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Review

# Multiple Myeloma Treatment

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**ABSTRACT**

Multiple myeloma (MM) is a cancer that begins in the plasma cells (PC) and progresses to the bone marrow. It is a recurring disease, as no definitive solution can be found despite the drugs and treatments applied. Therefore, correct care is vital for sick individuals. MM is known to be a disease that most commonly affects individuals between the ages of 40 and 60 and rarely occurs in individuals under the age of 40. Exposure to certain chemicals and radiation, weakened immune systems and viruses, are among the factors that cause disease. This review is aimed to explain the drugs and treatments developed for the treatment of MM.

**Keywords:** Multiple myeloma, myeloma, treatment and drugs.

Myeloma is a cancer disease that occurs as a result of abnormal changes in plasma cells, occurs in the bone marrow in the early stages of the disease, and affects the extramedullary region (outer part of the bone marrow) in the later stages. The existence of the first case was detected in 1844. Multiple Myeloma (MM) is a disease that destroys the skeletal structure and causes severe bone pain and bone fracture. As a result of the researchers, it has been announced that the survival time of individuals who are diagnosed and treated with MM is 3 years. Despite the development of new drugs and treatment methods, MM is a disease that cannot be cured completely and recurs within 5 years after treatment.[1-3] Since it is a relapsing disease, care should be taken in the care of individuals with this disease. After examining the bone marrow of the patients at the time of diagnosis of the disease, the presence of monotypic plasma cells was observed in the bone marrow. Monotypic cells are cells that contain cytoplasmic immunoglobulin. There are 5 types of MM. Immunoglobulin G (IgG) and Immunoglobulin A (IgA), which contain heavy chains in their structure and are frequently encountered, constitute 80% of them. Immunoglobulin M (IgM), Immunoglobulin D (IgD), and Immunoglobulin E (IgE), which are rarely encountered, constitute 20%.[4] It has been determined that patients diagnosed with MM are mostly between the ages of 40-60, it is rarely seen in individuals aged 40 and under and individuals over 60 years of age. In the USA, it has been observed that the incidence is gradually increasing and patients with MM are 70 years and older.[5] Studies have shown that weakening of the immune system, diet and diet, environmental factors, genetic factors, and exposure to radiation are among the factors that cause MM.[6]

## PATHOPHYSIOLOGY OF MULTIPLE MYELOMA DISEASE

There is an interaction between the mediators, osteoclasts and osteoblasts that mediate the reactions in the body. While osteoblasts are the immature cell type that is the precursor of the bone cell, osteoclasts are a type of bone cell that destroys

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bone tissue by destroying the bone matrix. After the interaction, osteoclastic activity increases while osteoblastic activity decreases. Following this, osteoblastic activity decreases. Therefore, damage to the bone marrow tissue occurs.[7]

## PATHOGENESIS OF MULTIPLE MYELOMA DISEASE

New treatments and drugs for MM disease have begun to be developed as pathogenesis of the disease has been better understood. It has been determined that there are protein kinases that support the growth of malignant plasma cells, and studies on these protein kinases have begun. Protein kinases cause structural changes by adding phosphate groups to proteins. In this condition, CK2 kinase, which constitutes a protection mechanism for mutated cells, and GSK3 kinase, which has a healing effect for diseases such as cancer and bipolar disorder, has been studied. It has been observed that CK2 kinase plays a role in the regulation of NF-κB and STAT3 signaling pathways and in inhibiting the proliferation of malignant tumor cells that cause cancer.[8] NF-κB and STAT3, a type of transcription factors, are present in all cells. They cause the growth of abnormal plasma cells, leading to the progression of cancer. CK2 inhibition leads to the degradation of these transcription factors and prevents the growth of MM cells. It has been observed that GSK3 has a healing effect on bone deformations caused by MM, which affects the bone development process. In addition, GSK3 takes part in cellular functions and then plays a role against the PI3K enzyme that causes cancer, inhibits the Wnt/β-catenin pathway, and prevents the growth of MM cells. By showing similar characteristics to CK2, they constitute a kind of barrier in signaling pathways to prevent the spread of malignant tumor cells.[9]

## SYMPTOMS OF MULTIPLE MYELOMA DISEASE

Fatigue, constipation, fever, frequent urination, nausea, severe bone pain, broken bones, tingling sensation in hands and feet, decreased physical and cognitive functions are among the most common symptoms of MM disease.[10]

When the bone tissues of a healthy individual and individuals with MM cancer are examined, it is seen that bone lesions occur in the bone of the cancer patient.[11]

## GENETIC FACTORS IN MULTIPLE MYELOMA DISEASE

MM, which is recognized by the anemia, kidney damage and bone destruction observed in the individual, causes point mutations in the breakage regions of the chromosome. There are translocations involving chromosomes 13 and 14, and nearly half of these translocations involve only one of the 5 chromosomal partners. Translocation is known as an abnormality that occurs when the broken part of one chromosome attaches to another chromosome.[12,13] In B cell tumor, it was observed that the translocation, which caused breaks in the double strand of DNA, occurred at the IgH (14q32) locus.[14]

## EVALUATION OF MULTIPLE MYELOMA DISEASE

### Plain radiographs and magnetic resonance imaging (MR)

It is a method for examining bone lesions that are limited to the bone marrow and do not progress to the cortex in great detail (the outer layer of an organ or structure). By reflecting a high level of magnetism, an image of living tissue is obtained.[15]

### Dual energy X-ray absorbtiometry (DEXA)

By measuring the mineral density in the bone structure, it is determined whether it is caused by MM and its effect on the bone. After the application of pamidronate, it was observed that the rate of bone change slowed down. Pamidronate is a drug with a curative effect, given intravenously in case of bone metastasis, bone marrow cancer (Multiple Myeloma), bone pain.[16]

### Chemotherapy and stem cell transplantation

It is a treatment method in which chemical drugs are used to kill the rapidly growing myeloma cells in the bone marrow. The drugs can be used alone or in combination. Of the 200 patients who received this treatment, 87% improved.[17] Stem cell transplantation is a method that is used in all malignancies, especially MM and is applied in patients up to the age of 65. Radiotherapy or chemotherapy treatments are applied to the patient before the transplant. Thanks to this method, MM disease can be treated.[18]

## DIAGNOSIS OF MULTIPLE MYELOMA DISEASE

Plasma cells in the body normally produce antibodies called immunoglobulin to fight infection. Myeloma produces abnormal plasma cells. Therefore, it creates antibodies called paraproteins that have no function. The diagnosis of myeloma involves looking at the presence of these paraproteins.

The International Working Group on Myeloma (IMWG) examined symptoms in the definition of MM. Diagnostic criteria for plasma cell disorders are as follows:

- Asymptomic MM requires the following criteria:

1. Serum monoclonal protein (IgG or IgA) ≥3 g/100 mL and/or clonal bone marrow plasma cells >10%.

- The following criteria are required for MM:

1. Clonal bone marrow plasma cells should be ≥10%.
2. Hypercalcemia: serum calcium should be 11.5 mg/100 mL.
3. Renal failure: serum creatinine should be >1.73 mmol/L.
4. Anemia: An individual with a low hemoglobin value should have a hemoglobin value >2 g/100 mL.[19]

## DRUGS USED IN THE TREATMENT OF MULTIPLE MYELOMA DISEASE

*Thalidomide:* The mechanism of action of thalidomide, which has a good effect at all stages of the disease, is unknown; nonetheless, it was discovered that it prevented the proliferation of myeloma cells in patients who got the drug. In one study, 113 patients were given thalidomide orally at a dose of 200 mg daily for 2 weeks. The dose was increased to 800 mg for asymptomatic MM and Relapsing Myeloma. Thalidomide, in new MM patients, 40 mg was given monthly, on days 1-4, 9-12, and 17-20 of the month, and was repeated monthly. Following the administration of drug therapy, it was observed that a large proportion of patients (58%) responded to treatment either partially or fully. In the remaining 42%, it was observed that there was no improvement. A significant reduction in MM cell growth was found in patients responding to treatment. Although thalidomide has a good effect on treatment, it has been discovered to cause limb differences in infants of mothers exposed to the drug during pregnancy. Thus, Thalidomide is a prohibited drug.[20]

*Lenalidomide and pomalidomide:* The presence of chromosomal deletions and point mutations in MM cell lines (HMCL) is recognized, although there is no alteration in the XG1LenRes and CRBN genes. Following the Lenalidomide and Pomalidomide treatment, it was observed that IRF4 regulates the protein in the down direction while CD147 is moving upwards. CD147 is a protein that prevents false plasma membrane localization through its transmembrane domain. IRF4 is the protein that causes B-cell lymphoma. Accordingly, it can be seen that Lenalidomide and Pomalidomide ameliorate B-cell MM illness by regulating IRF4 and boosting the protein CD147.[21,22]

Lenalidomide and Pomalidomide are drugs with a stronger anti-inflammatory effect than Thalidomide. They are seen to be more effective in inducing the proliferation of T cells, increasing the production of Interleukin-2 (IL-2) and Interferon-y (INF-y). IL-2 is used for cancer or tissue transplant patients as it provides an improvement in T cell response. INF-y's role is to ensure that the reaction in the immune system occurs.[23,24]

*Bortezomib:* Bortezomib inhibits the degradation of the inhibitory kappa B (IKKs) and, accordingly, stabilizes the (NF-κB) complex. Because IκB causes IκBα to dissociate from NF-κB, causing NFκB to migrate to the nucleus. In addition, Bortezomib increases the susceptibility to apoptosis by reducing the adhesion of myeloma plasma cells to stromal cells. Stromal cells are cells found in the connective tissue of cells.[25]

The Immunomodulatory Drugs (IMIDs) (Vincristine, Paclitaxel, Oxaliplatin, Cisplatin): The mechanism of action of IMID group drugs, which are used in the treatment of MM and give the best results among drug types, is still unknown. It has been understood that these drugs used for the treatment of MM have negative effects on the sensory nerve cells of individuals. Therefore, they are the types of drugs that are rejected for use.[26]

## TARGETING PATHWAYS IN MULTIPLE MYELOMA CELLS

*Ras/MEK/MAPK pathways:* IL-6, IGF-1, VEGF, and integrins induce the Ras/MEK/MAPK pathway, thereby inhibiting MM cell growth, increasing survival and drug resistance. IL-6 is both a

pro-inflammatory and anti-inflammatory cytokine that stimulates osteoblast and osteoclast formation. In excess, they increase inflammation and cause cancer. IGF-1 is a growth hormone and causes growth in childhood. An excess of VEGF can cause cancer metastasis. Integrins provide the regulation of the cell cycle and the organization of the cytoskeleton. For this reason, they are important structures in cancer, and signal pathways are needed to work regularly.

*PI3K/AKT pathways:* Perifosine targets AKT. Because the perifosine inhibits the phosphorylation of AKT. Prevention of programmed cell death (apoptosis) has been achieved by generating specific molecules to target this pathway. Therefore, the PI3K/AKT pathway is thought to be a good way to treat human malignancies.

*Status signaling pathways:* It is a signaling pathway in charge of producing cytokines, proteins, etc., which is required for many stromal cell types, including MM.

*Wnt signaling pathways:* Proliferation of stem cells and subsequent continuation of this proliferation occurs with the inability to activate Wnt signals normally. Wnt signaling pathways are activated by silencing the antagonist genes (the gene responsible for inhibition), resulting in a reduction in proliferation of MM cells.[27]

## DISCUSSION AND CONCLUSION

MM, which has no definitive cure, affects the living conditions of the individual. This disease, which causes damage to the bones, causes severe pain and limitation of movement in individuals and is a lifelong condition. Therefore, care should be taken in the care of individuals.

The morphology of plasma cells causing MM has been examined, and it has been observed that they can have different morphologies in many places in the body and around many organelles. Due to the paraproteins of erythrocytes, small or abnormally sized plasma cells are seen in the cytoplasm, around the Golgi apparatus, in a para-shaped structure, single or multinucleated. Considering these morphological differences, it can be concluded that we are faced with a disease that is difficult to treat. For this, many treatment methods and many drugs have been tried to be developed.

Some methods have been used to determine whether the response to treatment is positive in individuals receiving treatment for MM disease and how long it takes to respond. One of these methods, PFS, examines the time between the diagnosis of the disease and death; TTP is a method that monitors the progress of the disease until the death of individuals who have MM, but die for any reason other than this disease. DOR is the method used to follow the individual from the diagnosis of the disease until the next cancer stage. Thanks to these methods, the disease process of individuals can be examined in detail, the necessary treatment method can be determined, and the most accurate conclusions about the disease can be reached by examining the data.

It is known that IL-6 has both inflammatory and anti-inflammatory effects, and thanks to this effect, it can affect osteoblastic or osteoclastic activity depending on the amount it is expressed in the body. In other words, it has a direct effect on the formation of MM cancer. In addition, overexpression of growth hormones such as VEGF and IGF-1 can cause cancer metastasis. Keeping the levels of these and similar factors under control, and the ability of important signaling pathways to function properly are factors that will enable the healing process of the disease to evolve positively.

It is known that the average survival time of an individual with MM cancer is 3 years. After the data reviews, it was determined that the survival time after the discovery of new treatment methods and drugs was more than 10 years as of 2014.

In a study, patients who are treated with stem cell transplantation are followed for 9 years. It has been observed that relapses occur in nearly half of the patients, and these relapses generally manifest themselves within the first 40 months. It is determined that their lifespan after transplantation was 78 months.

Considering the treatment methods and the drugs developed; It has been observed that the recovery period of patients treated with Bortezomib and IMID drugs together is shorter than in patients treated with Bortezomib alone or IMID drugs alone. However, since thalidomide and some drugs have serious handicaps such as damage to sensory nerves, severe pain, loss of function in the limbs or difference during treatment, it is thought that MM treatment using methods such as stem cell transplantation is a more secure method.

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