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Case Report
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Hematological Side Effects Management of Paclitaxel - Carboplatin Chemotherapy in Lung Cancer

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Abstract

Background: Paclitaxel-carboplatin chemotherapy can cause hematological disorders. This regiment's hematological side effects include anemia, neutropenia, and thrombocytopenia. Data showed this regiment side effect occurs with grade iii/iv toxicity anemia, grade III/IV anemia by 41%, neutropenia (78%), and thrombocytopenia (41%). This hematological disorder occurs in bone marrow-producing areas due to chemotherapy. Each hematological disorder requires separate intervention.

Case Presentation: A 54-year-old woman was diagnosed with a progressive disease of left lung adenocarcinoma (Exon 21 mutation) with TKI and received paclitaxel-carboplatin chemotherapy. The patient experienced side effects of anemia, neutropenia, and thrombocytopenia. Anemia was treated with PRC transfusion, neutropenia corrected with Filgrastim, and thrombocytopenia with platelet transfusion. Chemotherapy was discontinued after five cycles because the Thrombocytopenia condition did not improve.

Conclusion: Hematological parameters are essential in preparing for lung cancer chemotherapy. Uncorrectable hematological disorders lead to discontinuation of chemotherapy.

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INTRODUCTION

Hematologic disorders can occur due to paclitaxel-carboplatin chemotherapy. Charles' 2016 study found anemia (87.9%), leukopenia (57.6%), and thrombocytopenia (27.3%) were side effects of paclitaxel-carboplatin chemotherapy.[1] These side effects can increase morbidity and predict mortality.[2] Hematologic toxicity will affect chemotherapy management. Toxicity grading must be determined as it may affect subsequent chemotherapy, based on the *World Health Organization* (WHO) Toxicity scale. Chemotherapy can only be performed if toxicity does not exceed grade three or hematologic side effects can be corrected, So toxicity levels are decreased.[3]

Guastala's 2018 study found the incidence of neutropenia in paclitaxel-carboplatin with WHO Toxicity grade III by 30% and grade IV by 23%. The incidence of thrombocytopenia with WHO Toxicity grade III was 3%, and grade IV was 1%.[4] Research by Leong in 2004, chemotherapy with a paclitaxel-carboplatin regimen had anemia with whom Toxicity grade III/IV occurred by 41%, thrombocytopenia by 41%, and neutropenia by 78%.[5] Yuliandra et al. study found the paclitaxel-carboplatin regimen can cause three toxicity parameters (anemia, leukopenia, and thrombocytopenia), that occurred in grade I - III who toxicity [3] Lee's study in 2011found that leukopenia can occur after the first cycle of paclitaxel-carboplatin chemotherapy. [6] The incidence of hematologic toxicity (anemia and neutropenia) In Asians was higher than non-Asians. The paclitaxel-carboplatin regimen is also associated with neutropenic febris. [2]

Anemia was treated with *package rage cell* (PRC) transfuse and *Erythropoietin Stimulating Agents* (ESA). Thrombocytopenia was treated with platelet transfusion, antifibrinolytic agents, and thrombopoietin receptor agonists. Neutropenia was treated with *Granulocyte-Colony Stimulating Factor* (G-CSF), i.e., Filgrastrim /tbo-Filgrastrim or pegfilgrastim.[7] Langa's research in 2015 showed that ESA was given to 90.2% of patients, 68.6% were given together with iron, and PCR transfusion was 9.8%.[8] Kuter's research in 2022, platelet transfusion was given to 9% of patients who experienced grade III/IV thrombocytopenia.[9] Hashigu-chi's research in 2015, the correction of neutropenia due to chemotherapy using G-CSF was 7.1%.[10]On data above, the author was interested in discussing the management of hematologic disorders that occur due to pacli-taxel-carboplatin regimen side effects, in adenocarcinoma lung cancer.

CASE PRESENTATION

A female, 54 years old, was admitted with chief complaints of breathlessness since three months ago, not shrinking, increasing with activity and cough, left chest pain felt since four months ago, not radiating, intermittent. The patient was diagnosed with left lung adenocarcinoma (exon 21 mutation) and re-ceived first-generation *Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor* (EGFR-TKI) therapy Gefitinib 1x250mg by a pulmonologist at Dharmais Cancer Hospital. The patient then continued treatment in Bengkulu. After 17 months of treatment, the pulmonologist at Bengkulu Regional Hospital concluded progresssive disease. The patient was then referred to General Hospital M Djamil. The patient had no history

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of pulmonary tuberculosis (TB) before. There was no history of malignancy in other organs. The patient was a housewife, non-smoker, with no history of exposure to environmental tobacco smoke and no history of cooking with firewood. The patient lived in a permanent house with tiled floors, no cracks, and no dug wells.

Physical examination revealed moderate pain with compos mentis consciousness. Blood pressure 125/75 mmHg, heart rate 82x/min, respiratory frequency 19x/min, body temperature 36.6^{0}C. Eye sclera was not icteric; conjunctiva was not anemic. Enlarged lymph nodes in the neck and other places were absent. Physical examination of the lungs showed there were no abnormalities in lung inspection, palpation, and or percussion. Lung's auscultation found the left breath sound weakened at RIC VIII and below, and the right breath sound bronchovesicular, no rhonchi or wheezing found.

Based on anamnesis, physical examination, and supporting examination. The patient was diagnosed with left lung adenocarcinoma (Exon 21 mutation) T3N1M1c (pleura, con-tralateral nodule, ribs, suprarenal) Stage IVb progressive disease with TKI. TKI therapy in the patient was stopped, and rediagnostics were performed. Rediagnostic results found adenocarcinoma. The patient was advised to do a molecular biology examination to determine the presence of the T790M mutation, but it cannot perform due to health insurance issues. The patient was managed with conventional platinum-based chemotherapy with a paclitaxel 250mg-carboplatin 450mg regimen.

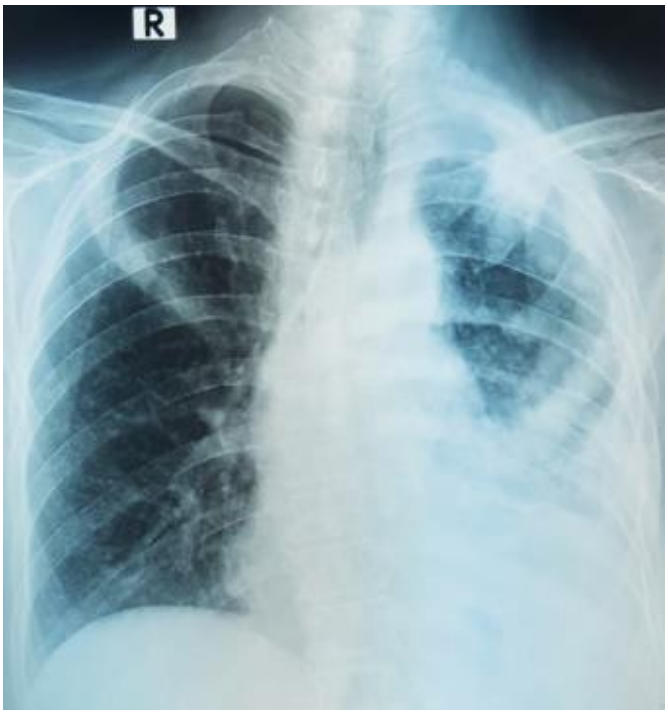

Figure 1: Thoracic photograph after administration of EGFR TKIs for 17 months, left pleural effusion impression.

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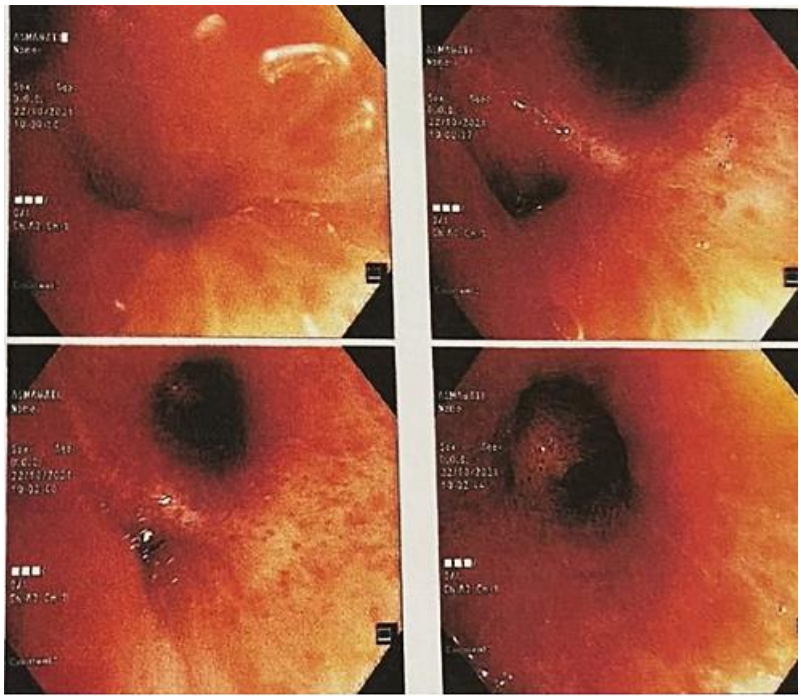

Figure 2. Bronchoscopic examination (rebiopsy): infiltrative mass found in the left lower lobe

In preparation for the first chemotherapy, the lab results were obtained: Hb 10,1 g/dl, leucocytes 11.620/mm^3, platelets 458.000 /mm^3, Hematocrit 28%, Diff count 0/3/0/72/19/11, Granulocytes 8.640, CCT urine 60.7, SGOT 18 IU/L, SGPT 9 IU/L, Ureum 19 IU/L, Creatinine 0,6 IU/L. Body weight 52 kg, height 155 cm with *body surface area* (BSA) 1.50 m^2. The patient is eligible for chemotherapy with a paclitaxel regimen of 250mg - carboplatin 450mg.

Preparation for the second chemotherapy, obtained laboratory results Hb 10,7 g/dl, leucocytes 4.490/mm^3, platelets 171.000/mm^3, hematocrit 32%, diff count 0/0/2/43/45/10, granulocytes 2020, CCT urine 61.7, SGOT 30 IU/L, SGPT 32 IU/L, Ureum 10 IU/l, Creatinine 0,6 IU/l. Body weight 52 kg, height 155 cm with BSA 1.50 m^2. The patient is currently eligible for chemotherapy with a regimen of paclitaxel 250mg - carboplatin 450mg.

Third chemotherapy laboratorium preparation, obtained lab results Hb 10,4 g/dl, leucocytes 2.490/mm^3, platelets 161.000/mm^3, hematocrit 33%, diff count 0/0/1/32/50/17, granulocytes 821.7, CCT urine 59.7, SGOT 32 IU/L, SGPT 21 IU/L, ureum 10 IU/L, creatinine 0,7 IU/L. Body weight 54 kg, height 155 cm with BSA 1.52 m^2. The patient experienced WHO toxicity grade III chemotherapy side effects (granulocytopenia). Granulocytopenia was corrected with filgrastim (leukogen®) 260 mcg once daily for three days. Lab evaluation results were eligible, and chemotherapy was performed with a paclitaxel 250mg - carboplatin 450mg regimen.

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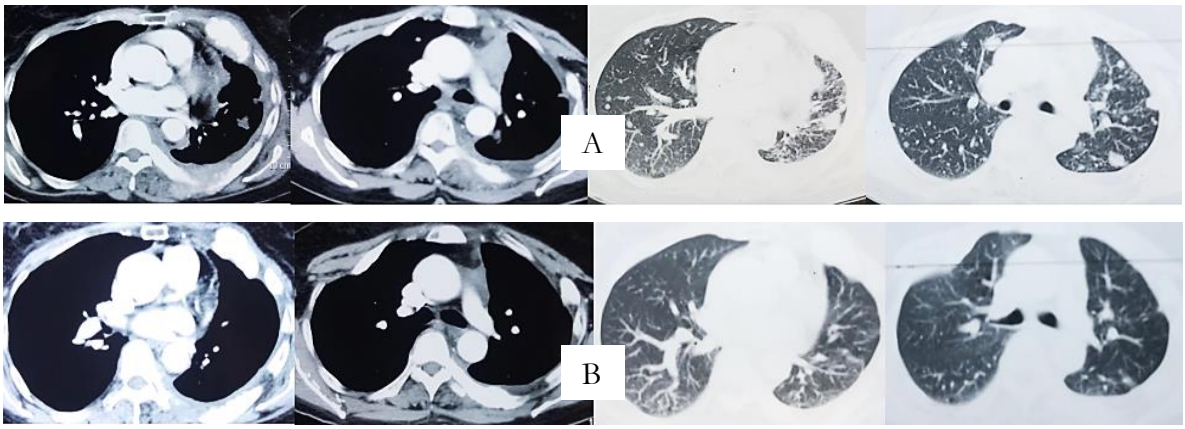

Figure 3. Comparison of thoracic CT scans with contrast up to suprarenal before therapy (A) with after chemotherapy three cycles (B)

After the third cycle of chemotherapy, *Response Evaluation Criteria in Solid Tumour* (RECIST) was performed. There was consisted of subjective response, semi-subjective response, and objective response. Subjective response assessment of complaints of shortness of breath and chest pain was reduced after che-motherapy. Semi-subjective response persis-ted. Objective response using thoracic CT-scan with contrast to the suprarenal, compared to conventional pre-chemotherapy CT-scan, obtained a solid mass reduced by 43% (partial response), so it was decided to continue chemotherapy until the sixth cycle.

Preparation for the fourth chemotherapy, lab results in Hb 10,1 g/dl, leucocytes 3.410/mm^3, platelets 71.000/mm^3, hematocrit 28%, diff count 0/2/2/31/50/5, granulocytes 1193.5, CCT urine 61.2, SGOT 18 IU/L, SGPT 9 IU/L, ureum 19 IU/L, creatinine 0,6 IU/L. Body weight 54 kg, height 155 cm with BSA 1.52 m^2. The patient had WHO toxicity grade I (granulocytopenia) and was corrected with filgrastim (leukogen®) 260 mcg 1x daily for three days. The laboratory evaluation results were eligible, and chemotherapy was performed with a regimen of paclitaxel 250mg - carboplatin 450mg.

Preparation for fifth chemotherapy, lab results Hb 9,1 gr/dl leucocytes 2.630/mm^3, platelets 36.000/mm^3, hematocrit 27%, diff count 0/0/0/29/57/14, granulocytes 762.7, CCT urine 65, total protein 7,4 g/dl, Albumin 4,3 g/dl, globulin 3,1 g/dl, SGOT 21 IU/L, SGPT 18 IU/L, ureum 19 IU/L, creatinine 0,6 IU/L. Body weight 54 kg, height 155 cm with BSA 1.52 m^2. The patient had pancytopenia with WHO toxicity grade III (anemia, thrombocytopenia, granulocytopenia). The patient was then transfused with ten bags of platelets, one bag of PRC, and filgrastim (leukogen®) 260mcq 1x daily for three days. The patient was further evaluated and eligible for fifth-cycle chemotherapy.

Preparation for the sixth chemotherapy, lab results in Hb 10.7 g/dl, leucocytes 2.940/mm^3, platelets 58.000/mm^3, Hematocrit 31 DC 0/0/1/30/52/17 Granulocytes 911.4 CCT urine 67.2 SGOT/SGPT 30/26 Ureum/Creatinine 13/0.7. Body weight 54 kg, height 155 cm with BSA 1.52 m^2. The patient had WHO toxicity grade III (granulocytopenia and thrombocytopenia). Thrombocytopenia corrects with

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five bags of platelet, one bag of afaresis, and filgrastim (leukogen®) 260 mcg once daily for three days. The patient was referred to oncology and assessed for labor correction. Lab evaluation: platelets from 58,000 to 68,000, then transfusion and stepwise evaluation. The platelets were given 40 units (in stages) and one bag of PRC (Hb dropped from 10 to 9.7). Chemotherapy was stopped because thrombocytopenia could not be resolved (post-correction platelets 58,000), so it did not meet the chemotherapy requirements.

DISCUSSION

Chemotherapy has cytotoxic characteristics cytotoxic and acts in the S (synthetic) phase of the cell cycle or during *deoxyribonucleic acid* (DNA) synthesis. Other agents, such as vinca alkaloids and taxanes, inhibit mitotic spindle formation in M (mitotic) phase. These agents work most effectively when cells enter the mitotic phase, the weakest phase of the cell cycle. Most of the agents mentioned interact with DNA or its precursors, inhibiting the synthesis of genetic material and causing extensive DNA damage in both normal and malignant cells.[11] This cytotoxic characteristic kills target cells and the body's normal cells.[12]

Blood has a variety of functions, including the transport of gasses transport, and all essential substances for cellular metabolism, maintenance of homeostasis, acidic (H+ pressure) balance, thermoregulation, mediation of immune responses, removal of waste substances, and more. Blood requires great regeneration ability to perform these functions. In healthy adults, blood cells (erythrocytes, granulocytes, and platelets) were produced at approximately 1-3 million cells per second. This ability makes blood and the hematopoietic system easy targets for drugs that suppress cell proliferation, such as most chemotherapy drugs.[13]

Hematopoiesis is used to describe the formation of blood cells. Hematopoiesis has two main branches, myeloid and lymphoid, which are derived from hematopoietic stem cells and produce various cell lines. The number of hematopoietic stem cells is estimated to be 1 in 20 million nucleated cells in the bone marrow.[13] Hematopoiesis begins with stem cell division, where one cell replaces the stem cell (self-renewal), and the other cell undergoes differentiation. These early progenitor cells express several transcription factors that can direct the cells into specific cell lines. Which cell line was selected for differentiation depends on the opportunity and external signals received by the progenitor cells.[13] Every second, the body produces 2 million erythrocytes, 2 million platelets, and 700,000 granulocytes, as shown in Figure 4. Cancer-related hematological disorders can cause various clinical symptoms, reduce the patient's quality of life, affect the patient's tolerance to treatment, and reduce the sensitivity of tumor tissue to treatment.[14] The baseline labor in this patient before chemotherapy with paclitaxel and carboplatin was within normal limits.

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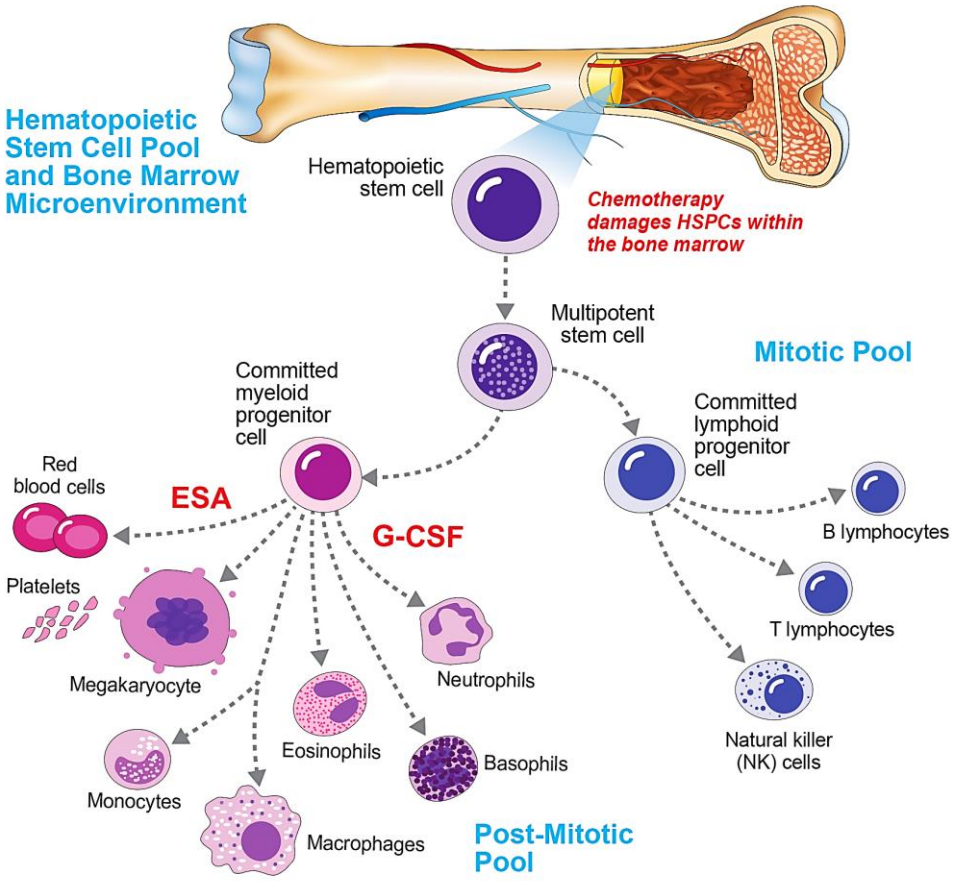

Figure 4. Chemotherapy-induced blood formation disorders. Abbreviations: BM, bone marrow; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte-colony-stimulating factor; HSC, hematopoietic stem cell; HSPC, hematopoietic stem progenitor cell. Quoted from (15)

Table 1. Degrees of Hematological Toxicity based on WHO.[13]

Hematology		0	1	2	3	4
Haemoglobin	g/100 ml	>11.0	9.5 – 10.9	8.0 – 9.4	6.5 – 7.9	<6.5
Leukocytes	1000/mm³	>4	3.0 – 3.9	2.0 – 2.9	1.0 – 1.9	<1.0
Granulocytes	1000/mm³	>2.0	1.5 – 1.9	1.0 – 1.4	0.5 – 0.9	<0.5
Platelets	1000/mm³	>100	75 – 99	50 – 74	25 – 49	<25
Hemorrhage		None	Peteci	Mild hemorrhage	Severe (gross) hemorrhage	Hemorrhage causing shock

Hematopoietic growth factors were produced by monocytes and bone marrow stromal cells, except erythropoietin which was produced by the kidney. The target destination is the hematopoietic point binding to hematopoietic progenitors via specific receptors on endothelial cells and osteoblasts.[13] Chemotherapy damages stem cells in the bone marrow, damaging all downstream cell lines, including committed progenitor cells, decreased *hematopoietic stem cell* (HSC) self-renewal, and decreased HSC reserve.

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Chemotherapy-induced myelosuppression (CIM) is the adverse effect of toxic compounds on blood-forming organs. Anticancer drugs (such as doxorubicin, carboplatin, cisplatin, lenalidomide, thalidomide, and vincristine) could cause myelotoxicity. Three types of chemotherapy-induced myelotoxicity are neutropenia, thrombocytopenia, and anemia.[13] The severity of anemia, neutropenia, and thrombocytopenia caused by chemotherapy are listed in Table 1.

The involvement of genetic polymorphisms (paclitaxel-carboplatin) made hematological toxicity. It depends on race and ethnicity. Single nucleotide polymorphisms 2677G> T/A and 3435C>T of the ABCB1 gene have been associated with neutropenia on paclitaxel chemotherapy. Several studies (polymorphisms in drug transport genes (ABCB1 and ABCG2), DNA repair pathway genes (ERCC4 and XCC), and apoptosis pathway genes (CASP 8 and CASP10)) were associated with severe hematological toxicity. It is due effects of paclitaxel-carboplatin.[1]

Chemotherapy-induced hematological toxicity can occur from the first to the eighteenth week. Severe toxicity was often experienced during the first cycle of chemotherapy. Toxicity events often appear in the fifth week or at the end of the second cycle.[16] Cycles of chemotherapy are reported to be directly proportional to the severity of toxicity. A more significant number of chemotherapy cycles, the patient experience more severe toxicity.[17] Paclitaxel causes myelosuppression by binding firmly to the microtubules of bone marrow cells. This process prevents depolymerization, leading to mitotic inhibition. Subsequently, apoptosis of cell division occurs.[18] However, thrombocytopenia is rare hematological toxicity of the platinum and paclitaxel combination.[19]

Anemia is a common finding in cancer patients, with an incidence between 30%-90%. Causes of anemia in cancer patients include metabolic and nutritional disorders, chronic disease, renal abnormalities, blood loss, decreased production due to bone marrow disease, peripheral destruction due to autoimmune disorders, drug-induced red blood cell aplasia, and chemotherapy-induced anemia.[20] Chemotherapy inhibits normal hematopoiesis mechanisms and cytokines action that will lead to anemia. Chemotherapeutic agents cause anemia directly by interfering with hematopoiesis. It includes synthesizing red blood cell precursors in the bone marrow. The nephrotoxic effects of specific cytotoxic agents can also induce anemia. This process occurs by decreasing erythropoietin production. Platinum-based regimens are known to cause anemia due to their toxic effects on the bone marrow and kidneys.[21,22]

Chemotherapy-Induced anemia can cause fatigue, pale skin, shortness of breath, drowsiness, depression, tachycardia, and dizziness. Chemotherapy-Induced anemia can lead to chemotherapy delays and adverse effects on quality of life. Hemoglobin concentration is also related to the quality of life, as shown in Figure 6.[23]

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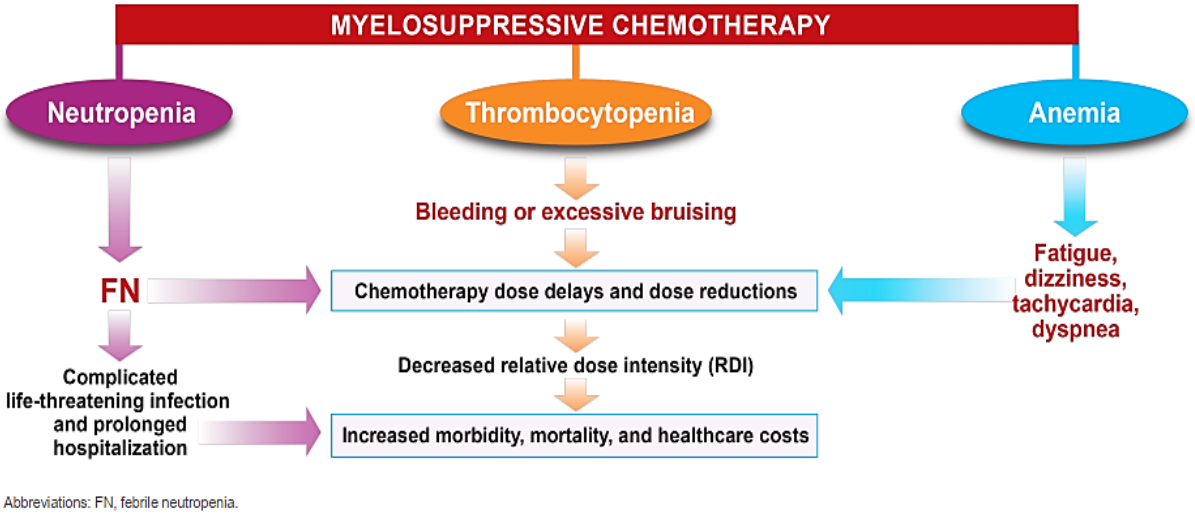

Figure 5. Myelosuppressive Consequences of Chemotherapy. Quoted from (2)

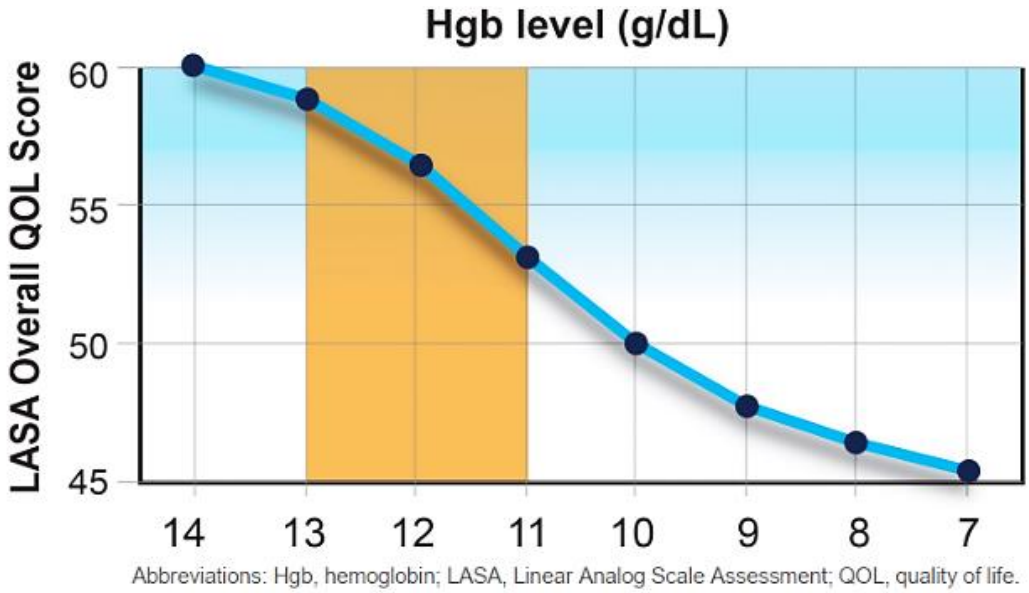

Figure 6. Haemoglobin Level Associated with Quality of Life (QoL) Quote from (23)

Packed Red Cells (PRC) transfusion should not be based solely on Hb values or anemia-inducing factors but on individual assessment of patient characteristics, the severity of anemia, comorbidities and their severity, and the physician's clinical experience. Packed red blood cell transfusion is the only therapy for chemotherapy patients who require immediate anemia correction. Transfusion of 1 unit of PRC can increase Hb by approximately 1gr/dL or hematocrit by 3% in adults of standard body size without bleeding.[12]

Red blood cell (RBC) production was generally controlled by erythropoietin, a cytokine produced by the kidney. Erythropoietin Stimulating Agent (ESA) administration is generally a long-term decision due to the risks involved. Erythropoietin Stimulating Agent is a synthetic

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recombinant human erythropoietin. It can stimulate erythropoiesis in patients with low RBC levels. Currently, two types of ESA are available in the United States: epoetin alfa and darbepoetin alfa.[23]

The administration of ESA should consider iron levels. Patients with functional iron deficiency should be given intravenous iron supplements.[24] The patient was not given ESA because it responded to PRC transfusion. Erythropoietin Stimulating Agent, in this case, can use epoetin alfa (Hemapo®). Insurance did not cover this drug, and the patient must purchase it.

The principle of action of epoetin alfa is erythropoietin. It stimulates the terminal differentiation of erythroid progenitors into mature erythrocytes, ultimately increasing red blood cell mass. Treatment of epoetin alfa is divided into two stages: a) Correction phase in non-dialysis patients: 100 IU/kg/week divided into three doses, and b) Maintenance phase Maintain the hematocrit between 30% and 35%, the dose should be 50-150 IU/kg/week divided into 2-3 doses (reduced to 2/3 of the previously administered amount). Hematocrit should be monitored once every 2-4 weeks to adjust the dose to keep the hematocrit at the right level and avoid erythropoiesis forming too quickly.[24]

Although *Chemotherapy-Induced Thrombocytopenia* (CIT) is expected, limited data are available on its incidence in the United States. Most standardized regimens have relatively low rates of CIT, lasting 4 to 6 days. The incidence of chemotherapy-associated thrombocytopenia is most associated with administering gemcitabine and platinum-based regimens. *Chemotherapy-Induced Neutropenia* (CIN) predisposes to infection. The most significant risk of neutropenia in chemotherapy was found in the first cycle of chemotherapy.[20] Several studies have shown that prophylactic administration of *Myeloid Growth Factors* (MGFs) could reduce the risk, severity, and duration of febrile neutropenia. MGFs are biological agents that regulate myeloid cell proliferation, differentiation, survival, and activation. *Granulocyte-Colony Stimulating Factor* (G-CSF) is a type of MGF that has shown promising results in clinical applications. Filgrastim, tbo-filgrastim, and pegfilgrastim were approved by the *Food and Drug Administration* (FDA) and used for prophylaxis of chemotherapy-induced neutropenia.[23]

CONCLUSIONS

Side effects of paclitaxel-carboplatin chemotherapy are anemia, neutropenia, and thrombocytopenia. Anemia was managed with PRC transfusion, neutropenia with filgrastim, and thrombocytopenia with platelet transfusion. These hematological disorders led to a delay in chemotherapy. Thrombocytopenia that did not improve after correction led to discontinuation of chemotherapy.

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