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Adverse events following infusion of T cells for adoptive immunotherapy: a 10-year experience

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Abstract

Background aims. The Food and Drug Administration (FDA) currently recommends at least 4 h of recipient monitoring after T cell infusions to detect early infusion reactions. Recent catastrophic reactions to 'first-in-man' biologic agents have emphasized the importance of this rule for initial studies of new products. The value of such monitoring for better established agents is less obvious. *Methods*. We reviewed infusion-related adverse events (AE) following administration of *ex vivo*-expanded T cell products (antigen-specific cytotoxic T lymphocytes, allodepleted T cells, and genetically modified T cells) on investigational new drug (IND) studies in our center. *Results*. From 1998 to 2008, we infused 381 T cell products to 180 recipients, enrolled on 18 studies, receiving T cells targeting malignancies or post-transplant viral infections. There were no grade 3–4 infusion reactions during initial monitoring or 24-h follow-up. Twenty-four mild (grade 1–2) AE occurred in 21 infusions either during or immediately following infusion (up to 6 h), most commonly nausea and vomiting (10/24, 41.6%), probably because of the dimethyl sulfoxide cryoprotectant, and hypotension (20.8%), attributable to diphenhydramine pre-medication. Twenty-two additional non-severe events were reported within 24 h of infusion, most commonly culture-negative fever, chills and nausea. An increased risk of adverse events was associated with age [incidence rate ratio (IRR) 0.98; 95% confidence interval (CI) 0.96–1.00, $P = 0.05$], while an increased risk of immediate infusion-related events was higher in patients reporting allergies (IRR 2.72, 95% CI 1.00–7.40, $P = 0.05$); sex, disease type and T cell source (allogeneic or autologous) had no effect on frequency of adverse events. *Conclusions*. Infusion of these T cell products was safe in the outpatient setting and associated with no severe reactions, so monitoring for 1 h after infusion is probably sufficient. As many of the AE were attributable to diphenhydramine premedication, a lower dose (0.25 mg/kg) should be selected.

Keywords: *adverse events, cytotoxic T lymphocytes, Epstein–Barr virus, infusion reaction, T cells*

Introduction

T cell therapies can benefit a range of disorders, including cancer, viral infections, invasive fungal disease and autoimmune and allergic disorders (1–9). The number of trials exploring this approach has increased substantially over the past decade and the clinical trials database currently lists 180 approved T cell immunotherapy protocols in 30 countries around the world (10). While clinical toxicities and adverse event (AE) profiles have been reported for other cell-based infusion products (11,12), there has been no comprehensive evaluation of infusion reactions after administration of *ex vivo*-manipulated T cells. Infusion of T cells could mediate a panoply of unintended effects, including fever and non-specific constitutional symptoms, as a consequence of inflammatory mediator release or cytokine secretion, by transmission of infectious agents, or following acute lung injury because of their entrapment in the pulmonary vasculature (13).

The Food and Drug Administration (FDA) currently recommends at least 4 h of recipient monitoring following administration of *ex vivo*-expanded T cells, and two recent severe AE after 'first-in-man' biologic agents have emphasized the importance of this rule for initial clinical studies using new

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products. In the first case, a patient received T cells modified to express a chimeric antigen receptor (CAR) specific to the B cell tumor antigen CD19 that also contained a co-stimulatory moiety (CD28). The patient was lymphodepleted with cyclophosphamide prior to the infusion. Within 48 h, the patient developed fever, hypotension, dyspnea, and renal failure, with negative blood cultures, and progressed to a fatal outcome (14). A second patient received T cells transduced with a chimeric antigen receptor targeting HER2/neu containing both the CD28 and 4-1BB co-stimulatory domains (15). Within 4 h of infusion, this patient developed rapidly progressive respiratory distress requiring ventilation (15) and subsequently died. Although these events are rare, they emphasize why a high level of monitoring is required for any 'first-in-man' study; however, the relevance for more established T cell infusion products is not known. We therefore retrospectively studied the incidence and severity of immediate and early AE occurring in patients enrolled on 18 different investigational new drug (IND) studies of *ex vivo*-manipulated T cells over a 10-year period at our institution.

Methods

Patient details

We reviewed the charts, infusion records, and AE reports of 180 patients who had received 381 infusions of *ex vivo*-expanded T cells on IND studies at the Center for Cell and Gene Therapy at Baylor College of Medicine, The Methodist Hospital and Texas Children's Hospital (Houston, Texas, USA) from 1 January 1998 to 20 November 2008. Included in this study were patients who received antigen-specific cytotoxic T cells, allodepleted T cells, or genetically modified T cells, on 18 FDA-approved IND studies. The infused T cells targeted malignancies or viral infections after hematopoietic stem cell transplant (HSCT). Cell doses were protocol specific and ranged from 10^4/kg up to $2 \times 10^8/m^2$. Patients were premedicated with intravenous diphenhydramine (0.5–1 mg/kg, with a maximum dose of 50 mg) and Tylenol (10 mg/kg up to a maximum dose of 625 mg) prior to infusion. All cellular products were cryopreserved using 10% dimethyl sulfoxide (DMSO) and administered intravenously over 1–15 min immediately after thawing. The types of cellular products are summarized in Table I.

All patients were treated on institutional review board (IRB)-approved protocols conducted under IND after approval by the FDA. If T cells were genetically modified or stimulated by antigen-presenting cells that were genetically modified, the studies were also reviewed by the Recombinant DNA Advisory Committee of the National Institutes of Health and the Institutional Biosafety Committee (Bethesda, MD). This collated analysis, combining data on infusion safety from all 18 studies, was also approved by the IRB at Baylor College of Medicine. AE were collected and graded on case report forms using National Cancer Institute (NCI) common toxicity criteria (version 2 or 3 depending on when the study was initiated). Outcome data from some of these studies have been reported elsewhere (16–26), but a detailed analysis of infusion-related AE has not been presented previously.

Statistical methods

We initially used descriptive statistics (mean, standard deviation, median, and range) to analyze the data. All patients who received T cell infusions were included in the analysis. AE data were summarized in the form of tables. Incidence tables were generated to summarize incidence of patients reporting at least one episode of each specific AE and incidence of serious AE. The total number of episodes for each event reported, the grade, and attribution to study therapy of each episode reported were summarized. The incidence of AE was also listed by age group, presence of an allergy, and source of T cells, and compared by Fisher's exact test. The association of the incidence of AE with the type of cells, gender, age at infusion, and presence of allergy was then analyzed further with a Poisson regression model using the generalized estimation equation (GEE) to account for the correlation of AE within patients, and we report estimates of the association and the robust 95% confidence intervals (CI). All *P*-values are 2-sided, with $P < 0.05$ considered statistically significant. All statistical analyses used R and STATA 9.0 software packages.

Results

Patient characteristics

A total of 381 T cell products were given to 180 patients [some studies infused more than two products (23) or had more than one infusion] during the 10-year period between 1998 and 2008. Patient characteristics are summarized in Table II. The types of T cell products infused are summarized in Table III.

AE resulting from the infusion were non-severe

Twenty-four grade 1–2 AE occurred in 21 infusions of 22 *ex vivo*-expanded T cell products (one patient was enrolled on a study where two products

Table I. Summary of studies.

Study name	T cell product	Dose range (cells/m^2)	Indication
ANGEL	Autologous EBV-specific CTL	2×10^7–2×10^8	Relapsed EBV-positive Hodgkin's disease lymphoma (17)
NCT00058617			
ANGELA	Autologous EBV-specific CTL	2×10^7–2×10^8	EBV-positive Hodgkin's disease post-autograft (17)
NCT00058773			
SCAEBV	Autologous EBV-specific CTL	1×10^7–1×10^8	Severe chronic active EBV infection (16)
NCT00608608			
EUCLID	Autologous EBV-specific CTL	2×10^7–1×10^8	Prevention and treatment of EBV lymphoma following solid organ transplantation (21)
NCT00058604			
NPC	Autologous EBV-specific CTL	2×10^7–2×10^8	Nasopharyngeal carcinoma (18)
NCT00609219			
CLANC	Autologous EBV-specific CTL	2×10^7–1×10^8	EBV-positive nasopharyngeal cancer after lymphodepletion (24)
NCT00608257			
NATELLA	Autologous (Latent membrane protein) LMP1/LMP2-specific CTL	2×10^7–2×10^8	Nasopharyngeal carcinoma
NCT00682864			
NESTLES	Autologous 14g2a-zeta-CAR-transduced CTL and 14g2a-zeta-CAR-transduced EBV-specific CTL	2×10^7	High-risk neuroblastoma (23)
NCT00085930			
ALASCER	Autologous or donor-derived LMP2a-specific CTL	2×10^7–1×10^8	EBV-positive lymphoma, Hodgkin's disease lympho-epithelioma or severe chronic EBV (22)
NCT00070226			
ALCI	Autologous or donor-derived LMP1/LMP2-specific CTL	2×10^7–1×10^8	EBV-positive lymphoma, lympho-epithelioma, or severe chronic EBV
NCT00671164			
ACDAL	Autologous or donor-derived LMP2a-specific CTL	2×10^7–1×10^8	EBV-positive Hodgkin's disease or non-Hodgkin's lymphoma after lymphodepletion
NCT00082225			
ETNA	Donor-derived EBV-specific CTL	2×10^7–1.2×10^8	Immune reconstitution in allogeneic/mismatch HSCT recipients (26)
NCT00058604			
LYPTAIST	Donor-derived adenovirus/EBV-specific CTL	5×10^6–1.35×10^8	Adenovirus and EBV infection post-allogeneic HSCT (25)
NCT00111033			
VICTA	Donor-derived CMV/adenovirus/EBV-specific CTL	1×10^7–1×10^8	Prophylaxis of CMV, adenovirus and EBV infection post-allogeneic HSCT (20)
NCT00078533			
CHALLAH	Third-party allogeneic adenovirus/EBV/CMV-specific CTL	2×10^7	Third-party CTL for persistent reactivation/infection with adenovirus/EBV/CMV after HSCT
NCT00711035			
RFT-DGA	Donor-derived allodepleted T cells	1×10^4–5×10^6[a]	Immune reconstitution post-haplo-identical stem cell transplant (19)
NCT00622297			
RAFAHS	Donor-derived allodepleted T cells	1×10^4[a]	Immune reconstitution post-haplo-identical stem cell transplant for Fanconi's anemia (19)
NCT00586274			
HIMRFT	Allodepleted T cells	1×10^3–1×10^4[a]	Immune reconstitution post-reduced intensity haplo-identical stem cell transplant (19)
NCT00586547			

[a]Cell doses are expressed per kilogram.
CTL, cytotoxic T lymphocytes; EBV, Epstein–Barr virus.

Table II. Patient characteristics.

Characteristic	T cell recipients
Age at infusion (years)	Range 9–80.4 Mean 26.6 Median 18.5
Male:female	109:71
Ethnicity	
White	86
Hispanic	41
Asian	25
Black	20
Others	8
Primary diagnosis	
Nasopharyngeal carcinoma	42
Hodgkin's lymphoma	28
Acute myeloid leukemia (AML)	18
Non-Hodgkin's lymphoma	16
Acute lymphoblastic leukemia (ALL)	15
Neuroblastoma	14
Post-solid organ transplant	11
Severe, chronic EBV infection	10
Lymphoproliferative disorders	5
Myelodysplastic syndrome	4
Beta-thalassemia	3
Hemophagocytic syndromes	3
Aplastic anemia	2
Chronic myelogenous leukemia (CML)	2
Multiple myeloma	2
Severe combined immunodeficiency (SCID)	2
Fanconi's anemia	1
Lympho-epithelioma	1
Acute biphenotypic leukemia	1

were administered), giving an incidence of 6.55%, either during infusion or the immediate post-infusion monitoring period (which lasted between 1 and 6 h). Figure 1 summarizes the observed events. Figure 2 enumerates an additional 22 events (incidence of reported or observed AE occurring in the 24-h window following T cell infusion). Again, no severe AE that was related to the T cell products was noted. Overall, we observed a total of 46 immediate (within 24 h) non-severe AE (12.56%) and no severe AE

Table III. Types of infusion.

Type of T cell product of infusions	
Allogeneic	
Adenovirus/EBV/CMV-specific CTL	24
Adenovirus/EBV-specific CTL	14
EBV-specific CTL	13
Allodepleted CTL	47
LMP2a-specific CTL	14
LMP1/LMP2a-specific CTL	4
Autologous	
EBV-specific CTL	139
CAR-transduced EBV-specific CTL	15
CAR-transduced OKT3 blasts	15
LMP2a-specific CTL	44
LMP1/LMP2a-specific CTL	52

CAR, chimeric antigen receptor.

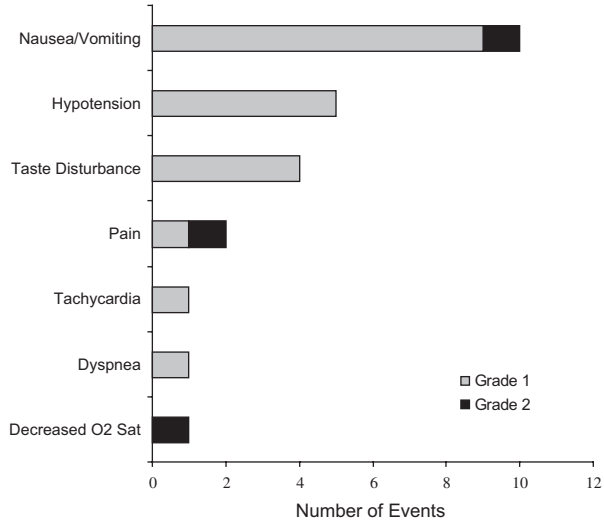

Figure 1. AE during T cell infusion/post-infusion monitoring. Twenty-four adverse reactions during infusion or the immediate post-infusion monitoring period amounted to an incidence of 6.5% AE in 366 infusions of 381 T cell products. Two grade 3 reactions, two grade 2 reactions and two grade 1 reactions were also reported but were considered to be unrelated to the T cell products. All AE that were possibly/definitely related to the T cell infusion were non-severe (grade 1–2). Adding the AE related to T cell infusion reported within 24 h resulted in an incidence of 12.5%.

following the infusion of *ex vivo*-manipulated T cells. The most common AE were nausea/vomiting and hypotension.

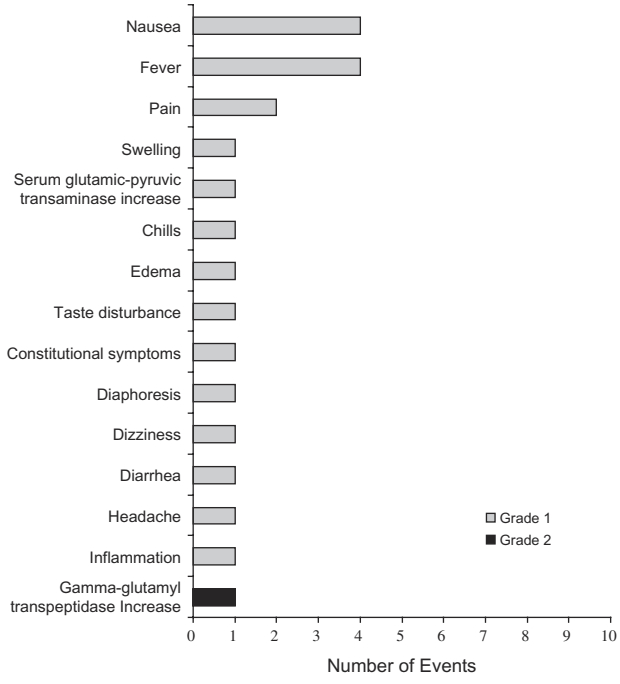

Figure 2. AE reported within 24 h. An additional 266 AE were reported within a day of infusion. A total of 22 events possibly or definitely related to the *ex vivo*-manipulated T cell product were listed (all of which were non-severe/grade 1–2). Both the frequency of each AE and the severity of the reaction were noted.

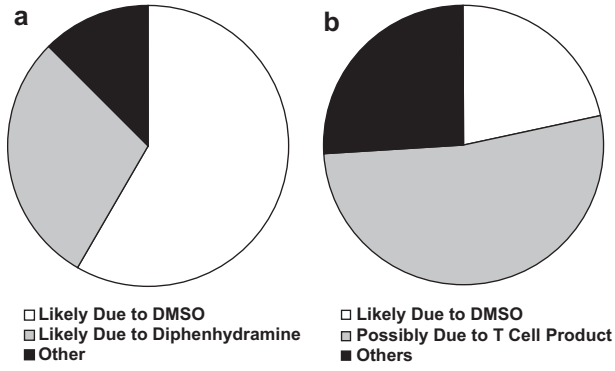

Figure 3. AE attributable to DMSO or diphenhydramine. Most of the (a) immediate AE seen during infusion and the post-infusion period were attributable to either DMSO or diphenhydramine. There were an additional five AE attributable to DMSO seen or reported (b) within 24 h of infusion, with most events at this time period conceivably resulting from a mild inflammatory process mediated by the T cell products. None of the AE was severe enough to be a cause of concern.

The majority of AE were related to DMSO or diphenhydramine

All infusions consisted of T cell products suspended in media containing 10% DMSO as a cryoprotectant and the cells were not washed prior to infusions. Patients received the infusions after premedication with diphenhydramine and acetaminophen, except when contraindicated by the presence of allergies or by concomitant medications that would produce unwanted interactions. As seen in Figure 3, most of the immediate AE noted were attributed to DMSO (e.g. nausea/vomiting and taste disturbance) or diphenhydramine (e.g. hypotension and transient hypoxia resulting from sedation).

Relationship of AE to other factors

For analysis, AE were defined as an event grade 1 or higher, possibly, probably, or definitely related to the T cell infusion. Because all AE were non-severe, no attempt was made to distinguish AE grades in the analysis.

Table IV. Incidence of AE analyzed by T cell infusion subgrouped by age.

No. AE	Age <18 years	Age >18 years
0	152	195
	92.12	90.28
1	8	16
	4.85	7.41
2	5	3
	3.03	1.39
3	0	2
	0	0.93
Total	165	216
Fisher's exact	0.360	

Table V. Incidence of AE analyzed by T cell infusion subgrouped by presence of allergies.

No. AE	No allergy	With allergy
0	190	157
	92.23	89.71
1	10	14
	4.85	8
2	5	3
	2.43	1.71
3	1	1
	0.49	0.57
Total	206	175
Fisher's exact	0.624	

AE were first summarized by infusion episode. Fisher's exact analysis of all T cell product infusions grouped by patient age, patient ethnicity, and cell source did not reveal any associations with increased risks for AE. The very young and very old were no more susceptible to untoward side-effects from T cell infusions (Table IV) than other patients. Neither the patients' ethnicity (Table V) nor increasing antigenic mismatch between donor and recipient cells (Tables VI and VII) contributed to a higher incidence of AE. T cells from both allogeneic and autologous sources resulted in similar rates of AE following infusions (Table VI), and allogeneic cells that were mismatched at more than two antigens are no more associated with AE than donor T cells matched at 5/6 and 6/6 HLA loci (Table VII).

Analysis by infusion episodes, however, was not very comprehensive, as AE within an individual patient were not statistically independent. We thus performed more rigorous data analysis of the data by individual patient. As the number of AE events from each individual should follow a Poisson distribution, we used a Poisson regression model with a generalized estimating equation (GEE) for correlated count data. We estimated the incidence rate (IR) per patient and, by covariates and in this multivariate Poisson regression model, we compared: autologous versus allogeneic stem cell source of T cells, patient gender, age at infusion, and the presence of allergies. We also fitted

Table VI. Incidence of AE analyzed by T cell infusion subgrouped by T cell source.

No. AE	Autologous	Allogeneic
0	241	106
	90.94	91.38
1	17	7
	6.42	6.03
2	5	3
	1.89	2.59
3	2	0
	0.75	0.93
Total	265	116
Fisher's exact	0.950	

Table VII. Incidence of AE in allogeneic T cell products subgrouped by extent of antigenic mismatch.

No. AE	4/6	5/6	6/6	Unspecified
0	50	6	39	11
	94.34	85.71	88.64	91.67
1	1	1	4	1
	1.89	14.29	9.09	8.33
2	2	0	1	0
	3.77	0	2.27	0
Total	53	7	44	12
Fisher's exact	0.458			

the Poisson regression model to the level of antigen mismatch for recipients of allogeneic T cells. Stratifying AE data by incidence rates per patient resulted in significantly lower incidences seen as patient age increased. Immediate AE rates were also increased in patients with documented allergies. In our analysis of patients with allergies, we classified patients whose allergy status was undocumented within the allergy group, to allow a more conservative estimate of the effects of allergies and avoid dropping any patients from our calculations. With this approach we found a significant effect of older age on the probability of both immediate and total AE. The presence of allergies also predisposed patients to develop immediate infusion reactions (Table VIII).

Discussion

Most complex biologic products, such as *ex vivo*-expanded T cells, are prepared following multistep procedures, including cell activation, *ex vivo* expansion using complex media, serum and cytokines, and genetic modification, all of which may increase the risk of subsequent infusion reactions from infection, contamination, and hypersensitivity (27). Several studies have previously looked at the safety profile of unmanipulated or minimally manipulated cellular therapies (11,12) but our study was aimed at evaluating the consequences of infusing *ex vivo*-expanded T cells. Our intent was to provide guidance for immediate safety monitoring after administration of these cellular products. We identified an overall AE incidence rate of 17.3%, and none of the AE was severe. This excellent safety record is similar to preliminary experience with other cell-based therapies (28). Of note, the majority of AE in our analysis could be attributed to either the cryoprotectant (DMSO) or the diphenhydramine used as premedication rather than to the T cells themselves.

Table VIII. Incidence of AE analyzed per patient.

Comparison	IRR	95% CI	*P*-value
Immediate AE			
Auto versus allo	0.27	0.07–1.11	0.07
Male versus female	0.59	0.23–1.52	0.28
Age at infusion	0.97	0.94–1.00	0.05
Allergy versus no allergy	2.72	1.00–7.40	0.05
AE after 24 h			
Auto versus allo	1.32	0.34–5.05	0.69
Male versus female	0.49	0.19–1.27	0.14
Age at infusion	0.99	0.96–1.01	0.27
Allergy versus no allergy	0.77	0.31–1.87	0.56
Total AE			
Auto versus allo	0.58	0.22–1.54	0.28
Male versus female	0.56	0.29–1.11	0.1
Age at infusion	0.98	0.96–1.00	0.05
Allergy versus no allergy	1.41	0.73–2.71	0.31

Of the AE observed, only mild immune/inflammatory responses (constitutional symptoms, mild fever and chills), reported on 10 occasions within 24 h of T cell infusion, were probably mediated by the *ex vivo*-generated T cell products; a similar rate of such symptoms has been reported in studies of other cell products (29). As we found an increased risk of infusion reactions in recipients with documented allergies, we recommend careful monitoring of those patients who report such predispositions. We observed no differences in AE rates if patients were grouped according to cell source used for infusion.

DMSO is a commonly used cryoprotectant, and a variety of methods have been proposed to minimize the adverse effects of this agent. Washing cells prior to infusion is effective but introduces additional variables into the analysis of product functionality that we believe is unjustified by the low rate and severity of infusion reactions. Fractionated cell infusions (30) and the use of strawberry-flavored lollipops (31) has been shown to decrease the incidence of DMSO-related clinical effects.

The patients in this series received relatively low infusion volumes (0.7–58 mL) and T cell numbers (3×10^5/kg to 2×10^8 cells/m^2). While larger quantities, or 'first-in-man' products, may have an entirely different safety profile because of, for example, pulmonary vascular congestion or cytokine storms (14), our experience with these more established, smaller scale infusions clearly shows immediate safety.

Hence we propose that 1-h monitoring post-infusion, with clear instructions to patients to report any AE they experience before the next clinic visit, should be sufficient to maintain this excellent safety record. Indeed, reduction of the dosage of diphenhydramine may reduce AE such as mild hypotension still further.

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