BARCELONA 2024 ESMO congress

804MO

Gut microbiota composition is predictive of CAR-T cells response and its modulation enhances CAR-T cells activity

L. Marcos-Kovandzic[1], J. Rengassamy[2], G. Ferrere[3], J. Srikanthan[4], S. Durand[5], L. Derosa[6], C. Bigenwald[7], L. Zitvogel[7]

[1] Unité 1015, Gustave Roussy, Villejuif, France, [2] Hematology Department, Institut Gustave Roussy, Villejuif, France, [3] Everimmune, Gustave Roussy - Cancer Campus, Villejuif, France, [4] Hematology Department, Gustave Roussy, Villejuif, France, [5] Gustave Roussy - INSERM U1030, Villejuif, France, [6] Medical Oncology Department, Institut Gustave Roussy, Villejuif, France[7] U1015, Institut Gustave Roussy, Villejuif, France

Background

Nowadays, anti-CD19 CAR-T cells represent the standard treatment for refractory B-cell lymphoma. However, there is still a 50% non-response rate in aggressive lymphoma cases. Some factors, such as gut microbiota composition, can influence T cell function and therapeutic response, mainly studied in the setting of immune checkpoint blockade and recently demonstrated to impact the efficacy of CAR-T cells in pre-clinical models and patients.

Methods

We prospectively and longitudinally collected fecal material from patients receiving commercial anti-CD19 CAR-T cells at different time-points (PIONEER NCT04567446). With no difference in alpha and beta diversity, the patient's fecal samples at baseline revealed a distinct bacterial composition associated with response at 6 months, showing a higher prevalence of Akkermansia spp. amongst responders. Then, we validated the effect of this specific bacteria in treatment efficacy by using our fully immunocompetent B-cell lymphoma anti-CD19 CAR-T cell murine model.

Results

We observed a significant increase in overall survival and a higher anti-tumoral effect in the mice receiving the combination treatment of *Akkermansia spp.* + CAR-T. Moreover, the supplementation of *Akkermansia spp*. lead to a higher CAR-T infiltration in all explored organs and tumors, highlighting a significant higher early infiltration in the bone marrow, indicating the relevance of this compartment at early treatment stages. The infiltrating CAR-T cells had a higher cytotoxic phenotype (CD8+CD44hiCD62 low) and higher IFNγ production when *Akkermansia spp*. was added. Moreover, the increased cytotoxic T cell effector function seems to occur via the aryl-hydrocarbon receptor on T cells, as suggested by the in vivo use of AhR agonists and AhR KO CAR-T cells in our experimental settings. Finally, the activation of this receptor via the administration of *Akkermansia spp*., could be through certain metabolites (e.g. indoles), exclusively produced by the gut microbiota.

Conclusions

This suggests that a favorable microbiota is associated with a better response to CAR-T cell therapy in B-cell malignancies and restoring this favorable microbiota by supplementing *Akkermansia spp*. may improve the response to treatment.

Clinical trial identification

PIONEER NCT04567446.

Legal entity responsible for the study

Institut Gustave Roussy.

Funding

European H2020 Marie Skłodowska-Curie Program.

Disclosure

All authors have declared no conflicts of interest.