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ABBAS Letissia & REGHID Lina

Study of hematotoxicity induced by chemotherapy drugs

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Last and first name*:*	***Grade***		
Mrs. METIDJI Karima	MCB	Bouira Univ.	President
Mr. BOURNINE Lamine	MCA	Bouira Univ.	Supervisor
Mrs. BENSMAIL Souhila	MCA	Bouira Univ.	Examiner

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With a fulfilled heart, I dedicate this work to:

To the person who inspired me the most, my source of patience and determination,

the soul who left this world but inhabits my heart, Dad "رحمة الله عليه"

To my mom, thank you for always being there, for lifting me up during the tough times, and for celebrating every achievement with me. This work is dedicated to you, with profound gratitude for your sacrifices and the countless ways you have enriched my journey. This achievement would not have been possible without your prayers.

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To all my friends, the source of joy and fun, who made this journey easier with their help. Thank you for being there.

With all my love and gratitude,

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Dedication

I dedicate this work to:

***My dear Dad**, whose name I proudly carry. Thank you for everything you have given me from birth until now, your love and your support. This success is the result of the countless sacrifices you have made for my education and training. May Allah bless you with good health and long life.*

***My Mother**, the best mom in the world. You are the precious person in my life. Thank you, a thousand times over, for always being there for me through good and bad times, and for your endless encouragement. Your prayers are the foundation of my success and achievements. May God bless you with a long and joyful life.*

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*My three favorites, my close-knit team: **LINA**, **SERIN**, and **BOUBA**. You are the brightest part of my university years. Thank you for every moment we shared. I hope our friendship lasts a lifetime, and I wish you success and happiness.*

*To all my **Friends**, you are the source of joy and laughter. Thank you for the wonderful memories and beautiful moments we've shared. Thank you for always being there.*

With much love,

Lety

Content table

List of abbreviations:

5FU: 5-Fluorouracil

ANC: Absolute neutrophil count

ATO: Arsenic trioxide

CBC: Complete blood count

CIT: Chemotherapy induced thrombocytopenia

CPT: Camptothecin

CPT11: Irinotecan

DNA: Deoxyribonucleic acid

EDTA: Ethylene-diamine tetra acetic acid

ESA: Erythropoietin stimulating agents

FN: Febrile neutropenia

G-CSFs: Granulocyte colony-stimulating factors

HGB : Hemoglobin

HNE : 4-hydroxynonenal

IL1 : Interleukin

IV : Intravenous

MDA : Malondialdehyde

MetHb : Methemoglobin

N : Nitrogen

NACL : Sodium chloride

NCI : National cancer institute

NSCLC : Non-small cell lung cancer

O: Oxygen

OS: Oxidative stress

PC: Platelets count

RBC: Red blood cell

RNA: Ribonucleic acid

ROS: Reactive oxygen species

TBA: Thiobarbituric acid

TBARS: Thiobarbituric acid reactive substances

TBAs: Tubulin binding agents

TCA: Trichloracetic acid

TOPO I: Topoisomerase I

TOPO II: Topoisomerase II

TPO: Thrombopoietin

TS: Thymidylate synthase

UMP: Uridine monophosphate

WBC: White blood cell

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Introduction

Introduction

Cancer become the main cause of death, increasing global life expectancy in the 21st century (Jang et al., 2023). Cancer treatment typically involves radiotherapy, surgery, and systemic therapy. While surgery alone can often cure low-risk patients in the early stages of the disease, many other cases necessitate a combination of these treatments. Systemic therapy, which comprises hormonal therapy, targeted therapy, immunotherapy, and chemotherapy, is the primary therapeutic mode in metastatic disease, as it facilitates access to disseminated cancer sites through the bloodstream (Dickens and Ahmed, 2018).

Chemotherapy is one of the most important treatments for killing cancer cells. It involves administering cytotoxic chemicals to eradicate or reduce the tumor (Nygren, 2001) by inhibiting cell proliferation and tumor multiplication, which prevents invasion and metastasis (Amjad et al., 2024). These drugs are frequently used either alone (monotherapy) or, more commonly, in combination with other chemotherapy or cytotoxic drugs for an extended period (Mooren, 2012).

This treatment can, on the one hand, provide a huge benefit to cancer treatment but also can cause a serious limitation, which is its lack of selectivity, resulting in several side effects such as hematological toxicity, nausea, vomiting, diarrhea, tiredness, hair loss, and toxicities affecting the heart, nervous system, and kidneys. Hematological toxicity is the primary side effect of most anticancer drugs, resulting in reduced production of rapidly dividing cells in bone marrow, including red blood cells, platelets, and white blood cells (Gasmi et al., 2021).

Several mechanisms of action of chemotherapeutic agents have been explored particularly oxidative stress (OS) (Conklin, 2004). OS is a dynamic and complex condition marked by an imbalance between the production of reactive oxygen species (ROS) and the availability and effectiveness of antioxidants, leading to tissue damage (Cauli, 2021). In vitro study has explored the membrane cytotoxicity of different anticancer drugs on RBCs caused by an exacerbation of OS (Mameri et al., 2021).

In addition, the toxic effects of chemotherapeutic drugs are attributed to their effects on the bone marrow (medullary effects) (Mameri et al., 2021). However, little is known about the direct effects of commonly used anticancer drugs on whole blood cells in clinical trials. Research indicates that the adverse effects experienced during chemotherapy

(doxorubicin and paclitaxel), are owing to direct contact of the intravenous infusion with RBCs and systemic oxidative damages generated during drug metabolism (Panis et al., 2012).

The aim of this study is to assess the direct impact of chemotherapy on the hematologic profile in cancer patients by comparing complete blood count (CBC) parameters before and immediately after the administration of the treatments and to investigate the molecular mechanism involved in this hematotoxicity.

This manuscript is divided into two parts. The first part contains a bibliographic review with general information about chemotherapy, the hematotoxicity induced by this treatment, and the link between chemotherapy and OS. The second part focuses on the experimental study, describing the material and methods, the results obtained, and their interpretations. Finally, this document ends with a conclusion and some research perspectives.

Chapter 01
Chemotherapy

I. Chemotherapy

I.1. Definition of chemotherapy

Chemotherapy, along with surgery and radiation therapy, is frequently used as a treatment option for numerous cancer cases in medicine (MacDonald, 2009).

Chemotherapy is the treatment of disease using chemicals. These chemicals aim to stop the growth of harmful cells, like cancer cells or infectious agents (such as bacteria or viruses). Ideally, these chemicals target the harmful cells with minimal impact on healthy cells in the body (Alam, 2018).

I.2. Treatment strategies for chemotherapy

I.2.1 Combination chemotherapy

Combination chemotherapy is a treatment strategy that involves administering multiple agents from different classes. Chemotherapy drugs are programmed in cycles according to the recovery of normal tissues from those agents (Dickens and Ahmed, 2018).

The significant advantage of combining chemotherapy is to decrease the risk of drug resistance development to any individual agent. Besides, administering the drugs at lower doses can help in minimizing side effects and toxicity (Alam, 2018).

I.2.2 Adjuvant chemotherapy

Chemotherapy is introduced after controlling the primary tumor through procedures like surgery or radiotherapy. The objective is to eliminate any tumor cells that may have evaded treatment from the primary tumor and could potentially lead to the development of metastases in the future (Alam, 2018).

I.2.3 Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is administered before local treatments like surgery, aiming to reduce the size and achieve better long-term control of the primary tumor (Alam, 2018).

I.3 Chemotherapy drugs

I.3.1 Alkylating agents

Alkylating agents represent the initial generation of anti-cancer agents employed in the treatment of cancer patients (Gate and Tew, 2011). These drugs possess a dual nature, acting as double-edged swords capable of causing significant damage but also facilitating

profound healing effects. While most alkylating agents operate through similar mechanisms, their clinical effectiveness varies (Ralhan and Kaur, 2007).

Because of their chemical properties, alkylating agents can interact with DNA either directly or after biological activation. This interaction can lead to DNA crosslinking, causing breaks in the DNA strands. Consequently, abnormal base pairing occurs, hindering cell division and ultimately leading to cell death (Ralhan and Kaur, 2007).

- Mechanisms of action

In traditional classification, alkylating reactions are typically categorized into two groups: mono-functional, which interacts with only one DNA strand, and bi-functional, which reacts with atoms on both DNA strands, resulting in the covalent crosslinking of the strands (Ralhan and Kaur, 2007).

Alkylating agents exert their effects through three distinct mechanisms, ultimately disrupting DNA function and culminating in cell death (Ralhan and Kaur, 2007).

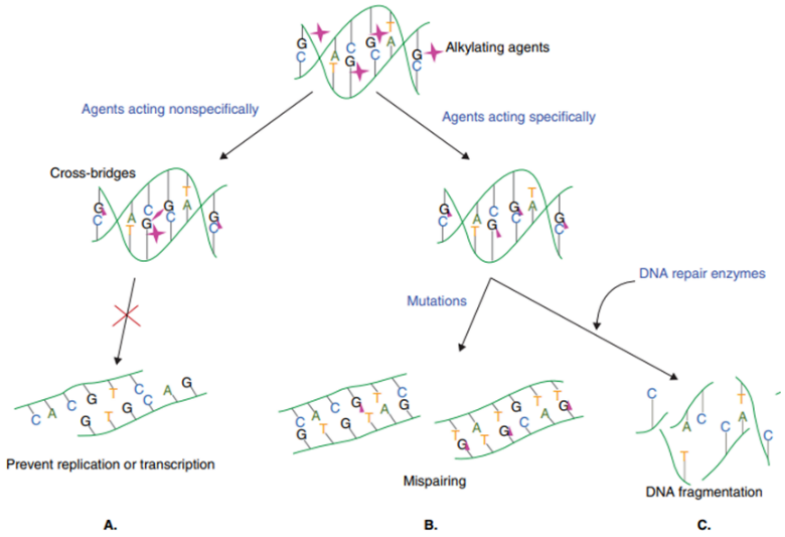

Figure 1: Mechanism of action of alkylating agents *(Ralhan and Kaur, 2007).*

A- Inhibition of replication or transcription: DNA damage induced by the formation of cross-bridges. During this process, bi-functional alkylating agents link two bases together. This cross-linking inhibits the separation of DNA strands necessary for synthesis or transcription to occur, as in the case of Melphalan (Ralhan and Kaur, 2007).

B- Mutation: induced by causing mispairing of nucleotides. For instance, alkylated guanine bases may erroneously pair with thymidine.

C- DNA fragmentation: Alkylating agents attach alkyl groups to DNA bases. Consequently, DNA repair enzymes endeavor to replace the alkylated bases, leading to DNA fragmentation (Ralhan and Kaur, 2007).

- Types of Agent

This class includes many types of citing:

- *Nitrogen Mustards:*

While numerous nitrogen mustards have been developed and assessed in preclinical models, only five are presently employed in chemotherapy. These are: mechlorethamine, cyclophosphamide, ifosfamide, melphalan, and chlorambucil. They share a bis-chloroethyl group and interact with nucleophilic sites via an aziridinium intermediate. They typically alkylate the N_7 of guanine, although they can also react with the O_6 of guanine, as well as the N_3 and N_7 of adenine (Gate and Tew, 2011).

- *itrosoureas*

Clinically valuable nitrosoureas are derived from methylnitrosoguanidine and methylnitrosourea agents, which were initially screened by the National Cancer Institute (NCI). These compounds demonstrated antitumor activities against experimental mouse cancer models (Gate and Tew, 2011).

I.3.2 Antimetabolites:

An antimetabolite is characterized as a drug that disrupts the regular metabolic processes within cells (Kaye, 1998).

Antimetabolites are analogs of essential cellular molecules. They function by substituting normal molecules in DNA and RNA synthesis or by competing for the catalytic site of key enzymes (Kaye, 1998).

Types

Among these antimetabolite drugs are gemcitabine, 5FU, capecitabine and methotexate.

- Gemcitabine

Gemzar® is a di-fluorinated analogue that has risen to prominence as a crucial agent in the treatment of several tumor types, notably pancreatic, non-small-cell lung, bladder, breast, and ovarian cancers (Kaye, 1998).

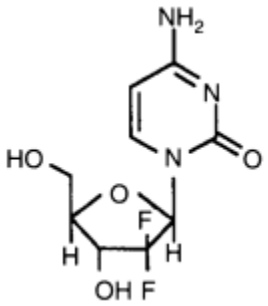

Figure 2: Gemcitabine structure

Its activity relies on the formation of a mononucleotide that is subsequently integrated into DNA. Another residue is then incorporated into the chain before chain termination occurs (Kaye, 1998).

This mechanism, known as 'masked chain termination,' renders the recognition and excision of the modified DNA challenging, thereby partly elucidating the drug's broad activity (Kaye, 1998).

Gemcitabine, when combined with the proteasomal synthesis inhibitor Velcade, demonstrated growth inhibition of non-small cell lung cancer (NSCLC) xenografts. Similarly, in combination with bortezomib, it inhibited the growth of bladder carcinoma xenografts (Tiwari, 2012). It is also used in combination therapy with cisplatin in the treatment of NSCLC (Kaye, 1998).

- 5-fluorouracil (5-FU):

5-fluorouracil (5-FU) is a fluoropyrimidine that belongs to the class of agents known as nucleoside analogs. Generally, these agents operate by substituting nucleosides in one or more normal cell functions due to their resemblance to naturally occurring substrates. They can be categorized into two main classes: those incorporated into DNA and RNA synthesis and those responsible for inhibiting enzymes essential to cell metabolism (Kaye, 1998).

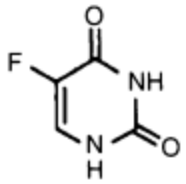

Figure 3: 5-fluorouracil structure

The precise mechanism of action of 5-fluorouracil (5-FU) remains unclear and is partly dependent on dose and schedule. However, thymidylate synthase probably serves as the primary target for the nucleoside of 5-FU, which binds to the active site of the enzyme similarly to dUMP (Kaye, 1998).

Following the binding of 5-fluorouracil (5-FU) to thymidylate synthase (TS), the enzyme is locked into an inhibited conformation resembling the transition state formed during the conversion of dUMP to thymidine. This binding is facilitated by the folate co-factor 5,10-methylenetetrahydrofolate. As a result, cellular levels of thymine are depleted, and the enzyme is rendered incapable of functioning normally (Kaye, 1998).

- Capecitabine:

Capecitabine is a prodrug of 5-fluorouracil (5-FU) that is administered orally. As a prodrug of 5-fluorouracil (5-FU), capecitabine offers two advantages over intravenous 5-FU: ease of administration (oral vs IV) and a potential for increased therapeutic effect. It is presently approved for use in the treatment of stage III colon cancer and metastatic breast cancer (Parker, 2009).

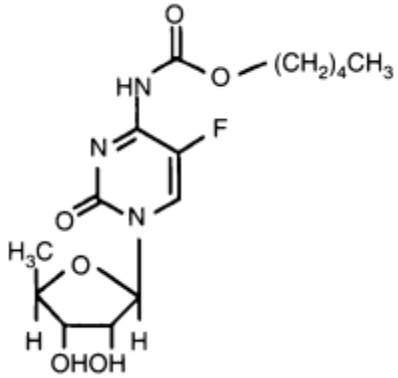

Figure 4: Capecitabine structure

Other recent studies have demonstrated that this cytidine analog, administered orally, passes through the intestinal mucosa unchanged. It undergoes activation through a series of

enzymatic reactions in both the liver and tumor cells, potentially leading to conversion to 5-fluorouracil (5-FU) in a tumor-selective manner by the enzyme thymidine phosphorylase (Kaye, 1998).

I.3.3 Anti-tumor antibiotics

Exert their effects by intercalating them into specific DNA sequences. This process generates free radicals that induce strand breakage (Dickens and Ahmed, 2018).

This class comprise doxorubicin, epirubicin, and bleomycin… the most commonly used in treatments is doxorubicin. Doxorubicin is an antineoplastic antibiotic derived either from a culture of *Streptomyces peacetime var. caesius* or synthesized chemically from daunorubicin (Vigevani and Williamson, 1981).

Doxorubicin is primarily utilized in the treatment of cancers affecting various organs such as the bladder, breast, lung, ovaries, soft tissue sarcoma, multiple myeloma, and Hodgkin's lymphoma (Rivankar, 2014).

- Mechanism of action

The precise mechanism of action of doxorubicin is intricate and not fully understood. Doxorubicin interacts with DNA by intercalation, thereby inhibiting macromolecular biosynthesis (Rivankar, 2014).

The precise mechanism by which doxorubicin exerts its cytotoxic effects is complex and involves multiple cellular processes. A key mechanism involves intercalation between DNA base pairs, which disrupts DNA function and hinders essential processes like DNA replication and transcription. This ultimately leads to the inhibition of macromolecular biosynthesis and contributes to cell death (Rivankar, 2014).

I.3.4 Topoisomerase inhibitors

DNA topoisomerases play a crucial role in stabilizing DNA supercoiling and resolving tangles. These enzymes are present in all cells and exist in two primary types: topoisomerase type I with single DNA cleavage activity and type II with double stands DNA cleavage activity. These enzymes play crucial roles in numerous essential cellular processes, encompassing DNA replication, transcription, recombination, and chromosome condensation (Jang et al., 2023).

Topoisomerase activity experiences a notable increase in rapidly dividing cells, such as those found in cancer. Consequently, topoisomerase inhibitors have proven to be an effective chemotherapy choice for treating various types of cancer(Jang et al., 2023).

- Mechanism of action

Camptothecin functions by attaching to and stabilizing the typically transient cleavable DNA-topoisomerase I complex, which occurs during replication. While the initial cleavage activity of topoisomerase I remains unchanged, camptothecin hinders the usual resealing of the parental DNA strand after the daughter strand has passed through. When the replication fork encounters this cleaved DNA strand, it triggers an irreversible double-strand DNA break, halting the cell division process and leading to cell death (Rothenberg, 1997).

Topoisomerase II inhibitors are classified into two types according to their mode of action: catalytic inhibitors and TOPO II poisons (Jang et al., 2023).

- Catalytic inhibitors impede the enzymatic functions of TOPO II by blocking the enzyme either before DNA cleavage or after DNA re-ligation. Consequently, these inhibitors do not promote the build-up of TOPO II-DNA cleavage complexes. The absence of TOPO II activity in unwinding DNA supercoils or untangling sister chromatids during mitosis can result in failed cell division and, ultimately, cell death (Jang et al., 2023).
- TOPO II poisons inhibit TOPO II from completing the catalytic cycle following DNA cleavage. Consequently, they enhance the accumulation of TOPO II-DNA cleavage complexes, inducing DNA damage that surpasses the cell's DNA repair capacity. This accumulation of DNA breaks ultimately triggers programmed cell death. Examples of TOPO II poisons include etoposide, doxorubicin, and amsacrine (Jang et al., 2023).

I.3.5 Tubulin-binding drugs

These drugs disrupt microtubule function, causing daughter chromosomes to misalign to the mitotic spindle in a bipolar manner. As a result, the cell is unable to pass through the checkpoints designed to regulate mitosis, causing it to halt at the metaphase/anaphase transition. This interruption ultimately triggers programmed cell death, known as apoptosis (Attard et al., 2006).

Tubulin-binding agents (TBAs) are highly effective mitotic poisons, categorized broadly into microtubule-stabilizing drugs (such as taxanes and epothilones) and

microtubule-destabilizing drugs (such as vincristine, vinblastine, and vinorelbine) (Kavallaris, 2010).

TBAs exert their effects by suppressing spindle microtubule dynamics, resulting in a delay or blockage at the metaphase–anaphase transition during mitosis. This disruption fails to satisfy the spindle assembly checkpoint, leading to an extended mitotic arrest, which ultimately can culminate in cell death (Kavallaris, 2010).

Cancer cells exhibit heightened susceptibility to the cell death induced by tubulin-binding agents (TBAs) compared to normal cells. As a result, these agents are frequently employed in combination with other drugs for the treatment of a diverse array of cancers (Kavallaris, 2010).

Taxanes were the pioneering microtubule-stabilizing drugs identified and are now commonly employed in the treatment of various solid tumors, including lung, breast, and ovarian cancers (Kavallaris, 2010).

Epothilones are utilized for treating drug-refractory advanced breast cancer, and are currently being evaluated for the treatment of a broader spectrum of solid tumors. Epothilones have demonstrated efficacy in a subset of tumors resistant to paclitaxel (Kavallaris, 2010).

Table 1: Recapitulative table of chemotherapy drugs (Dickens and Ahmed, 2018)

Drug class	Mechanism of action	Examples
Alkylating agents	Chemically capable of binding to various cellular macromolecules: DNA, RNA, proteins. Those agents substitute alkyl groups for hydrogen atoms in DNA. This class includes: the nitrogen mustard, nitrosourea, and platinum complexes	cisplatin, carboplatin, oxaliplatin, chlorambucil, cyclophosphamide
Anti-metabolites	Analogues of crucial cellular molecules. Act by substitute normal molecules in DNA and RNA synthesis or compete for the catalytic site of a key enzyme.	gemcitabine, 5-fluorouracil, capecitabine, methotrexate.
Anti-tumor antibiotics	Exert their effects by intercalating into specific DNA sequences. This process generates free radicals that induce strand breakage	doxorubicin, epirubicin, bleomycin
Topoisomerase inhibitors	They function by engaging with the essential nuclear enzymes, topoisomerase I and II, which play critical roles in DNA replication, transcription, and repair. The drug interaction with these enzymes, results in more permanent breaks in the DNA, disrupting its normal function	irinotecan, topotecan, etoposide

Tubulin-binding drugs	They attach to tubulin and hinder the formation of microtubules, crucial not only for mitosis but also for maintaining cell shape, facilitating intracellular transport, and supporting axonal function.	vincristine, vinorelbine, paclitaxel, docetaxel

I.4 Side effects of chemotherapy

All anticancer drugs exhibit cytotoxicity towards both cancerous and normal cells, which means that chemotherapy also destroys some cells that normally divide rapidly: the digestive tract, cells in bone marrow, and hair follicles (Alam, 2018).

In addition to these common side effects, there are others such as cardiac toxicity, hepatic toxicity, neurological effects, pulmonary toxicity, renal toxicity, and even some drugs induce oxidative stress, which leads to major damage in cells (Lowenthal and Eaton, 1996).

I.4.1 Gastrointestinal toxicity

-Nausea and vomiting:

Nausea and vomiting are a very common acute side effects of chemotherapy. The mechanisms of chemotherapy-induced nausea and/or vomiting are based central and peripheral neural processes (Di Fiore and Van Cutsem, 2009).

Table 2: Risk degree of drugs causing nausea and vomiting (Di Fiore and Van Cutsem, 2009).

Drugs	Risk degree
Cetuximab, bevacizumab, paclitaxel, docetaxel, etoposide, mitomycin, gemcitabine, fluorouracil	low risk
Oxaliplatin, irinotecan	moderate risk
Cisplatin, streptozotocin	high risk

- Acute Diarrhea:

Diarrhea can pose a significant, incapacitating, and potentially life-threatening challenge during anti-cancer therapy, particularly when coupled with neutropenia. This side effect observed in treatments with 5-fluorouracil (5-FU) and irinotecan (CPT11) (Di Fiore and Van Cutsem, 2009).

I.4.2 Alopecia

Alopecia is a troubling side effect frequently encountered in specific treatment protocols within oncology. Cytotoxic chemotherapy agents focus on attacking dividing cells,

inadvertently affecting highly proliferative hair matrix cells in the process (Chon et al., 2012).

I.4.3 Bone marrow toxicity

Myelosuppression induced by chemotherapy represents the primary dose-limiting and potentially life-threatening complication of cancer therapy. It occurs due to the destruction of proliferating progenitor cells responsible for producing the three primary cell lines within the bone marrow: platelets, neutrophils, and erythrocytes (Maxwell and Maher, 1992).

Neutropenia and thrombocytopenia emerge as the most prevalent acute toxicities due to the relatively brief half-lives of these cells. Thrombocytopenia exhibits a relatively lower occurrence rate compared to the rates of neutropenia and anemia. The primary risk associated with chemotherapy-induced thrombocytopenia is Hemorrhage resulting from decreased platelet levels (Kuhn, 2002).

In patients with solid tumors, neutropenia is typically defined as an absolute neutrophil count (ANC) below 500 cells/µL. Three-hour infusions of paclitaxel generally result in greater neurotoxicity compared to 24-hour infusions, which are more likely to induce neutropenia and anemia (Kuhn, 2002).

Chemotherapy-induced anemia tends to manifest as more persistent or chronic toxicity. It results from malignant infiltration of healthy tissue, causing blood loss, bone marrow infiltration that disrupts erythropoiesis, and functional iron deficiency resulting from inflammation (Bryer and Henry, 2018).

Chapter 02
Hematotoxicity

II. Hematotoxicity

II.1 Definition of hematotoxicity

Hematotoxicity pertains to the adverse impacts of toxins on blood-forming organs like bone marrow, as well as on various components of blood, encompassing platelets, leukocytes, erythrocytes, and broadly affecting the hematopoietic system (Shukla and Singh, 2015).

In a healthy adult, distinct blood cells (such as erythrocytes, granulocytes, and platelets) are produced at a rate of approximately 1–3 million per second. This characteristic makes the blood and hematopoietic system vulnerable targets for drugs intended to suppress cell proliferation as in the case of chemotherapy drugs (Shukla and Singh, 2015).

II.2 Hematotoxicity sources

II.2.1 Transplantation

Patients undergoing graft transfers experience hematotoxicity primarily attributed to the conditioning regimens administered immediately following transplantation, along with immunosuppressive medications(Shukla and Singh, 2015).

II.2.2 Drugs and chemicals

Several drugs and chemicals such as antiepileptic drugs, anti-hepatitis C drugs, antiviral drugs, pesticides, and anticancer drugs induce hematotoxicity, which leads to a decrease in Hemoglobin, RBCs, WBCs, depending on the type of drug (Shukla and Singh, 2015).

II.2.3 Disease conditions

As in the case of celiac disease, there's impaired absorption of several essential micronutrients like iron, folic acid, and vitamin B12, resulting in a secondary condition known as anemia(Shukla and Singh, 2015).

II.3 Hematotoxicity induced by chemotherapy

Currently, cancer chemotherapeutics represent the most commonly encountered causes of bone marrow suppression (Budinsky, 2000).

The alkylating agents employed in cancer chemotherapy are renowned for their propensity to harm the bone marrow, and they are frequently administered until the patient experiences bone marrow suppression (Budinsky, 2000).

Myelosuppression induced by chemotherapy affects those lines: platelets, neutrophils, and erythrocytes, which leads to thrombocytopenia, neutropenia, and anemia respectively (Kuhn, 2002).

II.3.1 Anemia

- Generalities

Anemia is determined as a dwindling in hemoglobin levels (Kuhn, 2002). Chemotherapy-induced anemia is a complex occurrence influenced by factors such as bone marrow function, erythropoiesis, red blood cell destruction, and overall erythrocyte mass (Kuhn, 2002). The National Cancer Institute classifies anemia severity based on hemoglobin levels (Bryer and Henry, 2018).

Table 3: Classification of anemia by the National Cancer Institute (Bryer and Henry, 2018).

Grade	Severity	[HBG] g/dL
0	Normal limits	12–16 g/dL women / 14–18 g/dL men
1	Mild	10–12 g/dL women / 10–14 g/dL men
2	Moderate	8–10 g/dL
3	Severe	6.5–8 g/dL
4	Life threatening	<6.5 g/dL

- Chemotherapy and anemia:

Approximately 70% of individuals undergoing chemotherapy are likely to experience anemia. Chemotherapy impacts sensitive erythroid progenitor cells, through a process called eryptosis. This process, similar to apoptosis, leads to the destruction and elimination of defective erythrocytes. Consequently, it prevents hemolysis and the release of Hemoglobin. Eryptosis, along with the ensuing deficiency in erythrocytes, exacerbates anemia and is worsened by insufficient compensatory erythropoiesis (Bryer and Henry, 2018).

In advanced hematologic malignancies, tumor cells primarily disrupt erythropoiesis through the release of cytokines. These cytokines, such as interferon-gamma, IL-1, and tumor necrosis factor, hinder the natural synthesis of erythropoietin in the kidneys and inhibit the differentiation of erythroid progenitor cells in the bone marrow (Bryer and Henry, 2018).

It can occur as a result of various anticancer treatments; however, platinum-based regimens commonly induce this condition (Bryer and Henry, 2018).

Non-platinum chemotherapy regimens, such as antimicrotubular agents, camptothecins, and biologics, can also exhibit significant myelosuppressive effects (Bryer and Henry, 2018).

- Treatment

Current approaches for managing anemia are transfusing packed red blood cells, administering erythropoietin stimulating agents (ESAs), and providing iron supplementation (Bryer and Henry, 2018).

II.3.2 Thrombocytopenia

- Generalities

Thrombocytopenia can result from the disease itself or its symptoms, but it is most commonly induced by chemotherapy that inhibits bone marrow function, and it occurs as a hematologic toxicity associated with myelosuppressive and ablative therapy. This can result in severe bleeding, sometimes fatal (Wu et al., 2009).

The primary risk associated with chemotherapy-induced thrombocytopenia is Hemorrhage due to reduced platelet levels, which is defined as platelet count (PC)≤ 150×10^9/L (Kuhn, 2002).

Thrombocytopenia prevalence is higher in patients with hematologic cancers, and there are individuals who have experienced this toxicity before beginning chemotherapy. Therefore, patients with severe CIT often opt to decrease the chemotherapy dosage to reduce the risk of bleeding. However, this decision may compromise the therapeutic effect and relative dose intensity (RDI), thereby negatively impacting the treatment process (Gao et al., 2023).

- Anticancer drugs and thrombocytopenia:

The therapeutic objective of chemotherapy is to achieve optimal tumor response while minimizing bone marrow suppression. However, certain anticancer drugs can induce thrombocytopenia via diverse mechanisms, although pancytopenia resulting from generalized bone marrow suppression is most prevalent (Liebman, 2014).

In this context, the frequency and severity of chemotherapy-induced thrombocytopenia depend on the specific chemotherapeutic regimen, individual drug dosages, and the number of treatment cycles administered (Wu et al., 2009).

Several studies have indicated that patients with CIT, particularly those undergoing carboplatin or oxaliplatin-based chemotherapy regimens, have a higher risk of severe thrombocytopenia (Wu et al., 2009).

Various chemotherapy drugs impact the megakaryocyte and platelet production pathway at distinct stages. Alkylating agents such as busulfan and carboplatin affect pluripotent stem cells. Cyclophosphamide spares hematopoietic stem cells due to their high levels of aldehyde dehydrogenase, but it does affect later-stage megakaryocyte progenitors (Kuter, 2022).

- Treatments and management

In patients suffering from severe CIT, the general goal is to prevent bleeding. There are several types of treatments available to manage this thrombocytopenia such as (Gao et al., 2023) :

- Vitamin K can be administered to correct blood coagulation in patients taking warfarin or those deficient in vitamin K-dependent coagulation factors (factors II, VII, IX, and X) (Gao et al., 2023).

- Oprelvekin (IL-11) has been approved for treatment. Clinical trials have demonstrated that recombinant human IL-11 (rhIL-11) is employed in managing severe (grade III or IV) thrombocytopenia. Its use has been shown to elevate platelet counts and decrease the risk of bleeding (Gao et al., 2023).

- But in fact, platelet transfusion is frequently the sole immediately accessible treatment option (Gao et al., 2023).

- However, to augment platelet production and elevate platelet counts there is growing interest in the using Thrombopoietin (TPO) which stands out as the primary cytokine responsible for regulating this process (Gao et al., 2023).

II.3.3 Neutropenia

- Generalities

Neutropenia represents the most severe hematologic complication of cancer chemotherapy, frequently constraining the tolerable dosage levels. The severity and duration of neutropenia determine the risk of infection. The Common Toxicity Criteria of the National Cancer Institute classified neutropenia by its severity degree (Crawford et al., 2004).

Table 4: Neutropenia grades (Crawford et al., 2004).

Grade	Absolute neutrophil count (10^9/L)
0	2-7.5
1	1.5–2
2	1–1.5
3	0.5–1
4	0.5

Neutropenia increases the likelihood of patients facing potentially life-threatening complications such as febrile neutropenia (FN), antibiotic administration, hospitalization, and heightened mortality rates (Blayney and Schwartzberg, 2022).

Chemotherapy increases the susceptibility of cancer patients to infections by inhibiting neutrophil production and exerting cytotoxic effects on the cells lining the gastrointestinal tract (Crawford et al., 2004).

The risk of neutropenia is largely influenced by the specific chemotherapy regimen utilized, with certain regimens exhibiting greater myelotoxic effects than others (Crawford et al., 2004).

- Treatment

- *G-CSF agents:*

G-CSF–based agents work by mobilizing mature neutrophils into the bloodstream and speeding up the maturation of neutrophil precursors in the bone marrow. Clinically, this leads to an increased neutrophil count within the first 4 days after starting G-CSF, postponing the neutrophil nadir to day 7 or 8 after chemotherapy, reducing the severity of the nadir, and achieving neutrophil recovery by day 14. Consequently, G-CSF agents lower the risk of febrile neutropenia and documented infections, as well as decrease the need for antibiotics and hospitalizations (Blayney and Schwartzberg, 2022).

- *Trilaciclib:*

Trilaciclib is a small-molecule inhibitor belonging to the class of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. In preclinical studies, trilaciclib induced a temporary and reversible G1 cell cycle arrest in both murine and human hematopoietic stem and progenitor cells (HSPCs), protecting murine HSPCs from chemotherapy-induced exhaustion (Blayney and Schwartzberg, 2022).

-Plinabulin

Plinabulin is a small molecule, distinct from G-CSF, that binds to a specific site on β-tubulin and inhibits microtubule polymerization.

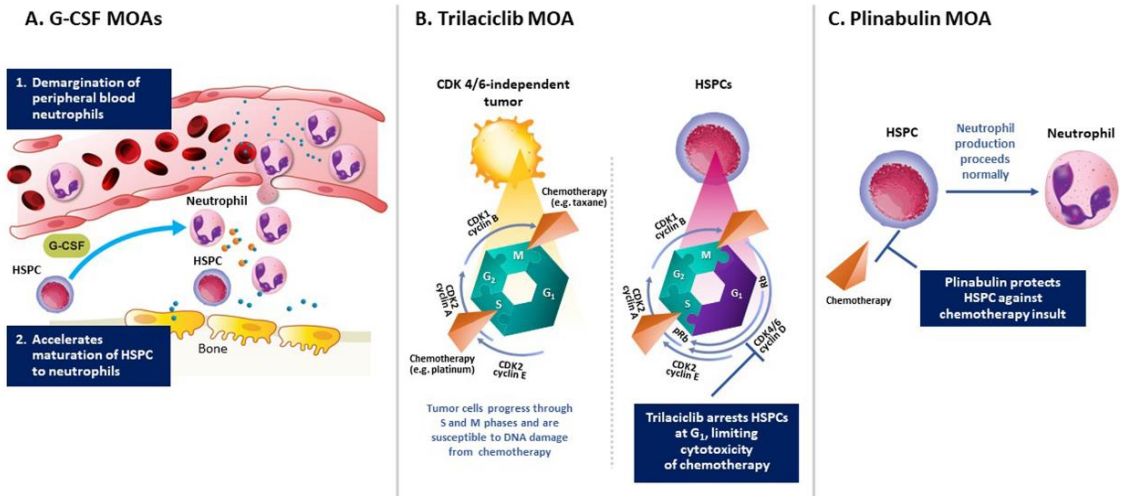

Figure 5: Agents preventing neutropenia and febrile neutropenia (Blayney and Schwartzberg, 2022) Abbreviations: CIN, chemotherapy induced neutropenia; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; HSPC, hematopoietic stem and progenitor cell; MOA, mechanism of action; G, gap; M, mitosis; S, synthesis.

Chapter 03
Oxidative stress

III. Oxidative stress

III.1 Definition

Oxidative stress (OS) is a biochemical condition that arises when intracellular antioxidants fail to counteract pro-oxidants, such as reactive oxygen species (ROS) (Jiang et al., 2023).

It refers to the cellular environmental conditions stemming from an imbalance between the generation of ROS and the response of the antioxidant defense systems (Zhang et al., 2018).

III.2 Reactive oxygen species (ROS)

Reactive oxygen species (ROS) are metabolites generated during normal cellular processes, playing crucial roles in promoting health, longevity, and antimicrobial phagocytosis by cells of the innate immune system. However, they can also trigger the activation of cell death processes, including apoptosis, providing a mechanism for cancer treatment (Zhang et al., 2018).

Table 5: Examples of ROS (Liou and Storz, 2010).

Reactive oxygen species(ROS)	
free oxygen radicals	**non-radical ROS**
superoxide (O_2•–)	hydrogen peroxide (H 2O2)
hydroxyl radical (•OH)	singlet oxygen ($^1O_2$)
nitric oxide (NO•)	ozone/trioxygen (O_3)
peroxyl radicals (ROO•)	organic hydroperoxides (ROOH)

III.3 Damage ways of oxidative stress

The primary mechanisms through which oxidative stress (OS) induces cell injury are lipid peroxidation of membranes, oxidative modification of proteins, and DNA damage (Zhang et al., 2018).

III.3.1 Lipid peroxidation

Process known as chain reaction of lipid peroxidation impacts cell membranes and other lipid-containing structures. This reaction produces hydroperoxides (LOOHs) as critical intermediate products, which can disrupt membrane integrity and pose a threat to cells. Additionally, the direct secondary products of lipid peroxidation include aldehydes, such as malondialdehyde (MDA) and 4-hydroxynonenal/4-hydroxy-2-nonenal (HNE) (Zhang et al., 2018).

These products are considered to be the markers of OS, and their unique property of a no-charge structure allows them to easily permeate through membranes and into the cytosol, thus causing far-reaching and damaging effects inside and outside the cells, rendering them superior to ROS. These products, regarded as markers of oxidative stress (OS), possess a distinctive property of a no-charge structure, enabling them to readily permeate through membranes and enter the cytosol. As a result, they exert extensive and detrimental effects both inside and outside cells, surpassing the impact of reactive oxygen species (ROS) (Zhang et al., 2018).

III.3.2 Oxidative Modification of Proteins

Proteins can be oxidized in two ways: directly by reactive oxygen species (ROS) or indirectly by 2^{ndry} by-products of OS. Secondary modifications involve oxidized carbohydrates and lipids interacting with proteins, unsaturated fatty acids within lipid molecules are likely oxidized, producing abundant lipid peroxidation products MDA and HNE. Studies have shown that these products can cause protein cross-linking and inactivation (Chakravarti and Chakravarti, 2007).

Proteins can be damaged by free radicals, as well as through glycation, also known as the Maillard reaction or nonenzymatic glycosylation (Chakravarti and Chakravarti, 2007).

III.3.3 DNA damage

ROS can damage DNA in several ways. This damage includes changes to the building blocks of DNA (bases and sugars), cyclization of sugar-base, the creation of bonds between DNA and proteins, and cross-links between DNA and proteins. All of this damage can ultimately lead to breaks in the DNA strands (Gonzalez-Hunt et al., 2018).

III.4 Chemotherapy and oxidative stress

Oxidative stress is indeed one of the most significant biological events in cancer progression, commonly observed in cancer cells and emerging as a hallmark of various cancers. Among the various methods used in cancer therapy, the use of chemotherapeutic agents is notable for generating reactive oxygen species (ROS) or other free radicals in patients undergoing treatment. Studies have demonstrated that many of these chemotherapeutic drugs can kill cancer cells by directly or indirectly promoting the accumulation of ROS. Examples include doxorubicin, cisplatin, 5-fluorouracil, and arsenic trioxide (ATO) (Jiang et al., 2023).

Pro-oxidant therapy can be achieved either through direct ROS production or indirectly by targeting and inhibiting cancer cells' endogenous antioxidant systems (Jiang et al., 2023).

Cancer treatment strategies focusing on oxidative stress (OS) and oxidative damage have demonstrated effectiveness. Chemotherapy drugs that interfere with cell division, such as Vinca alkaloids and taxanes, or those targeting nucleic acid synthesis, such as 5-fluorouracil, platinum complexes, and anthracyclines, can induce the production of reactive oxygen species (ROS) by disrupting mitochondrial functions. This ROS production contributes to their cytotoxic effects against cancer cells (Jiang et al., 2023).

Among these chemotherapy agents, anthracyclines belong to a class of anticancer antibiotics and are extensively utilized in both single-agent and combination chemotherapy regimens. They are valued for their potent ability to generate reactive oxygen species (ROS) and exert anticancer effects (Jiang et al., 2023).

- Anthracyclines (e.g., doxorubicin): there is ample evidence indicating that anthracyclines induce excessive reactive oxygen species (ROS) production through various mechanisms. Among the widely accepted theories are DNA intercalation and topoisomerase II poisoning. These processes contribute to the generation of ROS and ultimately to the cytotoxic effects of anthracyclines against cancer cells. Indeed, another accepted mechanism of anthracycline-induced cytotoxicity involves the formation of an anthracycline-iron complex. This complex promotes lipid peroxidation, protein oxidation, and DNA damage by enhancing reactive oxygen species (ROS) production, ultimately leading to apoptosis. This mechanism underscores the multifaceted nature of anthracycline-induced cytotoxicity against cancer cells (Jiang et al., 2023).
- Taxanes: (such as paclitaxel) are commonly used in the treatment of ovarian, breast, and prostate cancer. However, they are associated with side effects such as peripheral neuropathy. Taxanes exert their anticancer effects by disrupting microtubule dynamics, leading to mitotic arrest and cell death. Additionally, they generate reactive oxygen species (ROS) by impairing the axonal transport of mitochondria and affecting the morphology and function of mitochondria in nerve cells, contributing to peripheral neuropathy(Jiang et al., 2023).
- 5-Fluorouracil (5-FU): is utilized in the treatment of various cancers, including colorectal, breast, gastric, pancreatic, prostate, and bladder cancers. However, it can cause

cognitive disability and cardiotoxicity. 5-FU exerts its anticancer effects by inhibiting the enzyme thymidylate synthase, blocking DNA formation, and dysregulating mitochondrial phosphate metabolism. These mechanisms contribute to the generation of reactive oxygen species (ROS), which can further contribute to its cytotoxic effects and side effects (Jiang et al., 2023).

Material and Methods

IV. Material and methods

This study investigated the immediate hematotoxic effects of chemotherapy in cancer patients. We compared complete blood count (CBC) parameters before and immediately after drug administration. Additionally, we assessed oxidative stress markers, malondialdehyde (MDA) level, and methemoglobin generation.

IV.1 The study places

This work is carried out at the oncology service and in the medical analysis laboratory of the public health hospital (EPH) Mohamed Boudiaf–Bouira.

IV.2 Ethical considerations

The oncologist selected donor patients based on their health status and willingness to participate. Consent was formally documented with signed agreements from both the donors and the doctor.

IV.3 Population of the study

In this study, the samples collected from patients differ in sex, age, type of cancer, and treatment received (annex 1).

All patients received a premedication consisting of:

- Dexamethasone 20mg
- Zophren 8mg
- Ranitidine 50mg

IV.4 Materials

IV.4.1 Biological material

The blood is collected from cancer patients at EPH Bouira in EDTA tubes.

IV.4.2 Chemical products and equipment

Chemical products:

- Trichloracetic acid (TCA: 30%)
- Thiobarbituric acid (TBA: 1g /1l)
- Ethylene-diamine tetra acetic acid (EDTA)
- Sodium hydroxide (NaOH: 0.05 M)

- Sodium chloride (NaCl 0.9%)

Equipment used during experiment:

Table 6: Equipment

Equipment	Firm
Balance	Pioneer, Ohaus
Centrifuge	MPW-352R, MED. Instruments
Spectrophotometer UV- visible	Optima, SP-3000 nano
Water bath	Memmert
Vortex	VELP SCIENTIFICA
Hematology analyzer	Swelab Alfa

IV.5 Methods

IV.5.1 Test of hematotoxicity

Following informed consent, blood samples were collected from cancer patients before and immediately after chemotherapy using EDTA tubes to prevent clotting. Complete blood count (CBC) analysis was performed using a Swelab Alfa Basic hematology analyzer to assess various blood cell parameters.

These tubes were then centrifuged at 3000 rpm for 3 minutes to separate the serum and the pellet, which were subsequently transferred to eppendorf tubes (figure 6).

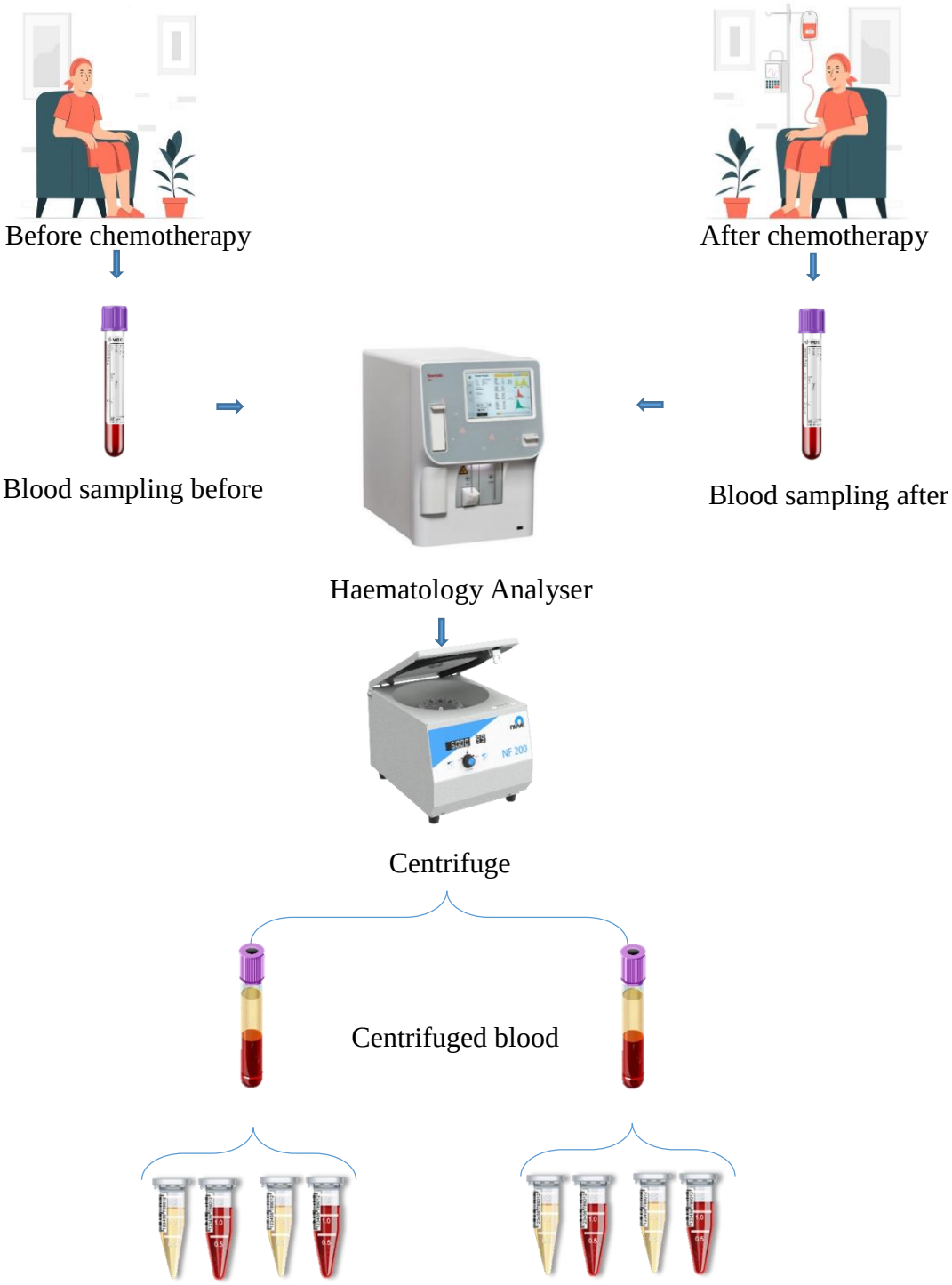

Figure 6: Hematotoxicity test scheme

IV.5.2 Oxidative stress assay

Following blood cell separation by centrifugation, both plasma and pellet fractions were used for MDA and methemoglobin analysis. Plasma and pellet samples were diluted with NaCl solution for further analysis.

- Measurement of malondialdehyde (MDA)

MDA was assessed through spectrophotometric measurement, serving as an indicator of lipid peroxidation.

A volume (µL) of sample was added to a volume (µL) of trichloroacetic acid (TCA). The mixture was incubated at 0°C for 2 hours. After incubation, the mixture was centrifuged at 3000 rpm for 10 minutes at 4°C. The supernatant was mixed with thiobarbituric acid (TBA) and EDTA. This mixture was incubated at 95°C for 15 minutes followed by cooling at 0°C for 5 minutes. The absorbance of the final solution was measured at 535 nm (figure 7) (Mameri et al., 2021).

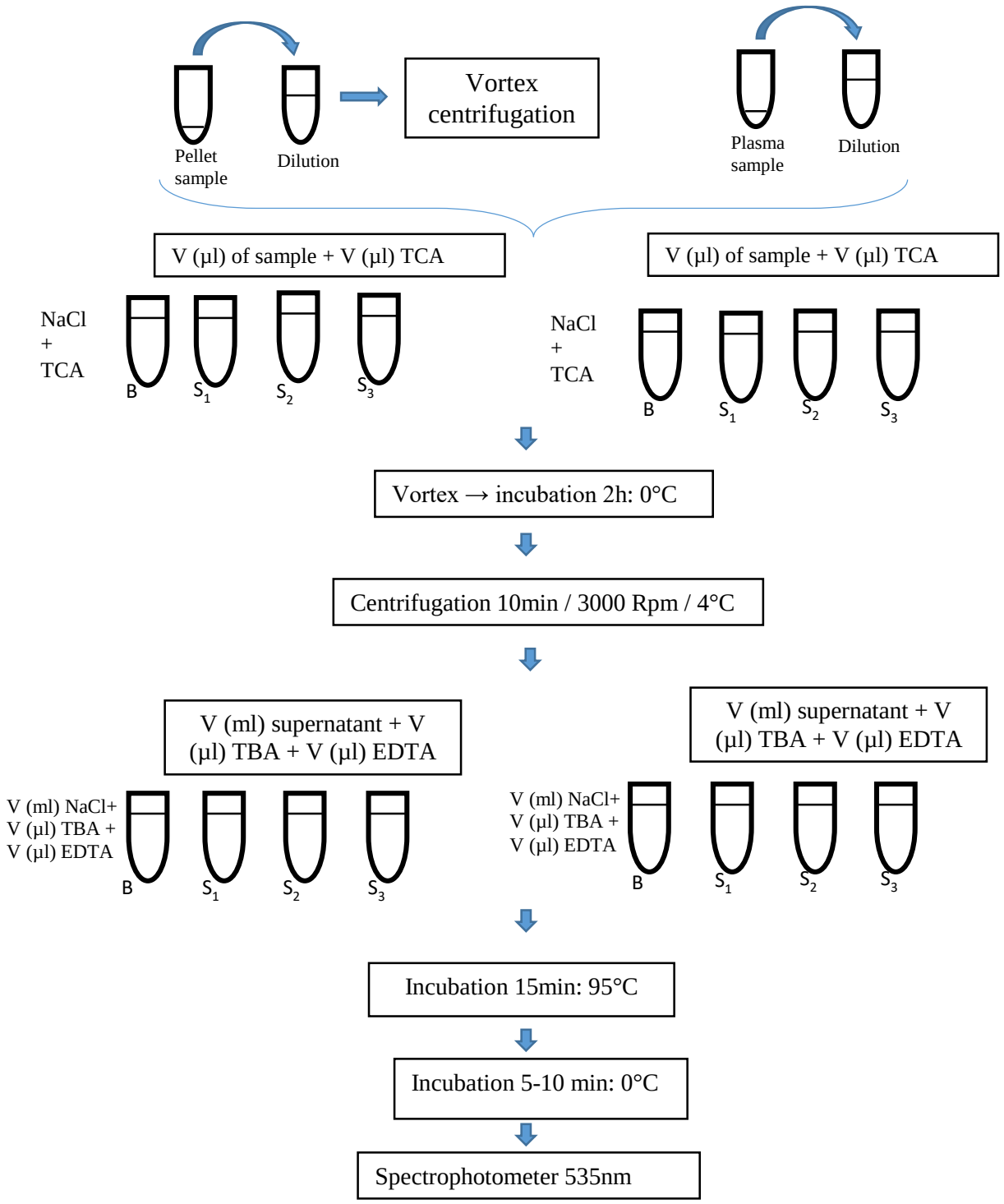

Figure 7: TBARS Protocol (Mameri et al., 2021).

- Methemoglobin measurement

Similarly to the MDA assay, plasma and pellet fractions were diluted (plasma with NaCl, pellet with distilled water) for methemoglobin analysis. The absorbance of both diluted samples was then measured spectrophotometrically at two wavelengths:

412 nm: for the absorbance of intact hemoglobin.

540 nm: for the absorbance of methemoglobin.

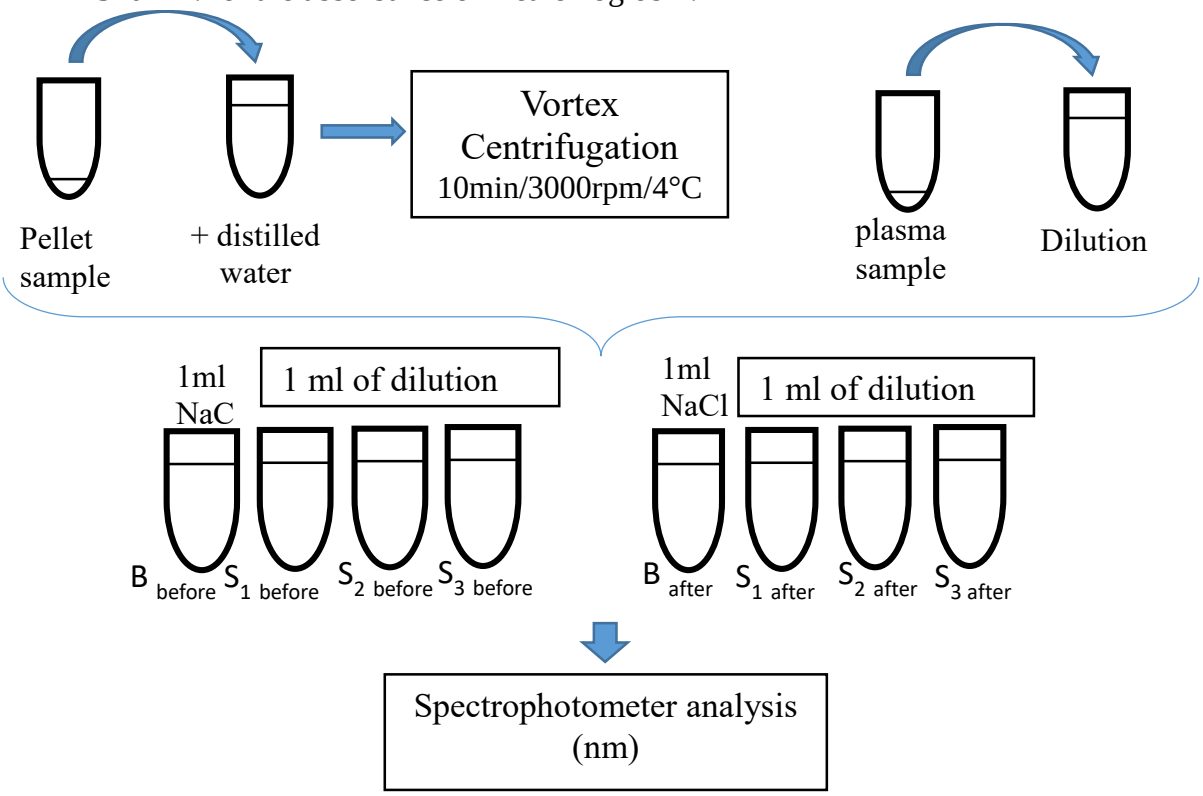

Figure 8: Methemoglobin protocol

IV.6 Statistical analysis

All experiments were performed in triplicate, and the data are presented as means ± standard deviation (SD). Statistical analysis was conducted using STATVIEW software (SAS Institute Inc., Version 5).

Results and Discussion

V. Results and discussion

V.1 Results

This section presents the overall results obtained, including:

- Study of chemotherapy-induced hematotoxicity by comparing the CBC parameters of patients before and after treatment.
- Determination of the molecular mechanism involved in this alteration by evaluating oxidative stress by measuring malondialdehyde (MDA) and methemoglobin (MetHb) levels.

The results illustrated in figure 09 shows the changes in white blood cell counts before and after chemotherapy. Our research revealed that both carboplatin and the combination of paclitaxel-carboplatin-bevacizumab led to a decrease in WBC count (6.2 x 10^9/L and 2.1 x 10^9/L, respectively) after treatment compared to before (8.3 x 10^9/L and 2.7 x 10^9/L, respectively). In contrast, treatment with oxaliplatin, combinations of carboplatin-paclitaxel, and adriamycin-cyclophosphamide resulted in an increase in WBC levels. Eribulin treatment registered an important increase (27.1 x 10^9/L) comparing to before treatment (19.7 x 10^9/L). While, paclitaxel exhibited low impact on white blood cell count.

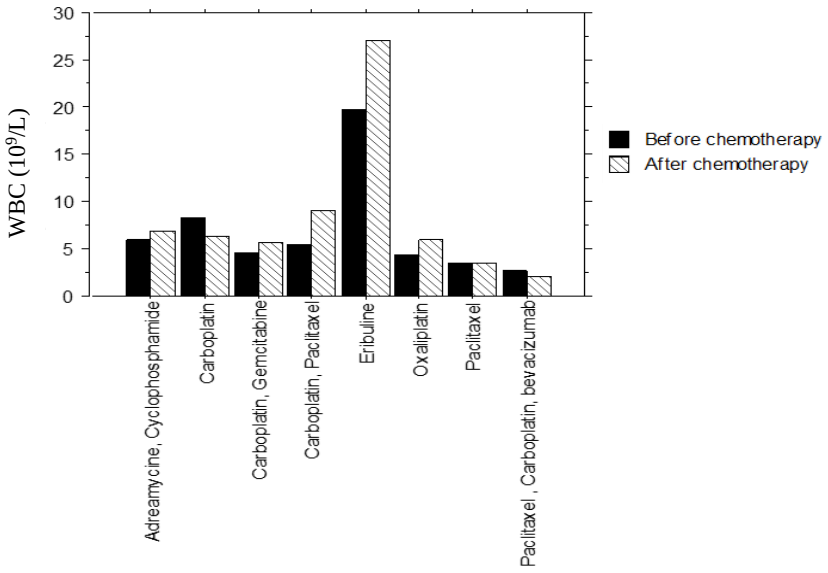

Figure 9: White blood cell number before and after chemotherapy.

The results shown in figure 10 indicate the lymphocyte numbers before and after chemotherapy. A significant decrease was observed after treatment with carboplatin (0.9 x 10^9/L), paclitaxel (0.8 x 10^9/L), a combination of these drugs (0.9 x 10^9/L), or a treatment

with paclitaxel-carboplatin-bevacizumab (0.5 x 10^9/L), and eribulin (1.7 x 10^9/L) compared to LYM levels before using these drugs (1.9 x 10^9/L), (1.1 x 10^9/L), (1.3 x 10^9/L), (1.4 x 10^9/L), and (2.5 x 10^9/L) respectively. Treatment with carboplatin-gemcitabine and oxaliplatin showed a slight decrease in the number of lymphocyte. A slight increase of these cells was observed with the combination of adriamycin-cyclophosphamide (0.9 x 10^9/L) compared to the value obtained before treatment (0.8 x 10^9/L).

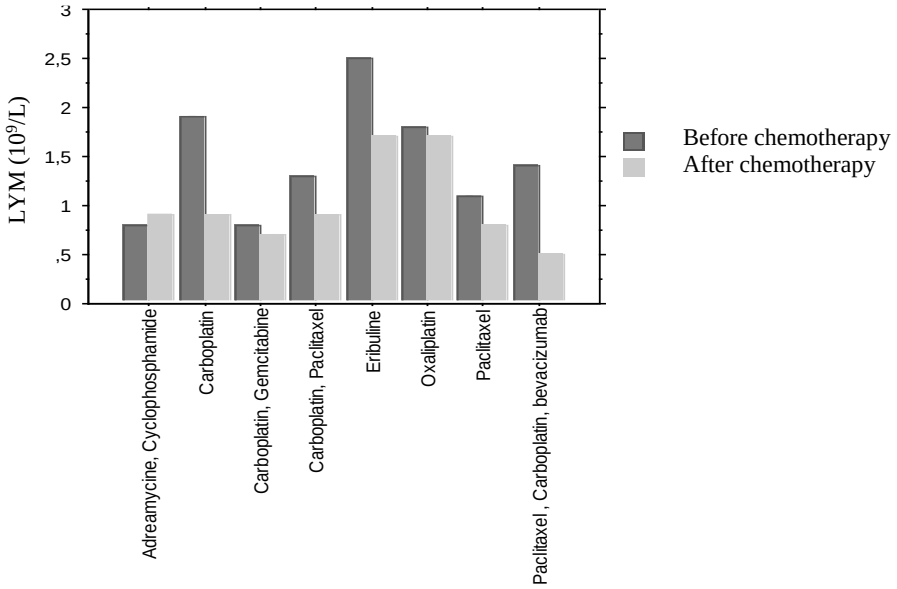

Figure 6: Lymphocyte number before and after chemotherapy.

Hemoglobin levels obtained before and after chemotherapy were illustrated in figure 11. The results indicate a significant decrease in hemoglobin levels after all treatments such as: oxaliplatin (11.2 g/dl), paclitaxel (8.5 g/dl), and a combination of carboplatin-paclitaxel (11.6 g/dl) when compared with hemoglobin values obtained before administration of these drugs: (13.9 g/dl), (10.5 g/dl), and (13 g/dl) respectively.

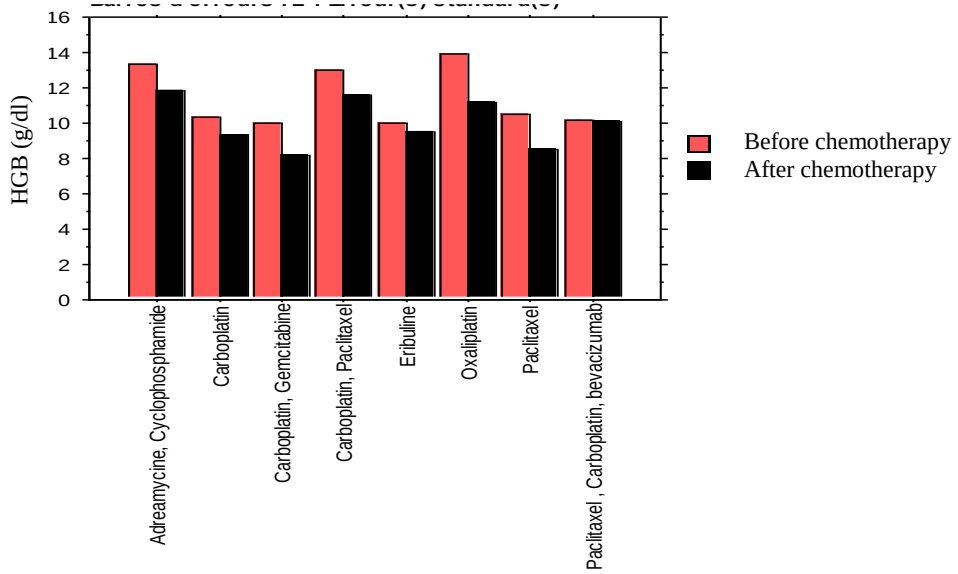

Figure 7: Hemoglobin level before and after chemotherapy.

Red blood cell numbers before and after chemotherapy are represented in figure 12. The results showed that all administered treatments, such as, oxaliplatin, paclitaxel, a combination of adriamycin-cyclophosphamide, and paclitaxel-carboplatin, have a direct impact on red blood cells and reducing immediately the cells numbers after treatments (2.81×10^{12}/L), (2.89×10^{12}/L), (3.72×10^{12}/L), (4.14×10^{12}/L) respectively, compared to before treatment (3.36×10^{12}/L), (3.32×10^{12}/L), (4.3×10^{12}/L), and (4.47×10^{12}/L) respectively.

Similarly, a small increase was observed after treatment with eribulin (3.52×10^{12}/L) and carboplatin-paclitaxel-bevacizumab (3.48×10^{12}/L) compared to before treatment ($3.48\times10^{12/}$L) and (3.39×10^{12}/L) respectively.

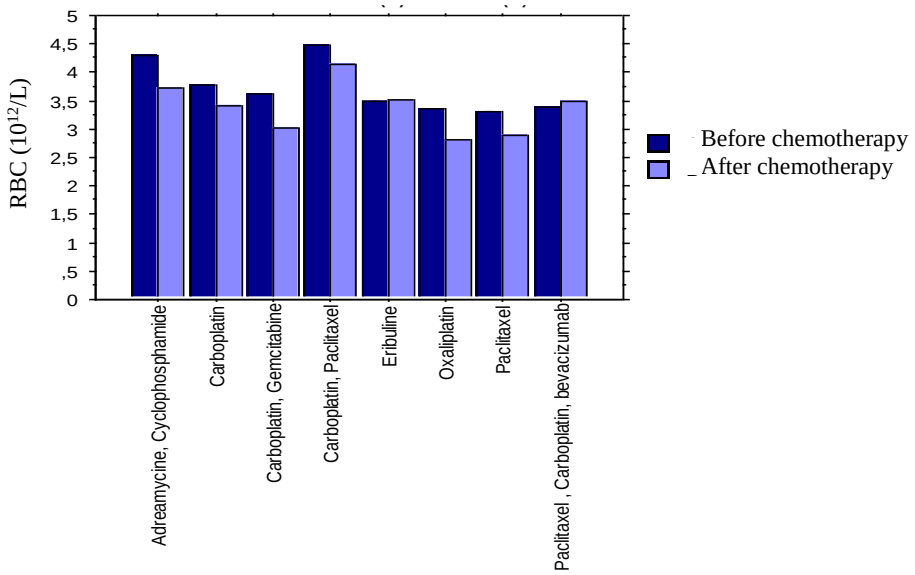

Figure 8: Red blood cell number before and after chemotherapy.

The results presented in figure 13 indicate the platelet number before and after chemotherapy. We observed a decrease in platelets after treatment with a combination of carboplatin-gemcitabine (333×10^9/L), eribulin (957×10^9/L), and carboplatin (153×10^9/L) compared to before treatment (366×10^9/L), (1016×10^9/L), and (169×10^9/L) respectively. There is a minor effect after the combination of carboplatin-paclitaxel-bevacizumab and adriamycin-cyclophosphamide.

In addition, an increase in RBCs was observed after treatment with oxaliplatin (211×10^9/L), paclitaxel (188×10^9/L), and also after the combination of paclitaxel-carboplatin (371×10^9/L) compared with before treatment (154×10^9/L), (171×10^9/L), and (329×10^9/L).

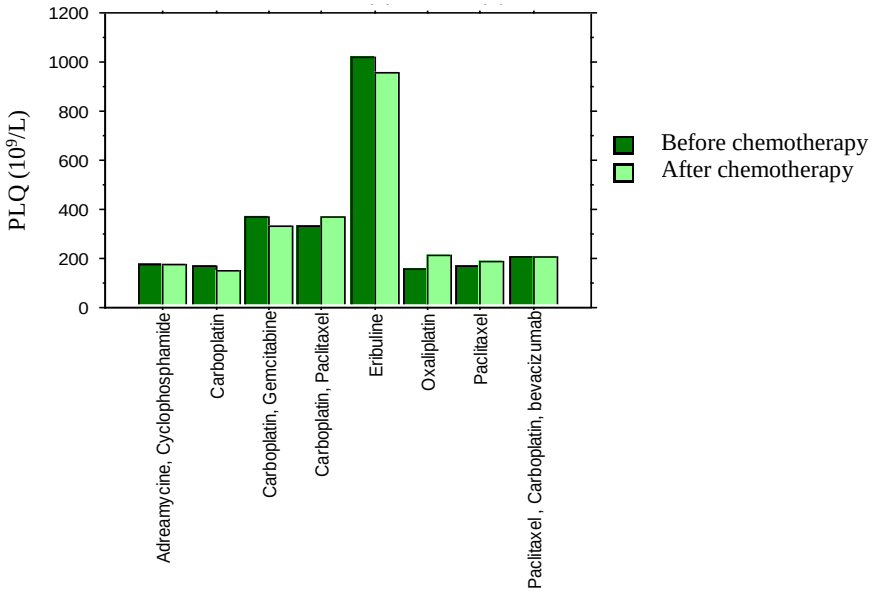

Figure 9: Platelets number before and after chemotherapy.

The graph in figure 14 illustrates the levels of MDA in serum before and after chemotherapy. The results show a significant increase in MDA levels in the serum after treatment with a combination of paclitaxel-carboplatin-bevacizumab (1.7±0.000), adreamycin-cyclophosphamide (1.7±0.000), and carboplatin (1.583±0.218). Additionally, a slight increase was noted after treatment with eribuline (1.585±0.093) and paclitaxel (1.164±0.151) compared to before treatments (1.164±0.101), (0.911±0.049), (1.434±0.000), (1.478±0.121), and (1.119±0.000) respectively. However, a minor decrease in MDA levels was observed after treatment with oxaliplatin.

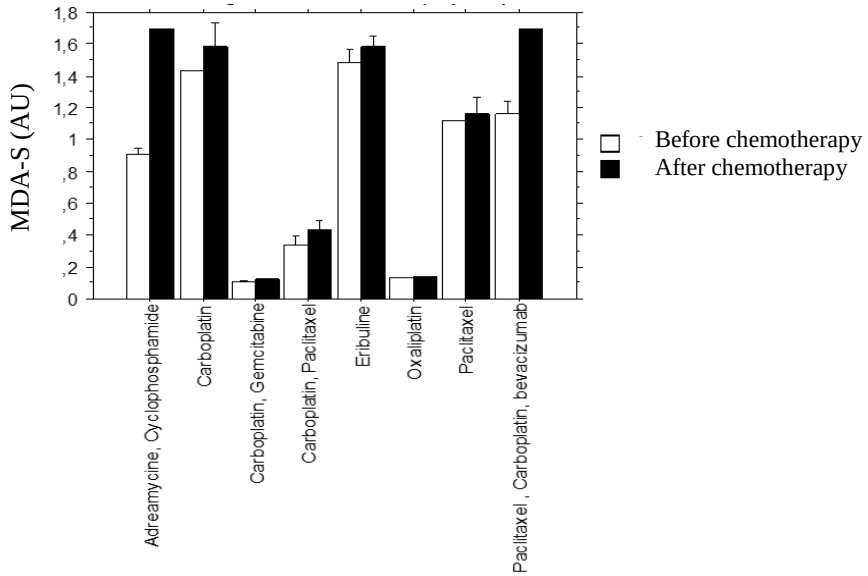

Figure 14: Serum MDA levels before and after chemotherapy.

The results illustrated in figure 15 represents MDA levels in pellet before and after chemotherapy, an important increase in MDA levels was registered after treatment with carboplatin (0.570±0.204) comparing with before (0.449±0.065). While a modest increase is observed after treatment with a combination of carboplatin-paclitaxel, eribuline, oxaliplatin and paclitaxel.

A decrease in MDA level after using a regimen combining Adreamycin-cyclophosphamide, carboplatin-gemcitabine and a significant decrease in a combination of paclitaxel-carboplatin-bevacizumab (0.176±0.020) comparing before (0.243±0.036).

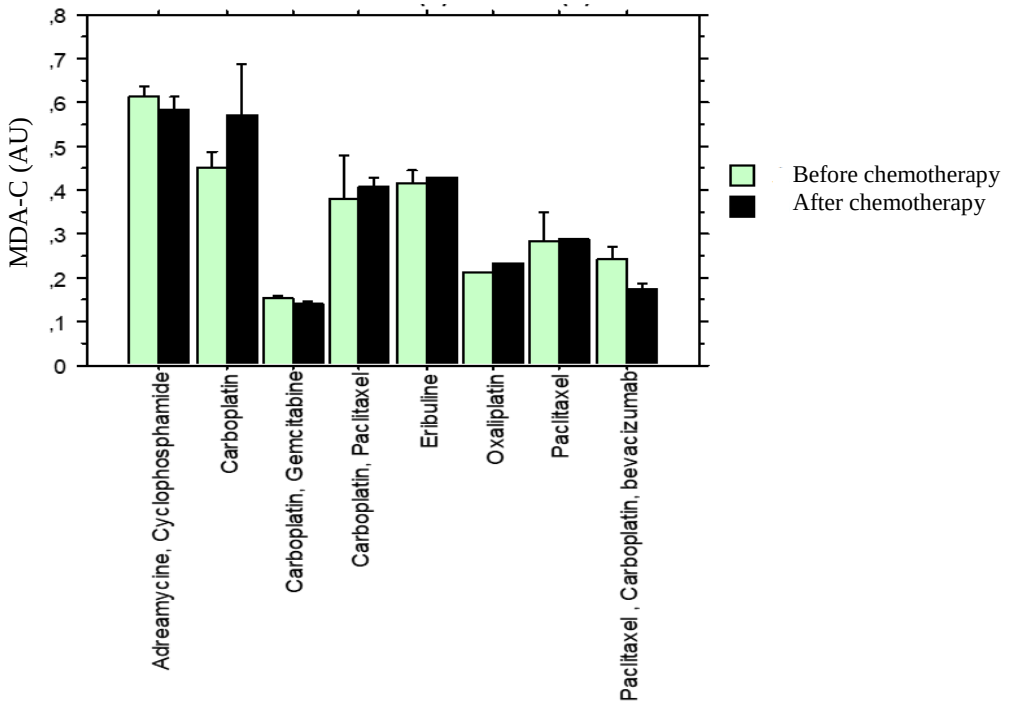

Figure 15: Pellet MDA levels before and after chemotherapy.

Figure 16 represents hemoglobin levels in serum before and after chemotherapy. We observed a decrease in the HGB level in serum after treatment combining carboplatin-paclitaxel (0.649±0.083) compared with before (0.988±0.000), while an increase was marked with all other treatments used.

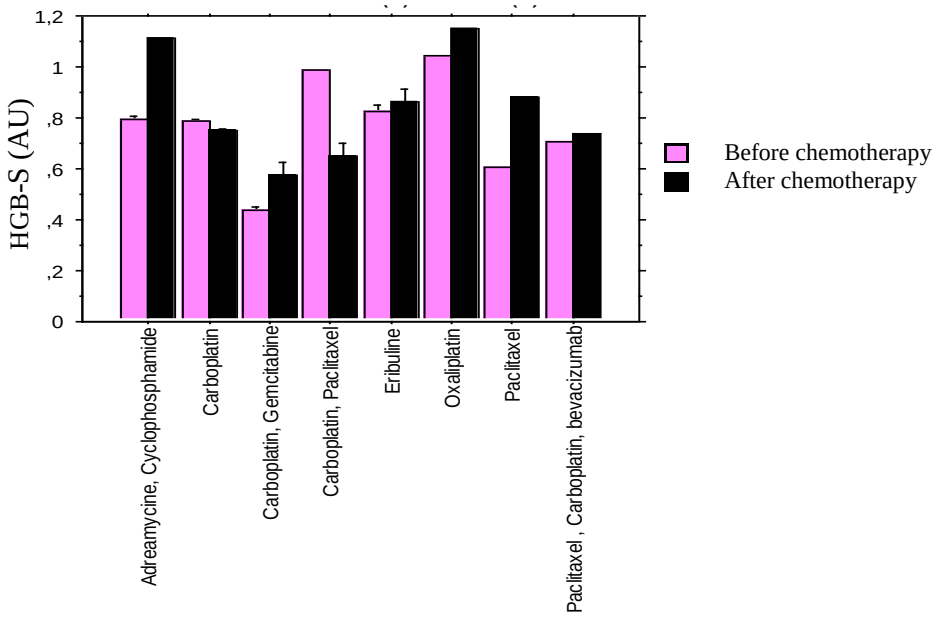

Figure 16: HGB levels before and after chemotherapy in serum.

Figure 17 illustrates MetHb levels in serum before and after chemotherapy. High levels of MetHb in serum are marked after a regimen combining adreamycin-cyclophosphamide (0.397±0.002), carboplatin-gemcitabine (0.285±0.022), and the administration of paclitaxel (0.399±0.003), oxaliplatin (0.315±0.000), and eribulin (0.377±0.040) compared with before (0.212±0.023), (0.207±0.026), (0.278±0.002), (0.265±0.000), and (0.359±0.052), respectively.

An insignificant increase was observed in carboplatin-paclitaxel treatment (0.221±0.024) and paclitaxel-carboplatin-bevacizumab (0.306 ±0.019). A slight decrease is marked after the use of carboplatin (0.317±0.004) when compared with MetHb levels before these drugs: (0.465±0.000), (0.524±0.066), and (0.335±0.003), respectively.

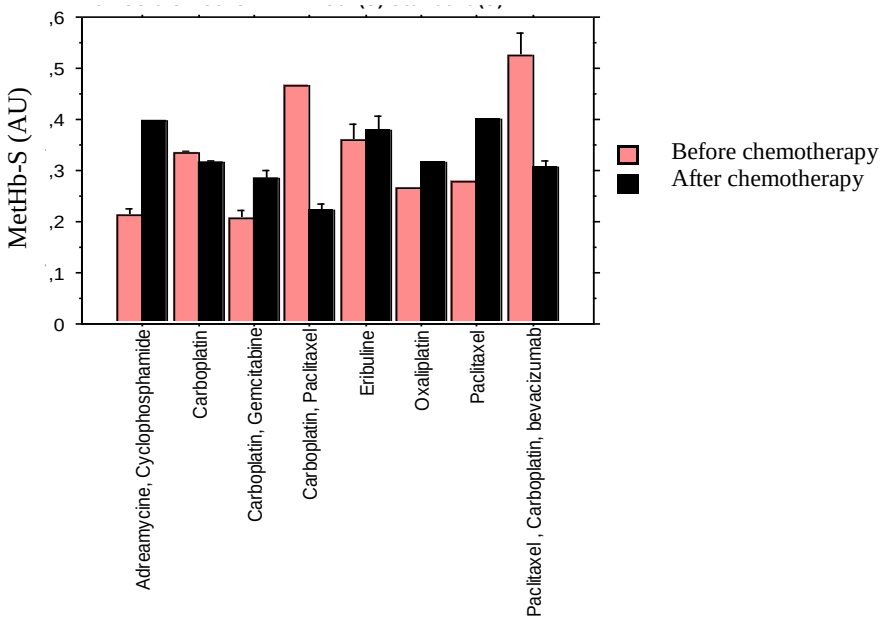

Figure 17: MetHb levels before and after chemotherapy in serum.

Figure 18 presents pellet HGB levels before and after chemotherapy. A significant increase was observed after treatment with paclitaxel (1.709±0.063), carboplatin (1.314±0.132), and their combination (2.328±0.244) compared with before (1.221±0.009), (0.518±0.008) and (0.515±0.053). However, a little decrease is noted following the adriamycin-cyclophosphamide combination (1.360±0.040), with substantial decreases after eribulin (1.601±0.037) when compared with HGB levels before administration of these drugs (2.591±0.025) and (2.158±0.049) respectively.

A decrease in pellet HGB level was also observed after treatment with oxaliplatin (2.1±0.000) and the combination of carboplatin-gemcitabine (1.602±0.027) and paclitaxel-carboplatin-bevacizumab (1.248±0.046) comparing with before levels (2.4±0.000), (1.844±0.071), and (1.634±0.123) respectively.

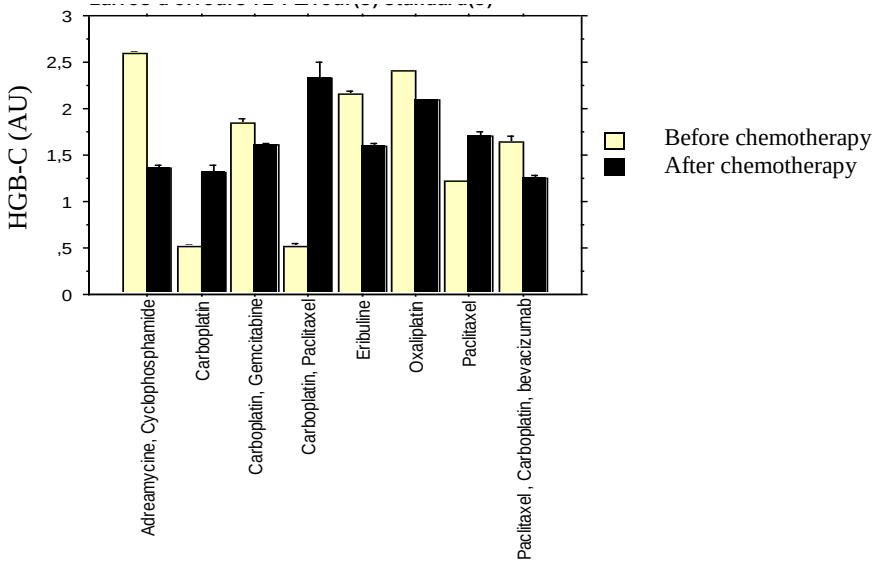

Figure 18: Pellet HGB levels before and after chemotherapy.

The findings presented in figure 19 illustrate pellet MetHb levels before and after chemotherapy. A significant drop in MetHb levels was observed immediately after treatment with the adriamycin-cyclophosphamide combination (0.18±0.001) compared with before (0.320±0.024), with notable decreases following treatments with eribulin (0.232±0.09) and for oxaliplatin (0.296±0.000), and the combinations of carboplatin-gemcitabine (0.190±0.000), and paclitaxel-carboplatin-bevacizumab (0.183±0.010) when compared with MetHb levels before (0.276±0.06), (0.316±0.000), (0.201±0.014), and (0.204±0.009) respectively. In contrast, paclitaxel and carboplatin exhibited a significant increase in MetHb levels, enhanced in the combination of both drugs (0.300±0.029) compared before (0.137±0.006).

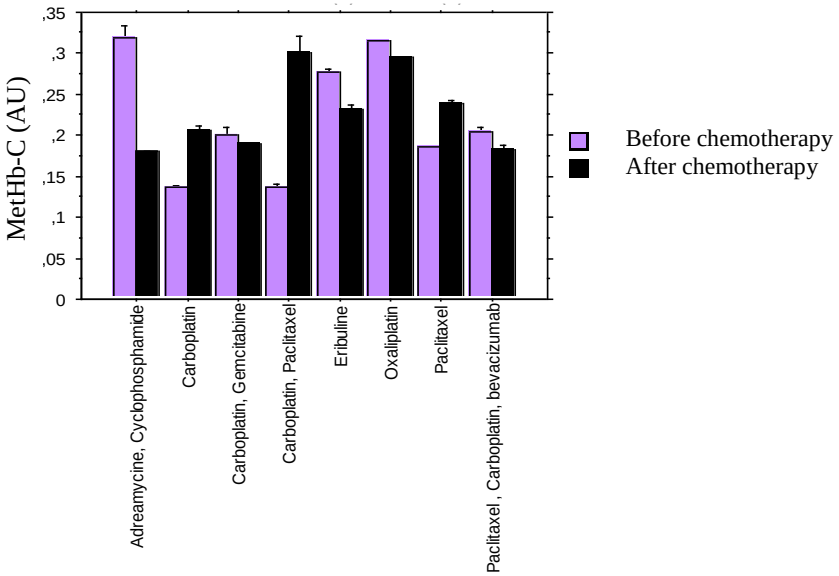

Figure 19: Pellet MetHb levels before and after chemotherapy.

V.2 Discussion

The antineoplastic agents can be crucial treatment for managing cancer, some research suggests a link between their use and the development of hematological disorders. This potential side effect arises because of many anticancer drugs work by inducing a state of high oxidative stress (OS) in the body. This OS triggers apoptosis (programmed cell death) in cancer cells. Unfortunately, current cancer therapies often lack perfect precision and can damage healthy cells along with cancerous ones (Shukla and Singh, 2015).

The primary role of blood is to maintain body fluid balance. It comprised of four main components: plasma, red blood cells, white blood cells, and platelets. Modifications in blood physiology in the development and progression of diseases. These changes can be caused by different xenobiotics such as anticancer drugs.

Despite extensive research on the effects of chemotherapy on the bone marrow (medullar effects), the immediate impact on blood cells upon contact with anticancer drugs remains under-investigated.

Our clinical study aims to explore this gap by highlighting the direct effect of chemotherapy on different blood components immediately after treatment. The assessment of the impact of chemotherapy on a patient's complete blood count (CBC) was evaluated by comparing values before and after treatment administration. Furthermore, we investigated whether oxidative stress plays a role in this chemotherapy-induced blood cell toxicity (hematotoxicity).

The results revealed that treatment decreased significantly the haematological profile in total patients immediately after receiving different chemotherapy drugs. In fact, lymphocyte decreased significantly after treatment with carboplatin, paclitaxel, eribuline, oxaliplatin, and also with a combination of paclitaxel-carboplatin-bevacizumab and carboplatin-gemcitabine. However, Lees et al. (2020) observed a decrease in WBCs in mice following oxaliplatin administration. It has been reported that an important decrease in lymphocytes within 72 hours of starting treatment that suggests a direct destruction of mature lymphocytes via apoptosis (Stahnke et al., 2001).

Indeed, carboplatin and gemcitabine, eribulin alone, and carboplatin alone induced thrombocytopenia. A decrease in platelet count is frequently observed in patients with solid cancers, which may be attributed to bone marrow suppression (Van Es et al., 2014). Interestingly, the clinical trials have demonstrated that 30% of patients receiving carboplatin

presented a decrease in platelet count (thrombocytopenia) (Boehm and Wallace, 1995). This finding suggests a direct impact of the anticancer drug used in our study on platelets.

The increases in platelet counts observed after treatment with oxaliplatin, paclitaxel, and even after the combination of paclitaxel and carboplatin, could be explained by the presence of platelet aggregates. Similarly, studies conducted on colorectal liver metastase patients proposed the hypothesis that oxaliplatin-based chemotherapy affects platelets in the liver. The results show that the administration of neoadjuvant chemotherapy to these patients leads to platelet aggregation in the liver's zone III (Tajima et al., 2015).

Patients treated with Paclitaxel alone or in combination with other types of therapy such as carboplatin, exhibited a significant decrease in red blood cells (RBCs) and Hb levels. This reduction can be explained by cell damage or an effect on the cell membrane (Panis et al., 2012).

Regarding carboplatin, which belongs to the same family as oxaliplatin and cisplatin, has a similar effect on RBCs by reducing their number in the bloodstream. These agents are known for their toxicity on RBCs, especially when combined with gemcitabine, as indicated in our results (Marani et al., 1996; Ohno et al., 1993).

Additionally, the oxaliplatin-based protocol showed a significant reduction on RBCs, which indicate that this treatment exhibited a direct effect on RBCs leading to the diminution in Hb levels.

Oxaliplatin has been shown to induce eryptosis in human RBCs, resulting in cell shrinkage and membrane scrambling. This is partly caused by OS (Fazio et al., 2015). In vitro studies conducted in mice have also demonstrated its direct interaction with hemoglobin (Lees et al., 2020). Also, according to Mameri et al. (2021), chemotherapy drugs cause OS in RBCs, resulting in altered cell membranes. Our findings on pellet MDA levels are consistent with this, as observed with oxaliplatin and paclitaxel.

Our results show that there is a decrease in hemoglobin (Hb) levels in the pellet and an increase in Hb levels in the serum. This suggests that hemoglobin may be released from the pellet to the serum, which could be linked to an increase in methemoglobin levels. This increase may also coincide with the observed rise in MDA levels. These findings indicate that OS may be affecting both the cell membrane and the intracellular compartments. The oxidation of Hb to methemoglobin (MetHb) triggers iron release, initiating ROS generation

and lipid peroxidation, which are the key mechanisms of OS. Additionally, other studies have indicated that cyclophosphamide administration leads to MetHb production (Shehadeh et al., 2003).

Conclusion

Conclusion

Chemotherapy is a cancer treatment that uses antineoplastic agents to target tumor cells and inhibit their growth through mechanisms that induce cell death. However, these treatments can also affect healthy normal cells that are naturally developing, leading to side effects and inducing toxicities in the body, mainly hematotoxicity, which includes neutropenia, anemia, and thrombocytopenia.

In our study, we performed complete blood counts (CBC) before and immediately after chemotherapy cycles in cancer patients. Our findings demonstrate that immediately after administering these anticancer drugs, there is direct contact between the drugs and the blood cells. This direct interaction affects the blood cells, resulting in significant cellular damage.

We also assessed lipid peroxidation products, specifically MDA and methemoglobin levels. Our results revealed that antineoplastic agents induce oxidative stress through lipid peroxidation and methemoglobin generation. This negatively impacts blood cells and their membranes, leading to membrane rupture.

More research is necessary in the future to further define and understand this chemotherapy-induced hematotoxicity and its relation with oxidative stress, particularly focusing on studying methemoglobin and its generation. Additionally, considering performing blood smears on cancer patients' blood may provide better insight into cell morphology.

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Annex

Annex 01 : Data of patients

ptient	age	sexe	weight	cancer type	Protocol	chemotherapy	dose	duration	date	cycle (21d)
1	49	F	48	lung	Protocol 01	Cisplatine	70 mg	1h	12/11/2023	C1
						Carboplatine	400mg	1h	03/12/2023	C2-C5
						Gemcitabine	1700mg	30min		
2	49	F	53	stomach	Protocol 01	Cisplatine	60mg	1h	11/07/2023	C1-C5
				colon	Protocol 02	oxaliplatine	85-120mg	2h	30/10/2023	C6
3	53	F	53	breast	Protocol 01	Paclitaxel	130-100mg	1h	24/09/2023	C1-C3
					Protocol 02	Carboplatine	455-420mg	1h	28/12/2023	C1-C3
4	44	F	60	brest oligometastic	Protocol 01	Epirubicine	160 mg	10min	16/11/2023	C1
						adréamycine	90-98mg	10min	07/12/2023	C2-C3
						cyclophosphamide	985mg	1h	25/01/2024	C4
					Protocol 02	Carboplatine	440mg	1h	15/02/2024	C1
						Paclitaxel	130mg	1h		
5	83	M	72	Leiomyosarcoma of the scrotum	Protocol 01	Gemcitabine	2200mg	1h40	04/06/2023	C1-C3 (d1-d8-d14)
					Protocol 02	dacarbazine	1830mg	1h	17/09/2023	C1-C3 (d1-d8-d14)
					Protocol 03	Paclitaxel	150mg	1h	10/12/2023	C1-C3 (d1-d8-d14)
6	53	F	47	brest cancer	Protocol 01	5FU	775mg	1h	23/06/2022	C1
						Epirubicine	155mg	10min	14/07/2022	C2
						cyclophosphamide	775mg	1h	04/08/2022	C3
					Protocol 02	Docetaxel	155mg	1h	25/08/2022	C1-C3
						Carboplatine	525-334mg	1h	15/09/2022 23/11/2022	C2-C3
					Protocol 03	Paclitaxel	270-200mg	3h	06/10/2022	C1-C2
						Carboplatine	525mg	1h	02/11/2022	
					Protocol 04	Gemcitabine	1550mg	1h	04/10/2023 26/10/2023	C1 C2
						bevacizumab	760mg	1h30	23/11/2023	C1
						capécitabine	3800mg	cp	14/12/2023	C2
					protocol 05	Eribuline	1,8mg	3-5min	17/01/2024 19/02/2024	C1 C2
7	48	F	68	Ovarian Cancer	protocol 01	Paclitaxel	290mg	3h	10/01/2024	C1-C3
						Carboplatine	630-600mg	1h	01/02/2024	
						bevacizumab	510-450mg	1h30-1h-30min	22/02/2024	
8	49	F	74	breast cancer	protocol 01	adréamycine	100mg	10min	26/12/2023	C1-C4
						cyclophosphamide	1000mg	1h	18/01/2024 08/02/2024 07/03/2024	

Abstract

Chemotherapy is a common treatment for cancer that destroys cancer cells. However, these treatments can cause severe side effects, including nausea, vomiting, diarrhea, fatigue, hair loss, and damage to organs like the liver and bone marrow. Bone marrow toxicity, also known as hematotoxicity, is a major concern with chemotherapy. Chemotherapy drugs can damage the blood cells in the bone marrow, leading to reduced production of blood cells and resulting thrombocytopenia, neutropenia, and anemia. This study aims to investigate the impact of chemotherapy on blood components and explore the role of oxidative stress (OS) as a molecular mechanism involved in this cytotoxicity. Blood samples showed a significant decrease in white blood cells (WBC) after carboplatin treatment (6.1 $x10^9$/L) comparing before treatment (8.3 $x10^9$/L). Platelets decreased with the carboplatin-gemcitabine combination from (366×10^9/L) to (333×10^9/L), and eribuline from (1016×10^9/L) to (957×10^9/L). Lymphocytes decreased significantly with carboplatin treatment ($0.9x10^9$/L) compared to before treatment ($1.9x10^9$/L), and with paclitaxel-carboplatin-bevacizumab combination from ($1.4x10^9$/L) to ($0.5x10^9$/L), eribuline from ($2.5x10^9$/L) to ($1.7x10^9$/L). Red blood cell (RBC) count was reduced with most treatments, especially with carboplatin-gemcitabine from (3.62 $x10^{12}$/L) to ($3.02x10^{12}$/L), with a decrease in hemoglobin (HBG) levels. Similarly, an increase in MDA and methemoglobin levels was registered, indicating that these drugs could cause membrane damage by exacerbating OS through membrane lipid peroxidation and hemoglobin oxidation. Further studies are crucial to understanding chemotherapy-induced toxicities. This knowledge can be used to develop strategies to mitigate these side effects and improve patients' outcomes in oncology.

Keywords: Chemotherapy, hematotoxicity, oxidative stress, lipid peroxidation, methemoglobin, MDA.

Résumé

La chimiothérapie est un traitement courant du cancer qui détruit les cellules cancéreuses. Cependant, ces traitements peuvent entraîner des effets secondaires graves, notamment des nausées, des vomissements, de la diarrhée, de la fatigue, une perte de cheveux et des lésions d'organes comme le foie et la moelle osseuse. La toxicité de la moelle osseuse, également appelée hématotoxicité, est une préoccupation majeure de la chimiothérapie. Les médicaments de chimiothérapie peuvent endommager les cellules sanguines de la moelle osseuse, entraînant une diminution de la production de cellules sanguines et provoquant une thrombocytopénie, une neutropénie et une anémie. Cette étude vise à analyser l'impact de la chimiothérapie sur les composants sanguins et à explorer le rôle du stress oxydatif (OS) en tant que mécanisme moléculaire impliqué dans cette cytotoxicité. Les analyses sanguines ont montré une diminution significative des globules blancs (GB) après le traitement au carboplatine (6,1 x 10^9/L) par rapport à avant le traitement (8,3 x 10^9/L). Les plaquettes ont diminué avec l'association carboplatine-gemcitabine de (366 × 10^9/L) à (333 × 10^9/L) et avec l'éribuline de (1016 × 10^9/L) à (957 × 10^9/L). Les lymphocytes ont diminué significativement avec le carboplatine (0,9 x 10^9/L) par rapport à avant le traitement (1,9 x 10^9/L), et avec l'association paclitaxel-carboplatine-bévacizumab de (1,4 x 10^9/L) à (0,5 x 10^9/L), et avec l'éribuline de (2,5 x 10^9/L) à (1,7 x 10^9/L). Le nombre de globules rouges (GR) a été réduit avec la plupart des traitements, en particulier avec la combinaison carboplatine-gemcitabine de (3,62 x 10^{12}/L) à (3,02 x 10^{12}/L), s'accompagnant d'une diminution des taux d'hémoglobine (Hb). De même, une augmentation des niveaux de MDA et de méthémoglobine a été enregistrée, indiquant que ces médicaments pourraient endommager les membranes en aggravant le stress oxydatif par la peroxydation lipidique membranaire et l'oxydation de l'hémoglobine. Des études complémentaires sont cruciales pour comprendre les toxicités induites par la chimiothérapie. Ces connaissances peuvent être utilisées pour développer des stratégies visant à atténuer ces effets secondaires et à améliorer les résultats des patients en oncologie.

Mots-clés : Chimiothérapie, hématotoxicité, stress oxydatif, peroxydation lipidique, méthémoglobine, MDA.

ملخص

العلاج الكيميائي هو علاج شائع للسرطان يعمل على تدمير الخلايا السرطانية. ومع ذلك، يمكن أن تسبب هذه العلاجات آثارًا جانبية شديدة، بما في ذلك الغثيان، القيء، الإسهال، الإرهاق، تساقط الشعر وتلف الأعضاء مثل الكبد ونخاع العظام. يُعدّ تأثر نخاع العظام، المعروف أيضًا بالسمية الدموية (hematotoxicity)، مصدر قلق كبير عند استخدام العلاج الكيميائي. يمكن أن تؤدي أدوية العلاج الكيميائي إلى إتلاف الخلايا المكونة للدم في نخاع العظام، مما يؤدي إلى انخفاض في إنتاج خلايا الدم، ويؤدي إلى حالات مثل قلة الصفاح (Thrombocytopenia)، قلة العدلات (Neutropenia)وفقر الدم (Anemia).تهدف هذه الدراسة إلى التحقيق في تأثير العلاج الكيميائي على مكونات الدم واستكشاف دور الإجهاد التأكسدي (Oxidative stress)كآلية جزيئية تشارك في هذه السمية الخلوية. أظهرت عينات الدم انخفاضًا ملحوظًا في خلايا الدم البيضاء بعد استخدام كاربوبلاتين (6.1×10^9/ لتر) مقارنة بالفترة التي تسبق العلاج (8.3×10^9/ لتر). انخفضت الصفائح الدموية مع استخدام مزيج كاربوبلاتين-جيمسيتابين من (366×10^9/ لتر) إلى (333×10^9/ لتر)، وانخفضت أيضًا مع استخدام إريبولين من (1016×10^9/ لتر) إلى (957×10^9/ لتر). انخفضت الليمفاويات بشكل ملحوظ مع استخدام كاربوبلاتين (0.9×10^9/ لتر) مقارنة بالفترة التي تسبق العلاج (1.9×10^9/ لتر)، ومع استخدام باكليتاكسيل-كاربوبلاتين-بفاسيزوماب من (1.4×10^9/ لتر) إلى (0.5×10^9/ لتر)، وكذلك مع استخدام إريبولين من (2.5×10^9/ لتر) إلى (1.7×10^9/ لتر). كما انخفضت خلايا الدم الحمراء مع استخدام معظم العلاجات، خاصةً مع استخدام مزيج كاربوبلاتين-جيمسيتابين من (3.62×10^{12}/ لتر) إلى (3.02×10^{12}/ لتر)، وذلك إلى جانب انخفاض في مستويات الهيموجلوبين يصاحبه ارتفاع في مستويات MDAوالهيموغلوبين المؤكسد (methemoglobin) تشير هذه النتائج إلى أن هذه الأدوية يمكن أن تسبب تلفًا في أغشية خلايا الدم عن طريق تفاقم الإجهاد التأكسدي من خلال بيروكسدة الدهون الغشائية وأكسدة الهيموجلوبين. هناك حاجة ماسة إلى إجراء المزيد من الدراسات لفهم سمية العلاج الكيميائي بشكل كامل. يمكن استخدام هذه المعرفة لتطوير استراتيجيات لتخفيف هذه الآثار الجانبية وتحسين نتائج علاج المرضى في طب الأورام.

الكلمات المفتاحية :العلاج الكيميائي، السمية الدموية، الإجهاد التأكسدي، بيروكسدة الدهون، الهيموغلوبين المصفر، مذنب البيروكسيد.