International Journal of Academic Health and Medical Research (IJAHMR)
ISSN: 2643-9824
Vol. 8 Issue 2 February - 2024, Pages: 166-170

CD30-expressing diffuse large-cell B lymphoma

R. Felk ; H. Masrour ; N. Alami ; N. Oubelkacem; M.Ouazzani ; Z. Khammar ; R. Berrady

Médecine interne et onco-hématologie, C.H.U Hassan II, Fès, Maroc

Auteur correspondant
FELK Rime
Tel : 00212661515667
E-mail : felk.rime@gmail.com

Abstract: *Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous disease for which great efforts have been made to build up molecular and immunophenotypic subgroups that could accurately indicate prognosis and give clues to therapy. Variable clinical outcomes are seen in response to standard R-CHOP combination therapy. That's why there is a need to identify biomarkers that can identify patients who may benefit from supplemental or alternative therapy and help guide therapeutic decisions. Recently, CD30 was reported as a useful predictor with favorable clinical outcomes. In addition, due to the development of targeted therapies such as an anti-CD30 monoclonal antibody drug conjugate, the identification and prognostic relevance of this biomarker have potential therapeutic impact. CD30 is a cell surface receptor expressed in classical Hodgkin lymphoma (HL), anaplastic large cell lymphoma (ALCL), and many other lymphomas to a variable degree. It has been identified as an important therapeutic target in lymphoma. Its expression in de novo diffuse large-cell B lymphoma defines a new histological entity whose characteristics and prognostic impact are currently being investigated. However, CD30 expression patterns and the clinicopathologic features of CD30-positive DLBCL are not well described thus far. This study aimed to investigate the positive expression rate and prognostic impact of CD30 in de novo DLBCLs and try to find the correlated influences.*

Keywords: CD30, diffuse large B cell lymphoma, prognostic, antibody-drug conjugate, immunohistochemistry.

Introduction:

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) in adults and a heterogeneous disease composed of many subtypes and entities [1]. Therefore, due to the heterogeneity of DLBCL, the best identification of risk groups to select patients for different therapeutic approaches is an important challenge today.

According to gene expression signatures or immunohistochemistry (IHC) using several algorithms as surrogates, most DLBCL cases can be placed into prognostically favorable germinal center B-cell-like (GCB) or prognostically unfavorable activated B-cell-like (ABC) subtypes [2] [3]. However, these immunophenotypic algorithms may not always correlate well with gene expression profiling (GEP) results and may show poor prognostic power [4] [5]. Although cell of origin (COO) stratification by gene expression signatures is able to provide a general perspective of clinical outcome, currently it is not practical to perform GEP routinely in the clinical setting.

One of the most consistent predictors of outcome is the International Prognostic Index (IPI).

Lymphomas were the first cancer to be cured in the 1970s with combination chemotherapy [6]. The invention and integration of rituximab, the first monoclonal antibody used in cancer, into the chemotherapeutic foundation improved the outcomes of B-cell lymphomas. In the last decade, there has been an explosion of novel monoclonal antibodies, antibody-drug conjugates, small-molecule inhibitors, and immunotherapy for various cancers, including lymphomas.

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) lead to cure in approximately 70% of patients [7] [8]. Unfortunately, there are few therapeutic options for high-risk DLBCL patients who do not respond to R-CHOP, and therefore, it is imperative to identify new therapeutic targets [9].

Identifying novel predictive biomarkers for individuals with DLBCL is a challenging task. Even though the R-CHOP regimen leads to clinical remission in approximately 60% of cases, the overall survival rates for these patients remain unfavorable[10]. Consequently, there is a need to explore new therapeutic targets, and the presence of the CD30 protein in certain cases could potentially serve as an alternative approach to enhance the clinical care of these patients.

CD30, a member of the tumor necrosis factor receptor family, is expressed on a small subset of activated T and B lymphocytes and is overexpressed in a variety of lymphoma subtypes [10].

CD30 was found to be expressed in approximately 30% of T-cell malignancies and 15% to 20% of B-cell malignancies [11], including DLBCL. Virtually, CD30+ DLBCL was emerging as a new immunophenotypic variant of DLBCL.

A few studies showed different positive incidences and controversial prognostic impacts of CD30 expression in DLBCLs [12], [13].

This highly restricted distribution of CD30 expression makes it an ideal target for monoclonal antibody therapy in patients with CD30+ lymphomas.

Patients and methods:

This is a retrospective, descriptive, and analytical study of newly diagnosed DLBCL-expressing CD30 patients followed up in an internal medicine and onco-hematology department between January 2018 and December 2021. Data were collected using a computerized system (HOSIX). Statistical analysis was performed with IBM SPSS Statistics. Survival analyses with corresponding P-values were calculated using the Kaplan-Meier method.

Results:

Among the 185 newly diagnosed cases, 4,34% expressed CD30. There were 8 patients, 7 women and 1 man. The mean age at diagnosis was 45.37 ± 16.69 years [19–71 years], and the mean time to diagnosis was 4 months ± 5.1 months. Seventy-five percent of patients had general signs at diagnosis and a tumor syndrome (adenopathy and/or splenomegaly). The PS was less than 1 in 5 patients (62.5% of cases). Histological studies showed Ki67 values below 80% in 75% of patients, and extension studies showed extensive involvement (stage III/IV) in 25% of patients. A bulky mass was described in half the patients and a mediastinal location in 3 patients (37.5%). The IPI score was less than or equal to 2 in 87.5% of patients, and 37.5% developed venous thrombosis.

Given the mediastinal location, 50 % of patients were placed on the RDEAPOCH protocol and the remainder on the RCHOP protocol. Fifty percent of patients responded to first-line treatment with complete remission, and 50% of patients died before completing their first-line treatment.

We found a significant correlation between CD30 expression and the localized form of DLBCL (p = 0.036), including 4 cases of primary mediastinal DLBCL and 1 primary pulmonary case, as well as the occurrence of thrombosis (p = 0.04). There was no significant association between death and CD30 expression (p = 0.081).

The overall survival of patients expressing CD30 was reduced compared with those not expressing CD30.

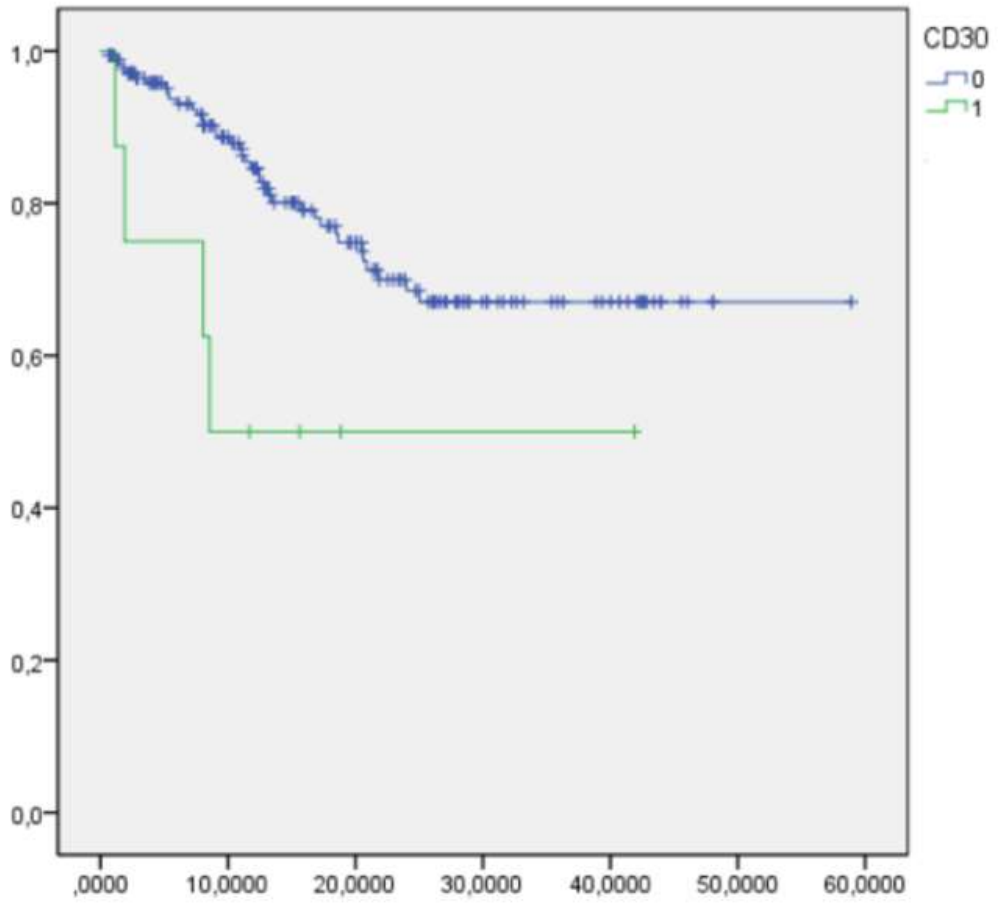

Figure 1: Survival of CD30+ DLBCL patients compared with non-CD30 patients.

Discussion:

Lymphomas are a heterogenous group of hematologic malignancies that are divided into Hodgkin (HL) and non-Hodgkin (NHL) subtypes. This high-grade neoplasm has a very complex and heterogeneous molecular basis, making the understanding of its pathogenesis very difficult.

The international prognostic index (IPI) remains a valuable tool for risk stratification of DLBCL patients in the rituximab era [14] [15]. However, it does not identify individual patients who will suffer a particularly aggressive clinical course, given that these patients can be found in the same subgroup. These prognostic variables are considered to be proxies for the underlying cellular and molecular variation within DLBCL.

Many attempts have been made to find biomarkers that can improve our outcome prediction beyond the IPI. This scarcity of knowledge impairs the development of more efficacious therapeutic approaches; therefore, the search for new biomarkers with prognostic potential that could be useful therapeutic targets remains desirable.

Recently, CD30+ DLBCL has emerged as a new immunophenotypic variant of de novo DLBCLs. A few studies focused on CD30 expression and its significance in DLBCLs [12] [16].

CD30, a member of the tumor necrosis factor receptor family, is expressed on a small subset of activated T and B lymphocytes and is overexpressed in a variety of lymphoma subtypes.

It is described as a transmembrane glycoprotein receptor (120 kD) of the tumor necrosis factor receptor superfamily 8 (TNFRSF8) [17]. The receptor has intracellular, transmembrane, and extracellular domains. Its ligand (CD30L, TNFSF8, or CD153) is a membrane-bound cytokine member of the TNF family and is expressed in activated lymphocytes, histiocytes, and granulocytes [10].

CD30 is universally expressed in classical Hodgkin lymphoma and anaplastic large cell lymphoma, as well as in cutaneous CD30-positive lymphoproliferative disorders, cutaneous anaplastic large cell lymphoma, and lymphomatoid papulomatosis. Other lymphoproliferative disorders, such as diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, peripheral T-cell lymphoma, mycosis fungoides, and adult T-cell leukemia/lymphoma, can express CD30 to variable degrees [18] [19] [20].

CD30 is variably expressed in DLBCL, at a frequency of up to 60% depending on the cut-off value [21] [22], but unexpectedly, some studies have suggested that the response to brentuximab vedotin treatment does not correlate with CD30 expression [23].

The extent of CD30 expression in DLBCL and its significance are not well established due to the lack of standardization of immunohistochemical techniques and the absence of consensus on the cut-off point. Previous studies have used cut-off values that range from 10% to 20% of CD30-positive cells per tumor to classify the tumor as positive. [24] [12] [25] [26] [13] [27]

Various studies have looked into the expression of CD30 in DLBCL and its prognostic significance. A population-based Canadian study explored CD30 expression characteristics in 386 immunocompetent de novo DLBCL patients who were treated with R-CHOP chemotherapy. Of 386 patients, 95 (25%) had CD30+ malignant lymphoma cells in the biopsy specimen. The study categorized the patients based on international prognostic score (IPI), molecular subtypes (Germinal Center vs. non-Germinal Center), and CD30 expression (0%, >0–10%, and >20% cells expressing CD30). At the 20% CD30 expression cutoff for positivity, CD30+ DLBCL had a non-significant trend towards improved OS and PFS. When the cut-off was changed to >0% positivity, the CD30+ GCB subtype had better OS (5-year survival: 86% vs. 64%, $p = 0.020$) and PFS (HR 2.65, 95% confidence interval: 1.13-6.23) [23]. This observation highlights the importance of standardizing the cut-off of CD30 expression for considering positivity [6].

A large-scale study conducted in British Columbia [25] agreed that CD30 was associated with favorable clinical outcomes but was merely elicited in the GCB group.

However, Campuzano-Zuluaga et al. [24] and Hao X et al. [26] argued that CD30 expression was positively associated with BCL2 expression and an inferior outcome.

A recent study from Collie et al. [28] showed that CD30 expression is a predictive factor of poor survival in DLBCL patients treated with R-CHOP. However, another study in a large cohort of de novo DLBCL patients revealed that CD30 expression could identify a superior clinical outcome subgroup of DLBCL patients. [12]

In our study, the overall survival of patients expressing CD30 was reduced compared with those not expressing CD30. However, it should be noted that this study was a retrospective analysis based on a relatively small number of patients.

Expression of CD30 in a subset of cases of DLBCL may make these lymphomas amenable to targeted therapy such as brentuximab vedotin, an anti-CD30 monoclonal antibody-drug conjugate approved by the Food and Drug Administration for the treatment of classical Hodgkin lymphoma and anaplastic large cell lymphoma since 2011. A recent clinical trial using brentuximab in patients with relapsed or refractory DLBCL showed promising results [29]. Although this study suggested that CD30 expression

imparts a more favorable prognosis with first-line R-CHOP therapy, other studies have not universally confirmed this finding, and the prognostic implications of CD30 expression at relapse are unclear [25] [28].

CD30 immunohistochemistry may be useful as a prognostic marker in R-CHOP-treated GCB-DLBCL, as it is associated with a trend towards a better outcome [25].

Conclusion:

CD30+ DLBCL may be a subset of de novo DLBCLs with characteristic clinicopathological features, but the prognostic role of CD30 is limited.

However, the prevalence of CD30 positivity is variable according to different studies, and the prognostic significance of CD30 is also controversial.

Anti-CD30 therapy is an attractive approach to treating CD30 DLBCL. Future studies examining the role of brentuximab vedotin in CD30-expressing DLBCL will demonstrate whether this approach will have a place in the therapeutic armamentarium of DLBCL.

References:

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375-90.
2. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000;403:503-11.
3. Visco C, Li Y, Xu-Monette ZY, Miranda RN, Green TM, Li Y, et al. Comprehensive gene expression profiling and immunohistochemical studies support application of immunophenotypic algorithm for molecular subtype classification in diffuse large B-cell lymphoma: a report from the International DLBCL Rituximab-CHOP Consortium Program Study. Leukemia. 2012;26:2103-13.
4. Ott G, Ziepert M, Klapper W, Horn H, Szczepanowski M, Bernd H-W, et al. Immunoblastic morphology but not the immunohistochemical GCB/nonGCB classifier predicts outcome in diffuse large B-cell lymphoma in the RICOVER-60 trial of the DSHNHL. Blood. 2010;116:4916-25.
5. Gu K, Weisenburger DD, Fu K, Chan WC, Greiner TC, Aoun P, et al. CELL-OF-ORIGIN FAILS TO PREDICT SURVIVAL IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION. Hematol Oncol. 2012;30:143-9.
6. Pierce JMR, Mehta A. Diagnostic, prognostic and therapeutic role of CD30 in lymphoma. Expert Rev Hematol. 2017;10:29-37.
7. Coiffier B, Lepage E, Brière J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP Chemotherapy plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma. N Engl J Med. 2002;346:235-42.
8. Pfreundschuh M, Trümper L, Osterborg A, Pettengell R, Trneny M, Imrie K, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol. 2006;7:379-91.
9. Coiffier B, Sarkozy C. Diffuse large B-cell lymphoma: R-CHOP failure-what to do? Hematol Am Soc Hematol Educ Program. 2016;2016:366-78.
10. Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, et al. Introduction of Combined CHOP Plus Rituximab Therapy Dramatically Improved Outcome of Diffuse Large B-Cell Lymphoma in British Columbia. J Clin Oncol. 2005;23:5027-33.
11. van der Weyden CA, Pileri SA, Feldman AL, Whisstock J, Prince HM. Understanding CD30 biology and therapeutic targeting: a historical perspective providing insight into future directions. Blood Cancer J. 2017;7:e603.
12. Sotomayor EM, Young KH, Younes A. Clinical roundtable monograph: CD30 in lymphoma: its role in biology, diagnostic testing, and targeted therapy. Clin Adv Hematol Oncol HO. 2014;12:1-22.
13. Hu S, Xu-Monette ZY, Balasubramanyam A, Manyam GC, Visco C, Tzankov A, et al. CD30 expression defines a novel subgroup of diffuse large B-cell lymphoma with favorable prognosis and distinct gene expression signature: a report from the International DLBCL Rituximab-CHOP Consortium Program Study. Blood. 2013;121:2715-24.
14. Xu J, Oki Y, Saksena A, Desai P, Lin P, Tang G, et al. CD30 expression and prognostic significance in R-EPOCH–treated patients with diffuse large B-cell lymphoma. Hum Pathol. 2017;60:160-6.
15. Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2007;109:1857-61.
16. Ziepert M, Hasenclever D, Kuhnt E, Glass B, Schmitz N, Pfreundschuh M, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28:2373-80.

17. Xu J, Oki Y, Saksena A, Desai P, Lin P, Tang G, et al. CD30 expression and prognostic significance in R-EPOCH-treated patients with diffuse large B-cell lymphoma. Hum Pathol. 2017;60:160-6.
18. Dürkop H, Latza U, Hummel M, Eitelbach F, Seed B, Stein H. Molecular cloning and expression of a new member of the nerve growth factor receptor family that is characteristic for Hodgkin's disease. Cell. 1992;68:421-7.
19. Stein H, Mason DY, Gerdes J, O'Connor N, Wainscoat J, Pallesen G, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood. 1985;66:848-58.
20. Horie R, Watanabe T. CD30: expression and function in health and disease. Semin Immunol. 1998;10:457-70.
21. Falini B, Pileri S, Pizzolo G, Dürkop H, Flenghi L, Stirpe F, et al. CD30 (Ki-1) molecule: a new cytokine receptor of the tumor necrosis factor receptor superfamily as a tool for diagnosis and immunotherapy. Blood. 1995;85:1-14.
22. Rodrigues-Fernandes CI, Abreu LG, Radhakrishnan R, Perez DE da C, Amaral-Silva GK, Gondak R de O, et al. Prognostic significance of CD30 expression in diffuse large B-cell lymphoma: A systematic review with meta-analysis. J Oral Pathol Med Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol. 2021;50:587-93.
23. Salas MQ, Climent F, Tapia G, DomingoDomènech E, Mercadal S, Oliveira AC, et al. Clinicopathologic features and prognostic significance of CD30 expression in de novo diffuse large B-cell lymphoma (DLBCL): results in a homogeneous series from a single institution. Biomark Biochem Indic Expo Response Susceptibility Chem. 2020;25:69-75.
24. Lobastova L, Lettau M, Babatz F, de Oliveira TD, Nguyen P-H, Pauletti BA, et al. CD30-Positive Extracellular Vesicles Enable the Targeting of CD30-Negative DLBCL Cells by the CD30 Antibody-Drug Conjugate Brentuximab Vedotin. Front Cell Dev Biol. 2021;9:698503.
25. Campuzano-Zuluaga G, Cioffi-Lavina M, Lossos IS, Chapman-Fredricks JR. Frequency and extent of CD30 expression in diffuse large B-cell lymphoma and its relation to clinical and biologic factors: a retrospective study of 167 cases. Leuk Lymphoma. 2013;54:2405-11.
26. Slack GW, Steidl C, Sehn LH, Gascoyne RD. CD30 expression in de novo diffuse large B-cell lymphoma: a population-based study from British Columbia. Br J Haematol. 2014;167:608-17.
27. Hao X, Wei X, Huang F, Wei Y, Zeng H, Xu L, et al. The Expression of CD30 Based on Immunohistochemistry Predicts Inferior Outcome in Patients with Diffuse Large B-Cell Lymphoma. PLOS ONE. 2015;10:e0126615.
28. Gong Q-X, Wang Z, Liu C, Li X, Lu T-X, Liang J-H, et al. CD30 expression and its correlation with MYC and BCL2 in de novo diffuse large B-cell lymphoma. J Clin Pathol. 2018;71:795-801.
29. Collie AMB, Hill BT, Manilich EA, Smith MR, Hsi ED. CD30 Immunohistochemical Expression In Diffuse Large B-Cell Lymphoma Is Associated With Decreased Overall Survival and The Non-Germinal Center Molecular Subtype. Blood. 2013;122:4318.
30. Jacobsen ED, Sharman JP, Oki Y, Advani RH, Winter JN, Bello CM, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. Blood. 2015;125:1394-402.