Targeted immunotherapy in Hodgkin lymphoma

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In this issue of Blood, Rothe et al introduce a new principle of targeted Hodgkin lymphoma (HL) immunotherapy in their report from a phase 1 study of the bispecific anti-CD30/CD16A antibody construct AFM13.1

It has been 15 to 20 years since Küppers et al2 demonstrated that the Hodgkin Reed-Sternberg (RS) cell is in fact the clonal cell of B-cell origin from which HL derives. However, the RS cell is a very atypical B cell that has lost most of the usual B-cell identity and gained some important other functions. The clonal cell makes up <1% of the tumor mass, but through effective organization of the much more numerous surrounding immune cells, it is able to generate a highly aggressive and potentially lethal malignancy. Also, through cytokine and chemokine activity, as well as through more direct interaction with the microenvironment, the RS cell exerts a number of mechanisms that enable the tumor to escape the normal immune system of the host.3 One example of this is the absence of specific cytotoxic T cells and natural killer (NK) cells in the cellular landscape of HL.4

Assuming that the ability of HL to escape the normal immune response is central to tumor survival and growth, modulating the immune system and its response to the disease is a logical novel therapeutic strategy. Different immunological approaches are currently the focus of clinical development in HL: (1) so-called checkpoint inhibition, eg, the promising activity of monoclonal antibodies targeting programmed cell death protein 1 (nivolumab5 and pembrolizumab6); (2) modulation of the immune status and tumor environment, eg, lenalidomide7; or (3) the direct engagement of cytotoxic immune effector cells, such as cytotoxic T or NK cells, to mediate tumor cell lysis. The most prominent example of the last is the engineering of T cells with chimeric antigen receptors (CAR-T cells). Another example is the bispecific antibody AFM13, which targets the CD30 receptor present on the surface of RS cells and via the CD16a antibody selectively attracts and activates NK cells.

Using the CD30 receptor as a target for HL therapy is not at new concept. Stein et al8 demonstrated this antigen on the surface of RS cells 30 years ago. Because it is almost consistently expressed on RS cells of classical HL and at the same time relatively specific to those cells, it is an attractive therapeutic target. However, naked anti-CD30 antibodies have shown little or no antitumor activity.9 Brentuximab vedotin is approved for the treatment of relapsed and refractory HL. This drug is an antibody–drug conjugate that combines a cytotoxic agent (monomethyl auristatin E) with an anti-CD30 antibody through a cleavable linker molecule.10 Thus, it uses the CD30 antigen not to modulate the function of the intracellular domain of CD30 but to achieve high-concentration delivery of chemotherapy within and around the RS cells. In the same way, AFM13 uses the CD30 receptor as a geographical target without exerting any clear influence on the transmembrane protein itself.

The study by Rothe et al is a phase 1 study and as such is not primarily designed to assess efficacy.1 The drug seems generally well tolerated, and the maximal tolerable dose was not reached. Although AFM13 treatment resulted in a significant NK-cell activation and decrease of soluble CD30 in peripheral blood, the demonstrated activity is not very impressive at first, with an overall response rate of 11.5% (all partial response [PR]) and an overall disease control rate (PR + stable disease [SD]) of 61.5% in a very heavily pretreated cohort of patients. However, because this was a first-in-human experience, a proportion of the patients were treated at extremely low doses (starting at 700 times less than the final dose level of 7 mg/kg). The activity was notably higher in the higher dose levels of >1.5 mg/kg (23% PR and 77% PR + SD) even though toxicity remained stable during dose escalation. The majority of patients only received 1 treatment cycle (4 weekly infusions), and no patient received >2 cycles. Furthermore, the weekly dosing schedule is hardly optimal for this construct, with a half-life of 19 hours. A subsequent phase 2 study will take these considerations into account and shed more light on the actual efficacy of this promising compound and targeted immunotherapy in general.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES
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**Toward optimizing pomalidomide therapy in MM patients**

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In this issue of *Blood*, Sehgal et al report on the clinical and pharmacodynamic analysis of pomalidomide dosing strategies in multiple myeloma (MM) and their impact on immune activation and cerebro targets. The particular novelty of this study lies in the direct correlation of immune effects triggered by pomalidomide with clinical responses in MM patients. Results of this study will stimulate many additional studies.1

Because of remarkable responses, the second-generation immunomodulatory drug (IMiD) pomalidomide (Pomalyst; Celgene) has been granted accelerated US Food and Drug Administration and European Medicines Agency approval in February 2013 and in August 2013, respectively, for the treatment of adult patients with relapsed/refractory MM who have received ≥2 prior treatment regimens, including lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. Functionally, preclinical data have shown that pomalidomide mediates direct anti-MM cell activity as well as immunomodulatory and antistroma support activities.2 Data on pomalidomide-mediated immune activation in vivo are limited. The optimal dosing schedules of both pomalidomide and concurrent steroids need to be clarified.

Sehgal et al randomized 39 patients with relapsed MM refractory to lenalidomide and bortezomib into 2 treatment cohorts using either continuous (2 mg for 28 of 28 days) or intermittent (4 mg for 21 of 28 days) pomalidomide dosing schedules. Using extensive analyses, the authors demonstrate that pomalidomide induces rapid changes in immune profile and function. Specifically, they show pomalidomide-induced increases of both T and natural killer (NK) cells and their activation in the peripheral blood as well as in the bone marrow. Objective treatment responses correlated with pomalidomide-induced increases in interferon-γ- and tumor necrosis factor-α-producing CD8+ and multifunctional T cells but not NK cells. Moreover, gene expression profiling analysis showed that genes altered by pomalidomide treatment in CD138-negative cells predominantly belong to immune pathways, ie, in lymphocytes. These data highlight the eminent role of immunomodulation as part of the pomalidomide-induced in vivo anti-MM activity. They also indicate that the biology of innate lymphocytes in the context of pomalidomide treatment requires further investigation. Comparable responses were observed under both dosing schedules, with significantly greater incidence of grade 3/4 side effects in the intermittent dosing schedule. These results suggest that the lower dosing schedule of pomalidomide may be sufficient in the clinical setting. However, future studies need to explore whether treatment holidays as part of intermittent dosing schedules restore sensitivity to pomalidomide. Importantly, baseline levels of CD4/CD8+ T cells did not predict response rates to pomalidomide treatment. Therefore, a high need remains for those biomarkers that determine which patients are likely to benefit from pomalidomide-containing immunotherapies. Moreover, previous data demonstrate that dexamethasone synergizes with pomalidomide in terms of tumor regression.3 Based on the present data, dexamethasone also blunts pomalidomide-mediated T-cell activation. Optimization of pomalidomide/dexamethasone combination therapy using intermittent or modified low-dose dexamethasone is therefore required.

Another important finding of this study is that pomalidomide treatment increases the expression of immune checkpoint modulators B- and T-lymphocyte attenuator (BTLA) on T cells and T-cell immunoglobulin and mucin-domain containing-3 (Tim-3) on NK cells in MM. These data indicate a potential therapeutic role for combining pomalidomide with next-generation immune checkpoint inhibitors directed against Tim-3 and BTLA in MM. Importantly, pomalidomide induced changes of Tim-3 and BTLA expression, but not PD-1, currently the best investigated immune checkpoint protein in T cells. In contrast to normal plasma cells, PD-1 ligand is expressed on primary MM cells and induced by cytokines and bone marrow stromal cells, highlighting the intimate functional interrelation of the nonimmune and immune compartments within the MM bone marrow microenvironment.4,5 The efficacy of inhibiting the PD-1/PD-L1 pathway has been demonstrated in several preclinical studies of MM.4,5 A clinical study that evaluates the activity of pomalidomide in combination with the anti–PD-1 inhibitor...
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