CD200 in High-Grade Lymphoma, Chronic Lymphocytic Leukemia, and Chronic Lymphocytic Leukemia–Phenotype Monoclonal B-Cell Lymphocytosis

To the Editor

CD200 has become an essential marker for the study of low-grade lymphoproliferative disorders by flow cytometry (FC) because of its high discriminative power between chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL). However, its behavior in high-grade lymphomas remains unknown. Thus, we read with interest the recently published article by Challagundla et al., in which they examined CD200 in 505 samples, of both healthy individuals and patients with lymphoproliferative disorders, including 52 cases of diffuse large B-cell lymphoma (DLBCL) and six cases of Burkitt lymphoma (BL). Also very interestingly, and previously unreported, Challagundla et al., found that CD200 in CLL, while always positive, was dimmer in those cases with trisomy 12.

In this setting, we report our experience regarding the expression of CD200 by FC in high-grade lymphomas and CLL as well as CLL-phenotype monoclonal B-cell lymphocytosis (MBL), with emphasis on their cytogenetic aberrations.

From November 2012 onward, we have used CD200 (clone MRC-OX104; Becton Dickinson) as part of the basic antibody panel for the study of lymphoproliferative disorders. From that date until December 2014, we studied by FC 44 samples suggestive of high-grade lymphoma
(34 lymph node biopsy specimens, three lymph node fine-needle aspirations, three peripheral blood, and one bone marrow), 36 of which have been confirmed by histologic tissue examination according to World Health Organization criteria. They were further subgrouped, according to their cell of origin, into germinal center B cell–like (GCB) and activated B cell–like (ABC). In the same time period, we studied by FC 106 CLL samples (101 peripheral blood, five bone marrow), as well as 106 CLL-phenotype MBLs. All MBLs included in this study were CLL-like; any other phenotype was excluded. Of those, 74 CLL and 51 MBL samples were also studied by either conventional cytogenetics or fluorescence in situ hybridization, and unless otherwise stated, all analysis and comparisons included only patients with known cytogenetic status.

FC was performed with a Beckman-Coulter FC 500, and the results were analyzed by CXP software. Mann-Whitney U test was used for all statistical comparisons except where specified.

Of 36 histologically confirmed high-grade lymphomas, four were BLs and 32 DLBCLs. CD200 was positive in seven (22%) of 32 DLBCLs, as well as four (36%) of 11 (36%) in ABC vs three (15%) of 20 in GCB (Fisher exact test, \( P = .14 \)) (in one CD200-negative case, the cell of origin could not be determined). In CD200-positive cases, CD200 mean fluorescence intensity (MFI) in ABC was similar to GCB (\( P = .4 \)). One of four BLs was CD200 positive, with a lower MFI than any other high-grade lymphoma in the series.

All 106 CLL samples studied by FC were CD200 positive. Fifteen had a trisomy of chromosome 12, and those cases showed dimmer CD200 MFI compared with the other cases (\( P = .0003 \)). CD200 expression in all other cytogenetic groups was similar. All 106 MBLs were CD200 positive. MFI in MBL cases with trisomy 12 (eight cases) was lower than in the rest of MBL cases (\( P = .019 \)).

Comparing only non–trisomy 12 MBL with non–trisomy 12 CLL, MFI in MBL was lower (\( P = .0023 \)) than in CLL. However, there were no differences between trisomy 12 CLL and trisomy 12 MBL (\( P = .84 \)).

This series studying the role of CD200 in several lymphoproliferative disorders showed that DLBCL is occasionally CD200 positive and that CLL-phenotype MBL is always CD200 positive, albeit at lower MFI than CLL when excluding trisomy 12 cases. This series also confirms that trisomy 12 CLL and MBL cases express CD200 with lower intensity than CLL and MBL (respectively) with other cytogenetic abnormalities or no abnormalities.

CD200 positivity was found in 22% of DLBCLs, with a wide range of positive cells and MFI, as described by Challagundla et al. This contrasts with previous reports that found that, by immunohistochemistry, CD200 was always or almost always negative.\(^7\) Indeed, the authors of those articles suggest that CD200 has a role in the differential diagnosis between classic Hodgkin lymphoma or primary mediastinal DLBCL, entities in which CD200 is positive in more than 90% of cases, and DLBCL, in which CD200 is almost entirely negative. According to the results presented here, this is clearly not the case by FC.

We found no differences between ABC and GCB subtypes in percentage of positive cases, although this might be due to sample size, and we consider it is worth examining further. In contrast with Challagundla et al,\(^1\) we did not find differences in MFI between the two subgroups. However, they notice, as we did, that MFI values overlap greatly. Our findings in BL (only one weakly positive case) also coincide with Challagundla et al.\(^1\)

CLL was always CD200 positive in this series, as has been well established.\(^1,4-6\) Indeed, its high sensitivity for CLL has given CD200 an important role in the diagnosis of lymphoproliferative disorders, and it is even the foundation of new FC approaches to clonal studies of the B-cell compartment.\(^7,8\) However, CLL with trisomy 12 expresses CD200 with a lower MFI than CLL with other cytogenetic abnormalities. The results obtained in this study seem to confirm the findings of Challagundla et al.\(^1\) Further backtesting these findings, we report that MBL cases with trisomy 12 already show weaker CD200 MFI than cases with other cytogenetic abnormalities or with no abnormalities.

CLL-phenotype MBL was, like CLL, always CD200 positive, although with a lower MFI than CLL. To our knowledge, this has not been reported yet, and it is somewhat surprising as this type of MBL has been reported to be, clinically and biologically, no different from CLL with a low burden of disease.\(^9,11\) It will be interesting to follow CD200 MFI in patients with MBL as they evolve into having CLL and find out whether CD200 MFI increases.

Finally, we also report one case of CD23+ MCL with partial CD200 positivity, as has been previously published,\(^1,4\) perhaps suggesting that CD23+ MCL might behave biologically closer to CLL than traditional MCL. Some reports already indicate that CD23 is more frequently positive in indolent, leukemic (more CLL-like) forms of MCL.\(^12\)

In conclusion, the role of CD200 by FC in the differential diagnosis of CLL and MCL has been clearly delineated, but its role in both CLL-phenotype MBL and DLBCL remains to be determined. In the case of the former, it is always positive, although with lower intensity than CLL; in the case of the latter, we still need to find out the origin of the differences between FC and immunohistochemistry, whether CD200 correlates with any of the DLBCL subtypes,
if it has any prognostic implications, and if it can be used as a therapeutic target.

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