Immunological age predicts clinical outcomes in older patients with multiple myeloma

Wassilis S.C. Bruins[1,2], Febe Smits[1-3], Carolien Duetz[1,2], Kaz Groen[1,2], Charlotte Korst[1,2], A. Vera de Jonge[1,2], Christie P.M. Verkleij[1,2], Rosa Rentenaar[1,2], Meliha Cosovic[1,2], Merve Eken[1,2], Inoka Twickler[1,2], Paola M. Homan-Weert[1,2], Pieter Sonneveld[4], Philippe Moreau[5], Jürgen Claesen[6], Niels W.C.J. van de Donk[1,2], Sonja Zweegman[1,2], Tuna Mutis[1,2]

[1]Amsterdam UMC location Vrije Universiteit Amsterdam, Hematology, De Boelelaan 1117, Amsterdam, Netherlands;

[2]Cancer Center Amsterdam, Cancer Biology and Immunology, Amsterdam, Netherlands;

[3]Department of Hematology, Haga Hospital, The Hague, Netherlands;

[4]Department of Hematology, EMN/Erasmus MC Cancer Institute, Rotterdam, Netherlands;

[5]Hematology Department, University Hospital Hôtel-Dieu, Nantes, France;

[6]Amsterdam UMC location Vrije Universiteit Amsterdam, Epidemiology and Data Science, De Boelelaan 1117, Amsterdam, Netherlands.

Background

Immunotherapy has transformed the treatment landscape of multiple myeloma (MM), a hematological cancer predominantly affecting older individuals. We here explored the impact of aging on the immune system of MM patients and assessed whether immunological aging predicts clinical outcomes.

Methods

We conducted comprehensive immune profiling of T-cells and NK-cells in peripheral blood (PB) and bone marrow (BM) samples from 124 older (median age 77; range 67-92 years) and 145 younger (median age 58; range 34-65 years) newly diagnosed patients enrolled in the HOVON-143 and CASSIOPEIA/HOVON-131 clinical trials. Computational data clustering was performed using the unsupervised clustering algorithm FlowSOM. To assess immunological age at the individual patient level, a LASSO-regularized machine learning model (immunological clock) was trained on high-dimensional phenotypic T-cell data using cross validation. Associations between immunological age and survival outcomes progression-free survival (PFS), progression-free survival on second line therapy (PFS2) and overall survival (OS) were assessed in the HOVON-143 trial using Kaplan-Meier and Cox regression analysis.

Results

At the group level, older patients displayed a more activated, differentiated and senescent T-cell compartment than younger patients in both PB and BM. More specifically, older patients exhibited a

higher $CD4^+$:$CD8^+$ ratio; increased frequencies of Tregs and activated $CD4^+$ - or $CD8^+$ T-cells; decreased frequencies of naive $CD8^+$ T-cells; and increased frequencies of effector memory $CD8^+$ T-cells re-expressing CD45RA (TEMRA) and senescent $CD8^+$ T-cells in both PB and BM. In addition, older patients had higher frequencies of $TIGIT^+CD8^+$ T-cells in PB, as well as LAG-3^+CD4^+ and LAG-3^+CD8^+ T-cells in BM. The impact of aging on the NK-cell compartment was minimal. Given the notable inter-individual variation in immune cell frequencies, we calculated the immunological age of individual patients using an immunological clock and discovered widely divergent immunological ages among patients of similar chronological age. Importantly, immunological age, rather than chronological age, showed significant association with PFS (HR 1.02, 95% CI 1.00-1.04, p = 0.048), PFS2 (1.03, 95% CI 1.01-1.06, p = 0.004) and OS (HR 1.04, 95% CI 1.01-1.06, p = 0.006) in older newly diagnosed patients receiving daratumumab-based therapy, even after adjusting for established risk factors such as WHO performance status, ISS stage, and IMWG frailty status.

Conclusion

We have demonstrated the feasibility of measuring immunological age in individual MM patients using high-dimensional T-cell data. Our findings furthermore underscore the potential of assessing immunological age as a composite measure of immune fitness to predict immunotherapy outcomes in MM. We propose further development of this methodology to improve predictions of immunotherapy outcomes in MM and other hematological cancers.