Clinical Implications of CD30 Expression in Aggressive B-Cell Lymphomas

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Abstract

US Food and Drug Administration approval of brentuximab for treatment of CD30-positive relapsed/refractory lymphomas initiated research focused on CD30 expression in lymphomas. We studied CD30 expression in various types of previously unstudied aggressive B-cell lymphomas, including Burkitt lymphoma, high-grade follicular lymphoma, grade III follicular lymphoma/diffuse large B-cell lymphoma (DLBCL), DLBCL type post-transplantation lymphoproliferative disease, and primary mediastinal B-cell lymphoma.

Background: US Food and Drug Administration approval of brentuximab vedotin for treatment of CD30-positive relapsed/refractory lymphomas, including classical Hodgkin lymphoma and anaplastic large cell lymphoma, initiated significant interest in researching CD30 expression in other therapy-resistant or relapsed lymphomas. We evaluated CD30 expression in 116 cases of aggressive B-cell lymphomas diagnosed at Penn State Milton S. Hershey Medical Center between 2000 and 2012 with the purpose of assessing the benefit of treatment with brentuximab. **Patients and Methods:** We studied CD30 expression in types of aggressive B-cell lymphomas not previously studied, including Burkitt lymphoma, high-grade (grade III) follicular lymphoma, mixed grade III follicular lymphoma/diffuse large B-cell lymphoma (DLBCL), posttransplantation lymphoproliferative disease large B-cell lymphoma, and primary mediastinal large B-cell lymphoma. **Results:** CD30 expression was found in 37.5% of DLBCL and 46.2% of other non-DLBCL aggressive B-cell lymphomas. **Conclusion:** Expression of CD30 in patients with both DLBCL and other aggressive B-cell lymphomas and the absence of MYC oncogene–driven proliferation in the majority of these tumors suggests that brentuximab may be a particularly effective form of targeted therapy in the subset of patients with high CD30 expression.

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Introduction

CD30 is a 120 kDa type 1 transmembrane protein that contains tumor necrosis factor receptor–associated factor binding sequences that can activate both nuclear factor κB (NF-κB) and extracellular signal–related kinase signaling pathways.[1] Expression of CD30 in healthy individuals is limited to activated B and T lymphocytes.[1] CD30 can also be expressed in a variety of lymphomas, including Hodgkin lymphoma, anaplastic large cell lymphoma, certain peripheral T-cell lymphomas, and primary mediastinal large cell lymphoma.[3,4] Its expression in other types of lymphomas has not been extensively studied, with the exception of recent studies of the frequency and extent of CD30 expression in diffuse large B-cell lymphoma (DLBCL). CD30 is an attractive target for monoclonal antibody–targeted drug therapy because of its limited expression on normal tissues and its high level of expression on the malignant cells of Hodgkin lymphoma and anaplastic large cell lymphoma.[2] Brentuximab vedotin is a novel antibody–drug conjugate consisting of the anti-CD30 antibody cAC10 conjugated to monomethylauristatin E, a potent antimicrotubule agent.[3] The drug has shown favorable results in the treatment of Hodgkin lymphoma recurring after allogeneic stem cell transplantation and in the treatment of conventional therapy–resistant anaplastic large cell lymphoma.[2-4] It was approved by the US Food and Drug Administration in August 2011 for treatment of patients with these diseases.

DLBCL is the most common subtype of lymphoma encountered in clinical practice. Several variants of DLBCL are recognized by

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the 2008 World Health Organization (WHO) classification. Depending on the subtype, the prognosis can vary, but generally it is classified as an aggressive lymphoma.[5] In 2013, Hu et al[6] described CD30 expression as a feature that defines a novel subgroup of DLBCL with distinct gene expression and favorable prognosis.

Prior studies of CD30 expression in subsets of DLBCL demonstrated an association with the anaplastic variant of DLBCL,[7] Epstein-Barr virus (EBV)-positive DLBCL,[8,9] primary mediastinal large B-cell lymphoma,[1] and BCL-2 (B-cell lymphoma 2)-positive non–germinal center type of DLBCL, particularly in younger patients (< 47 years).[10]

Although the expression of CD30 has been reported in DLBCL,[7,10-12] few studies have examined the prevalence of CD30 expression in other types of aggressive B-cell lymphomas, including Burkitt lymphoma (BL), grade III follicular lymphoma (FL), and unclassifiable B-cell lymphoma, with features intermediate between DLBCL and BL.

The intent of our study was to add to the database of knowledge of CD30 expression in DLBCL and further extend knowledge about CD30 expression in various other types of aggressive B-cell lymphomas. EBV is a known oncogenic virus with a strong association with BL, nasopharyngeal carcinoma, and T-cell lymphoma, as well as an association with the development of lymphomas in immunocompromised patients. EBV is also recognized in the pathogenesis of a subset of DLBCL with a particularly poor prognosis in the elderly population (EBV-positive DLBCL of the elderly).[8] We added investigation of EBV status as documented by in-situ hybridization (ISH) staining (EBV-encoded RNA [EBER]) and examined the relationship between EBV infection and CD30 expression in malignant B cells.

The prognosis of aggressive B-cell lymphomas included in our study varies significantly depending on a multitude of factors that reflect the underlying biology of these rapidly progressive tumors. We focused primarily on CD30 expression in various diagnostic subgroups of aggressive B-cell lymphomas in order to identify patients who may benefit from treatment with brentuximab, especially if their disease fails to respond to traditional therapeutic regimens or if the patients experience relapse.

Patients and Methods

In this retrospective study, we reviewed all cases of aggressive B-cell lymphomas evaluated in the Department of Pathology at the Penn State Milton S. Hershey Medical Center between 2000 and 2012. A standard institutional review board protocol at the Hershey Medical Center was created for this study. We limited cases of DLBCL to those evaluated between 2007 and 2012 because of a disproportionally high prevalence of this type of lymphoma. In addition to DLBCL, the following subtypes were examined: BL, DLBCL in the setting of posttransplantation immunodeficiency, FL, primary mediastinal large B-cell lymphoma, and unclassifiable B-cell lymphoma with features intermediate between DLBCL and BL. These entities were identified in accordance with the 2008 WHO classification system. The morphology of all studied cases was reviewed, and all samples were stained with CD30 and EBV.

CD30 staining by immunohistochemistry was performed using the Dako Monoclonal Mouse Anti-Human CD30 antibody clone Ber-H2 (Dako, Glostrup, Denmark).

EBV ISH staining was based on the Ventana EBER 1 DNP ISH probe (Ventana, Tucson, AZ).

Demographic information for each patient was collected and reviewed. The scoring system for qualifying a case as CD30 positive was defined in our study by the proportion of CD30-positive tumor cells (proportion score, PS) and the intensity of CD30 staining (intensity score, IS). PS was expressed by a 0- to 5-point scale with score of 0 equivalent to negative staining (0 cells positive), a score of 1 equivalent to less than 1% of CD30-positive neoplastic cells, a score of 2 equivalent to 1% to 10% of positive neoplastic cells, a score of 3 equivalent to 11% to 33% positive neoplastic cells, a score of 4 equivalent to 34% to 66% positive neoplastic cells, and score of 5 equivalent to $\geq$ 67% positive neoplastic cells. IS was defined as follows: 0 = no staining, 1 = weak staining, 2 = intermediate staining, and 3 = strong staining (Figures 1-3). A combined PS + IS score of $\geq$ 3 was interpreted as CD30 positive, and a combined score of 0 to 2 was interpreted as CD30 negative.[13]

Any positive cellular staining by EBV ISH was scored as positive, while a negative score was assigned when no positive cells were identified.

Each case was examined histologically by 2 hematopathologists and a hematopathology fellow, then scored as positive or negative on the basis of the above criteria. The association between the diagnosis group CD30 and EBV expressions was summarized by 2-way contingency tables and examined by the Fisher exact test. Associations between continuous variables (such as age) versus CD30 (and EBV) expression were examined by the nonparametric Wilcoxon rank sum test. All statistical analyses were performed by SAS 9.2 software (SAS Institute, Cary, NC). The level of statistical significance was accepted at $P < .05$.

Results

A total of 116 patients were analyzed in this study, 49 women (42%) and 67 men (58%). The mean (standard deviation) age at diagnosis was 58.3 (20.4) years. Anatomic sites represented in this study included 33 cases of nodal disease (28.5%), 66 cases in extranodal sites (56.9%), and 17 cases involving the central nervous system (14.7%).

CD30 and EBV expression did not statistically correlate with patient age, sex, or anatomic site of disease ($P > .05$, Fisher exact test).

All cases of BL were CD30 negative (Table 1). In the DLBCL group, 37.5% of cases were CD30 positive and 46.15% of the

Table 1 Association Between CD30 Expression and Diagnostic Group

Diagnostic Group	CD30 Negative	CD30 Positive	Total
Burkitt lymphoma	10 (100%)	0 (0%)	10
Diffuse large B-cell lymphoma	50 (62.5%)	30 (37.5%)	80
Other[a]	14 (53.9%)	12 (46.2%)	26
Total	74	42	116

$P = .0213$.
[a]Diffuse large B-cell lymphoma/grade III follicular lymphoma, grade III follicular lymphoma, primary mediastinal B-cell lymphoma, posttransplantation lymphoproliferative disease large B-cell lymphoma.