CLINICAL RELEVANCE OF RUNX1 MUTATION IN PRIMARY REFRACTORY EGYPTIAN ACUTE MYELOID LEUKEMIA PATIENTS.

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ABSTRACT:

Background: *Primary refractory acute myeloid leukemia (AML) represents a continuing obstacle in clinical management. The Runt-related transcription factor 1 (RUNX1) gene is a relatively uncommon mutational target in AML cases.*

Aim: *to investigate the role of RUNX1 mutation in newly diagnosed refractory AML patients receiving first-line induction chemotherapy.*

Methods: *Our research involved 50 newly diagnosed Egyptian AML patients; As a control group, 20 newly diagnosed AML patients who received the conventional first induction chemotherapy with complete remission (CR) and 30 newly diagnosed AML patients who received the same conventional first induction chemotherapy protocols but did not respond to the treatment.*

Results: *13.3% of the examined cases group had RUNXI mutations found, compared to 5% of the control group, RUNXI mutation was found statistically significant with cases group (P=0.01) and RUNX1 mutation and OS were significantly correlated (P=0.05).*

Conclusion: *RUNX1 mutation have a role in resistance to treatment and prognosis in AML. Therefore, measurement of RUNX1 level provides a new strategy to more aggressive treatments for primary refractory AML cases.*

Keywords: *Acute myeloid leukemia, RUNX1, genetic mutations, primary refractory AML.*

INTRODUCTION:

AML is a type of stem cell tumor caused by a disruption in hematopoiesis in the bone marrow. which becomes distorted by blast cells. This disorder caused bone marrow suppression, variable degrees of cytopenia and high mortality if untreated [(1)]. Cytogenetically normal acute myeloid leukaemia (CN-AML) is a broad cancer that accounts for roughly half of the AML population. Despite being classified as an intermediate risk group, CN-AML patients' clinical practices indicate that some of them have a good prognosis, while adverse outcomes are offered to others. In the context of these discoveries over the past 15 years, study on gene expression and mutations has added new prognostic data [(2)]. RUNX1 controls a variety of hematopoietic genes, which helps to regulate hematopoiesis. RUNX1 is an importnt regulator of myeloid precursor cell development into granulocytes, which are expected to be the most common chromosomal translocation target in human leukemia. Both loss of function RUNX1 mutations and chimeric RUNX1 gene involvement in leukemia can result in myeloid leukemia [(3)]. AML patients with RUNX1 gene mutations responded less favorably to standard treatment, achieving lower rates of complete remission (CR),

disease free survival (DFS), and overall survival (OS). Regard to this data, 2017 European Leukemia Net (ELN) risk stratification considered RUNX1 mutated AML as an adverse risk group. However, information of RUNX1 mutation impact on allogeneic stem cell transplantation (alloSCT) indication and outcome are limited and conflicting and reported from subgroup studies comprising small numbers of transplant candidate [(4)]. Accordingly, mutated RUNX1 AML is considered a new provisional entity in World Health Organization (WHO) classifications of myeloid malignancy [(5).]

AIM OF THE WORK:

Our research aims to investigate the relationship between RUNX1 mutation and therapy responsiveness in AML patients, as well as its influence on prognosis.

PATIENTS AND METHOD:

Patient Sample:

This prospective case control study involved 50 patients, including a control group of 20 newly diagnosed adult AML patients who had completed remission after receiving the first conventional induction chemotherapy and a case group of 30 recently diagnosed adult AML patients who had received the same first conventional chemotherapy protocols but were not responding**.** The enrolled Patients were diagnosed and selected among cases attended to the Adult Clinical Hematology unit, Ain Shams University Hospitals over the period from December 2019 to March 2021. Patients with severe comorbidities, a history of prior haematological disorder, a young age of less than 15 years, and cases of relapsed or refractory AML were eliminated from the study. A full blood count, blood film for morphological study, metabolic profile (liver and kidney function), and a bone marrow assessment for morphological features, immunophenotyping, and cytogenetics analysis are all performed on all patients.

All patients received standard chemotherapy according to NCCN guidelines 2017 [(6)]. They received 3+7 protocol which constituted of cytosine arabinoside 200mg/m ^{2} by 7-day constant IV infusion (D1-D7) plus doxorubicin 25 mg/m^2/day for 3days (D1-D3). At day 28 of first induction chemotherapy, evaluation of patients' responsiveness to chemotherapy has been done by assessment of bone marrow aspirate samples as well as peripheral blood smears. Patients were divided into responders and refractory in accordance with the criteria depicted by NCCN guidelines 2017 [(6)].

Overall survival (OS) definition is the extent of time from time of diagnosis to death or end of patients follow up any established first. Disease-free survival (DFS) definition is the period from CR occurrence to time of relapse, death, or patient follow-up termination whichever came first. De novo AML was diagnosed when the patient had no previous history of chemotherapy and no previous diagnosis of myelodysplastic syndrome or chronic myeloid leukaemia.

Methodology for RUNX1:[(7)]

Molecular study done to assess presence of RUNX1 mutation using Real Time PCR. Firstly, Extraction by using extraction kits (QIAamp DNA Blood Mini Kit) by manual extraction method. Then, Detection for RUNX1 mutation gene by Real Time PCR (RT-PCR) at day 28 after first conventional chemotherapy. After that, patients were followed for 1 year after treatment.

Statistical analysis[(7)]:

Data analysis is carried out using IBM SPSS advanced statistics version 21 (SPSS Inc.). When appropriate, numerical data were presented as mean and standard deviation or median and range. Frequency and proportion were used to convey qualitative information. Reasonable statistically methods were used according to different types of data. When $P< 0.05$, the p-value was considered significant, and $P< 0.01$ was considered highly significant.

RESULTS:

The control group was made up of 10 males and 10 females with a mean age of 45.412.6 years, whereas the resistant case group was made up of 17 males and 13 females with a mean age of 44.112.5 years (Table 1). White blood cell count (WBCs), hemoglobin concentration, chemistry (renal and liver function tests), platelet count, peripheral blast%, bone marrow blast%, types of AML, and the presence of comorbidities did not statistically differ between the two groups. A statistically significant difference existed when comparing CD33 between the two study groups (P=0.011), but not when comparing the other flow cytometric markers between the two groups. Cytogenetic analysis, the existence of the RUNXI mutation, and molecular markers did not show any significant statistical distinctions between the two groups. RUNXI mutations were found in 13.3% of the cases investigated and 5% of the controls (P=0.336) (Table 2). RUNX1 mutation had no correlation with demographic (age, gender), clinical (co-morbidity, chemistry), hematological (initial WBCs, initial hemoglobin, initial platelets, peripheral blat cell count, initial bone marrow blast percent, day 28 bone marrow blast count), cytogenetics, or molecular studies (Table 3). Flow cytometry markers and RUNX1 mutation did not correlate. Regarding the OS and DFS, all patients were followed for 1 year from Day 0. O.S of patients with RUNX1 mutation was 2.5±1.9 Months in contrast to those without the mutation whose had O.S 7.1±3.5. RUNX1 mutation and overall survival (P=0.05) and disease-free survival (P=0.031) were significantly correlated (Table 4). Analysis of the relation between RUNIX mutation and status of disease response revealed significant association of absence of RUNIX mutation with remission of the disease in cases group and presence of RUNXI mutation with refractory cases (P=0.01) (Table 5).

Table (1): Demographic data of included all studied groups.

Variable		Cases	Control	Test value	P value
Age	Mean ± SD	44.1±12.5	45.4±12.6	0.368	0.710*
Gender	Male	17 (56.7%)	10 (50%)		
	Female	13 (43.3%)	10 (50%)	0.214	0.643^{+}

*Using Independent T test, $^{+}$Using Chi-square test, p value ≤ 0.05 is significant

Table (2): Molecular and cytogenetic analysis of included all studied groups.

Variable		Case (n=30)	Control (n=20)	Test value	P value
Molecular analysis	Not done	15(50%)	14(70%)	5.542	0.353
	FLT3	4(13.3%)	0		
	NPM	3(10%)	3(15%)		
	5q-deletion	2(6.7%)	0		
	BCR-ABL	1(3.3%)	1(5%)		
	PML-RARA	5(16.7%)	2(10%)		
Cytogenetics	Not done	17(56.7%)	7(35%)	4.129	0.248
	Translocation (6-16)	4(13.3%)	5(25%)		
	Translocation (8-21)	4(13.3%)	6(30%)		
	Translocation (5-17)	5(16.7%)	2(10%)		
RUNXI	Positive	4(13.3%)	1(5%)	0.926	0.336
	Negative	26(86.7%)	19(95%)		

Using Fisher-exact test, p value ≤ 0.05 is significant

FLT3=fms-like tyrosine kinase 3, NPM= nucleophosmin, BCR-ABL=breakpoint cluster region-Abelson, PML-RARA=Promyelocytic Leukemia-retinoic Acid Receptor Alpha

Table (3): RUNXI mutation versus demographic, clinical, hematological, and molecular parameters in all studied groups.

Variable		RUNXI mutation		Test value	P value
		Present	Absent		
Age	Mean ± SD	56±10	43.8±12.3	1.881	0.070*
Gender	Male	3	14	0.632	0.613+
	Female	1	12		
Initial White Blood Cells	Mean ± SD	72.1±34.7	39.7±22.2	1.715	0.097*
Initial Hemoglobin %	Mean ± SD	8.2±2.1	8.1±2.2	0.157	0.876*
Initial platelet	Mean ± SD	58.2±29.5	63.7±27.8	0.362	0.720*
Peripheral blast%	Mean ± SD	43.5±21.1	31.6±16.3	1.247	0.223*
Initial BM blasts%	Mean ± SD	79.7±25.3	65.9±20.8	1.204	0.239*
Blast%(Day28)	Mean ± SD	51.5±16.7	40.9±18.1	1.096	0.282*
Chemistry	normal	3	23	2.707	0.258+
	Hepatic	0	2		
	Renal	1	1		
Comorbidities	Present	1	4	0.231	0.538+
	Absent	3	22		
Molecular analysis	Not done	3	12	9.231	0.100+
	FLT3	0	4		
	NPM	0	3		
	5q-del	0	2		
	BCR-ABL	1	0		
	PML-RARA	0	5		
Cytogenetics	Not done	2	15	6.075	0.108+
	translocation (6-16)	0	4		
	translocation (8-21)	2	2		
	translocation (5-17)	0	5		

*Using Independent T test, +Using Fisher-exact test, p value ≤ 0.05 is significant
FLT3=fms-like tyrosine kinase 3, NPM= nucleophosmin, BCR-ABL=breakpoint cluster region-Abelson, PML-RARA=Promyelocytic Leukemia-retinoic Acid Receptor Alpha

Table (4): RUNXI mutation versus patients' survival in all studied groups.

Variable		RUNXI mutation		Test value	P value
		Present	Absent		
Overall survival (months)	Mean ± SD	2.5±1.9	7.1±3.5	1.978	0.05*
Disease free survival (months)	Mean ± SD	0	4.1±1.5	2.267	0.031*

*Using Independent T test, +Using Fisher-exact test, p value ≤ 0.05 is significant

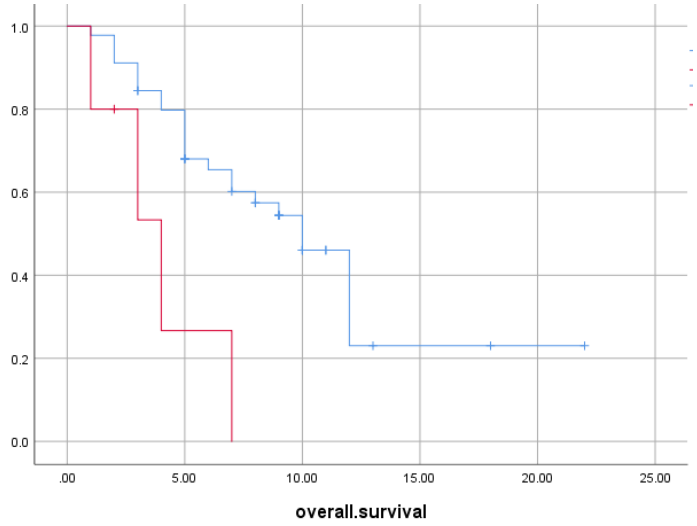

Figure (1): Survival plot of RUNIX mutation in all studied groups (Red line for positive mutation and blue line for negative mutation).

Table (5): Comparison of the status of disease response with RUNIX mutation.

		Status of disease response			Test value	P value
		Refractory	Remission	Relapse		
RUNIX mutation (Controls)	Present	0	0	1	0.702	0.402
	Absent	0	8	11		
RUNIX mutation (Cases)	Present	4	0	0	9.231	0.010
	Absent	6	14	6		

[+]Using Fisher-exact test, p value ≤ 0.05 is significant

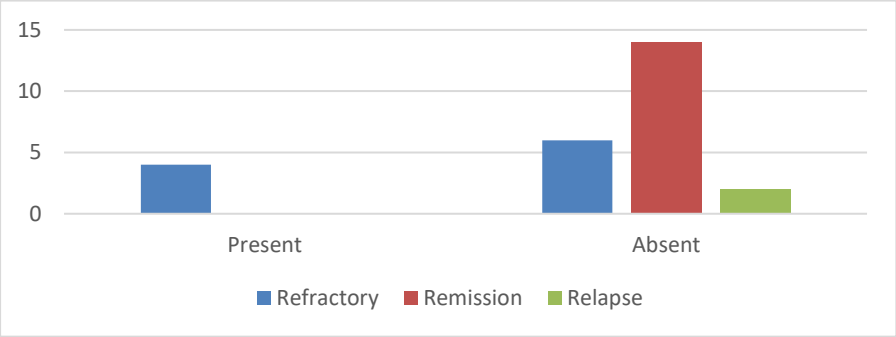

Figure (2): Comparison of the status of disease response with RUNIX mutation in cases group.

DISCUSSION:

AML prognosis is significantly dependent on the assessment of cytogenetic anomalies. Moreover, acquired molecular alterations have been associated with prognosis. The assessment of genetic aberrations in AML and understanding its relation to leukemogenesis process enhancing the evaluation of patient risk stratification especially regarding to molecularly and targeted based therapies. The mean aim of our study was to study the relation between resistance to treatment in acute myeloid leukemia cases and existence of RUNX1 mutations. In the present study, there were RUNXI mutation in 13.3% of the studied case group (4 out of 30) and in 5% in control group (1 out of 20) with no statistically significant difference (P=0.336)which is near to the results in the study was done by **Gaidzik *et al.*** [(9)]who

found that RUNX1 mutations were reported in 245 of 2439 (10.0%) of their studied group, secondary AML represent 24.2% and de novo AML represent 9.2%, that also Consistent with prior studies by **Tang *et al.*, Mendler *et al.* Greif *et al.*[10-12] .** Also, **Jalili *et al.* [13]** stated that the prevalence of RUNX1 mutation is quite low (5 to 16%) which was difficult to recognize its actual effect on clinical outcome**. You *et al.* [14]** found that RUNX1 mutations were reported in 33 (15.1%) of 219 patients. In the present study, RUNX1 mutation was positive in elder age (Mean=56 years old) than RUNX1 negative patients (mean=43.8 years old) but with no statistically significant correlation between age and RUNX1 mutations (P=0.070) which disagree with what reported in the study done by **Gaidzik *et al.*[9]** who found that RUNX1 mutations were identified in older age significantly (P<0.0001) and **Khan *et al.*[14]** found that mutant RUNX1 were detected more in patients older than 65 years of age, 24 (15.9%), in comparison to younger patients, 9 (5.1%) that may be due to the difference in number of the studied cases. This explained by cellular strain and compromised renovation of double-stranded DNA splits (e.g., after radiation exposure) buildup may promote to genomic fragility [16] and higher the incidence of genetic mutations, together with RUNX1[17,18]. In our study, there was male predominance in RUNX1 mutations than females but with no significant relation in between sex and RUNX1 mutations (P=0.613) which in agreement with **You *et al.* [14]** who found that the difference in the frequency of the RUNX1 mutation was negligible (P =0.139). But that disagree with **Gaidzik *et al.* [9] and Tang *et al.* [10]** who found that RUNX1 mutations was detected more frequent in male than female patients (18.4% vs 6.4%, P <0.001), (P = 0.02) respectively that may be due to the difference in number of the studied cases. In our study, there was no significant relation in between Initial WBCs and RUNX1 mutations with (P=0.097) but other studies showed that RUNX1-mutation was linked with lower WBC counts than subjects without mutation [12]. In this study, there was no significant relation between hemoglobin and RUNX1 mutations (P=0.876) which in the same way with the results in the analysis done by **Khan *et al.*[15] and Wang *et al.* [19]** as they stated that RUNX1 mutation did not correlate with WBC count and hemoglobin significantly. In this study, the mean platelet count was 58.2±29.5 in the RUNX1 mutation and 63.7±27.8 in cases of absent RUNX1 mutation but not statistically significant (P=0.720) which coincide with the results in the study done by **You *et al.*[14]** who found that patients with a RUNX1 mutation had lower median platelet count significantly than those with a RUNX1 wild type (P=0.013). On the other hand **Gaidzik *et al.*[9] and Khan *et al.* [15]** found that RUNX1 mutations were correlated with increased platelet counts (P=0.007), (P=0.012) respectively. As regard to bone marrow blasts and RUNX1 mutations, our results agree with **Gaidzik *et al.*[9] and Khan *et al.*[15]** that RUNX1 did not significantly correlate with bone marrow blasts. Regarding to Cytogenetic data, there was no significant relation in between Cytogenetic data such as translocation (6-16), translocation (8-21), translocation (5-17), 5q-deletion and RUNX1 mutations (P=0.108) which agree with **Ishikawa *et al.* [20]** who found that there was no significant difference between patients with KIT mutations and those without regarding cytogenetics abnormality. Also, in another study by **You *et al.* [14]** found that patients with RUNX1 mutations had less frequent cytogenetics abnormality (P = .089). But disagree with the results in the study done by **Gaidzik *et al.* [9]** who found that RUNX1 mutations were inversely correlated with Cytogenetic data. **Mendler *et al.* [11] and Greif *et al.* [12]** reported that the incidence became more than 10% in cases with intermediate cytogenetic risk group.

RUNX1 mutation and OS were significantly correlated in the current

research. (P=0.05) (Figure 1) and significant association of presence of RUNXI mutation with refractory cases (P=0.010) (Figure 2). Many reports have determined the constant and strong role of RUNX1 mutation in patient outcome stratification, but **Gaidzik *et al.*[9]** reported that no significant impact on DFS or OS within the cytogenetically normal AML (CN-AML) subgroup. **Jalili *et al.* [13]** reported that RUNX1 mutation linked to poorer prognosis. **Khan *et al.*[15]** found that there was no significant impact of RUNX1 status on CR rate. In contrast to **Wang *et al.* [19]** who found that mutant RUNX1 associated with lower rate of CR (P = .029). Also, **You *et al.* [14]** found that mutated RUNX1 patients had lower OS compared with those unmutated (median, 10.5 vs 14.95 months; P=0.074) and had noticeably worse DFS against those without (median, 12.4 months vs 15.9 months; P=0.045). These results are in line with other studies **Tang *et al.* [10] and Greif *et al.*[12]** on CN-AML patients. However, in another study, no significant impact on DFS or OS within the CN-AML subgroup [21]. **Stengel *et al.* [23]** reported that RUNX1 mutation with IDH2 mutation gave good outcome, but with mutations of ASXL1, SF3B1, SRSF2 and PHF6 gave worse outcome. Based on all reported in studies regarding poor outcome in assessed RUNX1 mutational AML, the 2016 WHO AML categorization system revision considered de novo AML with mutated RUNX1 as a provisional entity [24].

Based on our finding that the expression of RUNX1 mutation was more in refractory cases and there was significant correlation between RUNX1 mutation and overall survival, that means RUNX1 mutation plays an important role in prognosis of AML. The present study supports previous findings but more research involving large cohorts is still needed.

Conclusion:

The RUNX1 mutation might be utilized to predict prognosis and resistance to therapy in AML. Therefore, measurement of RUNX1 level provides a new strategy to more aggressive treatments for high-risk groups.

Declarations

Consent for publication:

Not applicable

Conflict of interest:

No conflict of interest.

Ethical approval: The Ain Shams University Faculty of Medicine's ethical committee's criteria and the 1964 Helsinki Declaration and its later amendments were followed in all procedures carried out in studies involving human subjects.

Informed consent:

All individual participants in the research gave their informed permission.

Availability of data and materials: The datasets used and/or analysed during the current investigation are accessible upon reasonable request from the corresponding author.

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تقييم طفرة عامل النسخ المرتبط برونت فى مرضى الليوكيميا الميلوديه الحاده المصريين المقاومين للعلاج الاولى

ناهد معوض ابراهيم ابراهيم وشذا عبدالوهاب أحمد وهناء فتحي عبدالسميع أستاذ أمراض الدم و ريهام عبدالفتاح موسى

قسم االأمراض الباطنية – أمؤاض الدم - كلية الطب جامعة عين شمس

المقدمه: سرطان فقر الدم النخاعي الحاد هو سرطان يصيب الخلايا الجذعية المكونة للدم ، حيث يترافق تراكم الخلايا النخاعية المختلة مع انخفاض إنتاج خلايا الدم السليمة. فقر الدم النخاعي الحاد ناتج عن عوامل مختلفة مثل الطفرات والإشعاع والمواد المسرطنة. المرضى الذين يعانون من فقر الدم النخاعي الحاد يحتفظون بالتعبير عن السيتوكينات المختلفة عند مستويات أعلى من تلك الموجودة في الأفراد الأصحاء

عامل النسخ ١ المرتبط ، المعروف أيضًا باسم بروتين اللوكيميا النخاعي الحاد ١ ، هو عامل نسخ مهم يشارك في تمايز الخلايا الجذعية المكونة للدم. إنها واحدة من أكثر الجينات المستهدفة شيوعًا لانتقال الكروموسومات في سرطان الدم ، وتسبب طفرة الخط الجرثومي لـعامل النسخ ١ المرتبط اضطراب الصفائح الدموية العائلي مع الأورام الخبيثة المرتبطة به.

لوحظت طفرات الخلايا الجسدية والتشوهات الصبغية ، بما في ذلك تلك الخاصة بـعامل النسخ ١ المرتبط ، في متلازمة خلل التنسج النخاعى ، وسرطان الدم النخاعي الحاد ، وسرطان الدم الليمفاوي الحاد ، وابيضاض الدم النخاعي المزمن بوتيرة عالية.

الهدف من الدراسة: يهدف هذا العمل إلى دراسة العلاقة بين مقاومة العلاج في حالات سرطان فقر الدم النخاعي الحاد ووجود طفرات فى عامل النسخ المرتبط ١.

لتوضيح هذا الهدف ، تم تشخيص ٣٠ مريضًا حديثًا من مرضى سرطان فقر الدم النخاعي الحاد البالغين بعد تلقي بروتوكولات العلاج الكيميائي التقليدية وعدم الاستجابة للخط الأول من العلاج. تم تضمين ٢٠ حالة تم تشخيصها حديثًا من سرطان فقر الدم النخاعي الحاد بعد تلقي نفس العلاج الكيميائي التقليدي والاستجابة له كمجموعة تحكم في هذه الدراسة.

نتائج الدراسة: - في هذه الدراسة ، اشتملت (المجموعة الأولى) على ١٧ من الذكور و ١٣ من الإناث بمتوسط عمر ٤٤,١ ± ١٢,٥ سنة ، بينما (المجموعة الثانية) تضمنت ١٠ ذكور و ١٠ إناث بمتوسط عمر ٤٥,٤ ± ١٢,٦ سنة

- وجدنا أن المجموعة الأولى لديها نسبة أعلى بكثير من BLASTs (المقدرة في اليوم ٢٨) مقارنة بمجموعة التحكم

- أظهرت مقارنة CD33 بين المجموعتين المدروستين أن هناك فروق ذات دلالة إحصائية

- لكن تحليل الواسمات الجزيئية والتحليل الوراثي الخلوي ووجود طفرة فى عامل النسخ المرتبط ١ لم تكشف عن أي فرق ذي دلالة إحصائية

- كان هناك ارتباط كبير بين طفرة عامل النسخ المرتبط ١ والبقاء الكلي للحالات

الاستنتاجات: - أوضحت دراستنا أن طفرة عامل النسخ المرتبط ١ ترتبط بالبقاء على قيد الحياة ، مما يشير إلى أن استراتيجية العلاج التي تستهدف عامل النسخ المرتبط ١ أكثر فعالية

- يمكن استخدام طفرة عامل النسخ المرتبط ١ كمؤشر حيوي التهابي لمقاومة العلاج في سرطان الدم النخاعي الحاد. لذلك ، يوفر قياس مستوى عامل النسخ المرتبط ١ إستراتيجية جديدة للعلاجات الأكثر قوة للمجموعات المعرضة للخطر

- تتنبأ طفرات عامل النسخ المرتبط ١ بمقاومة العلاج الكيميائي

التوصيات : - هناك حاجة إلى مزيد من البحث لتحسين فهمنا لطبيعة دور مستوى عامل النسخ المرتبط ١ في توقع لمقاومة العلاج فى مرضى سرطان فقر الدم النخاعي الحاد

- من المهم الآن المضي قدمًا في مجال الوقاية والعلاجات الأكثر قوة للمجموعات المعرضة للخطر في مرضى سرطان فقر الدم النخاعي الحاد