MultipleMyelomaHub

General MM

The effect of daratumumab on immune cell repertoire: depletion of CD38+ immune regulatory cells and T cell expansion

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In July 2016, Krejcik J. and colleagues from the Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands, along with collaborators at Janssen Biotech (Belgium and USA) and The Abramson Cancer Center, University of Pennsylvania, USA published a paper in Blood, which describes the effect of daratumumab (humanized IgG1 anti-CD38 monoclonal antibody) on the immune cell repertoire of Multiple Myeloma (MM) patients enrolled in two clinical trials.

Key Highlights

- Patients (pts) enrolled in two concurrent clinical trials were evaluated:
  - GEN501 (#NCT00574288) (n=42): phase 1/2 dose-escalation and dose-expansion study, patients had documented MM and had relapsed from or were refractory to ≥2 prior therapies
  - SIRIUS (#NCT01985126) (n=106): phase 2 study, pts had received >3 prior therapies, including a PI or an IMiD, or were refractory to both classes of agents
- Pt population was heavily pretreated: 76% received >3 prior lines of therapy, 91% were refractory to their last line of treatment, and 86% were refractory to both a PI and an IMiD

Daratumumab effect on regulatory cells expressing CD38:

- CD38 highly expressed on MM plasma cells, natural killer (NK) cells, monocytes, B cells, and T cells in PBMCs of both healthy donors and MM pts
- NK cells expressed highest levels of CD38, followed by subpopulations of B and T cells
- Co-cultured myeloid-derived suppressor cells (gMDSCs - (CD11b1CD14– HLA– DR– CD151CD331) were sensitive to daratumumab antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) *vs* isotype control
- Regulatory B cells (Bregs) in treated pts (n=16) produced IL-10, and were depleted following first dose of daratumumab (P= 0.0018, week 1), then remained low during treatment
- Novel subpopulation (10 ± 10%) of peripheral Tregs ($CD4^+CD25^+CD127^{dim}$) expressed high levels of CD38 prior to activation and were highly sensitive to treatment, with a significant decline following first dose and remained low throughout treatment: n=17 pts; P = 8.88×10^{-16}, 1.11×10^{-15}, and 1.50×10^{-11} at wks 1, 4, and 8, respectively, *vs* baseline
- $CD38^+$ Tregs suppressed proliferation of effector cells more effectively than $CD38^-$ Tregs

Daratumumab effect on helper and cytotoxic T cells:

- Significant increase in absolute count of PB total subsets (daratumumab 16-mg/mg treatment, on log scale per 100 days):
  - $CD3^+$ T cells: 0.16; 95% CI 0.14-0.19; ~44% average increase
  - $CD4^+$ T cells: 0.12; 95% CI 0.1- 0.14; 32% average increase
  - $CD8^+$T cells: 0.21; 95% CI 0.17-0.25), 62% average increase
- Ratios of CD8+:CD4+ and CD8+:Treg at weeks 8 and 16 of treatment and at week 12 ± 1 cycle increased significantly over time in PB and BM with daratumumab treatment; no significant differences were observed between responders and non-responders, except higher CD8+:Treg ratio at wk 8 in responders (P=0.00955)
- Overall reduction in PB Tregs likely to account for reduction in $CD38^+$ Tregs in response to daratumumab, rather than downregulation of CD38 expression
- Median max % increase in total CD3+, CD4+, and CD8+ T-cell counts in responders (n = 45) *vs* non-responders (n = 93): 86.76% *vs* 35.44% (P = 0.00012); 56.16% *vs* 26.97% (P = 0.00031), and 111.99% *vs* 42.5% (P = 0.00018), respectively

Other effects observed in daratumumab-treated patients:

- Significant increase in IFN-g secretion in response to viral and alloantigens; (n = 7) pts with a PR or better compared to baseline
- Increased proliferative capacity of virus-reactive T cells
- Increased TCR clonality in majority of pts (14 of 17 = 82%; P = 0.0056); this positively correlated with an increase in CD8+ T cells (Pearson's r = 0.76)
- Significant increase in Change in Abundance (CIA) for each expanded T-cell clone: P = 0.037; maximum CIA of individual clones: P = 0.048; significantly higher than in non-responders

Daratumumab was approved by the FDA in November 2015, after highly promising data from the SIRIUS clinical trial (see previous MMHub article). In this study, broad immunomodulatory effects of daratumumab in heavily pre-treated patients with relapsed and refractory MM are described. Specifically, daratumumab depleted the number of CD38+ immunosuppressive regulatory T and B cells and myeloid derived suppressor cells. In addition, an improved adaptive immune response was observed via activation of cytotoxic T cells and increased T cell clonality. The next step will be validation of direct anti-tumor effects.

Abstract

Daratumumab targets CD38-expressing myeloma cells through a variety of immune-mediated mechanisms (complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis) and direct apoptosis with crosslinking. These mechanisms may also target nonplasma cells that express CD38, which prompted evaluation of daratumumab's effects on CD38-positive immune subpopulations. Peripheral blood (PB) and bone marrow (BM) from patients with relapsed/refractory myeloma from 2 daratumumab monotherapy studies were analyzed before and during therapy and at relapse. Regulatory B cells and myeloid-derived suppressor cells, previously shown to express CD38, were evaluated for immunosuppressive activity and daratumumab sensitivity in the myeloma setting. A novel subpopulation of regulatory T cells (Tregs) expressing CD38 was identified. These Tregs were more immunosuppressive in vitro than CD38-negative Tregs and were reduced in daratumumab-treated patients. In parallel,

daratumumab induced robust increases in helper and cytotoxic T-cell absolute counts. In PB and BM, daratumumab induced significant increases in CD8(+):CD4(+) and CD8(+):Treg ratios, and increased memory T cells while decreasing naïve T cells. The majority of patients demonstrated these broad T-cell changes, although patients with a partial response or better showed greater maximum effector and helper T-cell increases, elevated antiviral and alloreactive functional responses, and significantly greater increases in T-cell clonality as measured by T-cell receptor (TCR) sequencing. Increased TCR clonality positively correlated with increased CD8(+) PB T-cell counts. Depletion of CD38(+) immunosuppressive cells, which is associated with an increase in T-helper cells, cytotoxic T cells, T-cell functional response, and TCR clonality, represents possible additional mechanisms of action for daratumumab and deserves further exploration.

References

1. Krejcik J. *et al.* Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood, 2016 Jul 21;128(3):384-94. DOI: 10.1182/blood-2015-12-687749. Epub 2016 May 24.
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