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The Clinical Significance of NOTCH 1 Mutations Detection among AML Patients

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Abstract

This study aimed to determine the prevalence and clinical impact of *NOTCH-1* mutations among Egyptian patients with acute myeloid leukemia. This study included a cohort of 50 AML patients. DNA extracted samples were analyzed by direct sequencing of PCR products expanding the heterodimerization (HD) domain (exon 26), exon 34 (tad domain) and exon 34 (pest domain) of *NOTCH-1* gene. *NOTCH 1* mutation was present in 6 cases out of 50 (12%). All *NOTCH-1* mutated AML cases have adverse cytogenetic finding. All cases with mutant *NOTCH-1* failed to achieve complete remission as compared to unmutated one (P=0.024). Mutant NOTCH-1 cases showed significantly shorter OS when compared to wild *NOTCH-1* cases (p<0.001). In conclusion: *NOTCH1* mutations had bad deleterious impact on AML patient's outcome.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by impaired differentiation and increased proliferation of myeloid progenitors. It is generally a disease of older people and is uncommon before the age of 45. AML is slightly more common among men than among women. With the widespread use of high-throughput sequencing techniques, AML has been genetically characterized as a complex polyclonal disease with multiple somatically acquired driver mutations and disease evolution over time [1].

NOTCH-1 is a highly conserved and fundamental signaling system that mediates cell–cell interactions during animal development through highly context-dependent and cell-type-dependent effects on cell growth, fate determination and survival. Aberrations in NOTCH-1 signaling or components of the signaling system underlie various human diseases including carcinogenesis [2;3].

The NOTCH-1 pathway is involved in lymphoid development and recurrent activating mutations in NOTCH-1 contribute to T lymphoblastic leukemias. (3) NOTCH-1 could be more expressed and activated in bone marrow, and such activation could be critical to mediate AML chemoresistance. NOTCH-1 mutation leading to drug resistance and associated with relapsed/refractory AML [4]. Other studies have described the involvement of NOTCH-1 in microenvironment-mediated chemoresistance [5]. These results suggest that NOTCH signaling inhibition, by overcoming the stromal-mediated promotion of chemoresistance, may represent a potential therapeutic target for AML [4]. In spite of that NOTCH-1 signaling is actively involved in the regulation of myeloid development, its role in the myeloid leukemogenesis is less clear due to conflicting reports. This study aimed to determine the prevalence and clinical impact of NOTCH 1 mutations among a cohort of AML Egyptian patients.

Patients and Methods

Patients

This study was conducted on 50 patients with acute myeloid leukemia at Mansoura university oncology center. The age of patients ranged from 24 to 59 years, 24 females and 26 males. The AML diagnosis was based on the morphological, immunophenotyping and cytogenic basis. Ethical committee approval and informed consents were obtained. Adult patients with AML, were treated with 3 + 7 protocol consists of 3 days doxorubicin (45mg/m2) and 7 days cytarabine (100 - 200 mg/m2 IV continuous infusion over 24 hours). The patients were followed up for a mean of 24 month.

Methods

All patients were subjected to full history taking, thorough clinical examination, and abdominal ultrasonography, routine laboratory Investigations (complete blood count, liver function

tests, creatinine, lactic dehydrogenase, bone marrow aspiration, cytochemical stains, cytogenetic analysis and immunophenotyping) and specific investigation for *NOTCH-1* mutations.

NOTCH-1 mutation analysis

NOTCH-1 mutation analysis by direct sequencing of PCR amplified *NOTCH-1* transcripts. Samples were analyzed by direct sequencing of PCR products expanding the heterodimerization (HD) domain (exon 26), exon 34 (tad domain) and exon 34 (pest domain) of *NOTCH-1* gene.

NOTCH-1 gene was amplified using polymerase chain reaction (PCR) from extracted DNA using the following primer pairs: Exon 26 FW: 5-GGAAGGCGGCCTGAGCGTGTC-3; exon 26 RV: 5-ATTGACCGTGGGCGCCGGGTC-3; exon 34 FW1: 5-GCTGGCCTTTGAGACTGGC-3; exon 34 RV1: 5-GCTGAGCTCACGCCAAGGT-3; exon 34 FW2: 5-CAGATGCAGCAGCAGAACCTG-3; and exon 34 RV2: 5-AAAGGAAGCCGGGGTCTCGT-3. Cycling conditions were 35 cycles with annealing temperature 67.5º for exon 26, 63º for exon 34tad and 64º for exon 34pest.

Statistical Analysis

The statistical analysis of data was done using excel program (Microsoft Office 2013) and SPSS (statistical package for social science) program (SPSS, Inc, Chicago, IL) version 20. Qualitative data were presented as frequency and percentage. Chi square and Fisher's exact tests were used to compare groups. Quantitative data were presented by mean, SD or median and range. Comparisons between two groups were done using t-test or Man Whitney (for non-parametric). Kaplan–Meier test was used for survival analysis and the statistical significance of differences among curves was determined by Log-Rank test. Cox regression analysis was used for prediction of OS. P-value less than 0.05 was considered statistically significant.

Results

Clinical and laboratory finding in AML

AML cases showed different clinical presentations at diagnosis; the most common was bleeding tendency (76%), followed by fatigue (64%), pallor (56%), fever/infection (48%), weight loss (40%), lymphadenopathy (28%), splenomegaly (20%), hepatomegaly (16%) and the least presentation was CNS infiltration (12%). AML cases were classified according to FAB classification; 20% were M2, 56% were M4, 20% were M5, 4% were M6 and M3 cases was excluded. (table 1)

Frequency of NOTCH-1 mutation in AML

NOTCH-1 mutation was detected in 6 cases out of 50 AML cases (12%). Two mutant cases were detected in the heterodimerization (HD) domain (exon 26) and 4 mutant cases were found in the proline, glutamic acid, serine, threonine-rich (PEST) domain (exon 34) of the NOTCH-1 receptor which were all predicted to result in enhanced NOTCH-1 signaling. Nucleotide and amino acid changes are shown in table (2).

Impact of NOTCH-1 mutation on laboratory finding and cytogenetic risk

No significant differences were found in blood counts data and FAB subtypes between wild and mutant NOTCH-1 groups in all studied AML groups. (table 3) NOTCH-1 mutated AML cases were associated with adverse cytogenetic risk, with significant association between cytogenetic risk and NOTCH-1 mutations in studied AML patients (table 4).

Impact of NOTCH-1 mutation on response to therapy

Thirty-four cases of studied AML cases achieved CR (68%), 16 cases failed to achieve CR (32%), 10 were refractory (20%) and 6 died during induction therapy (12%). Those who achieved

Table 1. Comparison of clinical and some laboratory presentations between wild and mutant NOTCH groups in all studied AML groups.

		AML patients with wild NOTCH1 (N=44)		AML patients with mutated NOTCH1 (N=6)		P value
		No	%	No	%	
Splenomegaly		6	13.6	4	66.7	0.091
Hepatomegaly		6	13.6	2	33.3	0.422
Lymphadenopathy		14	31.8	0	0	0.534
CNS infiltration		4	9.1	2	33.3	0.330
Positive HCV antibodies		6	13.6	4	66.7	0.091
FAB	M2	10	22.7	0	0	0.285
	M4	26	59.1	2	33.3	
	M5	6	13.6	4	66.7	
	M6	2	4.5	0	0	
Aberrant CD7+		1	4.5	2	66.7	0.180

Categorical data are expressed as number, percentage; compared using Fisher exact test.

Table 2. Types of NOTCH1 mutations in all studied AML cases.

No	domain	Nucleotide change	Amino acid change
1	Pest domain, exon 34	C7318A	Q2441k
1		Del 7344, insC7349, G7356A	S2450-2451A
2		C7550T	P2518L
1	HD-N exon 26	G5011A	V1672I
1		Del A4609	C1537L k1538Q

Table 3. Comparison of laboratory data between wild and mutant NOTCH groups in all studied AML groups.

	AML patients with wild NOTCH1 (N=44)		AML patients with mutated NOTCH1 (N=6)		*P* value
	Median	Range	Median	Range	
Total leucocytic count (X109/L)	14.5	3-420	13	1-99	0.546
Hemoglobin (g/dL)	8.5	5-12	8	7-10	0.932
Platelet count (X109/L)	57.5	13-907	39	11-106	0.358
Peripheral blasts (%)	66	21-85	45	30-80	0.844
BM Blast (%)	76	25-95	55	40-90	0.800

Table 4. Association between cytogenetic findings and NOTCH 1 mutations in studied AML patients.

Cytogenetic Risk	AML patients with wild NOTCH1 (N=44)		AML patients with mutated NOTCH1 (n=6)		*p*
	No	%	No	%	
Favorable (t(15;17), t(8;21), inv(16))	20	45.5	0	0	0.001
Intermediate (Normal karyotype AML)	21	47.7	1	16.7	
Adverse (-5, -7, -17, 11q23del), complex karyotypes	3	6.8	5	83.3	

CR, 12 cases continued CR (70.6%) and 5 cases relapsed (29.4%). AML patients with NOTCH-1 mutations failed to achieve CR, with significant difference from those with wild NOTCH-1. Mutant NOTCH-1 cases were significantly associated with death in aplasia. All studied mutant NOTCH-1 cases died during the study period, whereas, more than two third of wild NOTCH-1 cases still alive by the end of the study, with statistically significant difference.

Survival study

During the entire period of the study (24 months), 18 cases died (36%), while 32 were alive (64%). All mutant NOTCH-1 cases died during the study period, their mean overall survival (OS) was 1.2 months. Whereas, the mean OS for AML patients with wild NOTCH-1 cases was 21.2 months. Mutant NOTCH-1 cases showed significantly shorter OS when compared to AML patients with wild type (P<0.001). All AML patients with mutant NOTCH-1 were refractory or died during induction therapy, therefore no DFS was calculated for them. (Table 5,6 and figure 1)

Cox regression analysis

Cox regression analysis was conducted for prediction of OS within studied AML cases, using age, gender, clinical, laboratory, FAB subtypes, immunophenotyping and Notch mutation as covariates. The significant parameters in univariable analysis were introduce in multivariable. NOTCH-1 mutations were considered as poor prognostic factor for prediction of shorter OS within studied AML cases. (table 7)

Discussion

NOTCH1 mutations were observed in 6 out of 50 (12%) of AML patients in the current study. The previous reports demonstrated that the NOTCH-1 mutations in AML patients ranged from zero up to 8.3% [6-9]. This prevalence was different from those reported for T-cell ALL and CLL, in which more than half the cases had the mutations [6-10].

Based on morpho¬logical criteria, all patients with NOTCH-1 mutations were classified as AML M4 and M5 in the current study. This was in consistent with others who detected NOTCH-1 mutation in different FAB subtypes (M1, M3, M4 and M5a) [11].

In addition, NOTCH-1 mutation was detected in cell line derived from an AML M5 patient at relapse and M4 cell line [7]. NOTCH-1 mutations have also been described in patients with chronic myelomonocytic leukemia (CMML). (12) The recombinant NOTCH-1 ligand proteins could alter AML blast cells into macrophage-like cells morphologically. (13) However, other studies supported that NOTCH-1 mutations were as-

Table 5. Comparison of clinical outcome between wild and mutant NOTCH groups in all studied AML groups.

	AML patients with wild NOTCH1 (N=44)		AML patients with mutated NOTCH1 (n=6)		*P* value
	N	%	N	%	
Complete remission	34	77.3	0	0	0.024
Refractory disease	8	18.2	2	33.3	0.504
Induction death	2	4.5	4	66.7	0.029
Alive	32	72.7	0	0	0.037
Dead	12	27.3	6	100	

CR, Complete remission. Categorical data are expressed as number, percentage; compared using Fisher exact test.

Table 6. Comparison of OS between wild and mutant NOTCH groups in all studied AML groups.

	AML patients with wild NOTCH1 (N=44)	AML patients with mutated NOTCH1 (n=6)	*P* value
Two-year Cumulative OS (%)	65.50%	0%	<0.001
months (95 % CI)	21.2 (18.6-23.9)	1.2 (0.2-2.9)	

OS, overall survival; CI, confidence interval.

Figure 1. OS of AML case with wild NOTCH1 versus those with mutated NOTCH1 groups.

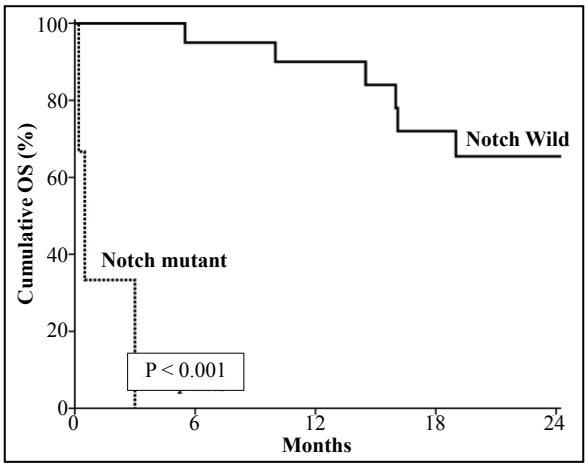

Table 7. Cox regression analysis for prediction of OS within studied AML cases.

	P	OR	95% CI	
Age	0.2	1.032	1.083	0.983
Gender	0.661	1.343	5.012	0.360
Total leucocytic count (X109/L)	0.609	0.998	1.007	0.988
Hemoglobin (g/dL)	0.554	1.129	1.687	0.756
Platelet count (X109/L)	0.391	1.001	1.004	0.998
Peripheral blasts (%)	0.294	0.986	1.012	0.961
BM Blast (%)	0.348	0.989	1.012	0.966
Positive HCV antibodies	0.633	1.468	7.085	0.304
infection	0.668	1.337	5.031	0.355
Bleeding tendency	0.71	1.348	6.52	0.279
Splenomegaly	0.6	1.524	7.359	0.316
Hepatomegaly	0.315	2.26	11.091	0.460
Lymphadenopathy	0.269	0.31	2.478	0.039
CNS infiltration	0.221	2.679	12.975	0.553
FAB	0.182	1.587	3.126	0.806
CD7+	0.568	0.631	3.058	0.130
Cytogenetic Categories	<0.001	1.587	1.102	3.298
NOTCH1 Mutations	0.001	5.287	22.265	1.028

OR, odds ratio; CI, confidence interval.

sociated with AML without mor-phological maturation (M0 or M1) [7;8;11;14;15]. This difference was attributed to rare prevalence in NOTCH-1 mutations in AML, and the fact that NOTCH-1 signaling inhibited a monocytic/granulocytic differentiation program in an early multipotent progenitor. (16,17,18)

Further examination of AML patients in the present study revealed enlargement of the spleen in 4 out of 6 mutant NOTCH-1 patients. This may be due to extramedullary hematopoiesis as they were FAB M4 and M5.

Bone marrow blasts in our mutant NOTCH-1 AML patients showed wide variation, it ranged from 40 to 90% [11]. reported that marrow blasts in NOTCH-1 mutant AML patients ranged from 68 to 97%.

Four of sex AML cases in the present study showed aberrant coexpression of CD7. This was in consistent with previous reports who found that CD7 was consistently highly expressed in all mutant NOTCH-1 AML specimens [8]. Others showed significant correlation between NOTCH-1 hyperexpression and coexpression of CD7 [14]. CD7, is known to be expressed by a considerable proportion of immature AMLs [19].

The previously reported mutations occur mostly in the heterodimerization (HD) domain (exon 26, 27) and proline, glutamic acid, serine, threonine-rich (PEST) domain (exon 34) of the NOTCH-1 receptor [8;20], which were all predicted to result in enhanced NOTCH-1 signaling [21;22]. Four out of 6 cases with NOTCH-1 mutant AML cases in the present study were detected in PEST domain and the other 2 cases were detected in HD domain. This agreed with previous studies [6-8;23].

Five AML cases with mutant NOTCH-1 in the current study showed adverse cytogenetic risk. This finding points that NOTCH-1 mutations might be bad prognostic marker in AML cases However, others reported that NOTCH-1 expression may be relevant prognostic markers in intermediate risk AML [24]. The association of NOTCH-1 mutation with adverse cytogenetic risk may be due to common dysregulation that affect DNA repair and stem-cell maintenance or certain aberrations in the stroma-microenvironment which might influence the evolution of malignant conditions and exhibit distinct genotypic and phenotypic features.

NOTCH-1 association with failure of CR. This may be due to conventional chemotherapies, often become ineffective due to the heterogeneity of leukemia cells [25]. While others showed similar outcome associated with NOTCH-1 mutation in adult AML [26]. On the other hand, Pediatric studies, showed an excellent outcome in NOTCH-1 mutated AML patients [27;28].

The difference in outcome association with NOTCH-1 could be due to small number of mutant NOTCH-1 patients in each study, association of comorbidities, different race and different treatment protocols.

In the present study, mutant NOTCH-1 cases showed significantly shorter OS when compared to wild NOTCH-1 cases. As all mutant NOTCH-1 cases were refractory or died during induction therapy, no DFS was calculated for them. Cox regression analysis was conducted for prediction of OS within studied AML cases, using age, gender, BM blasts, NOTCH-1 mutation as covariates. NOTCH-1 mutation was considered as poor prognostic factor for prediction of shorter OS within studied AML cases.

Association between inferior outcome and NOTCH-1 mutation or hyperexpression was also noticed by others in human samples [11;14;15;18;24;30].

This may explain by higher NOTCH-1 signaling that resulted from NOTCH-1 mutations that leads to truncation of the C-terminal PEST domain with decreased degradation of intracellular portion of NOTCH-1 receptor [31].

In conclusion our data indicate that NOTCH-1 mutation was detected in 12% and AML patients with NOTCH-1 mutation displayed bad clinical outcome. Therapeutic targeting of NOTCH-1 could be a potentially effective approach to combat master oncogenic drivers in AML thus likely beneficial for leukemia patients. Wide scale studies are recommended in order to validate the results detected in the present study.

Compliance with Ethical Standards

This study did not include animals. The research did not receive any specific grant from funding agencies in the public; or not for profit sectors.

Informed consent was taken from all subjects participate in this study.

The authors declare that there is no conflict of interest.

References

[1]. Saygin C, Hirsch C, Przychodzen B, Sekeres MA, Hamilton BK, Kalaycio M, et al. Mutations in DNMT3A, U2AF1, and EZH2 identify intermediate-risk acute myeloid leukemia patients with poor outcome after CR1. Blood Cancer J, 2008;8(1):40-49. PMID: 29321554.

[2]. Zheng B, Yu SF, Del Rosario G, Leong SR, Lee GY, Vij R, et al. An Anti–CLL-1 Antibody–Drug Conjugate for the Treatment of Acute Myeloid Leukemia. Clin Cancer Res. 2019 Feb 15;25(4):1358-68.

[3]. Francis OL, Chaudhry KK, Lamprecht T, Klco JM. Impact of Notch disruption on myeloid development. Blood Cancer J. 2017;7(8):e598. PMID: 28841212.

[4]. Takam Kamga P, Bassi G, Cassaro A, Midolo M, Di Trapani M, Gatti A, et al. Notch signaling drives bone marrow stromal cell-mediated chemoresistance in acute myeloid leukemia. Oncotarget. 2016 Apr 19;7(16):21713-27. PMID: 26967055.

[5]. Nefedova Y, Sullivan DM, Bolick SC, Dalton WS, Gabrilovich, DI. Inhibition of Notch signaling induces apoptosis of myeloma cells and enhances sensitivity to chemotherapy. Blood. 2008 Feb 15;111(4):2220-9. PMID: 18039953.

[6]. Fu L, Kogoshi H, Nara N, Tohda S. NOTCH1 mutations are rare in acute myeloid leukemia. Leukemia & lymphoma. 2006 Jan 1;47(11):2400-3.

[7]. Palomero T, McKenna K, O-Neil J, Galinsky I, Stone R, Suzukawa K, et al. Aster JC, Look AT, Ferrando AA. Activating mutations in NOTCH1 in acute myeloid leukemia and lineage switch leukemias. Leukemia. 2006 Nov;20(11):1963-6. PMID: 17008890.

[8]. Wouters BJ, Jordà MA, Keeshan K, Louwers I, Erpelinck-Verschueren CA, Tielemans D, et al. Distinct gene expression profiles of acute myeloid/T-lymphoid leukemia with silenced CEBPA and mutations in NOTCH1. Blood. 2007 Nov 15;110(10):3706-14. PMID: 17671232.

[9]. Kim YR, Eom HS, Min CK, Lee S, Chung NG, Yoo NJ, et al. Analysis of NOTCH1 extracellular juxtamembrane expansion mutations in acute leukemias and multiple myelomas. APMIS. 2009 Feb;117(2):147-8. PMID: 19239437.

[10]. Weng AP, Ferrando AA, Lee W, Morris JP, Silverman LB, Sanchez-Irizarry C. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science. 2004 Oct 8;306(5694):269-71.

[11]. Kannan S, Sutphin RM, Hall MG, Golfman LS, Fang W, Nolo RM, et al.

Notch activation inhibits AML growth and survival:a potential ther-apeutic approach. J Exp Med. 2013 Feb 11;210(2):321-37. PMID: 23359069.
[12]. linakis A, Lobry C, Abdel-Wahab O, Oh P, Haeno H, Buonamici S, et al. A novel tumor-suppressor function for the Notch pathway in myeloid leukemia. Nature. 2011 May;473(7346):230.
[13]. Yatim A, Benne C, Sobhian B, Laurent-Chabalier S, Deas O, Judde JG, et al. NOTCH1 nuclear interactome reveals key regulators of its transcriptional activity and oncogenic function. Mol Cell. 2012 Nov 9;48(3):445-58. PMID: 23022380.
[14]. Sliwa T, Awsa S, Vesely M, Rokitte D, Grossschmidt P, Jilch R, et al. Hyperexpression of NOTCH-1 is found in immature acute myeloid leukemia. Int J Clin Exp Pathol. 2014 Feb 15;7(3):882-9. PMID: 24695418.
[15]. Lutherborrow M, Bryant A, Jayaswal V, Agapiou D, Palma C, Yang Y, et al. Expression Profiling of Cytogenetically Normal Acute Myeloid Leukemia Identifies MicroRNAs that Target Genes Involved in Monocytic Differentiation. Am J Hematol. 2011 Jan;86(1):2-11. PMID: 20981674.
[16]. Tohda S, Kogoshi H, Murakami N, Sakano S, Nara N. Diverse effects of the Notch ligands Jagged1 and Delta1 on the growth and differentiation of primary acute myeloblastic leukemia cells. Exp Hematol. 2005 May;33(5):558-63. PMID: 15850833.
[17]. Mercher T, Cornejo MG, Sears C, Kindler T, Moore SA, Maillard I, et al. Pear WS, Aster JC, Gilliland DG. Notch signaling specifies megakaryocyte development from hematopoietic stem cells. Cell Stem Cell. 2008 Sep 11;3(3):314-26. PMID: 18786418.
[18]. Lobry C, Oh P, Mansour MR, Look AT, Aifantis I. Notch signaling: switching an oncogene to a tumor suppressor. Blood. 2014 Apr 17;123(16):2451-9. PMID: 24608975.
[19]. Bienz M, Ludwig M, Leibundgut EO, Mueller BU, Ratschiller D, Solenthaler M, et al., Risk assessment in patients with acute myeloid leukemia and a normal karyotype. Clin Cancer Res. 2005 Feb 15;11(4):1416-24. PMID: 15746041.
[20]. O'Neil J, Grim J, Strack P, Rao S, Tibbitts D, Winter C, et al. FBW7 mutations in leukemic cells mediate NOTCH pathway activation and resistance to gamma-secretase inhibitors. J Exp Med. 2007 Aug 6;204(8):1813-24. PMID: 17646409.
[21]. Chiang MY, Xu ML, Histen G, Shestova O, Roy M, Nam Y, et al. Identification of a conserved negative regulatory sequence that influences the leukemogenic activity of NOTCH1. Mol Cell Biol. 2006 Aug;26(16):6261-71. PMID: 16880534.
[22]. Malecki MJ, Sanchez-Irizarry C, Mitchell JL, Histen G, Xu ML, Aster JC, et al. Leukemia-associated mutations within the NOTCH1 heterodimerization domain fall into at least two distinct mechanistic classes. Mol Cell Biol. 2006 Jun;26(12):4642-51. PMID: 16738328.
[23]. Shiba N, Kanazawa T, Park MJ, Okuno H, Tamura K, Tsukada S, et al. NOTCH1 mutation in a female with myeloid/NK cell precursor acute leukemia. Pediatr Blood Cancer. 2010 Dec 15;55(7):1406-9. PMID: 20730882.
[24]. Xu X, Zhao Y, Xu M, Dai Q, Meng W, Yang J, et al. Activation of Notch signal pathway is associated with a poorer prognosis in acute myeloid leukemia. Med Oncol. 2011; 28 Suppl 1:S483-9. PMID: 20812035.
[25]. Desai UN, Shah KP, Mirza SH, Panchal DK, Parikh SK, Rawal RM, et al. Enhancement of the cytotoxic effects of Cytarabine in synergism with Hesperidine and Silibinin in Acute Myeloid Leukemia: An in-vitro approach. J Cancer Res Ther. 2015 Apr-Jun;11(2):352-7. PMID: 26148599.
[26]. Zhou L, Li LW, Yan Q, Petryniak B, Man Y, Su C, et al. Notch dependent control of myelopoiesis is regulated by fucosylation. Blood. 2008 Jul 15;112(2):308-19. PMID: 18359890.
[27]. Breit S, Stanulla M, Flohr T, Schrappe M, Ludwig WD, Tolle G, et al. Activating NOTCH1 mutations predict favorable early treatment response and long-term outcome in childhood precursor T-cell lymphoblastic leukemia. Blood. 2006 Aug 15;108(4):1151-7. PMID: 16614245.
[28]. Malyukova A, Dohda T, von der Lehr N, Akhoondi S, Corcoran M, Heyman M, et al. The tumor suppressor gene hCDC4 is frequently mutated in human T-cell acute lymphoblastic leukemia with functional consequences for Notch signaling. Cancer Res. 2007 Jun 15;67(12):5611-6. PMID: 17575125.
[29]. Zhang J, Ye J, Ma D, Liu N, Wu H, Yu S, et al. Cross-talk between leukemic and endothelial cells promotes angiogenesis by VEGF activation of the Notch/Dll4 pathway. Carcinogenesis. 2013 Mar;34(3):667-77. PMID: 23239744.
[30]. Czemerska M, Pluta A, Szmigielska-Kaplon A, Wawrzyniak E, Cebula-Obrzut B, Medra A, et al. Jagged-1: a new promising factor associated with favorable prognosis in patients with acute myeloid leukemia. Leuk Lymphoma. 2015 Feb;56(2):401-6. PMID: 24844362.
[31]. Rosati E, Sabatini R, Rampino G, Tabilio A, Di Ianni M, Fettucciari K, et al. Constitutively activated Notch signaling is involved in survival and apoptosis resistance of B-CLL cells. Blood. 2009 Jan 22;113(4):856-65. PMID: 18796623.