RESEARCH ARTICLE

Prognostic Factors and Survival in Acute Myeloid Leukemia Cases: a Report from the Northeast of Iran

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Abstract

Background: Acute myeloid leukemia (AML) is a clonal hematopoietic disorder resulting from genetic alterations in normal hematopoietic stem cells. The aim of this study was to evaluate prognostic factors and survival of AML patients in the Northeast of Iran. Materials and Methods: This retrospective study covered 96 patients with AML referred to Emam Reza Hospital, Mashhad city, Iran, from 2009 to 2015. Age, sex, blood group, type of AML, fever, consumption of amphotericin B, cytogenetic forms and survival were analyzed. Also, WBC, hemoglobin and platelet levels were checked. Mean follow-up was 30.5 months (60.4% mortality). Survival was plotted by GraphPad Prism 5 with Log-rank test. Results: The mean age for all AML patients at diagnosis was 40.4 years (range, 17-77 years). Some 42.7% patients were aged <35 years and 40.6% were male. In all patients, 76% had fever and 50% consumed amphotericin. T(15;17)(q22;q21) had the most prevalence (37.7%) compared to other forms. Out of 92 patients, O+(30.4%) was the most common blood group and AML-M5 (28.3%) the most common subtype. There was a significant difference in survival based on WBC and consumption of amphotericin B (P<0.05). Conclusions: WBC level, fever and consumption of amphotericin B proved to be factors for survival of AML patients. The mean age for patients in Iran is lower than other areas in the World and also survival in this study was higher than in other studies.

Keywords: AML - survival - amphotericin B - WBC - northeastern Iran

Asian Pac J Cancer Prev, **17 (3)**, 1547-1551

Introduction

Acute myeloid leukemia (AML) in adults is the most common malignant myeloid disorder and this disease is a heterogeneous clonal disorder of hemopoietic (blood-forming) progenitor cells. The median age at diagnosis for patients with AML is 70 years (Estey and Döhner, 2006). The etiology of AML is not well understood (Strom et al., 2012). A number of factors have been reported as affecting the outcome of the disease such as age, White Blood Cell (WBC) count in diagnosis, time to achieve complete remission, abnormal karyotypes and cytogenetics (Ayremlou et al., 2012). Cytogenetic analysis at the time of diagnosis is among the most important independent prognostic factors in patients with AML (Mrozek, 2008). The chromosomal abnormalities such as t(8;21) (q22;q22), t(16;16) (p13;q22), and t(15;17) (q22;q21) have a good prognosis (Mazloumi et al., 2012). The prognosis of elderly patients with AML is usually dismal, while the true survival of older patients not included in clinical trials is not known (Pulsoni et al., 2004). Advances in understanding of the pathophysiology of AML have not yet led to major improvements in overall survival of adults with this disease (Stone et al., 2004). AML is divided into subgroups that are distinguished by the morphology of the leukemia cells, specific chromosomal abnormalities, gene rearrangement patterns, and different clinical courses and response to therapy (Douer, 2003). AML is subdivided based on morphologic criteria by the French-American-British (FAB) classification (Walter et al., 2013). FAB group has classified AML cases into eight subgroups (M0-M7) (Ziaei, 2004). National and international studies have reported AML-M2 as the predominant FAB subtype of AML (Harani et al., 2005). More patients with AML are presented with fever (over 50%) (Hassan et al., 1993). Because of the increasing prevalence and changing microbiological spectrum of invasive fungal infections, some form of amphotericin B still provides dependable and broad spectrum therapeutic alternative (Hamill, 2013). Invasive fungal diseases cause morbidity and mortality in patients with AML (Girmenia et al., 2012). Amphotericin B associates with reducing of neutropenic fever in the majority of patients (Spitzer et al., 1989).

The aim of this study is to evaluate prognostic factors and affecting of them on survival in AML patients in the in the Northeast of Iran

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Materials and Methods

Patients

In a retrospective study from 2009 to 2015, 96 patients with AML referred to Emam Reza Hospital, Hematology-Oncology Clinic, Mashhad city, Iran. We analyzed age, sex, fever, blood group, type of AML, consumption of amphotericin B, forms of cytogenetic and survival in the patients. WBC, hemoglobin (Hb) and platelet were checked in the first referral for every patient. Overall survival for the patients was from date of diagnosis until death from any cause. Mean follow–up was 30.5 months (917 days) that in this time, 58 patients (60.4%) dead. The AML patients with systemic and infectious diseases and them who lost follow-up were censored from study.

Statistical analysis

Survival was plotted by GraphPad Prism 5 and Log-rank test was used for analysis of survival with risk factors. P<0.05 was statistically significant.

Results

The mean age for all AML patients at diagnosis was 40.4 years (range, 17-77 years). The mean and range of WBC, HB and Platelet have been shown in Table 1.

Table 2 shows the baseline variables for AML patients and their correlation with 5-year survival. The patients were divided to two groups (42.7%<35 years and 57.3%≥ 35 years), 40.6% were male. 59.4% patients, 25% and 44.8% had WBC<20×103/µl, Hb <7 g/dl and platelet<30×103/µl, respectively. Out of all patients, 24% had fever and 50% consumed amphotericin.

Table 3 shows the prevalence of forms of cytogenetic, blood group and type of AML in AML patients. In checked patients, t(15;17)(q22;q21) had the most prevalence(37.7%) compared to other forms. Out of 92 patients, O+(30.4%), A+(28.2%) and B+(26.1%) had the most percent and out of 81 patients, M5(28.3%), M3(26%) and M4(18.5%) had the most prevalence, respectively. 1-, 2-, 3-, 4-, 5-year survival rate for all patients were 56%, 42.8%, 34.6%, 32.5% and 26.6%, respectively.

The 5-year survival for patients based on prognostic factors had been shown in Figure 1 and Figure 2. There was a significant different for survival based on WBC

Table 1. The Mean Variables for Acute Myeloid Leukemia Patients (n=96)

Variables	Mean	Range(Min-Max)
Age, year	40.4	17-77
WBC(×10³/µl)	29.9	0.2-202.2
Hemoglobin, g/dl	8.4	2.3-14.1
Platelet(×10³/µl)	50.2	1.4-198

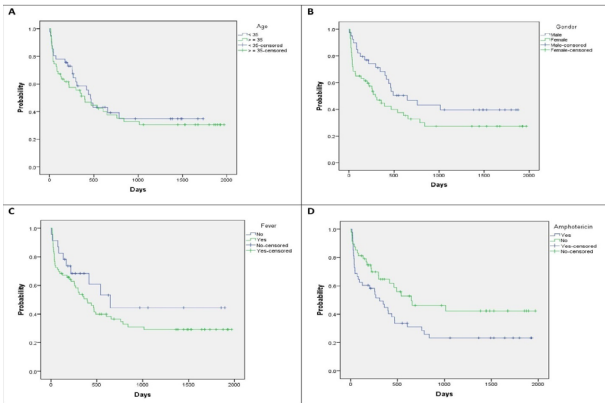

Figure 1. The 5-year Survival for Acute Myeloid Leukemia Patients Based on (A) age; (B) Gender or sex; (C) Fever; (D) Amphotericin

Table 2. The baseline variables for acute myeloid leukemia patients and correlation between 5-year survival with them (n=96)

Variables	n(%)	Survival rate (%)	Mean survival (day-month)	P-value*
Age, year				0.546
<35	41(42.7)	43.9	790-26.3	
≥35	55(57.3)	36.3	783-26.1	
Sex				0.078
Male	39(40.6)	46.1	951-31.7	
Female	57(59.4)	35.1	707-23.6	
WBC(×103/µl)				0.006
<20	57(59.4)	49.1	1016-33.9	
≥20	39(40.6)	25.6	462-15.4	
Hemoglobin, g/dl				0.524
<7	24(25)	33.3	767-25.6	
≥7	72(75)	41.6	821-27.4	
Platelet(×103/µl)				0.263
<30	43(44.8)	34.9	734-24.5	
≥30	53(55.2)	43.4	883-29.4	
Fever				0.228
Yes	73(76)	34.2	764-25.5	
No	23(24)	56.5	1003-33.4	
Amphotericin B				0.037
Yes	48(50)	27.1	636-21.2	
No	48(50)	52	1015-33.8	

Abbreviation: WBC, white blood cell; *P-value was calculated by Log-rank test for affecting of prognostic factors on 5-year survival

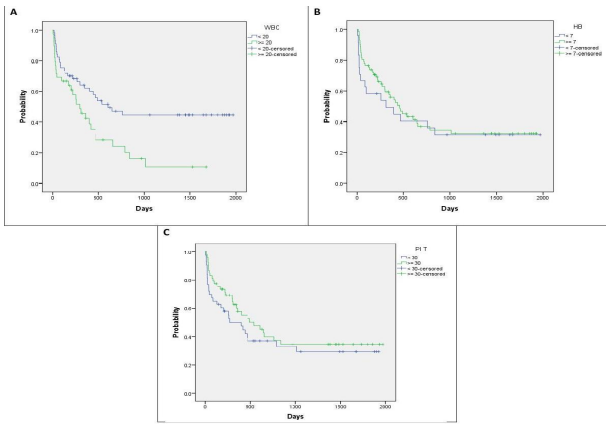

Figure 2. The 5-year Survival for Acute Myeloid Leukemia Patients Based on (A) WBC; (B) Hemoglobin; (C) Platelet

Table 3. The Prevalence of Forms of Cytogenetic, Blood Group Type of AML and Survival Rate for Acute Myeloid Leukemia Patients

Variables	n(%)
Form	
T(8;21)(q22;q22), n=43	
Positive	3(7)
Negative	40(93)
INV(16)(p13;q22), n= 42	
Positive	2(4.8)
Negative	40(95.2)
T(15;17)(q22;q21), n=53	
Positive	20(37.7)
Negative	33(62.3)
T(9;22)(q34;q31), n=39	
Positive	0(0)
Negative	39(100)
T(6;19)(p23;q34), n=40	
Positive	1(2.5)
Negative	39(97.5)
T(9;22)(q34;q11), n=40	
Positive	1(2.5)
Negative	39(97.5)
Blood group, n=92	
A+	26(28.2)
A-	4(4.3)
B+	24(26.1)
B-	1(1.1)
O+	28(30.4)
O-	2(2.2)
AB+	6(6.6)
AB-	1(1.1)
Type of AML, n=81	
M1	0(0)
M2	13(16)
M3	21(26)
M4	15(18.5)
M5	23(28.3)
M6	4(5)
M7	1(1.2)
MDS transfer to AML	4(5)

AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; WBC, white blood cell

(P=0.006) and consumption of amphotericin B (P=0.037) (Table 2).

Discussion

AML is a clonal hematopoietic(blood-forming) disorder resulting from genetic alterations in normal hematopoietic stem cells (Shipley and Butera,2009). Although older age by itself is probably the most important adverse risk factor for AML, it is insufficient to fully explain the poor outcomes observed in the older AML population (Oran and Weisdorf,2012). In one study, reported that the median age for 128 patients with AML was 67 years (range, 18 to 94) (Lerch et al., 2009). Other study, showed the median age of 17 patients with AML-M0 was 62 years that patients were male (Cohen et al., 1998). Data on 184 patients [MDS and AML], showed a the median age of 71.6 years (range, 29-92 years) (Merkel et al., 2013). The median age for AML patients in one paper (Gillis et al., 1996), was 40 years (range, 16-63 years). A report (Ghosh et al., 2003), in AML patients with ranged from 1 to 78 years showed a median age of 27.2 years that 72% were male. Patients in other research (Byrd et al., 1998), had a median age of 64 years (range, 16-79 years), 50% male. Three studies in Iran reported that: In study 1 (Ashrafi et al., 2013), patients' median age was 37 years (range, 15-68 years), 64.2% were male. In study 2 (Ayremlou et al., 2012), the mean age in AML patients was 44.7 years that 56.3% were male. In study 3 (Sepehrizadeh et al., 2014), the mean age of patients was 35 years (range, 15-63 years), 36.9% were male. In our study in Iran, the result was near to other studies in Iran. Therefore, the mean age for AML patients is lower in Iran compared to other area in the world.

A research on AML patients (Gillis et al., 1996), showed that the median WBC and platelet counts on discharge were 2.900×103/µl and 137.000×103/µl, respectively. The mean values for Hb was 6.8 g/dl, platelet count 63.3×103/µl (Ghosh et al., 2003). In this study, the mean WBC, Hb and platelet were 29.9×103/µl, 8.4g/dl, 50.2×103/µl, respectively, that was different to other studies. Regression analysis in one study (Ayremlou et al., 2012), showed that age, fever and WBC count were significant risk factors. There was no significant correlation between survival rate with Hb and platelet levels, but it was for WBC level. In this study, patients with higher WBC level and patient with fever had more death and lower survival, but just for WBC level was significant different. Therefore, higher WBC level and fever can be more risk factors in AML patients. In one study, 28.2% patients were diagnosed with AML type M2 and 19.6% with M4, respectively (Sepehrizadeh et al., 2014). A researcher (Ghosh et al., 2003), reported that the most frequency FAB subtype, in all age groups, was AML-M2. Other researcher showed that M4 and M5 subtypes are observed more frequently (Pedersen-Bjergaard et al., 1998). Other study (Hassan et al., 1993), reported that AML-M2 was the commonest FAB type with 32.2%, after that M1 and M4 (22.5% each), M5 (8.6%) and M6 and M7 (1.6% each), respectively. In this study, AML-M5 (28.3%), AML-M3 (26%), AML-M4 (18.5%) and AML-M2 (16%) had the most frequency, respectively. There was no AML-M1. In an article was observed that AML-M4 was the predominant FAB subtype (36.2%)

and after that M2 (30.2%), M3 (10.4%), M1 (8.7%), M0 (7.7%), M5 (6%) and M6 (0.8%), respectively (Harani et al., 2005). Frequency of FAB subtypes is different in the reports. Overally, M7 and M6 have lower frequency and M4 and M2 have higher frequency.

In AML patients in a research (Vadivelu et al., 2004), there were 14.3% patients with O blood group and in other research (Alavi et al., 2006), 28.8% patients were with A blood group. In this study, O blood group (32.6%) and A blood group (32.5%) had the highest prevalence. 91.3% patients had Rh-positive that the future researches can check affecting of Rh on AML patients as a risk factor. Several recurrent abnormalities such as t(3;3) (q21;q26) or t(6;9)(p23;q34) have very poor prognosis (Mrozek et al., 2008). In AML, t(8;21) (q22;q22), t(15;17) (q22;q21) and t(9;11) (p22;q23) were commonly seen (Mazloumi et al., 2012). In this study, t(15;17) (q22;q21) had the most frequency in AML patients (37.7%). A study reported that the 1- and 2-year survival rate for AML patients was 51% and 26%, respectively (Ashrafi et al., 2013). Two studies (Juliusson et al., 2009; Alibhai et al., 2009), reported 3-year survival rates was between 9-10% and 5-year survival was 3-8% in patients≥60 years, compared with 5-year survival rates of up to 50% for younger patients. Other study in the median follow-up with 97 months (Lerch et al., 2009), reported that 2-year survival rate was 16%. 1-, 2-, 3-, 4-, 5-year survival rate for AML patients in this study were 56%, 42.8%, 34.6% and 26.6%, respectively. Therefore, survival rate in our study was higher than other studies. Amphotericin B effectively reduces the duration of neutropenia by reducing the duration of fever (Heil et al., 1997). Amphotericin B is proven to be effective but toxic. This drug has a lot of severe adverse events including nephrotoxicity and infusion related side effects (Eriksson et al., 2001). A researcher reported in your study, 64% AML patients had fever (Ayremlou et al., 2012). In this study, although half of patients received amphotericin B, but 76% had fever and also in treated patients with this drug, survival reduced significantly (P<0.05). Therefore, patients who received amphotericin B had lower life expectancy because these patients were suffering fungal infection or due to lack of response to antibacterial drugs have been treated with amphotericin B.

In conclusions, WBC level, fever and consumption of amphotericin B can be more affective factors on survival of AML patients. The mean age for patients in Iran is lower than other areas in the World and also survival in this study was higher than other studies.

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