Yemeni Journal of Medical and Health Research

Changes in White Blood Cells in Solid Cancers Before First Cycle and After the Third Cycle of Chemotherapy

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DOI: https://doi.org/10.47372/yjmhr.2023(12).1.3

Abstract

Introduction: Chemotherapy is a nonspecific drug that kills or damages fast growing cells; cancer cells and noncancerous body cells including white blood cells (WBCs). Changes to the WBCs can begin as early as few days to a week after starting chemotherapy treatment. This study was conducted to assess the effect of three cycles of chemotherapy on white blood cells compared to that at diagnosis of solid cancers.

Methods: This is a prospective study included 100 patients diagnosed with solid cancers and subjected to chemotherapy in the National Cancer Centers in Aden and Taiz governorates, during 2020. Complete blood count was done for all patients prior to the first cycle and after the third cycle of chemotherapy.

Results: The mean total WBCs count, absolute neutrophil count (ANC), absolute eosinophile count (AEC) and absolute monocyte count (AMC) were statistically significantly lower after third cycle when compared to that before first cycle. Meanwhile, the mean Absolute Lymphocyte count (ALC) and absolute basophile count (ABC) did not show any significant difference. Only 9.0% of solid cancer patients had leucocytosis at diagnosis. The percentage of patients with low WBCs count significantly increased after the third cycle, while the percentage of patients with normal WBCs count significantly decreased after the third cycle. The ANC showed a significant statistical difference between the counts prior to the first cycle of chemotherapy and after the third cycle of chemotherapy. Normal ANC was observed among 74.0% of patients before the first cycle of chemotherapy and it decreased to 53.0% after the third cycle. Neutropenia with all grades of severity was statistically significantly higher after the third cycle. The mean total WBCs count decreased after the third cycle in all types of cancers, and this decrease was statistically significant in patients with breast cancers and lymphomas, while other cancers did not show such significance

Conclusion: This study concluded that in patients with solid cancer, WBCs and mainly the ANC significantly decreased after the third cycle of chemotherapy to a level that may be severe to affect patients' overall health.

Keywords: Solid cancers, WBCs, Chemotherapy, First cycle, Third cycle.

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التغيرات في خلايا الدم البيضاء في السرطانات الصلبة قبل الدورة الأولى وبعد الدورة الثالثة من العلاج الكيميائي

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ملخص الدراسة

المقدمة: العلاج الكيميائي دواء غير متخصص، يقتل أو يتلف الخلايا سريعة النمو كالخلايا السرطانية وخلايا الجسم غير السرطانية بما في ذلك خلايا الدم البيضاء، حيث تبدأ التغييرات على كرات الدم البيضاء في وقت مبكر من بضعة أيام إلى أسبوع بعد بدء العلاج الكيميائي. أجريت هذه الدراسة لتقييم تأثير ثلاث دورات من العلاج الكيميائي على خلايا الدم البيضاء مقارنة بتأثيرها عند بدء تشخيص السرطانات الصلبة.

المنهجية: هذه دراسة مستقبلية شملت 100 مريض تم تشخيص إصابتهم بالسرطانات الصلبة وخضعوا للعلاج الكيميائي في المراكز الوطنية للسرطان في محافظتي عدن وتعز خلال عام 2020. تم إجراء تعداد دم كامل لجميع المرضى قبل الدورة الأولى وبعد الدورة الثالثة من العلاج الكيميائي.

النتائج: كان متوسط إجمالي عدد كرات الدم البيضاء، والعد المطلق للعدلات، والحمضية، و الوحيدات أقل إحصائيًا بشكل ملحوظ بعد الدورة الثالثة بالمقارنة مع ذلك قبل الدورة الأولى. وفي الوقت نفسه، لم يُظهر متوسط العد المطلق للخلايا الليمفاوية و الخلايا القاعدية أي فرق كبير. فقط 9.0 ٪ من مرضى السرطانات الصلبة لديهم كثرة الكريات البيضاء عند التشخيص. زادت النسبة المئوية للمرضى الذين يعانون من انخفاض عدد كرات الدم البيضاء بشكل ملحوظ بعد الدورة الثالثة. في حين أن النسبة المئوية للمرضى الذين لديهم تعداد طبيعي لكرات الدم البيضاء انخفضت بشكل ملحوظ بعد الدورة الثالثة. أظهر عدد العدلات المطلق فرق ذات دلالة إحصائية بين الأعداد قبل الدورة الأولى من العلاج الكيميائي وبعد الدورة الثالثة من العلاج الكيميائي. لوحظ وجود الخلايا العدلية الطبيعي عند 74.0٪ من المرضى قبل الدورة الأولى من العلاج الكيميائي وانخفض إلى 53.0٪ بعد الدورة الثالثة. كانت قلة الخلايا العدلية مع جميع درجات الشدة أعلى إحصائيًا بشكل ملحوظ بعد الدورة الثالثة. انخفض متوسط العدد الإجمالي لكرات الدم البيضاء بعد الدورة الثالثة في جميع أنواع السرطانات ، وكان هذا الانخفاض ذا دلالة إحصائية لدى مرضى سرطان الثدي والأورام اللمفاوية ، بينما لم تظهر السرطانات الأخرى مثل هذه الدلالة.

الاستنتاج: خلصت هذه الدراسة إلى أن المرضى المصابين بالسرطانات الصلبة ، خلايا الدم البيضاء ، وبشكل رئيسي العدد المطلق الخلايا العدلية، انخفضت بشكل ملحوظ بعد الدورة الثالثة من العلاج الكيميائي إلى مستوى قد يكون شديدًاومؤثراً على الصحة العامة للمرضى.

الكلمات المفتاحية: السرطانات الصلبة، خلايا الدم البيضاء، العلاج الكيميائي، الدورة الأولى، الدورة الثالثة.

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Introduction

Cancer is a major public health problem worldwide and the second leading cause of death worldwide. In 2020, an estimated 18.1 million cancer cases around the world, of these, 9.3 million cases were in men and 8.8 million in women. The most common cancers globally are breast, lung and colorectal cancers [1].

The burden of cancer is substantial in countries of all income levels. The rates of many cancers are being brought under control in Western countries through decreasing prevalence of known risk factors, early detection, and improved treatment. In contrast, rates for cancers commonly found in high-income countries are now rising in many low-income countries due to increase in risk factors typical of western countries, such as smoking, excess body weight, physical inactivity, and changing reproductive patterns. Moreover, these countries continue to bear a disproportionate burden of infection-related cancers [2].

In Yemen, accurate cancer incidence is unknown due to limited diagnostic and clinical resources and poor quality of medical records. In addition to the ongoing civil conflicts that add a mystery to the current situation. According to the Global Cancer Observatory of the International Agency for Research on Cancer, the total number of cases reported in Yemen in the year 2020 was 16,476 new cases [3].

Chemotherapy treatments for cancer are drugs that kill or damage fast-growing cells. Cancer cells grow and divide quickly, so these drugs can kill cancer, potentially slowing tumor growth or even shrinking it. Chemotherapy is nonspecific and is often administered to the entire body, so that noncancerous fast-growing body cells may also be damaged and killed. Some rapidly dividing normal cells in the body, like those in the bone marrow that produce WBCs are affected [4].

These changes to the white blood cells can begin as early as a few days to a week after starting chemotherapy treatment. After that, it keeps dropping until a week or two after the chemotherapy treatment cycle finishes, then it begins to recover [5].

In the current study, white blood cells were estimated in solid cancers prior to the start of the first chemotherapy course and compared to that after the third cycle of chemotherapy, to assess the effects of chemotherapy on white blood cells, total and differential counts, after three cycles of chemotherapy.

Methods

Study design and setting

This is prospective descriptive study included 100 patients diagnosed with solid cancers and subjected to chemotherapy in the National Cancer Centers in Aden and Taiz governorates, during 2020. About (70.0%) were taken from Taiz Oncology Center and (30.0%) were taken from Aden Oncology Center.

Study population

The study included patients with any type of solid cancers, of any age, who started first line chemotherapy and continued till third cycle in the study area, during the study period. Patients presented with infection were managed prior to inclusion in the study. We excluded patients who were managed for relapsed or refractory solid cancers or those who discontinued treatment after first or second cycle.

Data collection

Data were collected by direct interview with patients and relatives in addition to collection of some data from patients' medical records. The included solid tumors were breast, gastrointestinal tract, head and neck, gynecological, pulmonary, hepatobiliary, pancreatic, lymphomas, sarcomas, retinoblastoma and neuroblastoma. The following variables were studied: sex of patient, age, type of solid tumor, the presence of metastasis. In addition, complete blood count was done for all patients prior to the first cycle and after the third cycle of chemotherapy.

Normal total WBCs count was considered (4.0-10.0x10^9/L), below (4.0x10^9/L) was considered low count, and above (10.0 x10^9/L) was considered high count [6].

The interval between the first and the third cycle was differing according to the type of protocol used for treatment. Some cycles were given every 2 weeks as in Hodgkin's lymphoma (HL) and gastrointestinal cancers, others every 3 weeks as in breast cancers and Non-Hodgkin's lymphoma (NHL) or every 4 weeks as in sarcomas.

Statistical analysis

Data collected were analyzed by the SPSS program version 24. Quantitative data were tested for normality using the Kolmogorov-Smirnov test, which revealed parametric distribution except for the age of patients. Operative parameters were presented as mean values with standard deviation and tests by the student t-test with a 95% level of significance. The age of patients was a non-parametric variable, presented as a median value with range and tested by the Mann-Whitney test. Qualitative variables were tested by the Chi-square and Fisher exact tests as appropriate. A p-value of ≤ 0.05 was considered statistically significant.

Ethical considerations: This study was approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, Aden University. All accessed patients were included after obtaining an informed verbal consent.

Results

During the study period, 100 patients with solid cancers were investigated prior to chemotherapy and after the third cycle of chemotherapy. The percentage of female patients (58.0%) was higher than that of male patients (42.0%) with solid cancers. The age of the studied cancer patients was ranging from 2 to 80 years and the median age was 50.0 years. For the age group, a higher percentage aged 50 years and more (63.0%) and the remainder (37.0%) were younger than 50 years of age. The common types of the studied solid cancers were breast cancers (23.0%), gastrointestinal tract cancers (18.0%) including colonic and anorectal cancers, head and neck cancers (12.0%), lymphomas (12.0%) including HL (7.0%) and NHL (5.0%), sarcomas (11.0%) including soft tissue sarcoma and Ewing's sarcoma, gynecological cancers (10.0%), and lung cancer (8.0%). Other solid cancers studied were hepatobiliary and retinoblastoma (2.0% for each), and pancreatic and neuroblastoma (1.0% for each). The studied patients with solid cancers were 51.0% with metastasis and 49.0% without metastasis as seen in Table 1.

Table 1: Sex, Age and Types of the Studied Solid Cancers (n=100)

Item	No.	%
Sex		
Female	58	58.0
Male	42	42.0
Age group (years)		
< 50 years	37	37.0
≥ 50 years	63	63.0
Median age (years) (Min. – Max.)	50.0 (2.0 – 80.0)	
Type of cancer:		
Breast cancer	23	23.0
Gastrointestinal tract cancers	18	18.0
Head and neck cancers	12	12.0
Lymphomas	12	12.0
Sarcomas	11	11.0
Gynecological cancers	10	10.0
Lung cancers	8	8.0
Other cancers*	6	6.0
Metastasis		
Yes	51	51.0
No	49	49.0

* Include: 2 hepatobiliary, 2 retinoblastoma, 1 pancreatic and 1 with neuroblastoma

When comparing WBCs counts (total and differential), it was found that the mean total WBCs count, the mean ANC, AEC and AMC were statistically significantly lower after the third cycle when compared to that before the first cycle (p<0.05). Meanwhile, the mean ALC and ABC, although were lower after the third cycle in comparison to that before the first cycle, did not show any significant difference (p>0.05), [Table 2]

Table 2: White Blood Cells Parameters before First Cycle and after the Third Cycle of Chemotherapy

White blood cells (x 10^9/L)	Before 1st cycle (n=100)	After 3rd cycle (n=100)	Statistics
	Mean ± SD (Min. – Max.)	Mean ± SD (Min. – Max.)	p #
Total White blood cells	6.42 ± 3.66 (1.51 - 27.22)	4.81 ± 2.50 (0.46 - 16.00)	0.001*
Absolute neutrophil count (ANC)	3.86 ± 1.12 (1.02 - 20.42)	2.59 ± 2.06 (0.08 - 13.12)	0.001*
Absolute Eosinophile count (AEC)	0.15 ± 0.18 (0.00 - 1.17)	0.09 ± 0.01 (0.00 - 0.70)	0.010*
Absolute Basophile count (ABC)	0.49 ± 0.31 (0.06 - 1.54)	0.41 ± 0.37 (0.00 - 2.25)	0.099
Absolute Lymphocyte count (ALC)	1.92 ± 0.87 (0.44 - 5.59)	1.72 ± 0.76 (0.18 - 3.95)	0.085
Absolute Monocyte count (AMC)	0.024 ± 0.007 (0.00 - 0.14)	0.006 ± 0.0009 (0.00 - 0.05)	0.001*

#Calculated by the Student t-test for two means. *p-value ≤ 0.05 is statistically significant.

Stratification of the total WBCs count into low, normal, and high counts showed that the percentage of patients with low WBCs count (<4.0 x109/L) significantly increased after the third cycle while the percentage of patients with normal WBCs count (4.0-10.0 x109/L) significantly decreased after the third cycle. Only 9.0% of solid cancer patients had leucocytosis at diagnosis and prior to the start of chemotherapy. These relationships were found statistically significant (p<0.05). The absolute neutrophil count when classified as normal versus neutropenia with variable severity, showed a significant statistical difference between the counts prior to the first cycle of chemotherapy and after the third cycle of chemotherapy (p<0.05). Normal ANC (≥ 2.0 x 109/L) was observed among the higher percentage of patients (74.0%) before the first cycle of chemotherapy and it decreased to 53.0% after the third cycle. Neutropenia with all grades of severity was statistically significantly higher after the third cycle when compared to the percentages observed before the first cycle of chemotherapy (p<0.05). [Table 3]

Table 3: Total White Blood Cells Level and Absolute Neutrophil Count before First Cycle and after the Third Cycle of Chemotherapy

Parameter	Before 1st cycle (n=100)		After 3rd cycle (n=100)		χ^2 *p*
	No.	%	No.	%	
White blood cells level (x 10^9/L)					
< 4.0	20	20.0	42	42.0	χ^2:11.02, *p*=0.011*
4.0 – 10.0	71	71.0	52	52.0	
> 10.0	9	9.0	6	6.0	
Absolute neutrophil count (x 10^9/L)					
Severe Neutropenia (< 0.5 x 10^9/L)	1	1.0	4	4.0	χ^2:10.8, *p*=0.012*
Moderate Neutropenia (0.5 - 1.0 x 10^9/L)	3	3.0	9	9.0	
Mild Neutropenia (1.01-1.99 x 10^9/L)	22	22.0	34	34.0	
Normal count (≥ 2.0 x 10^9/L)	74	74.0	53	53.0	

*p-value ≤ 0.05 is statistically significant.

The mean total WBCs were not statistically significant different between the studied types of solid cancers before the start of the first cycle as well as after the third cycle of chemotherapy. However, in comparison to the mean WBCs count after the third cycle, it was found that the mean total WBCs count decreased after the third cycle in all types of cancers, and this decrease was statistically significant in patients with breast cancers and lymphomas (p<0.05). While other cancers did not show such significance (p>0.05). Table4]

Table 4: Mean Total White Blood Cells According to the Type of Solid Cancer

Type of cancer	No.	Total White blood cells (x 10^9/L)		Statistics
		Before 1st cycle Mean ± SD (Min.-Max.)	After 3rd cycle Mean ± SD (Min.-Max.)	*p*
Breast	23	6.08 ± 2.99 (2.60 - 17.38)	4.52 ± 1.67 (2.75 -10.30)	0.034*
GIT	18	5.62 ± 2.47 (1.51 - 11.65)	4.30 ± 1.73 (1.99 -7.23)	0.072
Head and neck	12	5.47 ± 3.20 (2.46 - 14.60)	5.02 ± 1.59 (3.03 -8.81)	0.667
Lymphomas	12	6.50 ± 3.25 (2.97 - 12.90)	3.92 ± 1.98 (1.30 - 8.29)	0.027*
Sarcomas	11	9.72 ± 7.50 (2.10 - 27.22)	5.26 ± 2.85 (0.46 - 10.50)	0.080
Gynecological	10	6.08 ± 1.76 (3.90 - 8.81)	5.84 ± 4.60 (1.26 - 16.00)	0.879
Lung	8	6.52 ± 2.25 (3.57 - 11.01)	6.11 ± 3.80 (2.50 - 12.18)	0.797

Other cancers*	6	6.28 ± 2.15 (4.05 - 8.60)	4.59 ± 2.05 (2.46 - 8.10)	0.194
Total	100	$p^1 = 0.139$	$p^1 = 0.445$	--

GIT: Gastrointestinal tract, *p* was calculated by the Student t-test for two means , p^1 was calculated by the one way ANOVA test between all types of cancer, **p*-value ≤ 0.05 is statistically significant.

Discussion

White blood cells are heterogeneous group of nucleated cells that can be found in circulation for at least a period of their life. They play a most important role in phagocytosis and immunity and therefore in defense against infection [7]. This study was focused on WBCs count at the presentation of patients with solid cancers as well as after three cycles of chemotherapy.

The mean WBCs count at the presentation of the studied solid cancers was (6.42 ± 3.66 x10^9/l), which is not far from that observed by Wu *et al*.,[8]. among patients with colorectal cancer (5.78 x10^9/l), as well as the Saudi study among solid cancer female patients (8.35±3.94 x10^9/l) [9]. After the third cycle of chemotherapy, the current study noticed significantly lower mean total WBCs count, ANC, AEC and AMC ($p<0.05$). This significant difference was not observed with the mean ALC and ABC. In the Chinese study of Wu *et al*.,[8]. among patients with colorectal cancer, after adjuvant chemotherapy significant decreased in the values of total WBC and ANC and insignificant difference in the ABC, which are similar to our finding. However, they noticed an increase in the value of AEC and insignificant effects on the levels of AMC, which was not observed in our patients.

In the current study, most patients with solid cancers presented with normal WBCs count. In the study of Almehmadi in Taif, Saudi Arabia [9]. among female patients with solid cancers, a higher percentage of patients with normal WBCs count (81.4%) at diagnosis of solid cancer was found. This is not far from that reported in our studied solid cancers (71.0%).

The present study showed that only 9.0% of patients had leucocytosis at diagnosis of solid cancer. It is consistent with that observed in China by Qiu *et al*.,[10]. among patients with solid cancers, where 11.7% of their patients presented with leucocytosis. Elevated WBC count may be found in cancer patients at the time of diagnosis or during the follow-up period and it may be secondary to infections, bone marrow irritation or chronic steroid usage [11]. One possible mechanism of increased leucocytes at the presentation of solid cancers is the production of granulocyte and macrophage colony-stimulating factor (GM-CSF) by tumor cells, able to mobilize precursors in the bone marrow; interleukin-6, or vascular endothelial growth factor (VEGF) and both of which change cell differentiation [12].

Leukocytes may be actively involved in disease progression and cancer-associated thrombosis. Leukocytosis may be a marker of an underlying process such as more aggressive malignancy, more significant co-

morbidities, or inflammation. It has been demonstrated to be associated with increased mortality in several subgroups of cancer patients [13,14].

Leucopenia is a rare finding at the presentation of solid cancer patients. Paydas *et al*.,[15]. observed leucopenia among solid cancer patients who developed metastasis with subsequent bone marrow necrosis. In the current study, the percentage of patients with leucopenia at presentation was 20.0%, and all of them were found with metastasis.

Neutrophils play a critical role in the acute inflammatory response and host-defense mechanisms against bacterial infections. Damage to the host defense mechanisms by cytotoxic chemotherapy increases the risk of infection for cancer patients. Cytotoxic chemotherapeutic agents are widely known to cause immunosuppression, the extent of which is routinely ascertained by the absolute neutrophil count [16]. In the current study, it was found that the mean ANC at diagnosis and post-third cycle chemotherapies were 3.86 ± 1.12 x 10^{9}/L and 2.59 ± 2.06 x 10^{9}/L with a statistically significant difference (p= 0.01). This finding is consistent with that reported by Madu *et al*.,[17]. among 80 chemotherapy-naive patients with various solid cancers, where they reported the mean ANC pre-and post-chemotherapy were 3.7±2.2 x 10^{9}/L and 2.5±1.6 x 10^{9}/L with statistically significant difference (p= 0.010).

In the current study, normal ANC (≥ 2.0 x 10^{9}/L) was observed among the higher percentage of patients before the first cycle of chemotherapy (74.0%) and it decreased to (53.0%) after the third cycle. Chemotherapy-induced neutropenia is a dose-limiting toxicity of cytotoxic chemotherapy.

In the study of Abou Saleh *etal*.,[18]. in Oman, they reported chemotherapy-induced neutropenia among 50.0% of the studied 159 patients with solid cancers, which is not far from our finding (53.0%). However, a lower percentage was reported recently by Salako *et al*.,[19]. in Nigeria, who studied 113 patients with breast cancers, and reported chemotherapy-induced neutropenia among 31.9% of them. They further observed that the incidence of neutropenia decreased with increasing chemotherapy courses. They found only 12.7% with neutropenia after the third cycle of chemotherapy. Their lower percentage of chemotherapy-induced neutropenia was attributed to the introduction of GCSF in subsequent cycles of chemotherapy [19].

In relation to the type of solid cancers, it was found that the mean total WBCs count decreased after the third cycle in all types of cancers, and it was statistically significant in patients with breast cancers and lymphomas (p<0.05). Similar to our finding, what was reported by Madu *et al*.,[17]. among patients with breast cancers but not in lymphomas.

This study found a significant decrease in total WBCs and ANC after the third cycle of chemotherapy which can affect patients' health and overall quality of life. These findings mandate optimal intervention by oncologists to prevent disastrous consequences, especially in severe neutropenia.

Conclusion

This study concluded that in patient with solid cancer, WBCs and mainly the ANC, significantly decreased after the third cycle of chemotherapy to a level that may be severe to affect patients' overall health. This needs careful observation of patients after each cycle to manage as early as possible such morbid conditions.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022; 72: 7-33.
2. Torre L.A, Siegel R.L, Ward E.M, Jemal A. Global Cancer Incidence and Mortality Rates and Trends - An Update. Global Cancer Rates and Trends - An Update. Cancer Epidemiol Biomarkers Prev. 2016; 25(1): 16-27.
3. Bawazir A, Basaleem H, Badheeb A, Abdul Hamid G. General Oncology Care in the Republic of Yemen. In: Al-Shamsi H.O, Abu-Gheida I.H, Iqbal F, Al-Awadhi A. (eds) Cancer in the Arab World. Springer, Singapore. 2022: 2-20.
4. Lowenthal R.M, Eaton K. Toxicity ofchemotherapy. Hematology/Oncology Clinics. 1996; 10(4): 967-90.
5. Testart-Paillet D, Girard P, You B, Freyer G, Pobel C, Tranchand B. Contribution of modeling chemotherapy-induced hematological toxicity for clinical practice. Critical Reviews Oncol/hematol. 2007; 63(1): 1-11.
6. Stiene-Martin A. Leukocytes (also known as white blood cells or WBC) are so named because they are relatively colorless compared. In: Bernadette F. Rodak, Elaine M. Keohane, George A. Fritsma editors of Hematology: Clinical Principles and Applications. Chapter 12. Elsevier Saunders. China 2013; 134.
7. Wu J, Ge X.X, Zhu W, Zhi Q, Xu M.D, Duan, W, et al. Values of applying white blood cell counts in the prognostic evaluation of resectable colorectal cancer. Mol Med Rep. 2019; 19(3): 2330-40.
8. Almehmadi M.M. Association between random glucose level and leukocytes count in female cancer patients. Cureus 2020; 12(7): e8962.
9. Qiu M.Z, Xu R.H, Ruan D.Y, Li Z.H, Luo H.Y, Teng K.Y, et al. Incidence of anemia, leukocytosis, and thrombocytosis in patients with solid tumors in China. Tumor Biol. 2010; 31(6): 633-41.
10. Oguz A, Colak D, Ersoy U, Imamoglu I.G, Altinbas M, Unal D, et al. The effect of Haematological parameters on overall survival in advanced stage non small cell lung Cancer. Inter J Hematol Oncol. 2014; 2(24): 82-8.
11. Martins Tavares-Murta B, Murta E.F.C. Systemic leukocyte alterations in cancer and their relation to prognosis. Open Cancer J. 2008; 2(1): 53-8.
12. Gripp S, Moeller S, Bolke E, Schmitt G, Matuschek C, Asgari S, et al. Survival prediction in terminally ill cancer patients by clinical estimates, laboratory tests, and self-rated anxiety and depression. J Clin Oncol. 2007; 25:3313–20.

13. Schmidt H, Suciu S, Punt CJ, Gore M, Kruit W, Patel P, et al. Pretreatment levels of peripheral neutrophils and leukocytes as independent predictors of overall survival in patients with American Joint Committee on Cancer Stage IV Melanoma: results of the EORTC 18951 Biochemotherapy Trial. J Clin Oncol. 2007; 25:1562-9.
14. Paydas S, Ergin M, Baslamisli F, Yavuz S, Zorludemir S, Sahin B, et al. Bone marrow necrosis: of chemotherapy. Hematology/Oncolo gy Clinics. 1996; 10(4): 967-90.
Clinicopathologic analysis of 20 cases and review of the literature. Am J Hematol. 2002; 70: 300-5.
15. Lehman H.K, Segal B.H. The role of neutrophils in host defense and disease. J Allergy Clin Immunol. 2020; 145(6): 1535-44.
16. Madu A, Ocheni S, Ibegbulam O, Chukwura A, Madu K. Comparison of absolute neutrophil to CD4 lymphocyte values as a marker of immunosuppression in cancer patients on cytotoxic chemotherapy. Afr Heal Sci. 2015; 15(2): 581-9.
17. Abou Saleh M, Mafiana R.N, Za'abi A, Vaishnav R, Al Kindi S, Al-Zakwani I. Epidemiology of chemotherapy-induced neutropenia at a tertiary university hospital in Oman. Inter J Clin Pharmacy 2013; 35(6): 1036-9.
18. Salako O, Okunade K.S, Adeniji A.A, Fagbenro G.T, Afolaranmi O.J. Chemotherapy induced neutropenia and febrile neutropenia among breast cancer patients in a tertiary hospital in Nigeria. E-cancer Med Sci. 2021;15: 1188.