e-ISSN: 2980-0854

JCHOR

Journal of Current Hematology & Oncology Research

Volume: 2 Issue: 1 Year: 2024

MHA
MEDIHEALTH ACADEMY

Journal of Current
Hematology & Oncology
Research

EDITORIAL BOARD

EDITORS-IN-CHIEF

ASSOCIATE EDITORS-IN-CHIEF

EDITORIAL BOARD

Journal of Current
Hematology & Oncology
Research

EDITORIAL BOARD

Journal of Current
Hematology & Oncology
Research

EDITORIAL BOARD

Journal of Current
Hematology & Oncology
Research

EDITORIAL

Dear Colleagues,

I am pleased to announce that our journal has successfully completed its first year with great achievements. We have published a total of 12 original articles, 9 case reports, and 4 reviews, which have contributed significantly to the field of hematology-oncology. One of our short-term goals was to be indexed internationally, and I am proud to say that we have achieved it. Our journal is now indexed by indices that are considered international scientific journal indices, and this would not have been possible without the hard work and dedication of our editors, publishing team, authors, and the unwavering support of our relatives.

As we embark on the new year, I am delighted to inform you that our first issue has been published with 4 original articles, 1 case report, and 1 letter to the editor. This is a significant accomplishment, considering the challenges we faced in the past year. The earthquake disaster that struck our country has caused immense loss of lives, including some of our citizens and colleagues. We dedicate our first issue of the year to them, and we hope to continue their legacy by striving for excellence in the field of hematology-oncology.

Looking ahead, our goal is to expand our reach and contribute more to the scientific community. We aim to be included in other indexes and make a significant impact in the field. With your continued support and contributions, I am confident that we can achieve this goal and make our journal a valuable resource for researchers and practitioners in the field of hematology-oncology. Once again, I would like to express my sincere gratitude to everyone who has been a part of this journey and helped us reach this milestone. Let's continue to contribute more to the field of hematology-oncology with new publications.

Best Regards

Spec. Serhat ÇELİK, MD, PhD
Editor in Chief

Journal of Current
Hematology&Oncology
Research

CONTENTS

Volume: 2 Issue: 1 Year: 2024

ORIGINAL ARTICLES

CASE REPORT

LETTER TO THE EDITOR

Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0026

Effect of vitamin D on prognosis in patients with gastric cancer

Yasin Sezgin[1], İbrahim Aydın[2], Abdurrahman Biçer[2], Alper Can[3]

[1] Division of Medical Oncology, Department of Mecical Oncology, Faculty of Medicine, Yüzüncü Yıl University, Van, Turkiye
[2]Department of Internal Medicine, Van Training and Research Hospital, Van, Turkiye
[3]Department of Medical Oncology, İstinye University Medical Park Gaziosmanpaşa Hospital, İstanbul, Turkiye

Cite this article: Sezgin Y, Aydın İ, Biçer A, Can A. Effect of vitamin D on prognosis in patients with gastric cancer. *J Curr Hematol Oncol Res.* 2024;2(1):1-5.

Corresponding Author: Yasin Sezgin, dr.yasin1982@hotmail.com

Received: 08/12/2023 ◆ **Accepted**: 05/01/2024 ◆ **Published**: 12/02/2024

ABSTRACT

Aims: In the Eastern Anatolia Region of Turkiye it is estimated that the gastric cancer is seen more frequently compared to other regions. As is well known, a reduction in the incidence of certain cancers with high vitamin D value was identified, and vitamin D has been shown to have positive effects on the prognosis of these diseases. In our study, we aimed to investigate the relationship between vitamin D values before treatment and prognosis in patients with gastric cancer.

Methods: This study includes 76 patients who had diagnosis of gastric cancer for the first time and admitted to Oncology Clinic in Van Yüzüncü Yıl University (YYU) Faculty of Medicine Hospital. Patients inclusion criterias have been identified as lack of story for recently blood transfusion, treatment with any medication and being taken any mineral supplements. Patients vitamin D and tumor markers values were measured at diagnosis. Vitamin D values at diagnosis and stage of the disease, 6. 12. month mortality and disease progression were compared.

Results: A total of 76 patients were included in the study. Mean value of vitamin D was 16.1 (3-27). There was not a significant correlation between vitamin D value and stage of disease. Mean age was 60 (33-89). Of the patients 26 (34.2 percent) had no metastasis, 15 (19.2 percent) had only liver metastasis, 8 (10.5 percent) had only lung metastasis and 27 (35.5 percent) had two or more region metastasis.

Conclusion: In our study, vitamin D deficiency was present in all gastric cancer patients regardless of stage, indicating that vitamin D deficiency is a poor risk factor in gastric cancer.

Keywords: Gastric cancer, vitamin D value, prognosis

INTRODUCTION

Gastric cancer is one of the leading causes of cancer-related deaths worldwide, with a mortality rate of 9.4%.[1] Although the incidence and mortality of gastric cancer have decreased in recent years, it remains one of the top four causes of cancer-related deaths globally.[1,2] The reduction in mortality can be attributed to early detection of the disease.[3] The availability of laboratory tests and the widespread use of appropriate replacement therapies in cancer patients are estimated to decrease mortality. Gastric cancer is the fourth most common cancer worldwide. Early detection and control of risk factors are the most effective methods of prevention, given its low 5-year survival rate. According to data from the World Health Organization (WHO), the most common types of cancer worldwide are lung cancer (12.3%), breast cancer (10.4%), and colorectal cancer (9.4%). The leading causes of cancer-related deaths are lung cancer (17.8%), gastric cancer (10.4%), and liver cancer (8.8%).[5] Epidemiological studies indicate that smoking, Helicobacter pylori infection, and diet are significant risk factors for gastric cancer. Gastric cancer is believed to result from a complex interplay between environmental and genetic factors.[4]

Although vitamin D is primarily associated with calcium and bone metabolism, it has been shown to have various biological functions, including an anticancer effect. The first study in this area was Apprely's observation of the correlation between cancer mortality and solar radiation in North America.[6]

Intensive research on this subject began 35 years ago when Garland demonstrated the North-South relationship with cancer rates. High cancer incidences were found in the north and low in the south.[7] Gıovanunnuci's study supports the hypothesis that vitamin D is cancer-protective. These studies found that deaths from colon, prostate, and breast cancers were 30% lower in summer months compared to winter months. According to these studies, it is recommended that patients receive a daily replacement of 1000 IU of vitamin D, particularly during the winter months.[8]

It is estimated that gastric cancer is more prevalent in Eastern Anatolia than in other regions of Turkiye. High levels of vitamin D have been shown to reduce the incidence of certain cancers and have a positive impact on disease prognosis.[8] Studies have proven that high levels of vitamin D have a protective effect against prostate, breast, and colorectal cancers.[2-8] In this study, we aimed to investigate the relationship between pre-treatment vitamin D levels and the prognosis of patients diagnosed with gastric cancer.

METHODS

This study included 76 patients who were admitted to the Oncology outpatient clinic of Van Yüzüncü Yıl University (YYU) Faculty of Medicine Hospital and were diagnosed with gastric malignant neoplasm for the first time. The study population consisted of both genders and individuals over the age of 18. Patients were enrolled prior to the initiation of any treatment. The inclusion criteria for the patients were as follows: no recent history of blood transfusion and no current use of medication or mineral supplements for therapeutic purposes. All patients were questioned about their history of chronic liver and kidney disease, and a complete physical examination was performed.

Tumor markers and vitamin D levels were measured at the time of diagnosis. The study compared vitamin D levels at diagnosis with disease stage, 6- and 12-month mortality, and disease progression [radiologically or by positron emission tomography (PET)].

Venous blood samples (2-3 milliliters) were collected from each participant. Samples showing hemolysis were excluded. The blood was allowed to clot and then centrifuged at 3000 rpm for 15 minutes to separate the serum. The serum samples were stored in deionized polyethylene tubes and in a deep freezer at -80 degrees Celsius until the day of the study.

Biochemical analysis was conducted on blood samples obtained from the patients to determine CEA, CA 19-9, and vitamin D levels. The samples were analyzed using the chemiluminescence method on Arcitech CİI16200 (Abbott Agnostos IL USA).

The study received ethics committee approval from Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 05.05.2015, Decision No: 2015/13). The analyses were conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Descriptive statistics were used to express the emphasized characteristics as mean and standard deviation (Mean±SD). The groups were compared in terms of these characteristics using One-way analysis of variance (One-way ANOVA). A statistical significance level of 5% was used for calculations. The statistical package program SPSS for Windows version 13.0 was used.

RESULTS

A total of 76 patients who were diagnosed with gastric cancer and followed up and treated in the Department of Medical Oncology, Yüzüncü Yıl University Faculty of Medicine were included in the study. Of these, 47 (61.8%) were male and 29 (37.2%) were female. The male to female ratio was 1.62/1.

In the male group, 3 patients had stage 2, 11 patients had stage 3, 33 patients had stage 4 disease; in the female group, 4 patients had stage 2, 8 patients had stage 3, 17 patients had stage 4 disease. In total, 7 patients had stage 2, 19 patients had stage 3, and 50 patients had stage 4 disease.

The mean vitamin D level was 16.1 (3-27), 15.7 (13-18) in stage 2 patients, 16.9 (7-27) in stage 3, 15.9 (3-26) in stage 4 and no significant correlation was found between the stage of the disease and vitamin D level (**Table 1**).

Table 1. Vitamin D levels according to stages and comparison of vitamin D values according to stages

	Number	Mean	Std. Dev.	Std. err	Min.	Max.
Stage 2	7	15.7286	2.37397	.89727	13.20	18.90
Stage 3	19	16.9105	5.31318	1.21893	7.20	27.90
Stage 4	50	15.9660	4.52479	.63990	3.60	26.90
Total	76	16.1803	4.55927	.52298	3.60	27.90
	(I) Stage	(J) Stage		Std. err	P	
Tukey HSD						
	Stage 2	Stage 3		2.03417	.831	
		Stage 4		1.85665	.991	
	Stage 3	Stage 2		2.03417	.831	
		Stage 4		1.23991	.727	
	Stage 4	Stage 2		1.85665	.991	
		Stage 3		1.23991	.727	

The patients' mean age was 60 (33-89), with stage 2 patients having a mean age of 65 (46-89), stage 3 patients having a mean age of 60 (40-74), and stage 4 patients having a mean age of 60 (33-84). The mean CEA level for tumor markers was 57 (1-1000), and the mean CA 19-9 level was 189 (2-1200).

Metastases were absent in 26 patients (34.2%). The liver was the most common site of visceral metastasis. **Table 2** displays the frequency of metastases.

Table 2. Metastatic regions

	Frequency	Percentage
Null	26	34.2
Liver	15	19.7
Lung	8	10.5
2 and more regions	27	35.5
Total	76	100.0

Out of the patients, 28 (36.8%) received MDCF (modified docetaxel-cisplatin-5 fluorouracil), 10 (13.2%) received CF (cisplatin-5 fluorouracil), 11 (14.5%) received capecitabine, 16 (21.1%) received other treatments, and 11 (14.5%) received more than one treatment.

According to data from the World Health Organization, patients were divided into two groups based on their vitamin D levels: those with levels below 20 ng/ml[9] and those with levels above 20 ng/ml. At the 6-month tumor response evaluation, 34 patients progressed. All of these patients had vitamin D levels below 20 ng/ml. In contrast, no progression was detected in patients with vitamin D levels above 20 ng/ml at 6 months. There was a significant difference between these two groups (p:0.01) (**Table 3**).

Table 3. Progression according to 6. Month vitamin d levels

	Vitamin D		Total	Q-square
	<20	>20		P value
Progression at 6.month				0.01
No	30	12	42	
Yes	34	0	34	
Total	64	12	76	

At 12 months, progression was detected in 50 patients, 43 of whom had vitamin D levels below 20. The remaining 7 patients had vitamin D levels above 20. At 12 months, there was no significant difference in progression rates between the two groups (p=0.314). Please refer to **Table 4** for more information.

Table 4. Progression by 12th month vitamin d levels

	Vitamin D		Total	q-square
	<20	>20		P value
Progression at 12. month				0.314
None	16	5	21	
Yes	43	7	50	
Total	59	12	71	

DISCUSSION

Although the incidence and mortality rates of gastric cancer have decreased worldwide in recent years, it remains the 4th most common cancer and the 3rd most common cause of cancer-related deaths.[10] According to the Surveillance, Epidemiology and End Results (SEER) database, it accounts for 1.6% of new cancer cases in the United States.

In Turkiye, the situation is different, and stomach cancer ranks 5th in men and 6th in women in terms of incidence (Globocan 2013 data). Memik et al.[11] found significant differences in gastric cancer incidence between the eastern and western regions of the country. Gastric cancer accounted for 9.4% of all cancers. In a 2003 study of 1002 cases in the Van Lake basin, Tuncer et al.[12] reported that gastric cancer was the most common gastrointestinal malignancy, comprising 47% of cases. The study reported a male/female ratio of 2/1 and mean ages of 55 for women and 58 for men.

Vitamins are essential for the body and refer to substances that cannot be produced internally and must be obtained through food. Vitamin D, one of the most important vitamins, is also a hormone, unlike other vitamins. Approximately 80-90% of this steroid hormone is synthesized endogenously in the skin, while the remaining 10-20% is obtained exogenously from plant and animal sources through diet. The circulating serum concentrations of 1,25(OH)2D3 are approximately 0.1% of 25OHD3. Vitamin D synthesis is primarily regulated by the key enzyme 1α-hydroxylase, which is in turn regulated by parathormone, calcium, 1,25(OH)2D3, and fibroblast growth factor-23 (FGF-23). The activation of 1,25(OH)2D3 occurs through binding to vitamin D receptors. This receptor belongs to the steroid receptor family and is found in both the cytoplasm and nucleus. This receptor belongs to the steroid receptor family and is found in both the cytoplasm and nucleus. It regulates the expression of approximately 500 genes.

Vitamin D, which mainly regulates Ca and P metabolism, binds to nuclear receptors and increases intestinal Ca and P absorption by increasing the synthesis of proteins required for absorption. It also increases the reabsorption of Ca and P from the kidney. Stimulating osteoblasts in bone, increases Ca release, thus promoting bone mineralization and balancing the storage and release of Ca and P in bone. Vitamin D plays a major role in maintaining appropriate plasma Ca levels.

Vitamin D deficiency has been associated with various disorders, including diabetes, hypertension, cardiovascular diseases, infections, autoimmunity, asthma, obesity, skin diseases, muscle diseases, and cancer. It is estimated that 15-20% of the global population has a vitamin D deficiency. Studies in our country have also shown high rates of vitamin D deficiency, reaching up to 80% in women of reproductive age. The primary cause of vitamin D deficiency is insufficient exposure to sunlight. Low dietary intake, increased loss of vitamin D (such as in nephrotic syndrome), impaired vitamin D activation, and various drugs are causes of vitamin D deficiency.

The relationship between vitamin D and cancer was first established observationally by Frank L. Apeerly in 1940. People living in the north of the United States were found to have a 2 times higher risk of death due to cancer than those living in the south.

The incidence and survival of renal cell cancer were found to be affected by low vitamin D levels in the European Prospective Investigation into Cancer and Nutrition (EPIC) study conducted by Muller et al.[13] among renal cell cancer patients.

A review by Barreto et al.[14] explored the potential of vitamin D and its analogs in preventing and treating pancreatic cancer. The study found that pancreatic cancer tissue expresses vitamin D receptors and that vitamin D may have an impact on pancreatic cancer.

Another study published in the same year by Abulkhair et al.[15] observed that low levels of vitamin D at baseline in breast cancer patients increased the risk of triple negative breast cancer with poor prognosis.

A study conducted on American men found that the incidence and mortality of gastrointestinal cancer was higher in the black race compared to the white race. The study also found that low vitamin D levels were associated with high cancer incidence and mortality in the black race.[16]

In the early 1980s, Colston et al.[17] demonstrated that the doubling time of malignant melanoma cells was extended after incubation with active vitamin D. During the same period, Abe et al.[18] found that leukemia cells differentiated towards the macrophage series after incubation with vitamin D.

Vitamin D is believed to have anti-neoplastic properties through inhibiting proliferation, inducing differentiation and programmed cell death, as well as inhibiting angiogenesis and invasiveness.[19]

In a separate study, SCC cells were photographed two days after treatment with either ethanol or vitamin D. Flow cytometric analysis was then performed. The cells treated with vitamin D were found to be flattened, and there was a significant increase in the number of cells undergoing apoptosis with flow.[20]

The study found that vitamin D deficiency was an independent factor in cancer mortality but not a risk factor in cancer development.[21]

A study conducted in elderly women investigated the relationship between vitamin D and cancer-specific mortality. Another UK-based study investigated the relationship between vitamin D replacement and cancer incidence. In this randomised, placebo-controlled study, 2686 men and women over 65 years of age received vitamin D3 replacement at a dose of 100,000 IU every 4 months. The study found no significant difference in cancer incidence during the 5-year follow-up compared to the placebo group.[22]

The relationship between vitamin D and gastric cancer has been studied less than other types of cancer. Khayatzadeh et al.[23] found no significant relationship between vitamin D and gastric cancer risk. However, Ren et al.[24] discovered that

vitamin D deficiency was a poor prognostic factor in patients with gastric cancer. Patients with serum vitamin D levels of 50 nmol/L and above had significantly longer overall survival. In their 2012 publication, Sungmin Beak et al.[25] demonstrated that vitamin D treatment inhibits gastric cancer cells.

Abnet et al.[26] conducted a study on the relationship between vitamin D and upper gastrointestinal system tumours. The study found no significant correlation between serum vitamin D levels and the risk of upper gastrointestinal system cancer.

Most studies on the topic suggest a weak correlation between serum vitamin D levels and cancer incidence. However, most of the studies on the correlation between serum vitamin D levels and cancer incidence were conducted in regions with intense vitamin D deficiency, and they were mostly epidemiological or experimental. Therefore, it is unclear whether there is a negative correlation between serum vitamin D levels and cancer incidence in areas with normal serum vitamin D levels.

The role of vitamin D in the etiopathogenesis and prognosis of gastric cancer remains unclear. No significant evidence suggests a relationship between vitamin D levels and gastric cancer risk. This study analyses the vitamin D levels at the time of diagnosis and their relationship with overall survival in patients diagnosed with gastric cancer.

Despite being one of the sunniest regions of Turkiye, vitamin D deficiency is observed more frequently than expected in Van province and its surroundings. All patients diagnosed with gastric cancer in our study had low levels of vitamin D. This suggests that vitamin D may be involved in the development of the disease.

In our study, we compared patients with vitamin D levels below 20 ng/ml and above 20 ng/ml. When the progressions of these patients at 6 and 12 months were evaluated, a statistically significant difference in progression-free survival at 6 months and a numerical difference at 12 months was found in the group with vitamin D levels below 20 ng/ml.

The American Institute of Medicine's 2011 report highlighted the beneficial impact of vitamin D on skeletal health. However, the report also noted that there is insufficient evidence to support the use of vitamin D for cancer chemoprevention and treatment.

While vitamin D deficiency is a known cause of colorectal cancer, vitamin D treatment has been found to play a role in colon cancer. Additionally, vitamin D deficiency is an independent risk factor for prostate cancer. Low levels of vitamin D may contribute to the high incidence of gastric cancer in the Van-Erzerum region compared to other regions. Our study found that patients with all stages of gastric cancer had low levels of vitamin D.

Limitations

The study had limitations, including being single-centre, retrospective, and having a small number of patients. Additionally, hormonal disorders that affect calcium metabolism and conditions such as renal insufficiency were not analyzed, which were other limitations of this study.

CONCLUSION

Our study found that vitamin D deficiency is an independent risk factor for many cancers, particularly colon and prostate cancer. Low vitamin D levels were observed in all cases, and patients with lower vitamin D levels at the 6th and 12th months had worse PFS. Low vitamin D levels were observed in all cases, and patients with lower vitamin D levels at the 6th and 12th months had worse PFS. It is important to note that these findings are objective and not influenced by subjective evaluations. Based on this data, it is suggested that a low level of vitamin D may increase the incidence of gastric cancer and act as a poor prognostic factor. However, further support is required through multicentre, prospective studies with larger patient cohorts.

ETHICAL DECLARATIONS

Ethics Committee Approval

The ethics committee approval of the study was obtained from Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 05.05.2015, Decision No: 2015/13).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Shah MA, Kelsen DP. Gastric cancer: a primer on the epidemiology and biolgy of the disease and onerview of the medical management of advanced disease. *J Atl Compr Canc Netw.* 2010;8(4):437-447.
2. Holick MF. Vitamin D: its role in cancer prevention and treatment. *Prog Biophys Mol Biol.* 2006;92(1):49-59.
3. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. *CA Cancer J Clin.* 2002;52(1):23-47.
4. Boccia S, La Torre G, Gianfagna F, Mannocci A, Ricciardi G. Glutathione S-transferase T1 status and gastric cancer risk: a meta-analysis of the literature. *Mutagenesis.* 2006;21(2):115-123.
5. Stewart BW, Kleihues P, eds. World Cancer Report. IARCPress: 2003.
6. Apperly FL. The relation of solar radiation to canser mortality in North American. *Canser Res.* 1941;1(3):191-195.
7. Gerland FC, Gerland FC. Do sunlight and vitamin D reduce the likehood of colon canser? *Int J Epidemiol.* 1980;9(3);227-231.
8. Giovannuci E. Commentary: vitamin D and colorectal cancer-twenty-five years later. *Int J Epidemiol.* 2006;35(2):222-224.
9. Wacker M, Holick MF. Vitamin D-effects on skeletal and extraskeletal health and the need for supplementation. *Nutrients.* 2013;5(1):111-148.
10. Parkin DM. International variation. *Oncogene.* 2004;23(38):6329-6340.
11. Memik F, Gulten M, Nak SG, et al. The epidemiology of gastrointestinal cancer in Turkiye: a review of our accumulated experience. *J Environ Pathol Toxicol Oncol.* 1996;15(2-4):209-213.
12. Tuncer İ, Uygan İ, Kösem M, Özen S, Uğraş S, Türkdoğan K. The demography and histopathologic characteristics of upper gastrointestinal cancers appeared in Van and its vicinity. *Van Med J.* 2001;8(1):10-13.
13. Muller DC, Fanidi A, Midttun I, et al. Circulating 25-ydroxyvitamin D3 in relation to renal cell carcinoma incidence and survival in the EPIC cohort. *Am J Epidemiol.* 2014;180(8):810-820.
14. Barreto SG, Neale RE. Vitamin D and pancreatic cancer. *Cancer Lett.* 2015;368(1):1-6.

15. Abulkhair O, Saadeddin A, Makram O, et al. Vitamin D levels and breast cancer characteristics: findings in patients from Saudi Arabia. *J Steroid Biochem Mol Biol*. 2016;100(164):106-109.
16. Giovannucci E, Liu Y, Willett WC. Cancer incidence and mortality and vitamin D in black and white male health professionals. *Cancer Epidemiol Biomark Prevent*. 2006;15(12):2467-2472.
17. Colston K, Colston MJ, Feldman D. 1,25-OH(2)D3 and malignant melanoma: the presence of receptors and inhibition of cell culture. *Endocrinol*. 1981;108(3):1083-1086.
18. Abe E, Miyaura C, Skagami H, et al. Differentiation of mouse myeloid leukemia cells induced by 1,25- OH(2)D3. *Proc Natl Acad Sci*. 1981;78(8): 4990-4994.
19. Özkan B, Döneray H. D vitamininin iskelet sistemi dışı etkileri. *Çocuk Sağ Hast Derg*. 2011;54(2):99-119.
20. Mc Guire TF, Trump DL, Johnson CS. Vitamin D (3)-induced apoptosis of murine squamous cell carcinoma cells. Selective induction of caspasedependent MEK cleavage and up-regulation of MEKK-1. *J Biol Chem*. 2001;276(28):26365-26373.
21. Wong G, Lim WH, Lewis J, et al. Vitamin D and cancer mortality in elderly women. *BMC Cancer*. 2015;15(1):106.
22. Trivedi DP, Doll R, Khaw KT. Effect of four-monthlyoral vitamin D3 (cholecalciferol) supplementation onfractures and mortality in men and women living inthe community: randomised double blind controlledtrial. *BMJ*. 2003;326(7387):469.
23. Khayatzadeh S, Feizi A, Saneei P, Esmaillzadeh A. Vitamin D intake, serum Vitamin D levels, and risk of gastric cancer: a systematic review and meta-analysis. *J Res Med Sci*. 2015;20(8):790-796.
24. Ren C, Qiu MZ, Wang DS, et al. Prognostic effects of 25-hydroxyvitamin D levels in gastric cancer. *J Transl Med*. 2012;10(1):16.
25. Baek S, Lee YS, Shim HE, et al. Vitamin D3 regulates cell viability in gastric cancer and cholangiocarcinoma. *Anat Cell Biol*. 2011;44(3):204-209 doi: 10.5115/acb.2011.44.3.204
26. Abnet CC, Chen Y, Chow WH, et al. Circulating 25-hydroxyvitamin D and risk of esophageal and gastric cancer: cohort consortium vitamin D pooling project of rarer cancers. *Am J Epidemiol*. 2010;172(1):94-106.

Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0027

Do mean platelet volume and platelet count vary on a daily or gender basis?

Ömer Candar[1], Ömer Ekinci[2], Ali Doğan[3], Senar Ebinç[3]

[1]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Uludağ University, Bursa, Turkiye
[2]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Fırat University, Elazığ, Turkiye
[3]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Yüzüncü Yıl University, Van, Turkiye

Cite this article: Candar Ö, Ekinci Ö, Doğan A, Ebinç S. Do mean platelet volume and platelet count vary on a daily or gender basis? *J Curr Hematol Oncol Res.* 2024;2(1):6-9.

Corresponding Author: Ömer Candar, oeml6365@gmail.com

Received: 05/12/2023 ◆ **Accepted**: 16/01/2024 ◆ **Published**: 12/02/2024

ABSTRACT

Aims: Mean platelet volume (MPV) is a measurement based on platelet morphology. We aimed to investigate whether MPV and platelet count exhibit a daily change in relation to the days and gender.

Methods: Healthy blood donors aged 18–55 years with no history of the disease and/or drug use participated in the study. MPV values and platelet counts were analyzed with respect to the date of the blood test and the gender of the participant based on a 29–day calendar.

Results: A total of 14718 participants (7772 female) were included. The median age of the females and males was similar [38 (range 18–54), and 36 (18–55), p=0.254, respectively]. Median platelet count was 278×10^9/L (range 152–448) in females and 244×10^9/L (range 151–439) in males, with a significant difference (p<0.01). The median MPV was 8.9 (range 5.7–12.2) fL in females and 8.4 (range 5.9–12.8) fL in males (p<0.01). MPV and platelet counts were higher in females on all days of the month compared to males. Decreases in MPV values were observed in both females and males on days 9th, 12th, 20th, and 26th, whereas increases in both occurred on days 5th, 15th, 23rd, and 29th.

Conclusion: We demonstrated that MPV and platelet count exhibited a daily fluctuating in healthy individuals; MPV values and platelet count were overall higher in females. This study may give a different perspective on future studies of MPV and a lead for evaluating daily changes on other blood parameters.

Keywords: Mean platelet volume, platelets, daily changes

INTRODUCTION

Platelets, the smallest blood cells, are responsible for the allowance and maintenance of hemostasis in physiological and pathological conditions. Platelets are anucleate and discoidal, and form the cytoplasmic fragments of megakaryocytes during thrombopoiesis.[1]

Mean platelet volume (MPV) is a measurement based on the volume morphology of platelets that can be easily determined by hematological analyzers. Studies have shown that MPV can provide important information regarding the course and prognosis of numerous diseases,[2] including cardiovascular diseases, neoplasias, respiratory diseases, connective tissue diseases, inflammatory bowel diseases and diabetes mellitus.[3-8]

Although the information that exists concerning changes in MPV in the presence of pathological conditions, there is no clear data to show daily changes in MPV under the physiological conditions in healthy people. In this study, we aimed to investigate whether MPV and platelet counts exhibit a daily change in relation to the days.

METHODS

The study was carried out with the permission of Non-invasive Clinical Researches Ethics Committee of Van Yüzüncü Yıl University Faculty of Medicine (Date: 20.05.2019, Decision No: 329290). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

The participants in this study consisted of healthy individuals between the ages of 18 and 55 who registered with hospital's blood center and met the criteria for blood donation. We excluded all patients with any type of chronic disease, individuals who had had an infection within the previous month or those with an active infection, and those who had been on medication within the previous month or were currently on medication from the study. Participants were grouped according to their blood draw dates. The monthly cycle was set as 29 days, and each group consisted of participants who registered on the same day of the lunar

month, resulting in 29 groups. These groups were further divided into two separate subgroups, male and female, for a total of 58 groups, each group represented one day of the month. MPV values and platelet counts were then compared on the bases of gender and day of the month.

Haemogram Test

For the whole complete blood count (CBC), 2 ml of blood was drawn into a tube with ethylenediaminetetraacetic acid (EDTA), following which the sample was tested using the Beckman Coulter LH 780 analyzer, an operation lasting approximately 30 minutes. The blood of all the participants was tested on the same device and the whole blood count values were retrospectively analyzed. Cases with platelet count less than 150×10^9/L or exceeding 450×10^9/L were excluded from the study.

Statistical Analysis

Statistical analysis of the data was performed using the IBM SPSS 22 statistical package program. Descriptive statistics are expressed as [median (minimum–maximum)] for variables not exhibiting normal distribution in continuous data, and for categorical variables the frequency is expressed as a percentage (%). Two–way and repeated measures analysis of variance (ANOVA) was used to compare groups and measurement times with respect to these characteristics. The Tukey test was used to identify different groups following the analysis of variance. The level of significance was set at $p<0.05$.

RESULTS

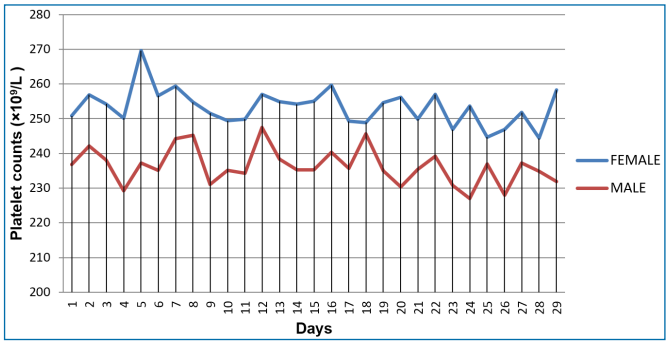
A total of 14718 individuals participated in this study, including 7772 females and 6946 males. The median age of the females was 38 (range 18–54) and that of the males was 36 (range 18–54). There were no significant differences with respect to the total numbers for each gender and age distributions of the participants ($p=0.142$ and $p=0.254$, respectively).

Median platelet count was 278×10^9/L (range 152–448) in females and 244×10^9/L (range 151–439) in males, a statistically significant difference ($p<0.01$). The median MPV was 8.9 (range 5.7–12.2) femtoliters (fL) in females and 8.4 (range 5.9–12.8) fL in males, also statistically significant ($p<0.01$) (Table 1).

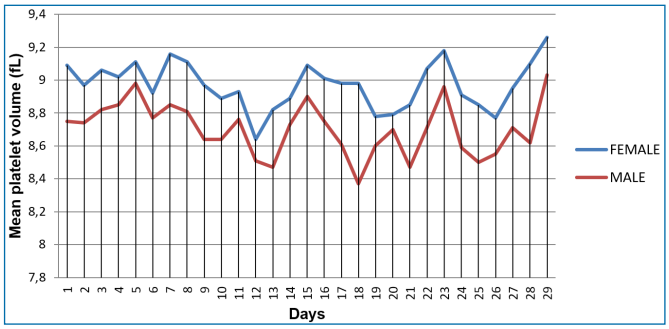
Table 1. Demographic and laboratory characteristics of the participants

Parameters	Female	Male	p–value
Number of participants, n (%)	7772 (52.8%)	6946 (47.2%)	0.142
Age (years)			0.254
Median	38	36	
Range	18–54	18–55	
Platelet counts ($\times10^9$/L)			<0.01
Median	278	244	
Range	152–448	151–439	
Mean platelet volume (fL)			<0.01
Median	8.9	8.4	
Range	5.7–12.2	5.9–12.8	

Additionally, the platelet counts were higher in females on all days of the month compared to males (Graph 1), as was the MPV values (Graph 2). In both females and males, decreases in MPV values were observed on the 9th, 12th, 20th, and 26th days of the month, while increases were observed on the 5th, 15th, 23rd, and 29th days (Table 2).



Graph 1. Distribution of daily platelet counts by gender



Graph 2. Distribution of daily MPV values by gender

Table 2. MPV status by gender and days

Parameters	Female (Mean±SD)	Male (Mean±SD)
Increase in MPV levels (fL)		
Day 5	9.11±1.16	8.98±1.36
Day 15	9.09±1.15	8.90±1.08
Day 23	9.18±1.14	8.96±1.21
Day 29	9.26±1.16	9.03±1.09
Decrease in MPV levels (fL)		
Day 9	8.87±1.23	8.67±1.08
Day 12	8.64±1.19	8.51±1.06
Day 20	8.79±1.12	8.70±1.10
Day 26	8.77±1.21	8.55±1.23

MPV: mean platelet volume

DISCUSSION

CBC is a blood test used to evaluate our overall health and detect a wide range of disorders, including anemia, infection and leukemia. Currently, the whole complete blood count is measured using modern hematologic analyzers in clinical laboratories. This yields valuable information regarding platelet count, MPV, platelet distribution width (PDW), and plateletcrit (PCT), which are basic platelet parameters. Recent studies have shown that platelet parameters can both contribute to the diagnosis of a patient and have prognostic value for some pathological conditions.[2,9] However, although routine assessments of these parameters have been presented in numerous studies over the years, their clinical importance is not yet fully understood and their application for diagnosis is still limited.

MPV values typically range from 7.5 to 12.0 fL and can easily be calculated using automatic hematologic analyzers. Under physiological conditions, MPV is considered inversely proportional to platelet count;[10] in such cases, with an increase in platelet count, a decrease in MPV is expected. As an example, in one study on immune thrombocytopenia, thrombopoiesis increased significantly while platelet count remained low and MPV increased.[11]

The volumetric distribution of platelets in peripheral blood is not homogeneous. MPV is correlated with platelet activity, with younger platelets exhibiting greater MPV (>15 fL) and activity.[12] Since large platelets contain more cell granules, express more adhesion molecules, and are more active, a greater risk of developing thrombus has been noted as a result.[13] MPV can thus be used as a marker of platelet activation in the diagnosis of specific diseases.[14]

The vast majority of studies on MPV have investigated its variability in pathological conditions such as cardiovascular diseases, cerebrovascular diseases, respiratory diseases, rheumatic diseases, diabetes mellitus, lymphomas, and carcinoma.[2] Additionally, a number of studies have reported that other factors such as age, gender, race/ethnicity, diet, and genetic factors may affect MPV.[15-18] However, information pertaining to physiological MPV changes is limited.

In the present study, we examined daily changes in MPV values and platelet counts in relation to the days of the month. As far as we know, this is the first study on physiological daily changes of MPV according to the day of the month. We used the lunar calendar, based on the moon's rotation around the earth and consisting of 29–day cyclical periods, to determine the daily changes of the MPV.

Previous reports in the literature on MPV values with gender relationships are inconsistent. In some studies, higher MPV values were reported for females,[19,20] while others observed higher MPV in males.[21] Several studies have reported no significant difference in MPV values for females and males.[22-24] In this study, we found that females had higher MPV values and higher platelet counts than males for all days of the lunar month.

Our study also detected periodic increases and decreases in MPV values for both genders. While increased MPV values were observed on the 5th, 15th, 23rd, and 29th days of the month, the values decreased on the 9th, 12th, 20th, and 26th days. We hypothesize that this variation may have occurred in accordance with the MPV's daily changes rhythm, suggesting that females may be more susceptible to thrombosis than males.

A morphological value that can be measured by routine whole blood count testing, MPV can provide important information regarding the disease course and prognosis in many cases of inflammation. However, it should be remembered that various factors may affect platelet activity, and therefore MPV may change under certain physiological and pathological conditions.

CONCLUSION

In this study, differences in MPV values and platelet counts between the genders were detected in healthy subjects, both parameters being higher in female participants compared with males. We also observed that MPV exhibits a variability that changes daily. We believe that this observation will lead to the adoption of a different perspective from which to proceed in future research on MPV and that it will open the door to the investigation of daily change patterns in various blood parameters. However, further studies are needed in order to make proper use of this aspect of MPV analysis in clinical applications.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Non-invasive Clinical Researches Ethics Committee of Van Yüzüncü Yıl University Faculty of Medicine (Date: 20.05.2019, Decision No: 329290).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Acknowledgments

Ömer Candar was responsible for the accuracy and integrity of this study. Ömer Candar, Ömer Ekinci, Ali Doğan and Senar Ebinç analyzed and interpreted the data, prepared the manuscript, performed the statistical analyses, and were responsible for the final editing.

REFERENCES

1. Machlus KR, Italiano Jr JE. The incredible journey: from megakaryocyte development to platelet formation. *J Cell Biol.* 2013;201(6):785-796.
2. Korniluk A, Koper-Lenkiewicz OM, Kaminska J, Kemona H, Dymicka-Piekarska V. Mean platelet volume (MPV): new perspectives for an old marker in the course and prognosis of ınflammatory conditions. *Mediators Inflamm.* 2019;2019:9213074.
3. Li NA, Yu Z, Zhang X, et al. Elevated mean platelet volume predicts poor prognosis in colorectal cancer. *Sci Rep.* 2017;7(1):10261
4. Feng Y, Yin H, Mai G, et al. Elevated serum levels of CCL17 correlate with increased peripheral blood platelet count in patients with active tuberculosis in China. *Clin Vaccine Immunol.* 2011;18(4):629-632.
5. Yavuz S, Ece A. Mean platelet volume as an indicator of disease activity in juvenile SLE. Clin Rheumatol. 2014;33(5):637-641.
6. Slavka G, Perkmann T, Haslacher H, et al. Mean platelet volume may represent a predictive parameter for overall vascular mortality and ischemic heart disease. *Arterioscler Thromb Vasc Biol.* 2011;31(5):1215-1218.
7. Liu S, Ren J, Han G, et al. Mean platelet volume: a controversial marker of disease activity in Crohn's disease. *Eur J Med Res.* 2012;17(1):27.
8. Rollini F, Franchi F, Muniz-Lozano A, Angiolillo DJ. Platelet function profiles in patients with diabetes mellitus. *J Cardiovasc Transl Res.* 2013; 6(3):329-345.
9. Budak YU, Polat M, Huysal K. The use of platelet indices, plateletcrit, mean platelet volume and platelet distribution width in emergency non-traumatic abdominal surgery: a systematic review. *Biochem Med.* 2016;26(2):178-193.
10. Thompson CB, Jakubowski JA. The pathophysiology and clinical relevance of platelet heterogeneity. *Blood.* 1988;72(1):1-8.
11. Kaito K, Otsubo H, Usui N, et al. Platelet size deviation width, platelet large cell ratio, and mean platelet volume have sufficient sensitivity and specificity in the diagnosis of immune thrombocytopenia. *Br J Haematol.* 2005;128(5):698-702.
12. Ntolios P, Papanas N, Nena E, et al. 2016. Mean platelet volume as a surrogate marker for platelet activation in patients with idiopathic pulmonary fibrosis. *Clin Appl Thromb Hemost.* 2016;22(4):346-350.
13. Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Mean platelet volume is a risk factor for venous thromboembolism: the Tromso Study, Tromso, Norway. *J Thromb Haemost.* 2010;8(1):157-162.

14. Kamath S, Blann AD, Lip GY. Platelet activation: assessment and quantification. *Eur Heart J.* 2001;22(17):1561-1571.
15. Kunicki TJ, Williams SA, Nugent DJ. Genetic variants that affect platelet function. *Curr Opin Hematol.* 2012;19(5):371-379.
16. Yazici M, Kaya A, Kaya Y, Albayrak S, Cinemre H, Ozhan H. Lifestyle modification decreases the mean platelet volume in prehypertensive patients. *Platelets.* 2009;20(1):58-63.
17. Noris P, Melazzini F, Balduini CL. New roles for mean platelet volume measurement in the clinical practice? *Platelets.* 2016;27(7):607-612.
18. Eicher JD, Chami N, Kacprowski T, et al. Platelet-related variants identified by exomechip meta-analysis in 157,293 individuals. *Am J Hum Genet.* 2016;99(1):40-55.
19. Biino G, Portas L, Murgia F, et al. A population-based study of an Italian genetic isolate reveals that mean platelet volume is not a risk factor for thrombosis. *Thromb Res.* 2012;129(4):e8-e13.
20. Santimone I, Di Castelnuovo A, De Curtis A, et al. White blood cell count, sex and age are major determinants of heterogeneity of platelet indices in an adult general population: results from the MOLI-SANI project. *Haematologica*. 2011;96(8):1180-1188.
21. Klovaite J, Benn M, Yazdanyar S, Nordestgaard BG. High platelet volume and increased risk of myocardial infarction: 39,531 participants from the general population. *J Thromb Haemost.* 2011;9(1):49-56.
22. Lippi G, Meschi T, Borghi L. Mean platelet volume increases with aging in a large population study. *Thromb Res.* 2012;129(4):e159-e160.
23. Vasse M, Masure A, Lenormand B. Mean platelet volume is highly correlated to platelet count. *Thromb Res.* 2012;130(3):559-560.
24. Butkiewicz AM, Kemona H, Dymicka-Piekarska V, Matowicka-Karna J, Radziwon P, Lipska A. Platelet count, mean platelet volume and thrombocytopoietic indices in healthy women and men. *Thromb Res.* 2006;118(2):199-204.

Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0028

Factors affecting prognosis in myelodysplastic syndrome: an 11 years' experience from a tertiary care center

Emrullah Doğan[1], Ekrem Küçükoğlu[1], Muzaffer Keklik[2]

[1]Department of Internal Medicine, Faculty of Medicine, Erciyes University, Kayseri, Turkiye
[2]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Erciyes University, Kayseri, Turkiye

Cite this article: Doğan E, Küçükoğlu E, Keklik M. Factors affecting prognosis in myelodysplastic syndrome: an 11 years' experience from a tertiary care center. *J Curr Hematol Oncol Res.* 2024;2(1):10-14.

Corresponding Author: Ekrem Küçükoğlu, dr.ekremkucukoglu38@hotmail.com

Received: 02/01/2024 ◆ **Accepted**: 29/01/2024 ◆ **Published**: 12/02/2024

ABSTRACT

Aims: Myelodysplastic syndrome (MDS) is a clonal bone marrow neoplasia characterized by morphological findings of dysplasia in hematopoietic cells, peripheral cytopenia(s), ineffective hematopoiesis, recurrent genetic abnormalities, and an increased risk of transformation to acute myeloid leukemia (AML). The International Prognostic Scoring System (IPSS) is the most commonly used prognostic classification system for MDS. Classification was made by a combination of morphology, cytopenia, and genetic studies. In this study, we aimed to examine the parameters that affect prognosis in MDS patients, show their effects on mortality, and evaluate their positive or negative effects on the course of the disease.

Methods: Two hundred twenty-nine patients who applied to Erciyes University Faculty of Medicine, Department of Hematology, and were diagnosed with MDS according to WHO classification between 2010 and 2020 were included in this retrospective study. Age, gender, comorbiditites, laboratory parameters, bone marrow biopsy materials, and genetic mutation analysis data were available. The bone marrow aspiration and biopsy examinations of each patient were evaluated and categorized according to the WHO classification. The prognosis was evaluated according to the data of the patients, survival-exitus, and survival after MDS-AML transformation. Risk scoring was analyzed with three different scoring systems (IPSS, WPSS, and R-IPSS).

Results: Of the 229 MDS patients included in the study, 57% (n=131) were male. The mean age of the patients was 67 years. Age, MDS-AML transformation times, disease duration, cellularity, and pathology blast rate were found to be statistically significant between the groups ($p<0.05$). Leukocyte, neutrophil, platelet, hematocrit, lymphocyte, monocyte, CRP, erythropoietin, ferritin, and LDH data were found to be statistically significant regarding survival ($p<0.05$). Age, IPSS risk status 3, and W-PSS risk status 3 were found to be independent risk factors affecting survival.

Conclusion: Age, IPSS high risk, and WPSS high risk status were found to be independent risk factors affecting survival. Although our study revealed important data in the analysis of MDS patients, single-center analysis of patients and retrospective analysis revealed the need for further studies.

Keywords: Mortality, myelodysplastic syndrome, prognosis

INTRODUCTION

Myelodysplastic syndromes (MDS) include a group of hematologic malignancies characterized by clonal hematopoiesis, cytopenia in one or more series (i.e., anemia, neutropenia, and/or thrombocytopenia), and abnormal cellular maturation.[1] MDS shares clinical and pathological features with acute myeloid leukemia (AML), but has a lower percentage of blasts in peripheral blood and bone marrow (by definition, blasts in bone marrow <20%). Patients with MDS are at risk of conversion to AML, which varies greatly according to subtypes and is frequently seen in advanced age.[2] As in many diseases, some models and scoring have been developed to predict prognosis and shape treatment in MDS. Over time, scoring systems and genetic-based models have improved in parallel with the rapid advances in the field of genetics.[3]

There are classification systems to indicate prognosis in MDS. The World Health Organization (WHO) classification system is based on a combination of morphology, immunophenotype, genetic, and clinical features.[4] The French-American-British (FAB) classification system partially subdivides patients with MDS according to the percentage of blasts in the bone marrow (BM). The International Prognostic Scoring System (IPSS) is the most widely used prognostic classification system for MDS. Classification was made with a combination of morphology, cytopenia, and genetic

studies.[5] In the Revised IPSS (R-IPSS), BM blast percentage, cytogenetics, hemoglobulin, platelet count, and neutrophil count were included.[6] The WHO Prognostic Scoring System (WPSS) was designed to include information on the need for erythrocyte transfusion, which has been shown to be an independent prognostic factor for patients with MDS.[7,8]

In this study, we aimed to examine the parameters affecting prognosis in patients diagnosed with MDS and to evaluate their positive or negative effects on the disease course. We planned to compare our current data with the currently used prognostic systems and present them in the literature.

METHODS

The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 08.09.2021, Decision No: 2021/571). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 229 patients over the age of 18 who were admitted to Erciyes University Faculty of Medicine, Department of Internal Medicine, Division of Hematology between January 2010 and December 2020 in a total period of 11 years and diagnosed with MDS according to WHO classification. The files of 229 patients were analyzed retrospectively.

Our patients had a bone marrow biopsy, genetic examinations, and flow cytometric examinations. Each patient's age, gender, comorbidities, laboratory data, bone marrow aspiration and biopsy examinations, blood product replacement status, cytogenetic abnormalities, and genetic examinations were evaluated and classified according to the WHO classification. Defining thresholds for anemia, leukopenia, and thrombocytopenia was based on the values defined in the R-IPSS classification. For the MDS-AML conversion threshold, the blast count threshold accepted by WHO was taken as 20%. In order to define the need for blood product transfusion, patients who received transfusions once every 8 weeks for at least 4 months from the time of diagnosis were considered to be in need of blood products, and those who did not comply with this condition were considered not in need. The use of azacitidine, decitabine, oxymetholone, eltrombopag, granulocyte colony stimulating factor, lenalidomide, and erythropoietin in the treatment of the patients was recorded, and the status of allogeneic bone marrow transplantation was added to the study. The effects of these treatments on overall survival and treatment response were grouped and recorded.

Three different scoring systems, including IPSS, WPSS, and R-IPSS, were used for prognosis evaluation.5-8 The final status and mortality of the patients, dependent on and independent of the transformation from MDS to AML, were recorded. The risk group in which the patients were placed according to their scores in the scoring systems was recorded.

In the data analysis section, descriptive statistics were presented with frequency, percentage, mean, and standard deviation values. In the study, X^2 (chi-square) analysis was used for proportional comparisons according to the characteristics of the patients, and Fisher's test was used for corrections. An independent sample t-test and an analysis of variance test were applied for comparisons of patients' measurements according to survival levels and durations. The Sidak test was applied to determine the groups found to be different in the analysis of variance. Logistic regression analysis was applied to analyze the multiple risk factors affecting the survival level of the patients in the study. Odds ratios and 95% confidence intervals (CI) were calculated for risk factors. Survival analysis was performed using Kaplan-Meier analysis. P values less than 0.05 were considered statistically significant (α=0.05). Analyses were performed with the SPSS 22.0 package program.

RESULTS

Demographic Data

Forty-three percent (n=98) of the patients were female, and 57% (n=131) were male. The mean age was 67 years. The mean age of female patients was 64.1 years, and the mean age of male patients was 69.5 years. Seventeen percent (n=39) had no comorbidity, 41% (n=97) had a single comorbidity, and 42% (n=93) had more than one comorbidity.

Twenty-one percent (n=49) had RCUD (refractory cytopenias with single-strand dysplasia), 3% (n=8) had RARS (refractory anemia with ring sideroblasts), and 19% (n=44) had RCMD (refractory cytopenia with multiple-strand dysplasia). 28% (n=63) were grouped as RAEB-1 (RAEB-1 with increased blast rate), 19% (n=44) as RAEB-2 (RAEB-2 with increased blast rate), 3% (n=7) as isolated 5q deletion, and 7% (n=14) as unclassified.

Transformation Status

Of the patients, 61% (n=140) had no conversion, 34% (n=78) had conversion with a survival of less than 1 year, and 5% (n=11) had a survival of 1-3 years. In the study, it was determined that age differed according to survival time. It was found that the age of patients with a survival time between 1-3 years was higher than the other groups (p=0.04). In the study, it was found that the duration of conversion from MDS to AML differed according to survival time. It was found that the duration of AML conversion from MDS was lower in patients with a survival period of less than 1 year compared to the other groups (p=0.01). In the study, it was determined that the duration of the disease differed according to the survival time. It was found that the disease duration of patients with a survival of less than 1 year was lower than the other groups (p=0.01). In the non-transformation group, the cellularity levels of the patients were found to be lower than the other groups (p=0.02). In the group with a survival of 1 year or less, the pathology blast rate of the patients was found to be higher than the other groups (p=0.01) (**Table 1**).

Table 1. Examination of patient measurements according to MDS survival time

	No transformation (X±S.D.)	Less than 1-year survival (X±S.D.)	1-3 Year survival (X±S.D.)	P
Age (years)	66.4±14.03	67.15±13.36	72.18±6.78	0.04*
MDS-AML transformation time	61.14±20.53	20.54±10.39	31.00±20.4	0.01*
Duration of illness	61.29±20.37	29.24±10.34	48.91±18.46	0.01*
Cellularity	55%±0.19	64%±0.21	74%±0.18	0.02*
Pathology blast rate	3%±0.02	9%±0.05	5%±0.03	0.01*

MDS: Myelodysplastic syndrome, AML: Acute myeloid leukemia *Significant relation at 0.05 level

Laboratory Data

Leukocyte, neutrophil, lymphocyte, and hemoglobulin levels did not differ according to survival time. Platelet and hematocrit levels differed according to survival time, and the group with a survival of less than 1 year was found to be lower than the other groups (p=0.01) (Table 2). It was observed that monocyte levels were different according to survival time, and the measurements of the group without transformation were lower (p=0.01)

Table 2. Analysis of complete blood count according to MDS survival time

	No Transformation (X±S.D.)	Less than 1 Year (X±S.D.)	1-3 Years (X±S.D.)	P
Leucocyte (µ/L)	5.40±6.47	6.09±11.13	6.56±6.2	0.18
Neutrophil (µ/L)	3.14±4.74	2.95±7.32	4.18±4.92	0.08
Hemoglobulin (g/dl)	10.35±2.54	9.21±2.13	11.22±2.55	0.17
Platelet (µ/L)	189.13±160.75	122.65±121.98	248.27±234.44	0.01*
Hemotocrit (%)	31.77±7.53	27.74±6.35	34.78±8.26	0.03*
Lymphocyte (µ/L)	1.39±0.84	1.42±0.98	1.45±0.69	0.13
Monocyteµ/L)	0.58±1.47	1.24±3.20	0.69±0.61	0.01*
Eritropoetin (u/mL)	75.44±134.34	138.06±210.51	341.73±885.27	0.01*
Fibrinogen (mg/dl)	331.81±105.45	347.76±117.01	334.18±128.21	0.53
CRP (mg/L)	19.85±39.89	37.63±111.26	20.64±29.86	0.02*
Ferritin (ng/mL)	559.55±777.98	867.54±857.1	582.55±580.05	0.04*
Lactate dehydrogenase (u/L)	292.77±164.86	683.42±896.03	760.09±599.88	0.01*
Albumin (g/dl)	4.04±0.57	3.87±0.67	3.8±0.33	0.25

*Significant relation at 0.05 level

Erythropoietin (EPO) levels were found to be different in the groups. The EPO level was found to be higher in the group with a survival time between 1 and 3 years (p=0.01). Fibrinogen and albumin levels did not differ according to survival time (p>0.05).

Ferritin and CRP levels were found to be different according to survival time, and the measurements of the group with a survival time of less than 1 year were found to be higher (p values of 0.04 and 0.02, respectively). Lactate dehydrogenase (LDH) levels were found to be different according to the survival time, and the measurements of the group with a survival time of less than 1 year were lower (p=0.01).

Treatment and Survival

In the treatment analysis according to MDS survival status, the total number of patients who received azacitidine was 58, 72% (42) of whom were exited and 28% (16) of whom survived. The total number of patients who received decitabine was 21, 95% (20) of whom were exited and 5% (1) of whom survived. The total number of patients who received oxymetholone was 7, 43% (3) of them had an exitus, and 57% (4) of them survived. The total number of patients receiving eltrombopag was 2, 50 (1%) of whom exited and 50 (1%) of whom survived. The total number of patients who received GCSF was 38, 71 (27.2%) of whom exited, and 29 (11.1%) survived. The total number of patients who received erythropoietin was 54, 63 (34%) of whom exited, and 37 (20%) survived. The total number of patients who received lenalidomide was 58, 75(3) % of whom exited, and 25(1) % survived.

MDS Risk Classifications and Survival

In our survival analysis according to MDS risk classification and treatment, survival response to treatment was evaluated according to WHO classification and R-IPSS classification (Table 3). IPSS Risk Status: It was found that patients in the middle-2 and high groups had a higher rate of survival below 1 year (p=0.02). R-IPSS Risk Status-3: patients in the high group had a higher survival rate of less than 1 year (p=0.01). W-PSS Risk Status-2; it was determined that patients in the high group had a higher survival rate of less than 1 year (p=0.01).

Table-3. Scoring risk distribution table according to MDS transformation status

	No Transformation	Less than 1 Year	1-3 Years	P
IPSS risk status				0.01*
Low	27.9%	1.3%	0.0%	
Medium-1	50.0%	11.5%	72.7%	
Medium-2	20.7%	51.3%	27.3%	
High	1.4%	35.9%	0.0%	
R-IPSS risk status				0.02*
Low	27.9%	1.3%	0.0%	
Low	24.3%	1.3%	9.1%	
Middle	51.4%	20.5%	45.5%	
High	12.9%	56.4%	45.5%	
WPSS risk status				0.01*
Very Low	20.7%	0.0%	0.0%	
Low	24.3%	3.8%	18.2%	
Middle	49.3%	29.5%	63.6%	
High	5.7%	64.1%	18.2%	
Very High	0.0%	2.6%	0.0%	

IPSS: The International Prognostic Scoring System , R-IPSS: Revised IPSS, WPSS: The WHO Prognostic Scoring System *Significant relation at 0.05 level

Evaluation of Independent Variables Affecting Survival

The data were evaluated by logistic regression analysis to investigate the independent risk factors affecting MDS survival. Age, IPSS risk status 3, and WPSS risk status 3 were found to be independent risk factors affecting survival. Other factors were found to be significant in univariate analyses but not in the multivariate model. If the significant variables are interpreted, patients younger than 60 years of age reduce the probability of survival level by 2.77 (95% CI 1.64-3.65) times. Patients with an IPSS risk score in the middle 2 reduce the survival level probability by 3.81 times (95% CI 1.39-5.28). Patients with a high WPSS risk score have a 3.67-fold (95% CI 1.22-5.07) lower probability of survival. At least 43% of survival was explained by the variables in the model, and the overall success rate of the model was 92% (Table 4).

Table-4. MDS survival independent risk factors logistic regression analysis table

MODEL	Wald	P	Odds Rate	95% GA Lower Limit	95% GA Upper Limit
Age (60<)	8.93	0.01*	2.77	1.64	3.65
IPSS Risk Status (MeHigh)	-7.58	0,01*	3.81	1.39	5.28
WPSS Risk Status (High)	-7.83	0.01*	3.67	1.22	5.07
ModelX2: 29,35; Success rate=92%					
Cox & Snell R2=0,43					

IPSS: The International Prognostic Scoring System , WPSS: The WHO Prognostic Scoring System

DISCUSSION

Myelodysplastic syndromes (MDS) include a group of hematological malignancies characterized by clonal hematopoiesis, cytopenia in one or more series (i.e., anemia, neutropenia, and/or thrombocytopenia), and abnormal cellular maturation.[1] In a multicenter retrospective analysis conducted by Stuart L. Goldberg et al.[9] on 2253 MDS patients, the proportion of male and female patients was 46.5% and 53.5%, respectively. Sekeres Mikkael A. et al.[10] in a multicenter cross-sectional analysis of 670 to 827 MDS patients in 4514 people, showed that 55% were male and 45% were female. In another study by Xiaomei Ma et al.[11] and Gregory et al.[12] on 7131 MDS patients, men had a significantly higher incidence rate than women. In our study, 43% of the patients were female and 57% were male. The median age of our patients was 67 years. In the results of the HAEMACARE project by Milena Sant et al.[13] on the incidence of hematologic malignancies in Europe according to morphologic subtype, the mean age was found to be 64 years in the data analyzed from a total of 97,521 patients.

Scores such as IPSS, R-IPSS, and WPSS used in MDS patients are effective in predicting prognosis.[5-8] In a single-center retrospective study conducted by Bektaş et al.[14] on 101 MDS patients in a tertiary care university hospital between 2003 and 2011, as the International Prognostic Scoring System (IPSS), World Health Organization Classification Based Prognostic Scoring System (WPSS), and revised IPSS (IPSS-R) risk categories increased, leukemia-free survival and overall survival decreased ($p<0.001$). When IPSS, WPSS, and IPSS-R prognostic systems were compared by Cox regression analysis, WPSS was the best at predicting leukemia-free survival ($p<0.001$), and WPSS ($p<0.001$) and IPSS-R were the best at predicting overall survival ($p=0.037$). All three prognostic systems were successful in predicting overall survival and leukemia-free survival ($p<0.001$). In a multicenter cohort study by Porta et al.[15] on 5326 MDS patients, WPSS and IPSS-R scores demonstrated an increase in mortality and leukemic transformation risk with increasing risk. In our study, it was determined that patients in the IPSS, medium-2, and high groups had a higher mortality rate. Similarly, R-IPSS and W-PSS at the time of diagnosis showed that patients in the high and very high groups had a higher mortality rate. Our study and other studies show in parallel that when leukemia-free survival and overall survival of patients are analyzed according to risk groups using IPSS, WPSS, and IPSS-R scoring systems, survival is directly affected as the risk group increases and stands out as direct predictive parameters for prognosis.

Low white blood cell count, low neutrophil count, and low platelet count, which are used as parameters in MDS prognostic risk scoring systems in the study by Guillermo-Montalban Bravo et al.[16] have very critical importance under the title of cytopenia. In the MDS study by Robert P. Hasserjian[17] persistent and unexplained cytopenia, which has a very important place in the diagnosis, was mentioned. A decrease in platelet values had a direct impact on disease prognosis in a single-center retrospective study by Strapatsas et al.[18] on 334 MDS patients. When the literature data and our study are evaluated together, leukocyte types and platelets have a direct effect on the diagnosis, survival, and prognosis of MDS. However, a point where the literature data and our study do not agree is that although hemoglobin values were low in our study, they were not found to be significant. The reason for this difference in our study may be the difference in the timing of blood product replacement and the lack of data availability in our retrospective study.

In a retrospective analysis of 47 patients diagnosed with MDS between 2002 and 2019, Belohlavkova et al.[19] analyzed the importance of LDH, CRP, and ferritin on MDS prognosis. Univariate analysis showed the impact of elevated LDH on survival ($p=0.041$): four-year survival was 70% versus 32% in patients with elevated LDH. CRP elevation was present in 47% of patients. The significance of the CRP value for survival could not be demonstrated in the study ($p=0.92$; $p=0.20$). Two values were taken as limits for ferritin. The limit for high levels was >1000 ng/mL. Patients with higher ferritin levels had similar four-year survival compared to patients with ferritin levels below 1000 ng/ml (46% vs. 48%; $p=0.76$). The importance of ferritin for survival has not been shown ($p=0.55$). Çelik et al.[20] showed that decreased fibrinogen levels decreased survival in patients with ACIT, including MDS. In our study, LDH, ferritin, and CRP levels were found to differ according to survival status. However, no relationship was observed between fibrinogen levels and survival.

In the study titled Recent Advances in the Treatment of Low-Risk Non-Del (5q) Myelodysplastic Syndromes by Almeida et al.[21] (2016), he drew attention to the importance of hypomethylated agents azacitidine and decitabine and mentioned the importance of erythrocyte stimulating agents, thrombopoietin receptor agonists, and GCSF used in patients. Malcovati et al.[22] mentioned the importance of hypomethylating agents, erythrocyte stimulating agents, thrombopoietin receptor agonists, and GCSF in the study titled Diagnosis and Treatment of Primary MDS in Adults. In the analysis conducted by Valeria Santini et al.[23] in 529 MDS patients divided according to 3 clinical groups and an IPSS risk group, the use of lenalidomide increased the mean survival compared to the placebo group. When our study was compared with other studies, the excess heterogeneity affected the treatment survival rates in the analysis of 229 MDS patients in our unit followed up in a retrospective 11-year period according to the risk group. Samples and study groups taken from the literature were categorized as high or low risk. Our study is not a study with the aim of consumable treatment and survival, but the treatment response according to risk status was analyzed according to survival, and the serious treatment response of patients with an increasing risk group decreased. Data analysis of treatment response and controls in our study, which included all MDS patients evaluated and followed up in our unit, was seriously complicated by confounders including patient compliance, a lack of file data, and treatment heterogeneity.

Limitations

This study has some limitations. First of all, the single-center experience limits the generalizability of the results. Retrospective and incomplete data is another limitation. Lack of complete genetic characteristics was another important limitation.

CONCLUSION

This single-center, retrospective study of 229 MDS patients analyzed the demographic, clinical, laboratory, survival, and treatment data of the patients; however, when the data are analyzed, heterogeneity in patients stands out.

Age, IPSS risk status, and WPSS risk status level were found to be independent risk factors affecting survival. Although our study reveals important data in the evaluation and analysis of MDS patients, single-center analysis of patients, and lack of data recording in the files, the number of patients participating in the study and retrospective examination revealed the need for further studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 08.09.2021, Decision No: 2021/571).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Pang WW, Pluvinage JV, Price EA, et al. Hematopoietic stem cell and progenitor cell mechanisms in myelodysplastic syndromes. *Proceed Nation Acad Sci.* 2013;110(8):3011-3016.
2. Moreno Berggren D, Folkvaljon Y, Engvall M, et al. Prognostic scoring systems for myelodysplastic syndromes (MDS) in a population-based setting: a report from the Swedish MDS register. *Br J Haematol.* 2018; 181(5):614-627.
3. Greenberg P, Hoffman R, Benz E, Shattil S. The myelodysplastic syndromes. Basic Principles and Practice. 3rd ed. Churchill Livingstone: 2000.
4. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood.* 2011;117(19):5019-5032.
5. van Spronsen MF, Ossenkoppele GJ, Holman R, van de Loosdrecht AA. Improved risk stratification by the integration of the revised international prognostic scoring system with the myelodysplastic syndromes comorbidity index. *Eur J Cancer.* 2014;50(18):3198-3205.
6. Groupe Francais de Morphologie Hematologique. French registry of acute leukemia and myelodysplastic syndromes. Age distribution and hemogram analysis of the 4496 cases recorded during 1982-1983 and classified according to FAB criteria. *Cancer.* 1987;60(6):1385-1394.
7. Naqvi K, Jabbour E, Bueso-Ramos C, et al. Implications of discrepancy in morphologic diagnosis of myelodysplastic syndrome between referral and tertiary care centers. *Blood.* 2011;118(17):4690-4693.
8. Della Porta MG, Malcovati L, Strupp C, et al. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. *Haematologica.* 2011;96(3):441-449.
9. Goldberg SL, Chen E, Corral M, et al. Incidence and clinical complications of myelodysplastic syndromes among United States Medicare beneficiaries. *J Clin Oncol.* 2010;28(17):2847-2852.
10. Sekeres MA, Schoonen WM, Kantarjian H, et al. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. *J Natl Cancer Inst.* 2008;100(21):1542-1551.
11. Ma X, Lim U, Park Y, et al. Obesity, lifestyle factors, and risk of myelodysplastic syndromes in a large US cohort. *Am J Epidemiol.* 2009;169(12):1492-1499.
12. Abel GA, Efficace F, Buckstein RJ, et al. Prospective international validation of the Quality of Life in Myelodysplasia Scale (QUALMS). *Haematologica.* 2016;101(6):781-788. doi: 10.3324/haematol.2015.140335
13. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood.* 2010;116(19):3724-3734.
14. Bektas O, Uner A, Eliacik E, et al. Comparison of myelodysplastic syndrome prognostic scoring systems. *Turk J Haematol.* 2016;33(2):119-126.
15. Della Porta MG, Tuechler H, Malcovati L, et al. Validation of WHO classification-based Prognostic Scoring System (WPSS) for myelodysplastic syndromes and comparison with the revised International Prognostic Scoring System (IPSS-R). A study of the International Working Group for Prognosis in Myelodysplasia (IWG-PM). *Leukemia.* 2015;29(7):1502-1513.
16. Montalban-Bravo G, Garcia-Manero G. Myelodysplastic syndromes: 2018 update on diagnosis, risk-stratification and management. *Am J Hematol.* 2018;93(1):129-147.
17. Hasserjian RP. Myelodysplastic syndrome updated. *Pathobiol.* 2019;86(1):7-13.
18. Strapatsas J, Barbulescu EC, Lauseker M, et al. Influence of platelet count at diagnosis and during the course of disease on prognosis in MDS patients. *Ann Hematol.* 2021;100(10):2575-2584.
19. Belohlavkova P, Vrbacky F, Smolej L, et al. Prognostic factors affecting the outcome after allogeneic haematopoietic stem cell transplantation for myelodysplastic syndrome. *Leuk Res Rep.* 2021;16:100274.
20. Çelik S, Kaynar L, Güven ZT, et al. The effect of danger-associated molecular patterns on survival in acute graft versus host disease. *Bone Marrow Transplant.* 2023;1-7.
21. Almeida A, Fenaux P, List AF, Raza A, Platzbecker U, Santini V. Recent advances in the treatment of lower-risk non-del(5q) myelodysplastic syndromes (MDS). *Leuk Res.* 2017;52:50-57.
22. Malcovati L, Hellstrom-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood.* 2013;122(17):2943-2964.
23. Santini V, Giagounidis A, Pelligra CG, et al. Impact of lenalidomide treatment on overall survival in patients with lower-risk, transfusion-dependent myelodysplastic syndromes. *Clin Lymphoma Myeloma Leuk.* 2022;22(9):e874-e883.

Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0029

Comparison of efficacy and tolerability of single agent and double agent chemotherapy regimens in first-line treatment of elderly patients with HER-2 negative metastatic gastric cancer

Gürkan Güner[1,2], Muslih Ürün[3]

[1]Department of Medical Oncology, Medical Point Hospital, University of Economy, İzmir, Turkiye
[2]Department of Medical Oncology, Van Training and Research Hospital, University of Health Sciences, Van, Turkiye
[3]Division of Medical Oncology, Department of Internal Medicine, Van Yüzüncü Yıl University Faculty of Medicine, Van, Turkiye

Cite this article: Güner G, Ürün M. Comparison of efficacy and tolerability of single agent and double agent chemotherapy regimens in first-line treatment of elderly patients with HER-2 negative metastatic gastric cancer. *J Curr Hematol Oncol Res.* 2024;2(1):15-19.

Corresponding Author: Gürkan Güner, gunergurkan@yahoo.com

Received: 08/01/2024 ◆ **Accepted**: 07/02/2024 ◆ **Published**: 12/02/2024

ABSTRACT

Aims: Chemotherapy remains a cornerstone in treating metastatic gastric cancer (GC), yet the management of elderly patients, who often face distinct challenges, lacks comprehensive guidelines. The aim of this study was to compare the efficacy and side effects of single-agent and double-agent chemotherapy regimens in first-line treatment of elderly patients with HER-2 negative metastatic GC.

Methods: We retrospectively evaluated HER-2 negative metastatic GC patients aged 80 years and older who were treated at Van Yüzüncü Yıl University Medical Faculty Dursun Odabaşı Medical Center Oncology Clinic between 2010 and 2023. Demographic characteristics, treatment regimens and responses, prognostic factors, grade 3-4 toxicity, progression-free survival (PFS), and overall survival (OS) were analyzed.

Results: The mean age of 56 patients was 82.6±2.3 years and 24 (42.9%) of them were women. Single-agent chemotherapy was administered to 33 (58.9%) patients, while 23 (41.1%) received double-agent chemotherapy. The median OS was 5 months (95% CI, 2.9 to 7.1) in the single-agent group and 10 months (95% CI, 4.2 to 15.8) in the double-agent group (p=0.237), although there was a numerical difference, it was not statistically significant. Median PFS was longer with double-agent chemotherapy, but not statistically significant (6 months vs. 4 months, p=0.668). No statistically significant difference was found in the side effect rates of patients receiving single and double-agent chemotherapy.

Conclusion: In our study, despite the absence of statistical significance in the survival rates among patients receiving double chemotherapeutic agents, their survival was twice as long as that of individuals receiving a single agent. Furthermore, no significant differences in terms of side effects were observed. These findings suggest that, even in individuals aged 80 years and older, a preference for double-agent chemotherapy should be considered when feasible.

Keywords: Chemotherapy, gastric cancer, elderly, first-line treatment

INTRODUCTION

Gastric cancer (GC) is a significant disease worldwide. With over one million new cases each year, it is the fifth most diagnosed malignancy globally. The mortality rate from GC is high as it is often at an advanced stage when diagnosed, and it is the third most common cause of cancer-related deaths with 768,793 deaths worldwide in 2020.[1]

Chemotherapy (CT) is the mainstay of treatment for metastatic GC and the median overall survival (OS) for patients treated with conventional chemotherapy is around 12 months.[2] The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend palliative chemotherapy for patients with HER2-negative locally advanced or metastatic GC with adequate organ function and immunotherapy as an adjunct for patients with accessibility.[3,4]

Age is one of the biggest risk factors for cancer and the incidence of most solid organ tumors increases with age. In the United Kingdom, more than one-third of new cancer diagnoses occur in individuals aged 75 and older each year, and it is expected that the number of elderly individuals living with cancer will triple from 2010 to 2040.[5] Aging is associated with a progressive decline in functional reserves and an increase in the prevalence of chronic diseases and cancer incidence. Increasing age is also associated with changes in the pharmacokinetics and pharmacodynamics of cancer treatment and increased susceptibility to treatment

complications.[6] Therefore, appropriate patient selection is crucial to deliver cancer treatment both effectively and safely.

Current guidelines for the management of GC are predominantly based on evidence from clinical trials in younger patients, but it has been shown that elderly cancer patients have worse OS compared to younger patients.[7] In a study evaluating patients aged 75 and older with metastatic GC, it has been demonstrated that chemotherapy is effective, and its side effects are tolerable.[8] In another retrospective study, 306 patients receiving chemotherapy treatment were divided into two categories under and over 70 years of age and no statistically significant difference was found in progression-free survival (PFS) and OS between the two groups.[9]

The aim of our study was to compare the efficacy and side effects of single-agent and double-agent chemotherapy regimens in the first-line treatment of patients with HER-2 negative metastatic GC aged 80 years and older, which is part of our routine practice.

METHODS

This study was conducted in accordance with the Declaration of Helsinki. The required approval for conducting the study was obtained from the Ethics Committee of Van Training and Research Hospital, University of Health Sciences (Date: 16.08.2023, Decision No: 2023/17-03).

We retrospectively evaluated HER-2 negative metastatic GC patients aged 80 years and older who were treated at Van Yüzüncü Yıl University Medical Faculty Dursun Odabaşı Medical Center Oncology Clinic between 2010 and 2023. Patients who were 80 years of age or older, had cytologically or histologically proven recurrent or metastatic GC, received at least two cycles of chemotherapy, were HER-2 negative, and received single or double-agent chemotherapy regimens were included in the study. Patients younger than 80 years of age, without a pathological or cytologic diagnosis, previously treated for metastatic/recurrent disease, without adequate physiologic organ function, not receiving chemotherapy or receiving one cycle of chemotherapy, receiving triple combination chemotherapy regimen, HER-2 positive, receiving any treatment other than chemotherapy, and patients with unavailable data were excluded.

Demographic characteristics, treatment regimens and responses, prognostic factors, grade 3-4 toxicity, PFS, and OS were analyzed. Patients were divided into two groups: single-agent chemotherapy and double-agent chemotherapy. PFS was determined by measuring the duration from the initiation of first-line treatment to the date of disease progression, death, or the last recorded visit for non-progressing patients. OS was calculated based on the duration from the commencement of first-line treatment to the date of death or last follow-up. Radiologic evaluations were performed every 8 weeks with computed tomography scans of the thorax and abdomen or PET-CT. Treatment response was evaluated according to RECIST 1.1. Toxicity assessment was performed according to the common criteria of the National Cancer Institute. Accordingly; it was graded as follows: 1: mild, 2: moderate, 3: severe, 4: very severe.

Statistical Analysis

Categorical variables were presented as numbers (percentages), while continuous variables with normal distribution were presented as mean±standard deviation (SD); non-normal variables were reported as median (minimum-maximum). As the quantitative variables did not follow a normal distribution, the Mann-Whitney U test was employed to compare two independent groups. To compare proportions in different groups, the Chi-square test was used. Survival analyses were conducted using the Kaplan-Meier method. Prognostic factors for survival were investigated through Cox regression analysis. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 15 (IBM Corp., Armonk, N.Y., USA).

RESULTS

A total of 56 patients, 32 (57.1%) males and 24 (42.9%) females, were included. The mean age was 82.6±2.3 years. In 64.3% of the patients, liver metastases were detected, while 21.4% had lung metastases, and 25% exhibited peritoneal metastases. Demographic and disease characteristics of the patients are summarized in **Table 1**. 33 (58.9%) patients received single-agent chemotherapy and 23 (41.1%) patients received double-agent chemotherapy. 14.3% of patients responded to first-line treatment. Treatment and follow-up of the patients are summarized in **Table 2**. There were no significant differences in laboratory values between the two groups (p>0.05).

Table 1. Demographic and clinical characteristics of the patients

	All patients (n = 56)
Age, years	82.6±2.3
Gender, female	24 (42.9)
HT	27 (48.2)
DM	7 (12.5)
ECOG PS	
0	4 (7.1)
1	22 (39.3)
2	27 (48.2)
3	3 (5.4)
History of surgery	
No	51 (91.1)
Yes	5 (8.9)
Surgery type	
Curative	3 (60)
Palliative	2 (40)
Adjuvant treatment	
No	44 (86.3)
Yes	7 (13.7)
Tumor Localization	
Cardia	17 (30.9)
Corpus	12 (21.8)
Antrum	20 (36.4)
Diffuse	6 (10.9)
Metastatic organ count	
1	38 (67.9)
2	16 (28.6)
3	2 (3.6)
Metastatic organ site	
Liver	36 (64.3)
Lung	12 (21.4)
Bone	2 (3.6)
Periton	14 (25)
Brain	-
Other	9 (16.1)

Data are given as n (%), mean ± SD. HT, hypertension; DM, diabetes mellitus; ECOG PS, Eastern Cooperative Oncology Group performance status

Table 2. Treatment patterns and responses of patients

	All patients (n=56)
Chemotherapy regimen	
Single-agent	33 (58.9)
Double-agent	23 (41.1)
Chemotherapy regimen	
Capecitabine	25 (44.6)
CapeOX	3 (5.4)
FUFA	4 (7.1)
FOLFOX	12 (21.4)
Cisplatin + 5-fluorouracil	8 (14.3)
Paclitaxel	4 (7.1)
Total number of CT cycles	3 (2-12)
Dose reduction	
No	38 (67.9)
Yes	18 (32.1)
Dose delay	
No	39 (69.6)
Yes	17 (30.4)
First-line treatment response	
CR	1 (1.8)
PR	7 (12.5)
SD	11 (19.6)
PD	37 (66.1)
Progression	
No	6 (10.7)
Yes	50 (89.3)
Second-line treatment	8 (14.3)
Follow-up period, months	5.5 (2-58)
Final situation	
Alive	13 (23.2)
Dead	43 (76.8)

Data are given as n (%), median (minimum-maximum). CapeOX, capecitabine and oxaliplatin; FUFA, 5-fluorouracil and folinic acid; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; CT, chemotherapy; CR, complete response; PR, partial response; SD, stabil disease; PD, progressive disease

Capecitabine, 5-fluorouracil, and folinic acid (FUFA), or paclitaxel were used as single-agent chemotherapy. Folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CapeOX) were used as a double chemotherapy regimen. The median overall survival was 5 months (95% CI, 2.9 to 7.1) in the single-agent group and 10 months (95% CI, 4.2 to 15.8) in the double-agent group (p=0.237), although there was a numerical difference, it was not statistically significant (**Figure 1**). The survival percentages for single-agent chemotherapy at 6 months, 12 months, and 36 months were 43%, 31.8%, and 9.3%, respectively; whereas for double-agent chemotherapy, the survival percentages at 6 months, 12 months, and 36 months were 65.2%, 42.5%, and 31.0%, respectively. Median PFS was longer with double-agent chemotherapy, but not statistically significant (6 months vs. 4 months, p=0.668) (**Figure 2**). No statistically significant difference was found in the side effect rates of patients receiving single and double-agent chemotherapy (**Table 3**).

Table 3. Treatment-Related Adverse Events

Adverse event	Single-agent CT	Double-agent CT	p
Grade 3-4 neutropenia	0	3 (13)	0.064
Grade 3-4 anemia	9 (27.3)	3 (13)	0.322
Grade 3-4 thrombocytopenia	0	1 (4.3)	0.411
Grade 3-4 mucositis	2 (6.1)	0	0.507
Grade 3-4 diarrhea	4 (12.1)	0	0.136
Grade 3-4 nausea-vomiting	4 (12.1)	1 (4.3)	0.639
Grade 3-4 peripheral sensory neuropathy	0	1 (4.3)	0.411
Grade 3-4 allergic reaction	1 (3)	1 (4.3)	1
Grade 3-4 thrombosis	1 (3)	1 (4.3)	1
Grade 3-4 hepatotoxicity	0	0	-
Grade 3-4 nephrotoxicity	3 (9.1)	0	0.261
Grade 3-4 cardiotoxicity	0	0	-

Data are given as n (%). CT, chemotherapy

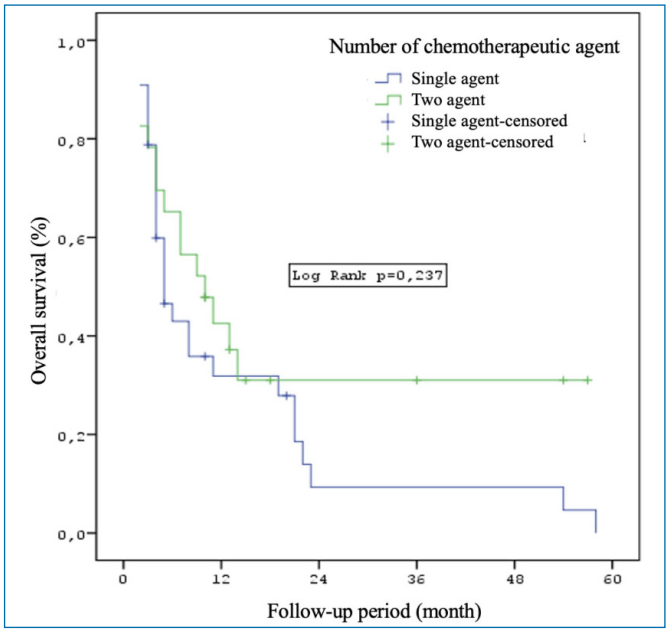


Figure 1. Survival curve for overall survival comparison between chemotherapy regimens

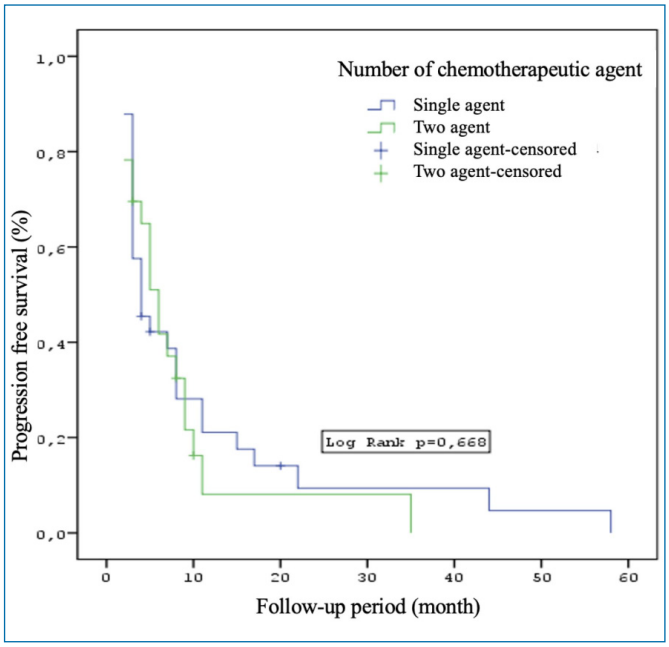


Figure 2. Survival curve for progression-free survival comparison between chemotherapy regimens

DISCUSSION

In our study, we found no statistically significant difference between double chemotherapy regimens and single chemotherapy regimens in terms of survival and side effects in the first-line treatment of patients aged 80 years and older with HER-2 negative metastatic/recurrent GC.

The survival benefit of systemic therapy, in addition to the best supportive care, compared with the best supportive care alone in patients with advanced GC has been demonstrated in several randomized trials.[10-12] In a comparison between chemotherapy and best supportive care, patients who received chemotherapy in addition to best supportive care for advanced GC had longer OS (8 vs. 5 months) and PFS (5 vs. 2 months).[10] In a meta-analysis by Wagner et al.[13] those receiving combination therapy for metastatic disease had an overall survival benefit compared to those receiving monotherapy. Also, as expected, the

frequency of side effects was higher in patients receiving combination therapy compared to monotherapy. In a phase III randomized trial, the addition of docetaxel to cisplatin-fluorouracil therapy improved radiological response rates and OS but was associated with significantly increased toxicity.[14]

The ESMO gastric cancer guideline supports dose-reduced oxaliplatin-based chemotherapy for elderly or frail patients, based on results from the phase III GO-2 trial15 showing lower toxicity and comparable survival outcomes compared to standard dose.[4] In a phase 2 study by Graziano et al.[16] evaluating cisplatin plus 5-fluorouracil treatment in GC patients aged 65 years and older, 58 patients were studied and the disease control rate was 43%, and grade 3-4 neutropenia was seen in 17% of patients. In our study, grade 3-4 neutropenia and grade 3-4 anemia were detected in 13% and 13% of patients using double-agent chemotherapy, respectively.

In a retrospective analysis using data from 3 large randomized trials, 257 of 1080 patients with gastro-oesophageal cancer were over 70 years of age. Response rates, overall survival, and incidence of grade 3 or 4 toxicity were similar between the two age groups, suggesting that patients over 70 years of age derive a similar benefit from chemotherapy to younger patients. Patients over 70 years of age received lower doses of chemotherapy, so results showing no increase in toxicity with age should be interpreted with caution.[17] In a phase III study in Korea in patients aged 70 years and older, adding oxaliplatin to capecitabine showed a survival benefit with acceptable toxicity.[18] In a study evaluating 178 patients aged 70 and older with metastatic GC, the use of single-agent and combination therapy was compared in the first-line treatment. No statistically significant difference was observed in PFS and OS.[19] In our study, although the survival between the groups was not statistically significant, the survival of patients using double agents was 5 months longer than those using single agents. This is extremely important for this disease and age group.

Despite the limitations of our study, including being single-center and retrospective, as well as having a relatively small sample size, it is noteworthy as the first study conducted in this patient group based on our review of the literature. Furthermore, our patient group was highly homogeneous, as HER-2 positive patients and those receiving treatment other than chemotherapy were excluded from the study. In the future, larger-scale, prospective, and well-designed studies are needed in this patient group.

Limitations

It was a retrospective study conducted in a single institution with a relatively small number of patients.

CONCLUSION

In our study, although the survival of patients receiving double chemotherapeutic agents did not reach statistical significance, the survival was twice that of patients receiving a single agent, and there was no statistically significant difference in terms of side effects. This indicates that even at the age of 80 years and over, we should be inclined to give a double agent if possible.

ETHICAL DECLARATIONS

Ethics Committee Approval

The required approval for conducting the study was obtained from the Ethics Committee of Van Training and Research Hospital, University of Health Sciences (Date: 16.08.2023, Decision no: 2023/17-03).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209-249.
2. Wagner AD, Syn NL, Moehler M, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev.* 2017;8(8):CD004064.
3. Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2022;20(2):167-192.
4. Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2022;33(10):1005-1020.
5. Maddams J, Utley M, Møller H. Projections of cancer prevalence in the United Kingdom, 2010-2040. *Br J Cancer.* 2012;107(7):1195-1202.
6. Hurria A, Lichtman SM. Clinical pharmacology of cancer therapies in older adults. *Br J Cancer.* 2008;98(3):517-522.
7. Coleman MP, Forman D, Bryant H, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet.* 2011;377(9760):127-138.
8. Sezigin Y, Urun Y. Chemotherapy efficacy and tolerability in metastatic gastric cancer patients aged 75 years and older. *EJMI.* 2023;7(4):487-493.
9. Liao PW, Cheng SB, Chou CW, et al. Chemotherapy for metastatic gastric cancer: does Age Matter? A single-center, retrospective, real-world study. *Clin Med Insights Oncol.* 2022;16:11795549221123617.
10. Glimelius B, Ekström K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol.* 1997;8(2):163-168.
11. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer.* 2011;47(15):2306-2314.
12. Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol.* 2012;30(13):1513-1518.
13. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol.* 2006;24(18):2903-2909.
14. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol.* 2006;24(31):4991-4997.

15. Hall PS, Swinson D, Cairns DA, et al. Efficacy of reduced-intensity chemotherapy with oxaliplatin and capecitabine on quality of life and cancer control among older and frail patients with advanced gastroesophageal cancer: the GO2 phase 3 randomized clinical trial. *JAMA Oncology*. 2021;7(6):869-877.
16. Graziano F, Santini D, Testa E, et al. A phase II study of weekly cisplatin, 6S-stereoisomer leucovorin and fluorouracil as first-line chemotherapy for elderly patients with advanced gastric cancer. *Br J Cancer*. 2003;89(8):1428-1432.
17. Trumper M, Ross PJ, Cunningham D, et al. Efficacy and tolerability of chemotherapy in elderly patients with advanced oesophago-gastric cancer: a pooled analysis of three clinical trials. *Eur J Cancer*. 2006;42(7):827-834.
18. Hwang IG, Ji JH, Kang JH, et al. A multi-center, open-label, randomized phase III trial of first-line chemotherapy with capecitabine monotherapy versus capecitabine plus oxaliplatin in elderly patients with advanced gastric cancer. *J Geriatr Oncol*. 2017;8(3):170-175.
19. Sun DS, Jeon EK, Won HS, et al. Outcomes in elderly patients treated with a single-agent or combination regimen as first-line chemotherapy for recurrent or metastatic gastric cancer. *Gastric Cancer*. 2015;18(3): 644-652.

Journal of Current Hematology & Oncology Research

Case Report

DOI: 10.51271/JCHOR-0030

Get two with one: bevacizumab treatment in hereditary hemorrhagic telangiectasia with concomitant cirrhosis

Serhat Çelik[1], Leylagül Kaynar[2]

[1]Department of Hematology, Yıldırım Beyazıt University Yenimahalle Training and Research Hospital, Ankara, Turkiye
[2]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Medipol Mega University, İstanbul, Turkiye

Cite this article: Çelik S, Kaynar L. Get two with one: bevacizumab treatment in hereditary hemorrhagic telangiectasia with concomitant cirrhosis. *J Curr Hematol Oncol Res.* 2023; 1(1): 15-17.

Corresponding Author: Serhat Çelik, serhatcelikmd@gmail.com

Received: 19/12/2023 ◆ **Accepted**: 04/01/2024 ◆ **Published**: 12/02/2024

ABSTRACT

Hereditary hemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu syndrome is a birth defect of the blood vessels that causes telangiectasias and arteriovenous malformations. HHT is a rare, autosomal dominant vascular disorder affecting approximately 1 in 8000 people. This multisystem angiogenic disorder is genetically and phenotypically variable, with the most common symptom being severe and recurrent epistaxis. ALK1, TGF-β, and VEGF are involved in its pathogenesis. VEGF increases mitotic activity in vascular endothelial cells, leading to uncontrolled angiogenesis and the formation of fragile vessels. Bevacizumab is used in the treatment of HHT by inhibiting VEGF. We present our patient, who developed hepatic encephalopathy due to hemorrhages with diffuse telangiectasias of the skin and tongue due to HHT and achieved an effective response to both conditions with bevacizumab.

Keywords: Bevacizumab, hereditary hemorrhagic telangiectasia, Osler-Weber-Rendu syndrome, telangiectasia

INTRODUCTION

Osler-Weber-Rendu syndrome, also known as hereditary hemorrhagic telangiectasia (HHT), is a developmental disorder of the vascular system that causes telangiectasias and arteriovenous malformations.[1] Although it is one of the most common monogenic disorders, it is usually undiagnosed. The most common features are epistaxis and telangiectasias on the lips, hands, and oral mucosa, which usually have a mild course. The management of vascular malformations in HHT is very important. Telangiectasias in the nasal and gastrointestinal mucosa and arteriovenous malformations in the brain may often present with bleeding.[2] Bevacizumab is a vascular endothelial growth factor (VEGF) inhibitor and reduces epistaxis, telangiectasia, and iron deficiency anemia.

We present our patient, who developed hepatic encephalopathy due to hemorrhage with diffuse telangiectasias on the skin and tongue due to HHT and achieved an effective response to both conditions with bevacizumab.

CASE

A 65-year-old woman was diagnosed with chronic liver parenchymal disease (CLD) and HHT. She was admitted to the hematology outpatient clinic due to the development of telangiectasias in the mouth, especially on the tongue, and in different parts of her body. Her cognitive functions declined, and laboratory tests revealed hemoglobulin (Hb) 9 g/dl and increased liver function tests. The patient was consulted for gastroenterology, and her ammonia level was 97 µmol/L. She was evaluated for decompensated cirrhosis and hepatic encephalopathy stage 1. With off-label admission, bevacizumab was started at a dose of 5 mg/kg at 2-week intervals. One week after the first dose, ammonia decreased to 51 µmol/L, and cognitive functions returned to normal. It decreased to 25 µmol/L at the end of the second week and always remained in the normal range (**Figure 1**). Hb levels increased to 12.1 g/dl in the fourth week without any other treatment (**Figure 2**). The patient's tongue telangiectasias completely normalized at the beginning of the second week.

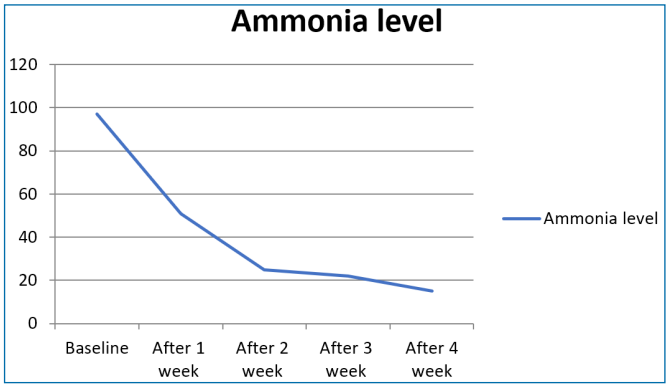


Figure 1. Ammonia levels (µmol/L) after bevacizumab treatment

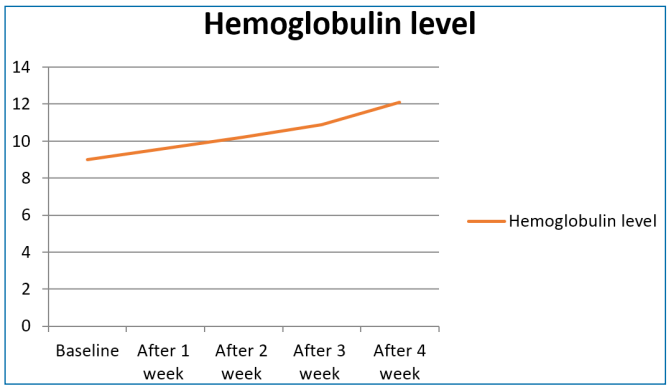


Figure 2. Hemoglobulin levels (g/dl) after bevacizumab treatment

DISCUSSION

HHT is a genetic disorder characterized by uncontrolled multisystem angiogenesis with epistaxis, telangiectasias, gastrointestinal bleeding, iron deficiency anemia, and arteriovenous malformations. It is usually associated with increased VEGF.[1] HHT is a rare, autosomal dominant vascular disease that occurs in approximately 1 in 8000 individuals.[1,2] This multisystem angiogenic disorder is genetically and phenotypically variable, and the most common symptom is severe and recurrent epistaxis. Other clinical features include mucocutaneous telangiectasias, gastrointestinal bleeding, iron deficiency anemia, and arteriovenous malformations, most commonly in the lung, brain, and liver.[3] ALK1, TGF-β, and VEGF play a role in its pathogenesis.[4]

VEGF increases mitotic activity in vascular endothelial cells and leads to uncontrolled angiogenesis and the formation of fragile vessels.[5] Bevacizumab is used in the treatment of HHT by inhibiting VEGF.

Hemorrhages in the CLD may lead to decompensation and the development of hepatic encephalopathy, as in our patient. After bevacizumab, ammonia levels normalized in our patient in two weeks.

Epperla et al.[6] gave bevacizumab to people who had bleeding and telangiectasias and saw that their Hb levels rose from 10 g/dl to 14.2 g/dl in 4 weeks without any other treatment to help. In our patient, an increase of 3 g/dl was observed during the same period. The treatment dose was 10 mg/kg/2 weeks in the case of Epperla et al. and 5 mg/kg/2 weeks in our case. Again, in this case, significant improvement was observed in telangiectasias during the same period as in ours.

CONCLUSION

In HHT, bevacizumab inhibited VEGF, preventing the development of fragile vessels and telangiectasias and preventing the development of decompensated cirrhosis and hepatic encephalopathy due to hemorrhage.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Fleagle JM, Bobba RK, Kardinal CG, Freter CE. Iron deficiency anemia related to hereditary hemorrhagic telangiectasia: response to treatment with bevacizumab. *Am J Med Sci.* 2012;343(3):249-251.
2. Sadick H, Riedel F, Naim R, et al. Patients with hereditary hemorrhagic telangiectasia have increased plasma levels of vascular endothelial growth factor and transforming growth factorbeta1 as well as high ALK1 tissue expression. *Haematologica.* 2005;90(6):818-928.
3. Bose P, Holter JL, Selby GB. Bevacizumab in hereditary hemorrhagic telangiectasia. *N Engl J Med.* 2009;360(20):2143-2144.
4. Oosting S, Nagengast W, de Vries E. More on bevacizumab in hereditary hemorrhagic telangiectasia. *N Engl J Med.* 2009;361(9):931.
5. Dupuis-Girod S, Ginon I, Saurin JC, et al. Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output. *JAMA.* 2012;307(9):948-955.
6. Epperla N, Hocking W. Blessing for the bleeder: bevacizumab in hereditary hemorrhagic telangiectasia. *Clin Med Res.* 2015;13(1):32-35. doi: 10.3121/cmr.2013.1205

Journal of Current Hematology & Oncology Research

Letter to the Editor

DOI: 10.51271/JCHOR-0031

Contributions of ELN2022 update and new genetic analysis tests in the risk assesment and treatment of acute myeloid leukaemia

Seda Yılmaz, Metin Bağcı, Abdulkadir Baştürk

Department of Adult Haematology, Konya City Hospital, Konya, Turkiye

Cite this article: Yılmaz S, Bağcı M, Baştürk A. Contributions of ELN2022 update and new genetic analysis tests in the risk assesment and treatment of acute myeloid leukaemia. *J Curr Hematol Oncol Res.* 2024;2(1):22-23.

Corresponding Author: Seda Yılmaz, dr46sedakurtulus@hotmail.com

Received: 10/12/2023 ◆ **Accepted**: 11/01/2024 ◆ **Published**: 12/02/2024

Dear Editor,

Acute myeloid leukaemia (AML) is a heterogeneous disease including cytogenetic and molecular abnormalities.[1,2] Age, performance status and specific genetic characteristics are important in prognosis.[3-5] Both directing consolidation treatment and having genetic-based treatment targets have made genetic results even more important.[6] The European LeukemiaNet (ELN) 2022 report was published by expanding the genetic mutation profile.[7] In order to question what this update has changed in clinical practice, we reviewed the data of patients with acute myeloid leukaemia in whom myeloid panel was studied by Next-Generation Sequencing (NGS).

The data of patients who were followed up in our clinic due to AML and whose myeloid panel was studied by NGS method at the time of diagnosis were analysed. The ELN 2017 and ELN 2022 risk categories of 10 patients were determined.

Among the participants, 30% were female and 70% were male. The median age of the participants was 60±18.41 (25-81) years. According to the ELN2017 AML classification, 20% of the patients were in the good, 50% in the intermediate, 30% in the poor risk group, while according to the ELN2022 AML classification, 20% were in the good, 20% in the intermediate, 60% in the poor risk group. FMS-like tyrosine kinase 3 (FLT3 -ITD) mutation, which can direct the treatment with myeloid panel, was found positive in myeloid panel (NGS) in 2 patients who were found negative with Polymerase Chain Reaction (PCR) method. In addition, EZH2, SF3B1, SRSF2 were found positive in 3 patients and were included in the poor risk group from the intermediate risk group. When the changes in the risk group were analysed, it was observed that 30% of the patients had a change. No statistically significant difference was found between patients with and without changes in risk status with the last ELN report in terms of gender, hemogram parameters at ECOG diagnosis, response to induction regimen and outcome. Targeted agents were added to the treatment of patients with myeloid panel reports (**Table**). In addition, allogeneic bone marrow transplantation was planned for patients in the high-risk group. A total of 60% of our patients are surviving (**Figure**).

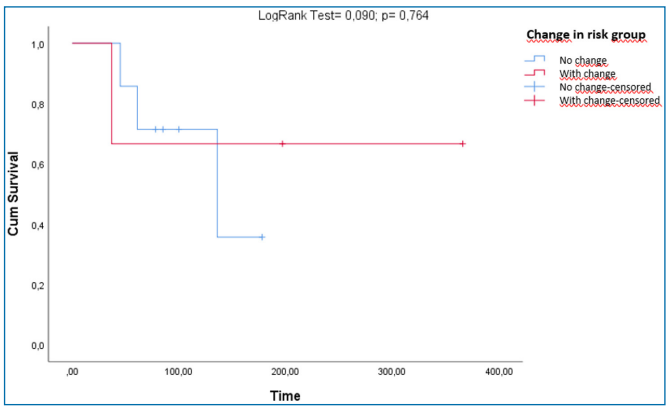


Figure. The relationship between BMI and WCM, BMI and BFP

Table. Genetic risk characteristics of patients and ELN classification

Patient	Genetic Outcome	ELN 2017	ELN2022	Mutations detected differently between tests
1	SRSF2, EZH2	Intermediate	Poor	
2	SF3B1, SRSF2	Intermediate	Poor	
3	NPM1	Good	Good	
4	t(8;21)	Good	Good	
5	FLT3(PCR)*, NPM1	Intermediate	Intermediate	
6	11q23	Poor	Poor	
7	-10,-12, del(5q), FLT3, U2AF1, ASXL1		Poor	FLT3(PCR) negative
8	EZH2, FLT3	Intermediate	Poor	FLT3(PCR) negative
9	No feature	Intermediate	Intermediate	IDH1
10	-7	Poor	Poor	

*Allelic ratio:0.8

ELN 2017 is a generally accepted risk classification.[8] The extent to which ELN 2022 recommendations will lead to changes in clinical practice is exciting. The main difference of ELN 2022 risk classification compared to ELN 2017 risk classification is the expansion of somatic gene mutation, definition of variant allele fraction, and removal of FLT3 mutation allele burden.[6,7] In our study, a change was found in

the risk category of 30% of our patients according to the new risk classification. In addition, while FLT3 was found negative by PCR in 2 patients, it was found positive by myeloid next generation sequencing panel. Again, thanks to this panel, IDH mutation, which is another targeted treatment chance, was detected.

We suggest that genetic risk analyses should be performed with as large a panel and different analysis methods as possible and these tests should be combined and evaluated.

Keywords: Acute myeloid leukemia, classifications, next generation sequencing, polymerase chain reaction

REFERENCES

1. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221.
2. Tyner JW, Tognon CE, Bottomly D, et al. Functional genomic landscape of acute myeloid leukaemia. *Nature*. 2018;562(7728):526-531.
3. Sekeres MA, Peterson B, Dodge RK, et al. Differences in prognostic factors and outcomes in African Americans and whites with acute myeloid leukemia. *Blood*. 2004;103(11):4036-4042.
4. Olesen LH, Aggerholm A, Andersen BL, et al. Molecular typing of adult acute myeloid leukaemia: significance of translocations, tandem duplications, methylation, and selective gene expression profiling. *Br J Haematol*. 2005;131(4):457.
5. Estey EH. Therapeutic options for acute myelogenous leukemia. *Cancer*. 2001;92(5):1059.
6. El Chaer F, Hourigan CS, Zeidan AM. How I treat AML incorporating the updated classifications and guidelines. *Blood*. 2023;141(23):2813-2823.
7. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood, J Am Soc Hematol*. 2022;140(12):1345-1377.
8. Tallman MS, Wang ES, Altman JK, et al. Acute myeloid leukemia, version 3.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2019;17(6):721-749.