The Survival of Patients with t(15;17)(q22;q12) Positive Acute Promyelocytic Leukemia: A Study in North-East of Iran

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ABSTRACT

Background & Objective: Acute promyelocytic leukemia (APL) with t(15;17)(q22;q12) is a relatively common subtype of acute myeloid leukemia (AML). Here, our objective was to ascertain the survival of patients with this leukemia in north-east of Iran.

Methods: Survival rates of 42 APL patients with t(15;17)(q22;q12) were assessed. Clinical information was obtained from archived medical records. Statistical analysis was performed by SPSS 18 software using log-ranked test and Kaplan Maier survival analysis.

Results: Females and males comprised 49% and 51%, respectively. The mean age at diagnosis was 34.3 ± 14.1 years old. During the study period, 17 demises occurred in males, while this number was 7 in females. The mean survival of patients (month) was 23.22 ± 3.57 (95% CI: 16.21 ± 30.2). The five-year survival rate obtained 30%. Regarding demographic and clinical features, the highest rates of 5-year survival were recorded in patients with 20-35 years old (47.6%), males (51%), white blood cell count $<10\times 10^9$ /l (48%), and platelet count $>140\times 10^9$/l (100%).

Conclusion: Younger age, lower WBC count and higher platelet count were significantly associated with longer survival in AML patients with t(15;17)(q22; q12).

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Introduction

Incidence of hematological malignancies has elevated in recent decades (1). Acute leukemia accounts for approximately 20,000 of cancers diagnosed annually in the United States (2). Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) constitute two principal categories of acute leukemia. Acute promyelocytic leukemia (APL) is a subtype of AML which is characterized by proliferation of malignant promyelocytes within blood and bone marrow. APL, comprising 5-8% of AML cases, is a unique form of AML regarding its strong association with the development of intravascular coagulation. Although clinically aggressive, APL is one of the most curable forms of AML which is sensitive to all-trans-retinoic acid (ATRA) (3). APL arises at a younger age, has a peak during adolescence and then reaches a plateau in early adulthood (4). APL represents M3 morphological subtype of French-British-American (FAB) classification system and is

currently categorized as APL with translocation t(15;17) (q24.1;q21.1) by world health organization (WHO) (5).

At cytogenetic level, 98% of APL cases are characterized by t (15;17)(q22;q12). This diagnostic feature may be confirmed by Fluorescence in situ hybridization (FISH) or by real-time PCR to detect Promyelocytic leukemia gene/ Retinoic Acid Receptor Alpha (PML-RARA) fusion gene (6). RARA gene is located at 17q21, and encodes a myeloid transcription factor. The expression of chimeric protein PML-RARA suppresses transcription of specific tumor suppressors favoring progression of APL. Rarely, RARA may be fused with genes other than PML. The alternative variant partners of RARA include PLZF (ZBTB16), NPM1 and STAT5b (7,8). The clinical importance of RARA fusion partners lies within differential responses to targeted therapies necessitating detection of classical t(15;17)(q22;q12).

ATRA and arsenic trioxide (ATO) are current medications for t(15;17)(q22;q12) positive AML. While ATO generally promotes favorable responses only in cases with PML-RARA fusion, ATRA is also effective in cases with NPM1, NUMA and FIP1L1 fusion partners (9-11).

Survival studies in patients with hematologic malignancies provide valuable insights into the identification of parameters associated with high mortalities and also provide us with opportunities to improve life expectancy of at-risk patients. Such studies help clinicians and researchers to develop a database providing essential information about the current updates on prognostic factors. To the best of our knowledge, there is no report regarding survival and prognostic features of APL patients in north-east of Iran. In the present study, survival analysis was performed on AML patients detected with t(15;17)(q22;q12) at Molecular Pathology Research Center of Qaem hospital, Mashhad city of Iran.

Materials and Methods

Patients

This was an epidemiological study performed during 2010-2015. The study was financially supported by the Molecular Pathology Research Center affiliated with Mashhad University of medical sciences. Our study was approved by the ethics committee of Mashhad University of medical sciences (Ethical code: A_908).

Our cohort constituted of 240 AML cases diagnosed at hematology department of Qaem hospital of Mashhad city. Clinical and laboratory information about 42 patients with positive t(15;17)(q22;q12) by routine karyotyping was gathered from available medical records at our center. Clinical symptoms and complete blood count parameters were documented at presentation before initiation of any treatment. The sample size was calculated considering 10% of the total population of AML with t(15;17), 95% confidence interval, and 0.05 standard error. Five-year survival rates for patients diagnosed with t(15;17)(q22;q12) were further documented by phone interviews.

The diagnosis was further scrutinized by observing abnormal promyelocytes in blood or bone marrow, staining bone marrow aspirations or peripheral blood smears for myeloperoxidase and investigating positive results for CD13, CD33, CD15 and CD 117 markers by flow cytometry. PML-RARA fusion gene was revealed by real-time PCR as well. Patients who received any treatments before the study initiation and patients with relapsed disease were excluded from the study.

The therapeutic protocol was according to the standard chemotherapy regimen for APL. Patients received a combination of Daunorubicin, cytarabine, and ATRA for both induction and consolidation therapies. For patients who acquired remissions, maintenance therapy was continued with ATRA.

Administration of antibiotics was performed for those with low white blood cell count. Blood products (packed red blood cells, and platelets) were given to eligible patients (patients with symptomatic anemia, and those at risk of bleeding due to low platelet count). Pain relieving agents were generally administered for patients with chronic pain.

RNA Extraction

Separation of mononuclear cells from bone marrow aspirated samples was carried out using Ficoll gradient centrifugation. RNA was extracted by Tri-Pure (Roche, Germany) according to standard instructions provided by the manufacture. Quality of extracted RNA was checked by agarose electrophoresis on 2% agarose gel.

cDNA Synthesis

cDNA synthesis kit was purchased from Fermentas (RevertAid™ H Minus First Strand cDNA Synthesis, USA), and the procedure was performed according to the manufacturer's instructions.

Detection of PML-RARA Fusion Gene

Real time PCR was carried out by an ABI thermocycler (Applied Biosystems, USA) in duplicate assays using Taqman. Sequences of specific primers and probes for fusion PML-RARA transcripts of three Break point Cluster Regions (BCR) were as forward primers; 5′-TCTTCCTGCCCAACAGCA -3′, 5′-ACCTGGATGGACCGCCTA -3′ and 5′-CCGATGGCTTCGACGAGT -3′, and reverse primer; 5′-GCTTGTAGATGCGGGGTAGAG -3′. Specific probe exploited was 5′ Fam-AGTGCC CAGCCCTCCCTCGC-Tamara-3′. ABL served as the reference gene with primer sequences of forward: 5′-TGGAGATAACACTCTAAGCATAACTAAAGGT-3′ and reverse; 5′- GATGTAGTTGCTTGGGACCCA-3′, with Specific probe of FAM-CCATTTTTGGTTTGGGCTTCACACCATT-Tamara. Each reaction tube contained 10 μL pre-mix Taqman, 0.5 μL ROX dye, 1.5 μL of each forward and reverse primers (10 pmol), 1.5 μL of specific probes, 2 μL of cDNA, and 3 μL of DEPC water. Thermal profile was set as initial denaturation (95℃) for 30 seconds and then 40 cycles of PCR phases as denaturation (95℃, 40 seconds), annealing (60℃, 32 seconds) and extension (72℃, 60 seconds).

Two types of positive controls (positive control of REH cell line, Biomed Reference, and a patient's sample confirmed with positive PML-RARA), and two types of negative controls (negative sample from known patients, and NTC) were used. Positive results were inferred as the presence of amplification curve at CT of 20-27.9 cycles, and negative results were considered as the absence of amplification curve at CT<36. The CT of the control gene was 23.5-27.7.

Statistical Analysis

Statistical analysis was performed in SPSS 18 (SPSS Inc., Chicago, Ill., USA). Descriptive statistics were used to analyze general demographic and laboratory features. Kaplan Mayer survival analysis

was performed to assess 5-year survival in t(15;17)(q22;q12) positive patients.

Results

From a total of 240 AML patients diagnosed according to standard procedures, 42 cases (17.5%) showed t(15;17)(q22;q12). The median age in t(15;17) negative group was 31.68+20.56 years old. In terms of sex, 49% were females and 51% were males. For patients with positive t(15;17), the mean age was 34.3+14.1 years old. Regarding age at diagnosis, 11.9% of these patients had <20 years old, 47.6% with 20-35 years old, 28.5% with 35-50 years old, and 11.9% had >50 years old. Of these, 35.7% were males and 64.3% were females. Characteristics of t(15;17)(q22;q12) negative and positive AML patients have been demonstrated in Tables 1 and 2, respectively. Splenomegaly and hepatomegaly were the most common clinical features, each was present at 28.6% of patients. All patients had at least two of symptoms including fever, anemia, petechia, oral bleeding, menorrhagia or CNS involvement upon admission.

Overall, 24 demises were observed. Death occurrence statistics were as follows; 3 in patients <20 years old, 11 in those with 20-35 years old, 8 in patients with 35-50 years old, and 2 in cases with >50 years old. Considering sex, 17 deaths occurred in males and 7 in females during the study period. Death occurrence in patients with WBC of $<10\times 10^9/l$, $10\text{-}49.9\times 10^9/l$, $50\text{-}100\times 10^9/l$, and $>100\times 10^9/l$ were 9, 11, 2, and 2 respectively. Regarding platelet count, death rates were 22, 2, and 0 cases in groups with $<70\times 10^9/l$, $70\text{-}140\times 10^9/l$, and $>140 \times 10^9/l$ respectively.

Median of 5-year survival in AML patients with t(15;17)(q22;q12) was obtained 23.22+3.57 month (95%CI: 16.21-30.29) with a 5-survial survival rate of 30%. Patients with positive t(15;17)(q22;q12) were subcategorized into four age groups; <20 years old, 20-35 years old, 36-50 years old, and >50 years old, each with respective 5-year survival rates of 11.9%, 47.6%, 28.5%, and 11.9%. Five-year survival rates based on the investigated features have been illustrated in Table 3, and Figure 1.

Table 1. Demographic and clinical characteristics of t(15;17)(q22;q12) negative and positive AML patients.

t(15;17) (q22;q12) negative AML		Total= 198 N(%)
Gender	Male	101(51)
	Female	97(49)
Karyotype	t(8;21)	15(7.6)
	Inv16	13(6.6)
	Normal	170(85.9)
		Total= 42
t(15;17)(q22;q12) patients positive AML		N(%)
Gender	Male	27(64.3)
	Female	15(35.7)
Hepatomegaly		12(28.6)
Splenomegaly		12(28.6)
Fatigue		42(100%)
Bleeding		29 (69%)
CNS involvement		8(19%)
Anemia		37(88.1)

Table 2. Features of AML patients with and without t(15;17)(q22;q12) cytogenetic abnormality.

	t(15;17)(q22;q12) negative AML			AML with t(15;17) (q22;q12) patients		
	Mean±SD	Minimum	Maximum	Mean±SD	Minimum	Maximum
Age (years)	31.6±20.5	1	78	34.3±14.1	4	70
WBC ($\times 10^9/l$)	33500±42923	400	233000	24200±34410	600	156000
RBC ($\times 10^{12}/ul$)	2.9±1.5	0.2	22.2	2.7±0.6	1.2	4.3
Hematocrit (%)	25.3±6	2.3	40.3	24.5±5.5	11.5	41
Hemoglobin (g/dl)	8±2	0.7	13.7	8.2±1.7	3.7	12.9
Platelet ($\times 10^9/l$)	72100±68193.5	3000	415000	49400±70189	8000	414000

A   B
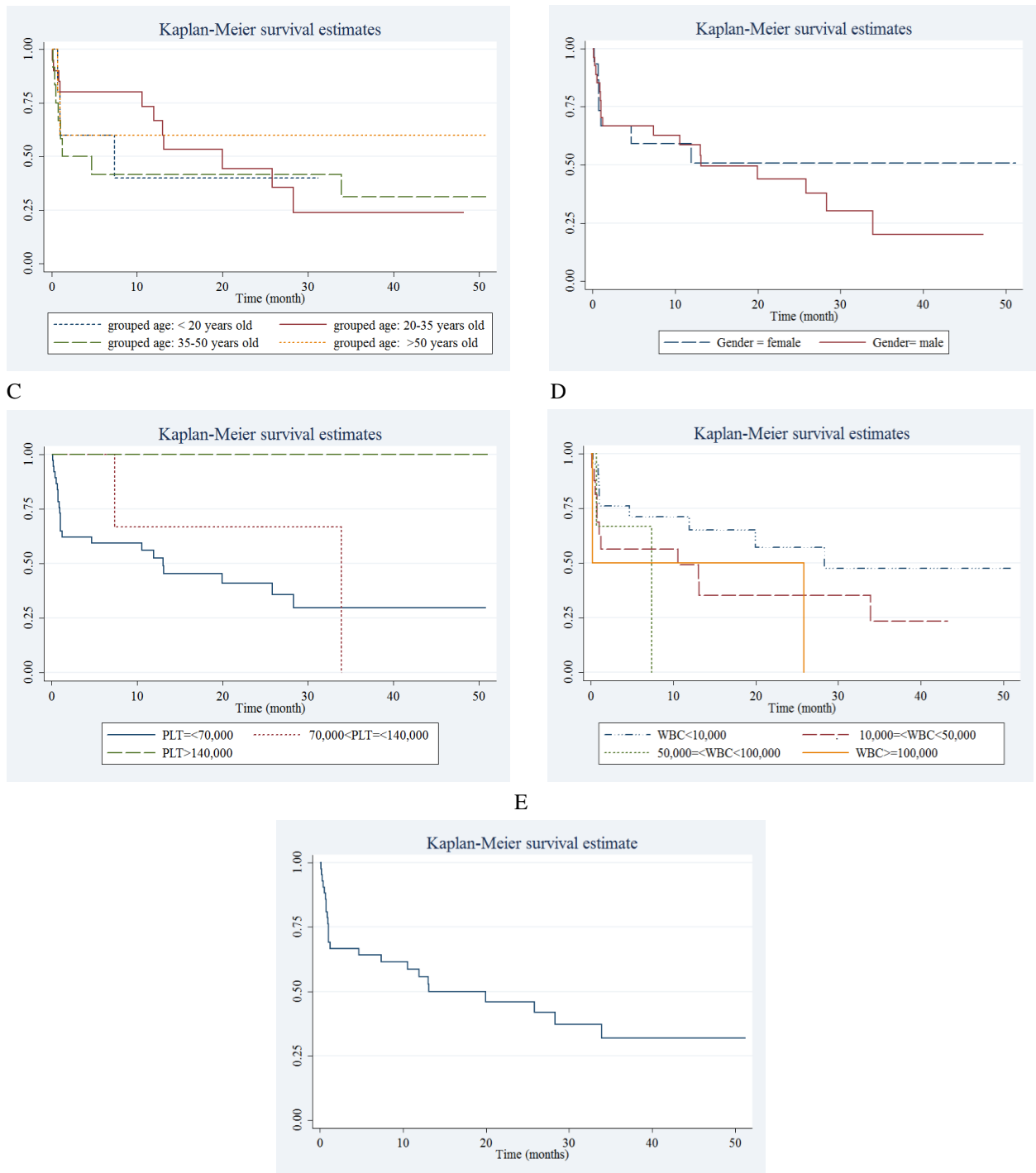
Fig. 1. Kaplan-Meier survival curves in patient with t(15;17)(q22;q12) positive AML. A) based on age groups, B) based on gender, C) based on platelet count, D) based on white blood cell count, and E) overall survival rate

Table 3. Survival of AML patients with t(15;17)(q22;q12) regarding different demographical and clinical parameters .

Parameters		t(15;17) positive N=42 n (%)	5-year survival (%)	Mean survival Index (month)	95% CI
Age distribution (years)	<20	5 (11.9)	11.9	14.2±6.2	2-26.5
	20-35	20 (47.7)	47.6	22.2±4.4	13.4-30.9
	35-50	12 (28.5)	28.5	20.2±6.6	7.1-33.3
	>50	5 (11.9)	11.9	30.8±10.9	9.3-52.2
Gender	Male	27 (64.3)	51	27.5±6.4	14.9-40.2

Parameters			t(15;17) positive N=42 n (%)	5-year survival (%)	Mean survival Index (month)	95% CI
Cell blood count ($\times 10^9/l$)		Female	15(35.7)	19.2	19.9±3.7	12.6-27.2
	WBC	<10	21 (50)	48	29.7±5.2	19.5-40
		10-50	16 (38)	24.6	16.9±4.5	8-25.9
		50-100	3 (7.1)	0	5.1±1.8	1.5-8.6
		>100	2 (4.9)	0	13±9	4.7-30.7
	Platelet	<70	37 (88)	29.3	21.1±3.8	13.6-28.5
		70-140	3 (7.1)	64.2	25±7.2	10.8-39.2
		>140	2 (4.9)	100	51.1	51.1-51.1

Discussion

In the current study, we evaluated 5-year survival rates of AML patients with t(15;17)(q22;q12) in north-east of Iran. Among 240 patients who diagnosed with AML during the study period, 42 (17.5%) were recognized with t(15;17)(q22;q12). In addition, frequencies of t(8;21)(q22;q22), and Inv (16) (p13; q22) subtypes of AML were 7.6% and 6.6% respectively, while no cytogenetic abnormalities were diagnosed in 170/240 (70.8%).

Kamaneh et al. evaluated 46 AML patients in north-west of Iran. Their findings showed that only 2.7% of patients harbored t(15;17)(q22;q12) (12). However, in a recent study conducted by Allahyari A et al. in the north-east part of Iran, t(15;17) subtype of AML was the most prevalent category with 37.7% (13). The incidence of APL was shown to increase from 1975 towards 2008 in the United States (14).

Overall, we recorded a 5-year survival rate of 30% for t(15;17)(q22;q12) positive AML patients, with median survival of 23.22+3.57 months. Similarly, Allahyari et al. reported 5-year overall survival of 26.6% in 96 AML patients from the north-east part of Iran (13). The lower survival rate in their study may be due to the higher mean age of their patients (mean age of 40.4 years old). Furthermore, the study of Allahyari et al. was performed on various subtypes of AML rather than only APL. In a study on 95 AML patients in Iran, median overall survival was reported 13 months, with one-year and two-year survival rates of 51% and 26% respectively (15). This was considerably lower than the survival observed in our study which may be due to the heterogeneity of AML subtypes in the before mentioned study. In another study on 222 Chinese AML patients with APL, 5-year overall survival was 80.9% (16). In an evaluation of 1397 APL patients during 1975-2008 in the United States, 5-year overall survival showed a remarkable increase from 10% during 1975-1990 to 64% during 2000-2008 (14). A report on 54 AML patients of M6 subtype in France showed 5-year survival of 17% with median overall survival of 9 months (17). Another research found that AML subjects with normal cytogenetics had a 5-year overall survival rate of 74% (18). The different survival rate of APL patients in our study compared with the studies in China and the United

States can be attributed to multiple factors such as different supportive therapy protocols, late diagnosis in our patients and subsequently late initiation of chemotherapy, or even unknown genetic factors. Evaluation of these parameters and their extent of contribution to this low survival rate needs another comprehensive study to be addressed.

Inconsistent results among different studies can be explained by different molecular and clinical characteristics of AML patients with t(15;17)(q22;q12). Besides, the role of therapeutic procedures is also of critical importance in the determination of survival in AML patients (19,20). Introduction of ARTA has been associated with an increased survival rate in t(15;17)(q22;q12) positive AML patients (16,21). ATRA induces differentiation in promyelocytes, and is considered a unique therapeutic approach among hematological malignancies. A high rate of 97% of 2-year survival has been reported in t(15;17)(q22;q12) positive patients who received ATRA+ATO as induction therapy (22). Furthermore, early initiation of therapy has been shown to significantly affect survival rates in AML patients (23). It was shown that 10-year overall survival in AML patients who underwent allogenic bone marrow transplantation were 63% (24).

In the present research, we found the highest rate of 5-year survival in patients with 20-35 years old (47.6%), while the lowest rate (11.9%) belonged to patients with <20 and >50 years old. An inverse relationship between survival and age at diagnosis has been noted in a majority of AML subtypes (2,16,25,26). Likewise, in a study carried out by Dores GM et al. on 1397 APL patients in the United States, age was suggested as the most prominent factor influencing survival, with a higher rate of 5-year survival reported for patients with 20-39 years old (14). Similarly, it was demonstrated that younger Iranian AML patients had a higher 5-year survival rate (13,27). In another study from the United States, 5-year survival was shown to be <10% for AML patients older than 60 years old (2). Age was also suggested as a poor prognostic factor in a cohort of 5480 AML patients aged 72-83 years old in the United States (23). In addition, Kent EE et al. found that children had better survival compared to adolescent-adults

considering all subtypes of leukemia (26). Furthermore, AML patients with >75 years old showed a higher risk of mortality than younger patients within 5 years (19). Redaniel MT *et al.* evaluated 54 AML patients of M6 subtype in France, they found that age higher than 60 years old rendered a poor prognosis (17).

We observed that patients with lower leukocyte and higher platelet counts had better survival and lower mortality rates. The best survival was recorded for patients with WBC $<10\times 10^9/l$ and platelet count $>140\times 10^9/l$. A pervious study addressed leukocyte count at presentation as a prominent prognostic factor in t(15;17)(q22;q12) positive AML patients (16). In Iranian AML patients, WBC $>10\times10^9/l$ was associated with higher mortality rate, while WBC $5\text{-}10\times 10^9/l$ demonstrated the highest survival rate in these patients (27). Likewise, Iranian patients with AML who were diagnosed with WBC> $20\times 10^9/l$ showed a significantly lower rate of 5-year survival (25.6%) than patients with WBC $<20\times 10^9/l$ (49.1%) (13).

Conclusion

We observed that t(15;17)(q22;q12) cytogenetic abnormality was the most common AML subtype in north-east Iran. The survival rate of our patients was associated with factors such as the age at presentation and initial leukocyte and platelet counts. To improve survival rate of these patients, it is recommended to use more accurate diagnostic procedures and provide timely and effective therapeutic support.

Acknowledgements

Conflict of Interest

The authors declared that there is no conflict of interest regarding the publication of this article.

References

1. Koohi F, Salehiniya H, Shamlou R, Eslami S, Ghojogh ZM, Kor Y, et al. Leukemia in Iran: Epidemiology and Morphology Trends. Asian Pac J Cancer Prev. 2015;16(17):7759-63. [DOI:10.7314/APJCP.2015.16.17.7759] [PMID]

2. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. Blood. 2012 Jan 5;119(1):34-43. PubMed PMID: 22086414. [DOI:10.1182/blood-2011-04-347872] [PMID] [PMCID]

3. Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. The Lancet. 2013;381(9865):484-95. [DOI:10.1016/S0140-6736(12)61727-9]

4. Sucic M, Zadro R, Burazer B, Labar B, Nemet D, Mrsic M, et al. Acute promyelocytic leukemia M3: cytomorphologic, immunophenotypic, cytogenetic, and molecular variants.J Hematother Stem Cell Res. 2002 Dec;11(6):941-50. [DOI:10.1089/152581602321080600] [PMID]

5. Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013;369(2):111-21. [DOI:10.1056/NEJMoa1300874] [PMID]

6. Welch JS, Ley TJ, Link DC, Miller CA, Larson DE, Koboldt DC, et al. The origin and evolution of mutations in acute myeloid leukemia. Cell. 2012;150(2):264-78. [DOI:10.1016/j.cell.2012.06.023] [PMID] [PMCID]

7. Grossmann V, Schnittger S, Kohlmann A, Eder C, Roller A, Dicker F, et al. A novel hierarchical prognostic model of AML solely based on molecular mutations. Blood. 2012;120(15):2963-72. [DOI:10.1182/blood-2012-03-419622] [PMID]

8. Stein EM, Tallman MS. Acute promyelocytic leukemia in children and adolescents. Acta Haematol. 2014;132(3-4):307-12. [DOI:10.1159/000365117] [PMID]

9. Huang J, Sun M, Wang Z, Zhang Q, Lou J, Cai Y, et al. Induction treatments for acute promyelocytic leukemia: a network meta-analysis. Oncotarget. 2016 Oct 04;7(44):71974-86. [DOI:10.18632/oncotarget.12451]

10. Testa U, Lo-Coco F. Prognostic factors in acute promyelocytic leukemia: strategies to define high-risk patients. Ann Hematol. 2016 Apr;95(5):673-80. [DOI:10.1007/s00277-016-2622-1] [PMID]

11. Tallman M, Lo-Coco F, Barnes G, Kruse M, Wildner R, Martin M, et al. Cost-Effectiveness Analysis of Treating Acute Promyelocytic Leukemia Patients With Arsenic Trioxide and Retinoic Acid in the United States. Clin Lymphoma Myeloma Leuk. 2015 Dec;15(12):771-7. [DOI:10.1016/j.clml.2015.07.634] [PMID] [PMCID]

12. Kamaneh EA, Asenjan KS, Akbari AM, Laleh PA, Chavoshi H, Ziaei JE, Nikanfar A, Kermani IA, Esfahani A. Characterization of Common Chromosomal Translocations and Their Frequencies in Acute Myeloid Leukemia Patients of Northwest Iran. Cell Journal (Yakhteh). 2016;18(1):37.

13. Allahyari A, Tajeri T, Sadeghi M. Prognostic Factors and Survival in Acute Myeloid Leukemia Cases: a Report from the Northeast of Iran. Asian Pac J Cancer Prev. 2016;17(3):1547-51. [DOI:10.7314/APJCP.2016.17.3.1547] [PMID]

14. Chen Y, Kantarjian H, Wang H, Cortes J, Ravandi F. Acute promyelocytic leukemia: a population-based study on incidence and survival in the United States, 1975-2008. Cancer. 2012 Dec 1;118(23):5811-8. [DOI:10.1002/cncr.27623] [PMID] [PMCID]

15. Ashrafi F, Shahnazari R, Samimi MA, Mehrzad V. Results of treatment of acute myeloid leukemia in central part of Iran. Advanced biomedical research. 2013;2:51. PubMed PMID: 24516851. [DOI:10.4103/2277-9175.114194] [PMID] [PMCID]

16. Xin L, Wan-jun S, Zeng-jun L, Yao-zhong Z, Yun-tao L, Yan L, et al. A survival study and prognostic factors analysis on acute promyelocytic leukemia at a single center. Leukemia research. 2007 Jun;31(6):765-71. [DOI:10.1016/j.leukres.2006.07.028] [PMID]

17. Colita A, Belhabri A, Chelghoum Y, Charrin C, Fiere D, Thomas X. Prognostic factors and treatment effects on survival in acute myeloid leukemia of M6 subtype: a retrospective study of 54 cases. Ann Oncol. 2001 Apr;12(4):451-5. [DOI:10.1023/A:1011133115435] [PMID]

18. Pastore F, Dufour A, Benthaus T, Metzeler KH, Maharry KS, Schneider S, et al. Combined molecular and clinical prognostic index for relapse and survival in cytogenetically normal acute myeloid leukemia. J Clin Oncol. 2014;32(15):1586-94. [DOI:10.1200/JCO.2013.52.3480] [PMID] [PMCID]

19. Redaniel MT, Pulte D, Jeffreys M. Survival disparities by age and country of diagnosis for patients with acute leukemia. Leuk Lymphoma. 2015;56(10):2787-92. [DOI:10.3109/10428194.2015.1014358] [PMID]

20. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. Haematologica. 2012 Dec;97(12):1916-24. PubMed PMID: 22773600. [DOI:10.3324/haematol.2012.066100] [PMID] [PMCID]

21. Warrell RP, Jr., Frankel SR, Miller WH, Jr., Scheinberg DA, Itri LM, Hittelman WN, et al. Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid). N Engl J Med. 1991 May 16;324(20):1385-93. [DOI:10.1056/NEJM199105163242002] [PMID]

22. Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013 Jul 11;369(2):111-21. [DOI:10.1056/NEJMoa1300874] [PMID]

23. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. Haematologica. 2012;97(12):1916-24. [DOI:10.3324/haematol.2012.066100] [PMID] [PMCID]

24. Mangantig E, Naing NN, Norsa'adah B, Azlan H. Survival and prognostic factors in Malaysian acute myeloid leukemia patients after allogeneic haematopoietic stem cell transplantation. Int J Hematol. 2013 Aug;98(2):197-205. [DOI:10.1007/s12185-013-1373-1] [PMID]

25. Quintás-Cardama A, Ravandi F, Liu-Dumlao T, Brandt M, Faderl S, Pierce S, et al. Epigenetic therapy is associated with similar survival compared with intensive chemotherapy in older patients with newly diagnosed acute myeloid leukemia. Blood. 2012;120(24):4840-5. [DOI:10.1182/blood-2012-06-436055] [PMID] [PMCID]

26. Kent EE, Sender LS, Largent JA, Anton-Culver H. Leukemia survival in children, adolescents, and young adults: influence of socioeconomic status and other demographic factors. Cancer Causes Control. 2009 Oct;20(8):1409-20. [DOI:10.1007/s10552-009-9367-2] [PMID] [PMCID]

27. Ayremlou P, Razavi SM, Solaymani-Dodaran M, Vakili M, Asadi-Lari M. Demographic and prognostic factors of 455 patients with acute leukemia admitted to two referral hospitals in tehran-iran during ten years (2001-2011). Iran J Cancer Prev. 2012;5(3):157.

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