



Comment on: A novel dominant-negative PD-1 armored anti-CD19 CAR T cell is safe and effective against refractory/relapsed B cell lymphoma

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Cancer immunotherapy has made a revolution in cancer treatment, it works by enhancing patient's immune system against the tumor. Chimeric antigen receptor therapy (CAR-T) works to enhance T-cell. Patients undergo large volume leukapheresis to collect peripheral blood mononuclear cells, these T cells get CAR gene RNA through CAR-encoding viral vectors, then this RNA reverse-transcribed into DNA resulting in permanent CAR gene incorporation. This CAR gene is designed to recognize a specific tumor-associated antigen like CD-19. Eventually, these cells undergo *ex vivo* expansion, then transplant back to the patient [1,2]. This process takes about three weeks.

CAR-T therapy has shown very promising results, and it is already being used to treat multiple malignancies including lymphomas, leukaemias and multiple myeloma and so far, five CD19-targeting CAR-T cell products have been approved by FDA.

Multiple factors can lead to poor response to CAR-T therapy or disease relapse, like the poor proliferation of T cells and CD19 loss variants [3]. The new generation of CAR-T is being designed to overcome these obstacles. For example, engineering CAR-T cells that target more than one gene at the same time to overcome the loss of targeted antigen which has led to relapse, or targeting alternative antigens (other than CD-19), or engineering CAR-T to secrete IL-12, or using CRISPR technology for precise integration [1].

Another mechanism for CAR-T resistance is that some tumor cells express programmed death-ligand 1 (PD-L1) that suppress the proliferation and function of CAR-T cells by binding to PD1 receptor on CAR-T cells, so scientists have been trying to overcome this obstacle by administering T cell with PD-L1 antibody, using PD-1 blocking molecule or recently by engineering T cell to be PD-1 dominant negative receptor [4].

Liu et al. [5] for the first time reported the safety and efficacy of PD-1 modified CD19-CAR-T cells in refractory/relapsed B cell lymphoma in phase 1 clinical study. This is the first clinical study to evaluate the

dominant-negative PD-1 armored anti-CD19 CAR-T-cell. The study included nine patients with different refractory/relapsed B cell lymphomas who did not have prior CD19-targeted therapy or CAR-T-cell therapy; four patients had diffuse large B cell lymphomas (DLBCL), two patients had transformed follicular lymphomas (TFL), and three patients had follicular lymphomas (FL). Of these 9 patients, 3 had PD-L1 positive (>20%) on tumor cells and 6 had PD-L1 negative (range 0–10%) on tumor cells.

The primary endpoint of the study was the objective response rate (ORR) defined by complete remission (CR) and partial remission (PR). The secondary endpoints included duration of remission (DOR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs). The median follow-up time was 20 months (range: 13–24 months).

The authors examined the efficacy by measuring the overall response rate (ORR) and complete response (CR) rate by doing a positron emission tomography-computed tomography (PET-CT) scan 30 days after CD19-CAR-T-cell treatment. Of the nine patients included in the study, seven (77.8%) found to have an objective response at one month; two patients (22.2%) achieved CR, five (55.6%) achieved PR and two (22.2%) had stable disease then had progressive disease. Of the five patients who had PR in the first month; two patients achieved CR at three months, one patient achieved CR at six months and two patients had progressive disease. By the end, the ORR was 77.8% and CR was 55.6%.

The authors also evaluated the adverse events by checking the cytokine release syndrome (CRS) and neurotoxicity. Grade 1 CRS occurred in eight patients (88.9%) and grade 3 CRS occurred in one patient (11.1%). The severity of CRS was not attributed to the CD19-CAR-T-cell expansion because the patient who had grade 3 CRS did not have a higher CD19-CAR-T-cells expansion compared to other patients and patients who had peaks of CD19-CAR-T-cell counts only had CRS of grade 1.

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Only one patient, who had grade 3 CRS, had grade 1 neurotoxicity presented with encephalopathy, tremor, delirium, and restlessness, whereas the other patients did not experience any neurotoxicity symptoms.

The main limitations in this study were the lack of PFS and OS evaluation due to the short follow up duration by the time the study was reported. Secondly, there was no head-to-head comparison group of unmodified CD19-CAR-T-cell. Thirdly, the study was an open-label study without sample size calculation.

While other studies looked at different mechanisms to overcome the PD-1/PD-L1 inhibition pathway either by using PD-L1 antibodies in clinical trials or using genetically silenced PD-L1 tumor cells in animal-based trials [6,7], this study is the first clinical trial to evaluate the efficacy and safety of this new mechanism by engineering modified CAR-T-cells.

Based on the results, this study indicates that dominant-negative PD-1 armored anti-CD19 CAR-T-cell is effective in treating refractory B cell lymphoma on both PD-L1 positive and PD-L1 negative tumor and these modified CD19-CAR-T-cells may be an alternative option to avoid the CAR-T-cells exhaustion and the inhibition of CAR-T-cell expansion induced by PD-1/PD-L1 axis. However, to fully validate the efficacy and safety of this new mechanism, further clinical trials are needed with a larger number of patients and comparison groups. Overall, the study provides a very important and new method to enhance CAR-T-cell therapy in refractory/relapsed B cell lymphoma.

Declaration of Competing Interest

None.

Authors' Contribution

FB: wrote the manuscript and approved the final version.

ZM: wrote the manuscript and approved the final version.

FAA: revised the manuscript, edited the language and approved the final version.

MGK: wrote the manuscript, revised it and approved the final version.

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