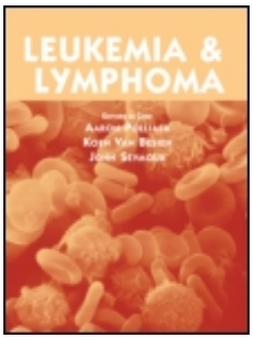

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

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To cite this article: Ashkan Emadi & Judith E. Karp (2013) CD30 in myeloid malignancies: hitting the bull's-eye with an available dart, Leukemia & Lymphoma, 54:4, 679-680, DOI: 10.3109/10428194.2012.728703

To link to this article: https://doi.org/10.3109/10428194.2012.728703

Leukemia & Lymphoma, April 2013; 54(4): 679–680

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2012.728703

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COMMENTARY

CD30 in myeloid malignancies: hitting the bull's-eye with an available dart

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CD30 is a 120 kDa cell membrane glycoprotein that shares sequence homology with tumor necrosis factor (TNF) receptors. It is known also as TNF receptor superfamily member 8 (TNFRSF8), with its gene located on chromosome 1p36 [1]. The receptor is expressed on activated B- and T-cells, and intercedes in signal transductions involving nuclear factor-κB (NF-κB) transcription factor. CD30 is expressed also on Reed–Sternberg cells of Hodgkin lymphoma and on a subset of non-Hodgkin lymphomas, including anaplastic large cell lymphoma (ALCL). When the extracellular segment of CD30 is enzymatically cleaved, soluble CD30 (sCD30) is released in the serum and can be measured [2]. Indeed, elevated sCD30 levels have been identified in Hodgkin lymphoma [3], ALCL [4] and non-Hodgkin lymphomas [5], and generally were associated with poor prognosis.

Brentuximab vedotin (Adcetris) is a CD30-directed antibody–drug conjugate comprising a chimeric immunoglobulin G1 (IgG1) anti-CD30 antibody, an anti-microtubule molecule monomethyl auristatin (MMAE), and a protease-cleavable linker that covalently attaches MMAE to the IgG antibody. Upon binding to CD30-expressing cells, the brentuximab–CD30 complex internalizes, and releases MMAE after proteolytic cleavage. Interruption of the microtubule assembly by MMAE culminates in cell cycle arrest and apoptosis [6]. In 2011, brentuximab vedotin was given accelerated approval by the United States Food and Drug Administration (FDA) for the treatment of patients with Hodgkin lymphoma after the failure of autologous stem cell transplant or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not transplant candidates, and also for the treatment of patients with systemic anaplastic large cell lymphoma after the failure of at least one prior multi-agent chemotherapy regimen. The approval was based on response rate, with no data available demonstrating improvement in survival or patient reported outcomes. The complete response (CR) rate in patients with Hodgkin lymphoma was 32% (95% confidence interval [CI] 23–42%), with a median response duration of approximately 21 months. The CR rate in patients with systemic anaplastic large cell lymphoma was 57% (95% CI 44–70%), with a median response duration of 13 months.

A variant of CD30, CD30v, presents mainly in the cytoplasm (with no transmembrane or extracellular domains) of alveolar macrophages and in cells of the HL-60 acute myeloid leukemia cell line, with constitutive phosphorylation [7]. In a small study, simultaneous expressions of CD30v and CD30-ligand (CD30L), mapped to chromosome 9q33, were found in 40% of patients with acute myeloid leukemia (AML), and were associated with increased blast cell and leukocyte counts, and decreased platelet levels compared to those cases of AML with no expression of CD30 [8]. AML is a very heterogeneous disease with several clinical, pathological, chromosomal and molecular subtypes. Investigating novel cellular and molecular markers in AML, such as CD30, with an agent already approved to target them in other malignancies, is of great value for the patient population and for translational and clinical scientists.

To further explore the presence and clinical relevance of CD30 expression on primary AML cells, in this issue of ***Leukemia and Lymphoma***, Fathi and colleagues reported an interesting retrospective analysis of 24 bone marrow biopsy samples from patients with AML for whom the presence of CD30 was assessed by semi-quantitative immunohistochemistry (IHC) using Ber-H2 antibody [9]. CD30 expression, with varying intensity, was detected in approximately half of the cases. The data also suggest the existence of positive associations between CD30 expression and internal tandem duplication (ITD) mutation of the fms-like tyrosine kinase 3 (FLT3) growth factor receptor, as well as between CD30 expression and leukocyte counts

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This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

greater than 20 000/mm^3. However, CD30 expression did not predict the achievement of CR following induction chemotherapy.

Notwithstanding the lack of validation in a large prospective cohort and despite being based on only a small sample size with limitations and biases common to retrospective analyses (including incomplete or missing documentation and poorly recorded information), the results of this study are profoundly provocative and underscore the importance of innovative new strategies for the treatment of AML with FLT3-ITD mutations. The presence of FLT3-ITD mutations has been associated with higher peripheral blast counts, normal karyotype and acute monoblastic leukemia, in particular French–American–British (FAB) M5 AML, and does not correlate with CR rate, but predicts high relapse rate and poor survival [10]. FLT3 inhibitors such as sorafenib, sunitinib, midostaurin, lestaurtinib, tandutinib, AC220 and KW-2449 when used as single-agent therapy have shown limited clinical benefit in patients with AML with FLT3-ITD mutations. The study by Fathi *et al*. provides interesting and important information for the planning of future prospective clinical trials to identify a subgroup of patients with AML with FLT3-ITD and CD30 expression for whom a combination of FLT3 inhibitor and anti-CD30 drugs might be beneficial. Furthermore, incorporation of correlative studies such as measurement of sCD30, as a potential biomarker, and investigation of common downstream pathways between FLT3 and CD30 may help not only to better understand the pathophysiology of this special type of leukemia, but also to introduce several important cancer therapeutic concepts and targets in the foreseeable future.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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