Chapter

Treatment and Disease-related Complications in Multiple Myeloma

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Abstract

Multiple myeloma is a clonal plasma cell neoplasm that is mainly characterized by anemia, renal insufficiency, hypercalcemia, and bone destruction. Since 1990, there is an increase in the incidence of myeloma globally by 126%. However, due to the presence of the new therapeutic agents such as proteasome inhibitors, immunomodulatory drugs, Chimeric antigen receptor T-cell therapy, bispecific antibodies, bisphosphonates, corticosteroids, melfulfen, iberdomide, cyclophosphamide, plerixafor, melphalan chemotherapy, nuclear transport inhibitor, and monoclonal antibodies, as well as upfront autologous and allogeneic hematopoietic cell transplantation in eligible patients, a decline in the age-standardized mortality rate has been seen. This leads to higher survival rates of patients with multiple myeloma in the last 15 years, and hence, patients with multiple myeloma for 10–15 years are no longer rare. However, it has been observed that even though the treatment goal was to prevent end-organ damage, improve or maintain quality of life (QoL), and achieve long-term disease-free survival; thus, new treatments have converted myeloma into a chronic disease, such as peripheral neuropathy (PN), venous thromboembolism, and cardiac toxicity. Notably, most patients remain on continuous treatment for extended time periods, which leads to various complications. Hence, management of immediate and late complications from disease and treatment is a critical component of survivorship care in myeloma.

Keywords: quality of life, disease, adverse effects, treatment, peripheral neuropathy

1. Introduction

Multiple myeloma (MM) is known to be one of the most common types of plasma cell cancer and is the third most hematological malignance after non-Hodgkin lymphoma cancer and leukemia. Moreover, it represents almost "21% of all cancer types globally and in the United Kingdom with a soar in the incidence rates since the mid-1970s" [1, 2]. Around 305 patients (128 females and 177 males) in Ireland are diagnosed with MM per year. In 2019, around 2000 people were living with myeloma in Ireland. Hence, various treatments are used to slow down, control, or prolong

survival rate of MM patients [3, 4]. The normal plasma cells that are located in the bone marrow (soft tissue within the bones) have a huge impact on the immune system, which consists of different cells, which aim to fight infections and various diseases. Lymphocytes including T cells and B cells are white blood cells in the immune system, which are located in various areas in the body, such as "lymph nodes, the bone marrow, the intestines, and the bloodstream." In the normal conditions, when an infection occurs, B cells would mature and progress into plasma cells. Thus, the antibodies (immunoglobulins) are formed by the plasma and aim to attack and kill germs [5].

In general, once the plasma cells grow out of control and become cancerous, this results in MM, which leads to malignant transformation of the plasma cells. Data from gene sequencing studies explain that the malignant clone in MM may arise from a late cell in B-cell development. Patients suspected of MM should be examined using screening tests, such as electrophoresis of serum and concentrated urine and then immunofixation to indicate any M protein present. To diagnose MM, radiographic skeletal survey, bone marrow aspiration, and biopsy are performed. As a result, plasma cells would lead to the formation of abnormal protein antibodies known as "monoclonal protein (M-protein) or paraprotein," which may lead to bone pain, fractures, anemia, infections, and other complications [6–8]. Chronic pain is extremely prevalent in patients with MM, and it is one of the most common symptoms upon diagnosis experienced by MM patients and could be an indicator of a relapse.

2. Complications of multiple myeloma

2.1 Infections

Moreover, MM is related to high rate of infections that could lead to death for MM patients. The increased susceptibility of patients to infections arises from the MM disease itself, therapies, age, and disease-related conditions. Moreover, the main leading cause of the infection is due to a multifactorial immunodeficiency caused by the disease itself and the novel therapies given during the different stages of treatment [9]. It was previously reported that MM patients exhibit a higher risk of developing a bacterial/viral infection compared with healthy individuals of the same sex and age. At 1 year of follow-up, high rate of infection was possessed in MM patients leading to death. The most common causes of infection in MM are gram-negative bacilli, *Streptococcus pneumoniae*, and viruses (influenza and herpes zoster) [10]. The most common infections resulted from MM are meningitis, septicemia, pneumonia, osteomyelitis, cellulitis, and pyelonephritis. Influenza infection and herpes zoster were the most frequent viral infections.

Hence, careful monitoring for infection and appropriate use of antibiotics are required with MM patients. In a randomized phase II study in 157 patients who were treated through autologous hematopoietic cell transplantation [HSCT], it was reported that administration of ciprofloxacin and vancomycin lowered the incidence of neutropenic fever without causing any effect on the total interval of hospitalization [11].

2.2 Renal complications

The kidney is one of the major target organs in MM. Thus, almost 40% of MM patients will develop kidney impairment, while 10 to 15% will require dialysis. Hence, renal impairment has a significant effect on the overall survival (OS) of these

patients and is a major complication of MM disease and can be presented as either Ig-dependent or Ig-independent [12], as in Ig-dependent that results from the toxic effects of monoclonal light chains, which can with other kidney lesions such as cast neuropathy, monoclonal immunoglobulin deposition disease, light chain amyloidosis, glomerulonephritis: membranoproliferative, diffuse proliferative, cryoglobulinaemic tubulointerstitial nephritis, Fanconi syndrome, minimal change disease membranous glomerulopathy, immunotactoid/fibrillary glomerulopathy, and thrombotic microangiopathy. The most common renal complication is the cast neuropathy, which results in acute kidney injury (AKI) and causes dehydration, infection, hypercalcemia, hyperuricemia, or nepthrotoxins and in most cases occurs in MM patients with serum light chains level greater than 100 mg/dl [12]. Hypercalcemia is the second most frequent reason of AKI in MM.

The most common glomerular lesion in MM patients is AL amyloidosis, which is a rapidly fatal systemic disease that involves extracellular deposition of congophilic fibrils in soft tissues.

Thus, renal insufficiency is associated with higher morbidity and mortality, and it is the second most common cause of death in MM patients, after infection, thus highlighting the importance of an early and aggressive treatment, because recovery of renal function is associated with increased survival [13].

2.3 Hyperviscosity syndrome (HVS)

Hyperviscosity syndrome is common in patients with multiple myeloma. It occurs as a result of increased serum viscosity usually resulting from increased circulating serum immunoglobulins leading to increased blood viscosity [14]. It can be caused due to the alternation of the shape of red blood cells or due to enhanced cellular or acellular components of blood, specifically immunoglobulins [15]. It has been previously reported that hypergammaglobulinemia is the most common cause of HVS particularly the monoclonal condition of Waldenstrom macroglobulinemia (WM) followed by myelomas, with the IgG type accounting for less than 5% of the cases.

2.4 Spinal cord compression

Previous findings have demonstrated that MM leads to 5–10% of all malignant tumors due to spinal cord compression (SCC) [16]. SCC is a devastating complication of MM and may lead to loss of neurological function. Hence, the common symptoms of SCC are back pain, motor weakness, and sensory change. Due to its complication, patient should be managed as soon as possible in order to forbid loss of neurological function [17].

2.5 Cytopenia

Initially, in the early stages of the disease, anemia is very common; however, in advanced stages, thrombocytopenia and neutropenia may develop leading to pancytopenia. Pancytopenia leads to decreases in all peripheral blood lineages, and its presence occurs when all three cell lines are under the normal reference range.

The main cause of pancytopenia is due to the plasma cell proliferation replacing normal hematopoietic cells, cytokine-mediated bone marrow failure, or renal failure-induced erythropoietin deficiency [18].

3. Complications of treatment of multiple myeloma

Unfortunately, the treatment options for MM are limited due to the fact that most of the drugs used in MM may cause peripheral neuropathy, which has been shown to negatively impact patient's quality of life [QoL] too.

3.1 Proteasome inhibitors and immunomodulatory drugs

Proteasome is a protease complex that maintains the optimal levels of intracellular proteins required for cell cycle progression, cell apoptosis, mitosis, DNA replication, DNA repair, and other normal cellular processes. The proteasome is a large multi-protein complex that is composed of multicatalytic proteases and aims at degrading or processing intracellular proteins *via* ubiquitin-dependent or ubiquitin-independent degradation pathways [19–23]. MM patients produce high levels of excess proteins including abnormal misfolded proteins by their cancerous cells as a consequence of genome mutations [24–26]. Examples of proteasome inhibitors are bortezomib, carfilzomib, and ixazomib. They can all cause nerve damage and increase the risk for certain infections [23].

Immunomodulatory drugs [IMiDs] modify the response of immune system, which can be beneficial for MM patients, **and** IMiDs have various uses and are mainly used as induction therapy for both transplant eligible and ineligible patients, in the posttransplant maintenance setting, and for relapsed/refractory disease [27].

In addition to this immunomodulatory action, these drugs have other actions in the body such as anti-angiogenic and cytotoxic. Examples of such drugs are lenalidomide, pomalidomide, and thalidomide. These IMiDs drugs can disrupt the myeloma cell-bone marrow stromal cell interaction by reducing the expression of cell surface adhesion molecules and decreasing IL-6 production [19, 27, 28].

3.1.1 Peripheral neuropathy

Peripheral neuropathy [PN] occurs as a result of damage to the peripheral (i.e., arms and legs) nervous system. Signals are being transmitted by the system between the central nervous system (the brain and spinal cord) and the rest of the body. This would lead to an alteration in feelings of the hands, fingers, legs, feet, toes, or lips causing pain, numbness, burning, or even tingling [29]. In case of tingling, burning pain, muscle weakness, sensitivity to touch prickling sensations, or even cold feel sensation develop; then, patient should report directly to his physician who will then adjust the myeloma treatment in order to manage the symptoms of PN [29, 30].

One of the main side effects of proteasome inhibitors [PI] and IMiDs is the treatment-induced PN. It is a common and debilitating toxicity in patients with multiple myeloma. Among the PI the major drug that leads to the highest incidence of PN is bortezomib with almost one-third of patients developing this toxicity [29]. It has been previously reported that subcutaneous and a once weekly dose administration of bortezomib causes a lower incidence of severe PN. Bortezomib mainly targets small nerve fibers and dorsal root ganglion leading to sensory polyneuropathy. Among the various proteasome inhibitors (PI), bortezomib was the first therapeutic agent effective against MM and has been used in clinical practice for the treatment of all stages of MM. Furthermore, daratumumab (DARA) was approved in 2015 by the Food and Drug Administration (FDA) in the United States of America (USA) for MM patients [31].

Moreover, thalidomide is one of the first-generation IMiD-causing PN and is usually observed in up to two-thirds of the patients [29]. It is usually noted beyond a daily dose of 200 mg and with a longer duration of treatment. In contrast to bortezomib, thalidomide may result in higher rates of motor and autonomic neuropathy [32]. Hence, it is reversible in almost a quarter of the patients and may last around 4–6 years. It has been previously seen that newer IMiDs such as lenalidomide and pomalidomide did not cause a high rate of peripheral neuropathy [32].

3.1.2 Infectious complications

Despite prolonging survival times of MM patients, both bortezomib and DARA caused an enhancement in infectious complications thus becoming a life-threatening issue in these patients. The main cause of infection is due to the change in lymphocyte count as well as due to the immunosuppressive effect of the disease [33].

3.1.3 Cardiac toxicity

Carfilzomib has demonstrated a high risk of cardiac toxicity with the incidence of all grade and higher than grade three toxicities being 18.1 and 8.2% and the risk ratio for high-grade cardiac toxicities being 2.2 [34, 35]. The most common cardiac toxicities with carfilzomib include heart failure (systolic or diastolic), cardiac chest pain, hypertension, arrhythmia, acute coronary syndrome, and pulmonary hypertension. Usually, almost 90% of cardiac toxicities occur during the first 3 months of treatment with a median time to first even being 31 days and a plateau in the incidence curve beyond 5 months [32].

It was previously reported [36] that administration of IMiDs to MM patients may result in cognitive impairment. For instance, in 2013, a 59-year-old male was diagnosed with MM. Upon reviewal of his medication, he was started on bortezomib and dexamethasone. Two months later, lenalidomide was added. However, 5 days later after initiating lenalidomide, the patient was taken to the emergency department as a result of cognitive decline and expressive aphasia (impaired word finding). Therefore, a decision was made to stop lenalidomide. Thalidomide was introduced instead, but the patient could not tolerate it due to extreme fatigue. Therefore, lenalidomide was reintroduced at a reduced dose of 5 mg daily and his symptoms did not recur upon follow-up after 16 months [37]. Hence, cognitive impairment caused by IMiDs is mostly reversible within days to weeks after dose discontinuation.

3.1.4 Venous thromboembolism

Furthermore, it has been previously reported that a high risk of venous thromboembolism (VTE) was associated with both thalidomide and lenalidomide. Hence, the incidence of VTE with IMiDs is the highest in the first 6 months of therapy and higher in newly diagnosed patients in contrast to relapsed settings.

IMiDs including lenalidomide, thalidomide, and pomalidomide are known to be the most effective therapies for MM; however, they cause an increase in the risk of VTE. In a previous meta-analysis study evaluating the effect of thalidomide, a 2–6-fold higher risk of VTE was observed, while an 8-fold higher risk of VTE was observed when thalidomide was combined with dexamethasone. A high incidence of VTE is particularly the highest seen during induction therapy of newly diagnosed MM patients [34].

Patients with MM have a high incidence of baseline cardiovascular co-morbidities, which is observed mainly with IMiDs and may induce arrhythmias, such as bradycardia and atrioventricular block.

3.2 Chimeric antigen receptor T cell therapy

Chimeric antigen receptor T-cell therapy (CAR-T) is an effective treatment of relapsed refractory MM that targets a protein called B-cell maturation antigen (BCMA) that is on the surface of myeloma cells but not healthy cells. However, CAR-T has shown high rates of infections from 23 to 63%. Furthermore, toxicities associated with CAR-T include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), cytopenias, tumor lysis syndrome, and hypogammaglobulinemia [38].

3.3 Bispecific antibodies

The main role of bispecific antibodies is to create an immunologic synapse by binding a target both on the malignant plasma cells and on cytotoxic immune effector cells (T-cells/natural killer (NK) cells) leading to T/NK cell activation and destruction of tumor [39]. Various adverse events have been seen throughout all early phase trials for bispecific antibodies including neurological events and cytopenia, such as neutropenia and lymphopenia and CRS in addition to hypogammaglobulinemia, which may lead to a high rate of infection [40].

3.4 Biphosphonates

The most widely used bisphonates (BPs) are pamidronate (Pam) and zoledronic acid (ZA) the most commonly used for the treatment of myeloma-related bone disease. Other BPs such as clodronate (Clo) and ibandronate (iban) have been less frequently used. Almost 40% of MM treated with biphosphonates emit an acute phase response post-administration of BP. Various side effects are found, such as flu-like symptoms, fever fatigue, malaise, and bone pain. A previous study showed nephrotoxicity from BPs and renal failure was observed in MM patients. It depends on the type of BP, and some are more nephrotoxic than others. Moreover, ZA is known to have a long renal tissue half-life, which could accumulate in the renal tissue causing renal damage [41, 42].

3.5 Corticosteroids

Corticosteroids, such as dexamethasone and prednisone either alone or in combination with other myeloma drugs such as immunomodulators or chemotherapeutics agents, are widely used in the treatment of MM. Inclusion of corticosteroids with other myeloma drugs increases the clinical response rates [43]. In addition, corticosteroids aid to decrease the nausea and vomiting that may result from the chemotherapy. The beneficial effects of corticosteroids in the treatment of MM are related to their anti-inflammatory and immunosuppressive effects [43]. These drugs can inhibit the movement of white blood cells to the areas where cancerous myeloma cells are causing damage, decreasing the degree of swelling and inflammation in these areas and mitigating the associated pain and pressure. Even at high doses, dexamethasone

can kill myeloma cells. The side effects associated with using corticosteroids are main concerns, especially it needs to be given at much higher doses than those given in other areas, which may affect patient QoL, especially in elderly patients [44].

As outlined previously, due to their anti-inflammatory and anti-immunosuppressive qualities, glucocorticoids have been shown to be effective in the treatment of MM. Nevertheless, both the short-term and long-term side effects of the use of glucocorticoids prove to be substantial, and it is certainly critical to address them. Glucocorticoids can increase insulin resistance by interfering with signaling pathways. These pathways and the abundance of insulin determine the glucose storage levels in skeletal muscles [35, 45]. Dexamethasone is a glucocorticoid commonly used for the treatment of MM. However, the use of dexamethasone has been demonstrated to trigger impairments in insulin-induced cascades, which then increases insulin resistance in skeletal muscles [46, 47]. The increased insulin resistance leads to a higher incidence rate of induced hyperglycemia in patients due to increased glucose levels. According to 13 studies observing the incidence rate of glucocorticoid-induced hyperglycemia, it was found that 32.3% of the patients involved in the studies developed hyperglycemia stimulated by glucocorticoid use [47, 48]. Furthermore, glucocorticoids evidently decrease bone mineral density [BMD], leading to osteoporosis. The use of prednisolone, another widely used corticosteroid, presents decreased intestinal Ca2+ absorption [47]. Therefore, the use of prednisolone eventually leads to the reduction of BMD, leading to osteoporosis consequently. Prednisolone is not the only glucocorticoid that portrays intestinal Ca2+ malabsorption, as dexamethasone proves to have similar effects on BMD [49, 50]. At least 50 percent of those who require extensive glucocorticoid therapy have osteoporosis. The incidence rate of osteoporotic fractures from long-term glucocorticoid oral use may be as high as 30–50% [34, 51]. The benefits of glucocorticoid treatments for MM certainly outweigh the negatives of the side effects; however, the side effects certainly remain significant and must be tackled by adjusting doses or using other medication to counter the effects. Additionally, corticosteroids may result in hypertension, cardiac Al amyloidosis, hyperviscosity, high output failure, and arteriovenous shunting [35, 37]. Other adverse events include alopecia, weight gain, dermatological rash, endocrine disorders, gastrointestinal disorders, leukocytosis, infections, musculoskeletal, ophthalmic, and psychiatric disorders. Therefore, as a result of this, steroids can adversely affect various boy systems and may exert an effect on patients, physical, social, and psychological functioning leading to decrease in quality of life and reduced treatment adherence. Thus, due to these adverse effects, less effective dosing may be required, which may negatively impact on treatment and survival outcomes [35].

3.6 Melfuflen

Cytopenia is common with melfuflen, especially thrombocytopenia. Therefore, it is essential to monitor cytopenias with melflufen and to ensure proper management and supportive care for platelet count recovery including dose reductions, growth factor support, and platelet transfusions. It has been previously reported that melflufen does not lead to alopecia despite working through an alkylator-dependent mechanism, and the incidence of mucositis is low [52].

3.7 Iberdomide

Iberdomide is a novel cereblon E3 ligase modulator with enhanced tumoricidal and immunostimulatory activity. Previous studies have shown that iberdomide

has the potential to overcome the resistance of IMiD and is compatible with dexamethasone, bortezomib, and daratumumab thus initiating enhanced apoptosis and antibody-dependent cellular cytotoxicity. When combined with dexamethasone, the novel agent iberdomide exhibited antitumor activity in patients with relapsed/refractory MM [53]. Despite its antitumor activity, it has possessed various adverse events including infection, neutropenia, anemia, fatigue, and gastrointestinal toxicities.

3.8 Cyclophosphamide

Cyclophosphamide is a medication primarily used in the management and treatment of neoplasms, including MM, sarcoma, and breast cancer that exerts its effect through alkylation of DNA [54]. However, various concerns were observed with cyclophosphamide regarding their adverse side effects. Bladder and gonadal toxicity are highly observed with this type of drug. Other various adverse side effects were reported such as hemorrhagic cystitis, amenorrhea, myelosuppression, alopecia, and spells of nausea and vomiting [55].

3.9 Plerixafor

Plerixafor is a CXCR 4 antagonist that is used for stem cell mobilization along with granulocyte colony-stimulating factor (G-CSF) in patients with MM [56]. As mentioned earlier, stem cell transplantation is one of the most effective treatment for MM; however, mobilization failure is an important concern with stem cell transplantations. Accordingly, stem cells are yielded from the peripheral blood *via* apheresis. Thus, the most commonly used mobilization agent that is administered subcutaneously for multiple days among patients and donors is the G-CSF. However, there are various adverse effects of G-CSF such as headaches, tiredness and weakness, bone and muscle pain, diarrhea, nausea, bruising or bleeding problems, breathlessness, shortness of breath, feeling sick, sore mouth, gut and back passage, and hair thinning. Accordingly, plerixafor has been reported to be used with G-CSF in patients who exhibited mobilization failure with G-CSF alone. Plerixafor has shown well tolerability by patients. The mild and transient adverse effects of plerixafor had overcome the adverse events due to G-CSF alone [57].

3.10 Melphalan

High-dose melphalan has been used as a common agent in treating refractory myeloma; however, due to complications of prolonged granulocytopenia, high mortality rates were observed [58].

3.11 Chemotherapy

Chemotherapy refers to the use of medicines to stop or slow the growth and longevity of cancer cells. These chemotherapeutic drugs go into blood and hence can reach all body parts to destroy myeloma cells. Chemotherapy can be used alone or in combination with other myeloma drugs. This can provide efficient control over MM and its symptoms or even may lead to complete remission in some cases [59]. Chemotherapy can be given alone as a main treatment for MM or it can be combined

with other myeloma drugs to get better clinical outcomes. It can be given before and even after stem cell transplant to make sure that the cancerous cells will not return. Examples of chemotherapeutic drugs used in MM include melphalan, cyclophosphamide, doxorubicin, and liposomal doxorubicin.

Chemotherapy may be an option for treating MM. However, there are various side effects that vary based on the medicine and the doses administered. Some of the most common side effects of chemo include hair loss, nausea and vomiting, mouth and throat sores, loss of appetite, fast and quick bleeding and bruising, extreme tiredness, and high risk for infection [60].

3.12 Stem cell transplantation

Stem cell transplant, also called a bone marrow transplant, can be effective in the treatment of MM. There are two types of stem cell transplants: autologous transplantation and allogeneic transplantation. In autologous transplantation, which is safer and more common, patient's own stem cells are taken before chemotherapy and then returned back after completion of the chemotherapy. On the other hand, in allogeneic transplantation, the stem cells are taken from a donor, mostly a close relative to the patient such as a sister or brother, whose cells are closely matched to the patient's cell type. MM patients should be exposed to high-dose chemotherapy prior to transplant to kill the cancerous cells; then after few days, the new stem cells are infused into the blood, and they go to settle in the bone marrow where they grow and develop into new blood cells.

Although autologous HSCT is not curative, it can improve the myeloma patient's quality. Stem cell transplant is an integral part of therapy in newly diagnosed MM young and fit elderly patients, or at the time of relapse [61].

High-dose chemotherapy and autologous HSCT is standard therapy for patients with MM. Even though autologous HSCT provides an enhanced survival rate to patients with MM, it can cause various complications such as infections (bacterial, viral, or fungal), chemotherapy-related toxicity, and organ failure [62]. Infections may arise due to damage to the mucosal surfaces and skin from preparatory regimens and central venous catheters, neutropenia, and immunodeficiency secondary to chemotherapy. Thus, patients would require prophylactic antibiotics. The major concern in this process is the development of resistant organisms and the presence of Clostridium difficile infections [63].

Furthermore, relapse rates are higher after autologous transplants than allogenic transplantation.

On the other hand, a lower risk for disease recurrence is found post-allogenic transplants compared to autologous transplantation. However, allogenic transplants may lead to fatal complications such as organ toxicity, graft failure, and graft-versus-host disease [64].

Hence, MM is the most frequent indication of autologous HSCT. It has been previously reported that melphalan 200 mg/m^2 is the gold standard conditioning regimen and the peripheral blood stems cell (PBSC) is the major source of cells. Accordingly, the PBSC is cryopreserved after harvesting using dimethyl sulfoxide (DMSO) as the cryoprotectant, which aims to prevent freezing damage to living cells. Even though DMSO is safe, it may cause mild adverse reactions such as cardiovascular, neurological, respiratory, renal, and hepatic dysfunction [65]. To reduce adverse effects, treatment before and after transplantation may be given, optimization of the infusion procedure, reduction of DMSO concentration or using alternative agents for cryopreservation, and removing DMSO prior to infusion [66].

3.13 Monoclonal antibodies

Immunotherapeutic agents such as monoclonal antibodies, which are proteins designed to attack antigens on the surface of the myeloma cells, play an important role in treatment of MM patients. This role relies on designing a target-specific antibodies produced from a single clone, monoclonal antibodies, which can directly target neoplastic cells and activate the immune system or disrupt a signaling pathway protecting neoplastic cells from immune-cell destruction. The first monoclonal antibody used for the treatment of multiple myeloma was daratumumab, a fully human IgG antibody [67]. Daratumumab was approved by the USA-FDA in 2015 and by the European Medicines Agency (EMA) in 2016 [68, 69]. More promising clinical outcomes were obtained when daratumumab was combined with IMiDs and PIs. Other examples of monoclonal antibodies used in the treatment of multiple myeloma are elotuzumab, isatuximab, and belantamab mafodotin.

Daratumumab may cause a certain drug reaction in people within several hours afterward, which can sometimes be severe. Symptoms may include coughing, wheezing, trouble in breathing, tightness in the throat, stuffy nose, dizziness, headache, rash, and nausea. It can also cause a drop in blood cell count, which may lead to a higher risk of infections and bleeding or bruising. Moreover, isatuzimab may cause drug respiratory infections such as pneumonia and cold leading to lower blood cell counts. Unfortunately, this drug may lead to high risk of developing a second type of cancer [70]. Furthermore, several complications may be observed with elotuzumab including fever, chills, feeling dizzy, wheezing, breathing problems, throat tightness, loss of appetite, diarrhea, constipation, cough, and nerve damage resulting in weakness or numbness in both hand and feet.

Common side effects of belantamab include tiredness, fever, nausea, severe problems in the eyes including blurry vision, dry eyes, vision loss, and damage to the cornea.

3.14 Nuclear transport inhibitor

The nuclear export protein expression in multiple myeloma cells is high. This intracellular nuclear export is responsible for transferring proteins out of the nucleus. Therefore, blocking this action by using a nuclear export inhibitors results in that the proteins build up inside the nucleus of the myeloma cells and consequently the cell dies. In July 2019, selinexor became the first nuclear export inhibitor approved for use in relapsed/refractory multiple myeloma. Clinical trials showed that this modern treatment is efficacious when used alone or in combination with dexamethasone, doxorubicin, bortezomib, or carfilzomib agents to treat multiple myeloma [71]. In addition, it was shown that SINEs also have an added benefit of reducing the progression of bone disease in multiple myeloma patients.

Selinexor may cause various adverse effects that include low platelet counts, low white blood cell counts, diarrhea, nausea, vomiting, not feeling hungry, weight loss, low blood sodium levels, and infections like bronchitis or pneumonia [70].

4. Conclusion

Due to the complications of treatment, myeloma is known to be transformed into a chronic disease. Therefore, focusing on immediate and late complications from the treatment is important to deliver higher survivorship care.

Various reports have demonstrated the importance of MM patients to continue with their daily activities and maintain good physical and mental well-being. Hence, their ability to continue with their daily routine and physical activities during treatment results in fewer side effects and lower fatigue and thus improves quality of life. Accordingly, the mental health and physical health of patient are extremely important during treatment [59].

An increase in prevalence of myeloma survivors has been observed; thus, monitoring and managing early and late complications is essential. Future investigational research is recommended to monitor the treatment-related complications, therefore improving the quantity and quality of life in patients with myeloma.

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