CD38: From positive to negative after Daratumumab treatment.

Case report.

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Abstract

A 63 years-old male patient diagnosed with relapsed / refractory multiple myeloma who requires Daratumumab as a part of treatment in the eighth line of management. The flow cytometry showed 63.5% of Plasma Cells with expression of CD38+.

Daratumumab + Lenalidomide + Dexamethasone regimen was ordered. After 4 cycles of treatment, an evaluation of response was performed and documented partial response. Nevertheless, flow cytometry revealed 4.8% of abnormal Plasma Cells in bone marrow CD38 Negative.

Regardless of the negative expression of CD38, the optimal response was continuously evident with daratumumab. A cessation of 6 months was required, but the response to daratumumab was sustainable again after restarting the medication.

Background

Daratumumab produces a direct apoptotic mechanism against multiple myeloma cells by binding to CD38 marker (1-3).

The CD38 expression on multiple myeloma cells has been considered as a factor of response to Daratumumab. Nevertheless, a wide spectrum of clinical responses after this treatment have not been demonstrated only by CD38 expression (4).

Objective

To describe a case of negativization of CD38 plasma cell (PC) marker after Daratumumab treatment, keeping the response even with an interruption of 6 months and posterior restarting.

Case Description

A 63 years-old male patient was diagnosed with IgA Kappa Multiple myeloma and treated in 2011 with PAD regimen as a front line. Complete response and posterior consolidation with Autologous stem cell transplant. He relapsed two years after ASCT. Several rescue treatments were given without any response: Rd, CyBorD, Kd, Cyclophosphamide+ Dexamethasone, VRD.

Flow Cytometry showed 63.5% of PC with expression of CD38+ (CD38/CD138=63.5% and CD38/CD56 = 63.5%), CD138, CD56, Beta-2 microglobulin, cytoplasmic kappa light chain.

Fig 1. Flow cytometry showed 63,5% of myeloma cells (red events)

Afterwards, a Daratumumab + Lenalidomide + Dexamethasone regimen was initiated. Partial response was documented. Nevertheless, flow cytometry documented 2,9% of abnormal PC in bone marrow CD38 Negative (CD38neg/CD138pos = 4.8%, CD38neg/CD56 = 4.8%). CD138+, CD56+, Beta-2 microglobulin, cytoplasmic kappa light chain. CD19 negative, CD45 Negative (Fig 2).

Fig 2. Flow cytometry showed 2,9% of myeloma cells (red events), CD38 negative

Due to the sustained clinical and biochemical response Daratumumab was continued. However, the patient suffered severe pneumonia requiring management in Intensive Care Unit. Daratumumab was interrupted. Pomalidomide + Cyclophosphamide + Dexamethasone was ordered but it was not authorized by the health insurance.

Six months after daratumumab was ceased, the patient presented progression with M-protein raising up and new bone lesions. After multidisciplinary consideration daratumumab was restarted with the same intensity of the cycle 1 according to the POLLUX protocol with antibiotic prophylaxis. CD38 was detected weak to negative expression by flow cytometry on bone marrow aspirate.

Clinical improving was documented early and the IgA levels reduced by 56% after just one cycle. (Fig 3)

IgA Levels

Fig 3. Levels of IgA in mg/dL

Discussion

Daratumumab activates cytotoxic immune effector, antibody-dependent cellular cytotoxicity, phagocytosis mediated by antibodies, and cytotoxicity through complement. In addition, it modulates CD38 enzyme activity diminishing adenosine levels (which normally produces immunosuppressive action), improving immune response against tumor (1-3).

The down-regulation by internalization of CD38 receptor after daratumumab exposure might explain a resistance route. However, many others mechanisms could explain the continuous response in this case. The downregulation is temporal because after 6 months cessation, CD38 expression raises again in PC. This has been shown in other studies (4-5).

Furthermore, becoming PC CD38neg produces loss of cell-cell and cell-matrix interaction, affecting growth and survival in the microenvironment of bone marrow, besides of adenosine regulation, being those mechanisms of action independent of the CD38 expression (4).

Nevertheless, a higher expression of CD55 and CD59 as anti-complement activity markers in PC when is associated with lower expression of the CD38 result in a poor response to Daratumumab. However, All-trans retinoic acid (ATRA) raises the level of expression of CD38, and reduced CD55 and CD59 to pre-treatment levels. This is an interesting alternative to re-sensibilize PC in progressive disease after daratumumab management (4-5).

References

1. Jansen JHM, Boross P, Overdijk MB, et al. Blood. 2012; 120(21). Abstract 2974.
2. Overdijk MB, Verploegen S, Bogels M, et al. MAbs. 2015;7(2):311-321.
3. Krejci J, Casneuf T, Nijhof IS, et al. Blood. 2016 Jul 21;128(3):384-94
4. Nijhof, Unger. Casneuf, Tienne. van Velzen, Jeroen, et al. Blood. 2016;128(7): 959-970
5. Nijhof IS, Groen RW, Lokhorst HM, et al. Leukemia. 2015; 29(10):2039-2049.