Pre-clinical translational studies of daratumumab in patients with myeloma or AL amyloidosis undergoing autologous hematopoietic stem cell transplantation (SCT)

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Background

- Clinical studies (GEN501 and MMY2002) of daratumumab (DARA) are in progress but its utility in conjunction with SCT has not been investigated.
- DARA is a human IgG1κ mAb that binds to a unique epitope in transmembrane glycoprotein receptor CD38 and kills tumor cells expressing CD38 through immune-mediated cytotoxicity (de Weers 2011, Overdijk 2013)
- CD38 is expressed on plasma cells in MM, AL and on myeloid progenitor cells (Drach 1994, Randall 1996)
- SCT remains a standard therapy for MM and AL. Thus, it is important to evaluate the effect of DARA on hematopoietic stem and progenitor cells (HPC).
- Ability of DARA to induce complement dependent cytotoxicity (CDC) of HPC was assessed in progenitor cell assay (PCA). DARA-mediated antibody-dependent cytotoxicity (ADCC) of HPC, its correlation with FcγRIIIA polymorphism and stem cell potential were examined using NK cells from post-SCT patients (N = 10, n = 6 MM and n = 4 AL) as effectors against a MM.1S target cell line

Materials & Methods

- We performed an IRB-approved clinical study with cells from MM and AL patients undergoing stem cell mobilization and collection for SCT
- With unselected and CD34 selected blood HHP, we assessed the effects of DARA on progenitor cell colony formation
- Using peripheral blood MNC at 3 weeks post-SCT, we quantitated CD3-/CD56+/CD16+ NK cells
- We performed ADCC using human myeloma MM.1S cells as targets (T) and patient NK cells as effectors (E) with E:T ratio of 10:1 in the presence of 100 ng/ml DARA or isotype control antibody
- We also performed PCR-based analysis of FcγRIIIA polymorphisms in each patient and correlated the specific lysis in ADCC with FCγRIIIA variants

Results

Figure 1. CD34+ Cells are CD38+

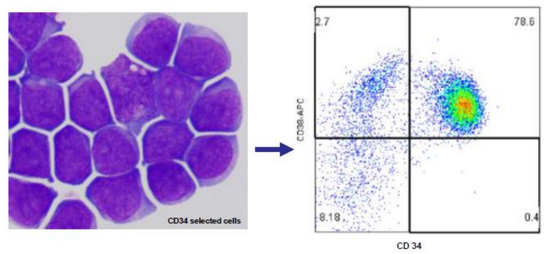


Figure 2. Progenitor cell assays with DARA or isotype control

Figure 3. Unselected mobilized peripheral blood progenitor cells (N=3)

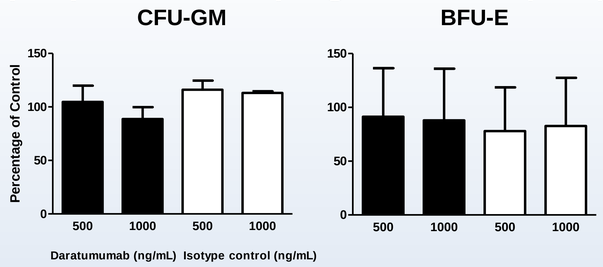
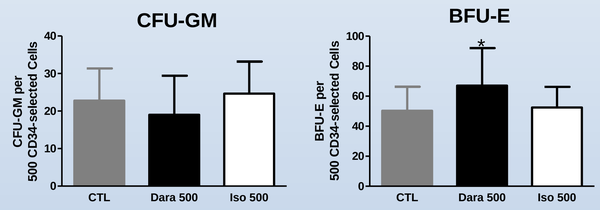
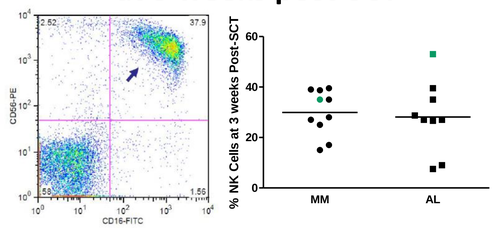


Figure 4. CD34+ mobilized peripheral blood progenitor cells (N=3)



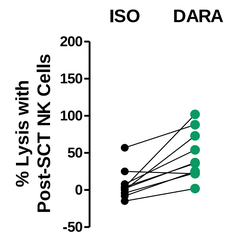
For these assays, fresh CD34-selected cells were incubated in complement-rich human serum with no antibody, DARA or isotype control for 1 hour and then plated directly in semisolid medium. For unclear reasons there were significantly more BFU-E (*) in plates with DARA than either control.

Figure 5. NK cells are increased at 3 weeks post-SCT



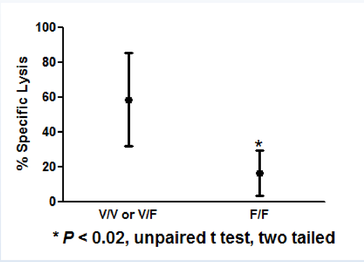
NK cell are identified by flow cytometry (arrow, left) and are maximum at the time of bone marrow recovery post-SCT,representing about 30% of peripheral blood mononuclear cells compared to about 10% at baseline.

Figure 6. ADCC assays with DARA



In ADCC assays with DARA at 100ng/mk and patient NK cells as effectors and MM.1S cells as targets at a 10:1 E:T ratio, average lysis was 40% compared to control. The individual assay results are shown (n=10).

Figure 7. *FCGR3A* (V158F) polymorphisms affect DARA ADCC



Conclusions

- DARA did not inhibit mobilized blood CD34+ progenitor cell growth
- DARA is active in ADCC assays with post-SCT NK cells from patients with MM or AL
- Activity of DARA correlates with the *FCGR3A-158V/F* polymorphism
- These findings support consideration of clinical trials of DARA post-SCT in MM and AL

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