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Evaluation of Hypogammaglobulinemia in Chronic Lymphocytic Leukemia Patients and Its Relation to Poor Prognostic Factors

Kronik Lenfositik Lösemi Hastalarında Hipogamaglobulineminin ve Olumsuz Prognostik Faktörler ile İlişkisinin Değerlendirilmesi

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Abstract

Aim: Chronic lymphocytic leukemia (CLL) is a heterogenous disease with variable clinical course. Rai staging system is used for at least 40 years to predict prognosis and need for treatment but more prognostic factors are needed. Infections have been known to have a significant impact on patients with CLL. It is postulated that hypogammaglobulinemia accounts for the high infection rate. The severity of hypogammaglobulinemia is correlated with disease stage and duration.

Methods: Data of patients who were diagnosed with CLL according to the the National Cancer Institute Working Group criteria were analyzed retrospectively. The patients were classified according to absolute lymphocyte count, immunoglobulin (Ig) levels, Rai stage, organomegaly, mass lymphadenopathy, lymphocyte doubling time (LDT), presence of B symptoms and treatment status.

Results: We found that low IgA levels were associated with LDT and splenomegaly indicating disease burden and activity. The patients with low IgA and IgM levels received more treatment than others with normal Ig levels.

Conclusion: In our study, we could not find a significant relationship between the stage and Ig levels but low IgA and IgM levels were significantly associated with need for treatment. Therefore, we suggest measuring IgA and IgM levels which is a simple and inexpensive test, to predict which patients may need treatment and should be observed closely.

Keywords: Chronic lymphocytic leukemia, hypogammaglobulinemia, chronic lymphocytic leukemia prognosis, immunoglobulins

Öz

Amaç: Kronik lenfositik lösemi (KLL) değişik klinik gidiş gösteren heterojen bir hastalıktır. Rai evreleme sistemi 40 yıldan uzun süredir prognozu ve tedavi ihtiyacını belirlemekte kullanılmakla beraber daha fazla prognostik faktöre ihtiyaç vardır. Enfeksiyonların KLL hastalarında önemli etkileri olduğu ve enfeksiyon sıklığındaki artışta hipogamaglobulineminin etkisi olduğu bilinmektedir. Hipogamaglobulineminin şiddeti ile hastalığın evre ve süresi ile ilişkilidir.

Yöntemler: Ulusal Kanser Enstitüsü Çalışma Grubu kriterlerine göre KLL tanısı almış olan hastaların verileri retrospektif olarak analiz edilmiştir. Hastalar, mutlak lenfosit sayısı, immünoglobulin (Ig) düzeyleri, Rai evresi, organomegali, lenfadenopati durumu, lenfosit sayısı ikiye katlanma zamanı, B semptomlarının varlığı ve tedavi durumuna göre sınıflandırılmıştır.

Bulgular: Düşük IgA düzeylerinin hastalık yükünü ve aktivitesini gösteren lenfosit sayısı ikiye katlanma zamanı ve splenomegali ile ilişkili olduğunu bulduk. Düşük IgA ve IgM düzeylerine sahip olan hastaların normal Ig düzeylerine sahip olanlara göre daha fazla tedavi aldıklarını saptadık.

Sonuç: Çalışmamızda, hastalık evresi ile Ig düzeyleri arasında anlamlı bir ilişki bulamadık fakat düşük IgA ve IgM düzeyleri ile tedavi ihtiyacı arasında anlamlı bir ilişki saptadık. Bu nedenle, hastaların tedavi ihtiyacını belirlemede basit ve ucuz birer test olan Ig düzeylerinin ölçülmesini ve yakın takibini öneriyoruz.

Anahtar Sözcükler: Kronik lenfositik lösemi, hipogamaglobulinemi, kronik lenfositik lösemi prognoz, immünoglobulinler

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Introduction

Chronic lymphocytic leukemia (CLL), is characterized by accumulation of mature B lymphocytes in peripheral blood, bone marrow, spleen and lymph nodes (1,2). Lymphocytes are recognised by the expression of at least one of the B antigens which is accompanied by expression of T cell marker CD5 (3,4). Generally, lymphocytosis (>5x10^9) is found, but in minority of cases, presence of lymphadenopathy is the major presentation (5). CLL is the most common form of leukemias. Annually, 1500 new cases are diagnosed in the United States of America (6,7). Average age at diagnosis is 65 years (1). Each year, 4500 Americans die from CLL complications (8).

Infections have been known to have a significant impact on clinical course of patients with CLL. 50-60% of patients are lost due to infections. It is postulated that hypogammaglobulinemia accounts for the high infection rate. The severity of hypogammaglobulinemia is correlated with the stage and duration of the disease. Hypogammaglobulinemia is probably related to non-clonal CD5 (-) B cell abnormality and down-regulation of B cell Ig synthesis by large granular lymphocytes found in CLL patients. There is no consensus about deficiency of which class of Igs causes susceptibility to infections (9-12).

In this study, we aimed to investigate the frequency of hypogammaglobulinemia in CLL patients and its relationship with poor prognostic factors.

CLL is a heterogeneous disease with variable clinical course. The Rai staging system has been used for at least 40 years to predict prognosis and need for treatment but more prognostic factors are needed. Conventional clinical prognostic factors are Rai or Binet stage, lymphocyte doubling time (LDT) and bone marrow infiltration pattern. Biological prognostic factors are elevated serum beta-2 microglobulin, thymidin kinase and soluble CD23 levels, presence of p53 expression, somatic mutations in immunoglobulin (Ig), variable heavy chain region, CLL cell surface expression of CD38, intracellular zeta-associated protein-70 (ZAP-70) positivity, some chromosomal abnormalities (e.g. del 17p), and more than 10% prolymphocytes in peripheral blood (13-23).

Methods

Data of patients, who were diagnosed with CLL according to the National Cancer Institute Working Group criteria, were analyzed retrospectively. Absolute lymphocyte, platelet counts, hemoglobin and IgG levels at the time of diagnosis were recorded. The patients were classified according to absolute lymphocyte count, Ig levels, Rai and modified Rai stage, organomegaly, mass lymphadenopathy (>7 cm LDT, presence of B symptoms, and treatment status).

IgA, IgG and IgM levels were analyzed by immunoturbidimetry (Beckman Coulter AU2700, California).

Study assessments and methods were approved by the local ınstitutional review board (Haseki Training and Research Hospital Ethics Committee, no: 28R/2018, dated 08.05.2018) and were conducted in accordance with the current version of the Helsinki Declaration. Written informed consent was obtained from all patients for inclusion and publication of anonymized data.

Statistical Analysis

Statistical analysis was done using SPSS version 16.0 statistical program. To evaluate the relationship between Ig levels and variables, the Student's t-test, Mann-Whitney U test, Fisher's exact test, and a chi-square were used. Correlation analyses were made by Pearson's correlation coefficient. A p value of less than 0.05 was considered statistically significant.

Results

Sixty six patients (37 male, 29 female) were enrolled in the study. Patient characteristics are shown in Table. The median age was 69 (range: 41-86) years. The median age was 74 for stage 0, 67 for stage 1, 61 for stage 2, and 58.5 for stage 4. Age and Rai stages were reversely proportional (p=0.021). Ig levels were not correlated with age and gender.

Percentage of Ig levels below reference values for each Ig class were 21.2% for IgA (<70 mg/dL), 10.6% for IgG (<700 mg/dL), and 37.9% for IgM (<40 mg/dL). We could not find a significant correlation between Ig levels and Rai stage. IgA and IgM levels were significantly lower in patients who received treatment (p=0.011 and p=0.030, respectively). The median absolute lymphocyte count was 25900/mm^3 (2900-131000/mm^3). Lower IgA (<70 mg/dL) and IgM levels (<40 mg/dL) were related to higher absolute lymphocyte levels (p=0.17 and p=0.10, respectively). Lymphocyte counts were found to be statistically significantly increased with disease progress (p<0.001).

Lower Ig levels were not correlated with presence of B symptoms. Shorter LDT (<6 months) was significantly correlated with low IgA levels (p=0.030) and higher Rai stage (p=0.0001).

Of 28 patients, in whom genetic analysis was made, karyotype abnormality was found in only eight patients. One patient had 46,XX/complex karyotype, one patient had 47,XY+8, one patient had del 11q22, one patient had del 11q23, and four patients had del 13q. There was no significant correlation between Ig subtype and each genetic abnormality. Karyotype abnormality was not associated with need for treatment.

Mass lymphadenopathy (>7cm) was not related with low Ig levels, but strongly correlated with higher Rai stages (p<0.001). Only low levels of IgA was significantly related with splenomegaly (p=0.001).

Discussion

CLL is the most frequent leukemia type in adults and has a variable clinical course. Infections are attributed mainly to hypogammaglobulinemia. Other risk factors are defects in cellular immunity and complement system, and immunosuppressive treatment applied to the patients. Our goal was to investigate the frequency of hypogammaglobulinemia and its relationship with poor prognostic factors.

Table. Patients characteristics

Age (years), median (min-max)	69 (41-86)
Gender, n (%) Male Female	 37 (56%) 29 (44%)
Hemoglobin level (g/dL), median (min-max)	12.5 (6.6-16.40)
Lymphocyte count/mm^3, median (min-max)	25900 (2900-131000)
Platelet count/mm^3, median (min-max)	210000 (67000-401000)
Rai stage, n (%) 0 1 2 3 4	 27 (40.9%) 11 (16.6%) 19 (28.7%) 7 (10.6%) 2 (3%)
IgA level, median (min-max)	155 (14.6-455 mg/dL) (RR: 70-400 mg/dL)
IgG level, median (min-max)	1047.5 (284-2365 mg/dL) (RR: 700-1600 mg/dL)
IgM level, median (min-max)	45.5 (8-241 mg/dL) (RR: 40-230 mg/dL)
Lymphocyte doubling time, n (%) <6 months >6 months Lost data	 8 (12.1%) 49 (74.2%) 9 (13.6%)
Lymphadenopathy, n (%) >7cm <7cm	 5 (7.5%) 61 (92.5%)
B symptoms, n (%) Yes No	 18 (27.2%) 48 (72.8%)
Splenomegaly, n (%) Yes No	 23 (34.8%) 43 (65.2%)
Treatment status, n (%) Yes No	 21 (31.8%) 45 (68.2%)

Min: Minimum, Max: Maximum, IgA: Immunoglobulin A, IgG: Immunoglobulin G, IgM: Immunoglobulin M, RR: Reference range

Parikh et al. (24) divided 3168 patients into two groups as under and over 55 years age and found that 44% of patients younger than 55 years of age had stage 0, 53% had stage 1-2, 3% had stage 3-4 disease. 57% of patients over 55 years had stage 0, 37% had stage 1-2, and 6% had stage 2-4 disease. Younger patients presented mostly with stage 1-2 disease. In the same study, 66% of patients under 55 years and 67% of patients over 55 years were male. In their study, Mauro et al. (25) also found that of 335 patients 65% were male and 35% were female. Another study evaluated 71 CLL patients of whom 76% were male, 24% were female and median age was 58 years. In the same study, 16.9% of patients were having stage 0, 69%, stage 1-2 and 14.1% were having stage 3-4 disease. In our study 56% were male, 44% were female, the male-to-female ratio was 1.27:1 and the median age was 69 years (range: 41-86). Twenty-seven patients (40.9%) had stage 0, 11 (16.7%), stage 1, 19 (28.8%), stage II, seven (10.6%), stage III, and two patients (3%) had stage IV disease. Compared to the literature, our male-to-female ratio was lower. The number of patients with advanced disease was higher because our clinic is a center where patients requiring treatment are commonly referred.

In previous studies, a significant relationship between absolute lymphocyte count and survival or response to treatment could not be demonstrated (25,26). In our study, we found a strong correlation between disease stage and absolute lymphocyte count (p=0.001). Also, patients with low IgA and IgM levels appeared to have higher absolute lymphocyte count, but there was no significant relationship between IgG and absolute lymphocyte count. Although not accepted as a poor prognostic factor in the literature, we believe further research are needed to elicit the importance of this variable which is frequently used during the follow-up of patients (27,28).

In several studies, chromosomal abnormalities have been reported in 53-77% of CLL patients (29-31). The most frequently genetic alterations were del 13q, trisomy 12, del 11q, del 17p and del 6q. It is known that, del 11q and del 17p are associated with high disease activity (30). el Rouby et al. (32) investigated p53 mutation in CLL patients and found that p53 mutation was associated with progressed disease. In our study, fluorescence *in situ* hybridization (FISH) analysis was made in 29 of 66 patients. In eight patients, different genetic abnormalities were found. Compared to the literature, the rate of FISH positivity in our study was low due to lack of genetic information. In four patients, del 13q, which is associated with good prognosis, was found. Poor prognostic del 11q was found in two patients, del 17p was not found in any of the patients. Due to low number of patients and poor prognostic cytogenetic abnormalities, we could not find

an association between karyotype abnormalities and high stage.

It is advised to use the International Workshop on CLL (iwCLL) criteria to initiate treatment in CLL patients (33). Otherwise, absolute lymphocyte count and hypogammaglobulinemia in the absence of iwCLL criteria do not indicate treatment. In their study, Parikh et al. (34) found that 26% of 1485 CLL patients had hypogammaglobulinemia. Poor prognostic factors like advanced Rai stage and CD49d expression were associated with greater risk of hypogammaglobulinemia and patients with low Ig levels progressed rapidly. In our study, we could not find a significant relationship between hypogammaglobulinemia and disease stage (p value for IgA, IgG and IgM: 0.162, 0.487 and 0.188, respectively). Shvidel et al. (35) analyzed Ig levels in 1113 patients from the Israeli CLL Study Group diagnosed with Binet A CLL in 25 years and found that age above 65, male gender, CD38 and ZAP-70 expression, elevated beta-2 microglobulin levels and lymphadenopathy were associated with shorter survival time but no relationship of survival time with hypogammaglobulinemia and paraproteinemia was found. Patients with low IgA levels needed treatment more than other groups.

In several studies, shorter LDT was found to be associated with poor prognosis (36,37). In our study, similar to the literature, there was a significant correlation between LDT and disease stage ($p<0.001$). Additionally, we found that patients with LDT shorter than six months, had lower IgA levels ($p=0.030$). According to the iwCLL guideline, a LDT of shorter than six months or elevation of lymphocyte count by 50% in two months are indications for treatment. Therefore, it is advisable to more frequently follow patients with a Rai stage 0-1-2 or Binet stage A-B and with low IgA levels.

In previous studies, it has been shown that hypogammaglobulinemia may precede CLL years before the disease emerges (38). In the sudy by Parikh et al. (34), it was found that low IgG levels were associated with progressed disease and high CD49d expression. Time to first treatment was shorter in patients with low IgG levels. In our study, we could not find a significant relationship between patients' stages and Ig levels (p value for IgA, IgG and IgM respectively; 0.162, 0.487 and 0.188), but low IgA and IgM levels were significantly associated with need for treatment ($p=0.011$ and $p=0.030$, respectively).

In the literature, it is mentioned that del 11q positivity is associated with mass lymphadenopathy, both indicating poor prognosis (39,40). In our study, mass lympadenopathy was related to advanced stage but not to low Ig levels (p value for IgA, IgG and IgM: 0.94, 0.462 and 0.36, respectively).

In several studies, it has been shown that splenomegaly is related to disease burden and poor prognostic factors (41,42). In our study, patients with low IgA levels had more severe splenomegaly but there was no significant relationship between Ig levels and B symptoms.

Conclusion

In our study, we found that low IgA levels were associated with LDT and splenomegaly which indicate disease burden and activity. Patients with low IgA and IgM levels received more treatment than others with normal Ig levels. Therefore, we suggest measuring IgA and IgM levels which is a simple and inexpensive test, to predict which patient may need treatment and should be observed closely.

Authorship Contributions

Surgical and Medical Practices: M.A. Concept: M.A. Design: M.A. Data Collection or Processing: M.A., Ç.M.A. Analysis or Interpretation: M.A., Ç.M.A., F.A.A., D.Ö., T.E. Literature Search: Ç.M.A., D.Ö., T.E., Writing: M.A., Ç.M.A., D.Ö.

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