Quantifying Anticancer Drug Toxicity on White Blood Cell Count in Cancer Patients: A Mathematical and Computational Approach

by Muhammad Adeel

Quantifying Anticancer Drug Toxicity on White Blood Cell Count in Cancer Patients: A Mathematical and Computational Approach

Abstract

Objectives: White blood cells (WBCs) are immune cells that fight infections and cancers. However, many cancers and their treatment with chemotherapy negatively affect the WBCs count. For oncologists and physicians, it is important to know how much the WBCs count is affected to optimize drug administration. The data of breast cancer patients were included in this study because the largest number of cancer patients were suffering from breast cancer in the under-study hospital. This study presents a computational and mathematical approach to measure the effect on the WBCs count of breast cancer patients treated with chemotherapy with two anticancer drug combinations: docetaxel with cyclophosphamide (TC) and doxorubicin with cyclophosphamide (AC).

Methods: Between July 2016 and October 2021, to breast cancer patients, 4 cycles of chemotherapy (one cycle of 21 days) were administered intravenously using TC (75 mg/m^2 + 600 mg/m^2). Similarly, varying in cases, intravenous AC (60 mg/m^2 + 600 mg/m^2) was administered in each of the 4 cycles. The WBCs counts of the subjects affected by both TC and AC combinations were observed for comparison. An equation was derived to calculate the effect of TC and AC on WBCs count (eWBCc). The eWBCc of 171 patients who received TC and 154 patients who received AC were calculated by implantation of the derived equation using Python 3.8.

Results: Comparing the results of 171 patients, it is observed that, TC affected WBC count of a patient at lowest level by 12.29%, at maximum level by 69.64%, and on average by 34.13%. Whereas, comparing the results of 154 patients, AC affected WBC count of a patient at lowest level by 19%, at maximum level by 65.03%, and on average, by 44.36%. A paired t-test was used to analyze the statistical differences between the eWBCc of both TC and AC cohorts. This test indicates a statistically significant difference

between the eWBCc by TC and AC, as evidenced by the P-value of 0.000, which is less than the chosen significance level (alpha) of 0.05.

Conclusion: We conclude that TC remains less toxic than AC in affecting white blood cells count of the studied patients.

Keywords: Breast cancer, white blood cells count, chemotherapy, equation for effect on WBC, impact of anticancer on WBC

1 Introduction

Cancer is a threatening disease that is treated by highly toxic anticancer drugs that leave many side effects (Adeel et al., 2019). The deficiency in white blood cells (WBCs) count is seen in different types of cancer and during chemotherapy using different anticancer drugs (Wu et al., 2019). WBCs also known as leukocytes play a major role in infection immunity. WBCs are of five major types including eosinophils, basophils, monocytes, lymphocytes (T cells, B cells, and Natural Killer cells), and neutrophils. WBCs make up 1% of human blood. MedlinePlus, US National Library of Medicine (developed by National Institute of Health, US), reported that a cancer patient can acquire a low WBCs count from the tumor or from its chemotherapy (Gersten 2021). Cancer in the bone marrow can cause fewer WBCs production. The WBCs count can also be decreased when cancer is treated with chemotherapy. The chemotherapy can negatively affect bone marrow hematopoiesis which causes the reduction of WBCs production.

Breast cancer in women has become a global cause for concern owing to its high occurrence all over the world (Kashyap et al., 2022). The most common cancers are breast cancer (in women) in the USA and lung cancer in China whereas lung cancer is the leading cause around the world (Xia et al., 2022). It was reported that through 23 years (between 1998 and 2020), 104753 women with breast cancer were admitted in three major hospital of Punjab province of Pakistan. The immune system of patients with breast cancer is affected by a deficiency in WBCs. Immune status is a useful marker for predicting the risk of primary, recurrent, or metastatic (secondary) breast cancer (Standish et al., 2008).

Anticancer drugs can be categorized into different types (Figure 1, see Supplementary Martial). Depending on the stage, grade, and immune system of the patient, different drugs are selected for chemotherapy in breast cancer patients. Chemotherapy for breast cancer comprises eight cycles

(Saarto et al., 1997). It was observed from the data of a government hospital that, in most breast cancer cases, patients were treated with two combinations. These combinations include docetaxel, cyclophosphamide (TC), and doxorubicin with cyclophosphamide (AC). Breast cancer and its treatment both affect WBCs (Park et al., 2019). These cells move through patients' tissues and bloodstream to respond to illness or injury by beating any strange microbes, such as viruses and bacteria that arrive in their body. Once a patient's WBCs reach the location of infection in the body, they attack the aggressor by supplying antibodies to the microbial tissue and clearing it.

Chemotherapy usually lowers the patient's WBCs count. Some cancer types that affect the bone marrow and blood can also decrease the WBCs count. These include lymphomas and multiple myeloma. A higher-than-normal range of monocytes or lymphocytes can signify the possibility of other types of malignancies. Some malignancies and their therapies may lead to neutropenia. Neutropenia is developed because of low counts of neutrophils which raises the possibility of microbial infections. To prevent a patient from developing neutropenia, clinicians lower the dose of chemotherapy, including diarrhea, sore throat, rash, chills, drainage from the ear, pain or burning with urination, fever, last longer cough, drainage from the central venous catheter site, stiff neck, any areas of warmth, redness, or other pain, which are sings of infections (Hassan et al., 2010). Thus, to improve the production of body neutrophils, clinicians usually prescribe medicine, such as WBC growth factors, in addition to antibiotics (Meckler and Lindemulder 2009).

For oncologists and physicians, it is important to know how much WBCs count is affected to optimize drug administration (Ono et al., 2022) and WBCs count is also associated with cancer mortality (Jee et al., 2005). Thus, this study presents a mathematical and computational method to determine the effect on WBCs count of breast cancer patients treated with chemotherapy for four cycles with TC followed by four cycles with AC. This study may help clinicians to assess 1) the administration of drug dosage, 2) the best time for chemotherapy, 3) the time for medication to cure infections, 4) to select or reject the type of understudied drugs, 5) the mathematical observation of WBCs count, 6) the drug's overall trend in affecting the WBCs count, 7) the formula for calculating the effect on WBCs count, and 8) the comparison of TC and AC in affecting WBCs count.

2 Material and Methods

The study was divided into two parts. In the first part, an equation was derived to calculate the effect on WBCs count in the understudied patients. The second part presents a comparative analysis of the data retrieved by the implementation of the derived equation using the WBCs count during the four cycles of chemotherapy for each cohort (TC and AC).

2.1 Study design

In this study, women with breast cancer treated chemotherapy in a governmental hospital were selected to observe the effect of TC and AC on their WBCs counts during four cycles of chemotherapy with both combinations. This work was permitted (approval number 675/2016) by the ethical review committee, in Faisalabad, Pakistan. All patients provided written informed consent for the use of their white WBCs. Data from 668 breast cancer patients treated with chemotherapy were collected. After applying the exclusion and inclusion criteria (see the next subsection), we examined 459 cases in our records. Out of the 459, 134 subjects were excluded from the study because they were being treated with other drugs including tamoxifen, paclitaxel, and epirubicin. Thus, 171 of the remaining 325 patients were treated or were being treated for four cycles of chemotherapy with TC, and 154 women with breast cancer received or were being treated for the next four cycles of chemotherapy with AC.

2.2 Inclusion and exclusion criteria

The records of this study had data from different patients, because other studies were conducted along with this work. Thus, only patients who met the inclusion criteria (Table 1) were included in this study.

Data from the participants' charts and their follow-up reports were saved for this study in different sets of weights, ages, and geographical areas. Figure 2 shows the comparison of age, weight, and area between the AC and TC cohorts.

2.3 Treatment

Intravenous TC (75 mg/m^2 + 600 mg/m^2) was administered in each of the 4 cycles of chemotherapy (one cycle was of 21 days).Varying in cases, intravenous AC (60 mg/m^2 + 600 mg/m^2) was administered in each of the 4 cycles. The WBCs counts of the subjects affected by both TC and AC combinations were observed for comparison.

2.4 Equation for the effect of anticancer drugs on patient's WBCs count

The percentage change in the new value in accordance with the old value was calculated mathematically using the following formula:

$$\% \text{ Change} = \frac{\text{BaseValue} - CurrentValue}{\text{BaseValue}} \times 100 \quad (1)$$

Based on the above formula, Equation 2 is derived which calculates the effect of TC and AC on WBCs count (*eWBCc*) of patients:

$$eWBCc = \frac{\sum_n \left(\frac{|bWBC - WBCn|}{bWBC}\right) \times 100}{n} \quad (2)$$

where *bWBC* is the base value of the number of WBCs to give the initial value that was observed before chemotherapy and WBC_n is the number of WBCs observed after *n* chemotherapy cycles (1, 2, 3, and 4).

3 Results

3.1 Effect of TC and AC on patient's WBCs count

Python 3.8 was used to implement Equation 2 providing a WBCs count of 154 patients during four cycles of chemotherapy with AC and a WBCs count of 171 patients during four cycles of chemotherapy with TC. Tables 2 and 3 show *eWBCc* values for AC and TC patients, respectively. From Table 2, it is observed that comparing the results of 154 patients obtained from the implementation of Equation 2, AC affects WBC count of patient number 110 at the lowest level is 19%. However, at the maximum level, in these patients, the WBC count of patient number 84 was affected 65.03% by AC. However, on average, AC remains toxic, affecting these patients WBC count of 44.36%. Interviewing patient no. 110, it was found that the food and environment provided to this patient collectively played a vital role in controlling his WBC count. The same factors affected the WBC count of patient no. 84 at the maximum level among these patients. It has also been reported that WBC count is controlled by these factors (Mahdi and Kadhim 2022). The WBC count of most of the patients in this study affected by AC remained in the range of 30% to 40%.

From Table 3, it is observed that comparing the results of 171 patients obtained from the implementation of Equation 2, TC affects WBC count of the patient number 133 at the lowest level of 12.29%. Whereas, At maximum level, in these patients, the WBC count of patient number 150 was affected 69.64% by TC. However, on average TC remains toxic in affecting these patients WBC count by 34.13%. Upon interviewing patient no. 133, it was found that the food and environment provided to this patient collectively played a vital role in controlling his WBC count. The same factors affected the WBC count of patient no. 150 at the maximum level among these patients. The WBC count of most of the patients in this study affected by AC remained in the range of 20% to 30%. The data listed in Tables 2 and 3 can be graphically observed in Figure 3, which shows a dramatic difference between the effects of TC and AC on the patient's WBCs count. Figure 3 shows that TC and AC both cause a low white blood cell count (neutropenia). However, the duration and magnitude of neutropenia varies between these two chemotherapies. AC is generally more likely to cause severe neutropenia than TC. The base WBC count normally takes place 7 to 10 days after TC administration and 5 to 7 days after AC administration. The retrieval of WBC count after administration of TC is faster than after the administration of AC. Patients treated using TC are required to have their WBC count monitored more closely than those receiving AC, as the start of a low white blood cell count is more rapid and the salvage is slower.

3.2 Comparative WBC between AC and TC

A paired t-test was applied to analyze the statistical difference between the overall effect of TC and AC on patient WBCs count. Table 4 presents the results of the analysis. From Table 4, it is found that the p-value is 0.000, which is less than the chosen significance level of 0.05. Therefore, we reject the null hypothesis and conclude that there is a statistically significant difference between the eWBCc by TC and AC.

4 Discussion

In this study, the drug dosage was optimized by assessing the *eWBCc* of patients. For example, the case of patient 1 was affected 14.29% by TC and 59.50% by AC (Tables 2 and Table 3). Based on these values, physicians can determine the dosage and duration of chemotherapy. Because TC affects 59.50% that means patient's immune system has been disturbed, so cannot receive chemotherapy. When a patient recovers a WBCs count in the normal range, it can be the best time for chemotherapy. Similarly, if a patient's *eWBCc* is adversely affected, it may lead to the development of any infection. This may assist doctors in deciding on the time to provide medication to cure any infection. Based on *eWBCc* of the patient, the doctor may also reject drugs and select a suitable drug for the patient. For example, in the case of patient 150, *eWBCc* was 69.64% that means doctor may change the drug for the remaining chemotherapy. Some studies have provided assistance with the administration of drug dosage. Several studies have discussed the optimal time for chemotherapy. Three papers discussed the time taken for medication to cure the infections. Four articles reported drug rejection or selection. The mathematical observation of WBCs count has been presented in a few studies. Table 5 presents a comparison of assistance observed in other studies.

The literature makes many important contributions by observing the white blood cell count of patients with cancer. A recent study have explored the medical importance of the perioperative counts of white blood cells count, along with other bio markers (Wang et al., 2021). Lien et al. found higher increase of WBCs with Chinese Herbal Medicine with chemo than with chemotherapy only in randomized controlled trials (Lien et al., 2021). The results of a study determined intracellular reactive oxygen species decline without impairing the chemotherapeutical activity of doxorubicin in K562 cells or inducing WBCs death (Dos Santos et al., 2018). Changes in the WBCs, platelet, neutrophil, and hemoglobin indices on fist day before chemo of small cell lung cancer patients and 5th, 8th, 11th,14th, 21st, and on 28th days after chemo were compared by a study among two different groups of medicines (Zhao et al., 2021). Hao et al. shown the predictive value of WBCs after chemotherapy of small cell lung cancer (Hao et al., 2018). A high lymphocyte-to-white blood cell ratio was observed by a study to predict the effectiveness of chemotherapy with the oxaliplatin and capecitabine regimen to gastric cancer patients (Tang et al., 2018). Yuksel et al. investigated WBCs counts and neutrophil to lymphocyte ratio in the identification of localized testicular cancer (Yuksel et al., 2016). A study investigated the analytical impact of elevated WBCs count of cervical cancer recurrence at the time of the diagnosis (Mabuchi et al., 2012). Shen et al. found that doxorubicin directly destroy neutrophils in a very short time and thus may not be used to make as a model chemo nanodrug to prepare an innovative cell chemotherapeutic drug (Shen et al., 2021). A study determined that the baseline, cycle-1 day-1 median absolute neutrophil count was lower in Black breast cancer patients versus Non-Black with same results at cycle-3 day-1 (Schreier et al., 2022). Hoshino et al. investigated the association between neutrophil-to-lymphocyte ratio change after neoadjuvant chemotherapy and histologic response and oncologic outcomes in patients of esophageal malignancy (Hoshino et al., 2022). Neutrophil-to-lymphocyte ratio was described to be related with diagnosis of patients of urothelial cancer who were receiving organized chemo or immunotherapy (Kobayashi et al., 2022). Though, even patients with high pre-chemo neutrophil-to-lymphocyte ratio attained favorable overall and progression-free survivals if they had the neutrophil-to-lymphocyte ratio decreased by chemo, while those with high pre-chemo neutrophil-to-lymphocyte ratio produced uncomplimentary overall and progression-free survivals if they had the neutrophil-to-lymphocyte ratio continued high after chemo, signifying that chemo may had disparity effect on the efficiency of following pembrolizumab medication in patients of urothelial cancer (Kobayashi et al., 2022). Méndez et al. evaluated the probiotic fermented milk management on the side effects of chemo drug, capecitabine and on its anticancer effects and they found that capecitabine organization reduced the number of WBCs compared to both the probiotic fermented milk and milk groups, without accomplishment of the control group standards (Méndez Utz et al., 2021). A study reviewed that many trials indicated that β-glucan concomitant administration with chemotherapy or with radiotherapy decreased immune decline due to such medications and enhanced the recovery of WBCs counts (Steimbach et al., 2021). Orhan et al. studied the data of perianal-complications and examined the association among the perianal lesion, WBCs to neutrophil count, and the kind of treatment in understudy patients with hematologic cancers in the neutropenic period. They derived a statistical significance consideration in favor of acute-myeloid-leukemia was found between those patient findings and anal-abscess-development and they also found that there was a converse relationship between the number of WBCs at hospitalization with an anal pathologic operation. They observed that patients with high WBCs counts underwent fewer operations due to anal pathology (Orhan et al., 2022).

5 Conclusions

The results of this study concluded that TC remains less toxic than AC in affecting white blood cells count of understudied patients. It was also concluded that both drugs disturbed the immune system of the patients, resulting in a slow recovery of their health. However, this study did not compare the levels of eosinophils, basophils, monocytes, and lymphocytes affected by anticancer drugs. In the future, we would like to formulate a calculation for the effect of chemotherapy on platelets of patients with cancer.

Research Ethics Approval

All methods adopted in this study were based on the standards of the ethical review committee of Faisalabad, Pakistan, who approved this study (approval number 675/2016). All patients provided written informed consent for using their data.

Disclosure of interest

The authors report no conflict of interest.

Data Availability

The data used for this study can be provided on request to corresponding author.

Funding

This research received no external funding.

Acknowledgments

The authors extend their appreciation to King Saud University, Riyadh, Saudi Arabia, for the Researchers Supporting Project (number: RSP2023R75).

References

Adeel, M., M. Asif, M. N. Faisal, et al., 2019. Comparative study of adjuvant chemotherapeutic efficacy of docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide in female breast cancer. Cancer management and research. 11 727.

Dos Santos, J. M., T. M. Alfredo, K. Á. Antunes, et al., 2018. Guazuma ulmifolia Lam. decreases oxidative stress in blood cells and prevents doxorubicin-induced cardiotoxicity. Oxidative Medicine and Cellular Longevity. 2018

Gersten, T. 2021, 4/28/2021. Low white blood cell count and cancer. Retrieved 6/26/2022, 2022, from https://medlineplus.gov/ency/patientinstructions/000675.htm.

Hao, L., J. Zhang, Y. Di, et al., 2018. Prognostic value of white blood cells detected for the first time after adjuvant chemotherapy in primary operable non-small cell lung cancer. Technology in cancer research & treatment. 17 1533033818802813.

Hassan, B. R., Z. Yusoff and S. B. Othman, 2010. Fever/clinical signs and association with neutropenia in solid cancer patients: bacterial infection as the main cause. Asian Pac J Cancer Prev. 11 (11) 1273-1277.

Hoshino, S., M. Takeuchi, H. Kawakubo, et al., 2022. Neutrophil-to-lymphocyte ratio change predicts histological response to and oncological outcome of neoadjuvant chemotherapy for esophageal squamous cell carcinoma. Esophagus. 1-10.

Jee, S. H., J. Y. Park, H.-S. Kim, et al., 2005. White blood cell count and risk for all-cause, cardiovascular, and cancer mortality in a cohort of Koreans. American journal of epidemiology. 162 (11) 1062-1069.

Kashyap, D., D. Pal, R. Sharma, et al., 2022. Global Increase in Breast Cancer Incidence: Risk Factors and Preventive Measures. BioMed Research International. 2022

Kobayashi, T., K. Ito, T. Kojima, et al., 2022. Pre-pembrolizumab neutrophil-to-lymphocyte ratio (NLR) predicts the efficacy of second-line pembrolizumab treatment in urothelial cancer regardless of the pre-chemo NLR. Cancer Immunology, Immunotherapy. 71 (2) 461-471.

Lien, C.-Y., C.-W. Lu, Y.-H. Lin, et al., 2021. Chinese Herbal Medicine, Guilu Erxian Glue, as alternative medicine for adverse side effects of chemotherapy in doxorubicin-treated cell and mouse models. Evidence-Based Complementary and Alternative Medicine. 2021

Mabuchi, S., Y. Matsumoto, T. Hamasaki, et al., 2012. Elevated white blood cell count at the time of recurrence diagnosis is an indicator of short survival in patients with recurrent cervical cancer. International Journal of Gynecologic Cancer. 22 (9)

Mahdi, M. S. and N. Q. Kadhim, 2022. The role of alpha klotho protein and FGF-23 in serum of breast cancer patients. AIP Conference Proceedings, AIP Publishing LLC.

Meckler, G. and S. Lindemulder, 2009. Fever and neutropenia in pediatric patients with cancer. Emergency Medicine Clinics. 27 (3) 525-544.

Méndez Utz, V. E., D. Pérez Visñuk, G. Perdigón, et al., 2021. Milk fermented by Lactobacillus casei CRL431 administered as an immune adjuvant in models of breast cancer and metastasis under chemotherapy. Applied microbiology and biotechnology. 105 (1) 327-340.

Ono, M., M. Tomaniak, W. Koenig, et al., 2022. Impact of white blood cell count on clinical outcomes in patients treated with aspirin-free ticagrelor monotherapy after percutaneous coronary intervention: insights from the GLOBAL LEADERS Trial. European Heart Journal-Cardiovascular Pharmacotherapy. 8 (1) 39-47.

Orhan, B., F. Özkalemkaş, V. Özkocaman, et al., 2022. THE ROLE OF WHITE BLOOD CELL COUNT IN PERIANAL PATHOLOGIES: A RETROSPECTIVE ANALYSIS OF HEMATOLOGIC MALIGNANCIES: Role of white blood cell count in perianal pathologies. Mediterranean Journal of Hematology and Infectious Diseases. 14 (1) e2022051-e2022051.

Park, B., H. S. Lee, J. W. Lee, et al., 2019. Association of white blood cell count with breast cancer burden varies according to menopausal status, body mass index, and hormone receptor status: a case-control study. Scientific Reports. 9 (1) 1-10.

Saarto, T., C. Blomqvist, P. Rissanen, et al., 1997. Haematological toxicity: a marker of adjuvant chemotherapy efficacy in stage II and III breast cancer. British journal of cancer. 75 (2) 301-305.

Schreier, A., L. Munoz-Arcos, A. Alvarez, et al., 2022. Racial disparities in neutrophil counts among patients with metastatic breast cancer during treatment with CDK4/6 inhibitors. Breast Cancer Research and Treatment. 1-15.

Shankar, A., J. J. Wang, E. Rochtchina, et al., 2006. Association between circulating white blood cell count and cancer mortality: a population-based cohort study. Archives of internal medicine. 166 (2) 188-194.

Shen, J., J. Hao, Y. Chen, et al., 2021. Neutrophil-mediated clinical nanodrug for treatment of residual tumor after focused ultrasound ablation. Journal of nanobiotechnology. 19 (1) 1-16.

Standish, L. J., E. S. Sweet, J. Novack, et al., 2008. Breast cancer and the immune system. Journal of the Society for Integrative Oncology. 6 (4) 158.

Steimbach, L., A. V. Borgmann, G. G. Gomar, et al., 2021. Fungal beta-glucans as adjuvants for treating cancer patients–A systematic review of clinical trials. Clinical Nutrition. 40 (5) 3104-3113.

Tang, C., X. Cheng, S. Yu, et al., 2018. Platelet-to-lymphocyte ratio and lymphocyte-to-white blood cell ratio predict the efficacy of neoadjuvant chemotherapy and the prognosis of locally advanced gastric cancer patients treated with the oxaliplatin and capecitabine regimen. OncoTargets and therapy. 11 7061.

Wang, Z., P. Zhang, Y. Chong, et al., 2021. Perioperative Circulating Tumor Cells (CTCs), MCTCs, and CTC-white blood cells detected by a size-based platform predict prognosis in renal cell carcinoma. Disease Markers. 2021

Wu, J., X. X. Ge, W. Zhu, et al., 2019. Values of applying white blood cell counts in the prognostic evaluation of resectable colorectal cancer. Molecular Medicine Reports. 19 (3) 2330-2340.

Xia, C., X. Dong, H. Li, et al., 2022. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. Chinese medical journal. 135 (05) 584-590.

Yuksel, O. H., A. Verit, A. Sahin, et al., 2016. White blood cell counts and neutrophil to lymphocyte ratio in the diagnosis of testicular cancer: a simple secondary serum tumor marker. International braz j urol. 42 53-59.

Zhao, F., Z. Wang, Y. Gao, et al., 2021. Randomized efficacy trial of conventional, TCM herb, and TEAS on bone marrow suppression in patients with small cell lung cancer after initial chemotherapy. Evidence-Based Complementary and Alternative Medicine. 2021

Zhao, Q., H. Du, J. Liu, et al., 2022. To Explore the Effects of Acupuncture and Medical Treatment at Different Times on the Gastrointestinal Reaction and White Blood Cell Count of Patients with Lung Cancer Chemotherapy. Applied Bionics and Biomechanics. 2022

Table 1: Inclusion and exclusion criteria for the patients for this study

Inclusion Criteria		Exclusion Criteria	
Gender	female	Gender	male
Age	above 26 and below 61 years	Age	below 26 and above 61 years
Stage	I-III	Stage	IV
Grade	1 and 2	Grade	3
Histology	invasive ductal carcinoma	Histology	Other than invasive ductal carcinoma
Diabetes	non-diabetic	Diabetes	diabetic
Renal function tests	normal	Renal function tests	abnormal
ECOG	0–1	ECOG	two and above
Ejection fraction in echocardiography	5%–70%	Ejection fraction in echocardiography	less than 50%

(ECOG, Eastern Cooperative Oncology Group)

Table 2: Effect (in percentage) on white blood cells count of patients by doxorubicin with cyclophosphamide (AC)

#	*eWBCc* by AC	#	*eWBCc* by AC	#	*eWBCc* by AC	#	*eWBCc* by AC	#	*eWBCc* by AC	#	*eWBCc* by AC	#	*eWBCc* by AC
1	59.50	**23**	62.00	**45**	44.00	**67**	46.00	**89**	39.80	**111**	33.00	**133**	48.33
2	63.03	**24**	56.00	**46**	44.00	**68**	37.00	**90**	37.00	**112**	32.00	**134**	42.00
3	48.33	**25**	51.00	**47**	42.00	**69**	49.00	**91**	36.00	**113**	34.00	**135**	39.33
4	44.00	**26**	50.00	**48**	55.00	**70**	48.00	**92**	38.00	**114**	37.00	**136**	49.20
5	61.00	**27**	44.00	**49**	58.50	**71**	63.00	**93**	31.50	**115**	46.00	**137**	39.80
6	47.20	**28**	43.00	**50**	62.03	**72**	57.00	**94**	41.00	**116**	35.00	**138**	37.00
7	37.80	**29**	35.00	**51**	47.33	**73**	48.00	**95**	62.00	**117**	40.00	**139**	30.43
8	35.00	**30**	44.00	**52**	39.00	**74**	33.00	**96**	56.00	**118**	46.00	**140**	36.00
9	42.00	**31**	35.00	**53**	38.33	**75**	37.00	**97**	60.50	**119**	61.00	**141**	31.50
10	43.00	**32**	39.00	**54**	46.20	**76**	33.00	**98**	64.03	**120**	55.00	**142**	36.00
11	38.00	**33**	46.00	**55**	36.80	**77**	36.00	**99**	49.33	**121**	46.00	**143**	62.00
12	43.00	**34**	61.00	**56**	34.00	**78**	45.00	**100**	61.00	**122**	51.00	**144**	56.00
13	61.00	**35**	60.50	**57**	32.00	**79**	36.00	**101**	40.33	**123**	54.00	**145**	59.50
14	39.00	**36**	64.03	**58**	33.00	**80**	37.00	**102**	48.20	**124**	31.00	**146**	63.03
15	37.00	**37**	49.33	**59**	34.00	**81**	47.00	**103**	38.80	**125**	34.00	**147**	48.33
16	35.00	**38**	43.00	**60**	33.00	**82**	62.00	**104**	36.00	**126**	43.00	**148**	34.00
17	33.00	**39**	40.33	**61**	34.00	**83**	61.50	**105**	39.00	**127**	34.00	**149**	39.33
18	36.00	**40**	48.20	**62**	35.00	**84**	65.03	**106**	35.00	**128**	59.00	**150**	47.20
19	45.00	**41**	38.80	**63**	41.00	**85**	50.33	**107**	30.50	**129**	45.00	**151**	37.80
20	36.00	**42**	36.00	**64**	46.00	**86**	34.00	**108**	34.00	**130**	60.00	**152**	35.00
21	41.00	**43**	41.00	**65**	53.00	**87**	41.33	**109**	35.00	**131**	59.50	**153**	39.00
22	47.00	**44**	39.00	**66**	35.00	**88**	49.20	**110**	19.00	**132**	63.03	**154**	54.00

(eWBCc, effect of AC on WBCs count)

Table 3: Effect on white blood cells count of patients by docetaxel with cyclophosphamide (TC)

#	eWBCc by TC	#	eWBCc by TC	#	eWBCc by TC	#	eWBCc by TC	#	eWBCc by TC	#	eWBCc by TC	#	eWBCc by TC
1	14.29	**26**	18.00	**51**	49.91	**76**	28.73	**101**	14.00	**126**	43.24	**151**	68.00
2	21.19	**27**	26.00	**52**	43.24	**77**	18.64	**102**	14.29	**127**	66.64	**152**	45.00
3	35.85	**28**	20.00	**53**	66.64	**78**	28.14	**103**	21.19	**128**	65.00	**153**	51.00
4	25.57	**29**	35.00	**54**	65.00	**79**	43.27	**104**	37.85	**129**	25.00	**154**	45.00
5	27.40	**30**	23.00	**55**	25.00	**80**	47.36	**105**	27.57	**130**	33.00	**155**	47.00
6	41.92	**31**	40.00	**56**	33.00	**81**	45.85	**106**	29.40	**131**	19.00	**156**	43.00
7	24.44	**32**	26.00	**57**	19.00	**82**	51.91	**107**	43.92	**132**	14.00	**157**	30.00
8	34.65	**33**	34.00	**58**	14.00	**83**	45.24	**108**	26.44	**133**	12.29	**158**	20.00
9	21.64	**34**	20.00	**59**	50.91	**84**	68.64	**109**	34.65	**134**	19.19	**159**	28.00
10	27.73	**35**	15.00	**60**	44.24	**85**	65.00	**110**	21.64	**135**	33.85	**160**	22.00
11	17.64	**36**	15.29	**61**	67.64	**86**	42.00	**111**	27.73	**136**	23.57	**161**	37.00
12	27.14	**37**	22.19	**62**	66.00	**87**	48.00	**112**	17.64	**137**	25.40	**162**	25.00
13	42.27	**38**	36.85	**63**	26.00	**88**	42.00	**113**	27.14	**138**	39.92	**163**	42.00
14	46.36	**39**	26.57	**64**	34.00	**89**	44.00	**114**	40.27	**139**	22.44	**164**	28.00
15	44.85	**40**	28.40	**65**	20.00	**90**	40.00	**115**	44.36	**140**	32.65	**165**	36.00
16	50.91	**41**	42.92	**66**	15.00	**91**	27.00	**116**	42.85	**141**	19.64	**166**	22.00
17	44.24	**42**	25.44	**67**	15.29	**92**	17.00	**117**	48.91	**142**	25.73	**167**	17.00
18	67.64	**43**	33.65	**68**	22.19	**93**	25.00	**118**	42.24	**143**	15.64	**168**	17.29
19	66.00	**44**	20.64	**69**	36.85	**94**	19.00	**119**	65.64	**144**	25.14	**169**	24.19
20	43.00	**45**	26.73	**70**	26.57	**95**	34.00	**120**	64.00	**145**	40.27	**170**	22.00
21	49.00	**46**	16.64	**71**	28.40	**96**	22.00	**121**	24.00	**146**	44.36	**171**	36.00
22	43.00	**47**	26.14	**72**	42.92	**97**	39.00	**122**	32.00	**147**	42.85		
23	45.00	**48**	41.27	**73**	25.44	**98**	25.00	**123**	18.00	**148**	48.91		
24	41.00	**49**	45.36	**74**	35.65	**99**	33.00	**124**	13.00	**149**	42.24		
25	28.00	**50**	43.85	**75**	22.64	**100**	19.00	**125**	49.91	**150**	69.64		

(eWBCc, effect of TC on WBCs count)

Table 4: Statistical difference between the overall effect of TC and AC on the patients WBCs count

Paired T-Test and CI: AC, TC

	N	Mean	StDev	SE Mean
AC	154	44.36	10.02	0.81
TC	154	34.62	14.60	1.18
Difference	154	9.74	17.68	1.42

95% CI for mean difference: (6.93, 12.56)

T-Test of mean difference = 0 (vs ≠ 0): T-Value = 6.84 P-Value = 0.000

(TC, docetaxel with cyclophosphamide; AC, doxorubicin with cyclophosphamide; WBC, White Blood Cells)

Table 5: Comparison of the assistance observed by this and other studies

Assistance for Observing	Wu et al. (Wu et al., 2019)	Park et al. (Park et al., 2019)	Shankar et al. (Shankar et al., 2006)	Ono et al. (Ono et al., 2022)	Jee et al. (Jee et al., 2005)	Zhao et al. (Zhao et al., 2022)	Hao et al. (Hao et al., 2018)	This study
the administration of drugs dosage	✓	×	✓	×	✓	×	✓	✓
the best time for chemotherapy	×	×	×	✓	×	×	×	✓
the time for medication to cure infections	×	✓	✓	×	✓	✓	×	✓
to select or reject type of understudy drugs	✓	×	×	✓	✓	×	✓	✓
the mathematical observation of WBCs count	×	×	×	×	×	✓	✓	✓
the drugs overall trend in affecting the WBCs count	×	×	×	×	×	×	×	✓
the formula for calculating effect on WBCs count	×	×	×	×	×	×	×	✓
the comparison of TC and AC in affecting WBCs count	×	×	×	×	×	×	×	✓

(TC, docetaxel with cyclophosphamide; AC, doxorubicin with cyclophosphamide; WBC, White Blood Cells)

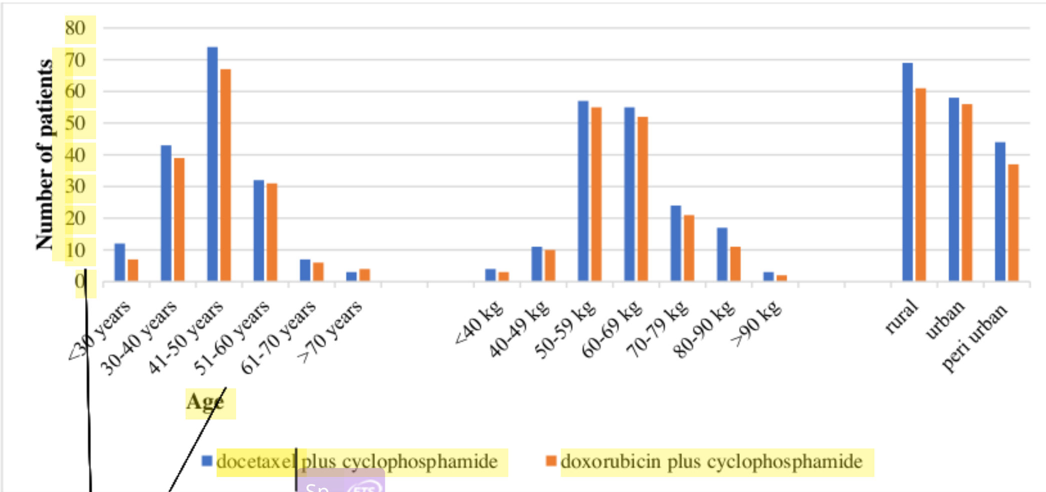

Figure 2: TC and AC cohorts' classification by age, weight, and geographical area

(TC, docetaxel with cyclophosphamide; AC, doxorubicin with cyclophosphamide)

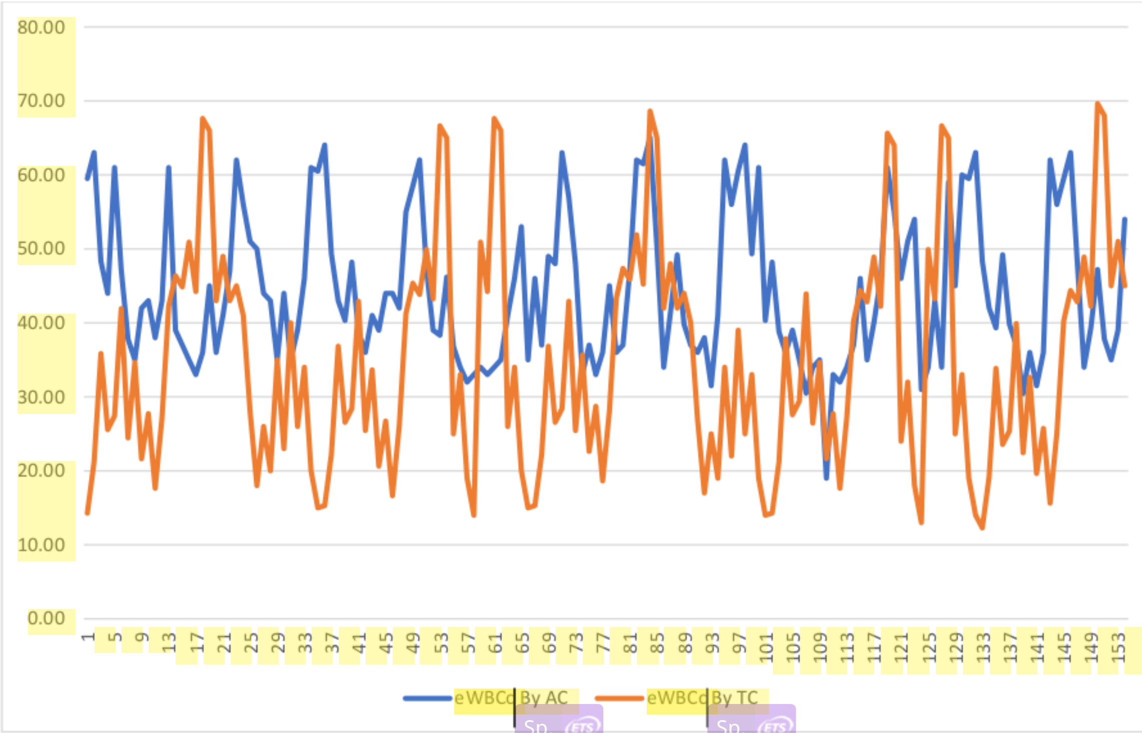

Figure 3: Difference between effects of TC and AC on patient's WBCs counts

(TC, docetaxel with cyclophosphamide; AC, doxorubicin with cyclophosphamide; WBC, White Blood Cells; eWBCc: effect of TC/AC on WBCs count)

Quantifying Anticancer Drug Toxicity on White Blood Cell Count in Cancer Patients: A Mathematical and Computational Approach

ORIGINALITY REPORT

13%	10%	8%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.dovepress.com Internet Source	1%
2	mjhid.org Internet Source	1%
3	link.springer.com Internet Source	1%
4	www.researchsquare.com Internet Source	1%
5	Muhammad Adeel, Muhammad Asif, Muhammad Naeem Faisal, Muhammad Hasanain Chaudary, Muhammad Sheraz Malik, Muhammad Khalid. "Comparative study of adjuvant chemotherapeutic efficacy of docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide in female breast cancer", Cancer Management and Research, 2019 Publication	1%

6	Ya Wen Shih, Mei Hua Wang, Karen A. Monsen, Ching Wen Chang, Yohanes Andy Rias, Hsiu Ting Tsai. "Effectiveness of Acupuncture for Relieving Chemotherapy-Induced Bone Marrow Suppression: A Systematic Review with a Meta-analysis and Trial Sequential Analysis", Journal of Integrative and Complementary Medicine, 2023 Publication	1 %
7	ecancer.org Internet Source	1 %
8	personel.trakya.edu.tr Internet Source	1 %
9	Submitted to University of Hong Kong Student Paper	<1 %
10	www.ijnrd.org Internet Source	<1 %
11	pubmed.ncbi.nlm.nih.gov Internet Source	<1 %
12	stars.library.ucf.edu Internet Source	<1 %
13	www.emerald.com Internet Source	<1 %
14	jnanobiotechnology.biomedcentral.com Internet Source	<1 %

15	www.mdpi.com Internet Source	<1%
16	Submitted to Yeditepe University Student Paper	<1%
17	Recent Results in Cancer Research, 1998. Publication	<1%
18	onlinelibrary.wiley.com Internet Source	<1%
19	studylib.net Internet Source	<1%
20	www.akadeum.com Internet Source	<1%
21	Lihu Gu, Bangsheng Chen, Dingcheng Zheng, Jiahang Mo et al. "Clinical significance of peripheral blood-derived inflammation markers in advanced gastric cancer after radical resection", Research Square, 2020 Publication	<1%
22	www.science.gov Internet Source	<1%
23	worldwidescience.org Internet Source	<1%
24	Tarik A. Elhadd, Gwen Kennedy, Alexander Hill, Margaret McLaren, Ray W. Newton, Stephen A. Greene, Jill J. F. Belch. "Abnormal	<1%

markers of endothelial cell activation and oxidative stress in children, adolescents and young adults with Type 1 diabetes with no clinical vascular disease", Diabetes/Metabolism Research and Reviews, 1999
Publication

25	core.ac.uk Internet Source	<1 %
26	www.cureus.com Internet Source	<1 %
27	www.frontiersin.org Internet Source	<1 %
28	"Natural Products and Human Diseases", Springer Science and Business Media LLC, 2021 Publication	<1 %
29	Imran Ahmed, Humaira Sardar, Hanan Aljuaid, Fakhri Alam Khan, Muhammad Nawaz, Adnan Awais. "Convolutional Neural Network for Histopathological Osteosarcoma Image Classification", Computers, Materials & Continua, 2021 Publication	<1 %
30	Tinker, . "Impact of a Reduced Dose Intensity of Adjuvant Anthracycline Based Chemotherapy in a Population-Based Cohort	<1 %

of Stage I-II Breast Cancers", ecancermedicalscience, 2008.
Publication

31	Zhou, Wenbin, Qiang Ding, Xiuqing Liang, Zhongyuan He, Xiaoming Zha, Xiaoan Liu, and Shui Wang. "The Risk of Amenorrhea Is Related to Chemotherapy-Induced Leucopenia in Breast Cancer Patients Receiving Epirubicin and Taxane Based Chemotherapy", PLoS ONE, 2012. Publication	<1 %
32	doaj.org Internet Source	<1 %
33	www.ncbi.nlm.nih.gov Internet Source	<1 %
34	Venetz, Carmen, José Labarère, David Jiménez, and Drahomir Aujesky. "White blood cell count and mortality in patients with acute pulmonary embolism", American Journal of Hematology, 2013. Publication	<1 %
35	Burstein, H.J.. "Prospective evaluation of concurrent paclitaxel and radiation therapy after adjuvant doxorubicin and cyclophosphamide chemotherapy for Stage II or III breast cancer", International Journal of Radiation Oncology, Biology, Physics, 20060201	<1 %

Publication

36	GÖKMEN, N. M. and GÖKMEN, E.. "Adjuvan kemoterapi alan erken evre meme kanserli hastalarda lenfosit alt tiplerinin flow sitometrik analizi", TUBITAK, 2011. Publication	<1 %

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

Quantifying Anticancer Drug Toxicity on White Blood Cell Count in Cancer Patients: A Mathematical and Computational Approach

PAGE 1

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to remove this article.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

P/V You have used the passive voice in this sentence. You may want to revise it using the active voice.

Article Error You may need to use an article before this word. Consider using the article **the**.

P/V You have used the passive voice in this sentence. You may want to revise it using the active voice.

Article Error You may need to use an article before this word. Consider using the article **the**.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

PAGE 2

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to use an article before this word.

Article Error You may need to remove this article.

Article Error You may need to use an article before this word.

Article Error You may need to use an article before this word. Consider using the article **the**.

PAGE 3

Article Error You may need to remove this article.

P/V You have used the passive voice in this sentence. You may want to revise it using the active voice.

Article Error You may need to use an article before this word. Consider using the article **the**.

PAGE 4

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to use an article before this word.

PAGE 5

Article Error You may need to use an article before this word.

Article Error You may need to remove this article.

P/V You have used the passive voice in this sentence. You may want to revise it using the active voice.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

PAGE 6

Article Error You may need to use an article before this word.

Article Error You may need to remove this article.

Article Error You may need to use an article before this word.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

PAGE 7

Article Error You may need to use an article before this word. Consider using the article **the**.

Article Error You may need to use an article before this word.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

P/V You have used the passive voice in this sentence. You may want to revise it using the active voice.

PAGE 8

Article Error You may need to use an article before this word. Consider using the article **the**.

Article Error You may need to use an article before this word. Consider using the article **the**.

P/V You have used the passive voice in this sentence. You may want to revise it using the active voice.

Article Error You may need to use an article before this word.

Article Error You may need to remove this article.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

PAGE 9

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

P/V You have used the passive voice in this sentence. You may want to revise it using the active voice.

Article Error You may need to use an article before this word.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to remove this article.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to use an article before this word.

Article Error You may need to use an article before this word.

Article Error You may need to remove this article.

P/V You have used the passive voice in this sentence. You may want to revise it using the active voice.

PAGE 10

PAGE 11

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to remove this article.

PAGE 12

Article Error You may need to use an article before this word. Consider using the article **the**.

Article Error You may need to use an article before this word.

PAGE 13

PAGE 14

PAGE 15

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to use an article before this word.

PAGE 16

Article Error You may need to remove this article.

Article Error You may need to use an article before this word.

Article Error You may need to use an article before this word.

Missing "," Review the rules for using punctuation marks.

PAGE 17

Prep. You may be using the wrong preposition.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to use an article before this word. Consider using the article **the**.

PAGE 18

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to use an article before this word. Consider using the article **the**.

PAGE 19

Garbled This sentence contains several grammatical or spelling errors that make your meaning unclear. Proofread the sentence to identify and fix the mistakes.

Article Error You may need to remove this article.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

PAGE 20

Prep. You may be using the wrong preposition.

Proofread This part of the sentence contains an error or misspelling that makes your meaning unclear.

Article Error You may need to use an article before this word.

Possessive Review the rules for possessive nouns.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

PAGE 21

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Prep. You may be using the wrong preposition.

Article Error You may need to use an article before this word.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Garbled This sentence contains several grammatical or spelling errors that make your meaning unclear. Proofread the sentence to identify and fix the mistakes.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to use an article before this word.

Article Error You may need to use an article before this word. Consider using the article **the**.

Article Error You may need to use an article before this word.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to use an article before this word. Consider using the article **the**.