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ORAL ABSTRACTS

703.CELLULAR IMMUNOTHERAPIES: BASIC AND TRANSLATIONAL

High Levels of Circulating Granulocytic Myeloid-Derived Suppressor Cells (G-MDSCs) Predict Failure of CD19-Targeting CAR-T Cell Therapy

Eugenio Galli[1], *Alessandra Battaglia*[2], *Marco Fossati*[3], *Ilaria Pansini*[4], *Silvia Bellesi*[5], *Alexia Buzzonetti*[3], *Nicole Zampetti*[3], *Stefan Hohaus*[5,4], *Andrea Bacigalupo, MD*[5], *Patrizia Chiusolo*[5,4], *Simona Sica*[4,5], *Andrea Fattorossi*[3], *Federica Sorà, MD*[5,4]

[1] Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy
[2] Dipartimento di Scienze della vita e sanità pubblica, Università Cattolica del Sacro Cuore, Rome, Italy
[3] Cytometry Facility, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[4] Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Rome, Italy
[5] Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Background

The mechanisms of resistance to CAR-T cell therapy may depend on the physical and biological characteristics of the tumor itself, on CAR-T cells in terms of efficiency and fitness, or on the microenvironment. Myeloid-derived suppressor cells (MDSCs) play a crucial role in hematological tumors, promoting immunosuppression and tumor progression. Their presence hampers the anti-tumor immune response, posing challenges for effective therapeutic interventions. The predictive role of myeloid-derived suppressor cells (MDSCs) of monocytic and granulocytic origin (M-MDSCs and G-MDSCs, respectively) in the context of CAR-T cell therapy is largely unknown.

Aim and methods

Our aim was to quantify circulating M-MDSC and G-MDSC in patients (n=26) receiving approved CAR-T cell products for high-grade B cell lymphoma or acute lymphoblastic leukemia.

Whole blood samples were collected at enrolment (time point 1), after leukapheresis (time point 2) and just after Cy/Flu lymphodepletion (time point 3). Stringent criteria for multicolour flow cytometry identification of M-MDSC (CD14/HLA-DR/CD124/CD11b/CD45 and light scattering) and G-MDSC (CD15/CD11b/CD66b/oxidized low-density lipoprotein receptor -1, LOX-1, /CD45 and light scattering) were used. Blood samples were examined immediately after collection to prevent artefactual G-MDSC changes.

Results

M-MDSC number, although very variable between patients, remained essentially constant from time point 1 to time point 3 in each individual (range 1.2-947 cells/ml at the latest time point) and was not associated with a higher risk of relapse.

Conversely, G-MDSC number, which was extremely low at time points 1 and 2, markedly increased at time point 3 (range 1.5-85.5 cells/ml). According to our preliminary data, at time point 3, mean G-MDSC were 39.3, 44.5, and 12.3 cells/ml in tisacel, axi-cel and brexu-cel, respectively. Mean G-MDSC were significantly lower in patients treated to receive brexu-cel (Figure 1). Responses were evaluated one, three, and six months after receiving CAR-T cells infusion. As we aimed at finding if G-MDSC could predict prognosis, we set a cut-off value of 30 G-MDSC/ml at time-point 3 (immediately after the completion of lymphodepletion); overall, approximately 35% of the patients had G-MDSC >30/ml at that moment. Kaplan-Meier survival analysis revealed that G-MDSC >30/ml at time point 3 associated with a higher risk of relapse, with a PFS of 80% vs 10% six months after CAR-T infusion (p= 0.0002) (Figure 1).

The sudden appearance of G-MDSC following the lymphodepletion is likely to reflect emergency granulopoiesis that favors an increased release of G-MDSC to the bloodstream and may be ideally customized with a tailored lymphodepletion.

Conclusion

In conclusion, here we show that the high circulating levels of G-MDSC induced by the lymphodepletion are associated with a lack of response to CAR-T cell therapy, thus representing a promising predictive biomarker of CAR-T cell therapy efficacy and possibly a hypothetical point of intervention for ameliorating CAR-T efficacy.

Disclosures No relevant conflicts of interest to declare.

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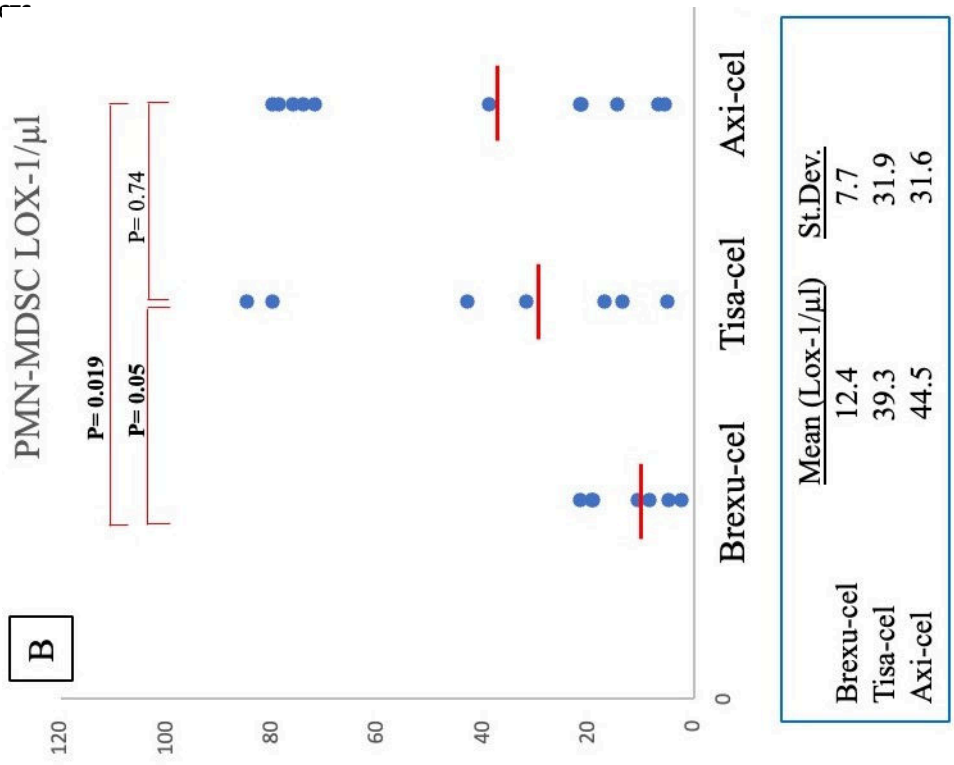

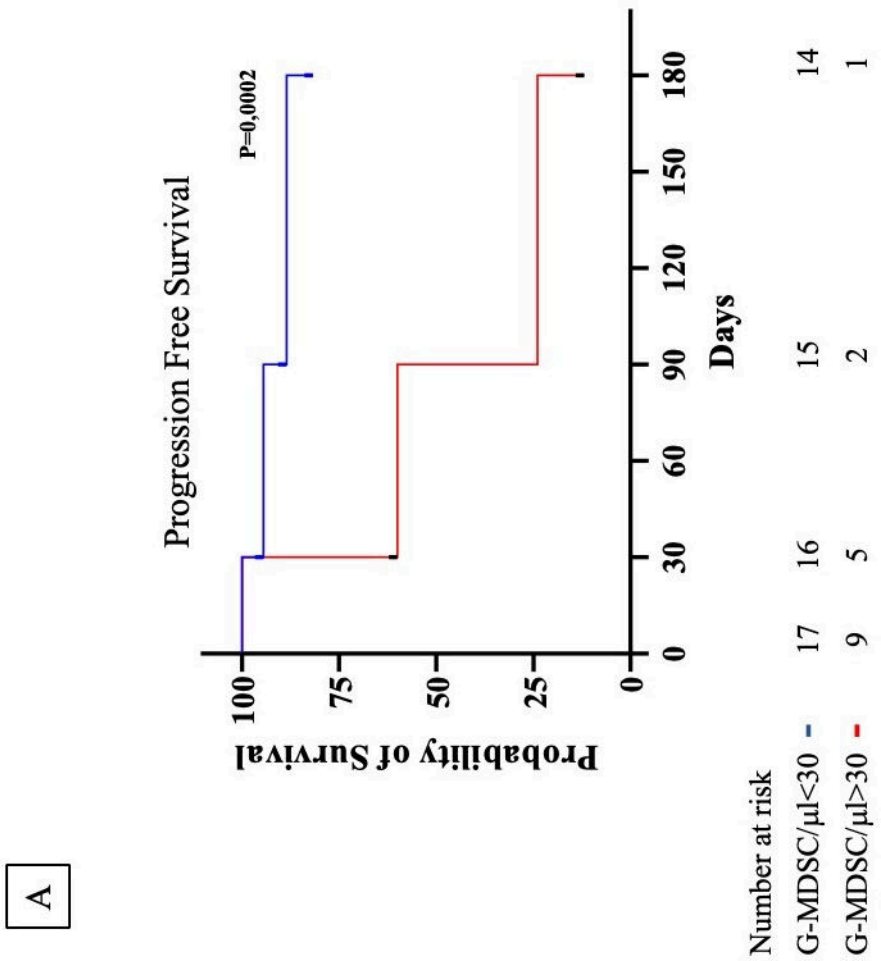

Figure 1