ELSEVIER

Blood 142 (2023) 6602–6603

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Senescent Immune Signature in Frail and Vulnerable Newly Diagnosed Myeloma Patients: A Cohort Analysis from the UK-MRA Myeloma XIV Fitness Study

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Introduction
Physical frailty is a key factor driving treatment tolerability and outcome in multiple myeloma (MM). There is a close interplay between physiological aging, frailty and immune dysfunction, with the presence of a malignant disease overlay adding an additional dimension to the host response biology. The UKMRA Myeloma XIV FiTNEss study is the first phase 3 randomised clinical trial to explore the utilisation of frailty assessment as a tool to guide and optimise treatment decision making and deliverability. Here we report on the relationship between physical frailty and T cell dysfunction in a cohort of patients within this landmark study.
Methods
Multiparameter flow cytometry was used to assess the baseline T cell phenotype in the peripheral blood of 49 participants with NDMM receiving treatment within FiTNEss. Patients were assessed for frailty using the IMWG frailty score and additionally assessed for clinical vulnerability using the UKMRA MRP score (Cook et al, Lancet Haematol. 2019). The IMWG frailty score combines activities of daily living assessment and co-morbidity burden with age to generate a validated, prognostic frailty score. The UKMRA MRP is a risk profile which uses routinely collected clinical data including age, WHO performance status, ISS stage and CRP to define prognostic risk categories with the high-risk category encompassing frailer individuals. Normal T cell subsets were assessed based on CD45RA and CD28 phenotype while dysfunctional subsets (exhausted and senescent) were defined using CD28 and KLRG1.
Results
The median age of participants was 79 (range 68-90) and 55% were male. The distribution by IMWG was fit 18%, unfit 33%, frail 49% and by MRP was low risk 31%, intermediate risk 28%, high risk 38%. Absolute lymphocyte count (ALC) decreased with increasing frailty (p=0.02), with no patients classified as fit by IMWG or low risk by MRP criteria having a lymphocyte count below the lower limit of normal. No relationship was seen between ALC and age. The ratio remained stable across the IMWG cohorts, suggesting a global reduction in lymphocyte subsets. An accumulation of CD8 TEMRA cells was seen in the MRP high risk cohort (p=0.0085). No differences were seen between cohorts based on the IMWG frailty score. The accumulation of CD8 TEMRA cells indicates a loss of T cell differentiation plasticity and is associated with a cytotoxic and pro-inflammatory immune response.
CD4 dysfunctional subsets were comparable across the cohorts. CD8 dysfunctional subsets were most marked in the frail and high-risk cohorts. The MRP high-risk cohort had a skewed ratio of exhausted to senescent cells (p=0.02), with a reduction in CD8 exhausted populations compared to the fit and unfit cohorts (p=0.0477) and a trend towards increased senescent cell

burden (p=0.07). This was echoed within the IMWG frail cohort where elevated numbers of senescent CD8 cells were identified (p=0.02). No relationship was seen between CD8 senescent burden and age, CRP, ISS or WHO PS when each variable was assessed independently, suggesting that the presence of this immune population is not directly related to disease burden or physiological aging alone, but reflects a more complex interplay between host response biology and disease characteristics. Principal component analysis demonstrated a high degree of immunological heterogeneity within the MRP low and intermediate risks cohorts, while the high-risk cohort had a more uniform immunological profile (Figure 1A). Significant overlap between a proportion of the non-high-risk cohorts and high-risk cohorts was seen and requires further exploration. A multivariable correlation analysis identified correlations between the CD4:8 ratio and CD8 cell senescent burden, MRP and ISS, highlighting the important interplay between immunological dysfunction, clinical vulnerability and disease burden (Figure 1B).

Conclusion

The T cell immunological landscape of the most vulnerable patient populations with newly diagnosed MM is characterised by an accumulation of senescent CD8 T cells which cannot be attributed to age or disease burden alone. Immune senescence is known to be associated with a chronic inflammatory state which may drive the acquisition of the physiological changes, such as sarcopenia, which characterise a frailty phenotype. This provides an opportunity for targeted intervention to address the biological drivers of disease related frailty.

Disclosures Seymour: *Takeda:* Honoraria; *Novartis:* Speakers Bureau; *Kite-Gilead:* Speakers Bureau; *Janssen:* Speakers Bureau. **Parrish:** *Takeda:* Honoraria, Speakers Bureau; *Janssen:* Speakers Bureau; *Jazz:* Speakers Bureau; *Gilead:* Honoraria; *Novartis:* Honoraria, Speakers Bureau; *BMS Celgene:* Consultancy, Speakers Bureau; *Everything Genetic:* Consultancy; *Abbvie:* Consultancy, Speakers Bureau; *Sanofi:* Consultancy, Speakers Bureau. **Cairns:** *Sanofi:* Research Funding; *Celgene BMS:* Honoraria, Research Funding; *Amgen:* Research Funding; *Janssen:* Honoraria; *Takeda:* Research Funding. **Pawlyn:** *Takeda:* Honoraria; *Sanofi:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy, Honoraria; *Amgen:* Honoraria; *BMS/Celgene:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *GSK:* Honoraria; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Jackson:** *Sanofi:* Consultancy, Honoraria, Speakers Bureau; *Oncopeptides:* Consultancy; *GSK:* Consultancy, Honoraria, Research Funding; *Pfizer:* Consultancy, Honoraria; *J&J:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Takeda:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Celgene BMS:* Consultancy, Honoraria, Speakers Bureau. **Cook:** *Janssen:* Consultancy, Research Funding; *Karyopharma:* Consultancy; *Takeda:* Consultancy, Research Funding; *BMS:* Consultancy, Research Funding; *Amgen:* Consultancy; *Sanofi:* Consultancy.

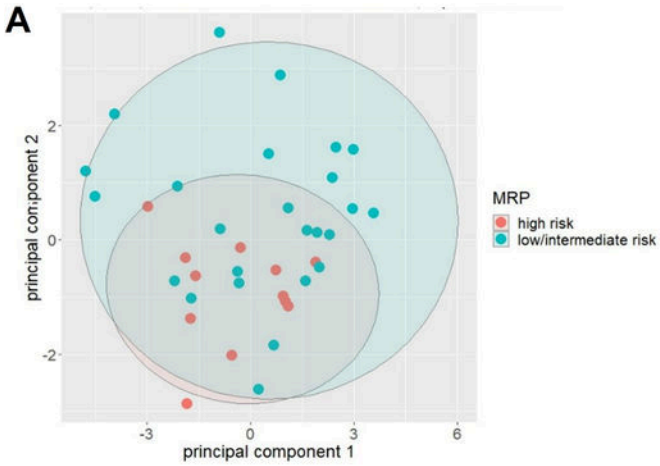

Figure 1A: Principal component analysis incorporating absolute lymphocyte count and T cell subsets (based on CD4, CD8, KLRG1, CD28, CD45RA expression). Ellipses show 95% CI.

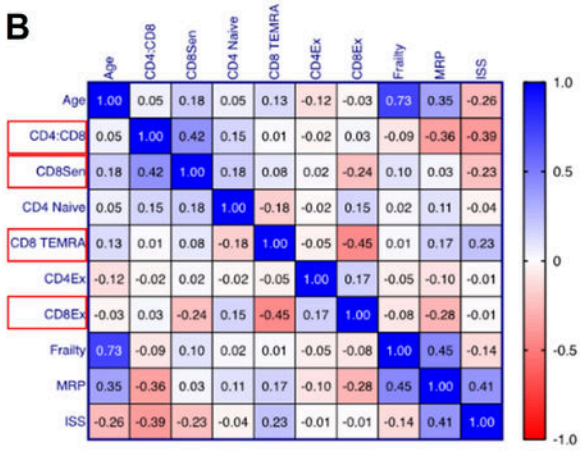

Figure 1B: Multi-variables correlation

Figure 1

https://doi.org/10.1182/blood-2023-184553