Research Article / Araştırma Makalesi

The Vitamin C Level in Cases with Hematological Malignancies

Hematolojik Maligniteli Olgularda C Vitamini Seviyesi

Gülden SİNCAN [1], Fuat ERDEM [1], Ahmet KIZILTUNÇ [2]

[1]Department of Hematology, Medical School, Atatürk University, Erzurum, TÜRKİYE
[2]Department of Medical Biochemistry, Medical School, Atatürk University, Erzurum, TÜRKİYE

Abstract

Background: Oxidative stress plays a significant role in the pathogenesis of hematological malignancies. Vitamin C, known for its antioxidant properties, has garnered attention in this context. Therefore, we investigated vitamin C levels in patients with hematological malignancies and evaluated the relationship between vitamin C levels and response to treatment.
Materials and Methods: Our study examined 150 cases of hematological malignancies and 30 healthy cases. The vitamin C levels of patients with hematological malignancies were compared with those of the healthy group.
Results: Vitamin C levels in cases of acute myeloblastic leukemia (n=30) (p<0.001), acute lymphoblastic leukemia (n=30) (p<0.001), Hodgkin lymphoma (n=30) (p<0.001), diffuse large B-cell lymphoma (n=30) (p<0.001), and multiple myeloma (n=30) (p<0.001) were significantly lower compared to healthy individuals. There was a significant relationship between vitamin C levels and the response to treatment in cases with acute myeloblastic leukemia, acute lymphoblastic leukemia, Hodgkin lymphoma, diffuse large B-cell lymphoma, and multiple myeloma (p=0.020, p=0.020, p=0.040, p<0.001, p<0.001, respectively). In Hodgkin and non-Hodgkin lymphoma cases, a negative correlation was found between vitamin C levels and LDH and beta-2 microglobulin levels (p=0.001; p=0.008; p=0.017; p=0.019, respectively).
Conclusions: Our study underscores the lower levels of vitamin C in patients with hematological malignancies compared to healthy individuals. Furthermore, the findings suggest that vitamin C levels could serve as a potential biomarker for predicting the response to treatment in these cases.

Keywords: Hematological malignancies, Vitamin C, Oxidative stress

Öz

Amaç: Oksidatif stres, hematolojik malignitelerin patogenezinde önemli bir rol oynamaktadır. Antioksidan özellikleri ile bilinen C vitamini, bu bağlamda dikkat çekmektedir. Bu nedenle, çalışmamız hematolojik malignitelerde C vitamini seviyelerini araştırmayı ve C vitamini düzeyi ile tedaviye yanıt arasındaki ilişkiyi değerlendirmeyi amaçlamıştır.
Materyal ve Metod: Çalışmamızda 150 hematolojik malignite vakası ve 30 sağlıklı vaka incelendi. Hematolojik malignite vakalarının C vitamini seviyeleri, sağlıklı grup ile karşılaştırıldı.
Bulgular: Akut miyeloblastik lösemi (n=30) (p<0.001), akut lenfoblastik lösemi (n=30) (p<0.001), Hodgkin lenfoma (n=30) (p<0.001), diffüz büyük B-hücreli lenfoma (n=30) (p<0.001) ve multipl miyelom (n=30) (p<0.001) vakalarında C vitamini seviyeleri, sağlıklı bireylerle karşılaştırıldığında anlamlı derecede düşüktü. Akut miyeloblastik lösemi, akut lenfoblastik lösemi, Hodgkin lenfoma, diffüz büyük B-hücreli lenfoma ve multipl miyeloma vakalarında C vitamini seviyeleri ile kemoterapiye yanıt arasında anlamlı bir ilişki bulundu (sırasıyla p=0.020, p=0.020, p=0.040, p<0.001, p<0.001). Hodgkin lenfoma ve non-Hodgkin lenfoma vakalarında, C vitamini seviyeleri ile laktat dehidrogenaz ve beta-2 mikroglobulin seviyeleri arasında negatif bir korelasyon bulundu (sırasıyla r=-0.59, p=0.001; r=-0.47, p=0.008; r=-0.43, p=0.017; r=-0.42, p=0.019).
Sonuç: Çalışmamız, hematolojik malignitelerde sağlıklı bireylerle karşılaştırıldığında C vitamini seviyelerinin daha düşük olduğunu vurgulamaktadır. Ayrıca, bulgular, C vitamini seviyelerinin bu vakalarda kemoterapiye yanıtı öngörmek için potansiyel bir biyobelirteç olarak hizmet edebileceğini önermektedir.

Anahtar Kelimeler: Hematolojik maligniteler, C vitamini, Oksidatif stres

Corresponding Author / Sorumlu Yazar

Dr. Gülden SİNCAN
Atatürk University Yakutiye Research Hospital Atatürk University Campus, 25240 Yakutiye/Erzurum

E-mail: guldensincan@gmail.com

Received / Geliş tarihi: 24.03.2024

Accepted / Kabul tarihi: 23.09.2024

DOI: 10.35440/hutfd.1458028

Introduction

The etiopathogenesis of hematological malignancies remains elusive, but oxidative stress is considered a key contributor to oncohematologic cancer development (1). This imbalance between reactive oxygen radicals and antioxidant defenses leads to an excess of reactive oxygen radicals, causing oxidative damage to proteins, lipids, and DNA (2). Oxidative stress induces oxidative modifications of proteins, lipid peroxidation, and DNA damage. Reactive oxygen radicals influence cell proliferation by affecting signaling pathways such as Ras/mitogen-activated protein kinase, nuclear factor κ-light-chain-enhancer of activated B cells, phosphatidylinositol 3-kinase/protein kinase B, and by increasing the release of vascular endothelial growth factor (3). Oxidative stress triggers the genetic expression of inflammatory cytokines, chemokines, and cell cycle regulatory molecules (1). All of these factors contribute to carcinogenesis by promoting cell proliferation and migration (4,5).

Hematopoietic cells are particularly susceptible to oxidative stress (6). Chronic inflammation fueled by oxidative stress, is a key driver in the etiopathogenesis of hematological malignancies (1). Oxidative stress has been implicated in the development of lymphomas, myeloma, and leukemias (7-10). In lymphoma, increased reactive oxygen radicals due to hypoxic conditions create a favorable microenvironment for cancer cell growth (10). In multiple myeloma, oxidative stress perpetuates an inflammatory tumor microenvironment and accelerates genetic mutations.

Vitamin C is an essential, water-soluble vitamin with antioxidant properties that protects DNA from damage caused by free radicals (11). Humans cannot produce vitamin C, so it must be obtained through the diet (12). Vitamin C serves as a cofactor for the enzymes required in hydroxylation reactions, maintaining metal ions within these enzymes in a reduced state to activate them and exhibit antioxidant effects (13). It also inhibits the formation of carcinogens like nitrosamines (14). The relationship between vitamin C and cancer is not yet fully understood. Vitamin C deficiency is more common in cancer patients, and this may be due to oral intake disorders in cancer patients (15). Additionally, metabolism disorders related to vitamin C, such as decreased bioavailability and increased vitamin C use, can occur in cancer patients (16). The effects of vitamin C treatment on cancer yield conflicting results (17,18). Vitamin C is also effective in reducing symptoms associated with cancer, such as loss of appetite, weakness, and insomnia (19).

Oxidative stress is a well-recognized contributor to the pathogenesis of acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), chronic myeloid leukemia (CML), and myelodysplastic syndrome (MDS) (20-23). Vitamin C is an antioxidant vitamin. However, the relationship between vitamin C levels and outcomes in hematological malignancies remains unclear. This study aimed to investigate vitamin C levels and their association with treatment response in patients with hematological malignancies.

Materials and Methods

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Atatürk University School of Medicine (date: 02.06.2022, approval number: B.30.2.ATA.0.01.00/460). An informed consent form was obtained from all participants.

The study included patients from the hematology clinic and outpatient clinic of Atatürk University School of Medicine Hospital who were newly diagnosed with AML, ALL, multiple myeloma (MM), Hodgkin Lymphoma (HL), and diffuse large B-cell lymphoma (DLBCL). Additionally, 30 healthy individuals were included as a control group. Control subjects were free from chronic systemic diseases, infections, and inflammatory conditions and were selected from patients undergoing routine blood tests in the internal medicine outpatient clinic. Hematological malignancies were diagnosed according to international guidelines (24-26). Initial treatment response was assesed as follows: Hodgkin lymphoma patients received 2 cycles of doxorubicin+vinblastine+dacarbazine+bleomycin (ABVD), DLBCL patients received 4 cycles of rituximab+cyclophosphamide+doxorubicin+vincristine+prednisone (RCHOP), MM patients received 4 cycles of bortezomib+cyclophosphamide+dexamethasone (VCD), AML patients received 1 cycle of cytarabine+anthracycline (7+3), ALL patients under 35 years received ALL-Berlin-Frankfurt-Münster (BFM) induction therapy, and ALL patients over 35 years received 1 cycle of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) treatment.

Response to treatment in HL and DLBCL cases was evaluated according to the International Harmonization Project criteria (27). If all FDG-avid lesions showed complete regression on post-treatment PET-CT and bone marrow biopsy was negative, it was considered a complete response. If there was more than a 50% reduction in lesion size and at least one lesion showed FDG uptake, it was considered a partial response. The disease was considered progressive if there were new FDG-avid lesions, more than a 50% increase in lesion size with FDG uptake, or new/relapsed bone marrow involvement. Response to treatment in MM cases was evaluated according to the criteria of the International Myeloma Working Group (28). Response to treatment in AML cases was evaluated according to the criteria revised by the European Leukemia Net group in 2022. Complete remission was defined as: bone marrow blasts < 5%, no blasts in peripheral blood, no extramedullary disease, absolute neutrophil count ≥ 1,000/μL, and platelet count ≥ 100,000/μL (25).

To determine the vitamin C levels, 10 ml of blood was collected from each subject and centrifuged at approximately 3000 RPM for 5 minutes. The isolated plasma was stored at -80°C until analysis. After thawing under appropriate conditions, all plasma samples were analyzed in a single session at the Medical Biochemistry Laboratory of Atatürk University Health Research and Application Center. A commercial human vitamin C ELISA kit (96 tests, BT-LAB) was used according to the manufacturer's protocol.

Routine laboratory tests performed on all patients included a complete blood count, sedimentation rate, C-reactive protein (CRP), and a comprehensive biochemical panel. Additional tests for beta-2 microglobulin, immunoglobulin levels, protein electrophoresis, and immunofixation electrophoresis were conducted in patients with lymphoma and MM. Genetic testing was performed on all patients according to international guidelines in the medical genetics laboratory (25,26). The results of these routine tests were obtained from the hospital database.

Lymphoma staging was conducted according to the Ann Arbor staging system (29). All DLBCL patients underwent bone marrow biopsy to assess bone marrow involvement. For HL patients, bone marrow involvement was initially evaluated with positron emission tomography-computed tomography (PET-CT). If PET-CT was negative for bone marrow involvement, a bone marrow biopsy was subsequently performed.

Statistical analyses was conducted using SPSS 20.0 (SPSS, Chicago, IL, United States). Normality of data distribution was assessed using the Kolmogorov-Smirnov test. Descriptive statistical methods were used to evaluate data. Independent sample T-test was used for two-group comparisons with normal distribution, while the Mann-Whitney U test was used for two-group comparisons without normal distribution. One-way analysis of variance (ANOVA) was utilized for comparing quantitative variables among more than two groups with normal distribution, and the Kruskal-Wallis test with Dunn's post-hoc test for non-normally distributed data. The correlation between quantitative variables was evaluated using Pearson and Spearman correlation analyses. Statistical significance was accepted at $p<0.05$.

Results

In our study, we examined a total of 30 HL, 30 DLBCL, 30 MM, 30 AML, and 30 ALL patients, as well as 30 healthy individuals. The groups were not similar in terms of age (p=0.018) but were similar in terms of gender distribution (p=0.820) (Table 1). The vitamin C levels of the HL (59.62±26.12), DLBCL (56.05±6.39), MM (47.37±18.17), AML (54.25±21.16), and ALL (62.6±20.97) subgroups were significantly lower than the control group (113.54±29.17) (p<0.001). However, the vitamin C levels among the hematological malignancy subgroups did not significantly differ from each other.

The relationship between disease stage, bulky disease, B symptoms, bone marrow infiltration, performance status, extranodal involvement, treatment response and vitamin C levels in HL patients shown in Table 2. A negative correlation was found between vitamin C levels and both lactate dehydrogenase and beta-2 microglobulin values (r=-0.59, p=0.001; r=-0.47, p=0.008).

Table 1. Distribution of Age and Gender in Groups

Parameters	Diffuse Large B-cell Lymphoma	Hodgkin Lymphoma	Multiple Myeloma	Acute Myeloid Leukemia	Acute Lymphoblastic Leukemia	Control Group	P Value
Age (M± SD)	52.8±12.1	45.7±12.6	54.1±7.5	49.03±10.97	44.03±17.27	46.08±13.4	0.018
Female n(%)	14 (46.7%)	15 (50%)	16 (53.3%)	14 (46.7%)	16 (53.3%)	15 (50%)	0.820
Male n(%)	16 (53.3%)	15 (50%)	14 (46.7%)	16 (53.3%)	14 (46.7%)	15 (50%)	

M- Mean; SD- Standart Deviation

Table 2. The Relationship Between Clinical Characteristics of Hodgkin Lymphoma Cases and Vitamin C.

Parameters		Vitamin C level	P value
Hodgkin Lymphoma Risk Group	Early Stage- Favorable	79.4±20.21	0.006
	Early Stage Unfavorable	66.11±13.75	
	Advanced Stage	48.95±17.8	
Ann-Arbor Stage	Stage 1	67.33±16.31	0.042
	Stage 2	64.22±25.56	
	Stage 3	60.92±7.59	
	Stage 4	34.92±17.16	
Bulky Mass	Present	54.2±5.04	0.050
	Absent	64.65 ±13.6	
B Symptoms	Present	52.45±25.23	0.040
	Absent	69.09±14.03	
Bone Marrow Infiltration	Present	53.12±7.2	0.040
	Absent	62.58±23.09	
Response to Treatment	Complete Remission	67.42±20.14	0.028
	Partial Remission	55.48±15.68	
	Progressive Disease	38.4±20.68	
ECOG Performance Status	ECOG 0	77.37±26.77	0.013
	ECOG 1	63.12±14.68	
	ECOG 2	55.83±7.94	
Extranodal Involvement	Present	51.1±14.77	0.040
	Absent	62.21±22.8	

The relationship between vitamin C levels and disease stage, bulky mass, B symptoms, bone marrow involvement, performance status, response to treatment, revised international prognostic score, and extranodal involvement in the DLBCL group was presented in Table 3. A negative correlation was found between vitamin C levels and LDH and beta-2 microglobulin values (r=-0.43, p=0.017; r=-0.42, p=0.019, respectively).

The relationship between vitamin C levels and disease stage, bone lesions and fractures, performance status, and response to treatment in the MM group was presented in Table 4. Vitamin C levels were negatively correlated with sedimentation rate, beta-2 microglobulin, plasma cell percentage in bone marrow, and globülin level (r=-0.51, p=0.004; r=-0.34, p=0.030; r=-0.48, p=0.040; r=-0.6, p=0.020, respectively).

Table 3. The Relationship Between Vitamin C Levels and Clinical Findings in Diffuse Large B-Cell Lymphoma Cases.

Parameters		Vitamin C level	P Value
Ann Arbor Stage	Stage 1	61.48±5.47	0.020
	Stage 2	55.48±4.9	
	Stage 3	54.02±5.71	
	Stage 4	52.5±6.52	
Bulky Mass	Present	50.16 ±1.63	0.030
	Absent	60.82±1.14	
B Symptoms	Present	44.04±1.83	0.020
	Absent	61.21±1.47	
Bone Marrow Infiltration	Present	43.32±1.33	0.030
	Absent	55.59±1.35	
Response to Treatment	Complete Remission	59.52±6.37	0.020
	Partial Remission	56.3±2.35	
	Progressive Disease	48.32±5.85	
ECOG Performance Status	ECOG 0	61.58±6.66	0.030
	ECOG 1	55.5±5.44	
	ECOG 2	54±4.64	
	ECOG 3	52.06±6.38	
Revised IPI Score	1	63.7±3.45	<0.001
	2	54.36±3.77	
	3	48.32±5.85	
Extranodal Involvement	Present	50.11±5.58	0.008
	Absent	57.53±5.77	

Table 4. The Relationship Between Vitamin C Levels and Clinical Findings in Multiple Myeloma Cases.

Parameters		Vitamin C level	P Value
Bone Fracture	Present	29.73±24.55	0.006
	Absent	51.77 ±13.55	
Bone Lesion	Present	43.45±18.9	0.030
	Absent	60.24±5.75	
International Staging System Stage	Stage 1	61.54±5.18	<0.001
	Stage 2	57.18±4.11	
	Stage 3	37.65±17.62	
Response to Treatment	Complete Remission	54.88±17.83	0.040
	Partial Remission	49.8±11.84	
	Very Good Partial Response	43.36±19.37	
	Progressive Disease	20.15±9.8	
ECOG Performance Status	ECOG 0	59.05±4.31	0.040
	ECOG 1	55.2±5.6	
	ECOG 2	50.12±54.14	
	ECOG 3	42.74±20.5	

The relationship between vitamin C levels and European Leukemia Net risk assessment, performance status, and response to treatment in the AML group was shown in Table 5. A negative correlation was observed between vitamin C levels and LDH, uric acid, and blast count in bone marrow (r=-0.8, p=0.040; r=-0.7, p=0.050, r=-0.6, p=0.040, respectively).

The relationship between vitamin C levels and central nervous system involvement, B or T-cell ALL, ALL risk group, performance score, and response to treatment in the ALL group was presented in Table 6. Vitamin C levels were negatively correlated with the blast count in the bone marrow and LDH values (r=-0.67, p=0.001; r=-0.58, p=0.020, respectively).

Table 5. The Relationship Between Vitamin C Levels and Clinical Status in Acute Myeloid Leukemia Group.

Parameters		Vitamin C level	P Value
European Leukemia Net Risk Group	Favorable	66.84±11.75	0.010
	İntermediate	50.9±26.6	
	Adverse	39.55±13.84	
Response to Treatment	Complete Remission	66.79±11.87	<0.001
	Not in Complete Remission	37.84±19.5	
ECOG Performance Status	ECOG 0	64.31±17.77	0.027
	ECOG 1	56.36±19.2	
	ECOG 2	35.18±20.91	

Table 6. The Relationship Between Clinical Features of Acute Lymphoblastic Leukemia Group and Vitamin C Levels.

Parameters		Vitamin C level	P Value
Central Nervous System Involvement	Present	58.09±15.54	0.040
	Absent	51.62 ±28.5	
ALL subtype	B-ALL	68.9±17.3	0.070
	T-ALL	55.37±22.5	
ALL risk group	High-risk group	46.33±24.36	0.010
	Non-high risk group	64.4±17.2	
Response to Treatment	Complete Remission	76.38±8.57	<0.001
	Not in Complete Remission	50.54±21.32	
ECOG Performance Status	ECOG 0	64.9±18	0.040
	ECOG 1	60.68±24.6	
	ECOG 2	53.78±17.7	

Discussion

Previous studies have reported lower vitamin C levels in patients with solid organ malignancies (30). Low vitamin C levels have also been reported in hematological malignancies such as leukemia, lymphoma, and myeloma (31-35). However, there is a lack of sufficient research on vitamin C levels in patients with hematological malignancies and its clinical and prognostic significance. Our findings corroborate previous research by demonstrating lower vitamin C levels in patients with hematological malignancies compared to healthy controls. Furthermore, the identification of significant correlations between vitamin C levels and specific prognostic markers suggests its potential as a predictive biomarker for treatment response.

Previous studies have reported decreased serum vitamin C levels in leukemia patients, attributed to increased white blood cell consumption and elevated hyaluronidase activity (31). Our findings align with these reports, demonstrating lower serum vitamin C levels in AML and ALL patients compared to healthy controls. Furthermore, the observed negative correlation between serum vitamin C levels and bone marrow blast count in both AML and ALL patients supports the hypothesis that increased blast cell proliferation contributes to vitamin C depletion.

In non-Hodgkin lymphoma patients, especially those with bulky masses, low vitamin C levels have been reported (33). The presence of a bulky mass, LDH, and beta-2 microglobulin levels are parameters associated with disease burden in lymphoma and myeloma patients. In our study, we found that patients with bulky masses in HL and DLBCL had lower vitamin C levels. Additionally, we observed a negative correlation between vitamin C levels and beta-2 microglobulin and LDH values in HL and DLBCL patients, as well as a negative correlation between vitamin C levels and beta-2 microglobulin levels in MM patients. In leukemia patients, we found a negative correlation between vitamin C levels and LDH values. The proposed mechanism by which vitamin C exerts its anti-tumor effects involves inducing hydrogen peroxide accumulation, leading to tumor cell growth inhibition and apoptosis (36). Consequently, lower vitamin C levels may correlate with a higher tumor burden.

Ottone et al. reported no association between vitamin C levels and genetic mutations, cytogenetic findings, or 2017 ELN risk classification in AML patients (34). Conversely, our study identified a negative correlation between vitamin C levels and the 2022 ELN risk classification in AML cases. This discrepancy may be attributed to the different methodologies employed for vitamin C level assessment, with our study utilizing an ELISA kit and Ottone et al. using isocratic high-performance liquid chromatography.

T-cell ALL has a worse prognosis compared to B-cell ALL. In our study, we also found that vitamin C levels were lower in patients with T-cell ALL compared to those with B-cell ALL. Furthermore, we observed that high-risk ALL patients had lower vitamin C levels compared to others. Vitamin C has antioxidant properties. In ALL, the production of reactive oxygen species increases and antioxidant system functions deteriorate. Low vitamin C levels can lead to increased oxidative stress in ALL, causing the disease to progress. Additionally, low vitamin C levels can lead to epigenetic changes in ALL cells, contributing to the pathogenesis of T-cell ALL.Therefore, it seems that patients with acute leukemia and a worse prognosis have lower vitamin C levels, making it a potential prognostic biomarker.

High doses of vitamin C inhibit cell migration and angiogenesis (37). It has been reported that vitamin C treatment

disrupts tumor growth and eliminates cancer stem cells. Therefore, in our article, we evaluated the relationship between vitamin C levels and extramedullar involvement in lymphoma cases. In our study, we found that vitamin C levels were negatively correlated with extranodal involvement and disease stage in patients with HL and DLBCL, supporting the notion that serum vitamin C levels could be used as a marker for disease burden.

Vitamin C deficiency can lead to symptoms such as fatigue, weakness, and musculoskeletal ischemic pain by increasing inflammation (38). These symptoms can affect the performance status of individuals. In our study, we also found that vitamin C levels were correlated with the Eastern Cooperative Oncology Group (ECOG) performance score in patients with hematological malignancies.

Since vitamin C cannot be synthesized by humans and must be obtained through the diet, low serum vitamin C levels are often associated with oral intake disorders, particularly in cases with solid organ cancers. However, in patients with hematological malignancies, low serum vitamin C levels are often attributed to different mechanisms (31-35). In our study, we found that vitamin C levels were lower in patients with AML, ALL, HL, DLBCL, and MM compared to healthy individuals.

The effectiveness of vitamin C therapy in patients with hematological malignancies cases has yielded conflicting results. In our study, we found that vitamin C levels were correlated with response to treatment in all patients. Therefore, further studies are needed to investigate the efficacy of vitamin C therapy among the treatment of hematological malignancies.

Ethical Approval: *Approval was obtained from the Ethics Committee of Atatürk University (date: 02.06.2022, approval no: B.30.2.ATA.0.01.00/460).*

Author Contributions:
Concept: G.S, F.E, A.K
Literature Review: G.S
Design : G.S, F.E, A.K
Data acquisition: G.S
Analysis and interpretation: G.S
Writing manuscript: G.S
Critical revision of manuscript: F.E, A.K

Conflict of Interest: *The authors have no conflicts of interest to declare.*

Financial Disclosure: *This work was supported by the Department of Scientific Research Projects (BAP) of Atatürk University (Grant number: TSA-2022-11098).*

References

1. Imbesi S, Musolino C, Allegra A, Di Salvo E, Aragona CO, Bongiovanni A, et al. Oxidative stress in oncohematologic diseases: an update. Expert Rev Hematol. 2013;6(3):317-25.
2. Singh RK, Tripathi AK, Tripathi P, Singh S, Singh R, Ahmad R. Studies on biomarkers for oxidative stress in patients with chronic myeloid leukemia. Hematol Oncol Stem Cell Ther. 2009;2:285–288
3. Zhang J, Wang X, Vikash V, Smith A, Johnson B, Williams C, et al. ROS and ROS-mediated cellular signaling. Oxid Med Cell Longev. 2016;2016:4350965
4. Cheng D, Zhao L, Xu Y, Lee S, Kim D, Park E, et al. K-Ras promotes the non-small lung cancer cells survival by cooperating with sirtuin 1 and p27 under ROS stimulation. Tumour Biol. 2015;36:7221–7232.
5. Weyemi U, Lagente-Chevallier O, Boufraqech M, Patel K, Garcia-Ruiz C, Lee J, et al. ROS-generating NADPH oxidase NOX4 is a critical mediator in oncogenic H-Ras-induced DNA damage and subsequent senescence. Oncogene. 2012;31:1117–1129.
6. Sayre LM, Lin D, Yuan Q, Zhu X, Tang X. Protein adducts generated from products of lipid oxidation: focus on HNE and one. Drug Metab Rev. 2006;38:651–675.
7. Ahmad R, Tripathi AK, Tripathi P, Singh S, Singh R, Singh RK. Malondialdehyde and protein carbonyl as biomarkers for oxidative stress and disease progression in patients with chronic myeloid leukemia. In Vivo. 2008;22:525–528.
8. Al-Gayyar MMH, Eissa LA, Rabie AM, El-Gayar AM. Measurements of oxidative stress status and antioxidant activity in chronic leukaemia patients. J. Pharm. Pharmacol. 2007;59:409–417
9. Zima T, Spicka I, Stípek S, Nováková O, Novák F, Novotný L, et al. Antioxidant enzymes and lipid peroxidation in patients with multiple myeloma. Neoplasma. 1996;43:69–73.
10. Bur H, Haapasaari KM, Turpeenniemi-Hujanen T, Soini Y, Karihtala P, Leppä S, et al. Oxidative stress markers and mitochondrial antioxidant enzyme expression are increased in aggressive Hodgkin lymphomas. Histopathology. 2014;65:319–327
11. Iqbal K, Khan A, Ali Khan Khattak MM. Biological significance of ascorbic acid (Vitamin C) in human health. A review. Pakistan Journal of Nutrition. 2004;3:5-13
12. Drouin G, Godin JR, Pagé B. The genetics of Vitamin C loss in vertebrates. Current Genomics. 2011;12:371-378.
13. Levine M. New concepts in the biology and biochemistry ofascorbic acid. N Eng. J Med 1986;314:892-902.
14. Barrita JLS, Sánchez MDSS. Antioxidant role of ascorbic acid and his protective effects on chronic diseases. Oxidative Stress and Chronic Degenerative Diseases-A Role for Antioxidants. 2013;449.
15. Huijskens MJAJ, Wodzig WKWH, Walczak M, Germeraad WTV, Bos GMJ. Ascorbic acid serum levels are reduced in patients with hematological malignancies. Results Immunol 2016;6:8–10.
16. Chen Q, Polireddy K, Chen P, Dong R. The unpaved journey of vitamin C in cancer treatment. Can. J. Physiol. Pharmacol. 2015;93(12):1055-1063
17. Ngo B, Van Riper J M, Cantley L C, Yun J. Targeting cancer vulnerabilities with high-dose vitamin C. Nat Rev Cancer. 2019;19(5):271-282.
18. Pawlowska E, Szczepanska J, Blasiak J. Pro-and Antioxidant Effects of Vitamin C in Cancer in correspondence to Its Dietary and Pharmacological Concentrations. Oxid Med Cell Longev. 2019:7286737.
19. Carr AC, Vissers M, Cook JS. The effect of intravenous vitamin C on cancer-and chemotherapy-related fatigue and quality of life. Front Oncol. 2014;4:283.
20. Battisti V, Maders LD, Bagatini MD, Barbosa NV, Battisti IDE, Belle LP, et al. Measurement of oxidative stress and antioxidant status in acute lymphoblastic leukemia patients. Clin Biochem. 2008;41:511–518.

21. Pawlowska E, Blasiak J. DNA repair-a double-edged sword in the genomic stability of cancer cells-the case of chronic myeloid leukemia. Int J Mol Sci. 2015;16:27535–27549.
22. Chung YJ, Robert C, Gough SM, Rassool FV, Aplan PD. Oxidative stress leads to increased mutation frequency in a murine model of myelodysplastic syndrome. Leuk Res. 2014;38:95–102.
23. Hole PS, Darley RL, Tonks A. Do reactive oxygen species play a role in myeloid leukemias? Blood. 2011;117:5816–5826.
24. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organisation Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748.
25. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.
26. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36(7):1703-1719.
27. Hutchings M, Specht L. PET/CT in the management of haematological malignancies. European journal of haematology. 2008;80(5):369-80.
28. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17:e328–46
29. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.
30. White R, Nonis M, Pearson JF, Rumball C, Izzard M, Williams L, et al. Low Vitamin C Status in Patients With Cancer Is Associated With Patient and Tumor Characteristics. Nutrients. 2020;12:2338.
31. Pujari KN, Jadkar SP, Mashal SN, Belwalkar GJ, Kulkarni A, Patil CG. Variations in vitamin C levels in leukemias. Biomed Res. 2012;23:307-311
32. Liua M, Ohtania H, Zhoua W, Ørskovb AD, Charletc J, Zhangd YW. Vitamin C increases viral mimicry induced by 5-aza-2'-deoxycytidine. PNAS. 2016;113:10238-10244.
33. Shenoy N, Bhagat T, Nieves E, Stenson M, Lawson J, Choudhary GS. Upregulation of TET activity with ascorbic acid induces epigenetic modulation of lymphoma cells. Blood Cancer J. 2017;7:e587.
34. Ottone T, Faraoni I, Fucci G, Martini M, Venditti A, Testi AM, et al. Vitamin C Deficiency in Patients With Acute Myeloid Leukemia. Front Oncol. 2022;12:890344
35. Sharma A, Tripathi M, Satyam A, Kumar L. Study of antioxidant levels in patients with multiple myeloma. Leuk Lymphoma. 2009;50(5):809-815.
36. Ohno S, Ohno Y, Suzuki N, Soma G, Inoue M. High-dose vitamin C (ascorbic acid) therapy in the treatment of patients with advanced cancer. Anticancer Res. 2009;29:809–815.
37. Mikirova NA, Ichim TE, Riordan NH. Anti-angiogenic effect of high doses of ascorbic acid. J Transl Med. 2008;6(1):1-10.
38. Klimant E, Wright H, Rubin D, Seely D. Markman M. Intravenous vitamin C in the supportive care of cancer patients: A review and rational approach. Curr. Oncol. 2018;25:139