Title: Molecular abnormalities in Waldenstrom's macroglobulinemia patients treated with rituximab, bortezomib, lenalidomide and dexamethasone: Whole exome sequencing analysis in KMM1803 study

Ga-Young Song[2], Juyeong Park[16, 17], Sung-Hoon Jung[2], Je-Jung Lee[2], Gyeong-Won Lee[3], Joon Ho Moon[4], Ho Jin Shin[5], Jun Ho Yi[6], Won Sik Lee[7], Young Rok Do[8], Hyo Jung Kim[9], Ji Hyun Lee[10], Chang-Ki Min[11], Ji-Hyun Kwon[12], Kihyun Kim[13], Jae Hoon Lee[14], Min Kyoung Kim[15], and Ho Sup Lee[1]

[1]Department of Internal Medicine, Kosin University College of Medicine, Kosin University Gospel Hospital, Busan, Korea; [2]Department of Hematology-Oncology,Chonnam National University Hwasun Hospital,Chonnam National University Medical School,Hwasun,Jeollanam-do,Korea; [3]Division of Hematology-Oncology, Department of Internal Medicine, Gyeongsang National University Hospital, Gyeongsang National University College of Medicine, Jinju, Republic of Korea; [4]Department of Hematology/Oncology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea; [5]Division of Hematology-Oncology, Department of Internal Medicine, Biochemical Research Institution, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Republic of Korea; [6]Division of Hematology-Oncology, Department of Medicine, Chung-Ang University, Seoul, Korea; [7]Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Korea; [8]Department of Hemato-Oncology, Keimyung University, Dongsan Medical Center, Daegu, Korea; [9] Department of Hematology-Oncology, Hallym University Medical Center, Hallym University College of Medicine, Anyang,Korea; [10]Division of Hematology-Oncology Department of Internal Medicine,Dong-A University College of Medicine, Busan, Korea; [11]Divison of Hematology, Department of Internal Medicine,Seoul St. Mary's Hospital, College of Medicine,The Catholic University of Korea; [12]Department of Internal Medicine, Hematology and Oncology ,Chungbuk National University, College of Medicine; [13]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [14]Gachon University Medical College, Division of Hematology, Gachon University Gil Medical Center,Incheon, South Korea; [15]Division of Hemato-Oncology, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea; [16]Theragen Bio Co., Ltd, Seongnam-si, Korea; [17]Department of Medicine, Yonsei University College of Medicine, Seoul, Korea

Corresponding Author:

Ho Sup Lee, MD, PhD. professor.

Division of hematology-Oncology, Department of Internal Medicine, Kosin University College of Medicine, Kosin University Gospel Hospital

262 Gamcheon-ro, Seo-gu, Busan, Korea 49267

Tel: +82-51-990-6363, Fax: +82-51-990-5820

E-mail: hs52silver@gmail.com, hs3667@hanmail.net, hs3667@kosin.ac.kr

Background

Waldenstrom's macroglobulinemia (WM) is an indolent lymphoproliferative disease with heterogeneous lymphoplasmacytic bone marrow infiltration and high immunoglobulin M production. *MYD88* and *CXCR4* are the most studied mutations and are present in 95-97% and 35-40% of Caucasian WM patients. Due to its rarity, representing 1-2% of hematologic malignancies, limited data is reported about molecular information other than *MYD88* and *CXCR4* of WM, especially in Asian population. We therefore performed whole exome sequencing (WES) of 28 WM patients who are enrolled in KMM1803 study.

Methods

Bone marrow aspirates of 28 patients who were diagnosed with WM were collected at diagnosis and buccal swabs were obtained as controls to filter out germline variants. Enrichment and generation of libraries was performed using MGIEasy Universal DNA Library Prep Kit(V5). Paired-end sequencing was carried out using the Illumina HiSeq 2000 platform. The correlations between genetic mutations and clinical characteristics were analyzed.

Results

The distribution and frequency of gene alterations is presented in Figure 1. Among the 28 patients, 20 (71.4%) patients had 1 or more mutations. The most frequent mutations were identified in *MYD88* (32%), *CDC29* (29%), *KMT2D* (14%), *TET2* (14%), *CD79B* (11%), *FNFAIP3* (11%), and *CXCR4* (7%). All *MYD88* mutations were the classical L265P and 2 cases of *CXCR4* mutations were both frameshift mutations affecting S412 and S390. All 3 cases harboring *CD79B* mutation were *MYD88* mutated patients. Unlike previously published reports of mutually exclusive patterns of CXCR4 and *CD79A/B*, *CXCR4* and *CD79B* mutations were detected simultaneously in 1 case. In *MYD88* wild type patients, *TET2* and *TNFAIP3* mutation was frequently detected. As for clinical factors, no significant correlation was observed between genetic alteration and risk stratification system such as international prognostic score (IPSS) or revised IPSS. Six patients who achieved a response of very good partial response or higher to the treatment were all MYD88 wild type.

Conclusion

The mutation frequency of *MYD88* in Korean is lower than the frequency of studies in Caucasians. *MYD88* wild-type patients showed a better response to rituximab, bortezomib, lenalidomide and dexamethasone treatment.

Figure1. Patterns of mutations observed in 28 patients with Waldenstrom's macroglobulinemia treated with rituximab, bortezomib, lenalidomide and dexamethasone.