Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2018 January ; 18(1): e19–e25. doi:10.1016/j.clml.2017.09.017.

Outcomes of patients with relapsed core binding factor-positive acute myeloid leukemia

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Abstract

Purpose—To determine the factors associated with outcomes in patients with core binding factor acute myeloid leukemia (CBF-AML) in first relapse.

Material and Methods—We conducted a retrospective analysis of 92 patients with CBF-AML in first relapse who presented to our institution from 1990–2014. Clinical and demographic parameters were included in univariate and multivariate Cox proportional hazards regression model to predict overall survival.

Results—Among the 92 relapsed patients, 60 (65%) patients had inv (16) and 32 (35%) had t (8; 21). The median survival for patients with inv(16) cytogenetic group was 15.6 months (range 10.32 to 20.88 months) while for the t(8;21) group was 9 months (range 3.68 to 14.32) ($p=0.004$). Univariate Cox model analysis showed that increased age, high white blood cell count, t (8; 21) cytogenetic group, and high bone marrow blast percentage were associated with poor overall outcome, while stem cell transplant intervention was associated with better survival. Additional cytogenetic aberrations at relapse were not associated with survival outcomes ($p = 0.4$). Multivariate Cox model analysis showed that t(8;21) cytogenetic group has more hazard of death after adjusting, age, marrow blast percentage, blood cell count, and stem cell transplant(hazard ratio 1.802; $p = 0.02$).

Conclusion—Among patients with relapsed CBF-AML, median survival was less than a year and half and the outcome was worse in patients with t (8; 21). Despite the relatively better outcomes, dedicated clinical trials are needed to improve the outcome in all patients with relapsed CBF-AML.

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Conflicts of Interest
None

Keywords

acute myeloid leukemia; core-binding factor positive; relapse; cytogenetic; remission

Introduction

Relapse remains the biggest challenge in patients with acute myeloid leukemia (AML) irrespective of prognostic groups based on cytogenetic and molecular aberrations. Core binding factor-positive AML (CBF-AML), which accounts for approximately 20% of AML, has been defined by the presence of translocations (8;21)(q22;q22) [abbreviated t(8;21)], inv(16)(p13q22) or t(16;16)(p13;q22) [abbreviated inv(16)].^{1,2} These chromosomal aberrations create the fusion genes RUNX1/CBFA2T1, which interrupts one of the subunits of CBF, and CBFB/MYH11, which interrupts the β subunit of CBF respectively. CBF is a heterodimeric transcription factor that helps regulate hematopoiesis.^{1, 2, 3} Although CBF-AML is considered a favorable cytogenetic subset of AML, there is substantial room for improvement in outcomes particularly after relapse.⁴ Reports from several groups of this 'favorable-risk' AML have indicated a 5-year overall survival (OS) rate of about 50% in the frontline setting.^{2,5} More recent reports however indicate better results.^{6,7} Relapsed CBF-AML is a heterogeneous disease, and understanding the variables that impact outcome will help risk stratification and development of innovative therapies. Second complete remission (CR2) is achieved in around 60–85% of the relapsed patients after salvage therapy but median OS in 5 years is again around 50%.^{8,9}

Although t (8; 21) and inv (16) are both considered drivers of CBF-AML, diseases associated with these translocations have emerged as separate entities in terms of disease kinetics, relapse incidence, and treatment.⁵ Conventional front-line treatment strategies with proven efficacy in CBF-AML include multi-cycle high-dose cytarabine based consolidation, ¹⁰ FLAG-IDA regimen (fludarabine, cytarabine, idarubicin, and granulocyte colony stimulating factor),¹¹ and use of gemtuzumab ozogamicin.¹² In addition, diligent monitoring of minimal residual disease adds additional prognostic refinement.¹³ Remission duration and survival after relapse may depend on clinical and disease related characteristics and/or on treatment regimens. In most cases, the treatment approach for relapse has been use of regimens similar to those used in front-line and stem cell transplantation (SCT) for patients with appropriate donors. To help define factors that can predict outcome in relapsed CBF-AML and thus identify patients requiring innovative therapies, we conducted a univariate and multivariate analysis of patient, disease and therapy related characteristics.

Material and Methods

We performed an individual patient data-based retrospective analysis of 92 patients evaluated at our institution between 1990 and 2014 who had relapse of CBF-AML after having achieved the first CR. Details such as patient demographics (age, sex and ethnicity), first remission duration, relevant diagnostic test results at the time of relapse (percentage of blast cells in the bone marrow, peripheral blood blast cells, white blood cell (WBC) count, platelet count, hemoglobin, serum albumin, lactate dehydrogenase, bilirubin, creatinine),

cytogenetics, treatment regimens, and response to therapy were reviewed. Clonal evolution was recorded as any additional chromosomal aberrations compared to baseline cytogenetics. Due to the historical nature of the analysis, limited data was available regarding CBF-AML relevant mutations, including FLT3-ITD, FLT3-D835, RAS, KIT, TET2, JAK2, and TP53.

Continuous variables were summarized using mean, median, standard deviations, and ranges. Categorical variables were summarized using frequencies and percentages. Kaplan-Meier curves¹⁴ were used to estimate unadjusted OS durations. OS was defined as the time from the date of relapse to death or last follow-up. The log-rank test was used to compare OS between groups (e.g., cytogenetic subgroups). Cox proportional hazards models were used to evaluate the ability of the covariates to predict OS. Because time to SCT from relapse varied among patients, hazard ratios (HRs) and 95% confidence intervals (CIs) were computed by using a time-varying covariate Cox proportional hazards regression model. For the continuous variables, if the data were highly skewed, natural log transformation was used to produce a more symmetric distribution for the corresponding variables. Variables showing a potential effect on OS ($p \leq 0.05$) in the univariate analysis were included in final model. For all analyses, $p < 0.05$ was considered statistically significant. All computations were carried out in SAS version 9.4 (SAS Institute, Cary, NC) and TIBCO Spotfire S+ version 8.2 (TIBCO Software Inc., Palo Alto, CA).

Results

Patient characteristics

A total of 92 patients who had experienced relapse after first CR were included in the study; 55 (60%) were male and 37 (40%) were female. The median age at relapse was 46 years (range 19 to 76 years). Sixty patients (65%) had inv (16) and 32 (35%) had t (8; 21). The median WBC count was $2.65 \times 10^9/L$ (range 0.10 to $95.20 \times 10^9/L$), median platelet count was $43 \times 10^9/L$ (range 6.00 to $242.00 \times 10^9/L$), and median bone marrow blast percentage was 25% (range 0.40 to 97.00%). Most of the patients (93%) had an Eastern Cooperative Oncology Group (ECOG) performance status¹⁵ of 1 or 2. The median duration for first complete remission (CR1) was 13.04 months (range 11.97 to 15.37 months) for inv(16) and 10.86 months (range 7.47 to 17.75 months) for t(8;21) ($p=0.90$). All patients received high-dose cytarabine (HDAC) as part of their induction regimen (1.5 to 2 g/m² IV for 4–5 days based on age). Additional agents in the induction regimens included any one of these: daunorubicin, idarubicin, gemtuzumabozogamicin, fludarabine, or topotecan, depending on the frontline regimen of that time period.

Table 1 shows the characteristics of patients stratified by the cytogenetic subgroups t (8; 21) and inv (16). There was a significant association between cytogenetic subgroup and ethnicity ($p = 0.01$). Most of the African American patients (6/8; 75%) had t (8; 21), while 43 of the 60 Caucasian patients (72%) and 15 of the 22 Hispanic patients (68%) had inv (16). Because only two Asian patients were included in the cohort, associations between this ethnicity and cytogenetic group could not be assessed. Age, sex, bone marrow blast percentage, WBC count, and platelet count were not associated with a particular cytogenetic subgroup.

No significant difference was observed between the incidence of additional cytogenetic abnormalities between patients with t (8; 21) and those with inv (16) (34% vs. 22% respectively; $p = 0.31$).

The most common cytogenetic abnormalities were trisomy 8 (9; 10%), trisomy 22 (9; 10%) and - Y (8; 8.9%). Limited mutation data was available in 20 patients; 12 with Inv 16 and 8 with t (8; 21). One patient in each group tested positive for FLT3-ITD mutation while one patient with Inv16 was positive for FLT3-D835 mutation. All tested patients were negative for KIT mutation. One patient with Inv 16 had both p53 and JAK2 mutation.

Salvage therapy and response

Three-fourths ($n=45$, 75%) of the patients with inv (16) cytogenetic group received salvage treatment with high dose cytarabine and 12 patients (20%) received other treatments, including intermediate-dose cytarabine. Twenty (63%) patients in t (8; 21) cytogenetic group received salvage therapy with high dose cytarabine and 6 (19%) patients had received other forms of salvage therapy, including intermediate-dose cytarabine. (Table 2) Three patients in each cytogenetic group received HMA as first salvage and all were older than 55 years.

A total of 40 patients (43%) had received SCT after relapse. Approximately three-quarters ($n=20$, 74%) of the patients with inv (16) underwent SCT in second complete remission (CR2) CR, while 4 patients (30.8%) with t (8; 21) group did so in CR2.

The CR2 rate was 75.4% for those who received salvage therapy high dose cytarabine, 16.7% for those who received hypomethylating agents or other salvage therapies. Of those who had received salvage therapy with HDAC, 84.5% ($n=38$) of the inv (16) patients achieved CR2 while the CR2 rate was 55.0% ($n=11$) for the patients with t (8; 21) ($p=$). Table 2 outlines the CR2 rate stratified by cytogenetic subtype. Additional cytogenetic abnormalities at relapse were not associated with OS ($p = 0.4$; Figure 1).

Clinical outcomes

The median OS for all the patients who relapsed was 12 months (7.88 to 16.12 months); 15.6 months (range 10.32 to 20.88 months) for those with inv(16) and 9 months (range 3.68 to 14.32 months) for those with t(8;21) ($p=0.004$; Figure 2). The CR2 rate for the inv (16) was 68% while for t (8; 21) was 47% ($p=0.045$). Among the patients who responded to the salvage therapy ($n=56$), patients with t (8; 21) ($n=15$) cytogenetic group had a median relapse-free survival (RFS) of 3.87 months (95% CI: 1.85–28.66) while the median of RFS for inv (16) was not reached ($p=0.002$) (Figure 3A).

Among the patients who received HDAC based salvage regimen, there was a significant difference in the median survival times between the two cytogenetic groups: 18.4 months (range: 12.146–24.654) for patients with inv (16) and 7.0 months (range: 0.47–13.53) for patients with t (8; 21) ($p=0.008$). OS durations were shorter for patients who underwent treatment with hypomethylating agents than for those who received other treatments, but the difference was not significant ($p = 0.13$; Figure 3B).

Univariate Cox analysis (Table 3) showed no differences in OS for sex ($p = 0.84$), ethnicity ($p = 0.81$), performance status ($p = 0.17$), or platelet count ($p = 0.7$). The $t(8; 21)$ cytogenetic group ($p < 0.01$), older age ($p = 0.04$), higher WBC count ($p = 0.04$), and higher bone marrow blast percentage ($p = 0.02$) were associated with worse survival while SCT intervention was associated with better survival ($p = 0.02$). Multivariable analysis (Table 4) showed that the $t(8; 21)$ cytogenetic group (HR 1.802; 95% CI 1.093–2.970; $p = 0.0209$) and older age relapse were associated with poor outcome (HR 1.033; 95% CI 1.015–1.051; $p = 0.0003$). Additionally, increasing bone marrow blast cell percentage was associated with poor outcome (HR 1.017; 95% CI 1.006–1.027; $p = 0.0013$). Those who underwent SCT had longer OS times than those who did not, but this difference was not statistically significant (HR 0.651; 95% CI 0.335–1.265; $p = 0.2054$) ($p = 0.2054$).

Discussion

Although CBF-AML is associated with favorable outcomes compared to AML with a normal karyotype or other chromosomal aberrations,^{16–21} over 50% of patients may relapse and relapse alone remains the most important factor for long term survival.^{4,22} In our study, we retrospectively analyzed a cohort of 92 patients who relapsed after achieving first CR.

There is increased recognition that the two subtypes of CBF-AML, namely $inv(16)$ and $t(8; 21)$, should be considered as two different clinical diseases owing to considerably different behavior, and prognosis,^{5,23,24} even though both of these cytogenetic variants are grouped under CBF AML.²⁵ Survival outcomes after relapse vary between the two groups as well.^{4,5,26} Our study also affirms that survival after first relapse in patients with $t(8;21)$ were worse than in those with $inv(16)$ with lower CR2 rates and shorter median duration of OS, which is similar to results reported previously.^{4,5,26}

Differences in the secondary chromosome aberrations between the two groups have also been noted. The most frequent secondary chromosome aberration in $t(8; 21)$ AML is the loss of a sex chromosome [LOS], followed by deletions of the long arm of chromosome 9 [Del (9q)] and trisomy 8, whereas the most frequent secondary chromosome aberration in $inv(16)$ AML is trisomy 22, followed by trisomies of chromosome 8 and 21, respectively.²⁴ In newly diagnosed CBF AML, del9q abnormality in the $t(8;21)$ group and trisomy 22 in the $Inv16$ group have been associated with better outcomes, the same effect has not been seen in the patients with relapsed disease.^{4,5}

KIT mutations particularly in exon 17 and 8 have been associated with higher relapse rates after frontline therapy in several studies.^{27,28} The relevance of KIT mutation in the salvage setting is unclear as loss of KIT mutation at relapse is not infrequent. The same is true for RAS, FLT3-TKD mutations.²⁹ Given the historical nature of our data, we have mutation information in less than a quarter of this cohort.

Studies have postulated that a poor prognosis in patients with $t(8; 21)$ can be explained by an increased number of structural chromosomal abnormalities after relapse.²⁶ The frequency of additional cytogenetic aberrations were comparable between the subgroups and no association was found between OS and these additional cytogenetic changes. The influence

of various cytogenetic changes in addition to either t(8;21) or inv(16) is largely debatable; trisomy 22 has been implicated as an independent prognostic factor in superior survival⁴, while reports on the impact of del(9q) on OS have been mixed.^{5,30} On the other hand, another study concurs with our findings in showing lack of any significant impact of these additional cytogenetic aberrations on clinical outcome.²² Ultimately, the prognostic significance of these additional changes remains controversial and requires further investigation.

There was no significant difference in the mean age at relapse between the two cytogenetic subgroups in our study [45.5 ± 17.5 years for inv (16) and 49 ± 16.7 years for t (8; 21); $p = 0.44$). However, increased age was associated with poor OS. This result is in agreement with other studies.^{31–34}

In this analysis racial background had no significant impact on OS ($p = 0.81$). This contrasts with other studies that have shown a prognostic impact of race on OS.³⁴ We noted that inv (16) was more prevalent in white and Hispanic patients, which should confer a better prognosis in these groups. Conversely, three-quarters of the black patients had t (8; 21), the variant associated with the worse prognosis. This imbalance in cytogenetic subgroups among racial subgroups can mask the impact of race on outcome.

We found no statistically significant difference in OS between patients who underwent SCT and those who did not. There is controversy about this in the current literature and limited literature addressing this issue specifically.^{9,35–37} In a cohort of 139 patients, Kurosawa et al reported no difference in outcome among patients with CBF AML who did or did not undergo SCT after first relapse but in subgroup analysis found that benefit from SCT is largely in the group of patients with t(8;21).²⁶ In a similarly sized retrospective analysis from Hospital et al, SCT was not associated with better OS in relapsed CBF AML.⁹ The recommendations put forth by Döhner et al suggest the limitation of SCT to specific subgroups, and thus necessitates improved risk stratification of relapsed patients.³⁸ Relatively lesser fraction of patients in our study went for SCT (even lower for t (8; 21)) and that does not allow for a subgroup analysis.

Our study has certain limitations; its retrospective nature, relative over-representation of inv 16 subgroup and the fact that a small fraction of patients were treated with regimens other than high dose cytarabine based regimens. Our study was conducted at a single center, and thus there may be under-representation of racial subgroups.

Conclusion

Our study reinforces the need for reporting outcomes among the cytogenetic subgroups of CBF AML separately and to incorporate standard reporting of additional cytogenetic abnormalities. This will allow for the creation of larger data sets and a better understanding of trends among these relatively rarer group of patients. With recent data with sub clonal mutations in CBF AML at diagnosis and shift in clones at relapse, access to more comprehensive mutational data along with variant allele frequency will be important in providing outcome predictions after relapse in CBF AML.

However, regardless of intervention, the median survival of relapsed CBF-AML patients remains short, which underlines the need to develop focused clinical trials to improve outcomes accordingly.

Clinical practice points

Although CBF-AML is considered a favorable risk subtype of AML, about half of patients experience relapse, and consequently have poor survival outcomes. At present, patients with either inv(16) or t(8;21) are considered and treated similarly. However we found on multivariable analysis that t(8;21) cytogenetics were associated with lower second complete remission rates and shorter median overall survival. These findings suggest that the two cytogenetic subtypes of CBF-AML should be considered as clinically distinct entities, and highlight the need for tailored treatment approaches to be developed for t(8;21) patients.

SCT is currently considered the best option for eligible patients with AML. Although our study was limited by its modest sample size and retrospective nature, we did not find SCT to significantly prolong survival. This does not allow for overreaching conclusions to be drawn, but nevertheless emphasizes the importance of careful review of individual patient prognostic factors to identify patients likely to benefit from novel investigational therapies.

Our work identifies factors that predict for poorer prognosis in relapsed CBF-AML patients and compounded with findings from larger cohorts, may in future help stratify high-risk patients eligible for clinical trials involving targeted therapy.

Acknowledgments

M.K. designed the study, collected and analyzed data, wrote the manuscript. M.A. collected the data. W.Q. and S.P. provided statistical analysis. J.C., F.R., and H.K. edited the manuscript. G.B. conceived the study, designed the study, analyzed data, and wrote the manuscript.

Funding

This research is supported in part by the MD Anderson Cancer Center Support Grant P30 CA016672

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Microabstract

Patients with CBF-AML who relapse have suboptimal outcomes. We retrospectively analyzed 92 CBF-AML patients at first relapse to identify factors associated with clinical outcome. Age, high white cell count, high bone marrow blast percentage and t(8;21) cytogenetic group were associated with worse prognosis. Our findings suggest that consideration of these factors, especially t(8;21) cytogenetics, can improve prognostic stratification of patients.

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Figure 1. Kaplan-Meier estimates of overall survival stratified by additional cytogenetic change
Figure includes clonal expansion and no change ($p = 0.4$). Patients with a diploid karyotype were excluded from this analysis.

Figure 2. Kaplan-Meier estimates of overall survival stratified by cytogenetic groups inv (16) and t (8; 21) ($p < 0.01$)

Figure 3A. Relapse-free survival for patients with inv (16) and t (8; 21) cytogenetic groups
 Patients with t (8; 21) (n=15) cytogenetic group had median relapse-free survival of 3.87 months (95% CI: 1.85–28.66) while RFS for inv (16) (n=41) could not be estimated (p=0.002).

Figure 3B. Kaplan-Meier estimates of overall survival stratified by salvage therapy ($p = 0.13$)
Patients who underwent stem cell transplantation were excluded from this analysis.

Table 1

Patient characteristics and treatment stratified by cytogenetic subgroup (n = 92)

Variable	Total No. (%)	No. (%)		p*
		inv(16), n = 60	t(8;21), n = 32	
Sex				0.66
Female	55 (60)	23 (38)	14 (44)	
Male	37 (40)	37 (62)	18 (56)	
Ethnicity				0.01
Asian	2 (2)	0 (0)	2 (6)	
African American	8 (9)	2 (3)	6 (19)	
Hispanic	22 (24)	15 (25)	7 (22)	
Caucasian	60 (65)	43 (72)	17 (53)	
Age at relapse, years				0.44
Median (range)		43 (21 – 76)	50.5 (19 – 74)	
White blood cell count, $\times 10^9/L$				0.29
Median (range)		2.3 (0.1 – 95.2)	3 (0.2 – 33.2)	
Platelet count, $\times 10^9/L$				0.94
Median (range)		43 (6 – 242)	43 (12 – 204)	
Bone marrow blast, %				0.53
Median (range)		25 (0.4 – 85.6)	26 (1 – 97)	
Additional cytogenetic change				0.31
Clonal evolution	23 (27)	12(22)	11(34)	
Diploid/none	63 (73)	42 (78)	21(66)	
First Salvage Treatment				0.09
High - dose cytarabine	65 (71)	45 (75)	20 (63)	
Hypomethylating agents	6 (7)	3 (5)	3 (9)	
Stem cell transplantation	3 (3)	0 (0)	3 (9)	
Other	18 (18)	12 (20)	6 (19)	
Stem cell transplantation in CR2 [†]				0.83
No	40 (43)	33 (55)	19 (59)	
Yes	52 (57)	27 (45)	13 (41)	
[‡] ECOG performance status ^[10]				0.48
0	37 (40)	23 (38)	14 (44)	
1	46 (50)	32 (53)	14 (44)	
2	5 (5)	3 (5)	2 (6)	
3	1 (1)	0 (0)	1 (3)	
Not available	3 (3)	2 (3)	1 (3)	

Abbreviations:

[†]CR2: second complete remission;

^xECOG, Eastern Cooperative Oncology Group;

^{*}Boldface indicates statistical significance

The Fischer exact test was used to calculate the p values for sex, ethnicity, cytogenetic change, treatment group, stem cell transplantation, timing of stem cell transplantation, and performance status.

The Wilcoxon rank-sum test was used to calculate p values for age, white blood cell and platelet counts, and bone marrow blast percentage.

Table 2

Complete response rate after salvage therapy stratified by cytogenetic subgroup

Salvage Therapy	Cytogenetic Group	N (%)	
		Complete Response	No Response
High-dose cytarabine	inv(16)	38 (84.4%)	7 (15.6%)
	t(8;21)	11 (55.0%)	9 (45.0%)
	Total	49 (75.4%)	16 (24.6%)
Hypomethylating agents	inv(16)	1 (33.3%)	2 (66.7%)
	t(8;21)	0 (0.0%)	3 (100.0%)
	Total	1 (16.7%)	5 (83.3%)
Other	inv(16)	2 (16.7%)	10 (83.3%)
	t(8;21)	1 (16.7%)	5 (83.3%)
	Total	3 (16.7%)	15 (83.3%)
Stem cell transplant	inv(16)	0 (0.0%)	0 (0.0%)
	t(8;21)	3 (100.0%)	0 (0.0%)
	Total	3 (100.0%)	0 (0.0%)

Table 3

Univariate Cox analysis of overall survival in patients with relapsed CBF-AML (n = 92)

Variable	Hazard ratio (95% confidence interval)	p [*]
Sex (male vs. female)	1.05 (0.65–1.7)	0.84
Ethnicity (white vs. nonwhite)	0.94 (0.57–1.54)	0.81
Cytogenetic subgroup [t(8;21) vs. inv(16)]	2.01 (1.25–3.26)	<0.01
ECOG performance status ^[10] (2 or 3 vs. 0 or 1)	1.89 (0.76–4.75)	0.17
Age at relapse	1.02 (1–1.03)	0.04
White blood cell count	1.24 (1.01–1.53)	0.04
Platelet count	1 (0.99–1)	0.7
Bone marrow blast percentage	1.01 (1–1.02)	0.02
[×] Duration of complete remission	1 (0.98–1.01)	0.77
Stem cell transplantation (yes vs. no) in CR2 [†]	0.47 (0.25–0.89)	0.02

Abbreviations: ECOG, Eastern Cooperative Oncology Group

^{*} Boldface indicates statistical significance[×] First complete remission duration from date of diagnosis to date of relapse[†] CR2 indicates second complete remission

Table 4

Multivariable Cox analysis of overall survival in patients with relapsed CBF-AML (n = 92)

Variable	Hazard ratio	95% confidence interval	p [*]
Cytogenetic subgroup [t(8;21) vs. inv(16)]	1.802	1.093 – 2.970	0.0209
Age at relapse	1.033	1.015 – 1.051	0.0003
White blood cell count	1.214	0.979 – 1.504	0.0766
Bone marrow blast percentage	1.017	1.006 – 1.027	0.0013
Stem cell transplantation (yes vs. no) in CR2 [†]	0.651	0.335 – 1.265	0.2054

* Boldface indicates statistical significance.

[†] CR2 indicates second complete remission.