

CAR T case study in acute myeloid leukemia

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My name is David Sallman. I would like to give a little bit of background into CAR therapy in acute myeloid leukemia patients. In B-cell malignancies, particularly diffuse large B-cell lymphoma, ALL, and others, CD19 has emerged as an optimal target in that you can go for disease eradication without a lot of toxicity on the normal bone marrow. In acute myeloid leukemia, the challenge is that you have the potential with CAR therapy of hurting normal stem cells. Basically, if you eradicate normal stem cells, these patients may no longer have hematopoiesis, and will be stuck with a more major problem than what they began with. Because of that, current CAR strategies often require either a backup allogeneic stem cell transplant, or some sort of novel mechanism in which to turn off the CAR; but of course, that is complicated in terms of the optimal way to do that. Because of this, in collaboration with Celyad, the THINK trial was brought about, which takes the activating receptor on NK cells called NKG2D, which targets a number of ligands that are preferentially expressed on transformed or cancerous cells, and not on normal cells. In particular, at least in evaluation of AML patient samples, nearly all patients will express at least one of these ligands on their blast. Because of this, that was the thought process in this trial.

A little bit on the THINK trial itself: the patients have apheresis of their own T-cells and then subsequently will receive three infusions of the CAR product spaced two weeks apart. To exemplify this excellent case, an exciting case with a responding patient, we had a 52-year-old gentleman who was refractory to initial induction. He was able to achieve a first remission after salvage chemotherapy, but unfortunately, he only had around a seven-month remission. He was being worked up for transplant, but there was some delay secondary to pulmonary issues at that time, and so eventually he developed worsening cytopenia. A bone marrow did confirm evidence of relapse disease with around 7% blasts, severe constitutional symptoms, and severe cytopenias. He then enrolled in our trial. The patient tolerated the three infusions very well. After the second infusion, he did have complete clearance of his blast and start of hematopoietic recovery. He subsequently had his third infusion and at day 57, this was confirmed with blast clearance and continued hematologic recovery. This continued up to about three months after the initial infusion at which point he was bridged to allogeneic transplant. At that time, he had a near complete remission, with platelets in the 90s and neutrophils in the 900, and again, resolution of all the symptoms before. The patient is currently six months out from transplant, in remission and doing well.

A couple of other things to exemplify is in this trial, the patients do not get preconditioning chemotherapy, so the CAR does not last long. Still, in this setting, without the use of preconditioning therapy – and this patient was on the first dose level of the trial – we were able to achieve a good remission and were able to successfully bridge him to transplant, which is still the standard of care in this patient group where we are looking for the curative intent for these patients.

In conclusion, the excitement at least showed some evidence that targeting NKG2D ligands can be of clinical utility, and showed successful CAR treatment of an AML patient without the need of preconditioning chemo, at least in this trial which is the first of its kind. Hopefully this will just continue excitement and further growth of CAR development in AML.

We are continuing to recruit on this trial. It is still in the dose escalation phase of the trial and patients or providers can look at the information on [clinicaltrials.gov](https://www.clinicaltrials.gov) or they are welcome to directly reach out to us at Moffitt Cancer Center for consideration. There will be potentially other trials with this technology, as well as other CAR options in the future as well.

Trial link: <https://www.clinicaltrials.gov/ct2/show/NCT03018405?term=CYAD&rank=4>

Reference:

Sallman DA, Brayer J, Sagatys EM, et al. NKG2D-based chimeric antigen receptor therapy induced remission in a relapsed/refractory acute myeloid leukemia patient. [*Haematologica*](#). April 2018;haematol.2017.186742; doi:10.3324/haematol.2017.186742