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Original Article

The factors affecting early death after the initial therapy of acute myeloid leukemia

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Abstract: There are some improvements in management of acute myeloid leukemia (AML). However, induction-induced deaths still remain as a major problem. The aim of this study is to assess clinical parameters affecting early death in patients with AML. 199 AML patients, who were treated with intensive, non-intensive or supportive treatment between 2002 and 2014 in Hacettepe Hematology Department, were analyzed retrospectively. In our study early death rate for elderly was found to be lower than previous reports whereas it was similar for those who were under age of 60. Better ECOG performance (ECOG performance score 0 and 1) and non-intensive treatment associated with lower early death rates, however APL-type disease associated with higher early death rates. ECOG performance score at diagnosis was found to be the most related independent factor with higher rate of early death in 15 days after treatment (P<0.001). Therefore we decided to understand the factors which were related with ECOG. WBC count at diagnosis was found to be the only related parameter with ECOG performance score. Leucocyte count at diagnosis appears like to have an indirect effect on early death in AML patients. It maybe suggested that in recent years there is an improvement in early death rates of elderly AML patients. The currently reported findings require prospective validation and would encourage the incorporation of other next generation genomics for the prediction of early death and overall risk status of AML.

Keywords: Acute myeloid leukemia, early death

Introduction

There are some improvements in management of acute myeloid leukemia (AML). However, induction-induced deaths still remain as a major problem. Many efforts have been spent to understand the predictors of early mortality however this issue is still unclear [1]. Minimal residual disease (MRD) level after induction therapy could be associated with the risk of relapse and survival [2]. The cost, availability, standardization, and validation represent a great problem for MRD. Thus, clinical routine parameters retain at the cornerstone in the therapeutic stratification of AML. However, using simple clinical parameters such as 'age' as primary basis for assignment of intensive, curative intent treatment in AML is also challenging [3]. The aim of this study is to assess clinical parameters affecting early death in patients with AML. Identification of the frequency, clinical features and possible risk factors for early mortality trends in AML is extremely important for the determination of overall management strategies of the disease course.

Materials and methods

199 AML patients, who were treated with intensive, non-intensive or supportive treatment between 2002 and 2014 in Hacettepe Hematology Department, were analyzed retrospectively. They had been prospectively recorded during clinical follow-up. All of the studied patients with AML had received their induction/re-induction chemotherapy protocols and other diagnostic/therapeutic standard clinical interventions when there is an absolute clinical indication. Meanwhile, all of the ethical considerations had been strictly followed in accordance

Table 1. The main parameters of the participants

Parameters	Patients with early ex in 15 days (N: 23)	Patients without early ex in 15 days (N: 176)
Age (Median, Range)	63 (17-85)	53 (16-86)
Gender (F/M)	11/12	69/107
Type of Disease (APL/non-APL/secondary to MDS/treatment-related)	6/15/2/0	19/130/23/4
Treatment type (Intensive treatment/non-intensive treatment/supportive treatment)	14/4/5	153/13/10
ECOG score (0/1/2/3/4)	0/4/7/4/8	35/99/20/12/10
ELN cytogenetic category (Favorable/non-favorable/unknown)	7/4/12	75/43/58
Charlson Index (2/3/4/5/6/7/8/9/10)	7/2/6/1/4/3/0/0/0	67/28/26/31/10/8/2/3/1
Hemoglobin at diagnosis (mg/dl) (median, range)	8 (4-13)	9 (4-16)
WBC at diagnosis (median, range)	68.1×10^3/μl (0.9-200×103/μl)	8.8×10^3/μl (0.6-300×10^3/μl)
Platelet at diagnosis (median, range)	30×10^3/μl (5-478×10^3/μl)	41×10^3/μl (4-400×10^3/μl)
LDH at diagnosis (U/L)	1059 (370-3000)	504.5 (160-16170)

Table 2. The relationship of intensive treatment with early death

	Intensive treatment Yes (n=167)	Intensive treatment No (n=32)	*P* value
Patients with exitus in 15 days	14	9	0.001
Patients without exitus in 15 days	153	23	
Patients with exitus in 21 days	22	9	0.033
Patients without exitus in 21 days	145	23	
Patients with exitus in 30 days	32	11	0.055
Patients without exitus in 30 days	135	21	

Note: Categorical data were compared by the Chi-square (or Fisher's Exact test if required by sample size).

with the Helsinki declaration. As a standard care/action of the hospitals of the Hacettepe Medical School, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standard of care. Parameters of age, gender, type of disease, primary or secondary disease, type of treatment, Charlson comorbidity score, lactate dehydrogenase (LDH), ECOG, white blood cell (WBC), hemoglobin and platelet levels, European LeukemiaNet (ELN) cytogenetic category were noted. We analyzed the parameters effecting early exitus. Early exitus defined as the death within first 15 days after the initial therapy since we targeted to exclude the effect of achieving complete remission in prognosis.

Statistical analyses

Categorical and continuous data were compared by the Chi-square (or Fisher's Exact test if required by sample size) and Independent-samples T-test, respectively. Bivariate correlation analysis for categorical variables was done by Spearman's correlation analysis. Univariate comparisons with a *P* value <0.1 were included in multivariate analyses in which statistical significance threshold was accepted as P<0.05. Logistic regression analysis was used to study simultaneous effect of selected variables. Statistical Packages for the Social Sciences v17.0 (SPSS Inc., Chicago, IL) software was used for statistical analyses.

Results

A total of 199 AML cases were analyzed. The demographic data of participants are given in **Table 1**. 23, 31 and 43 cases died within 15, 21 and 30 days after treatment, respectively. When we analyzed the treatment choices 112, none and 2 of the patients aged <60 had been treated with intensive, non-intensive and supportive treatments, respectively. On the other hand 55, 17, and 13 patients aged ≥60 were treated with intensive, non-intensive and supportive treatments, respectively. The difference between treatment choices according to age category was highly statistically significant (P<0.001) (**Table 2**). In order to neutralize the effect of achieving CR/PR, we decided to evaluate the factors effecting early death in 15 days after initiation of treatment. In this study we found an early death rate of 13.06% in 15 days after the initiation of treatment. In the patients who were under age of 60, the early death rate was 10.67% (11 dead versus 103 alive) whereas early death rate was 16.43% (12 dead ver-

Table 3. Univariate analysis of parameters affecting early death in 15 days after treatment

Parameters	Values		*p* value
	Exitus Yes	Exitus No	
Age	63 (17-85)	53 (16-86)	0.256
Gender (M/F)	12/11	107/69	0.665
Hemoglobin at diagnosis (gr/dl)	8 (4-13)	9 (4-16)	0.522
WBC at diagnosis ($\times 10^3/\mu l$)	68.1 (0.9-200)	8.8 (0.6-300)	0.004
Platelet at diagnosis ($\times 10^3/\mu l$)	30 (5-478)	41 (4-400)	0.754
LDH at diagnosis (U/L)	1059 (370-3000)	504 (160-16170)	0.349
ECOG performance score (0/1/2/3/4)	0/4/7/4/8	35/99/20/12/10	<0.001
ELN cytogenetic analysis (Poor/Intermediate/Good/Unknown)	2/2/7/12	16/27/75/58	0.322
Charlson Score 6 and above/lower than 6	7/16	24/152	0.038
APL/non-APL/secondary	6/15/2	19/130/27	0.099
Treatment type (intensive treatment Y/N)	9/14	23/153	0.001

Note: Categorical and continuous data were compared by the Chi-square (or Fisher's Exact test if required by sample size) and Independent-samples T-test, respectively. Bivariate correlation analysis for categorical variables was done by Spearman's correlation analysis.

Table 4. Multivariate analysis of parameters with P<0.1 in early death in 15 days after treatment

Parameters	Beta value	Odds ratio (95% confidence interval)	*P* value
WBC at diagnosis	0.000	1.000 (1.000-1.000)	0.271
ECOG performance score	0.959	2.609 (1.708-3.985)	<0.001
Charlson Score below 6*	-0.734	0.480 (0.115-2.003)	0.314
APL type AML**	2.993	19.953 (1.972-201.910)	0.011
Non-APL type AML**	1.635	5.128 (0.705-37.294)	0.106
Non-intensive treatment***	1.487	4.423 (1.106-17.686)	0.036

Note: Univariate comparisons with a *P* value <0.1 were included in multivariate analyses in which statistical significance threshold was accepted as P<0.05. Logistic regression analysis was used to study simultaneous effect of selected variables. *Charlson Score 6 and above was the reference group. **Secondary type disease was the reference group. ***Intensive treatment was the reference group.

sus 73 alive) for patients who were ages of 60 or above. If only patients who were given intensive treatment were considered, the early death rates were 8.73% (9 dead versus 103 alive) and 10% (5 dead versus 50 alive) for patients under age of 60 and 60 or above, respectively. The relationship between age, gender, treatment type (intensive treatment yes/no), WBC, hemoglobin, platelet and LDH levels at diagnosis, ECOG performance score, ELN cytogenetic analysis, Charlson comorbidity score, disease type (APL/non-APL/secondary), with early exitus in first 15 days was evaluated (**Table 3**). After univariate analysis, among the factors that had *P* value <0.1, were taken to multivariate analysis. In multivariate analysis, ECOG performance score at diagnosis was found to be the most related independent factor with higher rate of early death in 15 days after treatment (P<0.001) (**Table 4**). Therefore we decided to understand the factors which were related with ECOG (**Table 5**). After univariate analysis, among the factors that had *P* value <0.1, were taken to multivariate analysis. WBC count at diagnosis was found to be the only related parameter with ECOG performance score (**Table 6**).

Discussion

Early death rate is still needs to be improved in management of acute myeloid leukemia. In literature, death rates related with intensive therapy in AML were reported as 5-10% and 25% for patients under age of 60 and 60 or above, respectively [4, 5]. In our study early death rate for elderly was found to be lower than previous reports whereas it was similar for those who were under age of 60. This result may suggest that in recent years there is an improvement in early death rates of elderly AML patients. Baseline ECOG performance score along with APL-type disease and non-intensive treatment were independently associated with early death. Better ECOG performance (ECOG performance score 0 and 1) and non-intensive treat-

Table 5. Univariate analysis of parameters related with ECOG performance score

Parameters	Values		*p* value
	ECOG 0-1	ECOG 2-3-4	
Age	53 (16-86)	60 (20-85)	0.005
Gender (M/F)	81/56	38/23	0.674
Hemoglobin at diagnosis (gr/dl)	9 (4-16)	8.1 (4-16)	0.406
WBC at diagnosis ($\times 10^3$/µl)	6.1 (0.6-300)	20.1 (0.6-298)	0.008
Platelet at diagnosis ($\times 10^3$/µl)	42 (4-400)	34 (5-478)	0.783
LDH at diagnosis (U/L)	446 (160-8490)	922 (267-16170)	0.027
ELN cytogenetic analysis (Poor/Intermediate/Good/Unknown)	12/18/59/48	6/11/22/22	0.738
Charlson Score 6 and above/lower than 6	18/119	13/48	0.144
APL/non-APL/secondary	17/105/15	7/40/14	0.087
Treatment type (intensive treatment Y/N)	112/15	44/17	0.003

Note: Categorical and continuous data were compared by the Chi-square (or Fisher's Exact test if required by sample size) and Independent-samples T-test, respectively. Bivariate correlation analysis for categorical variables was done by Spearman's correlation analysis.

Table 6. Parameters related with ECOG performance score (Multivariate analysis of parameters that has *p* value <0.1 in univariate analysis)

Parameter	Beta value	Odds ratio (confidence interval)	*P* value
Age	0.012	1.012 (0.988-1.036)	0.337
WBC at diagnosis	0.000	1.000 (1.000-1.000)	0.015
LDH at diagnosis	0.000	1.000 (1000-1001)	0.114
Non-Intensive Treatment*	0.686	1.986 (0.761-5.183)	0.161
APL type AML**	-0.136	0.873 (0.188-4.047)	0.862
Non-APL type AML**	-0.651	0.522 (0.198-1.376)	0.189

Note: Univariate comparisons with a *P* value <0.1 were included in multivariate analyses in which statistical significance threshold was accepted as P<0.05. Logistic regression analysis was used to study simultaneous effect of selected variables. *Intensive treatment was the reference group. **Secondary type disease was the reference group.

ment associated with lower early death rates, however APL-type disease associated with higher early death rates. The main causes of early death in leukemias are usually hemorrhage, often associated with hyperleukocytosis and infection [6]. The management strategies for leukemia patients with hyperleukocytosis prone to early death include optimization of coagulation, hyperhydration, urate oxidase administration and avoidance of packed red blood cell transfusions which may increase blood viscosity. Nevertheless, early mortality in this leukemic subpopulation is not influenced by universal or selected use of leukapheresis or hydroxyurea/low-dose chemotherapy [7]. In the English literature, there are many studies that advert to early death rates. It is known that intensive chemotherapy is not suitable for elderly and these patients die early as a consequence of extra toxicity [8, 9]. A study conducted in USA, reported that age and performance status were the most important predictors of treatment related mortality within 28 days after initiation of intensive induction chemotherapy [3]. Also another study which was conducted with eighty-five patients with AML presenting with hyperleukocytosis revealed early death was more frequent in older patients [10]. However in our study age was not found as a predictor. Probably this was due to the fact that older patients, especially less fit cases were deliberately not treated with intensive protocols. In the past decade many predictive models developed in order to classify elder patients unfitted for intensive chemotherapy [9, 11-15]. A recent study conducted with 9380 patients with AML who were aged ≤65 years and were diagnosed and treated with chemotherapy between 1973 and 2010 revealed that although age was found to significantly influence the 1-month mortality for the period between 1973 and 1977, this difference in 1-month mortality were no longer significant among patients with AML who were treated more recently [16]. The results of this study and our study together may indicate that in recent years there is an improvement in the management of AML patients especially in

decision-making for intensive treatment. In some studies co-morbidity index was found to be related with early death. For example, a study conducted in Serbia with 145 acute myeloid patients reported that for early death the most significant predictor was co-morbidity, as scored by the Hematopoietic Cell Transplantation Co-morbidity Index (HCT-CI) [17]. Another study conducted with 177 patients over 60 years of age receiving acute myeloid leukemia induction therapy also reported that the hematopoietic cell transplantation co-morbidity index was predictive of early death rates [18]. However in our study we did not find Charlson co-morbidity score as a predictor for early death. Probably, HCT-CI is a better tool than the Charlson score for this aim. In our study, the ECOG performance score was the most important independent factor affecting early death. This effect of ECOG score is regardless of age. So it may be interpreted that performance of patients is not always parallel with age, elder patients may have fair performance. As we found age did not affect the early death rates whereas ECOG did; our results coherent with tendency of doctors who are currently more likely to consider elderly patients on an individual basis, and to consider physiological age, rather than chronological age in making choices about patients. After understanding that the ECOG performance score was the most important factor, we aimed to reveal the parameters associated with it. WBC at diagnosis was found to have a strong independent association with ECOG performance score. Therefore the WBC at diagnosis seems to have an indirect effect on early death in AML patients. There could be many still unknown factors effecting early death rates. An interesting study from Japan conducted in 193 de novo non-M3 acute myeloid leukemia patients proposed that the null genotype of glutathione S-transferase-T1 might play a role in increased early death after chemotherapy [19]. Therefore, it can be concluded that studies also including molecular and genetic factors should be performed in order to clarify the predictors for early death rate. Since the potential differences and heterogeneity in the AML patient populations and lots of conflicting data available, the predictive role and integrity of numerous important clinical parameters in the leukemic patients still need further improvement. The currently reported findings require prospective validation and would encourage the incorporation of other next generation genomics for the prediction of early death and overall risk status of AML. Stratification of the AML patients for current therapy protocols needs reasonable objective scoring systems that would be developed by future clinicobiological investigations.

In conclusion, in this study we found that in recent years there is likely to be an improvement in early death rates of elderly AML patients. Also, ECOG performance score was the most important factor affecting early death in 15 days after treatment and leucocyte count at diagnosis was found to have a strong relationship with ECOG performance score. For that reason, leucocyte count at diagnosis appears like to have an indirect effect on early death in AML patients.

Disclosure of conflict of interest

None.

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