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POSTER ABSTRACTS

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

Immune Profiling of Newly Diagnosed Multiple Myeloma (NDMM) Treated with Quadruplet Induction and Autologous Stem Cell Transplantation (ASCT) and Comparison with Achievement of Minimal Residual Disease (MRD) Negativity

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Background

Incorporation of anti-CD38 monoclonal antibodies (mAb) to the triplet backbone of proteasome inhibitor, immunomodulatory agent and corticosteroid has resulted in unprecedented depth of response including MRD negativity in transplant eligible NDMM. While numerous immunological mechanisms of modern quadruplet combinations are proposed, the modulation of the immunoprofiles bone marrow (BM) and peripheral blood (PB) with quadruplet therapy and ASCT are unknown. The baseline as well as longitudinal study of the composition and functionality of the immune microenvironment with treatment may have implications on disease response.

Methods

We prospectively collected clinically annotated patient (pt) samples from a phase II single institution clinical trial in transplant eligible NDMM (NCT04991103). Pts received quadruplet combination with daratumumab, bortezomib, lenalidomide and dexamethasone for six cycles followed by MRD adapted deferral of ASCT for pts who achieved MRD<10^{-5}. Pts deferring ASCT received three additional cycles of consolidation followed by maintenance. Pts who did not meet threshold for ASCT deferral received ASCT followed by maintenance therapy per protocol. We collected paired PB and BM samples at the time of screening (SCN), post-induction (I), and post-consolidation/ASCT (C). We purified and biobanked viable PB mononuclear cells (PBMCs). We thawed PBMCs, treated with FcR blocking Ab, stained with fluorochrome-labeled antibodies and a live/dead fixable stain, and then analyzed using the FACSymphony A5 SE flow cytometer. We identified immune cell subsets in PBMCs using FlowJo v10.2. We report data as percentage of each population within total live PBMCs.

Results

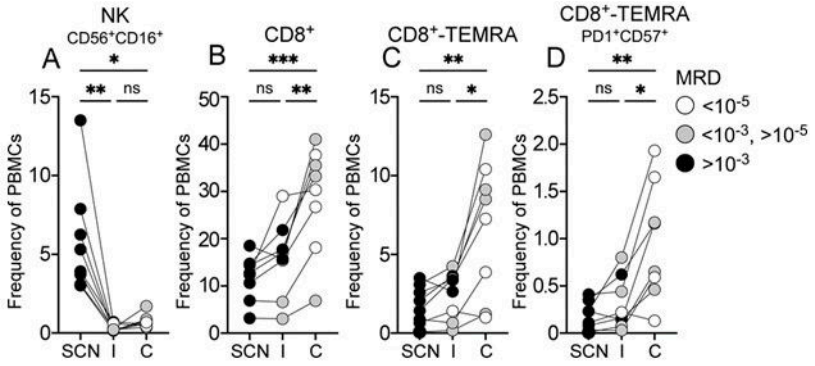
We collected 48 samples from 8 pts at three timepoints (SCN, I and C) and performed initial immunophenotyping analysis on the PBMCs. We observed no significant changes over time in the frequencies of peripheral CD45^{+}, CD3^{+}, NK T cells, monocytes or dendritic cells (not shown). We noted decreased frequencies of multiple B cell subsets, including naïve, transitional, memory and double negative cells (not shown), as well as CD56^{+}CD16^{+} NK cells (Fig. panel A) post-induction with no recovery following consolidation **.** While the frequencies of CD3^{+} T cells did not change with time, we observed a shift in the CD4:CD8 ratio, with an increase in the proportion of CD8^{+} T cells post-consolidation (Fig. panel B). Within the post-consolidation CD8^{+} T cell compartment, we noted increased frequencies of cells that presented with senescent (PD1^{neg}CD57^{+}), exhausted (PD1^{+}CD57^{neg}) or anergic (PD1^{+}CD57^{+}) profiles. Consistent with this, the frequencies of terminally differentiated effector memory cells re-expressing CD45RA (TEMRA) CD8^{+} T cells increased at consolidation (Fig. panel C) and many of these cells exhibited an anergic profile (CD57^{+}PD1^{+}, Fig. panel D).

Comparison of the baseline immune profiles and MRD levels post-induction revealed that the pt attaining MRD<10^{-5} had the highest frequency of-NK cells as well as proportionally higher T_{CM}/T_{EM} and lower TEMRA/T_{Naive} cells at diagnosis. This subject was able to defer ASCT per protocol and subsequently exhibited the lowest frequency of CD8^{+} TEMRA with an anergic phenotype (PD1^{+}CD57^{+}) post quadruplet consolidation. The subject with the least response to quadruplet induction and highest MRD post-induction had a high proportion of CD8^{+} T cells with an exhausted phenotype (PD1^{+}CD57^{neg}) at screening.

Conclusion

This is the first longitudinal analysis comparing MRD levels to the immune profiles of PB and BM cells derived from a cohort of NDMM patients prospectively treated with quadruplet induction and ASCT. We conclude that quadruplet induction negatively affects the NK cell and B cell compartment during induction and these compartments do not rapidly recover in the immediate post-transplant period. ASCT post quadruplet therapy is associated with preferential expansion of the effector CD8 $^{+}$ T cell compartments, including terminally differentiated TEMRA cells, which express markers associated with T cell exhaustion and anergy. Additional studies evaluating BM immune profile and T cell exhaustion are ongoing and shown at the meeting.

Disclosures Bal: *Bristol Myers Squibb:* Consultancy; *Janssen:* Consultancy; *AbbVie:* Consultancy; *Astrazeneca:* Consultancy; *Adaptive Biotechnology:* Consultancy; *MJH Lifesciences:* Other: Educational content development ; *Amyloid Foundation:* Research Funding; *Fate Therapeutics:* Research Funding; *Beigene:* Research Funding. **Costa:** *Janssen:* Consultancy, Honoraria, Research Funding; *Pfizer:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria, Research Funding; *Genentech:* Research Funding; *Adaptive biotechnologies:* Consultancy, Honoraria; *AbbVie:* Honoraria, Research Funding; *BMS:* Consultancy, Honoraria, Research Funding.



Phenotypic changes in CD8 T cell and NK cell compartments in PB of NDMM patients prospectively treated with quadruplet induction and ASCT. Flow cytometric analysis of PBMCs collected from 8 NDMM patients at the time of diagnosis (SCN), post-quadruplet induction (I) and following consolidation (C) with either ASCT (n=7) or 3 additional rounds of quadruplet therapy (n=1). The frequencies of $CD56^{-}CD16^{-}$ NK cells (**A**), $CD3^{-}CD8^{-}$ T cells (**B**), $CD3^{-}CD8^{-}CCR7^{neg}CD45RA^{-}$ TEMRA (**C**) and $PD1^{+}CD57^{-}$ TEMRA (**D**) cells at each timepoint are shown and reported as frequencies within the total PBMC compartment. Symbol and lines show changes in cell populations in each patient over time. Symbol color depicts MRD levels (black $>10^{-3}$, white $<10^{-5}$, grey $MRD>10^{-5}$-$MRD<10^{-3}$) for each patient at each timepoint.

Figure 1

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