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Adverse Events Following Infusion of T Cells for Adoptive Immunotherapy: A 10 Year Experience

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Abstract

Background—The FDA currently recommends at least 4 hours of recipient monitoring to detect early infusion reactions; recent catastrophic reactions to “first in man” biological 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 therefore reviewed infusion-related adverse events (AEs) following administration of ex-vivo expanded T cell products (antigen specific CTLs, 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 hour follow-up. Twenty four mild (grade 1-2) adverse events (AEs) occurred in 21 infusions either during or immediately following infusion (up to 6 hours), most commonly nausea and vomiting (10/24; 41.6%), likely due to the DMSO cryoprotectant, and hypotension (20.8%), attributable to diphenhydramine pre-medication. 22 additional non-severe events were reported within 24 hours of infusion, most commonly culture negative fever, chills and nausea. Increased risk of adverse effects was associated with age (IRR 0.98; 95% CI 0.96-1.00; p=0.05), while an increase 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 or T cell source (allogeneic or autologous) had no effect on frequency of adverse events.

Discussion—Hence infusion of T cells is safe in the outpatient setting and associated with no severe reactions, so that monitoring for one hour after infusion is likely sufficient. As many of the AEs were attributable to diphenhydramine premedication, a lower dose (0.25mg/kg) should be selected.

Keywords

T cells; Cytotoxic T Lymphocytes; Epstein-Barr virus; Infusion reaction; Adverse events

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 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 nonspecific constitutional symptoms, as a consequence of inflammatory mediator release or cytokine secretion, by transmission of infectious agents or following acute lung injury due to their entrapment in the pulmonary vasculature (13).

The FDA currently recommends at least 4 hours of recipient monitoring following administration of ex-vivo expanded T cells and two recent severe adverse events (AEs) after “first in man” biological agents have emphasized the importance of this rule for initial clinical studies using new 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 hours 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 costimulatory domains(15). Within 4 hours of infusion, this patient developed rapidly progressive respiratory distress requiring ventilation(15) and subsequently died. Although these events were 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 adverse events occurring in subjects enrolled on 18 different IND studies of ex vivo manipulated T cell cells over a 10 year period at our institution.

METHODS

Patient Details

We reviewed the charts, infusion records, and adverse event reports of 180 patients who 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 in Houston, Texas from January 1, 1998 to November 20, 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 investigational new drug studies. The infused T cells targeted malignancies or viral infections after hemopoietic stem cell transplant (HSCT). Cell doses were protocol specific and ranged from $10^4/\text{kg}$ up to $2 \times 10^8/\text{m}^2$. Patients were premedicated with intravenous diphenhydramine (0.5-1mg/kg, with a maximum dose of 50mg) and Tylenol (10mg/kg up to a maximum dose of 625mg) prior to infusion. All cellular products were cryopreserved using 10% DMSO and administered intravenously over 1-15 minutes immediately after thawing. The types of cellular products are summarized in Table 1.

All patients were treated on IRB approved protocols conducted under INDs after approval by the FDA. If T cells were genetically modified or if they were 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. This collated analysis, combining data on infusion safety from all 18 studies was also approved by the IRB at Baylor College of Medicine. Adverse events were collected and graded on case report forms using 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 (16-26) but a detailed analysis of infusion-related adverse events has not been previously presented.

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. Adverse event 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 adverse event and incidence of serious adverse events. 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 adverse events 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 further analyzed by the Poisson regression model using the generalized estimation equation (GEE) to account for the correlation of AE within subjects, and we report estimates of the association and the robust 95% confidence intervals. 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 ten year period between 1998 to 2008. Patient characteristics are summarized in Table 2. The types of T cell products infused are summarized in Table 3.

Adverse Events Resulting from the Infusion are Non-Severe

Twenty four grade 1-2 adverse events (AEs) occurred in 21 infusions of 22 ex vivo expanded T cell products (one patient was enrolled on a study where two products were administered), giving an incidence of 6.55%, either during infusion or the immediate post-infusion monitoring period (which lasted between 1 – 6 hours). Figure 1 summarizes the observed events. Figure 2 enumerates an additional 22 events (incidence of reported or observed adverse events occurring in the 24 hour window following T cell infusion). Again, no severe adverse events that were related to the T cell products were noted. Overall, we observed a total of 46 immediate (within 24 hours) non-severe adverse events (12.56%) and no severe adverse events following the infusion of ex vivo manipulated T cells. The most common adverse events were nausea/vomiting and hypotension.

The Majority of Adverse Events are 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. Subjects 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 adverse events noted were attributed to DMSO (e.g. nausea/vomiting, taste disturbance) or diphenhydramine (e.g. hypotension, transient hypoxia resulting from sedation).

Relationship of Adverse Events to Other factors

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

Adverse events were first summarized by infusion episode. Fisher's exact analysis of all T cell product infusions grouped by patient age, patient ethnicity, or cell source did not reveal any associations with increased risks for adverse events. The very young and the very old were no more susceptible to untoward side effects from T cell infusions (Table 4a). Neither the patient's ethnicity (Table 4b) nor increasing antigenic mismatch between donor and recipient cells (Table 4c & 4d) contributed to a higher incidence of AEs. T cells from both allogeneic and autologous sources resulted in similar rates of adverse events following infusions (Table 4c), and allogeneic cells that were mismatched at more than 2 antigens are no more associated with adverse events than donor T cells matched at 5/6 and 6/6 HLA loci. (Table 4d).

Analysis by infusion episodes, however, is not very comprehensive, as AE within a subject are not statistically independent. We thus performed more rigorous data analysis of the data by individual subject. Since 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 subject, and by covariates and in this multivariate Poisson regression model we compared: autologous vs allogeneic stem cell source of T cells, patient gender, age at infusion, and the presence of allergies. We also fitted the Poisson regression model to the level of antigen mismatch for recipients of allogeneic T cells. Stratifying adverse event data by incidence rates per patient results in significantly lower incidences seen as patient age increases. Immediate adverse event rates are also increased in patients with documented allergies. (IRR = incidence rate ratio, AE = adverse event) In our analysis of patients with allergies, we classified patients whose allergy status is undocumented within the allergy group, to make for a more conservative estimate of the effects of allergies and to avoid dropping any patients from our calculations. By this approach we found a significant effect of older age on the probability of both immediate and total adverse events. The presence of allergies also predisposed patients to develop immediate infusion reactions. (Table 5).

DISCUSSION

Most complex biological products such as ex-vivo expanded T cells are prepared following multi-step procedures – including cell activation, ex vivo expansion using complex media, serum and cytokines, and genetic modification, all of which may increase the risk for subsequent infusion reactions from infection, contamination or 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 adverse event (AE) incidence rate of 17.3%, and none of these AE's were severe. This excellent safety record is similar to preliminary experience with other cell-based therapies (28) Of note, the majority of AEs in our analysis could be attributed to either the cryoprotectant (DMSO) or the diphenhydramine used as premedication rather than to the T cells themselves.

Of the adverse events observed, only mild immune/inflammatory responses (constitutional symptoms, mild fever, chills) reported on 10 occasions within 24 hours of T cell infusion are likely mediated by the ex vivo generated T cell products; a similar rate of such symptoms have been reported in studies of other cell products (29). Since 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 adverse event rates if patients are 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 analysis of product functionality that we believed unjustified by the low rate and severity of infusion reactions. Fractionated cell infusions (30) and the use of strawberry flavored lollipops (31) have been shown to decrease the incidence of DMSO-related clinical effects.

The patients in this series received relatively low infusion volumes (0.7mL to 58 mL) and T cell numbers ($3 \times 10^5/\text{kg}$ to 2×10^8 cells/m²). While larger quantities, or first in man products may have an entirely different safety profile due, for example, to pulmonary vascular congestion or cytokine storms (14), our experience with these more established, smaller scale infusions, clearly shows immediate safety.

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

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Abbreviations

AEs	Adverse events (AEs)
CAR	Chimeric antigen receptor
CTLs	Cytotoxic T Lymphocytes
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GEE	Generalized Estimation Equation
HLA	Human Leukocyte Antigen
HSCT	Hemopoietic Stem Cell Transplant
IND	Investigational New Drug
IRB	Institutional Review Board

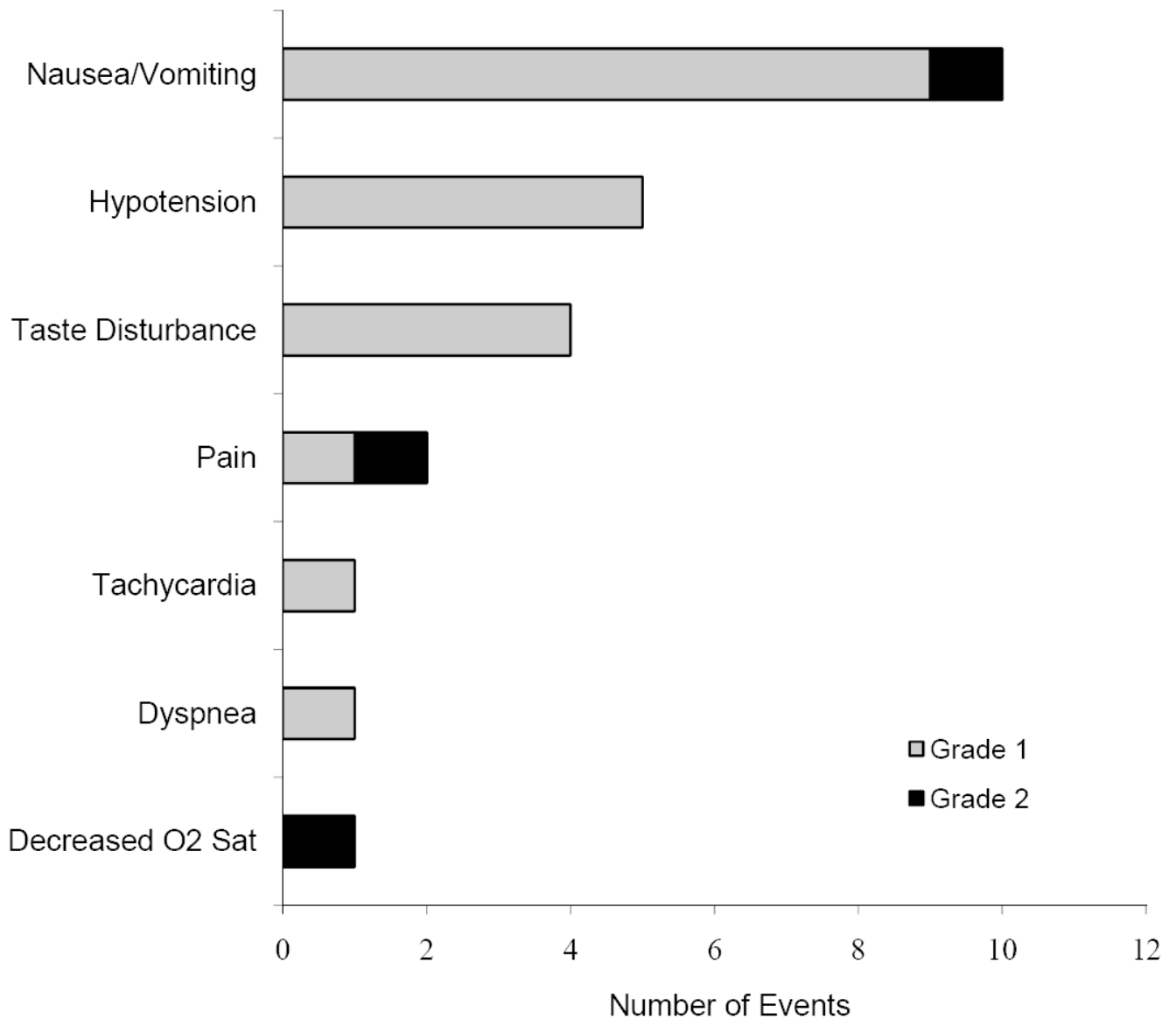


Figure 1. Adverse Events During T Cell Infusion/Post-Infusion Monitoring

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

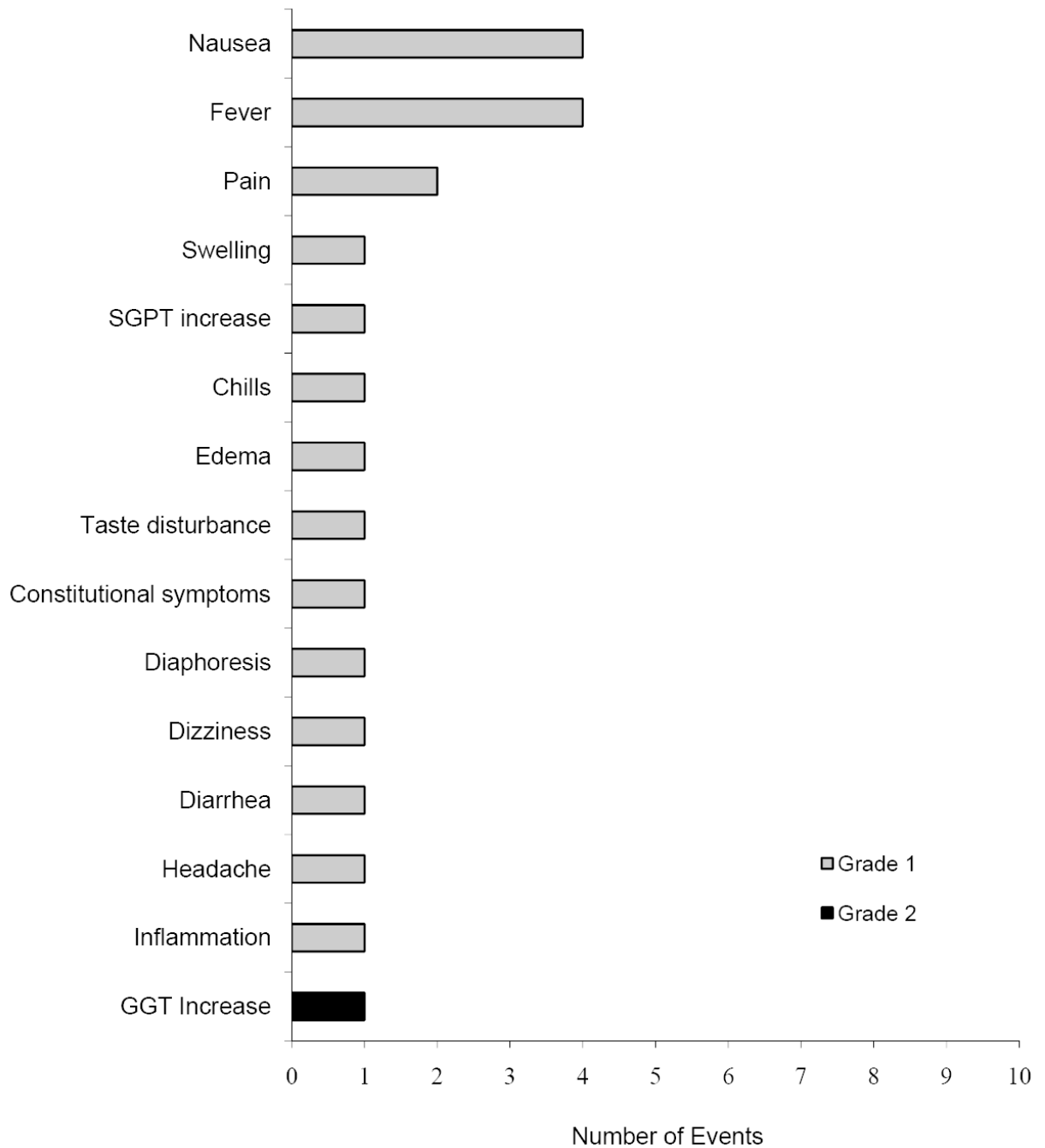


Figure 2. Adverse Events Reported Within 24 Hours

An additional 266 adverse events were reported within a day after infusion. A total of twenty two events possibly or definitely related to the ex vivo manipulated T cell product are listed here (all of which are non-severe/grade 1-2). Both the frequency of each adverse event and the severity of the reaction are noted.

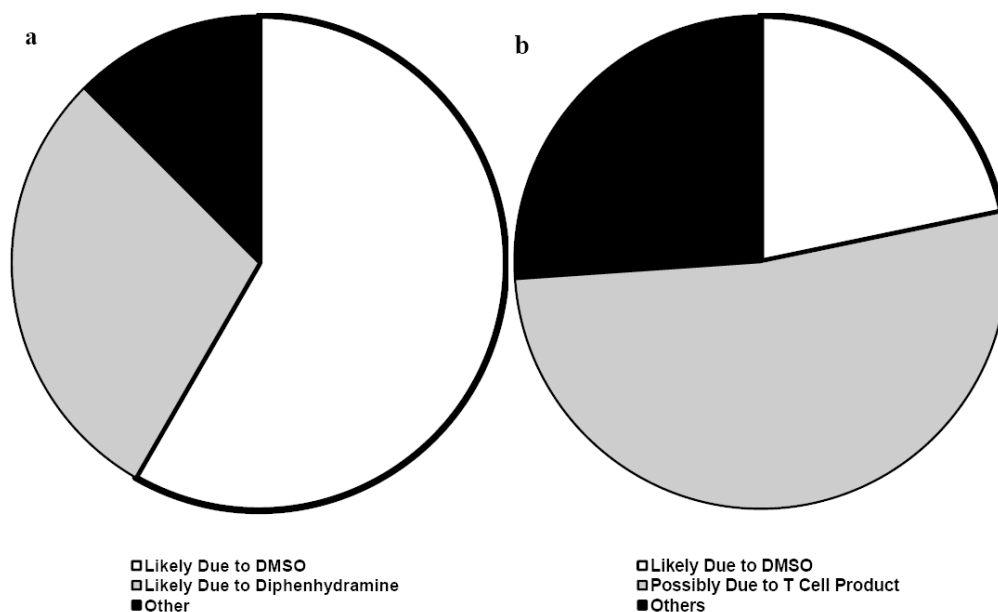


Figure 3. Adverse Events Attributable to DMSO or Diphenhydramine

Most of the (a) immediate adverse events seen during infusion and the post-infusion period are attributable to either DMSO or diphenhydramine. There were an additional five adverse events attributable to DMSO seen or reported (b) within 24 hours 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 adverse events were severe enough to be a cause of concern.

Table 1

Summary of Studies

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

* cell doses are expressed per kg

Table 2

Patient Characteristics

Characteristic	T cell Recipients
Age at Infusion	range 9 mo. to 80.4 y mean 26.6 y median 18.5 y
Male:female	109:71
Ethnicity	
White	86
Hispanic	41
Asian	25
Black	20
Others	8
Primary Diagnosis	
Nasopharyngeal carcinoma	42
Hodgkin's lymphoma	28
AML	18
Non-Hodgkin's lymphoma	16
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
CML	2
Multiple Myeloma	2
SCID	2
Fanconi's anemia	1
Lymphoepithelioma	1
Acute Biphenotypic Leukemia	1

Table 3

Types of Infusion

Type of T cell Product	
<u>Allogeneic</u>	
Adenovirus/EBV/CMV-specific CTLs	24
Adenovirus/EBV-specific CTLs	14
EBV-specific CTLs	13
Allodepleted CTLs	47
LMP2a-specific CTLs	14
LMP1/LMP2a-specific CTLs	4
<u>Autologous</u>	
EBV-specific CTLs	139
CAR-transduced EBV-specific CTLs	15
CAR-transduced OKT3 blasts	15
LMP2a-specific CTLs	44
LMP1/LMP2a-specific CTLs	52

Table 4

Incidence of Adverse Events Analyzed by T Cell Infusion

a. Adverse events subgrouped by age

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

b. Adverse events subgrouped by presence of allergies

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

c. Adverse events subgrouped by T cell source

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

d. Adverse events in allogeneic T cell products subgrouped by extent of antigenic mismatch

No. of AE	4/6	5/6	6/6	Unspecified
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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			

Table 5

Incidence of Adverse Events Analyzed Per Patient

	IRR	95% Confidence Interval	p-value
Immediate AE			
Auto vs Allo	0.27	0.07 – 1.11	0.07
Male vs Female	0.59	0.23 – 1.52	0.28
Age at Infusion	0.97	0.94 – 1.00	0.05
Allergy vs No Allergy	2.72	1.00-7.40	0.05
AEs After 24 Hours			
Auto vs Allo	1.32	0.34 - 5.05	0.69
Male vs Female	0.49	0.19 - 1.27	0.14
Age at Infusion	0.99	0.96 - 1.01	0.27
Allergy vs No Allergy	0.77	0.31 – 1.87	0.56
Total AEs			
Auto vs Allo	0.58	0.22 – 1.54	0.28
Male vs Female	0.56	0.29 – 1.11	0.1
Age at Infusion	0.98	0.96 – 1.00	0.05
Allergy vs No Allergy	1.41	0.73 – 2.71	0.31