Outcome of acute myeloid leukemia with recurrent cytogenetic abnormalities; A retrospective study in South Egypt Cancer Institute

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Abstract:

Acute myeloid leukemia (AML) is one of the world health problems especially in developing countries, as the majority of patients die in spite of the progress in therapy and supportive care. The response to therapy and the overall survival of AML patients depended on several risk factors.

Materials and Methods: Cytogenetic analysis was performed using Fluorescent In Situ Hybridization (FISH) analysis for 147 AML patients to detect the outcome and the overall survival of AML with certain cytogenetic abnormalities (t (15;17), t (8;21) and Inv 16).

Results:147 patients were classified as follow: 33 were AML M2, 53 were AML M3 and 61 were AML M4/M5. Cytogenetic analysis revealed that t (15,17) was positive in all AML M3 cases (53/53), t (8,21) was positive in 28/33 of AML M2 cases while inv 16 was positive in 23/61 of AML M4/M5 cases. Patients with t (15;17) or t (8;21) were associated with good prognosis and better outcome. WBCs count below $30x10^9$/L and age less than 60 years old had good prognostic impact on overall survival (OS) in AML.

Conclusion: t (15; 17) and t (8; 21) in AML were associated with good prognosis and better outcome in combination with other factors. The low WBCs count and the age of patients at presentation had good prognostic impact on overall survival(OS).

Keywords:

Acute Myeloid Leukaemia, Fluorescent in Situ Hybridization, overall survival, prognosis

Introduction

Acute Myeloid Leukaemia (AML) is a neoplastic blood disorder, characterizing by proliferation of blast cells in the bone marrow and blood, resulting in anemia, thrombocytopenia and granulocytopenia with or without leukocytosis **(1).**

AML is the most common acute leukemia in adults, accounting for ~80 percent of cases in this group. Within the United States, the incidence of AML ranges from three to five cases per 100, 000 populations. In 2015 alone, an estimated 20, 830 new cases were diagnosed, and over 10, 000 patients died from this disease **(2).**

New World Health Organization (WHO) classification of myeloid neoplasms and acute leukemias correlate morphology, cytochemistry, immunophenotype, karyotype, and molecular genetics with clinical features **(3).**

The clinical features of AML are the result of marrow replacement and failure of normal haematopoiesis, resulting in anemia, bleeding and increased risk of infections. The presenting feature in 15-20% of patients is fever. Organomegaly is in half of the patients with AML; however, lymphadenopathy is relatively infrequent **(4).**

The bone marrow aspirate, biopsy, Cytochemistry and flow cytometricimmunophenotyping (FCI) are the routine diagnostic work-up of AML **(5,6).** Conventional cytogenetics analysis is the mandatory component in the diagnosis of AML, approximately 55% of adult AML **(7).**

The diagnosis of AML is established by the involvement of more than 20% of the blood and/or bone marrow by leukemic myeloblasts, except in AML with recurrent genetic abnormalities (t (8;21), inv (16), and t (15;17)) as the presence of this genetic abnormality is diagnostic irrespective of blast percent **(8).**

Based on different cytogenetic abnormalities of AML, it becomes favorable, intermediate or poor risk. Favorable risk group included AML with core binding factor (CBF) abnormalities [t (8; 21) and inv 16/ t (16; 16)] as well as acute promyelocytic leukemia (APL) with t (15; 17) translocation which represent around 15% of AML cases in adults **(9)**.

The standard remission therapy for AML is induction regimen, 7 days of cytarabine (Ara-C) and 3 days of daunorubicin, producing CR in 62% to 71% of patients. The median overall disease-free survival (DFS) was 0.75 years and the 5-year DFS rate was 22%. The 5-year overall survival (OS) rate ranged from 9% to 33% for patients age < 55 years and from 6% to 13% for patients age 55 years **(10,11)**.

Suspicion of or established diagnosis of APL must trigger a distinctive therapy programme **(12).** If in doubt and/or if APL is a diagnostic possibility at presentation, oral all-trans retinoic acid (ATRA) should immediately be started, and only discontinued when APL has been specifically excluded in the diagnostic work-up of newly diagnosed AML.APL induction chemotherapy consists of ATRA as a differentiating agent and an anthracycline given simultaneously **(13).**

AML patients who achieved CR, intensified post remission chemotherapy and allogeneic stem cell transplantation (All-SCT), having prolonged survival **(14)**.

There are multiple challenges to achieve a higher cure rate for AML (**15**). Several risk factors, including clinical factors as the age, performance status **(16)** and previous hematological diseases (myelodysplastic (MDS) or myeloproliferative (MPD) **(17,18)** affect the prognosis and survival of AML.

The aim of the present study is to evaluate the outcome and the overall survival of adult patients with acute myeloid leukemia with certain cytogenetic abnormalities (t (15; 17), t (8;21) and

Inv 16) in SECI.

PATIENTS AND METHODS

This Retrospective study was conducted at South Egypt Cancer Institute (SECI) and Clinical Hematological Unit, Internal Medicine Department, Assiut University, including all adult AML patients during the time period from January 2014 to January 2017.In this period, 1231 acute leukemia patients of different age groups were admitted to SECI. 682 patients were diagnosed as ALL and the remaining 549 as AML. None of our patients were diagnosed as

"therapy-related AML ". A total number of 147 cases with accessible cytogenetic reports were included in our study. Clinical data (history and physical examination), Complete blood count, bone marrow aspirate and biopsy were done for all patients. Cytogenetic analysis was performed using Fluorescent in Situ Hybridization (FISH) analysis, data collected include t (15, 17), t (8; 21) and Inv 16. Responses to induction chemotherapy, the overall survival of patients in association with WBCs count and the age of patients at presentation were recorded.

Complete blood count:

CBC was done using cell counters: Abott Cell Dyn 1700 (Abott, USA) & Ruby Cell Dyn (Abott, USA). The data collected were WBCs count, haemoglobin (Hb) level and platelets count.

Bone marrow aspiration and biopsy:

a) The patient is placed in the lateral decubitus position, with the upper leg flexed and the lower leg straight.
b) Palpate the iliac crest, and mark the preferred sampling site with a pen.
c) Aseptic technique is employed, including sterile gloves and gown.
d) Islam needle is used.

e) The skin and the underlying tissue to the periosteum are infiltrated with a local anesthetic (e.g. approximately 8 ml of 1% xylocaine). A 10 ml syringe with a 22 gauge needle is used to inject an initial 0.5 ml directly under the skin, raising a wheal. Then to penetrate deeper into the subcutaneous tissue and the underlying periosteum, an area roughly 1 cm in diameter.
f) A skin incision is made with a small surgical blade, through which the BMB needle, with a stylet locked in place, is inserted. Once the needle touches the bone surface, the stylet is removed.
g) Using firm pressure, slowly rotate the needle in an alternating clockwise counterclockwise motion, and advance it into the BM cavity to obtain an adequate BM specimen.
h) Once the needle contacts the bone, it is advanced by slowly rotating clockwise and counterclockwise until the cortical bone is penetrated and the marrow cavity is entered. Contact with the marrow cavity is usually noted by a sudden reduction in pressure.
i) Once within the marrow cavity, the stylet is removed. Using a 20 mL syringe, approximately 0.3 mL of BM is aspirated.
j) Place the sample in an EDTA (ethylene diamine tetra acetic acid) anticoagulant containing tube for immunophenotyping and molecular genetics and Lithium Heparin anticoagulant containing tube for cytogenetic studies.

Fluorescent In Situ Hybridization

Done with microscope type: Carl Zeiss
AxioSkop 2 Mot FL

Objective types:

20x plan NeoFlaur,40x plan NeoFlaur, 63x Oil NeoFlaur, 100x Oil NeoFlaur

Camera Type: Leica CW 4000 FISH version 1.1, 29 Nov 2006

Software: Carlzeiss/ Cytovision, Axiovision control 3.1

Principle:

This technique involves the hybridization of fluorescently labeled specific DNA sequence probes with patient DNA, and the subsequent microscopic detection of the presence, absence, abnormal copy number or pathological location of a given fluorescence signal.

Data analysis:

Data collected and analyzed by computer program SPSS" ver. 21" Chicago. USA. Data expressed as mean, Standard deviation and number, percentage. T-test or Mann-Whitney if necessary was used to determine significant for numeric variable. Chi. Square or Fisher exact test was used to determine significance for categorical variable.

Survival data:

After a median follow-up of 18.8 months, the median overall survival (OS) was 18.8 months (95% CI: 18.54± 2.17 months) **(Fig.2).** Event free survival for included cases was 10.88± 3.86 months with a median of 8.9 months.

There was significantly longer overall survival for cases positive for t (8;21) compared to those with (p-value=0.3) (**Table 3).**

Results:

The median age was 34 years (range,18-72). 70/147 (47.6%) were males and 77/147 (52.4%) were females, with female to male ratio was 1.1:1. The patients presented with different clinical pictures, 88/147 (59.86 %) had bleeding tendencies ,71/147(48.2 %) were pale,45/147 (30.61 %) had recurrent infection and 12/147 (8.16%) had bone pain. While 34/147 (23.12 %) had hepatomegaly, splenomegaly in 27/147 (18.36 %) and Lymphadenopathy was found in 14/147 (9.52 %). The mean WBC count was 33.77± 19.30 x 10^9/L, mean hemoglobin (Hb) concentration was 7.8± 4.66 g/dL and mean platelet count was 58.95± 17.71 x 10^9/L (**Table 1).**

As regarding types of AML according to FAB classification, distribution of AML cases was as follow: the commonest FAB subtype in AML group in our series was AML (M4/M5) (35.26%) followed by AML M3 (30.63%) while AML M2 account for (19.07%), AML M1 represent (6.93%). AML M0 accounted only for (4.62%) of all AML cases. While AML M6 and AML M7 represent 2.0% and 4.0% respectively as shown in **(Fig 1**).

Cytogenetic analysis was performed using (FISH) analysis, the results showed that, t (15;17) was positive in all patients diagnosed as AML(M3) 53/53 (100%). t (8; 21) was positive in only 28 patients of 33 (84.8%) patients diagnosed as AML(M2), and negative in 5\33(15.2%). 61patients diagnosed as AML (M4, M5). Inv16 was positive in 23/61 patients (37.7%) and negative in 38\61(62.3%) **(Table 2).**

Out of 147 AML patients were included in our study, treated with induction chemotherapy. The outcome of AML patients was founded that 53 patients who were positive for t (15; 17), 44/53 (83%) were in remission while 9/53 (17%) were not in remission, with significant difference (p-value <0.001).

28 Patients who were positive for t (8; 21), 21/28 (75%) were in remission while 7/28 (25%) were not in remission, with significant difference (p-value=0.03).

Inv 16 were positive in 27 patients,13/27 (48.14%) were in remission and 14/27 (51.85%) weren't in remission with no significant difference

negative t (8;21). The median overall survival was 21.65 versus 7.48 (p-value<0.001) **(Fig.3).**

Our results evaluated that the overall survival was 12.86 months for patients less than 60 years in contrast to 7.95 months for patients more than60 years with statistical significance (p value <0.001) **(Fig.4),** and a significantly higher overall survival (21.63 months) in the patients with WBCs count lower than 30x 10^9/L at the time of diagnosis versus 5.02 months for patients with WBCs count of more than 30x 10^9/L (p-value<0.001) (**Fig.5).**

Table (1): characteristics of AML patients at presentation

Total no of patients= 147		
1. Age:		
Median:	34 years	
Range:	18-72 years	
2. Sex:		
Male:	70	47.6%
Female:	77	52.4%
Female: male ratio:	1.1: 1	
3. Clinical data:		
Pallor	71/147	48.2%
Lymphadenopathy	14/147	9.52 %
Bleeding tendency	88/147	59.86 %
Bone pain	12/147	8.16%
Hepatomegaly	34/147	23.12%
Splenomegaly	27/147	18.36%
Recurrent infections	45/147	30.61 %
4***. Hematological data:***		
WBC (x 10^9/L)	33.77 ± 19.30	
Hemoglobin (g/dL)	7.8 ± 4.66	
Platelets (x 10^9/L)	58.95 ± 17.71	

WBC: *White Blood Cell*

Table (2): Reported cytogenetic abnormalities in study group

Cytogenetic abnormality at presentation	**Total**	**Positive**		**Negative**	
		No.	**%**	**No**	**%**
t (15:17) in AML (M3)	53	53	100.0	0	0.0
t (8:21) in AML (M2)	33	28	84.8	5	15.2
inv (16) in AML with monocytic differentiation	61	23	37.7	38	62.3

T: *translocation;* ***AML:*** *acute myeloid leukemia****; Inv:*** *inversion*

Table (3): The outcome of AML patients with cytogenetic abnormalities (after induction chemotherapy)

Cytogenetic abnormalities at presentation			Patient outcome				P value*
			Remission		Not in remission		
Cytogenetic abnormality	**No**	**%**	**No**	**%**	**No**	**%**	
t (15:17) in AML(M3)	53/53	100%	44	83%	9	17%	**< 0.001****
t (8:21)in AML(M2)	28/33	84.84%	21	75.0%	7	25.0%%	**0.03***
Inv (16) in AML with monocytic differentiation	27/61	44.26%	13	48.14%	14	51.85%	**0.3n.s**

T: *translocation;* ***Inv:*** *inversion;* ***AML:*** *acute myeloid leukemia*

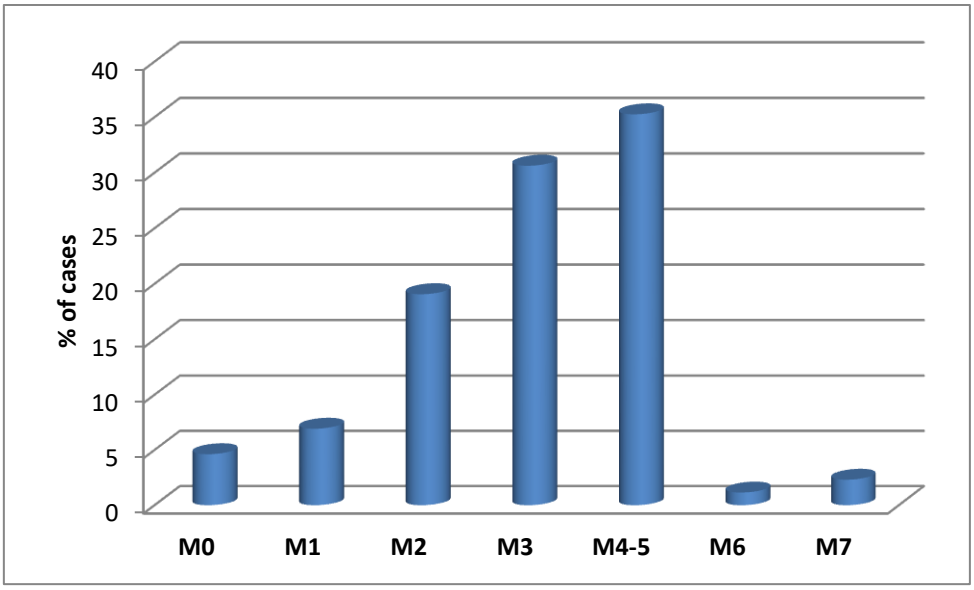

Fig (1): AML subtypes in study group according to FAB classification

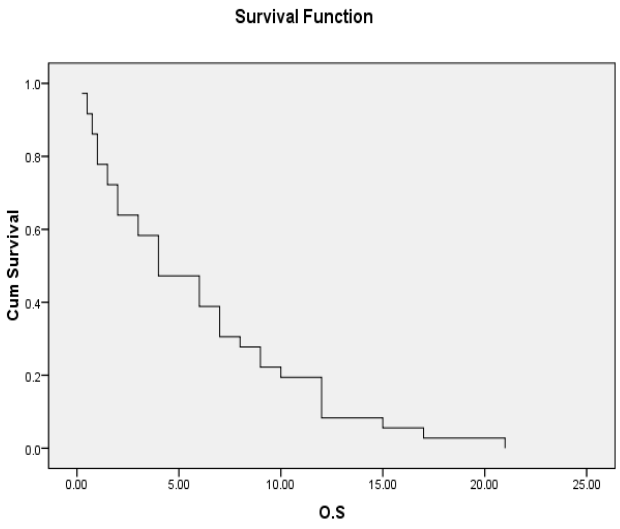

Fig (2): Overall Survival in months in study group

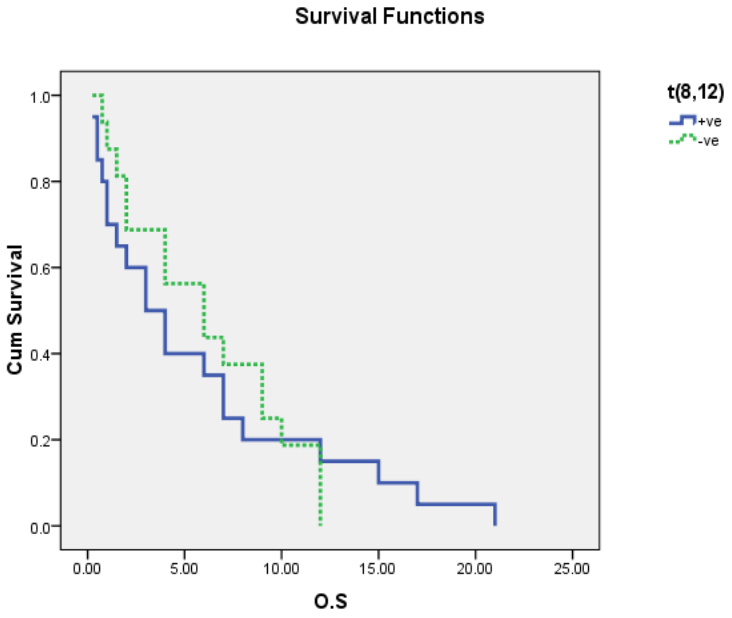

Fig (3): Relation between Overall survival in months & t (8, 21) in cases diagnosed as AML M2

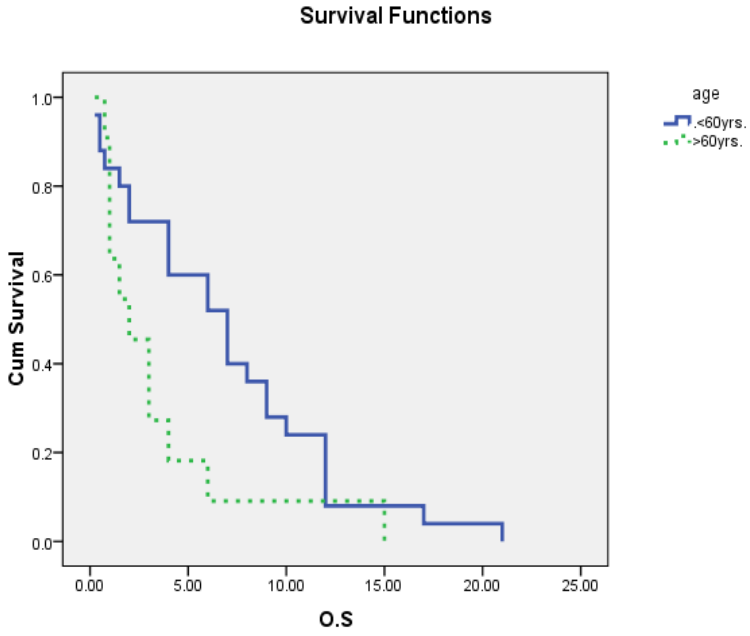

Fig (4): Overall Survival in relation to patients' age in study group

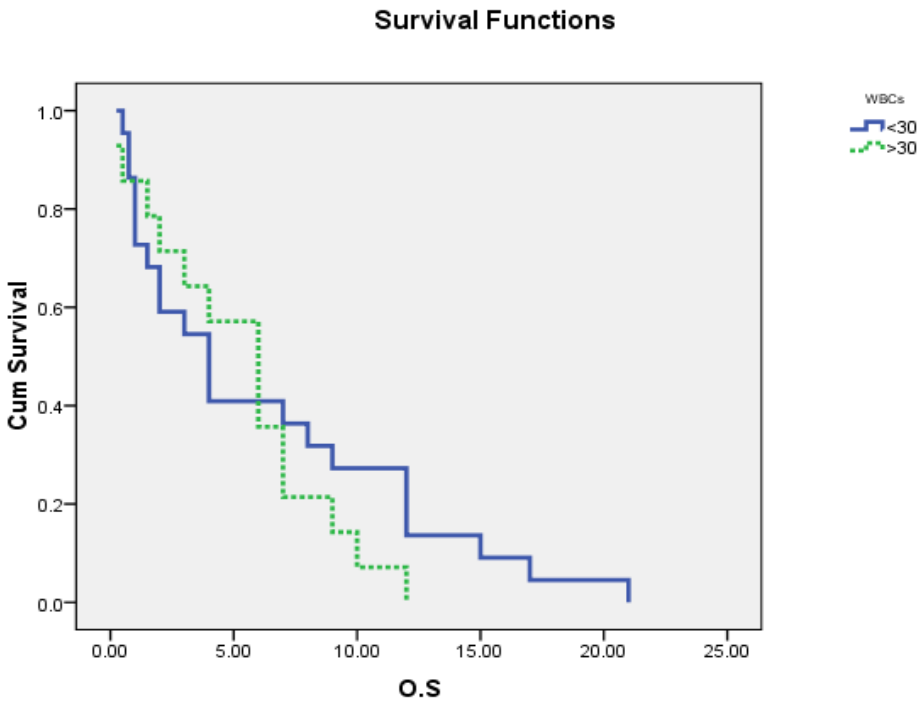

Fig (5): Overall survival in relation to White blood cells count

Discussion:

In our study, the median age at presentation was 34 years (range,18-72 years). This agrees with the studies of **Ashrafi et al., & Sepehrizadeh et al., (19,20)** who reported approximately close findings.

In the current study, there was slight female predominance which is different from ***Chang et al.,* (21)** who reported a female to male ratio of 0.84. This variation may be attributable to the non-random selection of cases in our study.

In our study, t (15;17) was positive in (100%) of cases with AML M3. There were multiple studies in agreement with our results, which evaluated the higher frequency of t (15;17) in AML M3**(22,23,24,25).** The t (15; 17) was exclusively observed in (71.0%) of patients with M3 **(26).**

Regarding AML M2, t (8;21) showed positivity in (84.4%) of cases. Our results were very close in percentage to that reported by (**Byun et al.,** who found that t (8; 21) was found in (85.0 %) of AML M2 patients (**23**).

AML with monocytic differentiation (i.e. M4/M5), Inv 16 was positive in (37.7%) of cases. Different results were described by ***Byun et al.*** as the reported incidence of inv 16 was (15%)**.**Also in ***Li et al.***study, inv 16 was detected in (15.2%) of AML M4 cases**.** This discordance seems to be due to that the previous two other studies were displayed in a large series of patients **(23), (26)**.

In the present study, we found that patients who are positive for t (15;17), 83% of them were in remission following induction chemotherapy, while 17% of patients were not in remission, with significant difference (p-value <0.001). Similar results were obtained from ***Vaskova et al.*** who documented that the best clinical results with respect to the ability to reach CR (100%) were observed in the t (15;17) positive patients **(27)**.

Patients who were positive for t (8; 21), 75% of patients were on remission following treatment, while 25% of patients didn't pass through remission, with significant difference (p-value=0.03). ***Gritsaev et al.*** reported occurrence of complete remission following induction in 97% of cases with t (8, 21) **(28)**.

In Inv 16 positive cases,13/27(48.14%) cases were in remission and 14/27 (51.85%) weren't in remission with no significant difference (p-value=0.3). Reportedinv16 as a favorable chromosomal change which is associated with higher rates of complete remission and event free survival **(29), (30).** It is possible that the discordance especially with inv 16 results may be due to the difference in the genetic makeup of the studied patients or regimens employed.

The overall survival in our study population was 18.54± 2.17 months with median of 18.8 months. The age of patients less than 60 years old had a good prognostic impact on OS as the overall survival for patients less than 60 years was 12.86 months versus 7.95 months for those more than 60 years with statistical significance (p value <0.001). In agreement with ***Padilha et al.*** study who reported that the OS for patients less than 60 years was 12.4 months versus 8.2 months for the group older than 60 years **(31)**. A significantly worse prognosis is documented in AML patients over 60 years of age **(27).**Our study found significantly higher overall survival in the group with WBCs count lower than 30×10^9/L at diagnosis ,as OS was 21.63 months versus 5.02 months for the group with WBCs count of more than 30×10^9/L at diagnosis (p-value<0.001).In agreement with ***Padilha et al.*** study who reported a significantly higher OS in the group with WBC count lower than 30×10^9/L at diagnosis with a median survival time of 23.6 months versus 4.7 months for the group with WBC count of more than 30×10^9/L at diagnosis **(31)**.

Conclusion:

T (15;17) and t (8;21) in AML patients at SECI were associated with good prognosis and better outcome in combination with other factors. The low WBCs count and the age of patients at presentation had good prognostic impact on overall survival(OS). However, inv 16 does not significantly affect the outcome.

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