Am J Blood Res 2025;15(4):80-89
www.AJBlood.us /ISSN:2160-1992/AJBR0163653

Original Article

Assessing glucose 6-phosphate dehydrogenase activity in children with acute lymphoblastic leukemia and its relationship to disease activity

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Received January 31, 2025; Accepted July 29, 2025; Epub August 15, 2025; Published August 30, 2025

Abstract: Objective: Glucose 6-phosphate dehydrogenase (G6PD) activity of red blood cells (RBC) may be helpful as a prognostic factor and a probable predictive indicator of disease activity in children with acute lymphoblastic leukemia (ALL). Materials and methods: This cross-sectional, case-control study was performed on almost 133 pediatric ALL cases from 2016 to 2020 in an oncology hospital. Patients with a history of blood transfusion within the last three months, acute hemolytic crisis, any other type of enzyme deficiency like pyruvate kinase and hexokinase, and chronic liver disease were excluded. The G6PD activity in RBC was measured using the spectrophotometric method. In addition, the G6PD activity was assessed in 133 normal individuals as a control group. According to the kit, the G6PD <1.5 IU/g of Hb level was recognized as severely deficient. The correlation of G6PD activity with disease activity and other parameters in ALL patients was determined using the Pearson correlation test. Data were measured by an independent t-test and a one-way ANOVA test. Results: The mean G6PD activity of RBC in the control (n=133) and patient group (n=128) was 9.1±2.08 IU/g of Hb and 11.12±3.8 IU/g of Hb, P<0.001, respectively. There was a significant difference in the G6PD activity of RBC in patients' blastic and non-blastic phases, t (128) =-2.48, P=0.014. Conclusion: The G6PD activity of RBC is higher in childhood ALL than in the control group. Moreover, the G6PD activity of RBC in the blastic phase of leukemia was higher than that of patients in remission.

Keywords: Red blood cells, acute lymphoblastic leukemias, enzyme disorders, red cells, acute leukemia, pediatric leukemia

Introduction

Glucose 6-phosphate dehydrogenase G6PD activity has been observed to increase in many cancers [1, 2]. A study in which nude mice were inoculated with fibroblasts overexpressing G6PD revealed that overexpression of G6PD can lead to malignant transformation [3].

The enzyme G6PD is involved in the initial stage of the pentose phosphate pathway (PPP), which maintains NADPH enzyme levels and, thus, cell energy. The main biological activities of G6PD include: NADPH production, antioxidant defense, lipid and nucleotide biosynthesis, cell proliferation and cancer, and immune response support [4-9] as shown in detail in **Table 1**. The primary physiological functions of G6PD include generating NADPH, a vital reducing agent essential for antioxidant defense through the regeneration of reduced glutathione, maintaining cellular redox homeostasis, supporting anabolic processes such as fatty acid and cholesterol biosynthesis, and safeguarding cells-especially red blood cells-from oxidative stress and associated cellular damage [5, 7-9].

NADPH, in turn, maintains glutathione levels in these cells, helping to protect red blood cells (RBCs) against oxidative damage from compounds such as hydrogen peroxide. Furthermore, G6PD is one of several glycolytic enzymes regulated by the transcription factor hypoxia-inducible factor 1α (HIF1α) [5, 10-12].

https://doi.org/10.62347/QFMM6731

Table 1. The main biological activities of G6PD [4-7]

Biological activity of G6PD	Description
NADPH production	Catalyzes the first step of the PPP, generating NADPH, a crucial cofactor in reductive biosynthesis and antioxidant defense
Antioxidant defense	Provides NADPH for glutathione reductase to maintain reduced glutathione (GSH), defending against oxidative stress
Lipid and nucleotide biosynthesis	Supplies NADPH for fatty acid and nucleotide synthesis, especially important in the liver, adipose tissue, and proliferating cells
Cell Proliferation and Cancer	Supports growth and survival of rapidly dividing cells (e.g., cancer cells) by fueling anabolic reactions and controlling reactive oxygen species (ROS) levels
Immune response support	Provides NADPH for the NADPH oxidase complex in phagocytes, enabling production of superoxide for microbial killing

Acquired enzymatic abnormalities of RBCs are often observed in patients with acute leukemia or after chemotherapy. The suggested causes for changes in erythrocyte enzyme activity in individuals with leukemia are (1) Intracellular stress and transient inhibition of glycolysis in erythrocytes, (2) post-translational molecular modification, and (3) genetic abnormalities of cell division (the cytoplasm or nucleus) associated with loss of function leading to defects in enzyme production [13, 14].

Devi G.S. and coworkers found in 1995 that leukocyte G6PD activity can be utilized as a diagnostic and prognostic tool for children with ALL [15].

A study by Devi GS et al. 1996 showed that RBCs' G6PD activity may be helpful as a predictive indicator of relapse in children with acute leukemia [16].

The study's objective is to evaluate G6PD activity in children with ALL and its relationship to disease activity because our country has a higher prevalence of G6PD deficiency.

Methods

Patients

One hundred thirty confirmed ALL pediatric patients from Amir Oncology Hospital, affiliated with Shiraz University of Medical Sciences, were enrolled in this prospective cross-sectional study from February 2016 to February 2020.

ALL was confirmed via bone marrow aspiration and biopsy, flow cytometry, and molecular cytogenetics.

The study was conducted using a convenience sampling method for patients who had confirmed ALL and were under 18 years old. We use the B-ALL trials of the Children's Oncology Group (COG) protocol to treat childhood ALL in our institute. Routine karyotyping was done on bone marrow (deletions, translocations, or extra chromosomes, hyperdiploid, and hypodiploidy) and also cytogenetic abnormalities, including [t(9;22), t(12;21), t(1;19), and t(4;11)] by PCR.

Individuals who have had a blood transfusion within three months, chronic liver disease, acute hemolytic crisis, or any other type of enzyme deficiency, like pyruvate kinase deficiency and hexokinase deficiency, were excluded. This study received approval from the local Ethics Committee of Shiraz University of Medical Sciences. (IR. Sums. MED. Rec. 1395. s187).

Written informed consent was obtained from each patient or legal guardian who participated in this study.

Sample collection

Blood samples were taken from the patients during their hospitalization or follow-up treatment after a detailed review of their files. Therefore, patients have the possibility of being in any phase of the disease. For instance, the blastic phase can be associated with a relapse or a newly diagnosed patient who needs hospitalization.

Samples were collected in two tubes using the venoject method and observing the standard sampling method.

1) K_2EDTA containing tube for complete cell count test (CBC), reticulocyte count, blood group, and isolation of RBCs.

2) Clot activator containing tube for isolation of serum to measure the level of total and direct bilirubin and lactate dehydrogenase (LDH) for excluding the patients after a severe hemolytic crisis, at which level of G6PD is unreliable.

Isolation of RBCs

Leukocytes, platelets, and serum typically exert minimal influence on G6PD activation. In cases of severe anemia, an elevated white blood cell to red blood cell ratio or diminished red cell G6PD levels can render their impact substantial. Consequently, G6PD activity is assessed in red blood cells following the centrifuging of whole blood for 5 minutes at 6000 RPM.

1) Isolate plasma and buffy coat by Pasteur pipette. 2) Wash the RBCs thrice with 1x PBS (Phosphate Buffer Solution) for 5 minutes at 6000 RPM. 3) The count of WBCs should be lower than 5×10^3/L; if it is higher, steps 1 to 3 must be done again. 4) Adjust the hemoglobin level to 150 g/L with 1x PBS.

Control group

We selected a control group of children referred to the same laboratory center for a checkup with written informed consent from parents and no family history of G6PD deficiency. The activity level of G6PD was measured similarly to the case group.

G6PD activity test

G6PD catalyzes the first step in the pentose phosphate shunt, oxidizing glucose-6-phosphate (G-6-P) to 6-phosphogluconate (6-PG) and reducing NADP to NADPH. This procedure is a modification of the spectrophotometric methods of Betke K, and Beutler E [17, 18], involving the following reaction:

$$\text{G-6-P} + \text{NADP}^+ \xrightarrow{\text{G6PD}} \text{6-PG} + \text{NADPH} + \text{H}^+$$

G6PD reduces $NADP^+$ in the presence of G-6-P. NADPH's formation rate is proportional to the G6PD activity and is measured spectrophotometrically as an increase in absorbance at 340 nm by an automated analyzer (Hitachi 911, Tokyo, Japan). According to the reaction below, the production of a second molar equivalent of NADPH by erythrocyte 6-phosphogluconate dehydrogenase (6-PGDH) is prevented by the use of maleimide, an inhibitor of 6-PGDH.

$$\text{6-PG} + \text{NADP}^+ \xrightarrow{\text{6PGD}} \text{Ribulose-5-Phosphate} + \text{NADPH} + \text{H}^+ + \text{CO}_2$$

Red cell G6PD is stable in whole blood for one week refrigerated (2-8°C) but is unstable in red cell hemolysates. Freezing of blood is not recommended.

Since activity is reported in terms of grams of hemoglobin or the number of white blood cells, the hemoglobin concentration or WBC count must be determined before performing the G6PD activity, and in the last step, it should be normalized.

Reticulocytes have higher G6PD activity than mature RBCs. To accurately determine the mean of G6PD activity in ALL patients, the mean of G6PD activity was measured in the control group and then compared.

The assays should not be performed after a severe hemolytic crisis, since G6PD levels could seem falsely elevated. Under those conditions, detection of deficiency may require an exact family history. Testing may be performed after the level of mature RBCs has returned to normal. To diagnose a severe hemolytic crisis, we should consider total and direct bilirubin, LDH levels, positive hemoglobin in urine, and reticulocyte count, in addition to clinical symptoms such as sudden weakness, pallor, jaundice, dark urine, and rapid heartbeat. According to the kit from Biolabo SA (Maizy, France), the level of G6PD <1.5 IU/g of Hb was identified as severely deficient, 1.5-6.5 IU/g of Hb was considered as partially deficient, and levels ≥6.5 IU/g of Hb were regarded as sufficient.

Elimination of possible anemia effects on the G6PD test

In this research, to eliminate possible anemia effects on the G6PD test measurement process, a hematocrit test was performed on all samples before performing the G6PD enzyme level test. Samples with hematocrit lower than normal were separated. These samples were

centrifuged at low speed for twenty minutes (800 RPM). After centrifugation, according to the normal hematocrit, plasma was removed from the surface of these samples. Using the following formula, the amount of plasma that had to be removed from the surface of the sample was determined for the hematocrit of the sample to be within the normal range.

Plasma volume to be withdrawn (PVW) = patient sample plasma volume - corrected final plasma volume (CFPV). The amount of (CFPV) can be calculated as follows.

CPVR = (100-normal hematocrit) * sample plasma volume/(100-patient hematocrit).

Therefore, after mixing the sample again, its hematocrit, according to age and sex, was in the normal range. In this way, the effect of all types of anemia in the false underexpression of the G6PD enzyme was eliminated.

Statistical analysis

Data were analyzed by SPSS software (SPSS Inc., Chicago, IL, USA) version 21. Descriptive data were presented as mean, standard deviation, and percentage. Quantitative and qualitative data were compared between the two groups using the Student t-test and the Chi-square test, respectively - Correlate G6PD activity levels with leukemia activity markers using Pearson or Spearman correlation. Compare G6PD activity between patient groups (e.g., active disease vs. remission) using t-tests or Mann-Whitney tests. Use regression models to adjust for confounders (age, treatment, anemia). A *P* value less than 0.05 was considered statistically significant.

Results

In this cross-sectional, case-control study, 133 patients (56.4% males and 43.6% females) met enrollment criteria. The mean age of the patients was 6.98±4.44 years (range: 1.2-17 years). Ninety-nine (74.4%) patients were between 1 and 10 years of age, receiving the ALL standard-risk chemotherapy protocol. In addition, 34 (25.6%) patients were over the age of 10 who had received the ALL-high-risk chemotherapy protocol (P<0.001, 95% CI: 29.7%-62.6%). The mean G6PD activity of RBC in the age group between 1-10 years was 11.0±3.8 IU/g of Hb. Moreover, the mean G6PD activity of RBC in the age group over ten years was 11.3±4.0 IU/g of Hb with P=0.73 and P=0.17, respectively. Laboratory findings, history of admission, and follow-up time as clinical variables in the patient study are shown in **Table 2**.

113 patients had B-cell ALL, of which 44 (33.1%) were high-risk B-cell ALL, and 69 (51.9%) were standard-risk B-cell ALL. The remaining 20 patients (15%) belonged to the T cell ALL group.

In addition, the G6PD activity in RBC was measured in the control group (n=133) with the exclusion of G6PD-deficient individuals (5 patients) from the control group. Therefore, the mean G6PD activity of RBC in the control (n=133) and patient groups (n=128) was 9.1±2.08 IU/g of Hb and 11.12±3.8 IU/g of Hb, respectively, P<0.001 (95% CI: 8.73-9.45 and 10.93-12.10, respectively).

The 3-year overall survival (OS) in our study patients in the standard-risk group ALL was 80%. In addition, the 3-year OS of high-risk group ALL was 70.2% (P=0.007). **Figure 1A** and **1B** show Kaplan-Meier survival curves in standard and high-risk group ALL.

The 3-year event-free survival (EFS) in standard-risk group ALL was about 85.4%, and in a high-risk group, ALL was 52.5% (P=0.01) (**Figure 1A** and **1B**).

In our study, there were five leukemia patients (3.75%) who had a severe deficiency in G6PD activity in RBC (<1.5 IU/g of Hb), so they were disqualified from the evaluation of G6PD activity in RBC.

Due to the small number of G6PD deficiency patients (3.75%), statistical analysis and comparisons are not reliable in G6PD-deficient patients. A Pearson product-moment correlation coefficient was calculated to assess the relationship between the G6PD activity of RBC and age. There was no correlation between the two variables: r=0.043, n=133, and P=0.62.

There was no significant difference in the mean G6PD activity of RBCs in the high-risk group ALL with masking the age as high risk (M= 11.01, SD=2.44) and standard-risk group ALL (M=11.18, SD=4.45), t (131) =0.24, P=0.807.

Table 2. Laboratory findings, history of admission, and follow-up time as clinical variables in the patient study

Variables		Mean ± SD	
Age in years Mean, (Range)		6.98±4.44, (1.2-17 y)	
ALL (%)	B cell	113 (85%)	High risk: 44 (33%) Standard risk: 69 (52%)
	T cell	20 (15%)	
Follow-up time in a month Mean, (Range)		24.71±9.35, (2-72 Mo)	
Karyotype and Cytogenetic abnormality	No	93 (69.9%)	
	Yes	40 (30.1%); • Favorable (n=20) • Unfavorable (n=17) • No prognostic significance (n=3)	
History of Admission due to complications	Yes	79 (59.4%)	
	No	54 (40.6%)	
Hemoglobin		9.8±1.7 g/dl	
Mean corpuscular volume (MCV)		83.5±7 fl	
White Blood Cell (WBC)		5672.4±10651.8/µl	
Red Blood Cell (RBC)		$3.8\times10^6\pm0.7\times10^6$/µl	
Platelet		150135.1±144338.5/µl	
Lactate dehydrogenase (LDH)		953±1038 U/L	
Total Bilirubin		2.5±1.41 mg/dL	

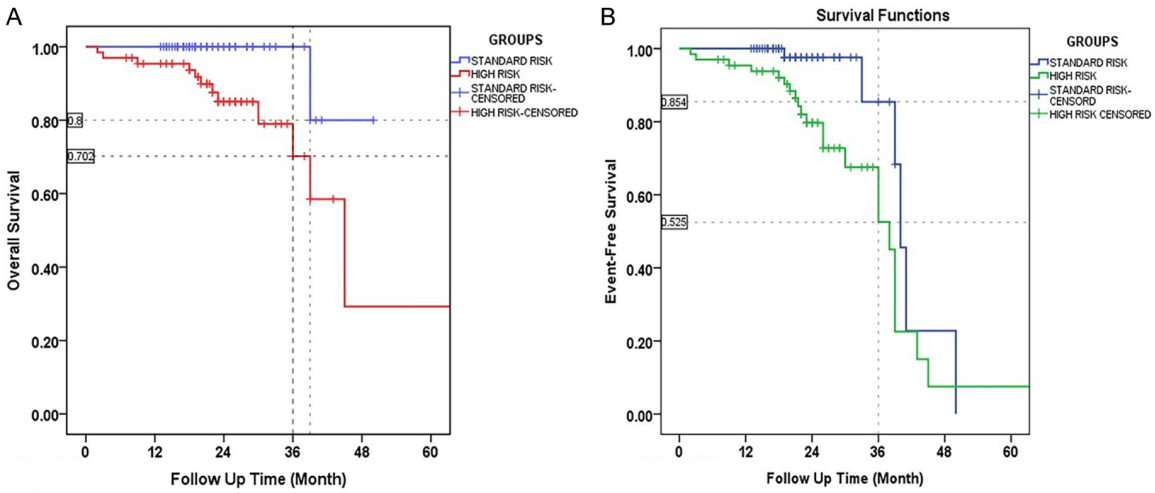

Figure 1. A. 3-Year overall survival in the study in standard and high-risk groups. B. 3-year event-free survival in the study in a standard and high-risk group.

Thirty-four studied patients (25.6%) had lymphoblasts during sampling (blastic phase) for G6PD activity in RBC.

In addition, the G6PD activity of RBC was measured in the blastic phase of ALL patients by the presence of lymphoblast cells in the peripheral blood smear documented with flow cytometry and compared with the non-blastic phase (patients in remission). There was a significant difference in the G6PD activity of RBC in the blastic and non-blastic phases of the disease, t (128) =-2.48, P=0.014.

Discussion

According to study results, the frequency of G6PD deficiency was 3.75% among leukemia patients in the study. In comparison, the prevalence of G6PD deficiency in our country is about

10-14.9% [19, 20], and also in our region, the prevalence of G6PD deficiency is about 12% [21]. Due to this, the prevalence of G6PD deficiency in leukemia patients seems low. To confirm this issue definitively, it is recommended to conduct studies with larger populations in areas with a higher frequency of G6PD deficiency. It may be due to the suppression of PPP in G6PD deficiency [22]. The blockage of PPP key enzymes, including G6PD, markedly influences cancer cell proliferation in vitro and in vivo [23].

Since then, the PPP has been a key in the glucose metabolism pathway, which is necessary for cancer cell growth and metastasis. Consequently, blocking PPP, as it occurs in G6PD deficiency, may correlate to the fact that G6PD-deficient subjects may have a lower prevalence of developing cancer and leukemia [6, 7, 22, 23].

The mean age of the study population was 6.98±4.44 years, compatible with the age prevalence of ALL in several studies [24-28]. For instance, Rahimi-Pordanjani et al. [29] analyzed the national registry and found a mean of 5.9 years, while hospital-based cohorts in Mashhad and Shiraz reported mean ages of ~5.6 and ~6.3 years, respectively [30, 31].

The mean G6PD activity of RBC was not statistically different between ALL patients of age group 1-10 years and over ten years (P 0.73). It seems that RBC's G6PD activity is not affected by age. Similarly, in a study performed by Azma, R. Z. et al. [32], there were no significant differences in G6PD activity of different age groups in pediatrics. However, there is little difference in age groups due to young RBCs in the bloodstream, which are more common in infants and gradually decrease with age. Young RBCs (reticulocytes) have higher G6PD activity than adult RBCs. Furthermore, contamination with high white blood cells during hemolysate preparation in infants may contribute to higher G6PD activity [32, 33].

The mean of G6PD activity in RBC was significantly higher in the ALL patient group compared to the control group (P<0.001). It is concluded that ALL patients have a higher G6PD activity, which is compatible with other studies that imply increased G6PD activity in cancer and leukemia [14, 16, 34, 35]. Batetta et al. showed that G6PD activity is strongly increased in leukemic cells (including in patients with hereditary G6PD deficiency) compared to normal peripheral blood mononuclear cells [36]. Silic-Benussi et al. revealed that mTOR inhibition downregulates glucose-6-phosphate dehydrogenase and induces ROS-dependent death in T-cell acute lymphoblastic leukemia cells. This work shows that T-ALL (a subtype of ALL) cells rely on high G6PD activity for survival [37].

It seems that the mechanism for increased G6PD activity in RBC may result from a derivation of some circulating red cells from the abnormal pluripotent stem cells in leukemia patients [14, 34, 35]. A pan-cancer analysis revealed that G6PD expression is upregulated in most cancers, including AML, and is linked to adverse prognostic factors such as shorter overall survival and progression-free interval. The increase in G6PD activity supports the enhanced pentose phosphate pathway flux, providing NADPH necessary for biosynthesis and antioxidant defense, which helps leukemic cells to proliferate and resist oxidative stress. [38-40]. Higher G6PD expression correlates with increased immune cell infiltration in the tumor microenvironment, suggesting a role in modulating immune responses [39]. Elevated G6PD levels are associated with resistance to various chemotherapeutic agents, indicating that G6PD may contribute to therapeutic challenges in leukemia treatment [40-42]. Yang et al. discovered that G6PD expression and activity are heightened in several malignancies. Numerous studies have shown elevated G6PD activity in tumor cells across various cancer types, including solid tumors such as bladder, endometrial, prostate, kidney, stomach, colon, lung, ovarian malignancies, and particularly in leukemias [43].

In the future, targeting the G6PD and PPP may probably help cancer therapy [35]. In addition, G6PD deficiency may have a protective role in cancer or be more sensitive to chemotherapy [22]. However, it is against the result of Ferraris AM (1988) that G6PD deficiency has no protective role in hematologic malignancies [13]. Xu et al. observed that SIRT2, a member of the sirtuin family of proteins, activates G6PD to promote leukemia cell proliferation and increase NADPH production. It illustrates that leukemia cells have increased G6PD activity, which facilitates their proliferation. Notably, clinical AML

samples exhibited a substantially higher G6PD catalytic activity than normal hematopoietic cells, thereby confirming that malignant leukemic cells upregulate the G6PD enzyme [44].

Catanzaro et al. showed that combining cisplatin treatment with inhibition of the PPP enzyme, like G6PD, can significantly increase the cytotoxic effects of cisplatin and can aid in overcoming cancer resistance to cisplatin treatment [45].

The blocking of PPP essential enzymes, including G6PD, significantly affects cancer cell proliferation in vitro and in vivo [23, 46]. G6PD is upregulated in several human cancers and is associated with poor prognosis [47]. Cancer patients with G6PD mutations, on the other hand, show more prolonged survival and decreased metastasis [48]. Additionally, G6PD activity can be controlled by oncogenes such as phosphatidylinositol 3-kinase (PI3K)-Akt, Ras, Src, mTORC1, or by oncosuppressors such as TP53 and TAp73 [6].

The 3-year OS and EFS in standard-risk ALL and high-risk ALL were 80% and 70.2% for OS and 85.4% and 52.5% for EFS, respectively (**Figure 1A** and **1B**). We should improve our care of high-risk patients, probably by using targeted or personalized therapy.

We can not evaluate and compare OS and EFS in G6PD deficient because the number of severely deficient patients was low and statistically not feasible.

The interesting finding in our study was the significantly higher G6PD activity of RBC in the blastic phase of leukemia (P=0.014). It seems that the existence of blasts in peripheral blood smears of leukemic patients, either in the acute phase or relapse phase, is associated with high G6PD activity. It may be due to hypoxia induced by a malignant cell that may cause overexpression of G6PD activity, leading to shunting the glucose flux into the PPP through activation of G6PD [12]. Therefore, overexpression of G6PD activity may be a warning sign for cancer patients. As shown in the study of Zhang Q et al. [49], high G6PD activity in patients with clear cell renal cell carcinoma is associated with metastasis, poor prognosis, and advanced disease. G6PD deficiency patients' leukemic cells showed higher levels of G6PD gene expression when compared to their normal counterparts [36]. Additionally, in a study by Dore MP et al. [50], G6PD deficiency is associated with decreased oxygen-free radical mutations and a decrease in nicotinamide-adenine dinucleotide phosphate to reduce replicating cancer cells and consequently reduce the risk of colorectal cancer.

In the study by Poulain et al., by using 6-aminonicotinamide, the G6PD inhibitor, the PPP can be targeted to create in vitro and in vivo cytotoxicity against AML cells and synergistically increase leukemic cells' susceptibility to chemotherapy. Their study shows that high levels of mTORC1 activity result in a specific vulnerability to G6PD inhibition, which could potentially be used as a new therapy for AML [51].

As a result, agents that target G6PD or PPP in ALL patients may help decrease malignant cell proliferation and antitumor activity; nevertheless, more extensive and multicenter studies with large populations are needed.

Conclusion

Assessing G6PD activity in leukemia patients may be pertinent for monitoring disease activity following a comprehensive multicenter study. The G6PD activity of red blood cells in the blastic phase of leukemia was elevated compared to that of the patient in remission (non-blastic phase). Consequently, factors that target G6PD or PPP in all patients may effectively diminish the proliferation of malignant cells.

Acknowledgements

This article was adapted from Dr. Nader Shakibazad's thesis on the subspecialty in pediatric hematology/oncology. The authors would like to thank the Research Vice-Chancellor of Shiraz University of Medical Sciences, Shiraz, Iran, for supporting the study with grant number 12037-01-01-95 and ethical research number IR.sums.med.rec.1395.s187. We greatly appreciate the Clinical Research Development Center and Ms. Neda Sadat Boyer as an editorial assistant.

Disclosure of conflict of interest

None.

Abbreviations

RBC, Red blood cell; WBC, white blood cells; G6PD, glucose 6-phosphate dehydrogenase; ALL, acute lymphoblastic leukemia; PPP, pentose phosphate pathway; HIF1α, hypoxia-inducible factor 1α; CBC, complete cell count test; LDH, lactate dehydrogenase; 6-PG, 6-phosphogluconate; 6-PGDH, 6-phosphogluconate dehydrogenase; OS, overall survival; EFS, event-free survival; PI3K, phosphatidylinositol 3-kinase.

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