Clinical Characteristics and Outcomes of Acute Myeloid Leukemia in Vajira Hospital-a 9-year Single Center Retrospective Study

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Abstract

Objective: To collect demographic data, management patterns and outcomes of acute myeloid leukemia (AML) patients in a tertiary hospital.

Methods: We collected data of newly diagnosed AML patients from 2008 to 2016, including clinical presentation and characteristics at the time of diagnosis. Survivals and factors affecting outcomes were evaluated.

Results: There were 106 patients enrolled in the study. More than half of the patients were in the younger age group, which had a median age 56.5 years (41.5-73.5). Initial symptoms at presentation were anemia, fever and bleeding tendency. The younger age group had a good performance status presented by Eastern Cooperative Oncology Group (ECOG) score of less than two. Intensive chemotherapy was utilized in treatment of most patients in the younger group (85.7%) as compared with the elderly group (18%). Better intensive chemotherapy significantly improved median survival (256 vs 79 days; $p < 0.001$).

Conclusion: AML patients who had received intensive chemotherapy had a survival advantage irrespective of age.

Keywords: acute myeloid leukemia, chemotherapy, performance status, survival

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ลักษณะทางคลินิกและผลการรักษาของโรคมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดมัยอีลอยด์ การศึกษาแบบย้อนหลัง 9 ปี ในโรงพยาบาลวชิรพยาบาล

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บทคัดย่อ

วัตถุประสงค์: การศึกษาจากข้อมูลย้อนหลัง 9 ปีเกี่ยวกับข้อมูลพื้นฐาน การรักษาและผลการรักษาในโรคมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดมัยอีลอยด์ในคณะแพทยศาสตร์วชิรพยาบาล

วิธีดำเนินการวิจัย: การศึกษานี้เก็บข้อมูลตั้งแต่ปีค.ศ. 2008 ถึง 2016 เกี่ยวกับอาการแสดง และลักษณะทางคลินิกเมื่อวินิจฉัย มีการประเมินการรอดชีพและปัจจัยที่ส่งผลต่อการรอดชีพ

ผลการวิจัย: ผู้ป่วยทั้งหมด 106 คนในการศึกษานี้ มากกว่าครึ่งของผู้ป่วยเป็นกลุ่มอายุน้อยกว่า ค่ามัธยฐานอายุอยู่ที่ 56.5 ปี (ระหว่าง 41.5 - 73.50) อาการแสดงนำได้แก่ ภาวะซีด ไข้ และภาวะเลือดออก กลุ่มอายุน้อยมักจะมีสมรรถนะร่างกายดีที่คะแนน Eastern Cooperative Oncology Group (ECOG) น้อยกว่า 2 ผู้ป่วยกลุ่มอายุน้อยได้รับยาเคมีบำบัดขนาดสูงที่ร้อยละ 85.7 เปรียบเทียบกับกลุ่มผู้ป่วยสูงอายุที่ร้อยละ 18 การได้รับยาเคมีบำบัดขนาดสูงเป็นปัจจัยเดียวที่เพิ่มอัตราการรอดชีพอย่างมีนัยสำคัญ (256 ต่อ 79 วัน; $p < 0.001$).

สรุป: ผู้ป่วยโรคมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดมัยอีลอยด์ที่ได้รับยาเคมีบำบัดขนาดสูงเพิ่มอัตราการรอดชีพได้โดยไม่ขึ้นกับอายุ

คำสำคัญ: โรคมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดมัยอีลอยด์, ยาเคมีบำบัด, สมรรถนะร่างกาย, การรอดชีพ

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Introduction

Acute myeloid leukemia (AML) is the most common leukemia among adults and can occur within all age groups, particularly increasing with advanced age[1]. AML is the heterogeneous disease in terms of etiology, risk factors, and genetic predispositions. Prognosis of disease depends on many factors[2]. The clinical manifestation of bone marrow failure is the indication to diagnose AML. Nowadays, survival has been improved dramatically due to more intensive strategies including, intensive chemotherapy, molecular-targeted therapies, stem cell transplantation and supportive cares. However, AML still has poorer prognosis when compared to other hematologic malignancies[3]. A single center study had previously reported the 5-year overall survival (OS) of only 22.2%[4]. Notably, the OS declined among elderly patients aged more than 60 years according to a recent study from Thai Acute Leukemia Working Group (TALWG)[5]. Clinical factors associated with better survival were younger age (Age < 60 years), good ECOG PS and less comorbidities[6]. Since the 1970's, the intensive "7+3 regimen" had been the standard of care which resulted in 30 – 40% chance of long-term remission among the younger age group[7]. The proportion of patients who were eligible for intensive induction chemotherapy depends on age and performance status. The aim of this study was to describe the patients' demographics, clinical characteristics at the time of AML diagnosis and management between age groups. Treatment responses and survival outcome were determined, and clinical factors associated with survival were evaluated.

Methods

This study was a nine-year retrospective cohort study conducted in the Division of Hematology, Department of Medicine, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University. Patients who were newly diagnosed from January 1, 2008, to December 31, 2016 were included. The inclusion criterion was age ≥ 15 years old at time of diagnosis according to the 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia[8-9]. Those with acute lymphoblastic leukemia (ALL), mixed phenotype acute leukemia, myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), relapsed disease, chronic myeloid leukemia (CML) with blastic phase and patients with unretrievable medical records were also excluded. The primary objective was to determine treatment response. Survival analysis and factors associated with better survival were the secondary objectives.

Terminology

The patients were categorized into two age groups. The ***younger age group*** included patients less than 60 yeas old. Those who aged equal to or greater than 60 years were defined as ***the elderly group***. The performance status was determined according to ECOG cancer research group. Anemia, fever and bleeding were documented as reported in the medical records. Cytogenetic results were classified according to WHO 2008 classification[8]. According to the definition defined in 2017 European LeukemiaNet (ELN) recommendation on the clinical outcomes: complete remission (CR) was determined when bone marrow blast < 5%, absence of circulating blasts and blasts with Auer's rod, absence of extramedullary blast, transfusion free, absolute neutrophil count > 1 x 10^9/L (> 1,000/μL) and platelet > 100 x 10^9/L (> 100,000/μL)[10].

Statistical Analyses

According to the data reported by frequency and percentage for categorical variables. Continuous variables were expressed as mean and SD or median and interquartile range if normality criteria. The continuous variables were compared between both age groups using Mann-Whitney *U* test and Student *t* test, as appropriate. The categorical variables were compared between both age groups using Fisher's exact test or Chi-square test, as appropriated. Overall survival between both age groups was estimated using Kaplan-Meier method

and compared by using log-rank test. Factors associated with survival were determined using Cox proportional hazards models. Hazard ration (HR) and 95% confidence interval across subgroups were reported, and *p*-value < 0.05 was determined as statistical significance. The data analyses were performed by STATA, version 13 (StataCorp, College Station, Texas, USA, 2013).

Result

There were 129 patients recruited in the nine-year period of this study, 23 patients were excluded according to the exclusion criteria. There were 106 AML patients were eligible for data analyses. There were 56 patients (52.8%) in the ***younger group*** and 50 patients (47.2%) in the ***elderly group*** (Figure 1). The median age was 56.5 years (IQR: 41.5 - 73.50). Half of them were male. Most of the participants were categorized into AML (69.8%). The rest of the patients were 21.7% AML with myelodysplastic-related change (AML-MRC) and 8.5% acute promyelocytic leukemia (APL). Leading clinical presentations at diagnosis were anemia (64.2%) and fever (60.4%), followed

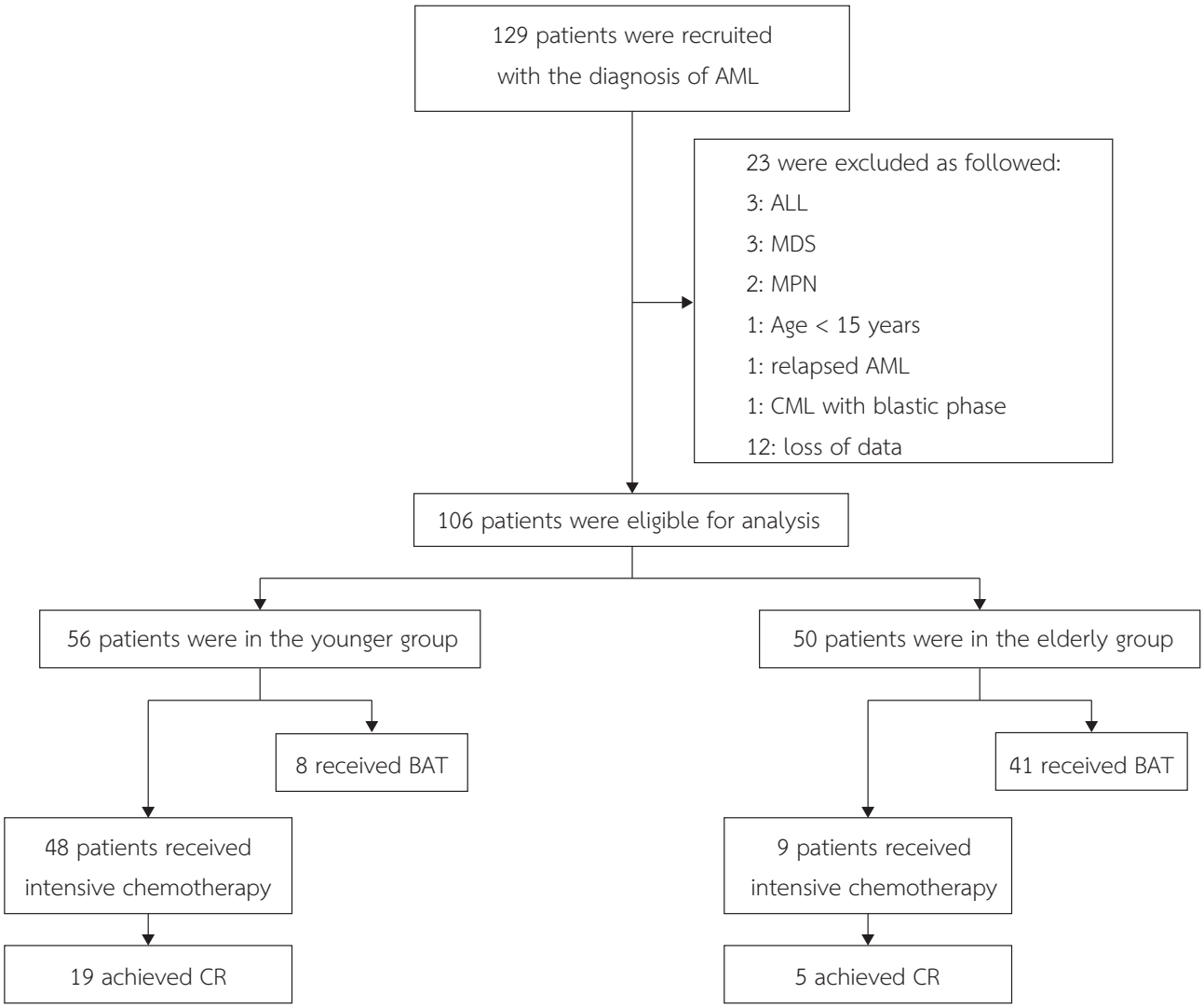

Figure 1: Patients recruitment in the study, treatment management and response. ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; BAT: best available therapy; CML: chronic myeloid leukemia; CR: complete response; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasms.

with bleeding (26.4%). More than half of the patients (51.9%) were in good performance status (ECOG 0 – 1). The initial blood counts at diagnosis were a mean hemoglobin of 8.6 g/dl (6.9 – 9.4), a median platelet count of 41 x 10^9/l (20.75-79.00), and a median white blood cell count of 17.35 x 10^9/l (4.8-68.9). A median peripheral and bone marrow myeloblast counts were 42.5% (13 – 69) and 50.6% (37 – 76), respectively. Most of the patients, especially those who were diagnosed in earlier years lacked the cytogenetic data. The cytogenetics results were available in 32 patients (30.2%). Normal karyotype was the most frequent result (12.3%) in this study. (Table 1)

Clinical presentation between younger and elderly group

The young age group had statistically significant better performance status (as defined as ECOG PS 0 – 1) compared with the elderly (82.1% vs 18.0%); $p < 0.001$). The younger age group had a greater percentage of fever (69.6% vs 50.0%; $p < 0.04$) and had higher hemoglobin level than the elderly group (9.0 g/dl vs 7.2 g/dl, $p < 0.001$). However, the bone marrow myeloblast cell counts were not different between both groups (50.6% vs 57.4%, $p = 0.86$). (Table 1)

Table 1:
Clinical characteristics and outcomes in the whole cohort, younger and older age groups of patients with AML

Characteristics	Total (n=106) (%)	AML in younger age group (n=56) (%)	AML in elderly age group (n=50) (%)	p-value
Age (year), Median (IQR)	56.5 (41.5-73.5)	44 (33-50)	73.5 (66-78)	
Male	52 (49.1)	30 (53.6)	22 (44.0)	0.33
Diagnosis				
Acute myeloid leukemia (n=74)	74 (69.8)	41 (73.2)	33 (66.0)	0.07
Acute promyelocytic leukemia	9 (8.5)	7 (12.5)	2 (4.0)	
AML with MDS-related change	23 (21.7)	8 (14.3)	15 (30.0)	
Clinical manifestation				
Anemia	68 (64.2)	31 (55.4)	37 (74.0)	0.05
Fever	64 (60.4)	39 (69.6)	25 (50.0)	0.04
Bleeding	28 (26.4)	17 (30.4)	11 (22.0)	0.33
Previous malignancy	5 (4.7)	1 (1.8)	4 (8.0)	0.19
Associated myeloid sarcoma				
Yes	5 (4.7)	2 (3.6)	3 (6.0)	0.67
ECOG				
0 – 1	55 (51.9)	46 (82.1)	9 (18.0)	<0.001
2 – 4	37 (34.9)	5 (8.9)	32 (64.0)	
NA	14 (13.2)	5 (8.9)	9 (18.0)	

Table 1:

Clinical characteristics and outcomes in the whole cohort, younger and older age groups of patients with AML (Continued)

Characteristics	Total (n=106) (%)	AML in younger age group (n=56) (%)	AML in elderly age group (n=50) (%)	p-value
Complete Blood Count				
Median Hb (IQR) (g/dl)	8.6 (6.9-9.4)	9 (7.9-10.3)	7.2 (5.6-8.9)	<0.001
Platelets (x 10^9/l)	41 (21-79)	38 (20-72)	49 (22-85)	0.41
WBC (x 10^9/l)	17.4 (4.8-69)	16.9 (5.1-66.6)	22.9 (3.5-70.2)	0.81
Myeloblast (%)	42.5 (13-69)	47.5 (17-69)	32 (11-74)	0.29
Bone marrow myeloblast (%)	51 (37-76)	51 (39-79)	57 (23-79)	0.86
Cytogenetics				
Normal cytogenetics	13 (12.3)	8 (14.3)	5 (10.0)	0.21
t(15;17)	6 (5.7)	4 (7.1)	2 (4.0)	
t(8;21)	1 (0.9)	1 (1.8)	0 (0.0)	
inv(16) or t(16;16)	3 (2.8)	3 (5.4)	0 (0.0)	
t(v;11q23) MLL rearranged	1 (0.9)	0 (0.0)	1 (2.0)	
Others	8 (7.5)	2 (3.6)	6 (12.0)	
Treatment				
Intensive chemotherapy	57 (53.8)	48 (85.7)	9 (18.0)	<0.001
Response				
Complete Response (CR) achieved	24 (22.6)	19 (33.9)	5 (10.0)	0.003

AML: acute myeloid leukemia, BM: bone marrow, ECOG: Eastern Cooperative Oncology Group, Hb: hemoglobin, IQR: Interquartile range, MDS: myelodysplastic, WBC: white blood cell.

Treatment and outcomes between the younger and elderly group

The standard of care for patients with AML were "7 + 3 regimen" (cytarabine 100 – 200 mg/m^2/day for 7 days, and idarubicin 12 mg/m^2/day for 3) and followed by 3 – 4 cycles of consolidation therapy with high dose cytarabine (3,000 mg/m^2 every 12 hours on day 1, 3, and 5) for patients who achieved complete remission after induction. All-trans retinoic acid (ATRA) and idarubicin were the induction protocol for APL. Hydroxyurea, a less intense chemotherapy regimen, and transfusion support were the best available therapy provided for non-fit or frail patients. Most patients (88.5%) in the younger age group were treated with intensive chemotherapy as compared to only 18% in elderly group. As expected, complete response was achieved more frequently in the younger group than in the elderly group (33.9% vs 10.0%; p = 0.003). Overall CR was achieved in 42.1% in all patients who had received induction chemotherapy.

The median follow-up of this cohort was 4.2 months. The median survival in the younger group was 6 months, compared to 3.6 months in the elderly group (Figure 2) which did not achieve a statistical significance (p = 0.062). Nine patients

with APL had excellent outcomes, which the median survival was not reached at the time of analysis and 55.6% of patients survived beyond 3 years. (Table 2)

In the univariate analysis, age group did not have an impact on either progression-free survival (PFS) or overall survival (OS). The mortality was significantly higher in the poor performance status group (HR = 2.49; 95%CI 1.58 – 3.93; $p < 0.001$), and intensive treatment decreased the mortality of disease (HR = 0.39; 95%CI 0.25 – 0.59; $p < 0.001$). A condition of hypoalbuminemia was a trend of negative impact to our survival (HR = 1.52; 95%CI 0.99 – 2.26; $p = 0.053$).

In the multivariate analysis, only intensive chemotherapy had positive impact on overall survival (HR = 0.39; 95%CI 0.19 – 0.81; $p = 0.01$). (Table 3) After multivariate analyses, patients who had received intensive chemotherapy significantly improved median survival (256 vs 79 days; $p < 0.001$). Moreover, one-fourth (15 in 56) of patients receiving intensive chemotherapy survived after 2-year follow up. (Figure 3) Interestingly, we found that more than more than half (55%) of elderly patients who had received chemotherapy achieved complete response.

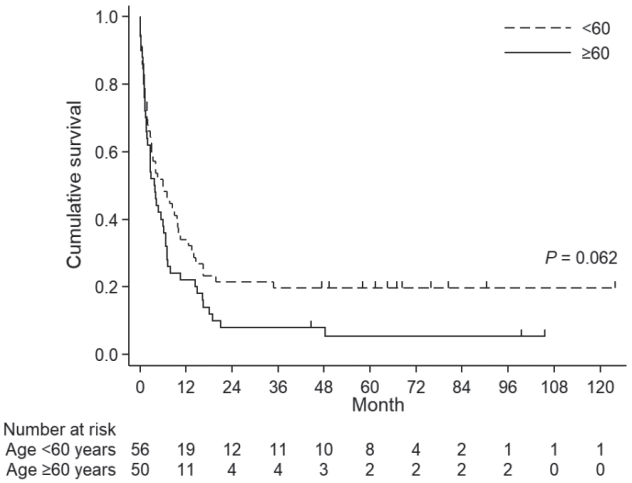

Figure 2: Cumulative survival between younger and older age groups of patients with AML.

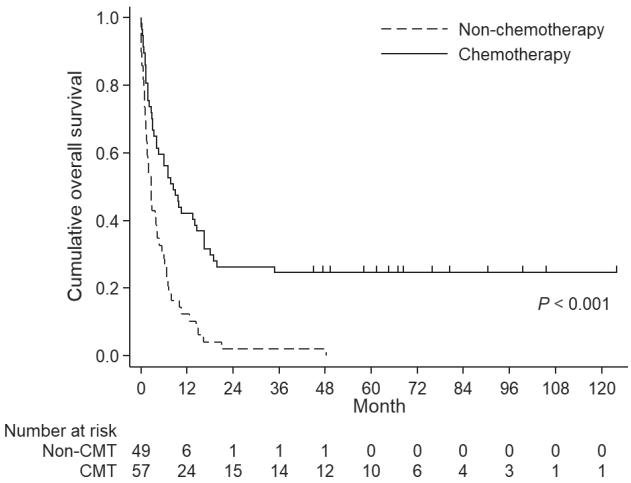

Figure 3: Cumulative survival between intensive chemotherapy and non-chemotherapy group. CMT (chemotherapy)

Table 2:

Univariate analysis of overall survival in different subtypes of AML

Variables	2-yr OS (%)		3-yr OS (%)		p-value
	Rate	(95% CI)	Rate	(95% CI)	
Acute myeloid leukemia	13.5	(6.9-22.3)	12.2	(6.0-20.7)	0.019
Acute promyelocytic leukemia	55.6	(20.4-80.5)	55.6	(20.4-80.5)	
AML with MDS-related change	4.4	(0.3-18.2)	4.4	(0.3-18.2)	

MDS: myelodysplastic

Table 3:

Univariate and multivariate analysis for mortality of patients with AML (n=106)

Factors	Mortality Outcome					
	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-value	HR_{adj}	95%CI	p-value
Age (year)						
<60	1.00	Reference				
≥60	1.47	(0.98-2.23)	0.06			
ECOG						
<2	1.00	Reference		1.00	Reference	
≥2	2.49	(1.58-3.93)	<0.001	1.76	(0.87-3.54)	0.12
Intensive Chemotherapy						
No	1.00	Reference		1.00	Reference	
Yes	0.39	(0.25-0.59)	<0.001	0.39	(0.19-0.81)	0.01
Albumin at diagnosis (g/dl)						
>3.5	1.00	Reference				
<3.5	1.50	(0.99-2.26)	0.053			

ECOG: Eastern Cooperative Oncology Group score

Discussion

Our study emphasized in clinical presentation, utilization of intensive chemotherapy and survival of AML patients in a real setting. Median age of AML patients diagnosed in this study was 56.5 years. Elderly patients accounted for 47%, their median age was 73.5 which was similar to Thai Acute Leukemia Study Group Registry in 2018[5] and Swedish registry at 71 years[11]. The proportion of the elderly AML was also similar to the Löwenberg's review in 2001[12]. The prevalence of AML-MRC was 21.7%, as compared to 7.2% in the reported by Kulsoom, et al., which may be due to a higher proportion of elderly patients in our study[13]. The current study also demonstrated the unmet need in older AML patients. Only a minority of the elderly patients (18.1%) who were aged between 60 – 67 years received intensive chemotherapy. However the CR rate of older patients who received intensive chemotherapy were 55.6% (5 out of 9 patients) which was greater than CR rate reported in the study from Brazil [14] but similar to the study report by Almeida AM. and Ramos F[15] The higher rate of CR in older patients in the current study was likely due to the higher proportion of APL in the older age group which the intensive inductions were more likely to be given. (Figure 4) The current study also confirmed that patients who received intensive induction chemotherapy has better survival that supportive care, even in the elderly patients. There data supported the survival benefit in elderly patients with AML in good performance who could tolerate intensive chemotherapy[5].

Despite the fact that older patients with AML are in vulnerable state, many studies have demonstrated the benefit of intensive induction chemotherapy when offered to a relatively younger subset of patients. Other factors which effect survival and proper delineation of frailty and comorbidities should be explored in future research to select appropriate patients for induction chemotherapy which could result in better outcomes.

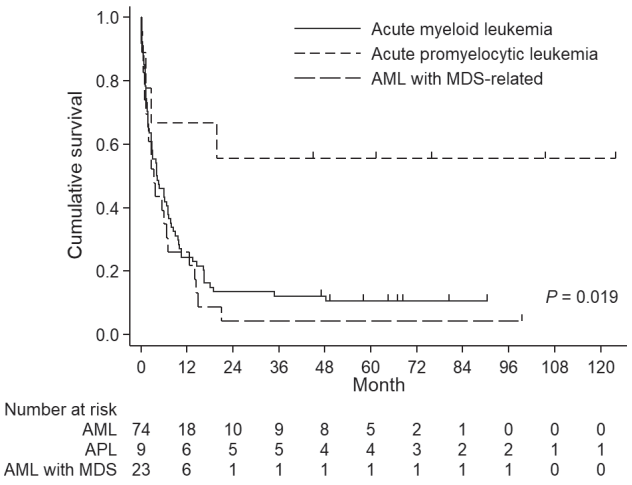

Figure 4: Survival and AML with specific subtypes. APL: acute promyelocytic leukemia, AML: acute myeloid leukemia, MDS: myelodysplasia

There are several limitations in this study. Firstly, the cytogenetics results which are surrogate marker for prognosis and risk stratification was not available in the majority of patients. The WHO classification of Tumours and Haematopoietic and Lymphoid Tissues had proposed a cytogenetic-based classification in 2008, however the official publication came out later and there was a lag in the implement of the treatment policy. Therefore, prognostic prediction and risk stratification according to genetic basis was not available in the current study. Secondly, due to limited sample size, the heterogeneity between the two age groups cannot be compared. The nationwide registration study with larger numbers of patients would offer better information than the current study.

Conclusions

Treatment with intensive chemotherapy had a significant impact on survival in AML. Good ECOG performance status reflects functionality and may predict tolerability for the treatment even in the elderly AML patients. Intensive chemotherapy significantly improves the survival irrespective of age.

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Disclosure

None

References

1. Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. The Lancet 2018; 392(10147):593-606.
2. Kaufman DW, Anderson TE, Issaragrisil S. Risk factors for leukemia in Thailand. Ann Hematol 2009;88(11):1079-88.
3. Sant M, Minicozzi P, Mounier M, Anderson LA, Brenner H, Holleczek B, et al. Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. The Lancet Oncology 2014;15(9):931-42.
4. Niparuck P, Chuncharunee S, Ungkanont A, Udomtrupayakul U, Aungchaisuksiri P, Rerkamnuatchoke B, et al. Long-term outcomes of de novo acute myeloid leukemia in Thai patients. J Med Assoc Thai 2009;92(9):1143-9.
5. Owattanapanich W, Utchariyaprasit E, Tantiworawit A, Rattarittamrong E, Niparuck P, Puavilai T, et al. Improved Survival of Elderly-fit Patients With Acute Myeloid Leukemia Requiring Intensive Therapy: 3-Year Multicenter Analysis From TALWG. Clin Lymphoma Myeloma Leuk 2018;18(12):e509-14.
6. Juliusson G, Lazarevic V, Hörstedt A-S, Hagberg O, Höglund M, Swedish Acute Leukemia Registry G. Acute myeloid leukemia in the real world: why population-based registries are needed. Blood 2012;119(17):3890-9.
7. Kantarjian H. Acute myeloid leukemia--major progress over four decades and glimpses into the future. Am J Hematol 2016;91:131-45.

8.S werdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press;2008.
9.V ardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009;114(5):937-51.
10.Dö hner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424-47.
11. Hulegårdh E, Nilsson C, Lazarevic V, Garelius H, Antunovic P, Rangert Derolf Å, et al. Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish Acute Leukemia Registry. Am J Hematol 2015;90(3):208-14.
12. Löwenberg B. Managing therapy in older adult patients with acute myeloid leukemia. Seminars in Hematology 2001;38(3 Suppl 6):10-6.
13. Kulsoom B, Shamsi TS, Ahmed N, Hasnain SN. Clinical presentation of acute myeloid leukaemia - A decade-long institutional follow-up. J Pak Med Assoc 2017;67(12):1837-42.
14. Rodrigues CA, Chauffaille MLLF, Pelloso LAF, Ghaname FS, Kerbauy DMB, Campos MGV, et al. Acute myeloid leukemia in elderly patients: experience of a single center. Brazilian Journal of Medical and Biological Research 2003;36(3): 703-8.
15. Almeida AM, Ramos F. Acute myeloid leukemia in the older adults. Leuk Res Rep 2016;6:1-7.