

Session IV: Scientific and Commercial Challenges

**Review of Selected
Adverse Events
July 2010 - August 2013**

Serious Adverse Events Reports

July 2010 – August 2013

- **About 40 SAEs reported that were possibly related to the genetically modified T cells**
- **Across TCR and CAR protocols the most commonly reported events involve fevers and hypotension that usually occur either in the immediate 24 - 48 hours after infusion or about a week after infusion.**
 - **In at least one case of fevers, hypotension, increased liver enzymes and thrombocytopenia, with elevations in cytokines occurred more than a month after infusion of cells.**

Serious Adverse Events Reports

July 2010 – August 2013

- In some cases, these symptoms resolve quickly with supportive care, but in about three-fourths of cases admission to intensive care required**
- In some cases, those with severe cytokine release syndrome are also reported to have significant tumor regression**
- Cytokine data reported on some events, with elevations in IFN gamma, IL-6 and TNF most often reported**
- Cytokine data sometimes used to distinguish infection from cytokine release syndrome due to cells**

Serious Adverse Events, cont.

- In four serious adverse events, a diagnosis of hemophagocytic syndrome/macrophage activation syndrome was made in subjects who developed constellation of symptoms that included fever/hypotension/dyspnea \pm increased liver enzymes or creatinine, together with elevations in serum ferritin levels that ranged from 40,000 to 160,000 $\mu\text{g/L}$ (normal 15-200 $\mu\text{g/L}$)
- Three of the four subjects recovered, but the fourth case was complicated by a new diagnosis of EBV lymphoproliferative disorder, which appears to have been related to immunosuppression, and sepsis

Neurological Adverse Events in CD 19 Trials

- A number of cases report mental status changes in conjunction with hypotension and fevers**
- At least 3 reports from two different CD19 protocols, reported more focal neurological changes, including aphasia and myoclonus.**
- In two of these cases, MRI of the brain showed transient white matter changes that resolved with 3- 10 days**
- Neurological symptoms resolved completely in two cases, with some residual neurological symptoms (tremor and some cerebellar signs) in the third**

On Target – Off Tissue

- **In addition to reports from trials targeting MAGE-A3, only one other trial for renal cell cancer reported an unexpected possible off-tissue targeting. The TCR in this trial targets the tumor antigen TNF-related apoptosis inducing ligand (TRAIL) bound to the DR4 receptor. After a case of reversible liver toxicity, subsequent analysis found that the modified T cells are able to recognize a biliary ductal adenocarcinoma cell line, indicating that the toxicity seen may be related to expression of the target antigen on normal bile ducts.**

Serious Adverse Events Treatment Strategies

- High dose steroids most often used**
- In five cases of cytokine syndrome reported on CD19 CAR trials, tocilizumab (Actemra) was administered due to elevated IL-6**
- Alemtuzumab (Campath), which targets CD52 on T cells, was reported to be used in one event**
- A suicide gene has not yet been tested in these situations**

Toxicities More Likely Related to Chemotherapy

- **In addition to reports of neutropenia/fever related to chemotherapy, and other toxicities expected from high dose IL2, additional serious adverse events reported in the last two years that were attributed to chemotherapy/ immunosuppression including:**
 - **Pancytopenia about two weeks after cells with no evidence of auto-reactivity of the gene modified cells against the blood**
 - **VZV infection with possible VZV-associated CNS vasculitis related to chemotherapy**
 - **Lymphoproliferative disorder consistent with diffuse B cell lymphoma in a subject with melanoma and EBV infection**
 - **Angioimmunoblastic T cell lymphoma in a subject with melanoma, but no evidence of vector sequences in the cells**
 - **Visual disturbance starting shortly after the initiation of chemotherapy, but before receipt of gene modified cells, progressing to complete visual loss about a month after cellular transfer.**

Availability of Summary SAE Data

Short summaries of significant adverse events that are possibly related to the gene transfer and are reviewed by the RAC Gene Transfer Safety Assessment Board are available on OBA's Website with the RAC Meeting quarterly meeting materials.

The screenshot shows a PDF document titled "Gene Transfer Safety Assessment Board Adverse Event Report" from the NIH Office of Biotechnology Activities, dated December 2012. The document lists two adverse events:

Event ID	Event Date	Event Description
11554	09/06/2012	Subject had received a total of six injections of either the gene transfer agent or placebo. About three weeks after the most recent injection, the subject was admitted to the hospital due to flu-like symptoms. Subject recovered and no source of infection found. Subject may have had a viral infection but a possible relationship to the study agent cannot be ruled out.
11605	10/24/2012	Subject who is a 55+ year-old male with relapsed acute lymphocytic leukemia, developed high-grade fevers approximately two days after last dose of the anti-CD19 engineered T-cells and developed fluid responsive hypotension (low blood pressure). Subsequently, the subject had a marked decline in mental status. Subject was transferred to the intensive care unit (ICU) for further care, including intubation (breathing tube) for airway protection due to the altered mental status. Four days later the subject had a seizure and was started on anti-convulsants and seizure activity stopped. The breathing tube was removed and the subject was transferred out of the ICU. A MRI of the brain demonstrated no evidence of acute infarct, hemorrhage or mass. Subject improved clinically and was discharged in stable condition.

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http://oba.od.nih.gov/rdna_rac/rac_meetings.html

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Discussion Points Managing the Unexpected – SIRS and other Adverse Reactions

- **What cytokine measurements are helpful and what have we learned?**
- **What is the role of steroids, and IL-6 antagonists?**
- **Pre-screening of subjects, what chronic conditions should be excluded from early trials and how is screening done?**
- **What needs to be included in the consent regarding risks?**