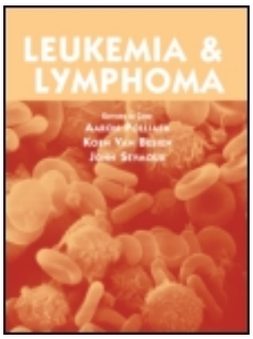

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# Time to look for CD30 expression in diffuse large B-cell lymphomas, along the way to immunotherapy

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COMMENTARY

# Time to look for CD30 expression in diffuse large B-cell lymphomas, along the way to immunotherapy

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In this issue of *Leukemia and Lymphoma*, Campuzano-Zuluaga and colleagues have analyzed the frequency of CD30 expression and its relation to other clinicopathological findings, in a large series (167 cases) of diffuse large B-cell lymphoma (DLBCL) [1]. CD30 is a type I transmembrane glycoprotein, a member of the tumor necrosis factor (TNF) receptor superfamily codified by the *TNFRSF8* gene mapped at chromosome 1p36 [2]. CD30 is expressed in a subset of activated B and T lymphocytes and natural killer (NK) cells but not on resting mature T or B cells, and is rarely expressed on non-neoplastic cells outside the immune system [2,3]. The role of CD30 in lymphocyte biology is not completely understood, but it seems that CD30 signaling participates in the generation and maintenance of both memory B and T cells, proliferation of B cells and enhancement of immunoglobulin production [4].

From the clinical perspective, CD30 is an important immunomarker for the diagnosis of classical Hodgkin lymphoma (cHL) and anaplastic large cell lymphoma (ALCL), but is also an excellent target for monoclonal antibody therapy in patients with CD30 positive malignancies [5,6].

Brentuximab vedotin (SNG-35, ADCETRIS™; Seattle Genetics) is an antibody–drug conjugate approved by the Food and Drug Administration for the treatment of cHL and ALCL since August 2011. This compound consists of the chimeric monoclonal antibody directed against CD30 (brentuximab) linked to 3–5 units of the antimitotic (antitubulin) agent monomethyl auristatin E. Brentiximab vedotin binds to the CD30 receptor in the cell surface, then the CD30–drug complex is internalized within the cell and the cytotoxic component (monomethyl auristatin E) is released by proteolytic cleavage in the lysosome. Kinetic studies on this agent have shown that relatively few brentuximab vedotin molecules are required for clinical efficacy, suggesting that this conjugated drug may well be effective in tumors with low CD30 expression [7].

ALCL and cHL are the natural tumors for testing the efficacy of brentuximab, as the tumor cells of both neoplasms strongly and uniformly express CD30. However, variable degrees of CD30 expression are detected in several other malignant hematopoietic and non-hematopoietic neoplasms. CD30 expression has been noted in a subset of DLBCL not otherwise specified (NOS), primary mediastinal large B-cell lymphoma, follicular lymphoma and Epstein–Barr virus (EBV)-positive lymphomas (lymphomatoid granulomatosis, EBV positive DLBCL of the elderly and primary effusion lymphoma), as well as large cell transformation of mycosis fungoides, among others. Expression of CD30 can also be detected in advanced systemic mastocytosis, and non-hematopoietic neoplasms including embryonal carcinoma, seminomas and a subset of melanomas and mesotheliomas [8–11].

DLBCL is the most common lymphoid malignancy in adults (approximately 30% of non-Hodgkin lymphomas diagnosed annually). In the USA alone, 70 130 new cases of non-Hodgkin lymphoma and 18 940 deaths from the disease were estimated for 2012. Although DLBCL is potentially curable with anthracycline-based therapy, variability in response is often observed, and about 40% of patients relapse and ultimately die. Therefore, new and effective therapeutic approaches are still needed for DLBCL. Because a subset of DLBCL expresses CD30, the addition of brentuximab vedotin to current or future chemotherapy protocols is a novel potential therapeutic approach that may increase the response rate of these tumors. However, the overall prevalence of CD30 expression in DLBCL NOS, the extent of CD30 positivity within individual CD30-positive DLBCL cases and the relation of CD30 expression to other biological variables are not well known.

In this issue of *Leukemia and Lymphoma*, Campuzano-Zuluaga and colleagues show evidence to support the potential use of anti-CD30 conjugate drugs in at least one of five patients with DLBCL NOS [1]. They demonstrated that after excluding specific subtypes of DLBCL, CD30 expression was detected in 21% of DLBCL, and when positive, it was expressed by a significant number of tumor cells. In 52% of the cases CD30 expression was detected in $>80\%$ of lymphoma cells, while in 84% of the cases 50% or more of lymphoma

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cells were positive for CD30. In addition, they also found that CD30 expression correlated with other clinicopathologic features in DLBCL: it was more common in BCL2-positive cases, in tumors with non-germinal center (GC) immunophenotype and in younger patients. Moreover, they report that the expression of BCL2 and CD30 were closely associated. In this series, only a few cases (7%) of BCL2 negative DLBCL expressed CD30. They also identify a subgroup of DLBCL with frequent expression of CD30, a subgroup represented by young patients with non-GC phenotype DLBCL positive for BCL2.

The stratification of DLBCL into subgroups is always of potential biological and clinical interest, as DLBCL is a very heterogeneous disease and stratification into smaller groups may result in biologically similar and clinically meaningful subgroups, which may have prognostic implications, perhaps facilitate more appropriate therapeutic decisions and stimulate further research to understand their pathogenesis. In their article, Campuzano-Zuluaga and colleagues do not address the issue of prognostic significance of CD30 expression in DLBCL [1]; however, recently Hu and colleagues have reported that CD30 expression is a favorable prognostic factor in DLBCL [12].

In summary, CD30 is a fascinating and poorly understood molecule that, in addition to being an important marker for the diagnosis of a subset of malignant lymphomas, is also gaining a lot of attention as a useful immunotherapeutic target in malignant lymphomas. CD30 is expressed in at least 20% of DLBCL, particularly in cases positive for BCL2 with a non-GC phenotype and in younger patients. The time to look for the presence of CD30 in DLBCL has arrived, and may have clinical implications for immunotherapy in the near 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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