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AML with Additional Cytogenetic Abnormalities to t(8: 21) has Poorer Survival than that with Isolated t(8;21): A Retrospective Multicenter Cohort Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author NABA performed lab analysis at KAMC, designed the study, wrote the protocol, managed the literature searches and wrote the manuscript. Author MMI designed the study, wrote the protocol, and wrote the manuscript. Author SAE performed the statistical analysis and revised the manuscript. Author AFA performed lab analysis at KFMC. Author EHA collected patient data and perform lab analysis at NCI. Author OE collected clinical data and revised the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim of the Study: To investigate the poor prognostic factors incriminated in AML with t (8; 21), particularly additional cytogenetic findings, clinicopathological presentation and their impact on survival rate in Egyptian and Saudi patients.

Study Design: Patients were collected from three centers: 9 cases from King Abdullah Medical City in Makah, between 2010 and 2013, 16 from King Fahad Medical City in Riyadh, Saudi Arabia between 2007 and 2013 and 16 patients from National Cancer Institute, Cairo University, Egypt 2010 and 2013.

Methodology: We studied 41 cases with t (8; 21). Immunophenotyping was performed using BD-FACS System. Conventional karyotypic analysis was done using standard culturing and banding techniques. Clinicopathological and cytogenetic data were correlated with disease outcome.

Results: There was no statistically significant difference between Egyptian and Saudi patients concerning the hematological parameters or immunophenotype markers expression, Thirty four (82.9%) out of 41 patients achieved complete remission. The follow up period for the whole group ranged from 2.1 to 170.3 weeks. The median survival was 146 weeks. The overall survival rate was 80% at one year and 70% at two years. Regarding the cytogenetic profile 33/41(80.5%) had isolated t(8;21) and 8 patients (19.5%) had a chromosomal aberration in addition to t(8;21); the commonest of which was + 8 that was found in 5 patients. The median overall survival of those 8 patients was 28.4 compared to 146.7 weeks in cases with isolated t (8; 21) p=0.002. Also, they had a lower one year overall survival rate (44%) than those with isolated t (8; 21) (86%) and their two years overall survival was zero.

Conclusion: AML associated with additional cytogenetic abnormalities to t (8;21) has poorer survival than that with isolated t(8;21). Trisomy 8 is mostly incriminated for this being the most commonly encountered in this study.

Keywords: AML; cytogenetic; t (8; 21); FLT3; survival.

1. INTRODUCTION

Acute myeloid leukemia (AML) with t (8; 21) (q22; q22) is usually associated with a good response to chemotherapy and a high complete remission rate with long term disease free survival [1]. Translocation (8; 21) abnormality is found in approximately 5-10% of all AML cases and 10 - 22% of AML cases with maturation corresponding to the previous FAB class M2 [2,3].

Translocation 8; 21 with breaks at 8q22 and 21q22.3 was first reported by Dr Janet Rowley in 1973 during the analysis of a leukemia patient sample, and today it offers a unique example of how a cytogenetic abnormality is used to define a distinct subgroup of patients [4]. The translocation fuses the AML1 gene (also called RUNX1) on chromosome 21 which encodes the alpha subunit of core-binding factor (CBF) that is essential for normal hematopoiesis with the ETO gene (also referred to as the RUNX1T1 or MTG8 gene) on chromosome 8, producing a novel chimeric gene, AML1–ETO which disrupts the CBF transcription complex and initiates the first step of leukemogenesis [5]. The AML1–ETO fusion protein is a multifunctional cellular protein that affects cell differentiation, proliferation, apoptosis and self-renewal. Evidences suggest that additional cytogenetic aberrations may act synergistically with AML–ETO in leukemogenesis [6].

The t (8; 21) abnormality is often detected together with additional cytogenetic or molecular genetic abnormalities. These abnormalities are often numerical, but other translocations or deletions can also be detected. The most common chromosomal abnormalities are loss of sex chromosome, del (9q), trisomy 8 and complex abnormalities while molecular abnormalities include c-KIT mutations and FLT3-ITD [7,8].

AML with t (8; 21)(q22;q22) is considered to have a favorable prognosis, however some patients rapidly giving in to the disease within a few months of diagnosis despite chemotherapy [9,10]. In patients with poor outcome, several adverse prognostic indicators have been suggested as possible explanations. Among these are additional cytogenetic aberrations, leukocytosis, CD56 expression and extramedullary manifestations. In the medical literature some suggested indicators, most

notably CD56 [11] and extramedullary involvement [12] were identified in relatively small studies. Identification of other indicators was based on groups of patients treated with different protocols [13,14] or groups of patients that included some secondary leukemia cases [15] rendering the conclusions liable to confounding.

1.1 Aim of the Study

To investigate the poor prognostic factors incriminated in AML with t (8; 21), particularly additional cytogenetic findings, CD56 expression and the overall clinicopathological presentation and their impact on survival rate in Egyptian and Saudi patients.

2. METHODS

2.1 Patient Selection

We searched the files of all newly diagnosed AML cases and selected only the cases that carried t (8; 21) (q22; q22) either as the sole cytogentic abnormality or combined with other abnormalities. All patients who had secondary leukemia or diagnosed as relapsed cases when first seen in these centers were excluded.

All the patients received induction protocol 3+7 that consisted of Idarubicin 12 mg/m^2 IV bolus daily or daunorubicin 60 mg/m^2 IV from day 1 to day 3. Cytarabine 100 mg/m^2/d continuous IV infusion from day 1 to day 7. Bone marrow aspiration and biopsy were done on day 14 where treatment is proceeded accordingly: In case of aplasia or severe hypoplasia (BM blasts <5%); await recovery, and in case of significant residual blasts (cellularity > 15%) a salvage Protocol will be used, and if significant cytoreduction (cellularity < 15%) with low % residual blasts, Re-induction with 3 & 7 protocol. All patients who achieved complete remission received HiDAC (High dose Ara-C) protocol as a part of their post-remission consolidation for 3-4 cycles [16,17].

Diagnosis was based on WHO criteria in addition to FAB classification. All cases had representative bone marrow aspiration together with trephine core biopsy specimens for evaluation, EDTA peripheral blood or bone marrow aspirate specimens for flow cytometry analysis of surface and cytoplasmic markers, and heparinised sample for cytogenetic study.

2.2 Immunophenotyping (IPT)

It was performed using BD- FACS-Canto II System or FACS Caliber cytometer (BD- Bio Science) and reagent system (BD- FACS Setup) as previously described [18]. A panel of monoclonal antibodies was performed, including the myeloid markers (MPO, CD13, CD33, CD14, CD 15 & CD 64) in addition to CD3, CD7, CD10, CD19, CD20, CD34 and CD117, as well as HLA-DR and TdT (terminal deoxynucleotidyl tansferase). CD56 was also performed in a subset of cases. Cell populations were designated as positive for a particular surface antigen if expressed in ≥ 20% of blasts events (stained beyond an appropriate isotype cutoff) and for intracellular antigen ≥ 10% [18].

2.3 Cytogentic Analysis

Conventional karyotypic analysis was performed on metaphase cells using standard culturing and G -banding techniques (Fig. 1), results were reported in accordance to the International System for Human Cytogenetics Nomenclature [19].

2.4 Statistical Analysis

Data were analyzed using SPSS statistical package version 21.0. Numerical data were expressed as mean ± SD or as the median, minimum and maximum according to the distribution of the values. Qualitative data were expressed as frequency and percentage. For comparisons between Egyptian and Saudi patients and between isolated t(8;21) and t(8;21) with other genetic aberrations, the Chi square test was used to compare categorical variables and the independent “t” test or the Mann Whitney test was used to compare numeric variables according to the type of data distribution.

Overall survival (OS) was measured from the date of diagnosis until death from any cause with observations being censored at the date of last contact for patients last known to be alive. The OS and impact of additional cytogenetic aberrations on survival were analyzed using the Kaplan–Meier method. A multivariate Cox proportional hazard model was used to analyze the impact of clinicopathological variables e.g. (age, gender, leukocyte count as well as CD19 or CD56 expression) on survival. For all comparisons, a two-sided alpha value was set at 0.05. Significance tests and confidence intervals

were not adjusted for multiple testing due to the exploratory nature of the study.

3. RESULTS

We had 41 cases fulfilling the previous criteria in the three centers: 9 cases from King Abdullah Medical City (KAMC) in Makah, diagnosed between 2010 and 2013, 16 patients from King Fahad Medical City (KFMC) in Riyadh, Saudi Arabia diagnosed between 2007 and 2013 and 16 patients from National Cancer Institute (NCI), Cairo University, Egypt seen 2010 and 2013. Data from Saudi Arabian patients were combined together, the patients being from the same genetic and ethnic background.

Clinicopathological data of the studied patients is shown in (Table 1). Egyptian patients had significantly higher incidence of hepatomegaly, splenomegaly, fatigue and pallor (P value = .009, .001, .05 and .05 respectively) while the Saudi patients had higher incidence of bleeding tendency (P =.006). Otherwise there were no significant differences between the two groups regarding the hematological parameters or marker expression by IPT.

Regarding the genetic profile, it was noted that all of the Egyptian patients had isolated t (8; 21) whereas 32% of Saudi patients had an additional genetic abnormality with their t (8; 21). None of the studied cases showed Internal Tandam Duplication (ITD) of FLT3 gene and the gene was in the wild type in all cases; Egyptians and Saudis. Thirty four out of 41(82.9%) patients achieved complete remission.

Secondly, the whole studied group were divided into two subgroups according to cytogenetic aberration for analysis of prognosis , group 1: isolated t(8;21); 33 cases (80.5%) and group 2: t(8;21) plus other cytogenetic aberrations; 8 cases (19.5%), these accompanying cytogenetic abnormalities were in the form of trisomy 8 in 5 cases, trisomy 7 in one case, trisomy 8 and other abnormalities in 2 cases [XX, t(8;21) ,+8,-5,-7, t(10;11)] and [XX t(8;21),+8,5q-,+19,+22] (Table 2). It is worthy to mention that there is a statistically significant higher achievement of complete remission and longer overall survival in group1 than group 2, P = 0.002. Otherwise there was no difference between the two groups regarding symptoms at clinical presentation, hematological findings or immunophenotyping markers.

Table 1. Clinicopathological features of the whole studied patients

Variable	Egyptian N=16	Saudi N=25	P-value
Age(mean ± SD)	22.6±18.3	27.8±14.6	0.32
Age category [no (%)]			
15 years or less	6(37.5%)	2(8.0%)	0.02
15 years more	10(62.5)	23(92.0%)	
Gender [no (%)]			
Male	9(56.2%)	10(40.0%)	0.29
Female	7(43.8%)	15(60.0%)	
***Clinical presentation [no (%)]**			
Hepatomegaly	9(56.2%)	3(15%)*	0.009
Splenomegaly	10(62.5%)	2(10%)*	0.001
Fever	12(75%)	10(50%)*	0.126
Fatigue	16(100%)	7(77.8%)*	0.05
Bleeding	2(12.5%)	7(63.6%) *	0.006
Pallor	16(100%)	7(77.8%)*	0.05
Hematological variables (mean ±SD)			
Total Leukocyte Count	14.6±9.8	26.6±29.9	0.08
Hb	8.1±1.2	8.1±2.2	0.91
Platelets	46.7±36.	38.7±32.4	0.47
Bone marrow blasts	59.5±24.9	66.1±24.9	0.42
FAB subtype [no (%)]			
M1	1(6.3%)	2(8.0%)	
M2	15(93.7%)	21(84.0%)	0.22
M4	-	2(8.0%)	
Cellularity [no (%)]			
Normocellular	0%	1(4.0%)	
Hypocellular	0%	2(8.0%)	0.32
Hypercellular	16(100%)	22(88.0%)	
***Selected Immunophenotyping markers [no (%)]**			
MPO	16(100%)	25(100%)	0.39
CD13	16(100%)	18(72%)	0.04
CD33	16(100%)	21 (84%)	0.13
CD34	14(87.5%)	20(83.3%)*	0.63
CD117	11(78.6%)*	22(95.6%)*	0.27
CD7	0(0%)	2(8%)	0.37
CD19	4(25%)	10(43.5%)*	0.23
Cytogenetics			
T(8;21)	16(100%)	17(68%)	0.012
T(8;21)with other cytogenetic aberrations	0	8(32%)	
Complete remission	15/34(44%)	19/34(56%)	0.77

** Denominators used to calculate these percentages represent the numbers of cases with available data.*
N.B.: p values refer to comparisons between Egyptian and Saudi patients

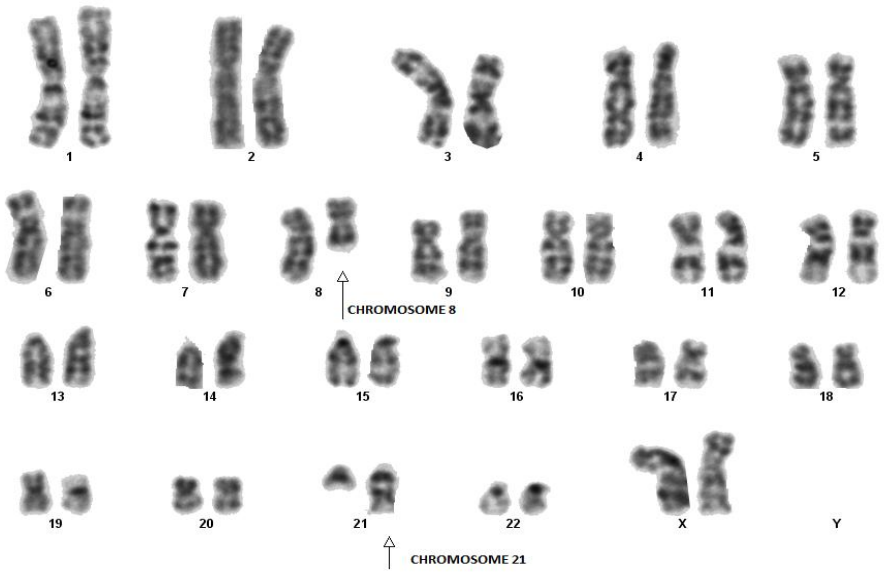

Fig. 1. Conventional karyotypic analysis performed on metaphase cells using standard culturing and banding techniques showing chromosome 8; 21 translocation

3.1 CD19 and CD56 Expression

CD19 was expressed in 14/41 (34.1%), with M2 FAB subtype.

Because this study is a retrospective study, CD56 was not available for most Egyptian patients as it was not part of the routine protocol for the time frame of collected data. Regarding the Saudi cases CD56 was expressed in 14/25(56%) with FAB subtype M2. Co expression of both CD19 and CD56 was noticed in 8 cases; 6 patients were M2 with isolated t (8; 21), while the other two patients had additional trisomy 8. Neither the expression of CD19 nor CD56 predicted the OS based on Cox Regression (*P=0.5* and *0.4* respectively).

3.2 Survival Analysis

The follow up period for the whole group ranged from 2.14 to 170.3 weeks, with a median of 27.7 weeks. The median overall survival (OS) was 146 weeks. The one year overall survival rate was 80% with 95% confidence interval (95% CI) of 64.3-95.7%. The two years overall survival rate was 70% (95% CI: 52.4-87.6%) (Fig. 2).

Survival analysis stratified by the type of cytogenetic abnormality shows that the median OS was 146.7 and 28.4 for the group with isolated t (8; 21) (Group 1) and that with t (8; 21) plus other cytogenetic aberrations (Group 2) respectively with P=0.002. The one year OS rate was 94 % (95% CI: 82.8-105.2%) for group 1 and 44% (95%CI: 7.0-80.8%) for group 2. The two years OS rate was 86% (95% CI: 68.0-104.0%) for group 1 and zero for group 2 (Fig. 3).

Neither age nor gender predicted OS, nor did the blast % (*P=.57, .48, and .45* respectively). Neither leucocytosis nor the expression of CD19 or that of CD56 correlated with the survival outcome (*P=.16, .51 and .43* respectively).

4. DISCUSSION

AML with t (8; 21) (q22;q22) is recognized as a distinct type of AML in the WHO classification [20]. Several adverse prognostic factors reported in AML with t (8:21) include leukocytosis, secondary cytogenetic aberrations, extramedullary manifestation and CD19 and CD56 expression. Many earlier studies were limited by small sample size or heterogeneous patient composition rendering it difficult to draw conclusions, especially regarding the role of secondary cytogenetic aberrations [21].

This study included 41 patients from three centers in Saudi Arabia and Egypt that were comparable to each other regarding hematological data, bone marrow (BM) cellularity, FAB subtypes, immunophenotyping

marker expression and FLT3. All the cases were newly diagnosed de novo AML cases and received the same treatment. Considering also the ethnic Arab background we could consider them as a homogenous group.

In the current work 36/41 (87.8%) cases were AML-M2 subtype, which is in accordance with the proportions reported in several other studies [20,21]. In this study, blasts were expressing CD19 in 14/41(34.1%) of cases in addition to the expression of myeloid markers. Aberrant expression of CD19 in AML with t (8;21) has been reported by several authors with different frequencies; the high rates were 54% and 66% [21,22] while lower rates were detected by others (20.9% and 14%) [23,24].

Table 2. comparison between cases with isolated t (8; 21) and cases with t(8;21) plus other cytogenetic aberrations in relation to the clinicopathological parameters

Variable	Isolated t (8;21) No (%) =33(80.5%)	t (8;21) with other cytogenetic aberrations No (%) = 8(19.5%)	P-value
Age category			
15 years or less	8	0	0.12
15 years more	25	8	
Gender			
Male	16	3	0.57
Female	17	5	
***Clinical presentation**			
Hepatomegaly	11(37.9%)	1(14.3%)	0.23
Splenomegaly	10(34.5)	2(28.6%)	0.76
Fever	19(65.5%)	3(42.9%)	0.27
Fatigue	18(94.7%)	5(83.3%)	0.36
Bleeding	6(28.6%)	3(50%)	0.32
Pallor	18(94.7%)	5(83.3%)	0.36
Hematological variables (mean ±SD)			
Total Leukocyte Count	22.1±24.7	17.4±21.2	0.62
Hb	8.3±1.8	7.9±2.2	0.61
Platelets	42.7±35.7	49.2±37.8	0.64
Bone marrow blasts	64.4±25.4	55.7±22.7	0.38
FAB subtype			
M1	2	1	
M2	31	5	0.05
M4	0	2	
BM Cellularity			
Normocellular	0	1(12.5%)	
Hypocellular	0	2(25%)	0.001
Hypercellular	33(100%)	5(62.5)	
***Immunophenotyping (selected markers)**			
MPO	33(100%)	8(100%)	0.47
CD13	29(87.9)	5(71.4)	0.26
CD33	31(93.9%)	6(75.0%)	0.10
CD34	28(87.5%)	6(75.0%)	0.37
CD117	25(80.6%)	8(100%)	0.17
CD7	1(3.1%)	1(14.3%)	0.22
CD19	11(33.3%)	3(37.5%)	0.82
CD56[a]	10(55.6%)	4(50%)	0.79
Complete remission	30	4	0.002
Overall survival (weeks)	146.7±46	28.4±1.6	0.002

** Denominators used to calculate these percentages represent the numbers of cases with available data.*
[a] CD56 was done in 25 Saudi cases

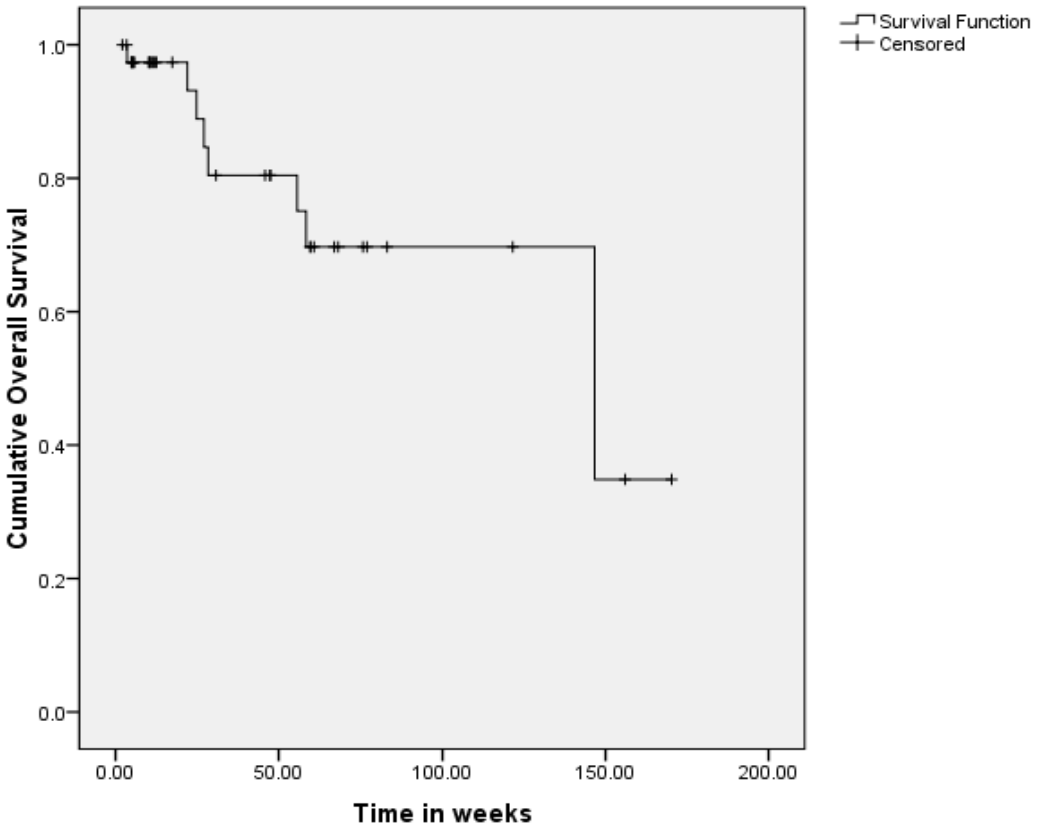

Fig. 2. Overall survival of studied patients N=41, the median survival was 146 weeks; the two years overall survival was 70%

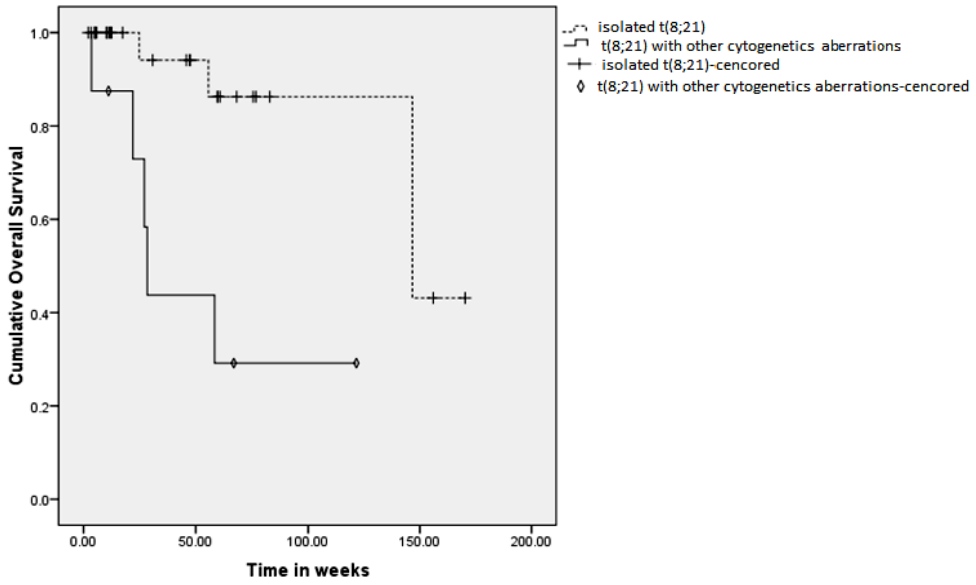

Fig. 3. Impact of cytogenetic aberrations on survival in AML studied cases

Regarding the Saudi patients in this study, CD56 was expressed in 14/25(56%) with FAB subtypes M2. This is in line with the findings of Fan et al. [22] and Chen Sw et al. [24] that showed CD56 expression in 66.7% and 58% of their t (8:21) - AML patients respectively.

In the current study the positive rate of stem cell markers of CD34, CD117, and HLA-DR were 85%, 84.6%, and 95% respectively. This also was comparable to what was reported by Fan et al. [22] who found the positive rate of the same stem cell markers respectively in 87.2%, 97.9%, and 95.7% of his studied cases.

The complete remission (CR) rate achieved by the patients included in this study was 82.9% which was comparable to the findings of earlier studies that reported rates of 96%, 82.7% and 95% [21,23,25]. However, a statistically significant higher achievement of CR was detected in patients with t(8;21) as a solo genetic abnormalities.

In this study we did not detect FLT3 (ITD); these results are in keeping with a study conducted on 20 patients with complex variants of t (8;21) by Xia [26]. A lower percentage of FLT3 detection (3.4%) was found by Kuchenbauer [27]. However several other studies showed higher percentages of 7.5%, 11%, and 10% [21,25,28].

The two years overall survival rate was 70% in our cases which was in accordance with the findings of Parihar et al. and Wu J et al., who reported 69% and 72% two years survival in their work [21,29]. A lower survival rate (56%) however, was reported by Pei Lin [28].

Further analysis could not confirm that age, leukocytosis, or expression of CD19 or CD56 was associated with poor survival in our patients, although this was suggested by other reports [23,29]. This could be due to the regular consolidation chemotherapy applied to our studied patients after CR.

We report here 8 cases with t(8:21) who had also been found to have additional chromosomal aberrations (19.5% of our cohort), with +8 as the most common additional aberration being found in 5 cases, trisomy 7 in one patient, and complex abnormality in the last two. In the literature, additional chromosomal aberrations are reported in different frequencies. In a study by Schoch et al. [30] it was found that (41/51) (80%) of their studied AML patients with t(8;21) had additional chromosomal abnormalities. They had detected a gain of chromosome 8 in 3 patients (6%) in addition to loss of a sex chromosome and deletion of the long arm of chromosome 9. In another more recent study by Parihar et al. [21] additional chromosomal aberrations were seen in 88% of patients with, trisomy of chromosome 8 in less than 5% of the total patients. In yet another study conducted by Pei Lin et al., most patients (60%) had other chromosomal aberrations in addition to t(8; 21), with trisomy 8 being detected in 4 patients (7%) and with 7 patients having complex karyotypes [28].

The effect of secondary cytogenetic aberration has different aspects and influences on the survival rate [30]. The main associated recurrent additional abnormalities reported are loss of sex chromosome, del (9q), trisomy 4 and trisomy 8 [28,31]. In the current work, we had 8 cases (19.5%) with additional chromosomal abnormalities to t (8;21). There were no statistically significant differences between those 8 patients (Group 2) and the 33 patients with isolated t(8;21) (Group 1) regarding their clinicopathological features (including hematological and immunophenotyping parameters), while there was a statistically significant higher achievement of complete remission in group1 than group 2, $P = 0.002$. The two years OS rate for Group 1 was 86% while none of the patients in Group 2 survived for two years. Some series demonstrate no deleterious effect of additional chromosomal aberrations on the outcome of patients with t(8:21) [32,33]. Our results, however are in accordance with those of other authors who reported shorter survival time of patients with additional abnormalities as compared to those with isolated t (8:21) irrespective of the type of additional aberration [23,31,34].

Our results show that AML associated with additional cytogenetic abnormalities to t(8;21) has a relatively lower rates of complete remission achievement and poorer survival outcome than that with isolated t(8;21). The additional chromosomal aberration mostly incriminated for this is trisomy 8 being the most commonly encountered in our group of patients and a further larger study is recommended to prove these results.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee.

The study was approved by KAMC IRB registered at National Biomedical Ethics committee, King abdulaziz city Science and Technology on 14-07-1433 (registration No.H-02-K-001) with IRB number 12-027.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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