INVESTIGATION OF MDM2 ONCOGENE COPY NUMBER ALTERATIONS IN CASES WITH CHRONIC LYMPHOCYTIC LEUKEMIA

Running Head: The MDM2 oncogene in Chronic Lymphocytic Leukemia

Sule Darbas¹, Cigdem Aydin², Ozan Salim³, Sibel Berker Karauzum¹

¹ Akdeniz University, Faculty of Medicine, Department of Medical Biology and Genetics, Antalya, Turkey
² Mehmet Akif Ersoy University, Bucak School of Health, Department of Nursing, Burdur, Turkey
³ Akdeniz University, Faculty of Medicine, Department of Hematology, Antalya, Turkey

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Conflict of interest

The authors declare that they have no conflict of interest.

Corresponding author: Prof. Dr. Sibel Berker Karauzum
Adress: Akdeniz University, Faculty of Medicine, Department of Medical Biology and Genetics, Antalya, Turkey.
Phone: +90 242 249 69 70
e-mail: sibelberker@akdeniz.edu.tr

Chronic Lymphocytic Leukemia (CLL) is a disease characterized by deposition of malignant monoclonal lymphocytes. Chromosomal abnormalities have been determined in 30-50% of patients with CLL (1). Most common chromosomal abnormalities are 13q14 deletion (51%), 11q22.3 deletion (17-20%), trisomy 12 (15%), 17p13 deletion (7%), 6q23 deletion (7%) and t(14;19) translocation (1-2%) (2,3).

In CLL patients, overexpression of MDM2 gene was shown in earlier studies at protein and RNA levels (4-6), and it was aimed to be shown at DNA level for the first time in this study.

The MDM2 gene amplification was investigated by the FISH method in 40 patients with CLL and 20 patients with Ph + Chronic Myeloid Leukemia (CML) as a control group. Modified Rai staging system was used for staging our patients. Also, conventional cytogenetic analysis and FISH analysis by using CLL-specific FISH probes for 17p13.1 (TP53), 13q14 (RB), 6q22-q23 (MYB), 11q22.3 (ATM) and chromosome 12 centromere were applied in all patients. The cytogenetic analysis were revealed in 3 of 40 patients. 47,XX,inv(9)(p11q13),del(13)(q14),+21[2],46,XY,del(17)(p13),dup(12)(q21q21)[8] and 46,XY,del(20)(q12)[6] karyotypes were observed in these patients. MDM2 gene
amplification could not detected neither in the patient nor in the control group. FISH analysis results were as follows in CLL cases; deletion of 17p13.1 in 16 cases (40%), 13q14 deletion in 13 cases (32.5%), trisomy 12 in 12 cases (30%), 11q22.3 deletion in 6 cases (15%) and 6q23 deletion in 1 case (2.5%). Frequencies of molecular cytogenetic findings have been observed in Figure 1A. As in the literature, frequency of deletion 17p13.1 in early stage CLL was reported between 7-10% (7,8), the higher rate observed in 75% of our CLL patients might be due to the differences of the methods and probe used, variability of laboratory cut-off values, in addition to the limited cases in this study. The clinical implication of having a 17p13.1 deletion in CLL cases might be more depended on the dosage of 17p13.1 deletion than the stage of the disease (9). In the present study, we have only 4 cases who have 17p13.1 deletion in >20 cells. Two of them were died because of progressive disease and the other two cases were lost of follow-up. If evaluated with this perspective, the high dosage of 17p13.1 deletion was observed in 10% of our cases. It has been observed that the patients with 17p13.1 and 11q2.3 deletion have a poor prognosis, and patients with isolated 13q14 deletion were related with slower progression and longer survival time (2). We observed that early stages patients with isolated 13q14 deletion showed more slowly progressive and these patients did not have treatment indication.

MDM2 have pivotal roles in the regulation and stabilization of p53 (10). In our study, amplification of MDM2 gene has not been determined in CLL patients, but 30 (75%) of 40 cases were clinically diagnosed as an early stage by FISH method (Figure 1B). We thought that the absence of MDM2 gene amplification in our patients might be related to the early stage of the disease. On the other hand, the reason for being unable to observe amplification of the MDM2 gene in 10 (25%) of 40 patients at advanced stages might be the presence of other abnormalities such as trisomy 12, deletions of 17p13.1, 11q22.3, and 6q23. We also suggest that reevaluation of MDM2 gene amplification in the patients having a relapse in the future is important for demonstrating the MDM2-CLL relationship. In previous studies, MDM2 overexpression was examined at mRNA and protein levels (4-6), amplification of the MDM2 gene at DNA level in CLL patients has been examined for the first time in our study.

References


Figure Legends

Figure 1a: Chromosomal abnormalities detected by routine FISH analysis of 40 CLL cases.

Figure 1b: Signal patterns in interphase nuclei of normal FISH results for the MDM2 gene.