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Secondary Immunodeficiency Frequency in Patients with Chronic Lymphocytic Leukemia: The Relationship with Stage and Treatment

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ABSTRACT

Background: Chronic lymphocytic leukemia (CLL) is one of the most common hematological malignancies. In patients with CLL, serum immunoglobulin levels decrease over time due to both the disease itself and the chemo-immunotherapeutic agents used. It was aimed to reveal the relationship between hypogammaglobulinemia and disease stage, and chemo-immunotherapies.

Materials and Methods: Data were obtained by retrospectively examining 74 patients who were followed-up between 2008-2019. The relationship between all parameters (demographic characteristics, RAI stages or therapy subtypes) and serum IgG levels was analyzed.

Results: Thirty-two of 74 patients received a therapy. Twenty-two patients were on combined therapy with rituximab or only rituximab and 10 were treated with chemotherapeutic agents only. The frequency of hypogammaglobulinemia was 5.4% at the diagnosis, this rate was 55% in patients receiving a therapy. Hypogammaglobulinemia was higher in advanced stages. In patients with rituximab, higher levels of IgG decrease were observed.

Conclusion: Serum IgG level was significantly lower in patients with advanced-stage, received chemotherapy, especially rituximab. In addition to basal IgG, immunoglobulin levels should be checked during treatment, and follow-up period. Early replacement intravenous immunoglobulins will be important to reduce severe infection attacks due to secondary immunodeficiency.

Keywords: Immunodeficiency; Chronic lymphocytic leukemia (CLL); Monoclonal antibody; Immunotherapy; Immunoglobulin G (IgG)

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disease originating from B-lymphocytes, with a frequency of 25-30% among hematological malignancies. The clinical progression and survival of CLL is very heterogeneous and can progress asymptomatically for years without any treatment indications. Even at the time of diagnosis, many patients with cytopenias, bone marrow infiltration, massive organomegaly, secondary immune deficiency and severe infections are encountered[1].

It is possible to say that the role of infections in mortality in CLL reaches up to 60%. Both the nature of the disease, the chemo-immunotherapeutic treatments preferred, and secondary immune

deficiency development are responsible for this situation[2]. It has been demonstrated that hypogammaglobulinemia may occur even 3 years before the diagnosis of CLL, and in some cases, it may be observed at the stage of monoclonal B lymphocytosis[3]. In the advanced stage, it is known that serum IgG level decreases progressively[4]. In addition, immunotherapeutic drugs used in CLL are known to decrease B lymphocyte count and cause hypogammaglobulinemia. The effects of the use of B lymphocyte (cell) receptor blockers and intracellular signal inhibitor targeting agents, which have been used more commonly and frequently in recent years , are not clear. It has been reported that humoral immune functions improve with the use of Bruton's kinase inhibitor "ibrutinib" in CLL[5]; however, there is no clear consensus on the impact of these new agents on immunity and hypogammaglobulinemia, and new studies are needed. Hypogammaglobulinemia is evaluated as a new prognostic marker in CLL.

Parikh et al. detected hypogammaglobulinemia in 26% of cases with CLL and the average of IgG was determined to be 624 mg/dL in this study. In the normal group, the average of IgG appears to be 1040 mg/dl. It is observed that those with hypogammaglobulinemia are at a more advanced stage of the disease (Rai stage III-IV; P = 0.001), and they also have a shorter treatment free survival (TFS) (3.8 years vs 7.4 years; P <0.001). Hypogammaglobulinemia has been reported to develop in 11% in 5 years, and 23% in 10 years[6]. Prophylactically, 0.35 g/kg of intravenous immunoglobulin (IVIG) is recommended for patients with frequent and serious infections in CLL, and who have secondary hypogammaglobulinemia. The level is recommended to be > 600 mg/dL[7].

In our study, we aimed to investigate the basal serum immunoglobulin G (IgG) level at the time of diagnosis of our patients who were followed up with the diagnosis of CLL in our hematology clinic, and the relationship between age, gender, disease stage (Rai and Binet stage) and basal IgG level. In addition, the difference in serum IgG values between patients who received and did not receive treatment was examined by subgroup analyzes. In the patients who received treatment, the additional effect of monoclonal antibody treatment regimens (anti CD20 monoclonal antibody: Rituximab) on the decrease in IgG level was investigated.

MATERIALS AND METHODS

In the hematology clinic of our hospital, the files of 74 CLL patients followed up with the diagnosis of CLL between 2008-2019 were analyzed retrospectively. The inclusion criteria for the cases in our study is determined to meet the "2016 CLL Diagnostic Criteria"[8] and the data of the cases should be complete. Exclusion criteria are identified as follows; patients with congenital immune deficiency; those receiving active IVIG therapy, those given new generation monoclonal antibody treatments other than rituximab, those being treated with new agents (such as ibrutinib and venetoclax), patients with a disease that affects serum IgG level (such as nephrotic syndrome, cirrhosis, etc.). The patients were subdivided into groups according to age, gender, Rai stage, whether they received chemotherapy and whether rituximab was used in those receiving chemotherapy. Both basal and post-treatment serum IgG levels were examined and analyzed in terms of statistical significance.

Ethical committee approval was received (Approval date and number: 22/9/2017 -1089) and the patients and control subjects gave informed consent before the beginning of the study. The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations.

Statistical analysis

Frequency and ratio values are used in the descriptive statistics of the data. The distribution of variables was measured by Kolmogorov Smirnov test. In the analysis of qualitative independent data, Chi-square test, Fischer test was used when Chi-square test conditions were not met. SPSS 22.0 program was used in the analysis. Statistical alpha significance level was accepted as p <0.05.

RESULTS

Seventy-four patients with CLL were included in the study. 44.6% of the cases were under 65 years old, 55.4% of them were 65 years old or older. 43.2% of the patients were female, and 56.8% were male (Table 1). Considering the Rai stages at the time of diagnosis; 29.7% were stage 0, 20.3% stage I, 33.8%

stage II, 8.1% stage III, and 8.1% were stage IV. 56.8% of the patients were followed without treatment; 43.2% had received a treatment. Twenty-two of those receiving treatment were treated with either rituximab or rituximab-based regimen, and the remaining 10 patients were given chemotherapy without rituximab. Basal IgG level was normal in 94.6% and low in 5.4% of the patients. Of the 32 patients who received treatment, only 20 had post-treatment IgG levels, of which 45% (n: 9) were normal and 55% (n: 11) were low. (Table 1).

Comparison Parameters in Different Case Groups

With serum IgG levels of patients (normal or high); when the relationship between age, gender, time of diagnosis, Rai stage and treatment status, whether or not it contains rituximab, is considered (Table 2). There was no significant difference in the level of serum IgG between those aged 65 and older. Similarly, there was no statistically significant difference between the IgG levels of the cases in terms of gender ($p>0.05$) (Table 2).

Regarding the relationship between patients' Rai stage and serum IgG level, 31.4% (n = 22) of patients with normal IgG level were stage 0, 21.4% (n = 15) stage I, 34.3% (n = 24) stage II. It was determined that 8.6% (n = 6) were stage III and 4.3% (n = 3) were stage IV. In the group with low IgG level, no patients were seen at 0, I, and III stages, while 25% were in stage II and 75% were in stage IV. It was statistically significant that the Rai stage of the group with low IgG level was higher than the normal ones ($p<0.05$) (Table 2). Sixty percent (n = 42) of the patient group with normal serum IgG never received a treatment, while all patients (100%, n = 4) with low serum IgG levels were treated. In addition, 27.1% (n = 19) of the patients with normal basal IgG levels received combined treatment containing rituximab or rituximab-based regimen, while 12.9% (n = 9) were treated with non-rituximab drugs. Twenty-five percent (n = 1) of the patients with low IgG levels were treated with non-rituximab drugs, while 75% (n = 3) treated with rituximab-based regimen. As a result, in the group with low IgG, the rate of receiving treatment and the rate of receiving the treatment regimen containing rituximab were significantly higher than the group with normal IgG level ($p <0.05$) (Table 2).

When the serum IgG levels are examined in relation to the patients' receiving a treatment or not; 45% of CLL patients receiving a treatment were found to have normal serum levels, and 55% had low serum IgG levels, while serum IgG level was normal in 100% of the untreated group. In the treated group, the IgG reduction after treatment was significantly higher than the untreated group ($p <0.05$) (Table 3).

When the subgroups receiving and not receiving rituximab among the patients receiving a treatment were evaluated in terms of IgG level; basal IgG level before treatment was normal in 86.4% of those receiving rituximab (n = 19), and low in 13.6% (n = 3). The treatment group without rituximab was normal in 90% (n = 9), and low in 10% (n = 1). If the difference between serum IgG levels in the group treated with and without rituximab was compared after treatment; 23.1% of patients given rituximab were normal (n = 3), and 76.9% were low (n = 10). Normal (n = 6) and low IgG levels (n = 1) were found in 85.7% and 14.3% of the patients treated without rituximab (Table 4).

While there was no statistically significant difference between these two groups receiving a treatment with or without rituximab in terms of low basal IgG level ($p >0.05$), serum IgG decrease in the treatment regimen with rituximab was significantly higher ($p <0.05$) (Table 4).

The serum IgG of the cases before treatment was 85% (n = 17) normal and 15% low (n = 3); after treatment, 45% (n = 9) of patients were normal and 55% were low. A significant decrease in serum IgG levels was observed after treatment ($p <0.05$) (Table 5).

Table 1: Demographic and clinical features of patients

		n	%
Age	<65	33	44.6 %
	≥65	41	55.4 %
Gender	Female	32	43.2 %
	Male	42	56.8 %
Rai Stage	0	22	29.7 %
	I	15	20.3 %
	II	25	33.8 %
	III	6	8.1 %
	IV	6	8.1 %
Treatment	No	42	56.8 %
	Yes	32	43.2 %
	Rituximab	22	29.7 %
	Non-Rituximab	10	13.5 %
Basal IgG	Normal	70	94.6 %
	Low	4	5.4 %
IgG Level After Treatment	Normal	9	45.0 %
	Low	11	55.0 %

Table 2: Results of comparison of parameters by groups

		IgG- Normal		IgG- Low		p
		n	%	n	%	
Age	<65	32	45.7 %	1	25.0 %	*0.624*
	≥65	38	54.3 %	3	75.0 %	
Gender	Female	30	42.9 %	2	50.0 %	*1.000*
	Male	40	57.1 %	2	50.0 %	
Rai Stage	0	22	31.4 %	0	1. %	*0.000*
	I	15	21.4 %	0	1. %	
	II	24	34.3 %	1	25.0 %	
	III	6	8.6 %	0	0.0 %	
	IV	3	4.3 %	3	75.0 %	
Treatment	No	42	60.0 %	0	1. %	*0.031*
	Yes	28	40.0 %	4	100 %	
	Rituximab	19	27.1 %	3	75.0 %	
	Non-Rituximab	9	12.9 %	1	25.0 %	

Table 3: Difference of IgG levels between treated and untreated groups

		Treatment (-)		Treatment (+)		p
		n	%	n	%	
IgG	Normal	42	100.0 %	9	45.0 %	*0.000*
	Low	0	0 %	11	55.0 %	

Table 4: Difference of IgG levels between subgroups with and without rituximab based regimen

		Rituximab		Non- Rituximab		*p*
		n	**%**	**n**	**%**	
Basal IgG Level	Normal	19	86.4 %	9	90.0 %	*1.00*
	Low	3	13.6 %	1	10.0 %	
IgG Level After Treatment	Normal	3	23.1 %	6	85.7 %	*0.007*
	Low	10	76.9 %	1	14.3 %	

Table 5: Decrease of serum IgG levels before and after treatment

		Before Treatment		After Treatment		*p*
		n	**%**	**n**	**%**	
IgG Level	**Normal**	**17**	**85.0 %**	**9**	**45.0 %**	***0.008***
	Low	**3**	**15.0 %**	**11**	**55.0 %**	

DISCUSSION

In this study, it was aimed to determine in which Rai stage hypogammaglobulinemia was more frequent, whether it was more frequent in the period of need for treatment, especially in patients receiving monoclonal antibody treatment. It was aimed to determine in which patient subgroups serum IgG levels should be examined and in which subgroup the need for replacement may be higher. It was found that 5.4% of our newly diagnosed CLL cases had hypogammaglobulinemia. Hypogammaglobulinemia was more common in advanced stages; in particular, the group receiving rituximab was the subgroup with the most frequent hypogammaglobulinemia.

Regarding the importance of IgG subgroup deficiency in CLL , in our study, it was found that 5.4% of our newly diagnosed CLL cases had hypogammaglobulinemia. In CLL Rai stage A, 19.9% decrease in IgG has been reported[9]; in advanced disease stage, serum immunoglobulin levels are lower and TFS decreases ($p < 0.001$ and $p = 0.006$)[10-12]. IVIG replacement given to these patients with hypogammaglobulinemia has been shown in the studies to decrease the risk of bacterial infection and hospitalization[13]. Freeman et al. also examined the deficiency of the immunoglobulin level (IgG, IgM, and IgA) and IgG subgroups of patients in a study conducted in 150 patients with CLL[14]. Patients are divided into groups based on their deficiency of Ig subtypes: 27.3% of patients had IgG, 30.7% IgA and 56.7% had IgM deficiency. Within the IgG subgroups, it was detected 28% IgG1, 19.3% IgG2, 52% IgG3 and 22.7% IgG4 deficiencies respectively. However, only 16% of cases had serious infection. In fact, it has been observed that half of those who have infection have normal IgG, and 50% of them have one of the subgroups' deficiency of IgG. In particular, IgG3 and IgG4 subgroup deficiencies were associated with the risk of infection. It is mentioned that IgG subgroup analysis can also be performed in those with frequent infection attacks in CLL. In another study examining the relationship between hypogammaglobulinemia and infection, and the effectiveness of IVIG replacement, Andrea et al.[15] reported a statistically significant relationship between hypogammaglobulinemia and increased risk of infection. In addition, these cases were reported to have a significant decrease in the frequency of major infections with IVIG replacement[16]. In line with the literature, it can be said that with the detection of early hypogammaglobulinemia and prophylactic IVIG

replacement in patients with CLL, there will be a decrease in serious infection attacks requiring hospitalization and therefore hospitalization-related costs and mortality will decrease. Despite the hypogammaglobulinemia rate, we reported in our study, we did not observe any infection with a mortal course.

Hypogammaglobulinemia was more common in advanced stages; in particular, the group receiving rituximab was the subgroup with the most frequent hypogammaglobulinemia. In the study in 2015, Parikh et al.[17] evaluated the prevalence of hypogammaglobulinemia at the time of diagnosis in CLL cases, and its relationship to TFS and overall survival. While 26% of CLL patients have hypogammaglobulinemia, it has been reported that more advanced Rai stage was observed in patients with hypogammaglobulinemia. (III-IV; P = 0.001) Although the median duration of TFS was shorter (3.8 years vs 7.4 years; P <0.001) compared to patients with normal IgG levels, there was no statistically significant difference in OS between these two groups. In a study conducted in Israel[18], among 857 CLL patients, 11% of patients in the Binet A stage had hypogammaglobulinemia. Moreover, Rozman[16] and Davey[19] et al. in the studies conducted by 10-44% of untreated CLL patients have been reported to have hypogammaglobulinemia. Our study results were also parallel to the literature.

In our study, only 20 (20/32) of the treated patients had post-treatment IgG levels. The rate of hypogammaglobulinemia (76.9%) in our patients who received rituximab-based treatment was significantly higher than those who received non-rituximab regimen (p = 0.007). In addition, in the comparison between IgG levels examined before and after rituximab treatment, the incidence of hypogammaglobulinemia increased after treatment (p = 0.008). In their study examining the relationship between rituximab and hypogammaglobulinemia, Fernandez Romero et al.[20] reported that 8 patients (4 with NHL, 2 with CLL and 1 with ITP) who received rituximab therapy for 20 months follow-up, six patients developed hypogammaglobulinemia, more frequent infections and four received positive responses with IVIG replacement. As a result of this study, the researchers stated that hypogammaglobulinemia developed significantly after rituximab and that immunoglobulin level control should be performed at certain intervals before and after treatment[20, 21]. In some studies from literature, with and without CLL and hypogammaglobulinemia; it was stated that there was no difference between the frequency and severity of the annual infection among the patients without IgG subclass deficiency (All infection frequency: 79.5% - 79.1%, p = 0.706) and IgG subclass measurement was not recommended[22, 23]. Raanani et al. stated that IVIG replacement does not contribute to survival in patients with hypogammaglobulinemia in CLL, and reported that it can be preferred only for some cases with severe infection attacks[24]. In another study, basal IgG levels of 211 patients diagnosed with B cell lymphoma and with rituximab-based regimen were reported to be low in 38% of cases and 6.6% of these cases were mentioned to need IVIG replacement for infection control. In another study, it was shown that hypogammaglobulinemia developed in 24% of patients (IgG <580 mg / dL) and decreased IgG1 and IgG2 in 1% of 114 patients who were given rituximab with different diagnoses[25, 26]. In addition to the nature of the disease, the progressive contribution of rituximab-containing treatments to hypogammaglobulinemia has been demonstrated in our study. Although no mortal infection was observed in our study, in parallel with the literature, the results are quite remarkable in terms of secondary immunodeficiency and the necessity of IVIG replacement. Hypogammaglobulinemia was observed more frequently, especially in advanced stage CLL patients and in patients receiving rituximab-based therapies. In future plans, especially in the choice of new agents and rituximab-based regimen, immunoglobulin follow-up at certain intervals will gain importance, especially in patients with advanced stage CLL.

The limitations of our study are as follows: The study consisted of 74 patients, partially heterogeneous screening of patient data, retrospective screening, differences in the treatment contents, and duration they received and different IgG level check-time periods after treatment. In 20 of our cases with CLL with treatment indication, the serum IgG level after treatment and the effect of rituximab and other chemotherapeutics on hypogammaglobulinemia can

be listed as other important disadvantages. In addition, the cases were not included in the study, considering the small number of cases that received new agents such as “Ibrutinib” or “Venetoclax” (B cell intracellular signal pathway inhibitor and Bcl-2 inhibitor) and may affect the study homogeneity. It can be said that further studies are needed on the effect of these new agents on hypogammaglobulinemia.

CONCLUSION

Considering the findings of our study, the following conclusion can be made in accordance with the literature: In CLL, hypogammaglobulinemia is more common in patients with Rai stage II and above, especially those who have frequent infection attacks. In these cases, serum immunoglobulin level determination should be checked intermittently. Basal serum IgG level should be monitored, and serum IgG level should be monitored after treatment, especially for patients with rituximab-based regimen. Our study offers limited data due to the disadvantages mentioned; however, the relationship of “CLL - development of secondary immunodeficiency-hypogammaglobulinemia" described above and our other results will shed light on the physicians dealing with this field and contribute to the conduct of larger studies.

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CONFLICT OF INTEREST

None to declare.

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Informed Consent

An informed consent was obtained from all of our patients to publish this study.

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