

T Cells Expressing Chimeric Antigen Receptors Can Cause Anaphylaxis in Humans

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Abstract

T cells can be redirected to overcome tolerance to cancer by engineering with integrating vectors to express a chimeric antigen receptor (CAR). In preclinical models, we have previously shown that transfection of T cells with mRNA coding for a CAR is an alternative strategy that has antitumor efficacy and the potential to evaluate the on-target off-tumor toxicity of new CAR targets safely due to transient mRNA CAR expression. Here, we report the safety observed in four patients treated with autologous T cells that had been electroporated with mRNA coding for a CAR derived from a murine antibody to human mesothelin. Because of the transient nature of CAR expression on the T cells, subjects in the clinical study were given repeated infusions of the CAR-T cells to assess their safety. One subject developed anaphylaxis and cardiac arrest within minutes of completing the third infusion. Although human anti-mouse immunoglobulin (IgG) antibodies have been known to develop with CAR-transduced T cells, they have been thought to have no adverse clinical consequences. This is the first description of clinical anaphylaxis resulting from CAR-modified T cells, most likely through IgE antibodies specific to the CAR. These results indicate that the potential immunogenicity of CARs derived from murine antibodies may be a safety issue for mRNA CARs, especially when administered using an intermittent dosing schedule. *Cancer Immunol Res*; 1(1); 26–31. ©2013 AACR.

Introduction

T cells engineered with chimeric antigen receptors (CAR) represent a promising novel form of adoptive immunotherapy (1). The CAR tumor-binding function is usually accomplished by the inclusion of a single chain antibody variable fragment (scFv), often of murine origin. Although there are several reports where CAR-T cells containing an scFv with murine sequences have been given to patients with cancer, and antibodies (IgG's) to the CAR have been detected (2, 3), to date adverse effects of these antibodies have not been reported in human studies. Similarly, human subjects given infusions of T cells engineered to express murine T-cell receptors (TCR) have developed antibodies to the TCRs without adverse effects (4).

Mesothelin is a tumor-associated antigen that is overexpressed in a variety of malignancies including malignant pleural mesothelioma, pancreatic, ovarian, and lung cancer (5, 6). We initially developed an investigational agent consist-

ing of autologous T cells expressing an antimesothelin CAR using lentiviral vector engineering (7). Mesothelin has relatively limited and low level expression in normal tissues, including the mesothelial cells that line the peritoneal, pleural, and pericardial cavities (6). It is a target of a natural immune response in mesothelioma and ovarian cancer (8), and has been proposed as a target for cancer immunotherapy (9). In studies testing a mesothelin-specific antibody–drug conjugate, the reagent was well tolerated with dose-limiting toxicity consisting of pleuritis (8). Because we have observed persistent B-cell aplasia following anti-CD19 CAR-T cell infusions (9, 10), an on-target, off-tumor toxicity, we developed an approach to transiently express the antimesothelin CAR on T cells by using electroporation of antimesothelin CAR mRNA. This approach offers the opportunity to test the safety and potential antitumor effects of mesothelin directed CAR-T cells (meso-RNA-CAR-T; ref. 11). In preclinical models, we showed that multiple infusions of antimesothelin and anti-CD19 RNA CAR-T cells have potent antitumor effects (11, 12).

On the basis of the above, we have been conducting a first-in-human study to test the safety of meso-RNA-CAR-T (NCT01355965; clinicaltrials.gov). Our approach is to test multiple infusions of T cells electroporated with mesothelin CAR mRNA, maximizing safety by allowing CAR expression for only a limited period. The intent of our study was that if adverse events were noted, we could terminate T-cell infusions with the expectation that toxicity would rapidly abate because mRNA CAR expression is limited to a few days, thus rendering adverse effects self-limiting. Here, we report the first incidence, to our knowledge, of anaphylactic shock

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following CAR-T-cell infusion, a toxicity that could not be managed by terminating T-cell infusions.

Materials and Methods

RNA CAR-T-cell manufacturing

Autologous T cells were engineered to express an extracellular single chain antibody (scFv) with specificity for mesothelin (13, 14), along with a transmembrane domain and an intracellular signaling molecule comprised the 4-1BB and TCR- ζ signaling modules (7, 15). The scFv is derived from the murine monoclonal antibody SS1, and thus contains murine sequences, whereas the cytoplasmic T-cell transgene signaling domains are entirely native human sequences. These studies used the same antibody region used in previous studies (8, 16), but the antibody sequences were in the form of an scFv displayed on T cells rather than a soluble antibody-toxin conjugate. The CAR-T cells were stimulated with bead immobilized anti-CD3 and anti-CD28 antibodies and cultured for 10 days in cell culture medium supplemented with human serum, electroporated with mRNA encoding the mesothelin CAR, and then cryopreserved in human serum albumin (11).

Clinical protocols

Subjects were enrolled on 2 clinical protocols using T cells transduced with the mRNA encoding the mesothelin CAR (NCT01355965 = UPCC 17510 and UPCC 21211 is a compassionate use protocol for a single patient). All subjects had serum collected at multiple predetermined time points after infusion for monitoring of cytokine production resulting from immune modulation and T-cell activation.

Soluble factor analysis

Whole blood was collected in red top (no additive) BD vacutainer tubes (Becton Dickinson), processed to obtain serum using established laboratory standard operating procedure, aliquoted for single use and stored at -80°C . Quantification of soluble cytokine factors was conducted using Lumines bead array technology and kits purchased from Life

Technologies. Assays were conducted as per the manufacturer protocol with a 9-point standard curve generated using a 3-fold dilution series as previously described (10).

Tryptase was measured retrospectively from serum samples collected as scheduled and cryopreserved after the serious adverse event (SAE). Serum samples were sent to ARUP Laboratories for measurement of tryptase levels. Cryopreserved or fresh serum samples were sent to Quest Diagnostics or LabCorp for measurement of human anti-mouse antibodies (HAMA) using an ELISA assay specific for human immunoglobulin (Ig)G and IgE antibodies.

Results and Discussion

Twenty-one infusions of meso-RNA-CAR-T cells have been given to 4 patients to date, and with the exception of 1 infusion, all have been well tolerated. One subject with pancreatic adenocarcinoma was treated with 8 intravenous infusions over 20 days (data not shown). Three subjects with malignant pleural mesothelioma were treated with single infusions of meso-RNA CAR-T cells spaced 1 week apart as shown (Fig. 1). Subjects were then eligible to enroll in an extended cohort with repeated infusions of meso-RNA-CAR-T cells (Fig. 1). Of the 3 subjects, 2 (101 and 105) were enrolled into the extended cohort; subject 102 developed progressive disease and died before enrollment on the extended cohort. Subject 101 tolerated an additional 6 infusions of meso-RNA-CAR-T cells well with minimal arthralgias and fatigue. However, subject 105 experienced a SAE within minutes of the first infusion on the extended cohort; this was his third infusion overall.

Case report

Subject UPCC17510-105 is an 81-year-old lifelong nonsmoking man with a past medical history notable for asthma and asbestos exposure. He was diagnosed with stage IV mesothelioma with bilateral pleural disease and mediastinal and peritoneal nodal involvement 3 years before enrollment on this protocol. He was treated with pemetrexed and carboplatin for 10 cycles followed by single-agent pemetrexed maintenance

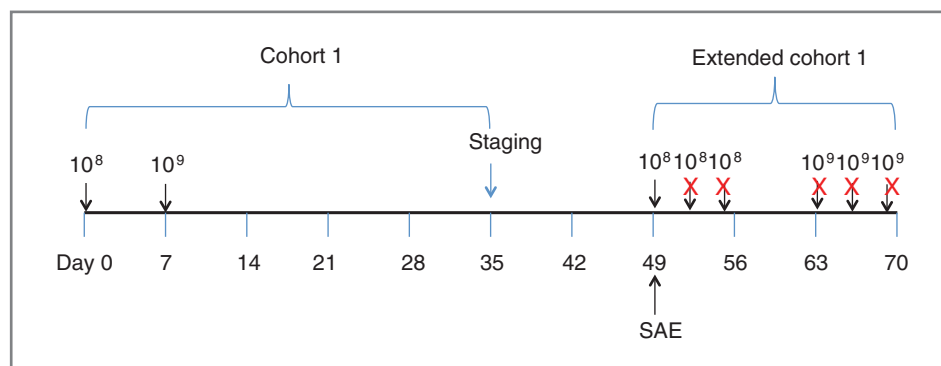


Figure 1. Clinical trial schema. The subject was originally enrolled onto cohort 1, where 10^8 meso-RNA-CAR-T cells were administered on day 0 and 10^9 meso-RNA-CAR-T cells were administered on day 7. Safety assessments were conducted between days 0 and 7, and repeat staging was conducted by computed tomography scan on day 35. The subject was then enrolled into an extended cohort to receive an additional 6 doses of T cells that were scheduled for Monday/Wednesday/Friday for 2 weeks. However, the subject developed anaphylaxis immediately after the third infusion (i.e., the first of extended cohort 1), and therefore did not receive any further infusions (marked with an "X").

therapy. Six months before this event, he was enrolled in a different study where he received gemcitabine and intrapleural adenovirus vector expressing IFN- α (17).

He was enrolled in the current study and underwent leukapheresis for T-cell collection. As part of cohort 1, he received 2 infusions of meso-RNA-CAR-T cells 1 week apart; the first dose was 1×10^8 T cells and the second dose was 1×10^9 T cells (Fig. 1). Each infusion was tolerated well with no side effects. Because of the short-lived nature of the study product, and the fact that he had tolerated prior infusions well, he was given the opportunity for a series of infusions to be given over the course of 2 weeks according to the amended protocol "Extended cohort 1."

Forty-nine days after the first infusion, the patient received 1×10^8 meso-RNA-CAR-T cells over 15 minutes (Fig. 1). The infused cells were an aliquot of cryopreserved cells from the same lot of cryopreserved cells that were used for the original infusions. Within 1 minute of completing the infusion, he developed plethora, tingling hands, shortness of breath, hypoxia, and then underwent cardiac arrest manifested as pulseless electrical activity. He was intubated, cardio-pulmonary resuscitation was conducted, and he was treated with epinephrine along with aggressive volume resuscitation, high-dose steroids, and vasopressors. All microbiology cultures were negative. The patient experienced a rapid recovery; pressors were withdrawn within 2 days and the patient was extubated on day 3. He was discharged to home 10 days after the SAE, on room air and a short prednisone taper. Overall, the patient experienced a complete clinical recovery and repeat imaging revealed a transient partial response of mesothelioma.

An anaphylaxis event

This infusion was the only infusion that was poorly tolerated of 21 infusions of meso-RNA-CAR-T cells in 4 patients. Moreover, the aliquot of meso-RNA-CAR-T cells was an aliquot of the same product lot administered in the previous 2 infusions. Therefore, we hypothesized that the SAE observed in subject 105 was a result of an acquired immune response to a component of the cell product, either related to the CAR itself or a carrier protein in the cell product, such as IgA or albumin. The clinical scenario was most consistent with an IgE-mediated anaphylaxis event triggered by systemic degranulation of mast cells (18) and basophils. To confirm the clinically suspected anaphylaxis event, tryptase levels were measured in cryopreserved sera in samples collected before and after the SAE (tryptase is stable in frozen serum for at least 1 year). Serum tryptase is the best clinically measurable indicator of recent mast cell degranulation, with levels typically peaking 15 to 60 minutes after symptom onset and declining with a half-life of about 2 hours (19). We found that tryptase levels were markedly elevated in the first few hours after the SAE, confirming that the event was anaphylaxis (Fig. 2).

Cytokine patterns

The serum cytokines in all subjects infused were consistent with transient T-cell activation, including mild elevations in MIP-1 β , granulocyte colony-stimulating factor (G-CSF), interleukin (IL)-6, and IL-17 for several days after each infusion

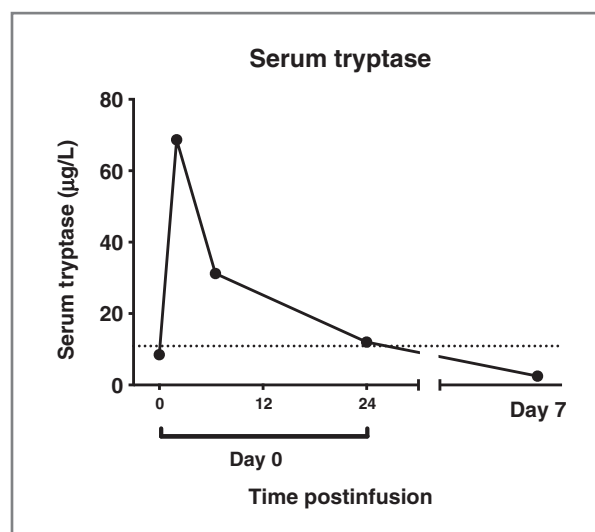


Figure 2. Serum tryptase in blood. Peripheral blood serum samples at baseline and several time points after the SAE were analyzed for levels of serum tryptase. The dashed line indicates the upper limit of reference range (0.4–10.9 $\mu\text{g/L}$).

(data not shown). In stark contrast, there was a rapid and significant elevation of several cytokines both in serum and in pleural fluid immediately after the third infusion (SAE event) of subject 105. Specifically, IL-6, G-CSF, MIP-1 β , MCP-1, IP-10, MIG, and IL-8 were all elevated up to 1,000-fold in serum within the first 24 hours of the event (Fig. 3A). Immediately after the event, IL-6 was elevated above the assay range. All cytokine levels returned to baseline by day 4 and remained at baseline through day 35. Cytokine analysis of pleural fluid obtained from the indwelling pleural catheter 1 day after the event revealed increased levels of IL-6 that were out of range for our assay, and increased levels of IL-8, G-CSF, and MIG (Fig. 3B).

Although the tryptase levels are pathognomonic of mast cell activation, anaphylaxis also produces significant elevations in other cytokines, particularly IL-6, IL-10, and IL-2 (20). In this case both the allergen (CAR-T cells) and the mast cells were potentially immunologically active and capable of secreting cytokines, which confounds determination of the source of cytokines observed in the serum, particularly in the first 24 hours after the infusion.

Detection of human anti-mouse antibodies

Serum samples were analyzed by ELISA testing for both IgG and IgE specific for mouse serum proteins. Results are shown for each patient in Table 1. Interestingly, subject 105 had a minimally positive IgG HAMA before enrollment (day -3), which increased after completing infusions in the first cohort (day 14, 21). Surprisingly, it returned to normal levels at day 107 (2 months after the SAE event) but was again elevated at day 219 (~7 months). Another IgG HAMA test sent to a different facility (LabCorp) using a fresh clinical specimen obtained at day 141 (3 months after the SAE) returned positive and out-of-range high for the assay (>600 ng/mL). Frozen serum samples were assayed and found to be negative for IgE specific for mouse serum proteins at all the same time points. This is not

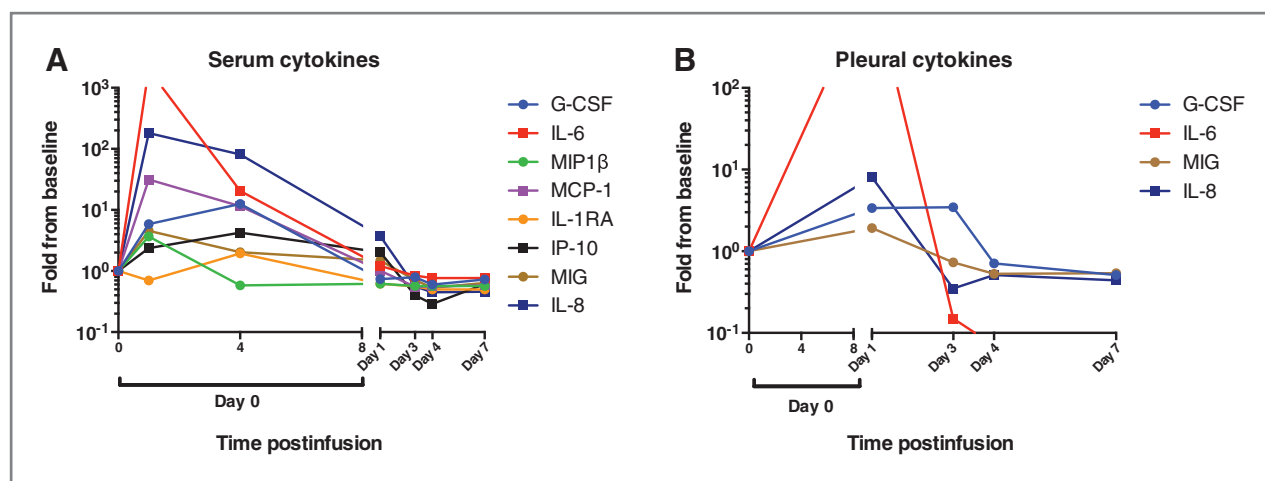


Figure 3. A, serum cytokines. Peripheral blood serum samples obtained at baseline and from several time points after the event were analyzed for levels of 30 cytokines. Only cytokines elevated at least 1.5-fold over baseline are shown. IL-6 levels at 1 hour after infusion were above the limit of quantification of the assay. B, pleural fluid cytokines. The subject had a pleurex catheter in place and pleural fluid was collected 24 hours after the event and periodically thereafter. The levels of 30 cytokines were measured but only the 4 that were elevated at least 1.5-fold above baseline are shown. IL-6 levels 24 hours after the event were above the limit of quantification of the assay.

unexpected because of the low levels of IgE in normal serum. Of note, subject 102 also developed a positive IgG HAMA test at day 21; he did not receive any further CAR-T cell infusions, and therefore the HAMA remained clinically silent in this patient.

These results establish that subject 105 had classical clinical and laboratory findings of anaphylaxis. It was possible, though, that the immune response was directed to the activated autologous T cells in addition to or instead of the CAR moiety. We have not previously observed anaphylaxis during our considerable experience with more than 400 patients infused with T cells cultured with immobilized mouse antibodies to CD3 and CD28 on beads, making it unlikely that the response was directed to antibody carry over, especially considering that the monoclonal antibodies are covalently attached to the beads (21). Furthermore, using the same T-cell manufacturing process with the exception of RNA electroporation, we found that CD4 ζ CARs were not immunogenic, as 41 of 43 patients had decade-long survival of the CARs (22). Another potential source of anaphylaxis induction relates to the *in vitro* T-cell production process; specifically, the CAR-T cells were cultured in media containing pooled human serum, and it is well

established that patients deficient in IgA can develop anaphylaxis upon exposure to human serum containing IgA. Quantitative immunoglobulins in subject 105 were normal, excluding IgA deficiency as the cause of anaphylaxis. In addition, total IgE levels were also normal, indicating no generalized pre-existing atopy in subject 105. Thus, we have concluded that meso-RNA-CAR-T cells triggered anaphylaxis most likely by inducing an IgE antibody specific for the murine-based antibody sequences present in the CAR-modified T-cell product. The elevated levels of human anti-mouse IgG, the finding that these levels increased with exposure to meso-RNA CAR-T cells, and the clinical scenario of anaphylaxis with highly elevated tryptase levels are all supportive of an IgE-mediated anaphylactic event.

Our data are consistent with the scenario that the IgE antibodies developed as a result of the dosing schedule consisting of 3 infusions given over a period of 49 days. On the basis of this event, in cases where multiple infusions are expected, we have modified the infusion schedule of RNA-CAR-T cells, such that infusions may not be separated by more than 10 days, and must be completed within 21 days. This schedule creates a window that would be too short for the time required for

Table 1. HAMA levels in serum of 3 subjects with mesothelioma

	Day -3	Day 14	Day 21	Day 107	Day 141	Day 219
101 ^a	36 ng/mL		30 ng/mL	40 ng/mL		
102 ^a	48 ng/mL		88 ng/mL			
105 ^a	80 ng/mL	87 ng/mL	119 ng/mL	63 ng/mL		79 ng/mL
105 ^b					>600 ng/mL	

NOTE: Bold values are above normal range.

^aReference range for (Quest) HAMA: <75 ng/mL.

^bReference range for (LabCorp) HAMA: <188 ng/mL.

isotype switching from IgG to IgE. While we have also considered using an ELISA-based HAMA assay as a screening tool, at present this is not feasible because (i) the turnaround time of such an assay produces a long gap between screening and infusion, (ii) findings would not be predictive of allergic reactions (23), and (iii) many of the positive HAMA antibodies are directed to mouse albumin or the Fc portions of mouse immunoglobulins (24), which are not present in the CAR-T cell product. Alternatively, if meso-RNA CAR-T cells are found to be safe from the standpoint of on-target off-tumor toxicity, a single infusion of stably transduced, long-lived CAR-T cells may be sufficient for efficacy. In such a case, CAR-T-cell infusion would not be expected to generate IgE antibodies because of the continuous, persistent exposure to the product, which is one principle of desensitization. Ultimately, constructs based on fully humanized antibodies (25) are expected to have minimal antigenic potential as allergens.

Disclosure of Potential Conflicts of Interest

B.L. Levine, Y. Zhao, and C.H. June have commercial research grants from Novartis, which provide Sponsored Research funds for CARs, and have ownership interest (including patents) in University of Pennsylvania, which holds patent applications. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.R. Haas, G.L. Beatty

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.V. Maus, A.R. Haas, B.L. Levine, M. Kalos

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