Original Contribution

CD43 Expression Is an Adverse Prognostic Factor in Diffuse Large B-Cell Lymphoma

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Abstract

Background: CD43 is a transmembrane glycoprotein expressed in different hematopoietic cells, including some subsets of B lymphocytes. About a quarter of diffuse large B-cell lymphomas (DLBCLs) express CD43, but its prognostic significance is unknown. **Patients and Methods:** We analyzed the prognostic effect of immunohistochemically determined CD43 expression in 119 patients with newly diagnosed DLBCL. All were treated with CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone)–like chemotherapy, 57 without and 62 with rituximab. **Results:** A total of 31 DLBCL cases (26%) expressed CD43. Patients with CD43+ and CD43− lymphomas did not differ regarding sex, International Prognostic Index (IPI) factors and score, rituximab treatment, presence of bulky disease, or germinal center subtype. Median follow-up was 45 months. Patients with CD43+ DLBCL had significantly lower complete response rates (59% vs. 80%; $P = .019$), 2-year event-free survival (EFS) rates (34% vs. 64%; $P = .003$), and overall survival (OS) rates (45% vs. 76%; $P = .002$). The prognostic significance of CD43 expression was retained in multivariate analysis (relative risk [RR] 2.04; $P = .013$ for EFS; RR 2.17; $P = .016$ for OS). In subgroup analysis, the effect of CD43 expression was significant in patients treated with rituximab and those with low IPI, whereas it was not reached in patients treated without rituximab. The effect was not observed in patients with high IPI. **Conclusion:** These results indicate that CD43 expression is an important independent adverse prognostic factor in DLBCL.

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Introduction

The CD43 molecule, also known as leukosialin, is a multifunctional type I transmembrane glycoprotein expressed in a variety of hematopoietic cells.[1] It is classified as a member of the cell-surface mucin family because of the heavily O-glycosylated extracellular domain.[2] The evolutionary conserved intracellular domain is involved in signal transduction through activation of several signaling cascades and might regulate cell activation and proliferation.[3-5] The physiologic role of CD43 was extensively studied but still remains controversial. Earlier studies on T cells suggested that CD43 is a negative regulator of T-cell function because of the rigid extracellular domain that acts as a barrier to cell-to-cell interactions.[6,7] However, more recent studies identified CD43 as the ligand for E-selectin responsible for T-cell migration to sites of inflammation.[8,9] In addition, CD43 is involved in T-cell maturation and survival by promoting[10] or inhibiting apoptosis.[11] The role of CD43 in B cells is even less clear. CD43 seems to play a role in stage and sublineage-specific maturation of precursor B cells in the bone marrow.[12] Mature plasma cells and B cells in the gastrointestinal mucosa also express this protein, but resting peripheral B cells do not.[13,14] Therefore, coexpression of CD43 and CD20 on peripheral B cells is suggestive of malignancy.[15] CD43 is differently expressed in various types of non-Hodgkin lymphomas (NHLs). Expression of CD43 in diffuse large B-cell lymphomas (DLBCLs) ranges from 16% to 28%.[16,17]

Diffuse large B-cell lymphoma is the most common lymphoid neoplasm, accounting for approximately 30%-40% of all NHLs. Today, about 60% of patients can be cured using a combination of anthracycline-based chemotherapy and rituximab.[18,19] However, the course of individual patients varies widely, and prognostic factors are needed to distinguish patients with favorable prognosis from those who require more intensive treatment and stem cell transplantation. Currently, the most important prognostic index for

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Table 1 Patient Characteristics and Response to Treatment According to CD43 Expression

Characteristic	CD43+ (n = 31)	CD43− (n = 88)	*P* Value
Demographics			
Median age, years (range)	51 (17-76)	48.5 (16-81)	.95
Number male sex (%)	20 (65)	44 (50)	.28
Disease Characteristics (%)			
PS ≥ 2	14 (45)	30 (34)	.27
Stages 3 and 4	15 (48)	38 (43)	.62
Age ≥ 60 years	10 (36)	29 (35)	.91
≥ 2 Extranodal sites	10 (32)	15 (17)	.074
Elevated LDH	18 (58)	51 (58)	.99
≥ 1 Extranodal site	21 (68)	40 (47)	.033
Bulky tumor (> 7.5 cm)	9 (29)	35 (40)	.37
GC subtype	10 (32)	38 (43)	.29
IPI			.21
0-2	18 (58)	62 (70)	
3-5	13 (42)	26 (31)	
Treatment (%)			
Rituximab treatment	17 (55)	45 (51)	.72
CHOP treatment	25 (81)	65 (74)	.45
Response (%)			
CR (u)	17 (59)	70 (80)	.019
PR, SD, PD	12 (41)	17 (20)	
Not evaluated	2	1	

Abbreviations: CHOP = cyclophosphamide/doxorubicin/vincristine/prednisone; CR (u) = complete remission (unconfirmed); GC = germinal center; IPI = International Prognostic Index; LDH = lactate dehydrogenase; PD = progressive disease; PR = partial remission; PS = performance status; SD = stable disease

DLBCL is still the International Prognostic Index (IPI) based on clinical characteristics.[20] Bulky disease also seems to be an adverse prognostic factor.[19] Gene-expression profiling is able to identify 2 or 3 distinct prognostic subgroups of DLBCL, the germinal center (GC)–derived subtype with favorable prognosis, activated B-cell (ABC) subtype with unfavorable prognosis, and a small third group that has a prognosis indistinguishable from the ABC subtype.[21,22] However, gene-expression profiling cannot be used in routine clinical practice. Therefore, immunohistochemical procedures to distinguish between the GC and non-GC DLBCL subtypes have been developed. The method developed by Hans et al[23] is used most frequently, although its prognostic importance in the rituximab era is still somewhat controversial.[24,25] In contrast, a more recent gene-expression profile study identified 3 signatures associated with survival both in patients who received CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) and patients who received rituximab plus CHOP (R-CHOP).[26]

To our knowledge, there are no data on the prognostic significance of CD43 expression in DLBCL. We therefore undertook this study to analyze the prognostic effect of CD43 expression in patients with DLBCL treated with anthracycline-based chemotherapy regimens with or without rituximab.

Patients and Methods

Patients and Treatments

This was a retrospective study performed on 119 patients with newly diagnosed DLBCL who were diagnosed and treated in our institutions since 1984. The group consisted of 62 patients treated with rituximab in combination with first-line chemotherapy and 57 patients who were treated before the introduction of rituximab with chemotherapy alone. Inclusion criteria were available diagnostic paraffin block, complete medical record, and first-line treatment with an anthracycline-based chemotherapy regimen. Patients with HIV-associated lymphoma, primary central nervous system lymphoma, or composite lymphoma were excluded. All consecutive patients meeting the entry criteria were included. Most patients who were not included in the study because of the unavailability of the diagnostic paraffin block were diagnosed at other institutions. There were no apparent differences in outcomes of these patients and the studied cohort (data not shown).

The chemotherapy regimen used in 90 patients was CHOP. The remaining 29 patients received CHOP-like regimens: CNOP (cyclophosphamide/mitoxantrone/vincristine/prednisone), COP-Blam (cyclophosphamide/doxorubicin/vincristine/prednisone/bleomycin/procarbazine), BACOP (cyclophosphamide/doxorubicin/vincristine/bleomycin/prednisone) or EPOCH (etoposide/cyclophosphamide/doxorubicin/vincristine/prednisone).

Ethics

The study was approved by the Ethics Committee of the Medical School, University of Zagreb, Croatia. Patients were not contacted directly because of the retrospective nature of the study.

Immunohistochemistry

Standard sections for routine hematoxylin and eosin staining were obtained from each specimen to demonstrate the presence of lymphoma cells within the material to be studied. All slides were reviewed by 2 hematopathologists. In all cases, the immunohistochemical stains for CD20 (clone L26; dilution 1:200; DAKO, Glostrup, Denmark), CD3 (clone PC3/188A; dilution 1:50; DAKO, Glostrup, Denmark), CD10 (clone 56C6; dilution 1:30; Novocastra, Newcastle, UK), Bcl-6 (clone PG-B6p; dilution 1:10; DAKO, Glostrup, Denmark), CD43 (clone DF–T1; dilution 1:25; DAKO, Glostrup, Denmark), and MUM1 (clone MUM1p; dilution 1:25; DAKO, Glostrup, Denmark) were performed using the streptavidin-biotin complex method. Bcl-6, CD10, and MUM1 expression were determined to distinguish GC and non-GC subtypes according to Hans et al.[23] The immunohistochemical result was considered positive if ≥ 30% tumor cells were stained positively with an antibody. In addition, CD43+ cases were stained for cyclin D1 (clone SP4, dilution 1:25, Neomarkers, Freemont, CA) to exclude mantle cell lymphoma and CD5 (clone 4C7, dilution 1:50, Novocastra, Newcastle, UK).

Statistics

The analyzed outcomes were response to treatment, event-free survival (EFS), and overall survival (OS). Response to treatment was assessed using standard criteria.[27] Event-free survival was calculated

Figure 1 Event-Free (A) and Overall Survival (B) According to CD43 Expression

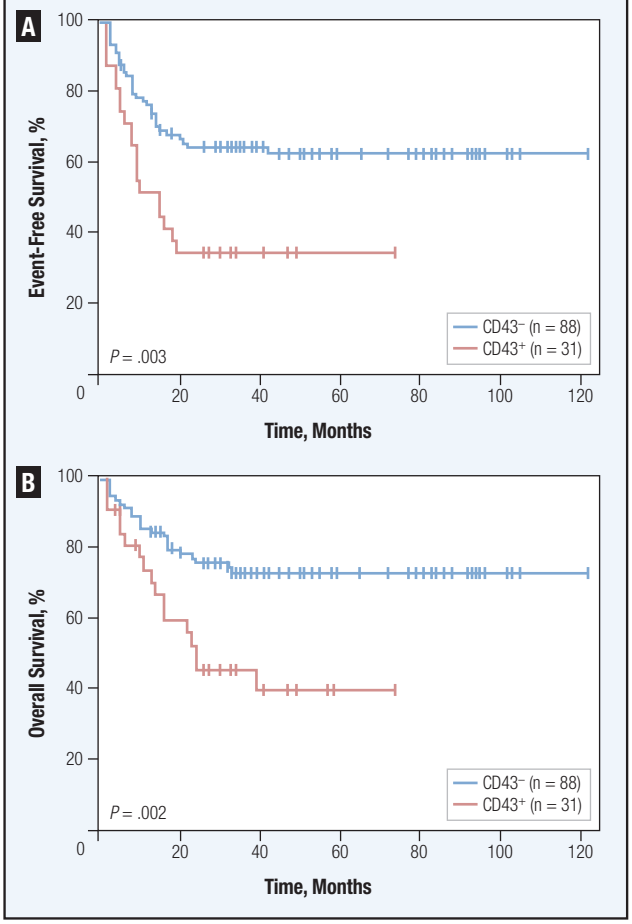
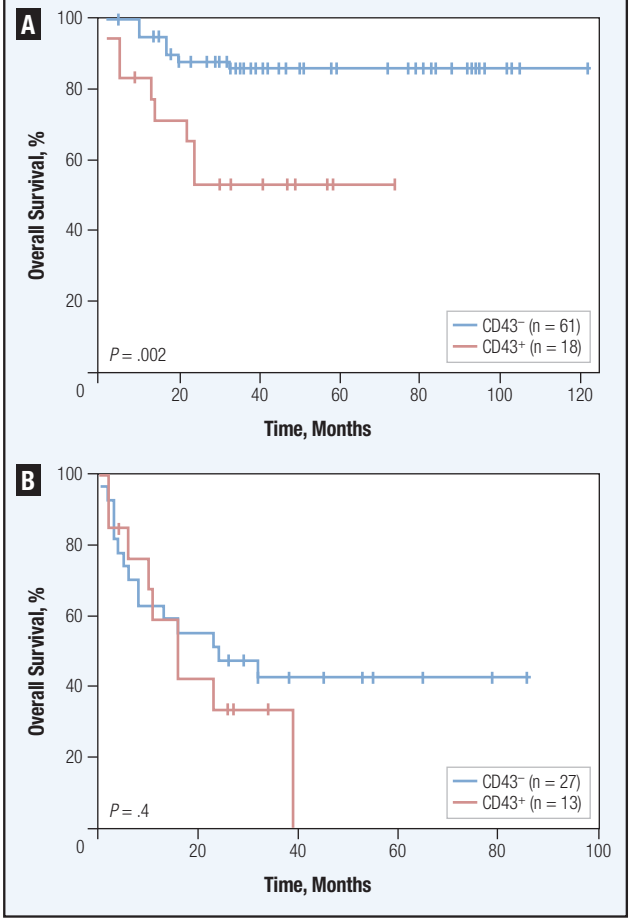


Figure 2 Overall Survival According to CD43 Expression and IPI Score



A. IPI score 0-2. **B.** IPI score 3-5.
Abbreviation: IPI = International Prognostic Index

from day 1 of the first treatment cycle until treatment failure (disease progression, institution of any unplanned antilymphoma treatment, relapse, or death from any cause) or last follow-up. Overall survival was calculated from day 1 of the first cycle of the treatment until the day of death or last follow-up. Pretreatment features and response were compared using the Pearson χ^2 test. Event-free survival and OS curves were calculated according to the Kaplan-Meier method; the log-rank test was used for comparison between groups. In addition, the effect of CD43 and factors included in the IPI score on response and survival were analyzed by logistic regression and Cox regression statistics. Statistica 7.0 software (StatSoft. Inc., Tulsa, OK) was used for data analysis. A P value of < .05 was considered statistically significant.

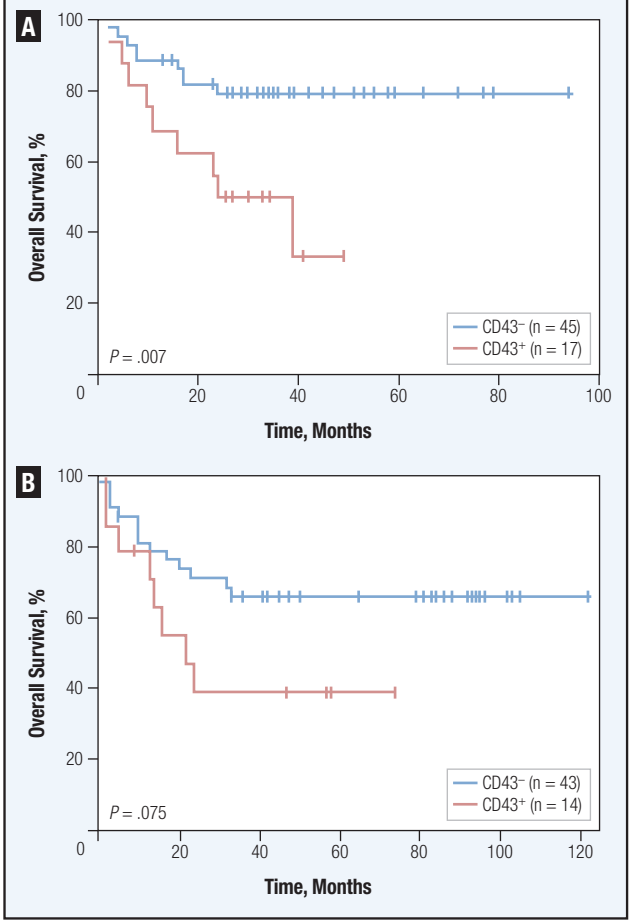
Results

CD43 was expressed in 31 (26%) of 119 DLBCL cases. In positive cases, the expression of CD43 was strong and ubiquitary, with > 90% of tumor cells expressing the antigen. All CD43⁺ cases were cyclin D1 negative, and 3 cases were CD5 positive. There were no differences between patients with CD43⁺ and CD43⁻ lymphoma regarding age, sex, performance status (PS), disease stage, > 1 extranodal localization, lactate dehydrogenase (LDH) level, IPI, bulky disease, and rituximab treatment (Table 1). Similarly, no differences between groups were observed regarding Bcl-6, CD10, and MUM1 expression and the frequency of GC versus non-GC lymphoma subtypes. The frequency of extranodal disease was somewhat higher in patients with CD43⁺ lymphoma (P = .033). Of the 116 patients evaluable for response evaluation, 87 patients (75%) had complete or unconfirmed complete remission (CR) after first-line treatment. The CR rate was significantly lower in patients with DLBCL expressing CD43 (59%) compared with those with CD43⁻ DLBCL (80%; P = .019).

Survival

After a median follow-up of 45 months for surviving patients, estimated 2-year EFS and OS rates for all patients were 56% and 68%, respectively. Patients with a CD43⁺ lymphoma had lower EFS and OS than those with a CD43⁻ lymphoma (Figures 1A and 1B). Two-year EFS was 34% in the former and 64% in the latter group (P = .003), and 2-year OS was 45% versus 76% (P = .002). As expected, the IPI score strongly influenced EFS and OS (data not shown; P < .001 for both measures). When patients were stratified in low- (IPI 0-2) and high-risk groups (IPI 3-5), CD43 expression was associated with inferior EFS and OS only in the low-IPI group (2-year EFS, 42% vs. 75%; P = .008; 2-year OS, 54% vs. 88%; P = .002) but not in the high-IPI group (2-year EFS, 23% vs. 40%; P = .29; 2-year OS, 34% vs. 47%; P = .4; Figures 2A and 2B). In groups of patients

Figure 3 Overall Survival According to CD43 Expression and Rituximab Treatment



A. Patients treated with rituximab and chemotherapy. **B.** Patients treated without rituximab.

stratified according to rituximab treatment, the adverse effect of CD43 expression on EFS and OS retained statistical significance only in the group treated with immunochemotherapy (2-year EFS, 41% vs. 73%; $P = .009$; 2-year OS, 50% vs. 80%; $P = .007$; Figure 3A). In the group treated with chemotherapy alone, the direction and magnitude of the effect were similar, but the level of statistical significance was not reached (2-year EFS, 25% vs. 55%; $P = .085$; 2-year OS 40% vs. 66%; $P = .075$; Figure 3B).

Multivariate Analysis

Variables included in the IPI and CD43 expression were entered in a multivariate analysis of response and survival. Complete remission rate was inversely related to a poor PS (relative risk [RR], 2.89; $P = .030$) and CD43 expression (RR, 3.10; $P = .032$). Using the Cox regression analysis, CD43 expression, age ≥ 60 years, and elevated LDH were significant independent factors associated with lower EFS, whereas CD43 expression, age ≥ 60 years, high LDH, and poor PS were significant independent factors associated with lower OS (Table 2). In a second multivariate analysis, we used IPI score as a single factor. CD43 expression remained a significant independent prognostic factor for EFS (RR, 2.74; $P < .001$ for IPI; RR, 2.04; $P = .013$ for CD43) and OS (RR, 3.93; $P < .001$ for IPI; RR, 2.17; $P = .016$ for CD43).

Table 2 Cox Proportional Hazard Regression Analysis of Survival

Risk Factor	Event-Free Survival		Overall Survival	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
PS ≥ 2	1.70 (0.94-3.08)	.08	2.37 (1.18-4.76)	.015
Stages 3 and 4	1.51 (0.71-3.17)	.28	0.84 (0.37-2.28)	.91
Age ≥ 60 Years	2.11 (1.16-3.83)	.015	2.60 (1.27-5.34)	.009
Elevated LDH	2.17 (1.05-4.50)	.037	3.21 (1.28-8.09)	.013
≥ 2 Extranodal Sites	1.54 (0.75-3.15)	.24	2.47 (1.03-5.95)	.043
CD43⁺	2.73 (1.50-4.97)	.001	2.43 (1.21-4.87)	.013

Abbreviations: LDH = lactate dehydrogenase; PS = performance status; RR = relative risk

Discussion

In our study, 26% of DLBCLs expressed CD43. This is comparable to results of other groups in which CD43 expression was observed in 16%-28% of cases.[16,17] The prognostic effect of CD43 expression was initially observed in a small study of patients with ocular adnexal lymphoma, where it was associated with inferior outcome.[28] In this study, we demonstrated for the first time a strong adverse effect of CD43 expression in patients with DLBCL affecting both response and survival. The negative influence of CD43 was independent of IPI, as demonstrated by multivariate analysis and of GC versus non-GC subtypes. Also, all CD43⁺ cases were cyclin D1 negative, whereas the expression of CD5, a well-known adverse prognostic marker in DLBCL, was comparable to other studies confirming that the CD43⁺ DLBCL cases were not misdiagnosed cases of mantle cell lymphoma.[29]

Different explanations for the adverse effect of CD43 expression can be found. CD43 expression could cause earlier and more widespread disease dissemination. The function of CD43 as a ligand for E-selectin on activated T cells mediating migration of activated T cells into sites of inflammation has been well established.[8,9] More recently, it was also demonstrated that CD43 plays a pivotal role in extravasation of leukemic B cells.[30] Manipulation of CD43 expression in vitro and in vivo significantly affects infiltration of extravascular tissues and engraftment of human pre-B leukemia cells. In solid tumors, CD43 expression in colon cancer could have a role in tumor dissemination, possibly by mediating tumor-cell adherence to the peritoneum.[31] Thus, CD43 expression might facilitate migration of DLBCL cells, particularly to extranodal sites, leading to more frequent progression of lymphoma or relapse. However, the fact that CD43 expression was not related to stage argues against this explanation.

An alternative explanation for the adverse effect of CD43 expression is based on its antiapoptotic role. Studies published in the previous decade investigated the role of CD43 in B-cell survival using transgenic mouse models.[32,33] When CD43 was transfected into CD43⁻ peripheral B cells, transgenic cells showed increased survival and decreased susceptibility to apoptosis.[32] In another study, CD43 cDNA was transfected into a CD43⁻ murine lymphoma.[33] In comparison with CD43⁻ cells, CD43⁺ cells had reduced susceptibility to G_1 arrest and better survival in culture upon serum depletion. More recent studies investigated molecular mechanisms involved in antiapoptotic activity of CD43 in different types of cells. The potential mechanism

of antiapoptotic activity might include resistance to FAS-mediated apoptosis in T cells.[11] A recent study identified CD43 as a potential contributor to tumor development through evasion of FAS-mediated apoptosis in nonhematopoietic tumors lacking p53.[34] The activation of nuclear factor (NF)–κB system observed in CD43+ B-lymphocyte progenitors could be another contributive factor.[35]

Unlike other immunohistochemical prognostic factors, such as Bcl-2, the adverse effect of CD43 expression is not mitigated by rituximab treatment.[36] Actually, the negative effect of CD43 expression seems to be more pronounced in patients treated with rituximab. This might be an artifact of limited patient numbers in subgroup analysis. Alternatively, the observed difference could be a result of improved outcome in the subgroup of patients with CD43− lymphoma. The mechanisms of rituximab action include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, induction of apoptosis, and increase in chemosensitization.[37] Because of the diverse and controversial role of both extracellular and intracellular domains of CD43, it is possible that CD43 antagonizes rituximab activity at different levels, for example, by impairing antibody or effector-cell binding to tumor cells,[37] causing activation of NF-κB[35] or resistance to FAS-mediated apoptosis.[11,34]

Another interesting observation in our study is that the adverse effect of CD43 is limited to, or at least more pronounced, in the group of patients with low IPI. Although subgroup analyses are unreliable, this suggests that CD43 expression might be used to identify a subgroup with increased risk of treatment failure in this otherwise favorable group of patients.

Conclusion

We have identified CD43 expression as a new important independent negative prognostic factor in DLBCL. Before being generally accepted, our results need to be confirmed in larger cohorts of patients from other centers. Further experimental studies are needed to elucidate the molecular pathways involved in pathogenesis and resistance to the treatment conferred by CD43. Introduction of novel agents should be considered in the treatment of patients with CD43+ DLBCL.

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Disclosures

The authors have no relevant financial relationships to disclose.

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