MYD88 mutation is associated with an unfavorable outcome of Primary Diffuse Large B-cell Lymphoma

Malignant lymphoma is a cancer of lymphocytes. This is actually a disease group consisting of multiple subtypes, among which diffuse large B-cell lymphoma (DLBCL) is characterized by diffuse proliferation of large B lymphoid cells. Primary DLBCL of the central nervous system lymphomas (PCNSL) is a rare subtype of DLBCL that arises within the brain or the eyes. PCNSL is treated with multi-agentdrug regimens. Treatment results have overall been unsatisfactory, although a substantial variation in outcome was noted among individual cases. Accordingly, clinical parameters have been proposed to predict the treatment outcome of PCNSL patients. These include patients' conditions such as altered mentation, increased age, poor performance status (the scores based on the activities of daily living), laboratory data such as elevated creatinine clearance, elevated serum lactate dehydrogenase level, and cerebrospinal fluid protein concentration, and structural information such as lymphoma involvement of deep brain (Taoka et al, 2010, Abrey et al, 2006). On the other hand, malignant lymphoma is a genetic disease driven by heritable and somatic mutations, just like the other types of cancers. Not only the topical specificity, but also the mutational profile of PCNSL is unique.

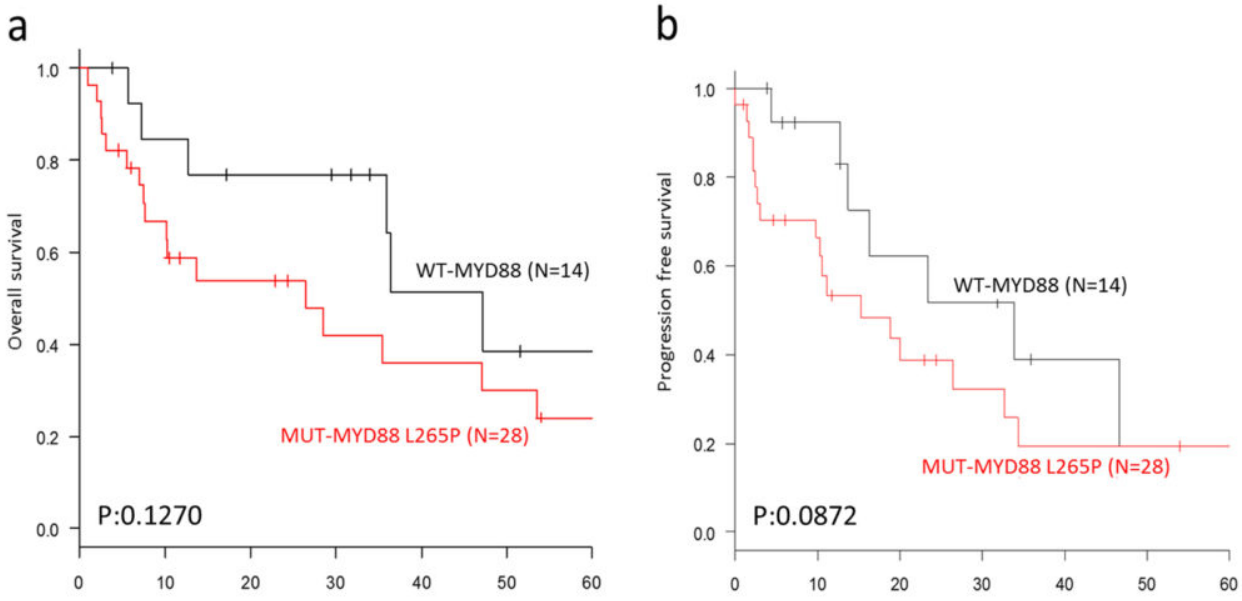

Fig. 1. Prognostic impact of MYD88 L265P mutation in PCNSL (univariate analysis).
Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan Meier method, and compared by the peto-peto generalized Wilcoxon test. PCNSL patients with MYD88 mutation (MUT-MYD88 L265P) had a tendency to be associated with inferior OS and PFS compared with PCNSL patients with wild-type MYD88 (WT-MYD88). (a) OS; (b)PFS.

Several gene mutations are more frequent in PCNSL than in general or other categories of DLBCL, although none of them are specific to PCNSL. The most representative one is *myeloid differentiation primary response gene 88 (MYD88:* 40?79%*)*, followed by *CD79b molecule, immunoglobulin-associated beta (CD79B:* 30?44?*)*, *pim-1 oncogene* (*PIM1*:20~44%*),* and *PR domain containing 1, with ZNF domain* (*PRDM1*:7~20%) (Braggio et al, 2015). Nevertheless, prognostic impact of these mutations in PCNSL remains to be elucidated, in contrast to the fact that the gene expression profile has been utilized to predict clinical courses of patients in many types of cancers including PCNSL.

We intended to integrate gene mutation profiles and clinical data. Forty-two newly diagnosed elderly PCNSL patients, treated with a regimen consisted of intermediate-dose methotrexate (MTX), were enrolled (Taoka et al, 2010). Gene mutations were examined for 12 genes. At least one mutation was detected in 38 out of 42 cases (90.4%). Similar to the previous reports, we found very frequent mutations in *MYD88* (33/42, 78.6%), most of which were located at the nucleotide, presumably resulting in substitution of leucine with proline at amino acid 265 (L265P *MYD88* mutation, 28/42, 66.7%). Our analysis ultimately reached a conclusion that the L265P *MYD88* mutation was a signi?cant risk factor for death, together with altered mentation. In addition, L265P *MYD88* mutation was signi?cantly associated with a higher risk of progression.

MYD88 functions as an adaptor molecule in the B-cell receptor and the toll-like receptor signaling pathways, as well as interleukin-1 receptor signaling pathways through binding to Bruton’s tyrosine kinase (BTK). L265P *MYD88* mutation has been detected in several B-cell malignancies. The importance of this mutation in clinical sequencing settings has been emerging. Frequent detection in Waldenström's macroglobulinemia (WM) emphasizes the diagnostic value of this mutation in WM (Arber et al, 2016). Our study demonstrates the negative impact of L265P *MYD88* mutation in PCNSL patients. L265P *MYD88* mutation has already been shown to be associated with an unfavorable outcome of DLBCL, not otherwise specified and cutaneous DLBCL of leg type (Fernandez et al, 2014; Pham et al, 2012). These findings together prompt us to investigate alternative treatment regimens for patients of B-cell malignancies, having *MYD88* L265P mutation. Ibrutinib, an inhibitor of BTK, was shown to be extremely effective in patients with WM (Treon et al, 2015), and activated B-cell type DLBCL, especially when the tumors had *MYD88* mutations (Wilson et al, 2015). The effectiveness of ibrutinib on PCNSL with *MYD88* mutations warrants clinical investigation. L265P *MYD88* mutation is a quite useful tool in many setting of clinical investigations, for the B-cell malignancies.

Keiichiro Hattori, Mamiko Sakata-Yanagimoto, Shigeru Chiba
Department of Clinical and Experimental Hematology,
Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

Publication

MYD88 (L265P) mutation is associated with an unfavourable outcome of primary central nervous system lymphoma.
Hattori K, Sakata-Yanagimoto M, Okoshi Y, Goshima Y, Yanagimoto S, Nakamoto-Matsubara R, Sato T, Noguchi M, Takano S, Ishikawa E, Yamamoto T, Matsumura A, Chiba S
Br J Haematol. 2016 May 10