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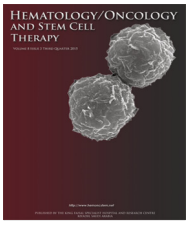

Prognostic Importance of *C-KIT* Mutations in Core Binding Factor Acute Myeloid Leukemia: A Systematic Review

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Abstract
Objective/background: Acute myeloid leukemia (AML) is defined as leukemic blast reproduction in bone marrow. Chromosomal abnormalities form different subgroups with joint clinical specifications and results. t(8;21)(q22;q22) and inv(16)(p13;q22) form core binding factor-AML (CBF-AML). *c-kit* mutation activation occurs in 12.8—46.1% of adults with CBF leukemia. These mutations occur in 20—25% of t(8;21) and 30% of inv(16) cases.
Methods: In this systematic review, we searched different databases, including PubMed, Scopus, and Embase. Selected articles were measured based on the inclusion criteria of this study and initially compared in terms of titles or abstracts. Finally, articles relevant to the subject of this review were retrieved in full text. Twenty-two articles matched the inclusion criteria and were selected for this review.
Results: In this study, *c-kit* mutations were associated with poor prognosis in AML patients with t(8;21) and inv(16). In addition, these mutations had better prognostic effects on AML patients with inv(16) compared with those with t(8;21).

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Conclusion: According to the results of this study, *c-kit* mutations have intense, harmful effects on the relapse and white blood cell increase in CBF-AML adults. However, these mutations have no significant prognostic effects on patients.

Introduction

Acute myeloid leukemia (AML) is defined as an increase of myeloid blasts in bone marrow [1]. The mean age of AML patients is 67 years; this means that AML occurs in old age [2]. Nonetheless, cytogenetic and molecular genetic abnormalities play a pivotal role in AML pathogenesis-the most prevalent AML chromosomal abnormalities are t(8;21)(q22;q22), inv(16)(p13;q22), and t(6;9)(p23;q34), which are described as core binding factor-AML (CBF-AML) [1,3,4]. According to previous studies, this group constitutes 5—8% of all AML cases [2—4]. In fact, AML with fused transcripts such as RUNX1-RUNX1T1 t(8;21) and CBFB-MYH11 inv(16) are recognized as CBF-AML; they are determined by their molecular level through gene infraction which encodes various CBF subunits [3]. t(8;21)(q22;q22) arises in approximately 8% of de novo AML patients and is associated morphologically with AML-M2 subtype [4].

Patients with CBF-AML consist of about 15% of all AML cases, which is usually more frequent in older patients. The median age of these patients is considerable lower and the prognosis is better compared with normal karyotype AMLs or other chromosome aberrations. This favorable consequence is associated with a higher complete remission (CR) rate and lower relapse incidence [5—7].

t(8;21) or inv(16) chromosomal rearrangements lead to novel chimeric fusion formation which contain a CBF complex gene. CBF complex is composed of *CBF-*α (*AML1*) and *CBF-*β gene infractions which encode CBF subunits. They are regulators of hematopoiesis that affects CBF-AML [8—10]. According to recent studies, this translocation is associated with a high white blood cell (WBC) count and it has been considered as a significant predictor in a study by Nguyen et al. [11,3,4]. Moreover, inv(16) and t(16;16)(p13;q22) are known to have a significant correlation with AML-M4Eo [3].

In general, CBF-AML has a high CR rate and extended CR time, particularly in the presence of high-dose cytarabine. It leads to a better prognosis of CBF-AML compared with cases with normal karyotypes or other chromosomal aberrations [4,11]. Mutations in Class III receptor tyrosine kinase coding genes, such as *c-kit*, cause other molecular disorders which lead to myeloid leukemia. *c-kit* expression occurs in myeloblasts and is present in 60—80% of AML patients [12]. Additionally, *c-kit* activation mutations happen in 12.8—46.1% of CBF leukemia adult patients [4,12]. These mutations mostly occur in exon 8 or 17 and are observed in 20—25% of t(8;21) and 30% of inv(16) cases [4,12].

To date CBF-AML has a high remission rate and survival possibilities. Nonetheless, because half of CBF-AML patients have not been treated yet, it is necessary to evaluate other markers to recognize patients who do not respond to usual therapy; better cognition of CBF-AML pathophysiology such as *c-kit* mutation which affects disease prognosis will help to develop new therapeutic methods [13—16]. Some studies have proposed that the presence of *c-kit* mutations or permanence of minimal residual disease may be correlated with a higher incidence of relapse and worse outcome [8—10].

Contradictory results have been reported about the prognostic significance of *kit* mutation. Several studies have shown that *kit* mutation is correlated with a decreased remission duration and overall survival (OS) of CBF-AML patients [4,13,15,16], while some studies expressed that *kit* mutations do not affect CBF-AML prognostic results [17,18]. *c-kit* mutation may be helpful to predict disease consequence of CBF-AML cases and it can be applicable as a novel remedial target for patients who underwent chemotherapy and did not have any therapeutic interventions. About 90% of CBF-AML patients achieve CR after anthracycline- and cytarabine-based induction chemotherapy [18—20].

A high dose of cytarabine which is used for postremission treatment (HiDAC; 3 g/m^2 twice a day on Day 1, Day 3, and Day 5) results in a better survival rate compared with intermediate and lower doses (400 mg/m^2 and 100 mg/m^2, respectively, as a continuous infusion on the 1st to 5th days). This finding is reported by Cancer and Leukemia Group B (CALGB) [5].

A study in 2011 by HOVON/SAKK group (Dutch Belgian Cooperative Trial Group for Hemato-oncology/Swiss Group for Clinical Cancer Research) achieved the same conclusions for CBF-AML patients who had been treated with multiagent chemotherapy with cytarabine at a cumulative dose of 13.4 g/m^2 (IDAC) and 26 g/m^2 (HiDAC). This study also showed similar event-free survival and OS for patients who treated with IDAC and HiDAC (event-free survival at 5 years: 58% vs. 47%; OS at 5 years: 64% vs. 67%) [19,21]. A case study showed that patients with t(8;21) and *c-kit* mutant gene have major molecular response to tyrosine-kinase inhibitor drugs always. They concluded that tyrosine-kinase inhibitor is useful to reduce *kit* positive AML symptoms [22,23]. A Japanese study in 2013 provided further evidence for HiDAC benefits in postremission treatment of CBF-AML compared with low-dose of cytarabine [5].

According to several studies, there is a significant correlation between age increment and *c-kit* activating mutations, which lead to a high relapse and low survival rate in CBF-AML groups [4]. Nevertheless, different OS rates have been reported for CBF-AML patients with *c-kit* mutations compared with others [3]. To our knowledge, prognosis of *c-kit* mutations in AML patients has not been assessed systematically. This systematic review aimed to evaluate the prognostic significance of *c-kit* mutations in CBF-AML patients within the age range of 15 to 90 years.

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Materials and methods

Search strategy and article selection

In this systematic review, we conducted a literature search in different databases, including PubMed, Scopus, and Embase databases. Cochrane extracted data until July 2015 and some key words were applied. The keywords used are as follows: *c-kit* and ''core binding factor acute myeloid leukemia", survival, *c-kit* and ''acute myeloid leukemia, prognosis", *c-kit* and ''core binding factor acute myeloid leukemia", ''stem cell factor receptor", ''core binding factor acute myeloid leukemia" and survival, and ''acute myeloid leukemia" and survival were in the cross-reference search of cohort articles. References lists of all primary studies were reviewed as well as review articles, in order to identify the studies which cannot be found via a computerized search.

To determine the competency of articles, titles and abstracts were investigated thoroughly by one of the researchers (Ayatollahi H). Eventually, only 22 articles were compatible with our inclusion criteria, and were reviewed in present study (Table 1). The search methodology is depicted in the preferred reporting items for systematic reviews and meta-analyses flow diagram (Fig. 1).

After measuring valid articles based on the inclusion criteria, the titles and abstracts were compared, and articles relevant to the subject of this study were retrieved in full text.

The inclusion criteria of this study were as follows: (1) published controlled clinical trials until July 2015; (2) published articles in English; (3) articles with survival data based on *c-kit* status (e.g., *c-kit* mutations and wild-type *c-kit*); and (4) articles with survival data in response to therapy (e.g., CR, disease-free survival, OS, and prognosis). The exclusion criteria of this study were as follows: (1) studies with sample sizes smaller than 10 patients; (2) published lectures, commentaries, review articles, case reports, and articles in any languages except English; (3) performed studies on extracted samples from cell lines and tissue cultures; (4) animal experiments and in vitro studies; (5) studies conducted on patients under 15 years of age; and (6) flow cytometry analyses.

Collected data for the present review included information about authors, publication year, place of study, patient characteristics (e.g., age range, median WBC count), *c-kit* mutations, OS rate, prognosis, number of participants in experimental groups, control groups, and inv(16) and t (8;21) subgroups.

Results

A detailed review of coherent data which were extracted from relevant papers is presented in Table 1. All selected articles were retrospective evaluations of the prognostic significance of the *c-kit* molecular marker. Studied populations of selected research were from different nationalities and clinical research groups. Besides, data in all the selected papers were obtained from evaluation of prognostic results of genetic tests prospectively. Also, all studies

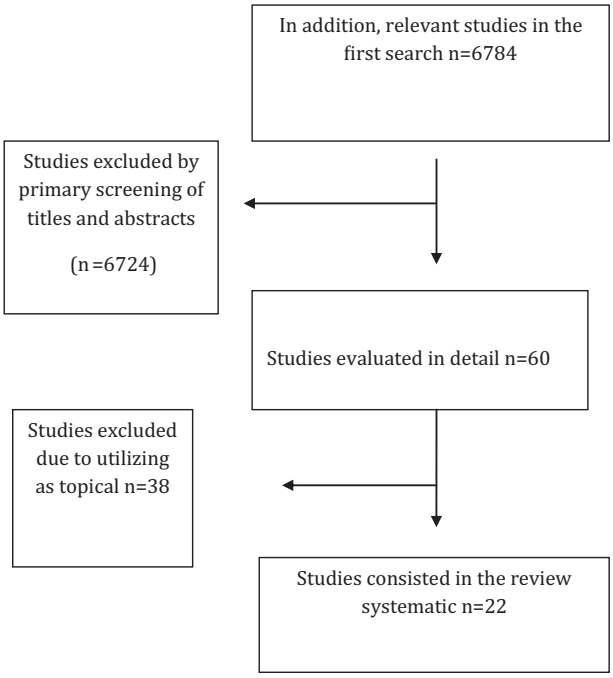

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses Flow Diagram: Screening Procedure of Selected Articles.

were conducted on CBF-AML patients with inv(16) and t (8;21) genetic abnormalities, and the number of studied cases were between 23 and 425.

Selected articles were classified into the following groups based on sample sizes: 20–100 patients (12 articles) [3,4,24–33], 100–200 patients (6 articles) [8,14,34–37], 200–300 patients (1 article) [7], 300–400 patients (2 articles) [16,38], and 400–500 patients (1 article) [16]. In total, *c-kit* mutations were detected in 10.9–46.2% of the studied patients (mean: 31%).

In this review, *c-kit* mutations were compared between two AML groups, including cases with t(8;21) and those with inv(16). These two categorizations were present in all the reviewed articles except for those listed in Table 2. The majority of the studies applied a direct sequencing method and different forms of polymerase chain reaction (PCR), including reverse-transcription PCR, methyl-binding PCR, and real-time PCR to detect *c-kit* mutations. In addition, four studies used high-performance liquid chromatography (HPLC) for *c-kit* mutations detection (Table 2) [16,24,34,35].

All the reviewed studies were retrospective with regards to the prognostic significance of *c-kit* mutations. Additionally, 11 studies reported *c-kit* mutation frequencies in inv (16) and t(8;21) patients separately. Mean WBC count separation was observed between patients with inv(16) and t(8;21) in only nine articles, all of which (expect one) [36] indicated that WBC counts had significant increments in inv(16) patients compared with t(8;21) cases [4,24,31,33,35,38,39]. Seven out of these articles expressed that *c-kit* mutations had significant increment in inv(16) patients compared with t(8;21) patients [4,8,14,24,33,35,38], while three articles stated

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Table 1 Data extraction from included studies investigating the effect of *C-KIT* in core binding factor-acute myeloid leukemia. NR: data not reported. Note: NR = data not reported; Ref. = reference.

Ref.	First author	Publication (region, year)	Participants, *n*	*c-kit* mutations (%)	inv(16) subgroup	t(8;21) subgroup	*c-kit* mutation	
							inv(16) subgroup	t(8;21) subgroup
[9]	Peter Paschka	Oldenburg, Germany, 2012	176	37	176	NR	37%	NR
[24]	Lars Bullinger	Palo Alto, CA, 2007	93	22	51	38	24%	16%
[25]	Yuan Wang	Beijing, China, 2014	92	64	NR	51	NR	64%
[26]	Roberto Cairoli	Bologna, Italy, 2013	58	25.9	58	NR	25.9	NR
[16]	Christopher Allen	London, UK, 2013	354	42	155	199	20	22%
[40]	Jung-Hoon Yoon	Seoul Korea, 2014	264	34.8	71	193	NR	
[39]	Di Wang	Hubei China, 2012	425	28.9	11	65	28.9	
[35]	Peter Paschka	Columbus, OH, 2006	110	34	61	49	20	14%
[38]	Ya-Zhen Qina	Beijing, China, 2014	351	36.5	62	188	10	26.5%
[27]	Satoshi Wakita	Tokyo, Japan, 2011	26	46.1	0	26	NR	46.1%
[36]	Hee-Jin Kim	Seoul, South Korea, 2009	121	26.4	0	121	26.4	NR
[37]	Baowei Jiao	Shanghai, China, 2009	118	31.3	NR	118	NR	31.3%
[28]	Sang Hyuk Park	Seoul, Republic of Korea, 2013	50	44	NR	50	NR	44%
[29]	Jungwon Huh	Seoul, Korea, 2012	96	23	35	63	23	NR
[8]	Sang Hyuk Park	Seoul, Republic of Korea, 2011	116	38	38	78	18	20%
[3]	Ludovica Riera	Turin, Italy, 2013	49	14.2	14	9	6	7.2%
[4]	Roberto Cairoli	Naples, Italy, 2006	67	46.2	25	42	20	26%
[14]	Nicolas Boissel	Paris, France, 2006	103	17	47	56	22	12%
[30]	Mayur Parihar	Tamil Nadu, India, 2012	88	6.5	NR	NR	6.5%	
[31]	JANA MARKOVA	Czech Republic, 2009	36	33.3	34	26	13	20.3%
[32]	O´scar Fuster,	Valencia, Spain, 2009	55	15	24	30	10	5%
[33]	Sang Hyuk Park	Busan, Korea, 2015	92	9.8	21	71	5	4.8%

Note. NR = data not reported; Ref. = reference.

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Table 2 Indication of Methods Used and Follow-up Periods.

Ref.	Author	Methods	Follow-up	Median age	
				c-kit mutation	
				inv(16) or overall	t(8;21)
[9]	Peter Paschka	RT-PCR, sequencing, DHPLC	6.04 y	41 (18–74)	NR
[24]	Lars Bullinger	RT-PCR, sequencing, DHPLC	NR	42 (19–72)	50 (19–73)
[25]	Yuan Wang	qRT-PCR, direct-sequencing	3 mo	NR	36 (18–54)
[26]	Roberto Cairoli	ARMS-PCR, sequencing	NR	42 (15–60)	NR
[16]	Christopher Allen	PCR/sequencing, DHPLC	10 y	39 (15–64)	39 (15–64)
[40]	Jung-Hoon Yoon	qRT-PCR	61.8 mo	39 (18–89)	
[39]	Di Wang	PCR, sequencing	21 mo	28 (16–64)	32 (13–70)
[35]	Peter Paschka	Sequencing, DHPLC./RT-PCR	5.3 y	49	38
[38]	Ya-Zhen Qina	RQ-PCR, bidirectional sequencing	10 mo	38 (15–73)	
[27]	Satoshi Wakita	MB-PCR/direct sequencing	3–112 mo	NR	50.3 (3–72)
[36]	Hee-Jin Kim	Direct sequencing	27 mo	38 (18–69)	44 (15–71)
[37]	Baowei Jiao	QRT–PCR, direct sequencing	2 y	NR	24 (3–72)
[28]	Sang Hyuk Park	RQ-PCR, direct sequencing.	24 mo	NR	33.5 (2.0–69.0)
[29]	Jungwon Huh	Direct sequencing	33.5 mo	41 (15–75)	
[8]	Sang Hyuk Park	RT-PCR, sequencing	NR	44.0 (18.0–69.0)	
[3]	Ludovica Riera	Q-PCR, direct sequencing	88 mo	51	
[4]	Roberto Cairoli	PCR, sequencing	34 mo	51 (17–88)	40.5 (16–76)
[14]	Nicolas Boissel	RT-PCR, sequencing	4.4 y	33 (1–75)	
[30]	Mayur Parihar	PCR, sequencing	25 mo	33 (16–61)	
[31]	Jana Markova	Q-PCR, direct sequencing	27.1 mo	40.5(20.4–72.2)	
[32]	Oscar Fuster	HRM, sequencing	17 mo	NR	
[33]	Sang Hyuk Park	PCR, sequencing	10 mo	47.0 (16.0–82.0)	41.0 (5.0–78.0)

Note. ARMS-PCR = amplification-refractory mutation system polymerase chain reaction; DHPLC = denaturing high performance liquid chromatography; HRM = high resolution melting; NR = data not reported; PCR = polymerase chain reaction; Q-PCR = quantitative polymerase chain reaction; RT-PCR = reverse transcription polymerase chain reaction; RQ-PCR = real-time quantitative polymerase chain reaction.

that this increase was more significant among patients with t(8;21) [3,31,39]. Furthermore, the majority of the reviewed studies evaluated other parameters such as OS, relapse-free survival (RFS), and follow-up outcome in terms of *c-kit* genotype marker presence or absence.

The effects of c-kit mutations on the OS of patients

With respect to *c-kit* mutations, CR rate was investigated in 16 studies on a CBF-AML population presenting with *c-kit* mutations and was estimated to be between 40% and 100% [3,8,14,25–31,33,34,36,37,39]. Effects of *c-kit* mutations on RFS were investigated in 17 studies ($p = .009–.34$), and it was reported as a significant variable among patients in three articles [35,39,40]. Moreover, three studies that compared the significance of RFS between CBF-AML patients with inv(16) and t(8;21) and AML patients with t(8;21), indicated its decline in the AML group; therefore, it can be concluded that RFS rate is significant in the t(8;21) group [8,11,38].

According to the results of 12 articles, RFS rate was estimated to be 2.98–88.8%, while nine studies reported a RFS rate reduction in the presence of *c-kit* mutations and wild-type *c-kit* [4,16,26,28,30,32,34,35,37,40].

However, two studies that evaluated the RFS rate in two groups of AML patients with inv(16) and t(8;21), expressed a RFS rate increment in the t(8;21) group compared with the inv(16) group significantly [8,33].

OS was found in 21 articles, with a p value ranging between .0004 and .9. In 18 papers, OS was measured in all CBF-AML patients; according to their findings, OS had a significant prognostic value ($p > .001$) [17,24–26,28,29,31,34], while OS was not significant *in c-kit* mutation prognosis determination in just one paper ($p < .001$) [3,33,39].

In addition, five studies evaluated OS in two subgroups of CBF-AML patients, including patients with inv(16) and t(8;21), and the rate was measured in each group [8,14,35,38,40]. OS rate was more significant in t(8;21) patients compared with the cases with inv(16) in three of these articles [8,38,40].

Among the reviewed articles, only two cases reported an OS rate as a more significant marker in patients with inv(16) [26,34] compared with t(8;21). Four other studies compared OS rate between the above-mentioned groups, and their findings were indicative of no significant differences between patients with t(8;21) and inv(16) [3,4,31,39]. In three studies, OS was measured in patients with t(8;21)

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only, and this variable was not reported to be significant among these patients [25,28,37].

In three articles, OS rate was not measured [27,30,32], while the increase was reported by 12 researches among *c-kit* mutant cases in a CBF-AML population [3,4,14,16,24,26,29,30,34,36,37,40]. In these studies, the follow-up period ranged from 3 months to 10 years.

Discussion

Genetic alterations, such as *c-kit* mutations, are considered as significant risk factors that provide essential prognostic information about CBF-AML [34]. According to a Cox model, some of the possible prognostic parameters of CBF-AML are age, sex, WBC count, *c-kit* mutations, and cytogenetic abnormalities of chromosome 22 [26].

CBF-AMLs are commonly associated with favorable prognosis; however, this prognosis can be changed. Correspondingly, only 50% of CBF-AML patients are able to preserve long-term remission without any relapse [29]. Also, allogeneic stem cell transplantation has not been administered in CBF-AML patients in CR [21,23].

Furthermore, based on the obtained results of this review, *c-kit* mutations organize the main genetic aberrations in the leukemogenesis of CBF-AML and are highly prevalent among these patients. Therefore, *c-kit* mutations are significant prognostic predictors in CBF-AML patients with t(8;21) and inv(16), which are associated with poor prognosis; however, current findings are inconsistent in this regard [29,33]. In the reviewed articles for the present analysis, about 3,284 patients were evaluated in terms of *c-kit* status. According to our findings, *c-kit* mutations have direct effects on relapse and result in poor RFS, especially with the D835 mutation; however, these mutations have no significant effects on OS rate. However, *c-kit* mutations can lead to WBC increments, especially in patients with inv(16). In the reviewed studies, no significant association was found between *c-kit* mutations and success rates of CR and OS among CBF-AML patients.

Conclusion

According to the results of current review, *c-kit* mutations have poor prognostic significance in AML patients with t(8;21); however, no definite results can be obtained according to the prognostic effects of these mutations in AML patients with inv(16). In the majority of the investigated articles, *c-kit* mutations were observed to have better prognostic effects on patients with inv(16) compared with those with t(8;21). Therefore, it can be concluded that *c-kit* mutations may cause relapse and WBC increments in CBF-AML adults without any significant prognosis in their survival.

One of the major limitations of present study was lack of prospective controlled studies in the review of the selected articles. Furthermore, due to limited data accessibility, findings of the current study can be used for AML prognosis evaluation and patients' guidance. It seems that it is necessary to recognize more efficient prognostic indicators and therapeutic strategies to determine AML risks.

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