial evaluation on admission, grade 3 or 4 cytokine release syndrome was identified in 23 (12%) of 194 patients. Within 24 h of admission to intensive care, grade 3 or 4 ICANS was identified in 38 (35%) of 108 patients, and grade 3 or 4 cytokine release syndrome was identified in 50 (25%) of 200 patients.

The initial evaluation found sepsis in 39 (16%) of 241 patients, from respiratory (n=12), digestive (n=9), urinary (n=5), or indwelling catheter (n=5) sources; the origin was unknown in eight patients. Appendix pp 2–3 shows patient characteristics according to the presence of infection. Neutropenia was found in 169 (70%) patients at admission to intensive care. Bacterial infection was microbiologically documented in 30 (12%) patients, including ten patients with cytokine release syndrome.

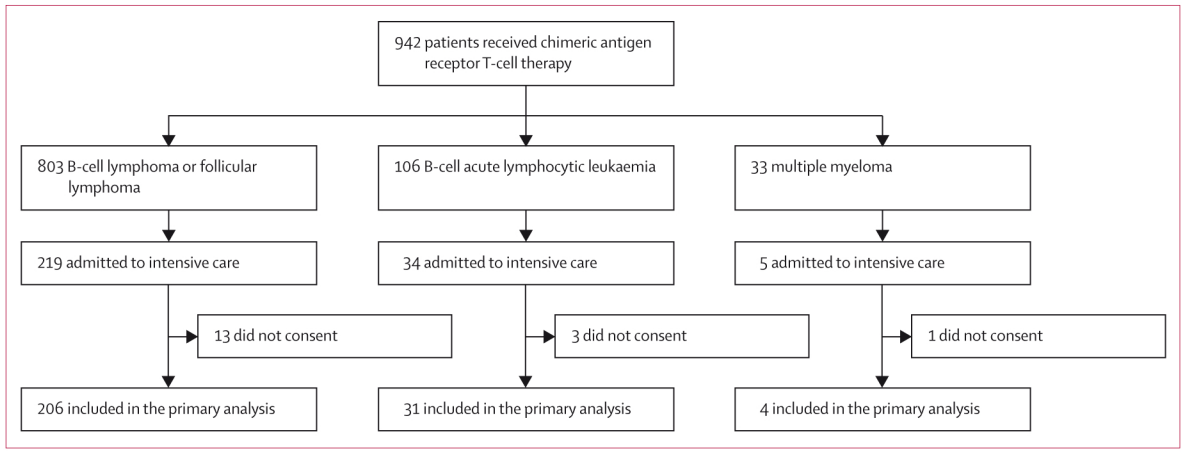

Figure 1: **Patient flow chart**

	Participants (n=241)
Age, years	58 (43–66)
Sex	
Female	97 (40%)
Male	144 (60%)
Any comorbid condition	75 (31%)
Cardiovascular comorbidity	60 (25%)
Clinical frailty scale	
1: very fit	23 (10%)
2: well	96 (40%)
3: managing well	71 (29%)
4: vulnerable	24 (10%)
5: mildly frail	5 (2%)
6: moderately frail	5 (2%)
7: severely frail	1 (<1%)
8: very severely frail	1 (<1%)
ECOG performance status	
0: fully active	70 (29%)
1: ambulatory and able to carry out light work	104 (43%)
2: ambulatory and capable of all selfcare but not work activities	46 (19%)
3: capable of only limited selfcare, confined to bed or chair >50% of waking hours	13 (5%)
4: Completely disabled, totally confined to bed or chair	1 (<1%)
Underlying malignancy	
B-cell lymphoma or follicular lymphoma	206 (85%)
Acute lymphocytic leukaemia	31 (13%)
Multiple myeloma	4 (2%)
Time since diagnosis of the malignancy, years	1·5 (0·8–2·8)
Previous stem-cell transplantation	
None	206 (85%)
Autologous	42 (17%)
Allogeneic	13 (5%)
(Table 1 continues in next column)	
(Continued from previous column)	
Number of chemotherapy lines before CAR T-cell therapy	3 (2–4)
Fludarabine plus cyclophosphamide-based lymphodepletion	231 (96%)
Time from CAR T-cell infusion to ICU admission, days	4·5 (2·0–7·0)
Clinical diagnosis upon evaluation in the wards	
Clinical sepsis	39 (16%)
Isolated cytokine release syndrome	101 (42%)
Isolated ICANS	7 (3%)
Cytokine release syndrome and ICANS	93 (39%)
Large pleural effusion related to disease progression	1 (<1%)
Cytokine release syndrome grade 3 or 4 at initial evaluation in the wards	23/194 (12%)
Cytokine release syndrome grade 3 or 4 within 1 day after ICU admission	50/200 (25%)
ICANS grade 3 or 4 within 1 day after ICU admission	38/108 (35%)
CARTOX score at ICU admission	7 (3–9)
Neutropenia at ICU admission	169 (70%)

Data are median (IQR), n (%), or n/N (%). CAR=chimeric antigen receptor. CARTOX=CAR T-cell therapy-associated toxicity. ECOG=Eastern Cooperative Oncology Group. ICANS=immune effector cell-associated neurotoxicity syndrome. ICU=intensive care unit.

Table 1: **Patient characteristics at ICU admission**

Compared with patients with no documented bacterial infection, patients with bacterial infection were admitted to the intensive care unit significantly later after the CAR T-cell infusion, were significantly more frequently febrile and hypotensive, and exhibited neurological signs significantly less frequently (appendix pp 2–3). Patients with bacterial infection were also more frequently diagnosed with isolated cytokine release syndrome, their platelet count was significantly lower, and they more frequently met criteria for disseminated intravascular coagulation (appendix pp 2–3). The ferritin concentration at admission was higher in patients with bacterial infection (appendix p 2), whereas daily C-reactive protein and lactate concentrations over the first week after admission to intensive care were not significantly different from those in patients without infection (appendix p 6). Antibiotic drugs were given to 215 (89%) patients, including 20 (8%) who started antibiotic drugs at admission to intensive care and 43 (18%) who escalated antibiotics at admission. 90-day mortality was significantly higher (40·0% [95% CI 22·5–57·5]) in patients with microbiologically documented infection than in patients with clinically suspected but not microbiologically documented infection (25·0% [7·7–42·3]) or without infection (19·2% [13·6–23·9]; p=0·020; appendix p 3).

Among the 200 patients with cytokine release syndrome within 24 h after admission to intensive care, all had a fever, 175 (88%) had been hypotensive, and 39 (20%) had acute kidney injury (including 11 with oliguria). Among all 241 patients, median C-reactive protein concentration was 76 mg/L (IQR 26–150) and median ferritin concentration was 1498 µg/L (626–3146), with no difference between patients with or without cytokine release syndrome (appendix p 6). 27 (14%) of 200 patients had an increase in cytokine release syndrome severity after admission to intensive care, 11 (6%) from grade 1–3 to grade 4, and 16 (8%) from grade 1–2 to grade 3.

Among the 108 patients with ICANS within 24 h of admission to intensive care, 76 (70%) had confusion and delirium, 52 (49%) had drowsiness or coma, 36 (34%) had aphasia, 21 (20%) had agraphia, 14 (13%) had tremor, 14 (13%) had epilepsy, ten (9%) had headache, nine (8%) had a focal deficit, six (6%) had myoclonus, five (5%) had dyscalculia, three (3%) had global muscle weakness, three (3%) had amnesia, and three (3%) had ataxia. The median CARTOX score was 7 points (IQR 3–9) at

	Alive at day 90 (n=187)	Died by day 90 (n=54)	p value
Age, years	58 (46–67)	60 (37–65)	0·56
Sex			
Female	79 (42%)	18 (33%)	0·31
Male	108 (58%)	36 (67%)	..
Any comorbid condition	55 (29%)	20 (37%)	0·37
ECOG performance status score ≥3	7 (4%)	7 (13%)	0·015
Clinical Frailty Scale score >3	20 (11%)	16 (30%)	0·0018
Underlying malignancy	..	..	0·041
B-cell lymphoma or follicular lymphoma	164 (88%)	42 (78%)	..
Acute lymphocytic leukaemia	19 (10%)	12 (22%)	..
Multiple myeloma	4 (2%)	0	..
Time since diagnosis of the malignancy, years	1·4 (0·8–3·3)	1·1 (0·2–2·1)	0·10
Allogeneic stem-cell transplantation	7 (4%)	6 (11%)	0·051
Number of previous chemotherapy lines	3 (2–4)	4 (3–5)	0·051
Time from CAR T-cell infusion to ICU admission, days	5 (3–7)	4 (1–8)	0·36
Clinical diagnosis at ICU admission	..	..	0·23
Clinical sepsis	27 (14%)	12 (22%)	..
Isolated cytokine release syndrome	77 (41%)	17 (31%)	..
Isolated ICANS	4 (2%)	3 (6%)	..
Cytokine release syndrome and ICANS	79 (42%)	22 (41%)	..
Neutropenia at ICU admission	127 (68%)	42 (78%)	0·22
C-reactive protein concentration, mg/L	35 (10–101)	92 (17–144)	0·14
Ferritin concentration, µg/L	1113 (596–2487)	3659 (1894–8653)	<0·0001
Lactate concentration, mmol/L	1·4 (0·9–2·0)	1·9 (1·0–2·9)	0·020
Disseminated intravascular coagulation	13 (7%)	16 (30%)	<0·0001
Documented bacterial infection	13 (7%)	16 (30%)	<0·0001
SOFA score at ICU admission	4 (2–5)	5 (3–7)	<0·0001
Cytokine release syndrome grade ≥3 at admission if cytokine release syndrome present	20/156 (13%)	3/39 (8%)	0·39
CARTOX score at ICU admission	7 (4–9)	6 (3–8)	0·29
Need for lifesaving therapy at ICU admission	49 (26%)	26 (48%)	<0·0001
High-flow nasal oxygen, non-invasive ventilation, or endotracheal mechanical ventilation	11 (6%)	14 (26%)	<0·0001
Fluid expansion >30 mL/kg	31 (17%)	13 (24%)	0·043
Vasoactive drugs	45 (24%)	20 (37%)	0·093
Renal replacement therapy	0	2 (4%)	0·071
Mechanical ventilation during the ICU stay	11 (6%)	14 (26%)	<0·0001
Length of ICU stay, days	3 (1–6)	5 (2–10)	<0·0001
Readmission to the ICU within 30 days	28 (15%)	15 (28%)	0·060
Length of hospital stay, days	14 (9–22)	21 (10–34)	0·050
ICU mortality	0	14 (26%)	<0·0001
Hospital mortality	1 (<1%)	35 (65%)	<0·0001

Data are median (IQR), n (%), or n/N (%). CAR=chimeric antigen receptor. CARTOX=CAR T-cell therapy-associated toxicity. ECOG=Eastern Cooperative Oncology Group (score ≥3 includes patients who are confined to bed or chair more than 50% of waking hours or completely disabled). ICANS=immune effector cell-associated neurotoxicity syndrome. SOFA=Sequential Organ Failure Assessment.

Table 2: **Factors associated with 90-day mortality by univariable analysis**

admission (calculated only among patients with ICANS). In addition to the 100 patients with ICANS at admission, 23 (10%) presented with new neurological symptoms on day 1, and 18 (7%) patients presented with new neurological symptoms on day 2.

Lifesaving therapy was required immediately at admission to intensive care in 75 (31%) patients: vasoactive drugs were required in 65 (27%) patients, invasive mechanical ventilation in 16 (7%) patients, high-flow nasal oxygen in 12 (5%) patients, and renal replacement therapy in two (1%) patients. The number of patients requiring immediate lifesaving therapies did not differ significantly between centres (data not shown). Outcomes according to the need for lifesaving therapies are shown in the

appendix (p 4). Overall, throughout the stay in the intensive care unit, mechanical ventilation was needed in 26 (11%) patients for a median of 3 days (IQR 2–6); high-flow nasal oxygen was needed in 14 (6%) patients for a median of 6 days (3–8); vasoactive drugs were needed in 74 (31%) patients for a median of 2 days (2–4); and renal replacement therapy was needed in 12 (5%) patients for a median of 3 days (2–3).

Tocilizumab was given alone to 44 (18%) patients or was followed by steroids in 122 (51%) patients. Steroids alone were given to 33 (14%) patients, whereas 42 (17%) patients did not receive any anti-inflammatory therapy in the intensive care unit.

Table 2 shows the results of the univariable analysis of factors associated with 90-day mortality. As shown in figure 2A, there was a significant association between the admission diagnosis and 90-day mortality, with increased mortality in patients who had sepsis (p=0·090) and isolated ICANS (p=0·020). There was no association between cytokine release syndrome grade or ICANS grade and 90-day mortality (figure 2B, C). Three factors were independently associated with 90-day mortality: a Clinical Frailty Score greater than 3 (hazard ratio [HR] 2·51 [95% CI 1·37–4·57]; p<0·010); microbiologically documented infection (HR 2·12 [1·11–4·08]; p=0·020); and need for lifesaving therapy within 24 h after admission to intensive care (HR 1·80 [1·05–3·10]; p=0·030). Based on the number of events, no further variables were tested.

In patients with cytokine release syndrome, median time to apyrexia was 4 days (IQR 2–6) in patients who survived and 5 days (3–7; p=0·050) in patients who did not survive. Median time to ICANS resolution was 5 days (2–9), with no significant association with mortality. Readmission to the intensive care unit was needed in 43 (18%) patients overall: 28 (15%) patients who survived, and 15 (28%; p=0·060) patients who died. Infections acquired in the intensive care unit were reported in 39 (16%) patients, including 11 (5%) with invasive fungal infections and two (1%) with invasive cytomegalovirus disease.

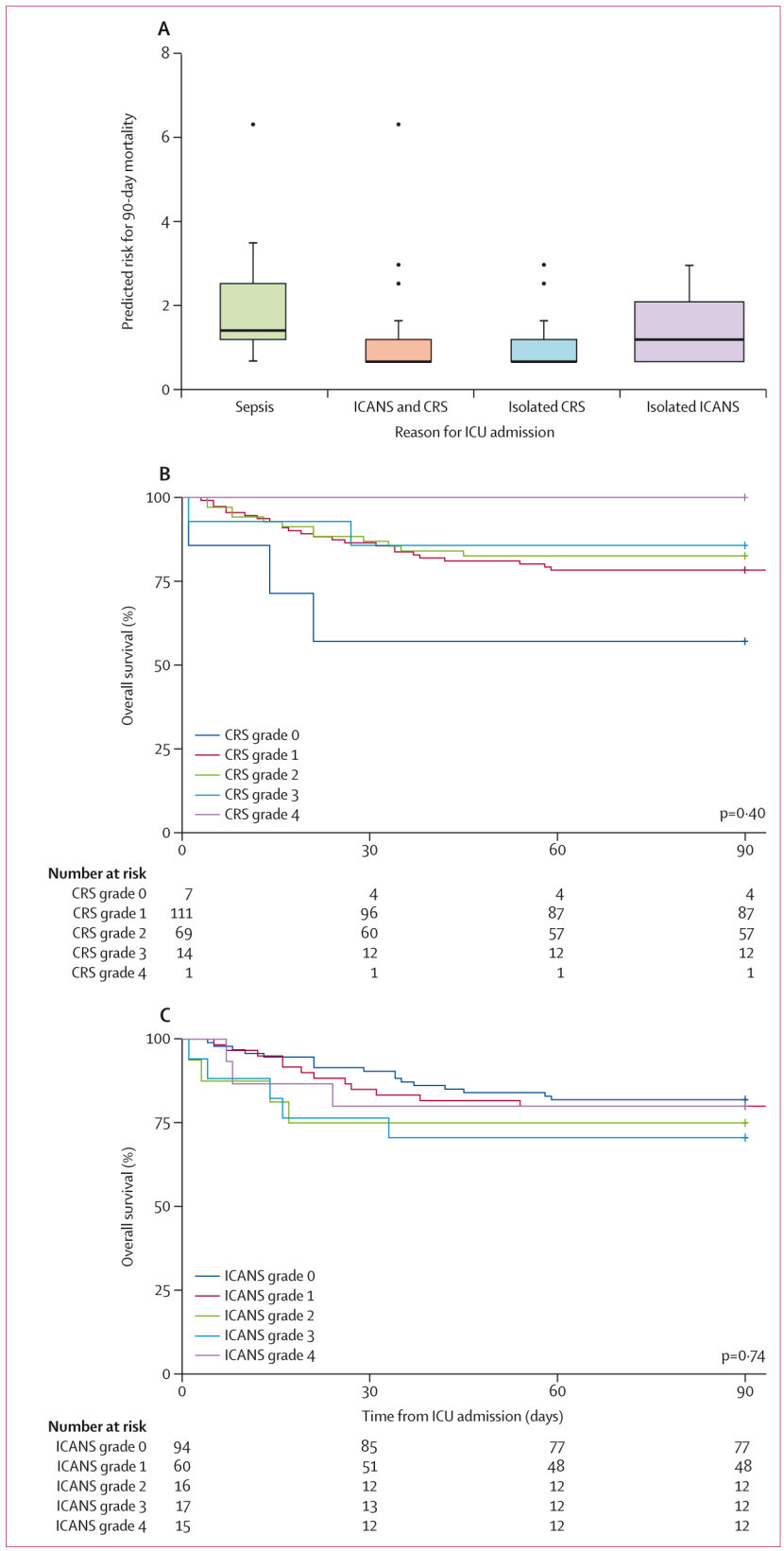

Figure 2: **Subgroup analysis of 90-day mortality and survival after ICU admission**

(A) Predicted 90-day mortality according to reason for intensive care unit admission. Sepsis was either clinically or microbiologically documented. p<0·0001 for the comparison between all four groups. Horizontal lines show the median, shaded areas show IQR, whiskers show the 9th and 91st percentile, individual points are outliers. (B) Cumulative overall survival as a function of CRS grade at ICU admission. For all groups, median survival was not reached (95% CI not reached–not reached), except for CRS grade 0 (median survival not reached [14 days–not reached]). (C) Cumulative overall survival as a function of ICANS grade at ICU admission. For all groups, median survival was not reached (not reached–not reached). In panels B and C, patients with sepsis (n=39) were excluded from the Kaplan-Meier analysis; no patients were lost to follow-up (n=0 for number censored at all timepoints). CRS=cytokine release syndrome. ICANS=immune effector cell-associated neurotoxicity syndrome. ICU=intensive care unit.

Discussion

This international study describes the management and outcomes of a large cohort of critically ill CAR T-cell recipients after admission to intensive care. More than a quarter of patients who received CAR T-cell therapy required admission to intensive care, all for cytokine release syndrome, ICANS, or sepsis. These three syndromes resulted in a 90-day mortality of 22·4% (95% CI 17·1–27·7), with the patients dying before the activity of CAR T-cell therapy could be assessed. Frailty, a need for lifesaving therapy within 24 h after admission to intensive care, and microbiologically documented bacterial infection were independently associated with increased 90-day mortality.

Several studies in patients with haematological malignancies have emphasised the prognostic relation of ECOG performance status with short-term mortality.[15,18] Using the ECOG scale, studies showed that patients with restricted activities of daily life consistently had higher mortality than patients with better performance. The Clinical Frailty Scale score is increasingly considered to be useful when planning intensive care unit treatments.[19] However, frailty has never been specifically studied in critically ill patients with haematological malignancies. Our results suggest that a frailty evaluation should be used to identify CAR T-cell recipients at increased risk of death should they develop cytokine release syndrome, ICANS, or sepsis. Our finding that frail patients are at increased risk of death even before the therapeutic response can be assessed suggests a need for specific monitoring to ensure earlier admission to intensive care. With this strategy, we can expect that immunotherapy will transform the landscape of refractory malignancies, even in the frailest patients.

In our study, the time from CAR T-cell infusion to admission to intensive care was not associated with mortality. However, mortality was significantly higher in patients who required lifesaving therapies within 24 h after admission to intensive care. Whether this increased mortality indicates a delay in admission or simply reflects a high degree of acute illness severity is unclear. The timing of admission to intensive care for CAR T-cell recipients with hypotension, pulmonary infiltrates, hypoxaemia, impaired alertness, delirium, or any mild organ dysfunction varies across grading systems and across institutions.[9] Overall, early admission to intensive care has been associated with improved overall survival in patients with haematological malignancies.[20] In a study of 1011 critically ill patients with haematological malignancies, hospital mortality was significantly higher in the patients admitted to intensive care more than 24 h after hospital admission (43·7% *vs* 33·9% in patients admitted earlier). In patients with acute respiratory failure, mortality at day 28 was 20% when admission to intensive care occurred within 2 days after hospital admission and 40% when time to admission was more than 3 days.[21] These data suggest that strategies to ensure timely admission to intensive care should be developed. Importantly, we found no association of cytokine release syndrome grade or ICANS grade with mortality. The usefulness of these grading systems for making admission decisions might need reappraisal.

Another independent determinant of mortality was microbiologically documented bacterial infection at admission to intensive care. In previous studies of patients with haematological malignancies, bacterial infections were associated with decreased mortality.[22,23] However, patients with bacterial infections were compared either with patients with fungal infection or with patients with no known cause of their acute respiratory failure. The adverse prognostic effect of bacterial infections in our study might be related to inadequate antibiotic therapy in patients receiving prophylactic but not targeted antibiotic drugs.[24] Along this line, neutropenia was found in 70% of the patients admitted to intensive care in our study. Moreover, source control, which has been associated with improved survival, might not have been optimal in patients believed to have cytokine release syndrome.[25,26] Additionally, our study confirms previous findings that a high proportion of patients who receive CAR T-cell therapy develop bacterial infections (16% of patients) and fungal infections (5%) while in intensive care. In the study by Hill and colleagues, infectious events within 28 days of CAR T-cell infusion were reported in 22·5% of patients, with 4% of patients presenting with fungal infections.[27] Corresponding figures were 41·5% for infectious events and 7·5% for fungal infections in the study by Park and colleagues.[28]

Our study has several limitations. First, the retrospective design is associated with risks of bias. However, the data were carefully abstracted from detailed patient files to a standardised electronic case report form. The missing data rate was very low. With a sample size of 241 patients, this international study is, to our knowledge, the largest reporting the critical care management of patients who have had CAR T-cell therapy. Second, the study focuses on the management of CAR T-cell recipients in intensive care, without providing information on the therapeutic response to the immunotherapy. However, we could only assess short-term outcomes of patients with organ dysfunction. An assessment of the response to CAR T-cell therapy would require a longer follow-up with specific investigations. Our analysis ignores progression as a deleterious event. However, tumour burden is a well established risk factor for CAR T-cell related toxicity. It is therefore difficult to make a well considered decision about whether the tumour directly or indirectly contributed to early deaths. Moreover, as the majority of deaths occurred before day 30, the effectiveness of CAR T-cell therapy could not be recorded. Third, in this study, patient management decisions were always made jointly by intensive care unit specialists and haematologists. Indeed, we believe that it is imperative that both specialists

work closely together in the management of these patients, as critical care is part of the care pathway. Fourth, only few data were available about patients not admitted to the intensive care unit for comparison with those who were admitted. Last, in this cohort study, the timing of admission to intensive care and of lifesaving therapies was not standardised. However, one of our goals was to learn from variations across centres.

In conclusion, intensive care management is an integral part of CAR T-cell therapy. As well as toxicity such as cytokine release syndrome and ICANS, infection occurs in a substantial number of patients and is associated with mortality. Studies aimed at standardising the management of CAR T-cell recipients admitted to intensive care are warranted.

Contributors

EA, MD, and SV designed the study. PH and JL monitored the data and supervised data entry, collected missing data, and checked for inconsistencies where needed. All authors approved the protocol, revised the electronic case report form, applied for their local institutional review board, collected informed consent, included patients and their data on the case report form, and contributed to revising the analyses, editing the manuscript and approving the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. EA, JL, PH, and MD had access to and verified the raw data.

Declaration of interests

EA has received personal fees and non-financial support from Pfizer, Gilead, Ablynx, Baxter, Alexion, and grants from Fisher & Payckle and Merck Sharp & Dohme, outside the submitted work. BL has received grants and personal fees from Amomed and Baxter, and personal fees from Novartis, outside the submitted work. BB has received personal fees from Johnson & Johnson and Novartis, grants and personal fees from Astellas, Kite/Gilead, Merck Sharp & Dohme, and Takeda, outside the submitted work. PS has received personal fees from Gilead and Novartis, outside the submitted work. VM has received personal fees from Gilead, outside the submitted work. MD has received personal fees from Gilead-Kite and Astellas, and grants and personal fees from Merck Sharp & Dohme, outside the submitted work. SV has received non-financial support from Pfizer and personal fees from Gilead-Kite, outside the submitted work. All other authors declare no competing interests.

Data sharing

The data collected for the study belong to each investigator of this study group and to their institutions. De-identified participant data collected for the study (including individual participant data and a data dictionary defining each field in the set) will be made available with the publication to others by contacting the first author by email who will then send the request to each participating centre. As the study protocol continues in the form of a registry, it will not be made available. A signed data agreement will have to be signed with each participating centre.

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