Original Article

Human Leukocyte Antigen-B Phenotype and Minimal Residual Disease in Chronic Myeloid Leukemia Patients Treated with Imatinib: Is There an Association?

Abstract

Background: Human leukocyte antigen (HLA) phenotype is a prognostic marker of cancer immunotherapy, and the expression profile of its alleles is associated with therapeutic rate. Therefore, there is the likelihood of a relationship between HLA phenotype and minimal residual disease (MRD) in chronic myelogenous leukemia (CML) patients treated with imatinib. The goal of this study was to assess the relationship between the expressions of HLA-B7, 8, 27, 5, and 51 molecules with MRD in CML patients who were treated with imatinib for the first time. **Materials and Methods:** Blood samples were collected from 33 CML patients who were subject to imatinib therapy for at least 6 months. The expressions of HLA-B molecules were evaluated using standard lymphocytotoxicity technique and MRD was measured by real-time polymerase chain reaction technique. **Results:** No significant association was found between the expressions of HLA molecules with MRD nor white blood cell, hemoglobin, and platelet counts ($P > 0.05$). However, CML patients expressing HLA-B5 and 51 molecules were more likely to show optimal response in imatinib therapy. **Conclusion:** We conclude that HLA-B5 and 51 molecules may have independent prognostic values in imatinib-treated CML patients, which suggests that they could be a prognostic marker for this disease. Nevertheless, investigation of HLA-B5 and 51 molecules in large-scale studies can be helpful in determining the true prognostic value of these molecules in predicting response rates to imatinib therapy among CML patients.

Keywords: *Chronic myeloid leukemia, human leukocyte antigen, imatinib, minimal residual disease*

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Introduction

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder, which is diagnosed in 90%–95% of cases with t(9;22)(q34; q11) BCR-ABL1 translocation in cells with a hematopoietic stem cell origin.[1,2] Currently, the BCR-ABL1 fusion gene is used as an indicator of prognosis and monitoring of imatinib therapy to classify patients.[3] Tyrosine kinase inhibitors (TKI) such as imatinib are among the most common drugs to treat CML patients.[4] Imatinib binds $P210^{BCR-ABL1}$, namely the translation product of BCR-ABL1 fusion gene (Ph chromosome) to inhibit its tyrosine kinase activity, which can alter the function of genes involved in mechanisms such as control of cell cycle, cell adhesion, and cytoskeleton organization, inducing apoptosis in Ph (+) cells.[5,6] In addition, because the increasing expression of BCR-ABL1 fusion gene in CML patients is associated with higher resistance to antitumor agents, the measurement of BCR-ABL1 fusion gene by real-time polymerase chain reaction (real-time PCR) for minimal residual disease (MRD) monitoring is employed to check the response to treatment and to predict the likelihood of future relapse.[7-9] MRD can be evaluated both quantitatively and qualitatively. The qualitative (yes vs. no) detection of MRD indicates the relative increase of relapse rates in CML patients. However, quantitative detection of MRD is a more accurate method that can be highly correlated with the probability of recurrence.[9-11] Besides BCR-ABL fusion gene, numerous prognostic factors including EVI-1, CYP2B6, cathepsin L, ABC, WT1, SLC, and human leukocyte antigen (HLA) have been discovered, each of which can independently affect

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leukemia progression and treatment. HLAs are a group of antigen-presenting proteins divided to HLA-I, II, and III, the changing expression of which on cancer cells can be related to decreased/increased ability of immune system in killing cancer cells, as well as inducing remission or relapse of various cancers.[12,13] To date, many studies have been conducted on the relationship between HLA expression, cancer prognosis, and response rates of cancer patients to therapy [Table 1]. In this respect, a number of studies suggest that HLA class I phenotype, especially HLA-B, could be used as a marker to determine the prognosis of leukemia. In this research, for the first time, we examined the relationship between HLA-B7, 8, 27, 5, and 51 molecules with MRD in CML patients treated with imatinib. The HLA-B alleles under study are examples of prognostic markers in various solid tumors and leukemias, which have been cited in various studies [Table 1].

Clinical significance

The expression of HLA molecules on cancer cells can be associated with a series of events such as stimulation or suppression of immune system, cancer metastasis and progression, as well as efficacy of the drugs used to treat cancer such as interferon-alpha (IFN-alpha) and TKI.[1,20,21] In this research, we examined the relationship between the expressions of HLA-B7, 8, 27, 5, and 51 molecules with MRD in CML patients who were treated with imatinib for at least 6 months. The results of this study can be useful in finding ways to predict the response to treatment, as well as improving the efficiency of the therapeutic methods for treatment of CML. Nevertheless, given the diversity of HLA polymorphisms across different races and nationalities worldwide, this investigation is only a prelude to future studies on larger populations of different races and nationalities worldwide.

Materials and Methods

Selection of patients

In this study, we assessed 85 CML patients who were referred to Shafa Hospital in Ahvaz, Iran, from December 8, 2018, to June 7, 2019. CML P21$^{BCR/ABL1}$ positive patients subjected to therapy with standard imatinib dose of 400 mg according to the European Leukemia Net (ELN) guidelines met the inclusion criterion,[22] and exclusion criteria were other diseases and genetic disorders recorded in patient history, <6 months of imatinib administration as well as consumption of other anticancer agents together with imatinib. Subsequently, we recruited 33 patients (21 males and 12 females) in our study [Figure 1]. This research was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1397.677) and was conducted in Thalassemia and Hemoglobinopathy Research center of this university. The samples were taken after obtaining informed consent from subjects.

Sample collection and HLA typing

Standard lymphocytotoxicity assay was used to determine the phenotype of HLA-B molecules among the patients participating in the study. We collected blood sample from each patient in a heparin-filled tube and used HISTO TRAY Disease HLA I Class Kit (BAG HEALTHCARE, Lich, Germany) for the assay. Furthermore, each patient sample was subject to laboratory investigations, including platelet (Plt) count, hemoglobin (Hb), and white blood cells (WBC) counts.

Table 1: An example of studies on the association between human leukocyte antigen expression and cancer

Study	Leukemia/ solid tumors	Result	References
Cortes *et al*., Texas	CML	In response to treatment with IFN-alpha, patients with HLA-B27 expression have a greater tendency to survive longer compared to patients without HLA-B27 expression	[1]
Fernández-Torres *et al*., Mexico	ALL AML	Decrease of HLA-B39 expression in ALL patients, decrease of HLAB15 expression, and increase of HLAB27 expression in AML patients, are associated with progression of ALL and AML, respectively	[14]
Locafaro *et al*., Italy	AML	The expression of HLA-G molecule on leukemic blasts and tolerogenic immune cells, DC-10 and CD4+ T-cells, is associated with increasing ability of these cells for escaping from host immune system	[15]
Rahman *et al*., India	APL	Triple-negative profile (CD34-/HLA-DR-/CD11b-) can be used for quick and accurate detection of APL	[16]
Posthuma *et al*., Netherlands	CML	The expression of HLA-B8, in particular when HLA-A3 is co-expressed, is associated with a reduced risk of CML development	[17]
Weiss *et al*., Texas	Lung cancer	The expression of HLA-Awl9 and HLA-B5 antigens is associated with prolonged survival in lung cancer patents	[3]
Yılmaz *et al*., Turkey	TCC	HLA-B51 was detected frequently in low-grade tumors	[18]
Lavado *et al*., Spain	Breast cancer	HLA-B7 is associated with the deterioration and progression of breast cancer	[19]

CML: Chronic myeloid leukemia, APL: Acute promyelocytic leukemia, AML: acute Myeloid leukemia, ALL: Acute lymphocytic leukemia, HLA: Human leukocyte antigen, DC-10: Dendritic cells-10, TCC: Bladder transitional cell carcinoma, IFN-alpha: Interferon-alpha

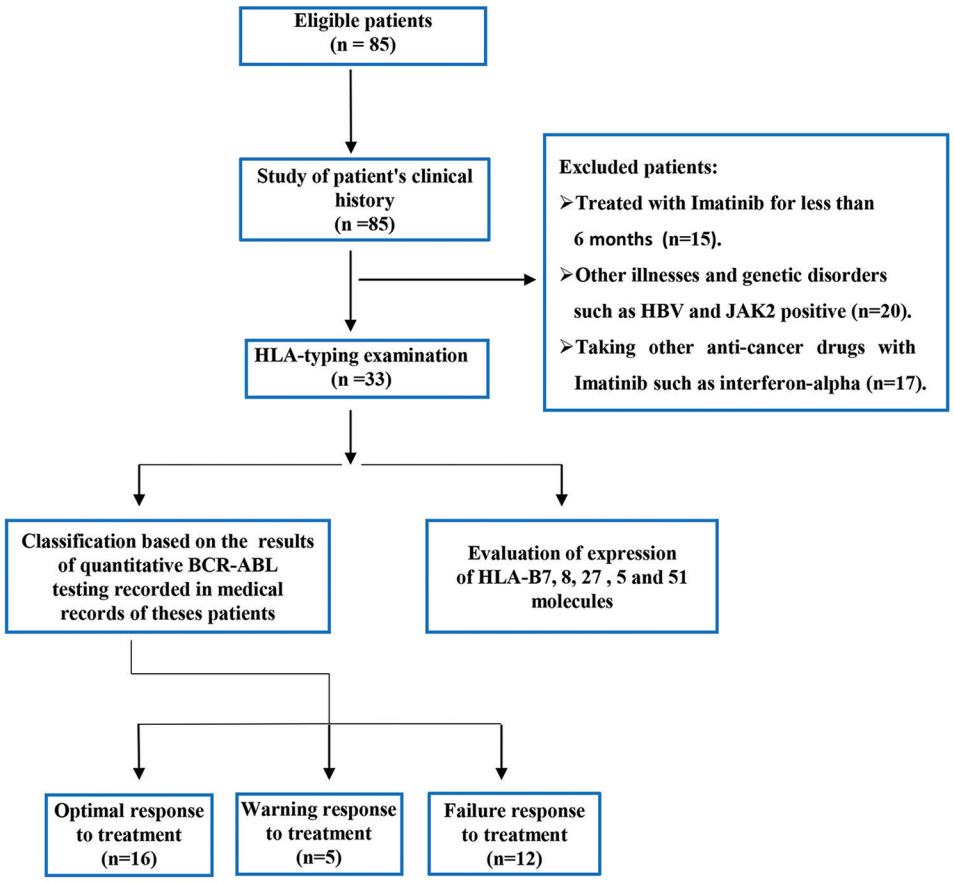

Figure 1: Flow diagram showing patient selection, evaluation of studied HLA molecules expression and response to treatment in CML patients

Real-time polymerase chain reaction

We employed real-time PCR to detect MRD in patients. In real-time PCR technique, after the isolation of mononuclear cells from peripheral blood samples of patients and RNA extraction from cells by observing the instructions of Ribo-Prep kit (Russia), optical density (OD) of the extracted sample was measured and cDNA synthesized by Qiagen kit (Germany) in case of OD260/OD280 ≥1.8. Afterward, according to the guidelines of real-time PCR kit (Ipsogen, USA), cDNA products were amplified by PCR for BCR-ABL gene. Subsequently, BCR-ABL1 results were normalized to international scale (IS) using ABL1 as the internal reference (Forward 10 pM: 5' GATACGAAGGGAGG GT GTACC 3' and Reverse 10 pM: 5' CTCG GCC AGGGTGTTGAA3') for normalization based on MIQE instructions.[23] In this research, all tests were done in duplicate.

Statistical analysis

For quantitative variables, mean and median were used to describe the data but standard deviation and interquartile range were employed to describe data dispersion. We used frequency and percentage to describe the data in qualitative variables. The normality of data was analyzed using Kolmogorov–Smirnov test and quantile–quantile (Q–Q) plots. For univariate analysis, Pearson's correlation coefficient, independent-*t*-test, ANOVA, and Fisher's exact test were used. Multivariable analysis was performed by multiple linear regression and multiple logistics regression. For normalization of variables, transformation of logarithmic variables, reverse transformation, and logarithm of (MAX + 1-variable) were employed and *P* value was considered equal to 0.05. All analyses were conducted using SPSS version 22 software. Due to the multicollinearity problem, one variable (either HLA-B8 or HLA-B27) was considered in multivariate analysis. Besides, given the equal expression of HLA-B5 and 51 molecules in all the patients, the HLA-B5 molecule was used to represent both HLA molecules.

Results

In this research, 33 CML patients (21 men and 12 women) participated with mean age of 46.3 ± 12.23 years who were subject to treatment with imatinib for no <6 months [Figure 1]. The data of patients are summarized in Table 2. We examined the expressions of HLA-B molecules in all patients to analyze the relationship between the expressions of these HLA molecules with patients' MRD (optimal, warning, and failure), as well as their correlation with WBC, Hb, and Plt counts. In this study, HLA-B7 expression was negative in all patients.

Table 2: Patients' data

Characteristics	CML patients (*n*=33)	Values and percentages
Sex, *n* (%)	Male	21 (63)
	Female	12 (36)
Age (minimum-maximum)		18-65
WBC (10^3*/mm^3), mean±SD	Total patients	24.5±58.4
	RT	
	Optimal	6.4±3.7
	Warning	4.8±0.4
	Failure	56.5±90.1
Hb (gr/dl), mean±SD	Total patients	12.1±2.2
	RT	
	Optimal	13.1±1.4
	Warning	12.5±1.8
	Failure	10.7±2.4
Plt (103*/mm^3), mean±SD	Total patients	321.3±292.4
	RT	
	Optimal	248.4±175
	Warning	171±105.8
	Failure	412±377.3
HLA-B7, *n* (%)	Positive	0 (0)
	Negative	33 (100)
HLA-B8, *n* (%)	Positive	2 (6)
	Negative	31 (94)
HLA-B27, *n* (%)	Positive	2 (6)
	Negative	31 (94)
HLA-B5, *n* (%)	Positive	10 (33)
	Negative	20 (67)
HLA-B51, *n* (%)	Positive	10 (33)
	Negative	20 (67)

Hb: Hemoglobin, HLA: Human leukocyte antigen, WBC: White blood cell, RT: Response to treatment, CML: Chronic myeloid leukemia, SD: Standard deviation

Correlation between HLA-B phenotypes and MRD

Patients participating in this research were divided into three groups using the results of their quantitative MRD test: optimal (n = 16), warning (n = 5), and failure (n = 12) of response to treatment based on ELN criteria.[22] According to the results of our research, most patients were positive for HLA-B5 (33%). From among the individuals expressing HLA-B5 molecule, 6 patients (60%) had optimal treatment response, 1 patient (10%) showed warning response, and 3 patients (30%) had failure of response (P = 0.7). However, a small number of patients were positive for other HLA molecules, including HLA-B8 (6%) and HLA-B27 (6%). In this investigation, among those expressing HLA-B8 molecule, only 1 patient showed optimal response to treatment and 1 patient had failed response (P = 1.0), while for patients expressing HLA-B27 molecule, treatment response was as follows: 1 patient with optimal response and 1 patient with warning response (P = 0.4). Considering $P > 0.05$, there was no significant correlation between the expressions of HLA-B8, 27 and 5 molecules with optimal, warning, and failure of treatment response groups [Table 3].

Expression comparison of different HLA molecules and laboratory data in CML patients

The mean (min-max) of WBC, Hb, and Plt were 24 (3–238) × 10^3/mm^3, 12 (7–16) g/dl and 321 (123–1554) × 10^3/mm^3, respectively. Laboratory data of patients are mentioned in Table 4. Although there was no significant relationship between expressions of different HLA molecules with WBC, Hb, and Plt counts ($P > 0.05$), statistical calculations showed that HLA-B5 among the studied HLA molecules had the highest influence on changes in WBC, Hb,

Table 3: Correlations between human leukocyte antigen expressions with minimal residual disease (optimal, warning, failure) in chronic myeloid leukemia patients

Variable	Univariate				Multivariate		
	Optimal	Warning	Failure	*P*	Ratio	OR	*P*
Age	43.4±12.3	46.4±10.3	50.1±12.8	0.368	Not calculated		
Sex (%)							
Male	12 (57.1)	3 (14.3)	6 (28.6)	0.383			
Female	4 (33.3)	2 (16.7)	6 (28.6)				
HLA-B8 (%)							
P	1 (50)	0	1 (50)	1.0	N to P*	0.94	0.972
N	15 (48.4)	5 (16.1)	11 (35.5)				
HLA-B27 (%)							
P	1 (50)	1 (50)	0	0.409	N to P	0.94	0.972
N	15 (48.4)	12.9 (4)	12 (38.7)				
HLA-B5** (%)							
P	6 (60)	1 (10)	3 (30)	0.682	N to P	2.41	0.303
N	10 (43.5)	4 (17.4)	9 (39.1)				

*Due to consideration of the warning and failure with each other (warning + failure), the result is quite similar to HLA-B27, **Due to equal expression of HLA-B5 and 51 molecules in all the patients, the HLA-B5 molecule was used to represent both HLA molecules (HLA-B5 and HLA-B51). P: Positive, N: Negative, HLA: Human leukocyte antigen, OR: Odd ratio

Table 4: Correlations between human leukocyte antigen expressions with hematological parameters (white blood cell, hemoglobin, platelet) in chronic myeloid leukemia patients

Variable	Univariate		Multivariate				
	Mean±SD, median (IQR)	*P*	Ratio	*B*	95% CI	β	*P*
WBC (10^3/mm^3)							
B8							
P	5.6±0.1, 5.6 (-)	0.6	N to P*		Not calculated		
N	25.7±60.1, 6.2 (3.4)						
B27							
P	5.5±1.1, 5.5 (-)	0.6	N to P	-0.014	−0.140, 0.111	-0.044	0.817
N	25.7±60.1, 6.2 (3.3)						
B5							
P	29.7±73.0, 6.5 (3.8)	0.7	N to P	0.014	−0.050, 0.077	0.080	0.663
N	22.2±52.5, 5.7 (2.9)						
Hb (gr/dl)							
B8							
P	11.5±0.7, 11.5 (-)	0.5	N to P*		Not calculated		
N	12.2±2.2, 12.3 (2.9)						
B27							
P	12.8±2.5, 12.8 (-)	0.7	N to P	0.79	−0.535, 0.693	0.039	0.739
N	12.1±2.2, 12.3 (2.6)						
B5							
P	12.1±1.8, 12.3 (2.3)	0.6	N to P	-0.050	−0.361, 0.261	-0.048	0.743
N	12.2±2.3, 12 (3.8)						
Plt (10^3/mm^3)							
B8							
P	197±18.4, 197 (-)	0.6	N to P*		Not calculated		
N	302.7±27.84, 221 (202)						
B27							
P	212±83.4, 212 (-)	0.7	N to P	0.248	−0.690, 1.185	0.104	0.592
N	301.7±27.8, 210 (197)						
B5**							
P	221.5±81.9, 215.5 (102)	0.4	N to P	0.222	−0.252, 0.687	0.3	0.345
N	328.7±316.7, 209 (215)						

*Due to consideration of the warning and failure with each other (warning+failure), the result is quite similar to the HLA-B27, **Due to equal expression of HLA-B5 and 51 molecules in all the patients, the HLA-B5 molecule was used to represent both HLA molecules (HLA-B5 and HLA-B51). P: Positive, N: Negative, HLA: Human leukocyte antigen, IQR: Interquartile range, B: Unstandardized coefficient, β: Standardized coefficient, CI: Confidence interval, WBC: White Blood cell, Hb: Hemoglobin, Plt: Platelet, SD: Standard deviation

and Plt counts. In this research, based on statistical calculations [Table 3], we can conclude that the patients expressing HLA-B5 molecules, which had a greater tendency to achieve optimal response in imatinib therapy, showed higher WBC counts, lower Hb levels, and Plt counts than those not expressing these molecules [Table 4].

Discussion

There have been several studies on the association between the expressions of HLA molecules on cancer cells with invasion, metastasis, and/or recurrence of various cancers and leukemia. For example, Alkhouly *et al*. showed that the expression of HLA-G molecule on ALL cells could be linked to the elusion of cancer cells from host immune system due to the downregulation of NK cells.[24] A number of investigations also suggest a correlation between the expressions of HLA molecules and response rates to therapy in cancer patients. For example, in a study conducted on the relationship between HLA phenotype and IFN-alpha therapy in CML patients, Cortes *et al*. found that patients treated with IFN-alpha who expressed HLA-B27 and HLA-A31 molecules had the highest response rates to IFN-alpha therapy and a tendency for long-term survival. In contrast, the patients expressing HLA-A2, HLA-B7, or HLA-B18 molecules showed the lowest response rates to IFN-alpha therapy and a trend for shorter survival.[1] Considering the diversity of HLA polymorphisms across nationalities and races around the world, the results of various studies may be different, so it is recommended that these investigations be separately conducted for each nationality and race. In this research, we first investigated the relationship between the expressions of HLA-B7, 8, 27, 5, and 51 molecules with MRD as well as WBC, Hb, and Plt counts in CML patients treated with imatinib.

The distribution of HLA-B7, 8, 27, 5, and 51 in the population under study is shown in Figure 2. As can be seen, HLA-B7 molecule is not expressed in our population and the HLA-B5 and 51 molecules (that are similarly co-expressed) are most prevalent in the population. Given the equal expression of HLA-B5 and 51 molecules in all the patients, the HLA-B5 molecule was used in methods and result sections of this article to represent both HLA molecules (HLA-B5 and HLA-B51). The findings show that patients with optimal response expressing HLA-B5 and 51 molecules are two times those with failure response, while no correlation was found between the expressions of other HLA molecules with MRD. The mechanisms involved in increasing tendency for optimal response in imatinib therapy through expression of HLA-B5 and 51 molecules on cancer cells remain unclear. Nevertheless, Barrett and Jiang in a study of CML patients found that the presentation of tumor antigens by HLA molecules on cell surface is a sequence-specific process. Thus, the binding and presentation of peptides derived from $p210^{BCR/ABL}$ that is an intracellular protein derived from BCR-ABL oncogene to cytotoxic lymphocyte cells and the stimulation of immune system can only be a function of specific HLA molecules.[25] On the other hand, it has been observed that in CML patients treated with imatinib, C-type lectin receptor NKG2D expressed on NK cells can activate NK cells and eventually the innate and adaptive immune systems after detection of the stress-induced ligand major histocompatibility complex Class I chain-related A (MICA) on the surface of cancer cells.[26] Imatinib has also been shown to play a significant role in enhancing this mechanism.[26] Moreover, Baranwal and Mehra showed that the MICA gene is located in the coding region of HLA-I molecule on short arm of chromosome 6 as well as at centromeric to HLA-B locus at a distance of 46.4 kb.[27] Therefore, considering the small distance between the genes encoding HLA-B molecules with MICA, we suggest that there may be a link between the

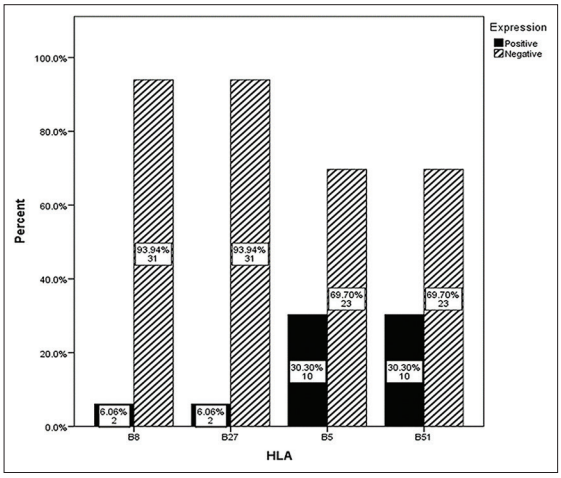

Figure 2: Expression pattern of Human leukocyte antigen-B8, 27, 5, and 51 molecules in the studied patients. The expression of human leukocyte antigen-B7 molecule was negative in all patients under study

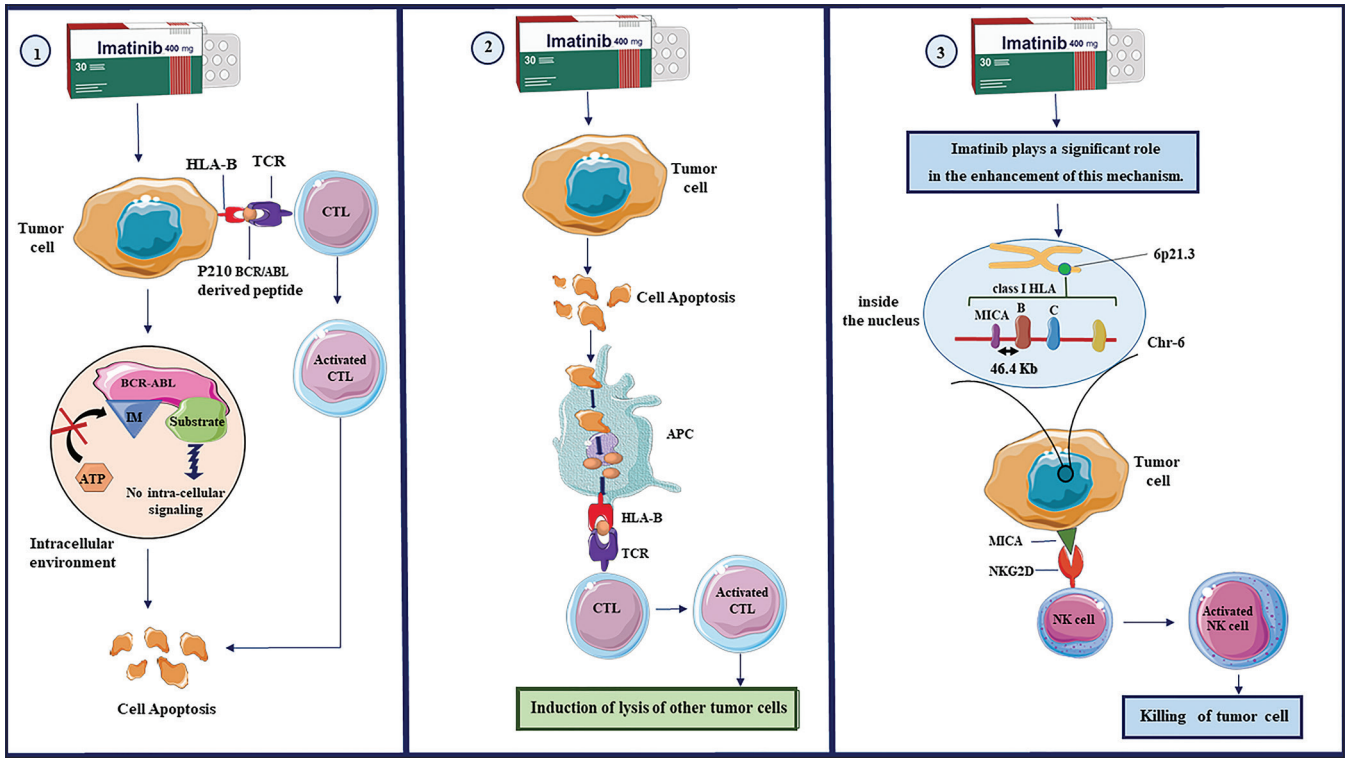

Figure 3: Correlation between HLA-B5, 51 with imatinib therapy in CML patients and the effect of this relationship on increased likelihood of recovery in CML patients, P: Positive, N: Negative, HLA: Human leukocyte antigen, IQR: Interquartile range, B: Unstandardized coefficient, Beta: Standardized coefficient, CI: Confidence interval, WBC: White blood cell, Hb: Hemoglobin, Plt: Platelet, CML: Chronic myelogenous leukemia

expressions of HLA-B5 and 51 molecules with increasing expression of the genes encoding MICA molecule. In summary, with respect to the mentioned studies in the field of HLA-typing and cancer, HLA-B5 and 51 molecules can be implicated in immune system stimulation in multiple pathways (direct/indirect) as well as increasing the likelihood of recovery in imatinib-treated CML patients. An example of these pathways is shown in Figure 3. In addition to the relationship between the expressions of HLA-B5 and 51 with optimal response in imatinib therapy, the statistical calculations of Table 4 show that among the studied HLA molecules, HLA-B5 and 51 played the most important roles in changes of WBC, Hb, and Plt counts. Hence, although no significant relationship was found between the expressions of these HLA molecules with MRD and WBC, Hb and Plt counts ($P > 0.05$), the findings of this study indicated that CML patients expressing HLA-B5 and 51 molecules, which had a greater tendency to achieve optimal response to imatinib therapy compared to other HLA molecules, had higher WBC counts, lower Hb levels and Plt counts than those not expressing these molecules. Considering the mechanisms mentioned above, it the increase in WBC counts was likely due to the stimulation of immune system against tumor antigens presented by HLA molecules.

Conclusion

Among the HLA molecules examined in this research, HLA-B5 and B51 had the most crucial role in changes of laboratory parameters and the induction of optimal response in imatinib therapy. In conclusion, HLA-B5 and 51 may have independent prognostic value in imatinib-treated CML patients, and we suggest that these molecules could be a prognostic marker for this disease. Nevertheless, investigation of HLA-B5 and 51 in large-scale studies can be helpful in determining the true prognostic value of these molecules for predicting the response rate to imatinib therapy in CML patients.

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Conflicts of interest

There are no conflicts of interest.

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