RESEARCH ARTICLE

DOI: 10.4274/tjh.galenos.2022.2022.0045
Turk J Hematol 2022;39:237-244

The Impact of Cytogenetic Aberrations in the Clonal Evolution of Chronic Myeloid Leukemia: A Single-Center Experience Among 450 Turkish Patients (Cohort Study)

Kronik Myeloid Löseminin Klonal Evolüsyonunda Sitogenetik Aberasyonların Etkisi: 450 Türk Hastadan Oluşan Kohort Çalışmasında Tek Merkez Deneyimi

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Abstract

Objective: Chronic myeloid leukemia (CML) is a clonal hematologic disorder characterized by t(9;22) translocation, in which cytogenetic aberrations can occur in Ph(+) and (-) clones. These aberrations develop due to clonal evolution as well as treatment and they have prognostic significance. They are grouped as major and minor route anomalies in terms of their effects on prognostic parameters, such as treatment response, overall survival (OS), disease stage, complete cytogenetic response (CCyR), and major molecular response (MMR). It is stated that major route anomalies have unfavorable prognostic effects compared to minor route anomalies. We aimed to investigate the frequency and prognostic effects of cytogenetic anomalies detected in Ph(+) and (-) clones.

Materials and Methods: In this study, we retrospectively analyzed the cytogenetic results of 450 patients diagnosed with CML between 2005 and 2020.

Results: We detected cytogenetic aberrations in Ph-positive and negative clones in 41 of 450 patients. The most common anomalies were trisomy 8 (+8), additional Ph chromosome (+Ph), and loss of chromosome Y. Rarely, aneuploidy of the Y chromosome, dup (22), +11, and +6 were seen in CML patients. We observed that these identified aberrations negatively affected MMR and CCyR, and generally resulted in changing imatinib treatment for second-generation tyrosine kinase activity inhibitors. Our results are compatible with the literature.

Öz

Amaç: Kronik myeloid lösemi (KML), t(9;22) ile karakterize olan, Ph(+) ve (-) klonlarda sitogenetik aberasyonların gelişebildiği bir lösemi tipi olarak bilinmektedir. Bu aberasyonlar klonal evolüsyon ve tedaviye bağlı gelişmekte olup, prognostik etkileri olduğu bilinmektedir. Literatürde; tedavi yanıtı, toplam sağkalım (OS), hastalık evresi, tam sitogenetik yanıt (TSY) ve majör moleküler yanıt (MMY) gibi prognostik parametreler üzerine olan etkileri açısından bu anomaliler majör ve minör yolak anomalileri olarak gruplandırılmaktadır. Majör yolak anomalilerinin minör yolak anomalilerine göre prognozu olumsuz yönde etkilediği belirtilmektedir. Biz de, Ph(+) ve (-) klonda saptanan sitogenetik anomalilerin sıklığını ve prognostik etkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Bu çalışmada, 2005-2020 yılları arasında KML tanısı almış 450 hastanın retrospektif olarak sitogenetik sonuçlarını inceledik.

Bulgular: Bu hastaların 41/450' inde Ph(+) ve/veya (-) klonda sitogenetik aberasyonlar saptadık. En sık gözlenen anomaliler trizomi 8 (+8), ek Ph kromozomu (+Ph) ve Y kromozom kaybı idi. Ayrıca KML hastalarında nadir görülen dup (22), +11, +6 ve Y kromozom artışı; ve daha önce literatürde saptanmayan inv(1) anomalisini tespit ettik. Saptanan bu aberasyonların MMY ve TSY olumsuz etkilediğini ve tedavide de genellikle 2. nesil tirozin kinaz aktivite inhibitörlerin tercih edildiğini gözledik. Elde ettiğimiz sonuçlar, literatür verileri ile uyumluluk göstermektedir.

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Received/Geliş tarihi: February 4, 2022
Accepted/Kabul tarihi: October 5, 2022

Abstract

Conclusion: We suggest that cytogenetic aberrations detected in Ph(+) and (-) clones should be a warning sign in terms of treatment and require close observation. The use of cytogenetic methods for the identification of these anomalies is also important.

Keywords: Chronic myeloid leukemia, Cytogenetics, Clonal evolution, Prognostic aberrations, Philadelphia chromosome

Öz

Sonuç: Sonuç olarak, Ph(+) ve (-) klonda saptanan sitogenetik aberasyonların hastaların tedavisi ve yakın takibi için "uyarı" niteliği taşıdığını savunmaktayız. Ayrıca bu kromozomal anomalilerin saptanması açısından sitogenetik yöntemlerin öneminin yadsınamaz olduğunu düşünmekteyiz.

Anahtar Sözcükler: Kronik myeloid lösemi, Sitogenetik, Klonal evrim, Prognostik aberasyon, Philadelphia kromozomu

Introduction

Chronic myeloid leukemia (CML) is characterized by the Philadelphia chromosome (Ph), which is detected in approximately 90% of patients. Most of these patients are sensitive to imatinib, and so the t(9;22) translocation is accepted as a good prognostic marker in CML [1].

Additional cytogenetic aberrations (ACAs) can be detected in clones with t(9;22) in some cases. It is known that these aberrations are associated with genomic instability, and clonal evolution has an adverse effect on prognosis. ACAs are mostly observed in the blastic phase (BP). CML patients with ACAs progress from the chronic phase (CP) to the BP [2]. In addition, clonal cytogenetic aberrations (CCAs) can be detected in Ph(-) clones in some cases of CML. These CCAs, like ACAs, contribute to clonal evolution and adversely affect prognosis. It has been stated that these aberrations develop after tyrosine kinase inhibitor (TKI) treatment, and they are more common in advanced-phase CML patients [3].

In some studies, the ACAs and CCAs detected in CML have been grouped as major and minor route anomalies. The major route anomalies (MRAs) include trisomy 8 (+8), isochromosome 17q [i(17q)], additional Ph (+Ph), trisomy 19 (+19), monosomy 7 (-7), and 3q26 rearrangements. Other anomalies are grouped as minor route anomalies (MiRAs). It has been reported that the prognostic effects of MRAs are worse than those of MiRAs in CML [4,5]. Hehlmann et al. [6] grouped ACAs as high-risk and low-risk based on disease survival. They defined +8, +Ph, i(17q), +17, +19, +21, 3q26.2, 11q23, -7/7q, and complex karyotypes as being of high risk and other anomalies as low risk.

In this study, we aimed to evaluate the results of cytogenetic studies of both newly diagnosed and follow-up CML patients who applied to our center between 2005 and 2020. We also aimed to examine the frequencies of detected ACAs and CCAs and their effects on prognosis.

Materials and Methods

Cases

Four hundred fifty patients with CML who underwent conventional cytogenetic, fluorescence in situ hybridization (FISH), and reverse transcription polymerase chain reaction studies were included in this work. The patient group consisted of 213 women and 237 men.

This study was conducted according to the guidelines presented in the Declaration of Helsinki, and it was approved by the relevant Clinical Practice Ethics Committee (2021-49). Each individual provided a signed consent form.

Genetics Tests

Conventional cytogenetic studies were performed on unstimulated bone marrow samples and analyzed using the CytoVision System (Leica, UK). Simultaneous molecular cytogenetic analysis (FISH testing) was performed using t(9;22) translocation probes (Vysis LSI BCR/ABL Dual Color, Dual Fusion Translocation Probe Kit, Abott, USA; CytoCell BCR/ABL(ABL1) Translocation, Dual Fusion, Sysmex, Japan; ZytoLight SPEC BCR/ABL1 Dual Color Dual Fusion Probe, ZytoVision GmbH, Germany). Analyses were performed using an Eclipse 80i fluorescence microscope (Nikon, Japan).

All chromosomal anomalies were reported according to the 2020 guidelines of the International System for Human Cytogenomic Nomenclature. The p210, p230, and p190 transcripts of the *BCR/ABL1* fusion gene were analyzed by real-time reverse-transcription polymerase chain reaction using the manufacturer's suggested protocol [geneMAP BCR-ABL1 p210 (Mbcr) Detection Kit (BCR210-RT48), geneMAP BCR-ABL1 p190 (mbcr) Detection Kit (BCR190- RT48), and geneMAP BCR-ABL1 p230 (µbcr) Detection Kit (BCR230-RT48), GenMark, USA]. The major molecular response (MMR) and complete cytogenetic response (CCyR) rates of these cases were evaluated according to the 2020 criteria of European LeukemiaNet [7].

Statistical Analysis

We statistically compared patients with ACAs and CCAs (n=41) and also evaluated only Ph(+) patients (n=50) in terms of CCyR, MMR, OS, and disease stages. Data analyses were performed with IBM SPSS Statistics 21 and R Studio. Categorical variables were presented as counts and percentages. Mean survival times of the groups were given. The Kaplan-Meier method was used to obtain survival functions. Proportional hazard assumptions were checked with goodness-of-fit tests. Log-rank tests were used to compare survival functions. Chi-square analyses were performed to assess the relationships between qualitative variables. Values of $p<0.05$ were considered significant.

Results

In cytogenetic and FISH analysis, ACAs and CCAs were detected in 41 of 450 cases (9.11%). We detected CCAs in 12 and ACAs in 29 of our patients. The mean age of these patients was 55±16.18 years, and 15 (37%) were female while 26 (63%) were male.

While additional anomalies detected in 29 of these 41 patients were determined to be ACAs, they developed as CCAs in the remaining 12 cases. Patients with CCAs were treated with imatinib (n=5), dasatinib (n=1), nilotinib (n=2), and azacitidine (n=2). We observed that these patients used second-line TKIs, switching from first-line imatinib treatment to dasatinib and nilotinib. Two patients were in the BP and the rest were in the CP of the disease. MMR was achieved in 3 of 9 cases, and CCyR was achieved in 1 of 8 cases. Three of these patients remained under follow-up. Three of ten (30%) of the patients were dead while the survival information of 2 patients could not be obtained (Tables 1 and 2).

Fourteen of 29 patients with ACAs were treated with imatinib, 5 with dasatinib, 7 with nilotinib, and 1 with azacitidine. Twenty-two of these patients were in the CP of the disease, 5 were in the BP or experienced transformation to acute leukemia, and 1 patient was in the accelerated phase. MMR was achieved in 8 of 26 cases, and CCyR was achieved in 10 of 23 cases. Seven of the patients remained under follow-up. Eight of 28 (28.57%) of the patients were dead and the survival information of 1 patient could not be obtained (Tables 1 and 2).

Results of conventional cytogenetic analysis revealed a great variety of ACAs and CCAs among 41 patients. The most common aberration was +8 in 16/41 patients (39.02%). Trisomy 8 was found in the Ph(-) clones of 5/16 patients (31.25%). In addition, LOY was found as an ACA in 4/41 patients (9.75%), and +8 was accompanied by LOY in 1 of these cases. An additional Ph chromosome was detected in 9/41 patients (21.95%). A complex karyotype was detected in 2/41 patients (4.87%) (Figure 1). Additionally, MRAs and MiRAs were detected at a rate of 9.11% among 450 CML patients.

Since the number of patients with ACAs and CCAs was very low, we jointly evaluated the clinical effects of ACAs and CCAs in 41 CML patients. We compared the statistical data of these patients with cases of only Ph(+) and cytogenetic abnormalities. The presence of only Ph(+) is known to be a good prognostic marker in CML patients because there is unresponsiveness to TKIs in CML patients with ACAs and CCAs. Furthermore, response rates are low in cases of Ph(+) acute leukemia treated with TKIs. We found a significant difference in MMR rates of the two groups ($p<0.05$), but we did not find a statistically significant difference in OS between the two groups (p=0.892) (Table 3).

Discussion

The Ph chromosome has both diagnostic and prognostic importance in CML. Therapies targeting the tyrosine kinase activity of the *BCR/ABL1* fusion gene are very successful in CML. However, it is stated that cytogenetic aberrations develop in cases of Ph(+) and Ph(-) clones, and these aberrations have important effects on prognosis [3,7]. The incidence of these aberrations has been reported to be 5%-12.7% among CML patients [8,9]. We think that the variability in this rate is likely due to the clinical heterogeneity of the cases and the different sizes of case groups in different studies. In our study, the rate of these aberrations was determined to be 9.11%, which is consistent with the literature.

Aberrations detected in CML have been reported to have negative effects on many prognostic parameters. Particularly, they are known to have effects on MMR, CCyR, and sensitivity to TKIs. Two different study groups were reported in which CCAs and ACAs negatively affected the MMR rate, CCyR rate, and TKI sensitivity (especially for imatinib) [1,10]. In our patient group, MMR and CCyR were evaluated in 34 and 30 patients, respectively. We observed nonachievement of MMR in 67.64% of the patients and nonachievement of CCyR in 50%. We also statistically determined the negative effect of ACAs and CCAs on MMR (p=0.042). We observed that 15 patients were switched from first-line imatinib treatment to dasatinib and nilotinib. It was reported that ACAs and CCAs were often seen in the advanced phase of CML, and these aberrations were particularly detected in the accelerated phase of the disease [1]. However, it is noteworthy that 80% of the aberrations detected in our study were seen in CP-CML (Table 2). In a study by Gong et al. [11], it was shown that ACAs can develop during treatment with TKIs and at the time of the initial diagnosis, and they are associated with blastic transformation. In our study, we observed that CCAs and ACAs developed after TKI treatment in 8 of 32 patients. However, we could not show a statistically significant difference due to the small number of patients.

Table 1. Karyotypes and clinical parameters of CML cases.

Case no.	Gender	Age	Karyotype	MMR	CCyR	Therapy	Phase	OS (months)
1	M	59	47,XY,+6[2]/48,XYYY[1]	A	A	Imatinib	Chronic	192
2	F	60	47,XX,+mar[5]	F	A	Imatinib	Chronic	192
3	F	72	47,XX,+8[10]	F	A	NK	Chronic	NK
4	M	47	47,XY,+6[1]/46,XY[14]	F	A	Imatinib -> nilotinib	Chronic	144
5	F	69	47,XX,+8[1]/46,XX [14]	A	A	Imatinib -> nilotinib	Chronic	156
6	F	69	47,XX,+8[8]/46,XX[18]	NK	A	Imatinib	Chronic	132
7	M	59	47,XY,+8[19]/46,XY[4]	F	F	Imatinib -> dasatinib	Chronic	48
8	M	47	47,XY,+mar[2]/46,XY[20]	F	A	Imatinib	Chronic	NK
9	M	87	47,XY,add(20)(p12),+der(21)[2]/47,XY,del(4)(q31),add(20)(p12),+der(21)[9]/46,XY[5]	NK	C	NK	Chronic	6, died
10	M	87	47,XY,+8[12]	A	C	Azacitidine	Blastic	3, died
11	F	85	47,XX,+11[8]	NK	C	Azacitidine	Blastic	9, died
12	M	40	46,XY,t(9;22)(q34;q11)[2]/47,XY,+8[7]/47,XY,+8,der(12)del(12)(p12?)[2]	F	F	Imatinib	Chronic	41
13	F	73	46,XX,t(9;22)(q34;q11)[1]/47,sl,+8[19]	F	F	Interferon + imatinib -> dasatinib + cytosine arabinoside	Accelerated	60, died
14	M	66	46,XY,t(9;22),sl,+8[6]/46,XY[10]	A	A	Imatinib -> nilotinib	Chronic	96, died
15	F	48	46,XX,t(9;22)(q34;q11),add(21)(q22)[20]	F	F	Imatinib	Blastic	12, died
16	F	59	46,XX,t(9;22)(q34;q11)[2]/47,sl,+8[6]/48,sdl1,+der(22)t(9;22)[10]/49,sdl2,+der(22)t(9;22)[2]/50,sdl3,+der(22)t(9;22)[2]	NK	C	NK	Chronic >acute	Died
17	M	54	46,XY,t(9;22)(q34;q11)[8]/47,sl,+8[2]/46,XY[10]	F	A	Imatinib -> dasatinib	Chronic	144
18	M	67	nuc ish(ABL1X3),(BCRX3),(ABL1 con BCRx2)[54]/(ABL1X4),(BCRX4),(ABL1 con BCRx 3)[47]/ (ABL1,BCR)x2[67]	NK	C	NK	NK	Died
19	M	51	46,XY,t(9;22)(q34;q11)[10]/47,sl,+der(22)t(9;22)[2]	A	A	Imatinib > nilotinib	Chronic	120
20	F	78	46,XX,t(9;22)(q34;q11),+der(22)t(9;22)[20]	A	A	Imatinib	Chronic	108
21	M	42	45,X,-Y,t(9;22)(q34;q11)[20]	F	F	Dasatinib	Chronic	120
22	M	44	47,XY,t(9;22)(q34;q11),+der(22)t(9;22)[5]	F	F	Imatinib	Chronic	180
23	M	47	46,XY,t(9;22)(q34;q11)[10]/47,sl,+der(22)t(9;22)[2]/46,XY[10]	A	A	Imatinib	Chronic	108

Table 1. Continued.

Case no.	Gender	Age	Karyotype	MMR	CCyR	Therapy	Phase	OS (months)
24	F	43	46,XX,t(9;22)(q34;q11)[12]/47,sl,+8[5]	F	C	Imatinib -> dasatinib	Chronic	84
25	M	64	46,XY,t(9;22)(q34;q11)[18]/45,X,-Y,t(9;22)(q34;q11)[6]	F	A	Imatinib -> nilotinib	Chronic	72
26	F	40	46,XX,t(9;22)(q34;q11)[10]/47,sl,+8[7]/46,XX[1]	A	F	Imatinib	Chronic	72
27	M	27	46,XY,t(9;22)(q34;q11)[2]/47,sl,+8[2]	A	A	Imatinib	Chronic	72
28	M	35	nuc ish(ABL1X3),(BCRX3),(ABL1 con BCRx2)[10]/(ABL1X4),(BCRX4),(ABL1 con BCRx 3)[80]/ (ABL1,BCR)x2[90]	F	F	Imatinib	Chronic >acute	24, died
29	F	72	46,XX,t(9;22)(q34;q11)[16]/47,sl,+mar[2]/46,XX[1]	A	A	Imatinib	Chronic	53
30	M	44	46,XY,t(9;22)(q34;q11)[9]/47,sl,+8[2]	F	F	Azacitidine	Blastic	12, died
31	F	27	nuc ish(ABL1X4),(BCRX4), (ABL1 con BCRx 3)[200]/ (ABL1,BCR)x2[1]	F	F	Imatinib -> nilotinib	Chronic	36
32	M	59	46,XY,t(9;22)(q34;q11)[2]/46,X,-Y,+8,t(9;22)(q34;q11)[1]	A	A	Imatinib -> nilotinib	Chronic	45
33	M	81	46,XY,t(9;22)(q34;q11)[2]/47,sl,+der(22)t(9;22)[10]	F	C	Imatinib + hydroxyurea	Blastic	12, died
34	M	26	46,XY,t(9;22)(q34;q11)[5]/47,sl,+der(22)t(9;22)(q34;q11)[5]	F	F	Imatinib	Chronic	36
35	F	30	46,XX,t(9;22)(q34;q11),inc[9]	F	C	Imatinib	Chronic	24
36	M	60	46,XY,t(9;22)(q34;q11)[2]/49,XYY,sl,+8,+der(22)t(9;22)(q34;q11)[3]	F	A	Imatinib -> dasatinib	Chronic	24
37	F	55	46,XX,t(9;22)(q34;q11)[6]/46,XX,sl,der(1)add(1)(p?)[2]/46,XX[3]	F	F	Imatinib -> nilotinib	Chronic	12
38	M	63	46,XY,t(9;22)(q34;q11),+der(22)t(9;22)(q34;q11)dup(22)(q11?)[12]	F	F	Imatinib -> dasatinib -> nilotinib	Chronic	24
39	M	41	46,XY,t(9;22)(q34;q11)[2]/46,sl,inv1(p31?q23?)[3]	NK	C	Imatinib	Chronic	24
40	M	41	45,X,-Y,t(9;22)(q34;q11)[5]	C	C	Imatinib	Chronic	NK
41	M	48	46,XY,t(9;22)(q34q11.2)[14]/47,XY,sl,+der(22)t(9;22)(q34.1q11.2)[6]	F	F	Imatinib -> nilotinib, dasatinib, and bosutinib	Chronic	96

M: male, F: female, MMR: major molecular response, CCyR: complete cytogenetic response, A: achieved, F: failure, C: continuing, NK: not known, OS: overall survival.

Due to the low number of cases and the high number of anomaly types, we discussed the effects of anomalies observed as ACAs and CCAs individually. Trisomy 8 is known as a moderate prognostic factor causing clinical heterogeneity in CML because the increased expression of the *c-MYC* gene has been associated with the aneuploidy of chromosome 8 [12]. In our study, +8 was detected as both an ACA (n=11) and CCA (n=5). Bacher et al. [3] stated that +8 detected as a CCA generally develops after treatment. MMR could not be evaluated in 1 of 5 cases in which trisomy 8 was detected as a CCA, while 2 of the remaining 4 cases did not have MMR. In the cases with +8 detected as an ACA, the MMR information for 1 case could not be obtained, and MMR could not be achieved in 5 of the remaining 9 cases. However, in 1 of these cases, it was observed that +8 was accompanied by an additional Ph chromosome and an extra Y chromosome (case #36). In another case, trisomy 8 was accompanied by a derivative chromosome 12 (case #12). Wang et al. [13] reported that the most common anomalies accompanying +8 were Ph(+) chromosomes and LOY in CML cases, respectively. They further stated that the anomalies accompanying +8 are associated with unresponsiveness to TKIs, and the Ph(+) chromosome accompanying +8 negatively affects

prognosis. However, the LOY anomaly does not contribute to prognosis. These findings support the conclusion that trisomy 8 does not confer poor prognostic effects, as stated in the literature [14]. However, treatment unresponsiveness should be investigated in cases where trisomy 8 is detected as an isolated anomaly or is accompanied by a Ph chromosome and MMR is not taken into consideration.

The LOY aberration provides proliferative advantages to cells in the S phase of the cell cycle, and it has been associated with the development of malignancy [15]. The LOY aberration is generally known as a good prognostic marker in CML patients, but Issa et al. [17] and Lippert et al. [18] reported that this anomaly identified as an ACA or CCA affected prognosis negatively and studies have concluded that LOY is associated with failure to achieve MMR or CCyR and reduced OS [16,17,18]. Our patients with LOY aberrations as ACAs (cases #21, 25, 32, and 40) also had failure to achieve CCyR or MMR and they were unresponsive to imatinib (Table 1).

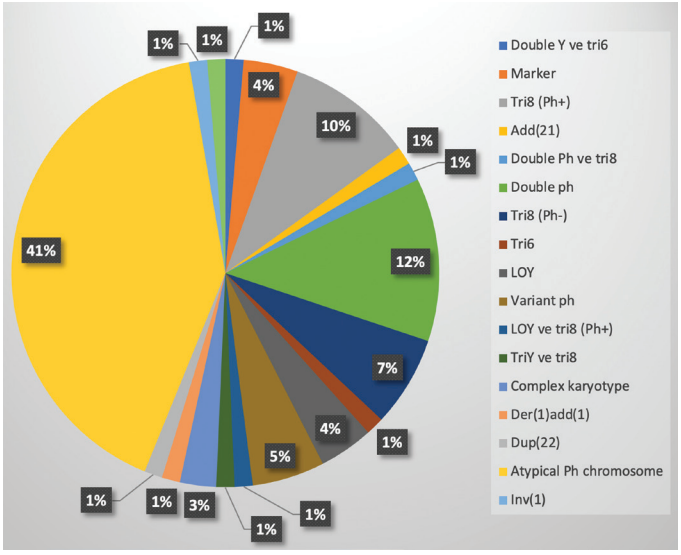

Figure 1. Variant and atypical Ph chromosomes as well as all cytogenetic aberrations detected in our CML patients in 2005-2020.

When we examined our data, we found that there were some very rare chromosomal anomalies detected as ACAs and CCAs. First, we detected aneuploidy of the Y chromosome aberrations (YCA) as a CCA and an ACA in cases #1 and #36, respectively. YCA is rarely seen in the case series in the literature and its prognostic effect is unknown. However, it has been stated that

Table 2. Various transcripts and prognostic parameters in two groups.

		CCAs (n=12)	ACAs (n=29)
MMR	A	3	8
	F	6	18
CCyR	A	7	10
	F	1	13
TKIs	Imatinib	5	14
	-> nilotinib	2	7
	-> dasatinib	1	5
	Azacitidine	2	1
Phase	Chronic	10	22
	Accelerated		1
	Blastic	2	3
	->acute		2
OS	Death	2	8
Transcripts	P210	12	28
	P230		1

MMR: major molecular response, CCyR: complete cytogenetic response, A: achieved, F: failure, TKIs: tyrosine kinase inhibitors, CCAs: clonal cytogenetics abnormalities, ACAs: additional cytogenetics abnormalities, OS: overall survival.

Table 3. Statistical comparison of clinical parameters between groups of patients with chronic myeloid leukemia.

		Group		p
		CML patients with only Ph(+) (n=50)	CML patients with CCAs and ACAs (n=41)	
Survival	Alive	25 (71.4%)	27 (71.1%)	1.000
	Deceased	10 (28.6%)	11 (28.9%)	
MMR	Failure	17 (41.5%)	23 (67.6%)	**0.042**
	Achieved	24 (58.5%)	11 (32.4%)	
CCyR	Failure	6 (27.3%)	14 (45.2%)	0.300
	Achieved	16 (72.7%)	17 (54.8%)	
Therapy	1st TKI	20 (60.6%)	18 (52.9%)	0.699
	2nd TKI	13 (39.4%)	16 (47.1%)	
Stage	Early stage	33 (97.1%)	32 (83.8%)	0.109
	Advanced stage	1 (2.9%)	6 (16.2%)	

CML: chronic myeloid leukemia, Ph: Philadelphia chromosome, CCAs: clonal cytogenetics abnormalities, ACAs: additional cytogenetics abnormalities, MMR: major molecular response, CCyR: complete cytogenetic response, TKI: tyrosine kinase inhibitors. The full clinical data of some patients were not available.

aneuploidies of chromosomes occur due to centrosome defects in CML and cause karyotypic instability [19]. We think that this aberration developed in our patients by a similar mechanism because we observed that +6 (case #1) and Ph(+) and +8 (case #36) accompanied this anomaly. For our patients, however, we did not have clear data on the prognostic effects of this aberration (Table 1).

Trisomy 6 as a rare cytogenetic abnormality has been reported for the Ph(-) clone of BP-CML after imatinib treatment [20]. In the present study, trisomy 6 was detected as a CCA in 2 cases. While it was observed to be isolated in case #4, this patient did not achieve MMR. In case #1, we first found +8 as a CCA; then a normal karyotype was detected and then +6 developed, and a normal karyotype was detected again during the treatment process. Most recently, the patient's karyotype was reported to be 47,XY,+6[2]/48,XYYY[1]. The prognostic impact of trisomy 6 is unknown. Zamecnikova et al. [20] reported a case with a history of +8 and found +6 as a CCA, and they emphasized that even though these patients may obtain MMR, the treatment strategy should be carefully clarified.

Trisomy 11, which is usually detected in AML cases, was identified in only 1 CML case in the literature and that patient died 8 months after starting combined therapy [21]. In case #11 in the present study, we detected trisomy 11 as a CCA and this patient died 9 months after the diagnosis.

We detected dup(22) as an ACA in case #38. Dup(22) is also rare and it is seen in advanced-phase CML patients in the literature. Additionally, it was reported that this aberration is associated with clonal evolution and that it develops after imatinib treatment. The aberration is also known as BCR-ABL amplification and masked Ph chromosome in cytogenetics [22]. In our study, case #36 was a patient with CP-CML who developed dup(22) after imatinib treatment due to clonal evolution. There was a failure to achieve CCyR or MMR in this case.

Finally, we detected inv(1) as an ACA in case #39, which has not been previously reported in CML. This patient with CP-CML responded to imatinib treatment, but we could not obtain information on whether he achieved MMR or not. Based on the available data, we think that inv(1) does not have poor prognostic effects.

Study Limitations

Our study has limitations including difficulty in the achievement of metaphase plaques, a small sample size, and the lack of complete follow-up data. As we included patients from only one center, we could detect cytogenetic aberrations and discuss their prognostic effects for only a small group of cases (n=41). To define the unfavorable prognostic effects of this small group, the control group comprised only Ph(+) patients (n=50), since Ph(+) is known as a good prognostic marker for CML patients.

Conclusion

We determined that ACAs and CCAs have negative effects on MMR, and the results of our study support the findings of previous reports in the literature. We suggest that the categories of MRA and MiRA are insufficient for newly defined anomalies in Ph(-) and Ph(+) clones. These anomalies should be classified as being of high or low risk according to their effects on the prognostic parameters of the 2020 ELN guidelines. Detection of these cytogenetic aberrations is important as they offer warning signs for CML treatment and patient follow-up. Additionally, as more chromosomal abnormalities are reported, their prognostic significance will become more clear. Finally, these anomalies can only be detected by cytogenetic methods, indicating that the conventional cytogenetic method is still the gold standard.

Ethics

Ethics Committee Approval: This study was conducted according to the guidelines presented in the Declaration of Helsinki, and it was approved by the relevant Clinical Practice Ethics Committee (2021-49).

Informed Consent: Each individual provided a signed consent form.

Authorship Contributions

Concept: S.I., G.G., H.Ü.T., O.M.A, N.O.D., V.A., M.K., H.Ö., O.Ç., S.A., B.D.A.; Design: S.I., G.G., H.Ü.T., O.M.A, N.O.D., V.A., M.K., H.Ö., O.Ç., S.A., B.D.A.; Data Collection or Processing: S.I., G.G., H.Ü.T., O.M.A, N.O.D., V.A., M.K., H.Ö., O.Ç., S.A., B.D.A.; Analysis or Interpretation: S.I., G.G., H.Ü.T., O.M.A, N.O.D., V.A., M.K., H.Ö., O.Ç., S.A., B.D.A.; Literature Search: S.I., G.G., H.Ü.T., O.M.A, N.O.D., V.A., M.K., H.Ö., O.Ç., S.A., B.D.A.; Writing: S.I., G.G., H.Ü.T., O.M.A, N.O.D., V.A., M.K., H.Ö., O.Ç., S.A., B.D.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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