A Review on the use of Carfilzomib and Bortezomib in the Treatment of Multiple Myeloma

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
Brac University
September 2024

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "A review on the use of carfilzomib & bortezomib in the treatment of multiple myeloma" submitted by Jannatul Ferdous (20146059) of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) in September 2024.

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Ethics Statement

This study does not involve any animal or human trial.

Abstract

Many people worldwide suffer from multiple myeloma, a blood cancer that is fatal and difficult to treat. Therapy has advanced significantly, but recurrence and treatment resistance remain significant issues. Two important medicines in the proteasome inhibitor class that have revolutionized the treatment of multiple myeloma are carfilzomib and bortezomib. Bortezomib, the first proteasome inhibitor approved by the FDA, has shown considerable promise in extending life and triggering remission. However, newer medications have been developed as a result its reversible inhibition and adverse effects, like peripheral neuropathy. It has been demonstrated that carfilzomib, a second-generation proteasome inhibitor, is more beneficial in instances that have not responded to prior treatments or have relapsed. Carfilzomib permanently stops the enzyme which can cause multiple myeloma. It is a superior option for certain patients because it has also been demonstrated to have a lower risk of side effects like neuropathy. This review compares the efficacy, safety, and long-term performance of carfilzomib versus bortezomib based on data from clinical trials. Making better decisions concerning the treatment of multiple myeloma and planning for future treatments can be aided by the information provided.

Keywords: Multiple myeloma, carfilzomib, bortezomib, clinical trial, monoclonal gammopathy of unknown significance (MGUS), progression free survival, overall survival.

Dedication

Dedicated to my respected supervisor Namara Mariam Chowdhury Ma'am, whose guidance and support made this journey possible.

Acknowledgement

First of all, I want to give thanks and appreciation to God for granting me good health as well as patience, dedication and knowledge I needed to finish the thesis.

To my project supervisor, Namara Mariam Chowdhury, Program Coordinator and Senior Lecturer, School of Pharmacy, Brac University, I would like to convey my profound gratitude for all of her help and support throughout my research. Working under her direction was a great honor and privilege.

I would like to thank my parents for their constant motivation and support. I would also like to thank everyone who has helped me whenever I required it.

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List of Acronyms

WHO	World Health Organization
DNA	Deoxyribonucleic acid
MM	Multiple myeloma
MGUS	Monoclonal Gammopathy of Undetermined Significance
SMM	Smoldering Multiple Myeloma
IgD	Immunoglobulin D
IgE	Immunoglobulin E
MRI	Magnetic resonance imaging
FDA	Food and Drug Administration
PIs	Proteasome Inhibitors
HDACis	Histone deacetylase inhibitors
IκB	Inhibitory kappa B
NFκB	Nuclear factor kappa B
CAR-T	Chimeric antigen receptor-modified T
ASCT	Autologous stem cell transplant
RRMM	Relapsed or refractory multiple myeloma
PFS	Progression-free survival
OS	Overall survival

VAL-4	Very late antigen-4
IGF-1	Insulin-like growth factor-1
ER	Endoplasmic reticulum
UPP	The ubiquitin proteasome pathway
IV	Intravenous
RNA	Ribonucleic acid
mRNA	Messenger ribonucleic acid

Chapter 1

Introduction

1.1 Introduction to Multiple Myeloma

Multiple myeloma (MM), referred to as plasma cell myeloma, and myeloma means malignancy affecting plasma cells, a subset of leukocytes responsible for antibody production. Frequently, no acute symptoms are observed at beginning. As the condition advances, osteoporosis, anemia, renal failure, and infections may develop. Possible complications such as elevated blood calcium levels and amyloidosis. The condition can result in bone marrow failure leading to anemia, immunological paresis triggered by infection, bone discomfort and fractures, elevated calcium levels, and renal failure. Recent years, we have seen a significant expansion of therapeutic alternatives for the treatment of MM, resulting in an extended length of survival. Despite these advancements, multiple myeloma (MM) remains an untreatable cancer for most people; the majority of patients will succumb to their illness as it develops resistance to therapy. (Bird & Boyd, 2019).

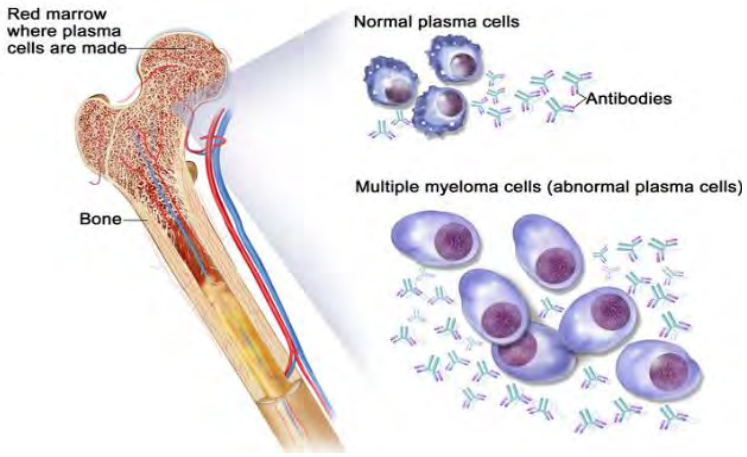

Figure 1 Multiple myeloma (National Cancer Institute, 2023)

Multiple myeloma (MM) is a neoplastic disease of B-cells that specifically affects a particular type of cells called long-lived plasma cells. Terminally differentiated, non-dividing cells that

persist in the bone marrow for months to years and generate immunoglobulin specific to antigens are essential components of the immune defense system (Bianchi & Munshi, 2015). Carcinogenic plasma cell clones produce an excessive amount of a particular immunoglobulin (consisting of two heavy chains and two light chains) as well as an excess of extra light chains. These proteins are detectable in the bloodstream and have utility in both the diagnosis and surveillance of multiple myeloma (MM).

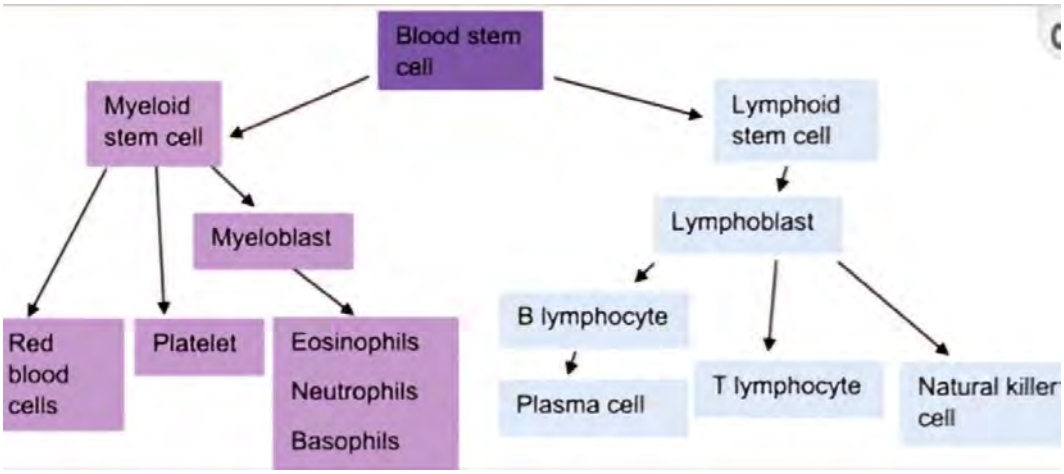

Figure 2 Hematopoietic stem cell differentiation pathways (Bird & Boyd, 2019).

1.2 Etiologies of Multiple

The precise cause of multiple myeloma remains unidentified. Nevertheless, various mutations and relocations in the promoter genes, particularly chromosome 14, are frequently observed in multiple myeloma and are believed to contribute to the development of the disease (Chesi et al., 1998). Furthermore, the genes NRAS, KRAS, and BRAF may also be involved in the proliferation of plasma cells (Pasca et al., 2019). Additional factors that contribute to the development of diseases include obesity, alcohol usage, environmental components such as pesticides, organic solvents, agent orange, and radiation exposure (Dhodapkar, 2016) (Bumma et al., 2020).

1.3 Signs, Symptoms and Prodromes

In many cases, multiple myeloma does not exhibit early signs. This can complicate the medical diagnosis during the early phases. Potential manifestations of multiple myeloma may include:

Fractures: Myeloma cells initiate the irreversible damage to the adjacent bone. The portion of bone having reduced strength is more prone to fracture. This condition is referred to as a pathological fracture. Musculoskeletal pain: particularly in the central and/or inferior region of the back, rib cage, or hips. The pain experienced can vary in intensity from mild to severe, contingent upon the magnitude of the multiple myeloma, the rate of its development, and the presence of fracture or nerve compression. Anemia caused by myeloma can result in fatigue and/or shortness of breath, characterized by a sensation of shortness of breath during physical activity or increased exhaustion. Confusion: Multiple myeloma can result in elevated blood calcium levels and/or renal failure. Confusion may arise because of this. Furthermore, confusion can be associated with hyper viscosity, which refers to excessively thick blood. Neuropathy or paralysis: Multiple myeloma is occasionally linked to nerve compressions, resulting in numbness in the extremities. Moreover, hyper viscosity might result in facial, arm,

or limb weakness or numbness. Leg edema: Multiple myeloma induces renal impairment, so impeding their optimal functioning. This indicates that your body is unable to eliminate excess salts and fluids, resulting in the formation of edema. Changes in appetite: Elevated calcium levels in the bloodstream and/or renal failure can also lead to a reduction in appetite, subsequent weight loss, and feelings of nausea. Frequent infection: Myeloma cells, by displacing normal white blood cells responsible for fighting infection, increase the likelihood of infection. Myeloma infections commonly manifest as pneumonia, bladder or kidney infections, sinusitis, and skin infections. Heightened thirst caused by elevated blood calcium levels and renal impairment (Multiple Myeloma, 2015).

1.4 Classification of Multiple Myeloma

There exist two primary sub-types of multiple myeloma:

The hyperdiploid (HMM) condition. Myeloma cells possess an abnormal genetic number of chromosomes. This subtype constitutes around 45% of all instances of multiple myeloma and typically exhibits slightly less aggressive behavior. Non-hyperdiploid or hypodiploid. Myeloma cells exhibit a reduced number of chromosomes compared to the usual count. Approximately 40% of those with the condition are affected by this more aggressive kind.

There are different kinds of multiple myeloma. There are also various precancerous disorders that can occasionally result in the development of multiple myeloma. Such as:

a) Light chain myeloma: Affecting 20% of myeloma patients, light chain myeloma leads to the production of an incomplete immunoglobulin known as light chain antibodies, which can build up in the kidneys and cause renal impairment.

b) Non secretory myeloma: Non-secretory myeloma is a medical diagnosis in which patients with multiple myeloma do not generate sufficient amounts of M proteins or light chains to be detected by a bone marrow biopsy.

c)Solitary Plasmacytoma: When plasma cells undergo malignant transformation and proliferate uncontrollably, they have the potential to give rise to a neoplasm known as plasmacytoma, often affecting a bone or other bodily tissues. These tumors are collectively referred to as solitary plasmacytomas. Multiple myeloma refers to the presence of many myelomas spread in distinct areas.

d)Extramedullary Plasmacytoma: The origin of these tumors is outside the bone marrow, namely in the soft tissues of the body. Commonly, they occur in the pharynx, sinuses, nasal passages, and larynx (or vocal folds). An estimated 30% of individuals diagnosed with extramedullary plasmacytomas will develop multiple myeloma. Interventions include radiation therapy, surgical procedures, or a combination of both.

e) Monoclonal Gammopathy of Undetermined Significance (MGUS): A disorder called MGUS can cause aberrant antibodies and M proteins, which can thereafter result in active myeloma. Active myeloma affects one in five patients with MGUS, but therapy is typically not required unless adverse symptoms arise. M protein levels are tracked through routine laboratory testing.

f) Smoldering Multiple Myeloma (SMM): A precancerous form of myeloma which is known as smoldering multiple myeloma and is more prone to develop in persons with elevated levels of M proteins or plasma cells. Approximately 50% of these patients are diagnosed after 5 years.

g) Immunoglobulin D (IgD) Myeloma: This relatively uncommon variant impacts a little 1% to 2% of the entire myeloma population. Males below the age of 60 are particularly susceptible to acquisition. The diagnostic criteria and manifestations are identical to those of other forms.

h) Immunoglobulin E(IgE) Multiple myeloma of the IgE subtype is the least common form present. Multiple myeloma of this kind has identical signs and symptoms as other forms of the

disease. The disease is often aggressive and rapidly advances to plasma cell leukemia or proliferates beyond the bone marrow (Types of Multiple Myeloma, 2023).

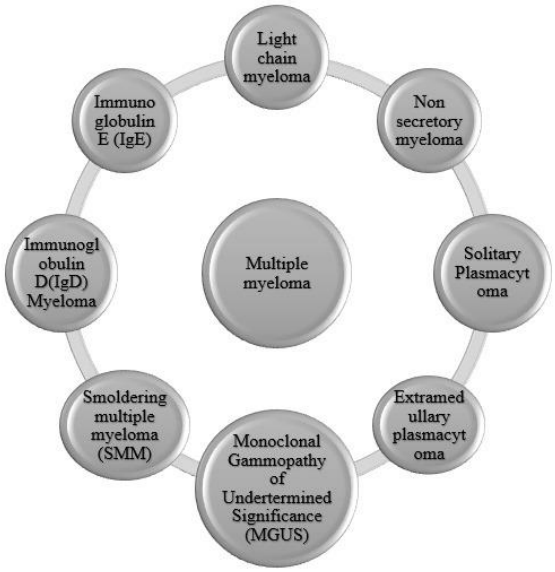

Figure 3 Types of Myeloma

1.5 Pathophysiology

Basically, multiple myeloma is a step within the monoclonal gammopathy spectrum. monoclonal gammopathy of unknown significance (MGUS) is a pre-malignant, asymptomatic phase of clonal plasma cell development that is assume to be cause of it .Finding monoclonal immunoglobin in the blood or urine without any indication of end- organ damage is known as MGUS. This is rather prevalent and has been seen in more than 3% of adults over 50. The cell of origin seems to be a post-germinal center plasma cell. This is usually a benign condition, although as mentioned above, there is a 1% annual risk of it progressing to multiple myeloma (Röllig et al., 2015) (Kyle et al., 2018). The precise factors contributing to the development and advancement of MGUS to MM are still to be determined. Nevertheless, as previously mentioned, genetic modifications can lead to an upregulation of promoter genes or resistance to apoptosis, both of which lead to elevated plasma cell proliferation and population. Under the

"second hit" hypothesis, the advancement of the disease may also result from the acquisition of further cytogenetic defects by the initial plasma cell clone, which can be attributed to either genetic instability or abnormalities in the hematopoietic microenvironment (Weinhold et al., 2016).

1.6 Existing Treatments

The remarkable advancements in survival observed in the last few decades can be attributed primarily to improved treatments, such as new medications, autologous stem cell transplantation, and improved supportive care. Although there is no known cure for multiple myeloma, there are numerous effective treatment options available, with new ones being developed every day. Supportive care therapies, associated with myeloma treatment, are interventions that aid in the control of myeloma symptoms and the adverse effects of treatment.

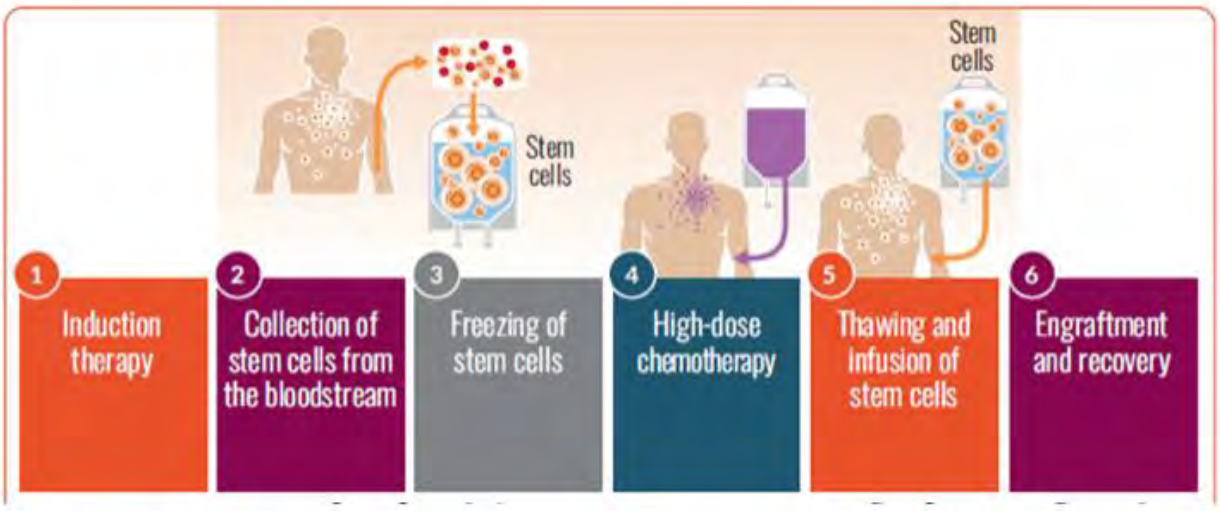

Figure 4 Multiple myeloma treatments (MMRF, 2024)

The active drugs of multiple myeloma are given below:

- ➔ Corticosteroids: Steroids continue to be a primary pharmacological intervention in multiple myeloma (MM), with dexamethasone or prednisolone initially as integral components of most therapy protocols. Glucocorticoids, when used

alone, exert their effects on myeloma cells by stimulating a wide spectrum of processes that reduce inflammation and suppress the immune system (Burwick & Sharma, 2018).

- ➔ Standard Chemotherapy: Both alkylating agents (e.g., cyclophosphamide, melphalan, and bendamustine) and anthracyclines (e.g., doxorubicin and idarubicin) are chemotherapy drugs that, although by distinct mechanisms, target deoxyribonucleic acid (DNA) for the treatment of various hematological and solid organ malignancies. Because malignant cells multiply more rapidly and have fewer DNA error-correcting capacities, DNA damage tends to impact malignant cells more than healthy ones. Administration of high-dose melphalan continues to be the established method for initiating stem cell transplantation (Hoskin, 2020).
- ➔ Proteasome inhibitors: According to US Food and Drug Administration (FDA), bortezomib approved as the first-in-class proteasome inhibitor (PI) in 2003. Subsequently, carfilzomib and ixazomib have been developed as newer treatments. Protein complexes known as proteasomes are intracellular organelles that break down proteins that are no longer necessary for the cell. Proteasome inhibitors (PIs) augment apoptosis by interfering with the proteasomal breakdown of proteins implicated in various essential cellular pathways. A fundamental process in multiple myeloma (MM) is the suppression of the degradation of inhibitory kappa B (IκB), resulting in the stabilization of the nuclear factor kappa B (NFκB) complex. The inhibition of NFκB translocation to the nucleus results in the deactivation of several downstream pathways that are recognized as crucial in the signaling of myeloma cells (Field-Smith et al., 2006).

- ➔ Immunomodulatory Drugs: Thalidomide was taken off the market in 1961 because of a documented link to congenital birth problems, although it was first prescribed as a sedative anti-emetic in Europe for hyperemesis gravidarum. Later research revealed that it possessed anti-angiogenic qualities as well as widespread immunomodulatory and anti-inflammatory effects. (Palumbo et al., 2008). After its initial discovery in the late 1990s, analogues including pomalidomide and lenalidomide were created and put into clinical usage for the treatment of multiple myeloma (Singhal et al., 1999).
- ➔ Histone deacetylase inhibitors: Histone deacetylase inhibitors (HDACis), like panobinostat, include a novel category of pharmaceutical therapy for the treatment of multiple myeloma (MM). Epigenetic modifications means to alterations in the structure of DNA rather than the sequential arrangement of nucleotides, which are gaining recognition as significant factors in the DNA transcription of genes that prevent the growth of tumor and also the genes associated with cancer. Molecular chromatin, which is DNA encased around histones, serves as the repository for genetic information within cells. Histone deacetylase inhibitors induce histone hyperacetylation, resulting in modifications in chromatin structure and in turn gene expression (Deleu et al., 2009).
- ➔ Monoclonal Antibodies: Daratumumab is licensed for use in the relapsed setting and was the first monoclonal antibody approved by the FDA for the treatment of MM. This human monoclonal antibody targets CD38, a protein on the cell surface that is expressed frequently on malignant plasma cells. There are several ways in which daratumumab causes cell death: apoptosis, antibody-dependent cellular phagocytosis, complement-dependent cytotoxicity, and antibody-

dependent cell-mediated cytotoxicity (Sanchez et al., 2016) . In addition to its approval for the treatment of multiple myeloma (MM), elotuzumab specifically targets SLAMF7, a cell surface protein that is abundantly expressed on normal plasma cells, malignant plasma cells, and natural killer (NK) cells (Lonial et al., 2015).

1.7 Aims and Objectives

Analysis of the clinical trial data for the multiple myeloma drugs carfilzomib and bortezomib is the objective of this study. The examination of clinical trial data pertaining to carfilzomib and bortezomib would provide noteworthy findings, which may thereafter be juxtaposed with the existing conventional therapy for multiple myeloma. This comparison will be used to assess the superior effectiveness of the new medication and determine if the possible advantages of this medicinal product surpass the associated side effects. A further aspect to be addressed is which medication demonstrates fewer adverse effects. The primary objective is to offer a succinct and efficient overview of this medication's therapeutic possibilities in several forms of myeloma. This will be achieved by comparing diverse clinical trial data obtained from many sources. Subsequently, a decisive conclusion will be drawn on the potential of these drugs.

Chapter 2

Novel Drug for Multiple Myeloma

2.1 Reasons for developing new drugs:

The hematological cancer, also known as multiple myeloma (MM) is identified by the bone marrow's growth of cancerous plasma cells. Even with the advancement in medicine, such as monoclonal antibodies, immunomodulatory drugs, and proteasome inhibitors, many patients eventually experience some situation relapses and become resistant to their current treatments. The following factors lead to the need for new medications:

Many patients can develop resistance to carfilzomib and bortezomib. Both carfilzomib and bortezomib have some serious adverse effects like cardiotoxicity and nephrotoxicity. Searching for more specific targeted therapy which can give more accurate therapeutic effects. There is currently no known treatment for multiple myeloma. Nonetheless, people are living longer thanks to recent medical advancements, and research into possible treatments is still ongoing. Researchers never stop looking for novel therapeutic targets, tailored strategies, and new pharmacological targets. Let’s examine the necessity of new medications:

Plasma cell directed therapy: A typical course of treatment includes taking three or four medications that target the immune system directly. The goal of these treatments is to regulate aberrant plasma cells (National Cancer Institute (US), 2024).

Bone marrow transplant: A person's own stem cells are infused after high-dose chemotherapy to aid in the regeneration of healthy bone marrow. In children, multiple myeloma is an uncommon malignant plasma cell condition; only about 0.3% of cases are identified before the age of thirty. According to Kimbrely, Andrew, Anders (2018), Although pediatric multiple myeloma is rare, it is crucial to provide additional information about the effectiveness of

therapies. Studies provide evidence suggesting that allogeneic transplantation may have a potential benefit in young, previously healthy individuals (Davidow et al., 2018).

CAR-T therapy: For hematological malignancies, chimeric antigen receptor-modified T (CAR-T) cells have demonstrated astounding clinical efficaciousness in cancer immunotherapy. With this novel method, a patient's T cells are trained to identify and target myeloma cells directly (Ma et al., 2019).

Monoclonal Antibodies: Since 2010, synthetic proteins known as monoclonal antibodies have been developed. They attach antigens on myeloma cells, therefore enhancing diagnostic results (*Multiple Myeloma: Improved Prognosis with the Latest Treatments*, 2024).

The availability of newer medications differs globally. While some physicians are quick to adopt new treatment approaches, others deliberately take time to update them (News-Medical, 2024).

Continual pharmaceutical research guarantees that patients worldwide experience the advantages of the most recent innovative discoveries. In brief, the pursuit of novel pharmaceuticals in the treatment of multiple myeloma arises from the aspiration to improve patient results, reduce adverse reactions, and finally discover a remedy. All stakeholders, including researchers, physicians, and patients, are essential contributors in the pursuit of improved management and optimism for the future.

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2.2Mechanism of action of Proteasome Inhibitor

Large protein structures which are called proteasomes cut proteins in cells into more smaller pieces called peptides. Different types of proteasomes have different regulatory subunits, catalytically active subunits, and proteins which are connected to them. The name of one

important group of drugs used to treat multiple myeloma and mantle cell lymphoma is proteasome inhibitors. These drugs are also being looked into for use in other illnesses (Fricker, 2020).

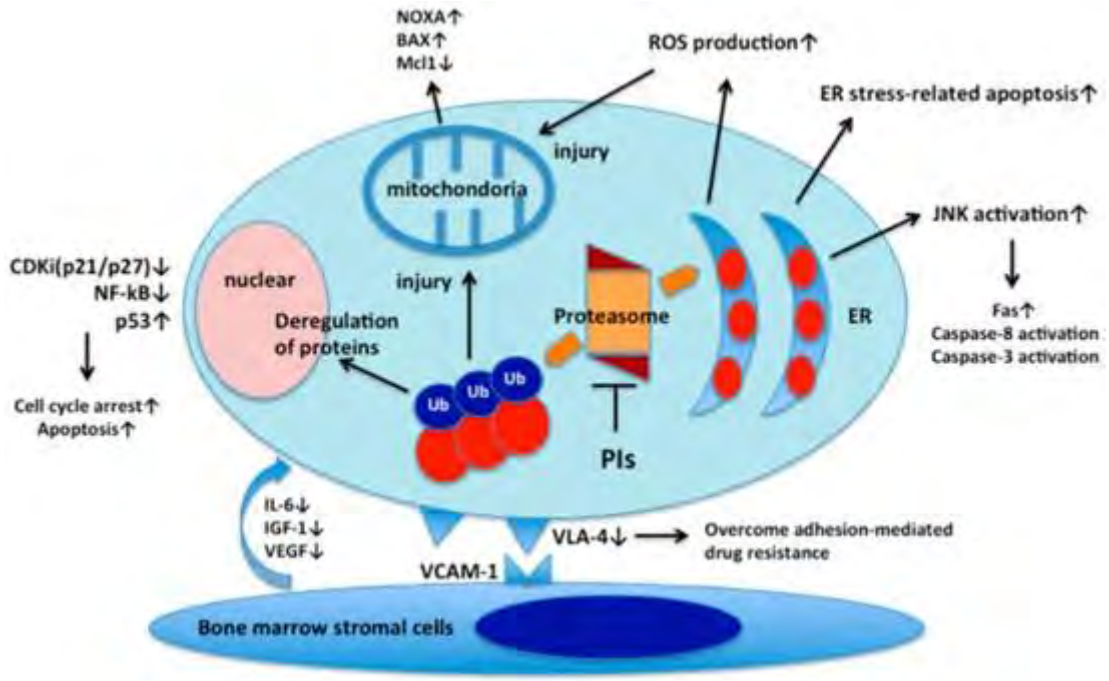

Figure 5 Molecular effects of proteasome inhibition on multiple myeloma cells (Ito, 2020a)

The ubiquitin proteasome pathway (UPP) is the most important and main pathway that eukaryotic cells break down proteins in the nucleus and cytoplasm. A big group of proteins which called the proteasome is made from different types of proteases that work together to break down or process proteins inside cells. There are also four stacked rings that make up the 20S proteasome. From them each ring has 28 protein parts. There are seven α-subunits in two of these rings and seven β-subunits in the other two. There are seven β-subunits, and three of them (β1, β2, and β5) have proteasome functions that have been described as chymotrypsin-like (Groen et al., 2019). Monoclonal proteins are made and released in large amounts by MM cells. When the proteasome isn't working, proteins that aren't formed correctly build up in the endoplasmic reticulum (ER). This is called ER stress. ER stress sets off proliferative and

antiproliferative signals, messes up the control of the cell cycle, starts apoptosis pathways, and finally kills the cell (Adams, 2004) (Niewerth et al., 2015). More recently, it was shown that blocking β1 or β2 activity along with β5 activity effectively stops the proteasome and kills MM cells (Besse et al., 2019). It's interesting that only high-dose carfilzomib from the PIs that are currently on the market has been shown to provide β2/β5 co-inhibition and kill MM cells more effectively. These results make it more likely that high-dose carfilzomib could work on other MM cells that are resistant to PI (Ito, 2020). From figure 01, we can see that, Apoptosis caused by ER stress can be stopped by proteasome inhibition. Proteasome inhibition also has other molecular effects on affected cells. The primary mode of action of bortezomib in multiple myeloma (MM) cells is to suppress the activation of the nuclear factor-κB (NF-κB) pathway, a crucial regulator of lymphomagenesis (Chauhan et al., 2005) (Li et al., 2008). Proteasome suppression of p53 cell can lead to the accumulation and phosphorylation of pro-apoptotic proteins, also including NADPH oxidase activator (NOXA) and Bcl-2-associated X protein (Bax). This can triggers apoptosis through mitochondrial malfunction which is characterized by the release of cytochrome-c and dysregulation of membrane potential. Additionally, Bortezomib reduces the expression of many cell adhesion molecules, including very late antigen (VLA)-4, which results in the resensitization of adhesion-mediated drug resistance in multiple myeloma (MM) cells (Noborio-Hatano et al., 2008).The buildup of unfolded and misfolded proteins, resulting in apoptosis and cell death, is induced by proteasome inhibitors (PIs) by various mechanisms including endoplasmic reticulum stress, generation of reactive oxygen species, activation of JNK and p53, inhibition of cyclin-dependent kinases, and stimulation of pro-apoptotic proteins. Bortezomib suppresses the synthesis of cytokines including IL-6, insulin-like growth factor-1 (IGF-1), and VEGF in cells of the bone marrow stroma. Furthermore, Bortezomib suppresses the expression of VLA-4, hence overcoming drug resistance mediated by cell adhesion (Ito, 2020).

2.3 Drug of Interest

Let's discuss about the pharmacokinetics and pharmacodynamics of carfilzomib and bortezomib:

Pharmacokinetics of carfilzomib

A two-compartment model with linear distribution (mean total clearance of 133 L/h) best characterized the pharmacokinetics of carfilzomib. The activities of proteasomes were most accurately described using a turnover model that includes irreversible inactivation. Excellent accuracy was achieved by estimating all parameters (Lin et al., 2023).

Pharmacodynamic of Carfilzomib

Carfilzomib exerts its pharmacodynamics by selectively and irreversibly inhibiting the 20S proteasome, a critically involved pathway in the degradation of unnecessary or impaired proteins. The inhibition of this function by Carfilzomib results in the buildup of proteins, which induces cellular stress and triggers apoptosis, especially in malignant cells such as multiple myeloma. This phenomenon arises because cancer cells are highly dependent on proteasome activity for their survival, due to their rapid turnover of proteins. Furthermore, the medication interferes with crucial signaling pathways, including NF-κB, therefore enhancing apoptosis. The irreversible nature of its action results in long-lasting effects, ongoing even after the drug is eliminated (Wang et al., 2012).

Pharmacokinetics of Bortezomib

The pharmacokinetics of Bortezomib manifest as fast absorption and distribution subsequent to intravenous or subcutaneous delivery. The volume of distribution suggests thorough penetration into tissues. Primary metabolism of bortezomib occurs through the action of

cytochrome P450 enzymes which are called CYP3A4, CYP2C19, and CYP1A2, resulting in the formation of inactive metabolites. And the primary route of elimination is through the biliary system, also with little excretion by the kidneys. The medication exhibits a biphasic half-life characterized by an early brief distribution phase followed by a prolonged terminal elimination phase. This property renders it appropriate for incorporation into cancer treatment regimens such as multiple myeloma (Reece et al., 2010).

Pharmacodynamic of Bortezomib

The mechanism of action of Bortezomib is its ability to reversibly block the 26S proteasome, an essential enzyme complex that breaks down misfolded or damaged proteins. The inhibition of this processed by Bortezomib interferes with the regular protein turnover which resulting in the buildup of faulty proteins, cellular stress, and the initiation of apoptosis, especially in malignant cells such as those found in multiple myeloma. Furthermore, proteasome inhibitors suppresses the NF-κB signaling pathway, which is involved in cell survival and proliferation, therefore by enhancing the death of cancer cells while minimizing the injury to most normal cells because of their reduced dependence on the proteasome (Tan et al., 2018).

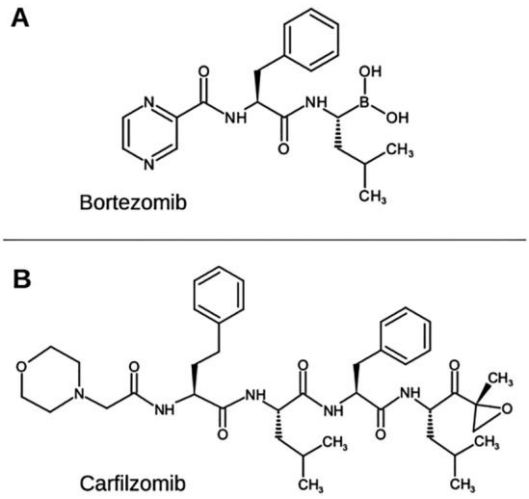

Figure 6 Chemical structure of carfilzomib & bortezomib (Malacrida et al., 2021)

Chapter 3

Methodology

3.1 Study Selection

Several web databases were used to gather information for the article's introduction. Such as PubMed, ScienceDirect, ctg.gov, SpringerLink, these were the databases that are used for extract primary information. This information was found in April 2024. A malignant plasma cell condition, multiple myeloma (MM) accounts for about 10% of all hematologic tumors. It typically develops from "monoclonal gammopathy of unknown significance,"(MGUS) a premalignant stage of clonal plasma cell growth that is asymptomatic (Kyle & Rajkumar,2008) . Most cases of multiple myeloma are diagnosed in those between the ages of 60 and 70. We also know that the incidence of myeloma in Blacks is two to three times higher and occurs around ten years earlier in Blacks than in Whites. The likelihood of developing multiple myeloma may also be raised by a family history of the illness (Ferrara, 2024). In this study, Only the most recent and pertinent articles were selected from a vast collection of articles for the intended subject.

3.2 Study Selection for Clinical Trial:

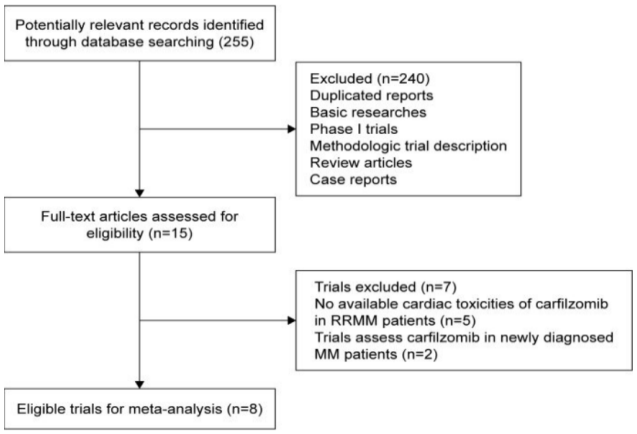

Figure 7Search criteria for carfilzomib & bortezomib clinical trial data (Zhao et al., 2018)

The objective was to collect at least eight clinical trial data points for each of the two drugs of interest—carfilzomib and bortezomib. To find the available clinical trial data, the search term called "Carfilzomib and bortezomib" was used on the international clinical trials registry platform. The preceding section provides a comprehensive explanation of the search approach. For each drug, eight clinical trial data sets met the qualifying requirements, and all of them were selected. The number of clinical trial data required was met, hence no other databases were searched. The clinical trial data that have been chosen are exclusively for combination therapy using carfilzomib or bortezomib.

3.3 Inclusion and Exclusion Criteria

3.3.1 Inclusion Criteria

For this investigation, clinical trials that satisfy the inclusion requirements have been chosen. The criteria for inclusion are as follows:

1) Phase 3 clinical trials

2) Clinical trials with complete results

3) Combination therapy

4) Patient number more than hundred

5) Progression free survival and overall survival

6) Therapy that is only used for multiple myeloma.

7) Combination therapy either with bortezomib or carfilzomib

3.3.2 Exclusion Criteria

Clinical studies that did not meet the exclusion criteria were not included in this analysis and were discarded. Here is the exclusion's foundation:

1) Phase 1 and phase 2 clinical trial

2) Clinical trials without complete results

3) If patients number less than 100

4) Any other physical condition without multiple

5) Clinical trials without both progression free survival and survival rate

6) Combination therapy without carfilzomib or bortezomib

7) There is no requirement for specific dose

Chapter 4

Result and Discussion

4.1 Result

Table 1Phase 3 clinical trial data of carfilzomib

Participant no.	disease	Intervention	dose	End points	Side effects	Reference
1)478 patients	Multiple myeloma	Carfilzomib Melphalan Prednisone	carfilzomib (IV)dose was at 20 mg/m² on cycle 1, days 1 and 2 followed by 36 mg/m² thereafter. On days 1 to 4, melphalan was administered at 9 mg/m² and prednisone was administered at 60 mg/m².	Progression-Free Survival (PFS): 22.3 Overall Survival (OS): 31.5	Anemia, Febrile neutropenia, Hemolytic uremic syndrome, Neutropenia, Cardiac disorders, Eye disorders, Gastrointestinal disorders, Hepatobiliary disorders, Immune system disorders, Infections and infestations, Injury, poisoning and procedural complications, Metabolism and nutrition disorders	(Clinical Trials.gov, 2019.)

2)464 patients	Multiple myeloma	Carfilzomib Dexamethasone	Participants received 20 mg/m² carfilzomib administered by IV infusion on Days 1 and 2 of Cycle 1, followed by 56 mg/m² on Days 8, 9, 15, and 16 of Cycle 1 and for each 28-day cycle thereafter. Additionally, participants received 20 mg dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle.	Progression-Free Survival (PFS): 18.7 Overall Survival (OS): 47.6	Anemia, thrombocytopenia, angina pectoris, atrial fibrillation, cardiac failure, myocardial infarction, diarrhea, vomiting, chest pain, bronchitis, Broncho pneumonia, gastroenteritis, lungs infection, pneumonia, respiratory tract infection, urinary tract infection	(Clinical Trials.gov, 2012)
3)240 patients	Multiple myeloma	Carfilzomib dexamethasone	Participants received carfilzomib administered by IV infusion (20 mg/m² on	Progression-Free Survival (PFS):	Anemia, cardiac failure, asthenia ,fatigue, pyrexia, infection, influenza , lung infection,	(Clinical Trials.gov, 2022)

			day 1 of cycle 1 and 70 mg/m² thereafter). Participants also received 40 mg dexamethasone IV or orally	11.2 Overall Survival (OS): 13.2	pneumonia bacterial, septic shock, pathological fracture, plasma cell myeloma, acute kidney injury, pulmonary embolism,	
4)312 Patients	Multiple myeloma	Carfilzomib, Dexamethasone and Daratumumab	Carfilzomib was administered intravenously (IV) at 20 mg/m^2 in Cycle 1, The 56 mg/m^2 dosage was continued in Cycles 2 Dexamethasone was taken by IV infusion at 20 mg on Cycle 1 Daratumumab was administered by IV at 8 mg/kg on	Progression-Free Survival (PFS): 35.3 Overall Survival (OS): 84.3	Anemia, thrombocytopenia, acute myocardial infraction, atrial fibrillation, cardiac failure, myocardial ischemia, cataract, diarrhea, fatigue, pyrexia, bronchitis, influenza, lower respiratory tract infection, pneumonia, respiratory tract infection, sepsis, septic shock, UTI, Covid 19 pneumonia, acute kidney injury, dyspnea,	(Clinical Trials.gov, 2020)

			Cycle 1		Pulmonary embolism, Pulmonary edema	
5)396 patients	Multiple myeloma	Carfilzomib Lenalidomide, and Dexamethasone	Carfilzomib 20 mg/m² was administered intravenously (IV) Lenalidomide 25 mg was administered orally on days 1 to 21 of every cycle. Dexamethasone 40 mg was administered orally or IV	Progression-Free Survival (PFS): 26.3 Overall Survival (OS): 48.3	Anemia, febrile neutropenia, thrombocytopenia, acute myocardial infraction, atrial fibrillation, cardiac Failure, myocardial infraction, cataract, abdominal pain, diarrhea, pyrexia, bronco pneumonia, gastroenteritis, pneumonia, respiratory track infection, UTI, Basal cell carcinoma, acute renal failure Pulmonary embolism, Deep vain thrombosis	(Clinical Trials.gov, 2015)

6)238 patients	Multiple myeloma	Carfilzomib Dexamethasone	Participants received carfilzomib administered by intravenous (IV) infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20 mg/m² on days 1 and 2 of cycle 1 and 27 mg/m² thereafter). Participants also received 40 mg dexamethasone IV or orally on days 1, 8, 15 and 22 for the first 8 cycles; starting with cycle 9, dexamethasone was administered only on days 1, 8, and 15.	Progression-Free Survival (PFS): 7.6 Overall Survival (OS): 18.1	Anemia, cardiac failure, asthenia, fatigue, pyrexia, infection, influenza , lung infection, pneumonia bacterial, septic shock, pathological fracture, plasma cell myeloma, acute kidney injury, pulmonary embolism	(Clinical Trials.gov, 2022)

7)157 patients	Multiple myeloma	carfilzomib	Carfilzomib: 20mg/m² IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m² IV on Days 8,9,15, and 16 of Cycle 1 and continuing on Days 1,2,8,9,15, and 16 of Cycles 2 through Cycle 9. Cycles 10 and beyond will receive 27 mg/m² IV on Days 1,2,15, and 16 (alternatively, the investigator could choose to continue the dosing frequency on the original dosing days [Days 1, 2, 8, 9, 15, 16] for individual	Progression-Free Survival (PFS): 3.7 Overall Survival (OS): 10.2	anemia, febrile neutropenia, thrombocytopenia, Cardiac arrest, cardiac failure, pyrexia, Broncho pneumonia, urinary tract infection, tumor lysis syndrome, pathological fracture, acute renal failure, renal Impairment	(Clinical Trials.gov,2017)

			subjects).			
8)154 patients	Multiple myeloma	Carfilzomib Dexamethasone	Carfilzomib was administered intravenously (IV) at 20 mg/m^2, Dexamethasone was taken by IV infusion at 20 mg	Progression-Free Survival (PFS): 44.2 Overall Survival (OS): 43.6	Anemia, thrombocytopenia, acute myocardial infraction, arterial fibrillation, cardiac failure, myocardial ischemia, cataract, diarrhea, fatigue, pyrexia, bronchitis, influenza, lower respiratory tract infection, pneumonia, respiratory tract infection, sepsis, septic shock, UTI, Covid 19 pneumonia, acute kidney injury, dyspnea, Pulmonary embolism, Pulmonary edema	(Clinical Trials.gov, 2022)

Table 2 Phase 3 clinical trial data of Bortezomib

Participant no.	disease	Intervention	dose	End points	Side effects	Reference
1)242 patients	Multiple myeloma	Dexamethasone, Lenalidomide, Bortezomib	Patients receive dexamethasone PO QD on days 1, 2, 4, 5, 8, 9, 11, and 12; lenalidomide PO QD on days 1-14; and bortezomib IV over 3-5 seconds on days 1, 4, 8, and 11. Treatment repeats every 21 days for 8 courses in the absence of disease progression or unacceptable toxicity.	Progression-Free Survival (PFS): 43 Overall Survival (OS): 75	cardiac ischemia, atrial fibrillation, STV and nodal arrhythmia, sinus bradycardia, diarrhea, hemorrhage, vomiting, edema: limb, fatigue, flu like syndrome, pain	(ClinicalTrials.gov, 2024)
2)387 patients	Multiple myeloma	Panobinostat Bortezomib Dexamethasone	Panobinostat was given 20 mg hard gelatin capsules.	Progression-Free Survival (PFS):	Anemia, thrombocytopenia, angina pectoris	(ClinicalTrials.gov, 2015)

			Bortezomib was given at 1.3 mg/m2 as a 3 to 5 second bolus intravenous (IV)injection. Dexamethasone was given as an oral dose of 20 mg/day.	11.99 Overall Survival (OS): 40.28	abdominal pain, diarrhea, Gastro intestinal hemorrhage, vomiting, asthenia, pyrexia, lower respiratory tract infection, long infection, pneumonia, sepsis, upper respiratory track infection	
3)278 patients	Multiple myeloma	Lenalidomide Bortezomib Dexamethasone	For Cycles 1 - 8: 1.3 mg/m2/dose For Cycles 9 onwards: 1.3 mg/m2/dose DEX (Dexamethasone) For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old)	Progression-Free Survival (PFS): 7.10 Overall Survival (OS): 31.61	anemia, hyper viscosity syndrome, thrombocytopenia, cardiac failure, constipation, diarrhea, nausea, vomiting, general Physical health deterioration, pyrexia, influenza, lower respiratory tract infection, lung infection,	(ClinicalTrials.gov, 2023)

			For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old)		pneumonia, upper respiratory tract infection, acute kidney injury	
4)254 patients	Multiple myeloma	lenalidomide, bortezomib and dexamethasone.	All patients will undergo a first autologous peripheral blood stem cell (PBSC) transplant with high dose melphalan (200 mg/m^2 IV) (lenalidomide 15 mg/day dexamethasone 40 mg bortezomib 1.3mg/m2 e,	Progression-Free Survival (PFS): 57.8 Overall Survival (OS): 85.4	Atrial fibrillation, colitis ischemic, bile duct Stone, bone pain, acute myeloid Leukemia, myelodysplastic syndrome, syncope	(ClinicalTrials.gov, 2018)
5)357 patients	Multiple myeloma	Lenalidomide Bortezomib Dexamethasone	RVD cycle duration:21 days R: 25 mg oral on days 1-14 V: 1.3 mg per square	Progression-Free Survival (PFS): 46.2 Overall	Anemia, febrile neutropenia, leukocytosis, leukopenia, lymphopenia, neutropenia,	(ClinicalTrials.gov, 2023)

			meter of body surface area IV or subcutaneous on days 1, 4, 8, and 11 D: 20 mg oral (cycles 1-3) or 10 mg (cycles 4-8) on days 1, 2, 4, 5, 8, 9, 11, and 12	Survival (OS): 79.2	thrombocytopenia, diarrhea, gastrointestinal bleed, Gastrointestinal hemorrhage, mucositis, nausea, stomach pain, vomiting, chest pain, edema, fatigue, fever, clostridium difficile infection, sepsis	
6)465 patients	Multiple myeloma	Bortezomib and dexamethasone.	Participants received bortezomib 1.3 mg/m² administered intravenously (IV) or subcutaneously (SC) on Days 1, 4, 8, and 11 of a 21-day cycle plus dexamethasone (DEX) 20 mg administered on Days 1, 2, 4, 5, 8, 9, 11, and	Progression-Free Survival (PFS): 9.4 Overall Survival (OS): 40.0	Anemia, febrile neutropenia, acute myocardial infarction, atrial fibrillation, cardiac failure, pyrexia, gastroenteritis, pneumonia, respiratory tract infection, sepsis, septic shock, upper respiratory tract infection, urinary tract	(ClinicalTrials.gov, 2022)

			12 of each 21-day cycle.		infection , urosepsis, platelet count decreased, dehydration, hyperkalemia, arthralgia, syncope, confusional state, acute renal failure, orthostatic hypertension	
7)281 Patients	Multiple myeloma	Pomalidomide, Bortezomib, Dexamethasone, lenalidomide	4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone)	Progression-Free Survival (PFS): 11.20 Overall Survival (OS): 35.58	Anemia, febrile neutropenia, thrombocytopenia, acute coronary syndrome, acute Myocardial Infarction , angina unstable, atrial fibrillation, cardiac arrest, cardiac failure, cardiac failure congestive, coronary artery disease, sinus node disfunction,	(ClinicalTrials.gov, 2023)

					abdominal pain, diarrhea, gastric hemorrhage, pyrexia, bronchitis, Escherichia urinary tract infection, lower respiratory tract infection, influenza, lung infection , pneumonia, pulmonary sepsis, sepsis, septic shock, urinary tract infection, dehydration, Basil cell carcinoma, acute kidney injury, deep brain thrombosis	
8)365 patients	Multiple myeloma	Lenalidomide Bortezomib Dexamethasone, autologous stem cell transplant	RVD cycle duration:21 days R: 25 mg oral on days 1-14 V: 1.3 mg per square meter of body	Progression-Free Survival (PFS):	Anemia, febrile neutropenia, leukopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopen	(ClinicalTrials.gov, 2023)

		(ASCT)	surface area IV or subcutaneous on days 1, 4, 8, and 11 D: 20 mg oral (cycles 1-3) or 10 mg (cycles 4-8) on days 1, 2, 4, 5, 8, 9, 11, and 12	67.5 Overall Survival (OS): 80.7	ia, congestive heart failure, myocardial infarction, diarrhea, gastrointestinal bleed, edema, fatigue, fever, influenza, pneumonia, sepsis, upper respiratory tract infection, elevated liver enzymes, dehydration, hypocalcemia, hypophosphatemia, bone pain, acute myeloid leukemia, myelodysplastic syndrome, squamous cell carcinoma, sensory peripheral neuropathy, anxiety, depression, hypertension	

Table 3 Comparison of the efficacy of Carfilzomib and Bortezomib

Trial no	Combination of carfilzomib PFS	Combination of bortezomib PFS	p-value
1	22.3	43	0.305112599
2	18.7	11.99	
3	11.2	7.10	
4	35.3	57.8	
5	26.3	46.2	
6	7.6	9.4	
7	3.7	11.20	
8	44.2	67.5	
Mean	**21.1625**	**28.22714286**	
Trial no	Combination of carfilzomib OS	Combination of bortezomib OS	p-value
1	31.5	75	0.096038267
2	47.6	40.28	
3	13.2	31.61	
4	84.3	85.4	
5	48.3	79.2	
6	18.1	40.00	
7	10.2	35.58	
8	43.6	80.7	
Mean	**44.25**	**58.415**	

4.2 Discussion

The main objective is to use a proteasome inhibitor to treat multiple myeloma. The proteasome inhibitors—like carfilzomib and bortezomib—are essential to treating multiple myeloma. Proteasomes are essential for all parts of the cell cycle, including mitosis, apoptosis, DNA replication, translation, transcription and the coordinated degradation of cyclin-dependent kinases (CDKs), which sustains signaling cascades. In addition, proteasomes are known to play a major role in breaking down of misfolded and mutant proteins as well as in signal transmission and the stress response, among other regular physiological processes. Because proteasome inhibition affects a variety of pathways that can contribute to antitumor actions, the proteasome has thus been accepted as a particularly appealing therapeutic target for cancers (Jayaweera et al., 2021). With the approval of bortezomib, a first-in-class reversible proteasome inhibitor, for the cure of relapsed/refractory multiple myeloma (MM), the proteasome has become an important target for cancer therapy. However, a considerable number of patients suffer a lack of response to bortezomib, while others develop resistance, indicating the need of other inhibitors with higher efficacy. So, we assessed carfilzomib, a new, irreversible proteasome inhibitor associated with epoxomicin (Kuhn et al., 2007). As compared to bortezomib, carfilzomib significantly and clinically decreased the chance of death (Dimopoulos et al., 2017).

A phase 3 trial was conducted (Clinical Trials.gov registration no. NCT01818752) on 478 patients suffering from multiple myeloma with the combination of carfilzomib, melphalan, prednisone. where the median of progression free survival was 22.3 and the median of overall survival was 31.5. The trial no 2 for carfilzomib was conducted (Clinical Trials.gov registration no. NCT01568866) on 464 patients suffering from multiple myeloma with the combination therapy of Carfilzomib Dexamethasone. where the median of progression free survival was 18.7 and median of overall survival was 47.6. The trial no 3 for carfilzomib was conducted

(Clinical Trials.gov registration no. NCT02412878) on 240 patients suffering from multiple myeloma with the combination therapy of Carfilzomib Dexamethasone. where the median of progression free survival was 11.2 and median of overall survival could not be estimated due to the low number of events. The trial no 4 for carfilzomib was conducted (Clinical Trials.gov registration no. NCT03158688) on 312 patients suffering from multiple myeloma with the combination therapy of Carfilzomib, Dexamethasone and Daratumumab. where the median of progression free survival was 35.3 and median of overall survival was 84.3. The trial no 5 for carfilzomib was conducted (Clinical Trials.gov registration no. NCT01080391) on 396 patients suffering from multiple myeloma with the combination therapy of Carfilzomib Lenalidomide, and Dexamethasone. where the median of progression free survival was 26.3 and median of overall survival was 84.3. The trial no 6 for carfilzomib was conducted (Clinical Trials.gov registration no. NCT02412878) on 238 patients suffering from multiple myeloma with the combination therapy of Carfilzomib and Dexamethasone. where the median of progression free survival was 7.6 and median of overall survival was 18.1. The trial no 7 for carfilzomib was conducted (Clinical Trials.gov registration no. NCT01302392) on 157 patients suffering from multiple myeloma with the monotherapy of Carfilzomib. where the median of progression free survival was 3.7and median of overall survival was 10.2. The trial no 8 for carfilzomib was conducted (Clinical Trials.gov registration no. NCT03158688) on 154 patients suffering from multiple myeloma with the combination therapy of Carfilzomib and Dexamethasone. where the median of progression free survival was 44.2 and median of overall survival was 43.6. Compared to these phases 3 clinical trial of carfilzomib we can say that combination of Carfilzomib, Lenalidomide, and Dexamethasone and the combination of Carfilzomib Dexamethasone both show a good result for progression free survival and overall survival.

A phase 3 trial was conducted (Clinical Trials.gov registration no.NCT00644228) on 242 patients suffering from multiple myeloma with the combination of Dexamethasone,

Lenalidomide, Bortezomib .where the median of progression free survival was 43 and the median of overall survival was 75.The trial no 2 for Bortezomib was conducted (Clinical Trials.gov registration no.NCT01023308) on 387 patients suffering from multiple myeloma with the combination therapy of Panobinostat Bortezomib , Dexamethasone . where the median of progression free survival was 11.99 and median of overall survival was 40.28. The trial no 3 for Bortezomib was conducted (Clinical Trials.gov registration no. NCT01734928) on 278 patients suffering from multiple myeloma with the combination therapy of Lenalidomide, Bortezomib, Dexamethasone. where the median of progression free survival was 7.10 and median of overall survival was 31.61. The trial no 4 for Bortezomib was conducted (Clinical Trials.gov registration no. NCT01109004) on 254 patients suffering from multiple myeloma with the combination therapy of lenalidomide, bortezomib and dexamethasone. where the median of progression free survival was 57.8 and median of overall survival was 85.4. The trial no 5 for Bortezomib was conducted (Clinical Trials.gov registration no. NCT01208662) on 357 patients suffering from multiple myeloma with the combination therapy of Lenalidomide Bortezomib, Dexamethasone. where the median of progression free survival was 46.2 and median of overall survival was 79.2. The trial no 6 for Bortezomib was conducted (Clinical Trials.gov registration no. NCT01568866) on 465 patients suffering from multiple myeloma with the combination therapy of Bortezomib and dexamethasone. where the median of progression free survival was 9.4 and median of overall survival was 40.0. The trial no 7 for Bortezomib was conducted (Clinical Trials.gov registration no. NCT01734928) on 281 patients suffering from multiple myeloma with the combination therapy of Pomalidomide, Bortezomib, Dexamethasone, lenalidomide. where the median of progression free survival was 11.20 and median of overall survival was 35.58. The trial no 8 for Bortezomib was conducted (Clinical Trials.gov registration no. NCT01208662) on 365 patients suffering from multiple myeloma with the combination therapy of Lenalidomide, Bortezomib, Dexamethasone, autologous stem

cell transplant (ASCT). where the median of progression free survival was 67.5 and median of overall survival was 80.7. Comparison of these eight clinical trial data of bortezomib clearly shows that lenalidomide, bortezomib and dexamethasone shows better results.

4.3 Evaluation of Usefulness of the Drug

Carfilzomib, a second-generation proteasome inhibitor, was first licensed in 2013 for treating relapsed refractory multiple myeloma in patients who had previously had lenalidomide and bortezomib. It is believed to be more powerful than bortezomib. The initial phase 1/2 trial evaluating the carfilzomib-melphalan-prednisone combination therapy in newly diagnosed multiple myeloma patients who are not suitable for transplantation demonstrated satisfactory tolerability, with a low incidence of peripheral neuropathy. (Xie et al., 2022). Studies have shown that carfilzomib, a second-generation proteasome inhibitor, is efficacious in the treatment of patients with multiple myeloma, including those who have experienced relapse or have not responded to prior therapies. Multiple clinical trials have established a correlation between it and extended progression-free survival as well as elevated response rates compared to bortezomib. Bortezomib inhibits both the chymotrypsin-like and caspase-like activities of the proteasome, but carfilzomib specifically targets the chymotrypsin-like active site inside the proteasome. This special selectivity of carfilzomib may lead to increased specificity and reduced toxicity (Rajkumar & Dispenzieri, 2020). Carfilzomib is a second-generation proteasome inhibitor called a keto-epoxide tetrapeptide proteasome inhibitor. This carfilzomib highly effective when it is used alone to treat relapsed refractory myeloma. Carfilzomib, a second-generation proteasome inhibitor, is a highly selective irreversible proteasome inhibitor that specifically binds to the N-terminal threonine active sites of the proteasome. But, bortezomib,1st generation drug, has a slowly reversible impact on the proteasome and also has some cross-reactivity with serine proteases with some other side effects. The bortezomib inhibits both the chymotrypsin-like and caspase-like activities of the proteasome, while

carfilzomib specifically targets the chymotrypsin-like active site inside the proteasome. This drug selectivity may lead to improved specificity and reduced toxicity (Rajkumar&Dispenzieri,2014). In addition to, carfilzomib also has a unique toxicity profile which is characterized by reducing the peripheral neuropathy but potentially has stronger impacts on cardiac and pulmonary functions. Carfilzomib, which is a second-generation irreversible selective proteasome inhibitor and was granted FDA approval in 2012 for the treatment of relapsed and refractory multiple myeloma (RRMM). Carfilzomib, which is irreversible, is more effective and expected to have a longer-lasting therapeutic effect compared to bortezomib. By the ENDEAVOR study, a randomized phase 3 trial, compared the effectiveness of the drug combination bortezomib and dexamethasone (Vd) to carfilzomib and dexamethasone (Kd) in patients with relapsed multiple myeloma (RRMM). The study also demonstrated a significant improvement in both progression-free survival (PFS) and overall survival (OS) for patients treated with Kd. Furthermore, the use of carfilzomib in conjunction with lenalidomide and dexamethasone shown a notable enhancement in progression-free survival (PFS) and overall survival (OS) in patients with relapsed or refractory multiple myeloma (RRMM). Carfilzomib has received approval for use in combination with daratumumab (a monoclonal antibody that targets CD38) and dexamethasone. This combination therapy has identified by a noteworthy improvement in the median progression-free survival (PFS) without any occurrence of new adverse events in the daratumumab and dexamethasone group. From the result we can see that , the Carfilzomib-based combinations therapies have risen as the preferred proteasome inhibitor (PI)-based therapy for patients with relapsed and refractory multiple myeloma (RRMM) which also includes those who are resistant to bortezomib (Georgiopoulos et al., 2023) .And the carfilzomib-based combinations treatments did not provide any substantial advantage when compared to bortezomib-based combinations in newly diagnosed multiple myeloma patients who are not suitable for therapies

like autologous stem cell transplantation (ASCT).The carfilzomib combinations therapies exhibit increasing cardiac and renal toxicity and appears to be a significant risk which could negate any advantages in terms of multiple myeloma and the progression and overall survival in this group of patients, particularly among the elderly patients. Carfilzomib-containing treatment plans have been diagnosed in younger patients who are eligible for transplantation for more good outcomes (Georgiopoulos et al., 2023). However, choosing between carfilzomib and bortezomib is influenced by a number of factors, such as patient characteristics, treatment history, and individual tolerability to side effects. Unlike bortezomib, which affects the proteasome slowly and exhibits significant cross-reactivity with serine proteases, carfilzomib is a highly selective, irreversible proteasome inhibitor that binds only to the N-terminal threonine active sites of the proteasome. Overall, carfilzomib and bortezomib are both effective treatments for multiple myeloma; however, the best option will depend on a number of criteria, such as patient characteristics, treatment goals, history of drugs, and tolerance to side effects. These factors must be considered by healthcare providers when determining the best course of action for each patient.

Chapter 5

Conclusion

5.1 Limitations

There are many different kinds of limitation of the study, and they are mention below:

1)There are so many clinical trial data are available for the desirable drug, but all are not fully complete. only a few clinical trial data are fully completed. among them most of the clinical trial data are from phase 2. but for this study we only need Phase 3 fully completed clinical trial data

2) Multiple myeloma is a disease associated with gene mutation, so the treatment of the disease is also associated with so many side effects. And most of the clinical trial data are not completed due to a smaller number of participants.

3) All clinical trial data have different Endpoints so comparing and analyzing them is quite difficult. Also, the dose is not specific.

There are also some more limitations like:

Carfilzomib:

1.Cardiovascular side effects: Carfilzomib is linked to elevated occurrences of cardiovascular complications, including hypertension, heart failure, and ischemic heart disease (Dimopoulos et al., 2019).

2.Administration: Carfilzomib needs intravenous administration, which can provide inconvenience for patients and escalate healthcare expenditures (Azab et al., 2016).

3.Resistance: Resistance to carfilzomib may occur in some patients, which can reduce the long-term efficacy of the treatment (Irimia et al., 2024).

Bortezomib:

1.Peripheral Nephropathy: One of the most important adverse effects of bortezomib is peripheral neuropathy. This can affect a patient's quality of life and be quite severe (Dimopoulos et al., 2019).

2.Administration: Just like carfilzomib, bortezomib is also administered by intravenous or subcutaneous routes that may not be convenient compared to oral drugs (Azab et al., 2016).

5.2 Future Studies

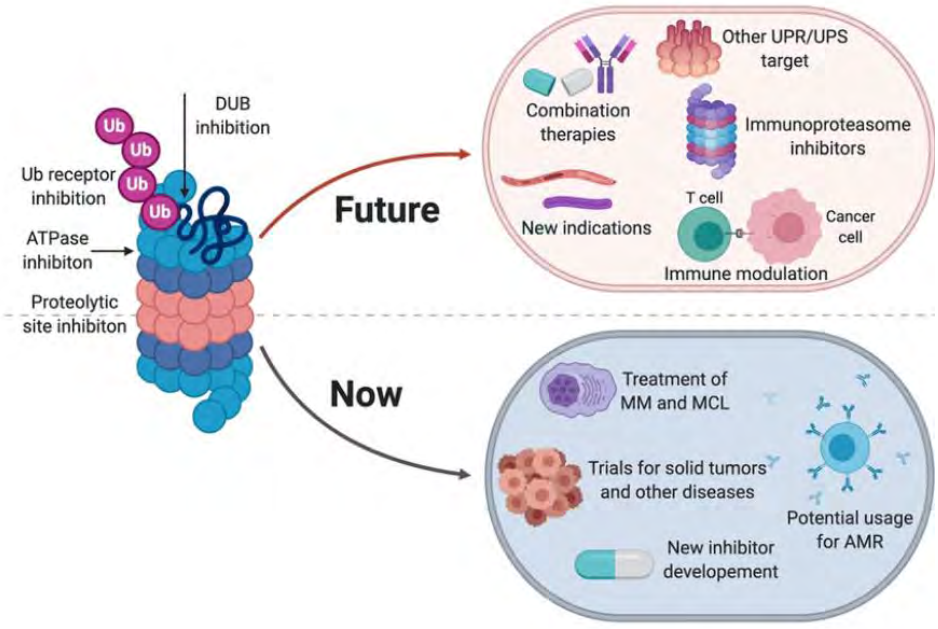

Figure 8: More scope for the future (Figure 4. State of Proteasome Inhibitors, Including Summary of Current. . ., 2020.)

Additional studies which are required to determine the drug's range of activity to find whether it is broad or narrow, and to include a larger number of patients in these trials. Additional articles which analyze the outcomes of the clinical studies to determine its effectiveness are also required. The proteasome serves as the core element of the primary cellular mechanism for protein breakdown. Over the last forty years, researchers have uncovered the crucial role of

the proteasome in many important bodily functions, and its activity has been associated with a range of human illnesses. The proteasome serves crucial functions such as preventing the buildup of misfolded proteins, regulating the cell cycle, and controlling the immunological response. Proteasome inhibitors have been authorized for the treatment of multiple myeloma and mantle cell lymphoma as a therapeutic target (Sherman & Li , 2020).

Conducting research in the areas described in Figure:7 could lead to revolutionary advancements and significantly decrease the incidence of severe side effects in patients. An in-depth discussion of the etiology of multiple myeloma, the route of proteasome inhibitors, and the resistance associated with it, together with ongoing research in this field, could potentially provide insights into strategies for enhancing survival rates.

Emerging research on proteasome inhibitors for the therapy of multiple myeloma is concentrating on various very promising areas:

1. Other Combination Therapy: Proteasome inhibitors, which are extremely effective for the treatment of multiple myeloma, have considerably increased the therapy options available for this disease. Also, with advancements in treatment regimens for multiple myeloma, achieving a complete response still necessitates a novel therapeutic approach with notable variations in results. Proteasome inhibitors trigger two essential processes for the maintenance of protein homeostasis which are autophagy and endoplasmic reticulum stress. Co-administration of the proteasome inhibitors with the autophagy inhibitors has identified triggering cell death in multiple myeloma cells (Salimi et al., 2022).

2. Novel Proteasome Inhibitor: Pharmacological trials are now underway to develop and evaluate novel proteasome inhibitors. These next-generation inhibitors seek to enhance effectiveness and minimize adverse effects in comparison to current medications such as bortezomib and carfilzomib (Ito, 2020).

3. Ongoing Clinical Trials: There are so many clinical trials that explores various aspects of proteasome inhibitors used in the treatment of multiple myeloma. By the help of these clinical trials, we can further know about different combination therapy, doses regimen and alternative treatment which can improve patients' survival (Merin & Kelly, 2014).

4. Individualized Medical Treatment: Inhibiting the ubiquitin-proteasome system to modulate intracellular protein turnover is a novel approach in cancer treatment, particularly effective against multiple myeloma. Initially approved as a single treatment for patients in the relapsed/refractory situation, the first-in-class proteasome inhibitor, bortezomib, has recently been proven to provide even greater advantages when used in rationally designed combos to overcome chemoresistance (Shah & Orlowski, 2009).

5.3 Conclusion

The proteasome inhibitors such as Carfilzomib and Bortezomib are used in the treatment of multiple myeloma, which is a malignancy affecting plasma cells. The first medicine in this family, Bortezomib, functions by reversibly blocking the 26S proteasome, resulting in the death of cancer cells by interrupting protein degradation. The second-generation inhibitor carfilzomib provides irreversible proteasome inhibition and enhanced potency, particularly in cases of relapse or resistance to treatment. Both medications leverage the reliance of myeloma cells on proteasome activity, rendering them very efficacious in enhancing results for patients with this complex tumor. Carfilzomib and Bortezomib gives substantial advantages in the treatment of multiple myeloma, for example enhanced overall survival rates, specific targeting of malignant cells, and efficacy in combination therapy. In individual patients who have been previously treated with Bortezomib, Carfilzomib effectively overcomes problems like drug resistance. Both drugs give powerful therapeutic alternatives with controllable adverse effects, therefore also enhancing the results for patients with relapsed and resistant multiple myeloma. The

therapeutic efficacy of both Carfilzomib and Bortezomib in the management of multiple myeloma has been well established, especially in patients who have experienced relapse and resistant like problems. The first proteasome inhibitor, bortezomib has been very successful for increasing the number of people who survive and respond to treatment. Patients who are no longer responding to Bortezomib are better treated with Carfilzomib and which is a stronger and permanent inhibitor. When carfilzomib used with other treatments like lenalidomide and dexamethasone, both drugs work better, and many people have deeper responses and longer remissions. Because this kind of treatments stop the proteasome from working, they can kill cancer cells, making them essential treatments for multiple myeloma. Carfilzomib is usually considered to be better treatment than Bortezomib for some patients because it stops the proteasome in a way that can't be reversed and works better in cases where a patient has become resistant to Bortezomib. It also works better at stopping the disease from getting worse and may have a lower chance of some side effects, like peripheral neuropathy. But Bortezomib is still widely used and even recommended in some situations because it has been used for a long time, is easier to administer (subcutaneously), and has been used in more clinical settings. Which one to use depends on the patient's health and what treatments they have had in the past (Kumar et al., 2020).

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