2-1-2017

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Recommended Citation
https://doi.org/10.1186/s40364-017-0088-5

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Diagnosis and treatment of CD20 negative B cell lymphomas

Tasleem Katchi and Delong Liu*

Abstract
CD20 negative B cell non-Hodgkin lymphoma (NHL) is rare and accounts for approximately 1-2% of B cell lymphomas. CD20- negative NHL is frequently associated with extranodal involvement, atypical morphology, aggressive clinical behaviour, resistance to standard chemotherapy and poor prognosis. The most common types of these include plasmablastic lymphoma, primary effusion lymphoma, large B-cell lymphoma arising from HHV8-associated multicentric Castleman’s disease, and ALK+ large B cell lymphoma. This review provides an overview of the diagnostic and treatment modalities for CD20 negative B cell NHL.

Background
CD20 is a glycosylated phosphoprotein expressed on the surface of all B cells (except early pro-B cells and plasma cells). Human CD20 molecule is encoded by the MS4A1 gene located on chromosome 11q12.2 [1, 2]. CD20 molecule is a tetra-transmembrane polypeptide with 297 amino acid residues. It plays a role in the differentiation, maturation and activation of B cells. CD20 is involved in the phosphorylation cascade of intracellular proteins by binding to Src family tyrosine kinases, such as Lyn, Fyn, and Lck. The CD20 molecule remains on the membrane of B cells without dissociation or internalization upon binding of CD20 antibody. CD20 expression varies in different lymphoma subtypes [3–5]. It is present from late pro-B cells through memory B cells, but not on early pro-B cells, plasmablasts and plasma cells. Plasma cell differentiation of B cells results in acquisition of plasma cell markers and loss of B cell antigens including the expression of CD20. CD20 was first defined by the murine monoclonal antibody (MoAb) tositumomab [6, 7]. Rituximab, a chimeric CD20 MoAb, was later developed and approved for treatment of human B cell malignancies. Rituximab destroys B lymphoid malignancies through complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). The addition of rituximab, to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has dramatically improved the survival of patients with diffuse large B cell lymphoma (DLBCL) [8, 9]. R-CHOP has since become the gold standard for the treatment of newly diagnosed DLBCL. In addition, rituximab has been found highly effective in a variety of B cell malignancies as well as relapsed and refractory lymphomas. Through recombinant DNA technology, second- and third- generation CD20 MoAbs were developed [2]. Among these, ofatumumab and obinutuzumab have been approved for clinical treatment of B cell malignancies, such as chronic lymphoid leukemia, and follicular lymphoma [10–15].

Genetic mutations of MS4A1 leading to conformational changes in the protein have been speculated to be a molecular mechanism of the CD20 negative phenotype [16]. The loss of CD20 expression is associated with extranodal involvement, a more aggressive clinical course, loss of responsiveness to rituximab and conventional chemotherapy, leading to poor prognosis. It poses a diagnostic and therapeutic dilemma and further studies need to be undertaken to establish the standard of care in this group of patients.

CD20 negative non-Hodgkin lymphomas
The pan-B lymphocyte markers include CD19, CD20, CD79a, and PAX-5 [2, 17–19]. Almost all B cell NHLs are positive for CD20. CD20- negative NHLs are rare with a rate of 1–2% of all B cell NHLs [20]. The most common types of these include plasmablastic lymphoma, primary effusion lymphoma, large B-cell lymphoma arising from...
Molecular analysis using cytogenetics or FISH (fluorescent in-situ hybridization) to detect rearrangements or translocations of Bcl-2, Bcl-6 and MYC is an important part of diagnosis. BCL-2 mutation was found frequently in human B cell lymphomas [34, 35]. Rearrangements or translocations of both BCL-2 and MYC are hallmarks of “double-hit” lymphomas which are typically more resistant to R-CHOP and portent poor prognosis. More intensive chemotherapy regimens and new agents like ibrutinib and lenalidomide appear to improve responses in these double-hit lymphomas [36].

**Treatment strategies**

There is still no standard of care for CD20 negative B cell lymphomas. Response to standard CHOP chemotherapy is inadequate. CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate alternating with ifosfamide, etoposide, cytarabine) [37–44], dose-adjusted EPOCH (infusional etoposide, vincristine and doxorubicin along with high-dose methotrexate and cytarabine) [48–52], are the suggested therapies. Upregulation of the expression of CD20 in CD20-negative B cell acute lymphoblastic leukemia following treatment with 5-azacytidine has been reported [53]. In addition, good response to bortezomib in combination with infusional dose-adjusted EPOCH for the treatment of plasmablastic lymphoma has also been reported [54]. Upregulation of CD20 expression by epigenetic agents may be another option to re-sensitize B lymphoma to CD20 antibodies [55]. Plerixafor, a CXCR4 antagonist, has been shown to enhance rituximab-induced killing of lymphoma cells [56]. It would be interesting to examine whether plerixafor can have similar effect in CD20 negative lymphomas.

**Conclusion**

CD20 negative lymphoma is uncommon and has poor prognosis. It poses a diagnostic and therapeutic dilemma. Further studies need to be undertaken to establish the standard of care for this group of patients. Novel agents targeting B cell signalling pathways, such as, inhibitors of Bruton tyrosine kinase and phosphoinositol-3 kinase, may play important role in the therapy of this rare entity of B cell lymphomas [57–62]. PD-1 antibodies are active in lymphomas [63–65], it remains important to evaluate whether immune check point inhibitors have activity in CD20 negative lymphomas. Bcl-2 inhibitors may be another option for CD20 negative lymphomas and warrant further investigations [34, 66, 67].

**Abbreviations**

CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CODOX-M/IVAC: cyclophosphamide, vincristine, doxorubicin, methotrexate
alternating with ifosfamide, etoposide, cytarabine; EPOCH: etoposide, vincristine and doxorubicin along with bolus cyclophosphamide and prednisone; HyperCVAD: cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and cytarabine; MoAbs: monoclonal antibody

Acknowledgement

We are indebted to our families for their unconditional support.

Funding

There was no funding involved in this study.

Availability of data and materials

This is not applicable.

Author’s contributions

DL designed the study. TK and DL drafted the manuscript. All authors involved in manuscript preparation and revisions. Both authors read and approved final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

This is not applicable.

Ethics approval and consent to participate

This is not applicable.

Received: 23 December 2016 Accepted: 3 February 2017

Published online: 07 February 2017

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