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Original contribution

CD43 expression in diffuse large B-cell lymphoma, not otherwise specified: CD43 is a marker of adverse prognosis☆

Xiao-Bo Ma MD, PhD[a], Yan Zheng PhD[a], He-pei Yuan PhD[a], Jing Jiang MD, PhD[b], Yin-Ping Wang MD, PhD[a,*]

[a]*Department of Pathology, The First Hospital of Jilin University, Changchun 130021, China*
[b]*Division of Clinical Epidemiology, The First Hospital of Jilin University, Changchun 130021, China*

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Summary CD43 (leukosialin) is a transmembrane glycoprotein expressed in a variety of hematopoietic cells, including B lymphocytes, and a variety of malignancies including lymphoma, leukemia, and solid tumors. CD43 plays an important role in the development of many diseases, and coexpression of CD43 and CD20 on peripheral B cells is a predictive factor of hematopoietic malignancy. Although CD43 is expressed in approximately 25% of diffuse large B-cell lymphomas (DLBCLs), its prognostic significance remains unclear. To analyze CD43 expression in DLBCL, not otherwise specified (DLBCL, NOS), and assess its prognostic value, we analyzed clinical data from 160 patients with DLBCL, NOS. We observed that CD43 expression was detected in 47 (29.4%) of 160 cases. CD43 expression was positively correlated with old age (>60 years), high serum lactate dehydrogenase level, B symptoms, non–germinal center type, and DLBCL, NOS, mortality. Patients with CD43-positive DLBCL, NOS, had poorer overall survival ($P < .001$, log-rank test) and event-free survival ($P < .001$, log-rank test) than CD43-negative patients. Univariate analysis showed that CD43 expression, age, sex, Ann Arbor stage, International Prognostic Index category, and germinal center phenotype were prognostic factors for DLBCL, NOS, patient survival. Multivariate analysis showed that CD43 expression was an independent significant prognostic factor for event-free survival ($P < .001$) and overall survival ($P < .001$). Based on these data, we conclude that CD43 expression is a novel adverse prognostic factor for patients with DLBCL, NOS.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive disease composed of a heterogeneous group of lymphomas in terms of morphology, immunophenotype, molecular abnormalities, and clinical behavior [1]. Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) is the most common subtype of DLBCL, comprising 25% to

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* Corresponding author. Department of Pathology, The First Hospital of Jilin University, 71 Xinmin ST, Changchun 130021, Jilin Province, China.
E-mail address: wyppath@163.com (Y. -P. Wang).

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30% of non-Hodgkin lymphoma in Western countries and is more prevalent in developing countries [2]. The primary treatment of DLBCL, NOS, is combination therapy with cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), and prednisone (CHOP) [3]. Cyclophosphamide, hydroxydaunorubicin, Oncovin, and prednisone therapy has recently been improved by the addition of rituximab or etoposide or the administration of high-dose CHOP at 2-week intervals (CHOP-14); however, 20% to 30% of patients still experience relapse or refractory disease [4,5]. These patients could benefit from alternative therapies if their clinical outcome could be more accurately predicted at the time of diagnosis. Therefore, it is important to identify biologic prognostic factors that could identify high-risk patients with DLBCL, NOS.

Currently, International Prognostic Index (IPI) is considered the most important prognostic factor for DLBCL, NOS, but is insufficient for an accurate prognosis because it does not reflect the underlying biologic differences in each case [6]. By gene expression profiling, DLBCL, NOS, has been divided into at least 2 subgroups that can predict disease outcome: germinal center (GC) derived, and the non-GC or activated B-cell type. The GC subtype has a better outcome compared with the activated B-cell type [7]. In addition, several biomarkers have been shown to predict the outcome of DLBCL, NOS, but few have made their way into clinical practice [8,9].

CD43 (leukosialin), also known as sialophorin, was first identified in 1981 [10]. CD43 is a heavily glycosylated transmembrane protein expressed on the surface of most hematopoietic cells including B lymphocytes of definite phase as well as some lymphomas, leukemias, and solid tumors. The physiologic role of CD43 has been extensively studied but still remains controversial. The 235 amino acid extracellular domain of CD43 usually contains mainly sialylated O-linked glycans [11] and can regulate cell adhesion both positively and negatively [12]. The intracellular C-terminal domain of CD43 is evolutionarily conserved and involved in signal transduction [11]. CD43 also plays a role in locomotion, apoptosis modulation, differentiation, and immune homeostasis [13].

Abnormal expression of CD43 has been implicated in autoimmune diseases such as diabetes, systemic lupus erythematous, Wiskott-Aldrich syndrome, and human immunodeficiency virus infection [14-17]. Recent studies have focused on the relationship between CD43 expression and tumorigenesis, particularly hematopoietic malignancies. CD43 appears to be involved in the tumor metastasis and can serve as a marker of malignant transformation [18]. Moreover, combined application of anti–CD43 antibodies and anti–CD5 antibodies can differentiate tumor cells from normal T cells and B cells [19], and coexpression of CD43 and CD20 on peripheral B cells is associated with malignancy [20]. CD43 is expressed in approximately 25% of patients with DLBCL; however, its prognostic significance remains unclear. In the present study, we analyze the expression of CD43 in DLBCL, NOS, and assess the predictive values of CD43 for patients with DLBCL, NOS.

2. Materials and methods

2.1. Patient cohort

The retrospective study was approved by the ethics committee of the Medical School, University of Jilin, Changchun, China; patients were not contacted directly. We searched the database of our hospital from January 1, 2004, to December 30, 2013, for cases of B-cell lymphoma that met the criteria for DLBCL, NOS. The medical records of 160 patients, for which follow-up information was available, were reviewed to collect clinical data. Diagnosis of DLBCL, NOS, was based on the World Health Organization classification system [2]. No patient was serologically positive for human immunodeficiency virus or human T-cell lymphotropic virus type 1, and there were no cases of iatrogenic immunodeficiency-associated lymphoproliferative disorders. All patients received either CHOP or rituximab plus CHOP (R-CHOP) with a median of 5 cycles (3-8 cycles).

2.2. Morphological and immunophenotypic analysis

Biopsy samples collected at the time of diagnosis were fixed in formalin, embedded in paraffin, sliced, and stained with hematoxylin and eosin for histologic analysis. Immunohistochemical analysis was carried out using the dextran-polymer method (EnVision+; Dako, Glostrup, Denmark) using monoclonal antibodies against CD20 (1:200 dilution, clone BC-1; Santa Cruz Biotechnology, Santa Cruz, CA), CD3 (1:200 dilution, clone PC3/188A; Santa Cruz Biotechnology), CD43 (1:200 dilution, clone DF-T1; Santa Cruz Biotechnology), CD10 (1:200 dilution, clone SP67; Santa Cruz Biotechnology), Bcl-6 (1:200 dilution, clone GI191E/A8; Santa Cruz Biotechnology), MUM-1 (1:200 dilution, clone MUM1P; Santa Cruz Biotechnology), FOXP1 (1:500 dilution, clone JC12; Abcam, Cambridge, United Kingdom), GCET1 (1:100 dilution, clone RAM341; Abcam). Samples were classified as GC or non-GC phenotypes using the Choi algorithm [21]. Immunohistochemical positivity was defined as 30% or more of tumor cells positively stained with the antibody for CD10 and Bcl-6 and 80% or more of tumor cells positively stained with the antibody for MUM1, FOXP1, and GCET1 [21]. In addition, CD43-positive cases were stained for cyclin D1 (1:150 dilution, clone 72-13G; Santa Cruz Biotechnology) and CD5 (1:200 dilution, clone CD5/54/F6; Santa Cruz Biotechnology) to exclude cases of mantle cell lymphoma. All the histopathology samples and immunohistochemical analysis were reviewed by 2 expert hematopathologists.