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CYAD-01, an autologous NKG2D-based CAR T-cell therapy, in relapsed or refractory acute myeloid leukaemia and myelodysplastic syndromes or multiple myeloma (THINK): haematological cohorts of the dose escalation segment of a phase 1 trial

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Summary

Background

CYAD-01 is an autologous chimeric antigen receptor (CAR) T-cell product based on the natural killer (NK) group 2D (NKG2D) receptor, which binds eight ligands that are overexpressed in a wide range of haematological malignancies but are largely absent on non-neoplastic cells. Initial clinical evaluation of a single infusion of CYAD-01 at a low dose in patients with relapsed or refractory acute myeloid leukaemia, myelodysplastic syndromes, and multiple myeloma supported the feasibility of the approach and prompted further evaluation of CYAD-01. The aim of the present study was to determine the safety and recommended phase 2 dosing of CYAD-01 administered without preconditioning or bridging chemotherapy.

Methods

The multicentre THINK study was an open-label, dose-escalation, phase 1 study for patients with relapsed or refractory acute myeloid leukaemia, myelodysplastic syndromes, or multiple myeloma, after at least one previous line of therapy. Patients were recruited from five hospitals in the USA and n. The dose-escalation segment evaluated three dose levels: 3×10^8 (dose level or 10^8 evel two), and 3×10^9 (dose level three) cells per infusion with a 3+3 Fibonacci stu igr

using a schedule of three infusions at 2-week intervals followed by potential consolidation treatment consisting of three additional infusions. The occurrence of dose-limiting toxicities post-CYAD-01 infusion was assessed as the primary endpoint in the total treated patient population. The trial was registered with ClinicalTrials.gov, NCT03018405, and EudraCT, 2016-003312-12, and has been completed.

Findings

Between Feb 6, 2017, and Oct 9, 2018, 25 patients were registered in the haematological dose-escalation segment. Seven patients had manufacturing failure for insufficient yield and two had screening failure. 16 patients were treated with CYAD-01 (three with multiple myeloma and three with acute myeloid leukaemia at dose level one; three with acute myeloid leukaemia at dose level two; and six with acute myeloid leukaemia and one with myelodysplastic syndromes at dose level three). Median follow-up was 118 days (IQR 46–180). Seven patients (44%) had grade 3 or 4 treatment-related adverse events. In total, five patients (31%) had grade 3 or 4 cytokine release syndrome across all dose levels. One dose-limiting toxicity of cytokine release syndrome was reported at dose level three. No treatment-related deaths occurred, and the maximum tolerated dose was not reached. Three (25%) of 12 evaluable patients with relapsed or refractory acute myeloid leukaemia or myelodysplastic syndromes had an objective response. Among responders, two patients with acute myeloid leukaemia proceeded to allogeneic haematopoietic stem-cell transplantation (HSCT) after CYAD-01 treatment, with durable ongoing remissions (5 and 61 months).

Interpretation

Treatment with a multiple CYAD-01 infusion schedule without preconditioning is well tolerated and shows anti-leukaemic activity, although without durability outside of patients bridged to allogeneic HSCT. These phase 1 data support the proof-of-concept of targeting NKG2D ligands by CAR T-cell therapy. Further clinical studies with NKG2D-based CAR T-cells are warranted, potentially via combinatorial antigen targeted approaches, to improve anti-tumour activity.

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