

What are the safety concerns moving forward with CAR-T cell therapy in multiple myeloma?

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Welcome to *Managing Myeloma*. I am Dr. Adam Cohen. A common question that I am often asked is, "What are some of the safety concerns that might be seen moving forward with CAR-T cell therapy in the myeloma population?" We know from extensive experience using CD19 directed CAR-T cells in B-cell malignancies that two of the biggest safety issues are cytokine release syndrome and neurotoxicity. It does look like these are going to be potential issues in the myeloma trials as well. Cytokine release syndrome results from rapid proliferation and activation of the infused CAR-T cells with release of IL6 and other inflammatory cytokines. The symptoms can range from just fevers, malaise, and myalgia that can be managed just with supportive care, to more serious hemodynamic instability including hypotension that can require pressors, or even hypoxia requiring ICU level care and intubation. Fortunately, the rate of severe cytokine release syndrome has been fairly low so far in the BCMA-specific CAR-T cells within myeloma and do not seem that different than what is seen in the CD19-directed CAR cells. Cytokine release syndrome can be managed by administering antibodies that block IL6 signaling, and the one that is most commonly used is called tocilizumab, it is an IL6 receptor blocker. Prompt administration of this drug at signs of hemodynamic instability, severe fevers, or organ dysfunction leads to usually very rapid resolution of fevers and stability of hemodynamic function. Fortunately, this does not seem to impact the ability of the CAR-T cells to expand and provide anti-tumor efficacy.

The other safety concern with CAR-T cells is neurotoxicity, and this again has been seen in the majority of CAR-T cell studies in B-cell lymphoma, ALL and CLL, and has been seen in some of the myeloma studies as well. This can range from just mild confusion or delirium in the setting of high fevers, to a more serious encephalopathy-like picture with confusion and obtundation, even seizures and focal neurologic deficits. In some of the CD19-directed CAR studies, there have been deaths from cerebral edema. Fortunately, there have not been any deaths seen in the myeloma studies so far, but this is something that we need to keep in mind. In the vast majority of patients, this neurotoxicity is self-limited and improves just with supportive care and, in some cases, a short course of steroids. The other safety concerns that were seen in the CD19-directed CAR-T cells, such as long-term B-cell aplasia, fortunately have not been as much of an issue with BCMA-directed CAR cells since BCMA is primarily on plasma cells and only a small subset of B-cells, so the majority of B-cells in these patients remain intact. Thank you for viewing this activity.