



Building a better mousetrap in the immunologic treatment of acute myeloid leukemia

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Sallman *et al.* report on the successful use of chimeric antigen receptor modified T cells (CAR-T cells) utilizing a Natural Killer Group 2D (NKG2D) target in a patient with acute myeloid leukemia (1).

CAR-T cells have been successfully used in the treatment of chronic lymphocytic leukemia (CLL) (2), B-cell acute lymphoid leukemia (B-ALL) (3), and non-Hodgkin lymphoma (NHL) (4) via direct targeting of cluster of differentiation 19 (CD19). The clinical utility of CAR-T cells has led to Food and Drug Administration (FDA) approval for this therapy in the setting of relapsed/refractory B-ALL and B cell large cell lymphoma and is tied to the ability to target and effectively deplete CD19+ cells including normal B cells. In addition to the toxicities that can occur these patients also require administration of intravenous immunoglobulins to compensate for the loss of the B cells. Acute myeloid leukemia (AML), on the other hand, has proven to be a more difficult malignancy in which to target surface markers. Thus far CAR-T cells have been developed against AML surface antigens (5-7) with resultant pre-clinical success. Their clinical utility, however, has been limited because of resulting myelosuppression that occurs since normal hematopoietic stem cells also express the same surface markers as AML.

The effectiveness of CAR T cell therapy is dependent on the identification of an antigen specifically expressed on cancer cells that avoids off-target effects and limits the development of toxicities. The authors explain that AML cells usually express one or more of the NKG2D ligands which bind to natural

killer (NK) and CD8+ activated T cells. The resultant binding triggers cytotoxicity of stressed, infected and malignant cells. Preclinical studies have not observed off-target effects and ligand expression is minimal to zero on normal cells making NKG2D ligands ideal targets for attack.

In their report, the authors utilized CYAD-01 autologous T cells in this report of a single male patient with relapsed/refractory AML who is part of the larger THINK trial. These T cells are genetically modified to express a CAR composed of the human full-length NKG2D receptor with the CD3 ζ signaling domain. A previous study had shown an encouraging signal for activity of single CYAD-01 infusions in one AML patient prompting development of the current THINK trial (NCT03018405) in which multiple CYAD-1 infusions are employed.

Their patient had primary refractory disease to initial 7+3 induction characterized cytogenetically as +8/del (7) (q22q36) and molecularly by *DNTMT3A* R822H. He was able to attain a remission following additional multi-agent salvage chemotherapy with cladribine, cytarabine, G-CSF, and mitoxantrone followed by cladribine/cytarabine consolidation. At his subsequent relapse at 7 months based on worsening cytopenias, constitutional symptoms, and 7% blasts in his bone marrow the patient was enrolled on the THINK trial. Notably no lymphodepleting chemotherapy was given prior to cell infusion of 3×10^8 CYAD-01 cells per injection (flat dosing) every 2 weeks for 3 total administrations. Infusions were well tolerated. By day 28 he had reached a morphologic complete remission based

on 2% blasts. His morphologic CR persisted on day 56 marrow assessment with improving hematopoiesis. FISH, however, showed 7% cells with del (7q) while next generation sequencing (NGS) revealed persistence of *DNMT3A* R882H as well as a new *IDH2* R172K mutation. Infusions were well tolerated with no evidence for cytokine release syndrome and only non-related Grade 1 adverse events. This patient then went on to allogeneic stem cell transplant (allo-SCT). On day 100 post transplant bone marrow assessment showed a complete molecular remission via NGS with 100% donor chimerism. The patient has remained in remission 6 months post allo-SCT and 9 months post initial CYAD-01 infusion.

Pre-infusion analysis of the patient's bone marrow showed positive staining for NKG2DL on neoplastic cells only with no involvement of normal marrow cells. CYAD-01 cells persisted in the periphery at low levels until day +4 post infusion and were composed primarily of effector memory CD8+ T cells. Persistence and *in vivo* expansion of cells was thought to be poor based on lack of transgene detection post infusion.

In conclusion, CYAD-01 autologous T cells appear efficacious but are short lived which limits their toxicities but also likely limits their long-term effectiveness. Notably the reported patient had a very low leukemic burden at the time of treatment which may be necessary given that this is cell based monotherapy without pre-conditioning lymphodepleting chemotherapy. The advantage in targeting NKG2D ligands is the lack of expression of this surface marker on normal cells. Antigen escape, however, may still occur given the development of a new *IDH2* clone in this patient prior to allo-SCT. Whether this antigen escape is secondary to lack of *in vivo* expansion and the resultant persistent immunologic surveillance of activated effector cells or not is unclear. Therefore, the clinical utility of CYAD-01 autologous T cells may still be to serve as a bridge to allo-SCT rather than definitive curative therapy for AML. We will watch with interest the further reports in this trial, particularly those results with further dose escalation, in order to see if continued efficacy is observed without toxicity regardless of initial tumor burden. We agree with Sallman and colleagues that the clinical utility of CYAD-01 CAR-T cells require additional study, particularly

in the setting of NKG2D ligand expression at diagnosis and after subsequent infusions, in order to advance this important therapy further.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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