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CLINICAL TRIALS AND OBSERVATIONS

Comment on Dimopoulos, page 1154

Dexamethasone as a partner of isatuximab

M. V. Mateos and V. González-Calle | University Hospital of Salamanca

In this issue of *Blood*, Dimopoulos et al report that dexamethasone improves the rates of response and progression-free survival with treatment using the anti-CD38 monoclonal antibody isatuximab. There were no significant deleterious effect on safety.[1] Dimopoulos, in the 1980s and 1990s as a young hematologist, worked with giants in myeloma, participating in several studies showing the benefit of dexamethasone as single agent in patients unresponsive to standard therapy. He also showed how dexamethasone was the key player when combined with vincristine and doxorubicine.[2] He reported later on its benefit in newly diagnosed myeloma patients and showed a beneficial dexamethasone effect in patients with hypercalcemia, in patients with pancytopenia, or in those who required simultaneous radiotherapy for a pathological fracture.[3] Despite the advances of the last 40 years, dexamethasone is still prescribed for patients with hypercalcemia, cord compression, and even acute renal failure.

High-dose dexamethasone was the control arm of phase 3 clinical trials conducted for relapse at the beginning of this century. Once the proteasome inhibitor bortezomib and immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide entered the myeloma landscape, the experimental arm still often included dexamethasone.

As more agents have become available for the treatment of myeloma, the attributes of successful new therapies have evolved. New agents should have activity as a single agent, be well tolerated, and be at least additive when combined with other drugs. Successful agents will be used earlier during the course of therapy and eventually incorporated into treatment guidelines.

Isatuximab, as single agent, has shown activity in an open-label, multicenter dose-escalation study in patients with relapsed-refractory myeloma. The overall response rate was 23.8% with a reasonable safety profile, including 51% mostly mild, infusion-related reactions.[4] These efficacy and safety results are similar to that reported in the isatuximab control arm of this published study by Dimopoulos et al.

Isatuximab is a monoclonal antibody, and it is therefore classified as immunotherapy. The addition of dexamethasone could potentially inhibit naive T-cell differentiation, causing a detrimental effect on CD8 T lymphocytes and impairing the immunomodulatory effect. Dimopoulos, likely influenced by his prior work with dexamethasone in myeloma, conducted this phase 2 randomized trial combining isatuximab with dexamethasone showing, once again, how the addition of corticosteroids improved the overall response rate up to 43.6% with a median progression-free survival of 10.2 months, more than double that of isatuximab as a single agent.

These data are similar to those reported by the Intergroupe Francophone du Myeloma. In their 2014-04 trial, daratumumab, another anti-CD38 monoclonal antibody, was combined with dexamethasone in heavily pretreated myeloma patients, but this is a single-arm study with no control arm.[5]

How relevant are these findings? From the scientific point of view, this study supports that anti-CD38 monoclonal antibodies can be combined with dexamethasone. The lack of deleterious effect on the T cells and NK cells was confirmed in ancillary studies. However, it is also important to note that (i) this was not a phase 3 randomized trial powered to detect a difference between the 2 arms; (ii) there was no difference in overall survival between the arms; (iii) although safety profile seems to be comparable, the addition of dexamethasone resulted in more psychiatric and gastrointestinal adverse events with no reduction in the incidence of infusion-related reactions; and (iv) the quality of life of the patients has not been evaluated, and it is well known how some patients do not tolerate dexamethasone.

Will we be able to offer corticosteroids-free regimens to our patients with myeloma? It will be difficult because dexamethasone continues to be the salt that flavors all combinations. Because of the synergistic effect reported here, all isatuximab-based combinations should include dexamethasone, as is the case already for pomalidomide or carfilzomib. Meanwhile, the best we can do is to inform the patient well about the potential side effects and treat them, since the benefit of dexamethasone in combination with other agents has again been demonstrated in the study by Dimopoulos et al in this issue of *Blood*.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Pignarre et al, page 1166

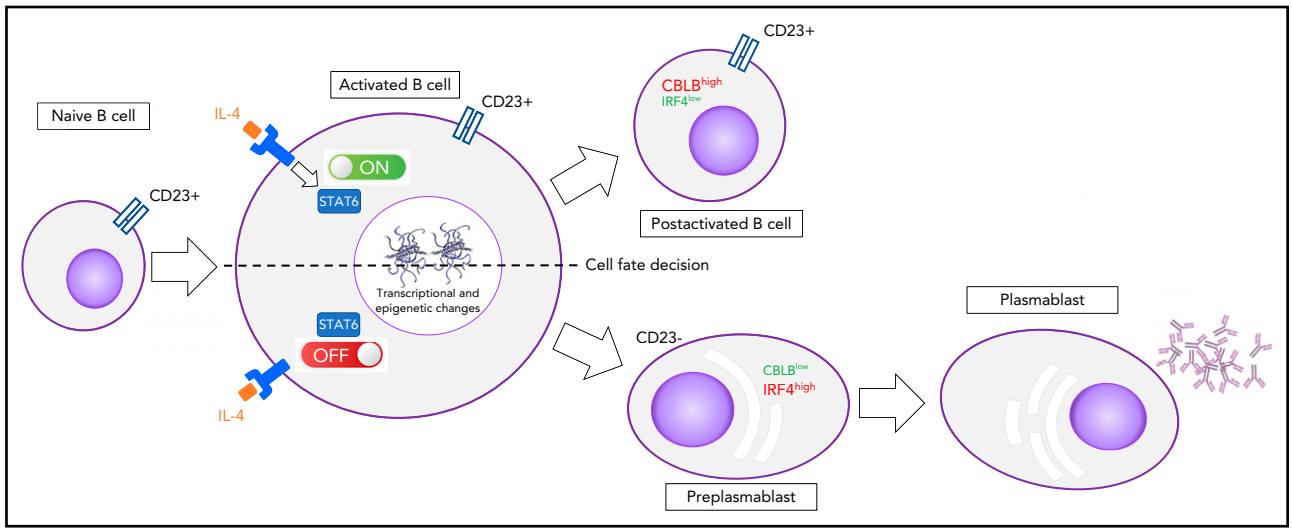
The origin of preplasmablastic cells

Jerome Moreaux | CHU Montpellier; Institute of Human Genetics; University of Montpellier UFR Medicine; Institut Universitaire de France

In this issue of *Blood*, Pignarre et al characterize the genomic events involved in the cell fate decision between activated B cells and plasmablasts.[1] Plasma cells (PCs) play an important role in humoral immunity by synthesizing and secreting antibodies.[2] Understanding the biological processes that control the production of PCs is critical to both ensure efficient immune response without autoimmunity or immune deficiency and prevent tumorigenesis. The production of interleukin-4 (IL-4) by follicular helper T cells drives B-cell amplification and maturation.[3] However, the full molecular mechanisms behind these functions are not fully understood.

Pignarre et al report new biological events driving normal B- to plasma-cell differentiation. Using an in vitro model, naive B cells were cultured in a 2-step process, which results in differentiation into plasmablasts,[4] and the authors demonstrated that cells are destined to differentiate into PCs if there is an early response to IL-4, which results in downregulation of the CD23 cell-surface protein and IL-4/STAT6 signaling. However, B cells maintaining IL-4 signaling did not differentiate. Furthermore, the differentiation of CD23$^-$cells is associated with CBLB E3 ubiquitin ligase downregulation, coinciding with IRF4 induction and with specific chromatin and transcriptional modifications (see figure). The changes were identified by ATAC sequencing and hydroxymethylation profiling. However, no major changes in expression of epigenetic factors were noted. CBLB is known to prevent premature germinal center (GC) exit promoting IRF4 degradation in light zone B cells.[5] Pignarre et al reported potential STAT6 binding sites in the CBLB promoter, suggesting potential direct regulation, hence the interest in characterizing STAT6 targets, using chromatin immunoprecipitation. CD23$^-$ B cells, postactivation, have the characteristics of preplasmablasts with a significant increase in chromatin accessibility at immunoglobulin heavy chain coding loci. Full transcriptomic characterization of the proposed model at a single-cell level would be particularly useful in deciphering the heterogeneity and transcriptional trajectories during B- to plasma-cell differentiation.

The major transcriptional and epigenetic changes reported by Pignarre et al may be associated with changes in nuclear organization during terminal B-cell differentiation. Gene regulation depends on the 3-dimensional chromatin organization



After activation, B cells that are committed to differentiate into PCs downregulate the CD23 cell-surface protein, IL-4/STAT6 signaling, and CBLB activity concomitantly with IRF4 induction. B cells that maintain the IL-4 signaling will not differentiate.