
# Plasma Cells Gone Awry

*Advances in the Treatment of Multiple Myeloma*

Multiple myeloma is a type of cancer that forms in plasma cells. Plasma cells are a type of white blood cell that make antibodies crucial in identifying and fighting infections in the body. Cancerous plasma cells in multiple myeloma multiply very quickly and accumulate in the bone marrow. Over time, healthy blood cells will be crowded out and the cancerous plasma cells can weaken bone structures, causing increased susceptibility to fractures. As the number of cancerous plasma cells increases, the production of healthy red blood cells, white blood cells and platelets drops, resulting in anaemia, easy bleeding and frequent infections. These cancerous plasma cells can also secrete cancer proteins, also referred to as monoclonal protein which can gradually accumulate throughout the body and cause organ damage, for which the kidneys are most susceptible.

Myeloma typically afflicts those in their 60s and above. However, patients as young as those in their 40s can also be afflicted. Myeloma has a lower incidence among Asians compared to American Blacks who are most at risk, followed by Caucasians. Research has implicated various possible factors in multiple myeloma's etiology, including genetic, occupational or environmental causes; monoclonal gammopathy of undetermined significance; radiation exposure; infections; and chronic inflammation. Some studies have found an increased risk among those individuals with significant exposure to chemicals in agricultural and petrochemical occupations. However, the majority of multiple myeloma cases appear in those with no risk factors. Myeloma incidents are rising mainly because of earlier detection and an aging population. Although most patients first present with bone pain, kidney failure or anaemia, it is not uncommon for asymptomatic patients to be diagnosed when they go for their routine health screening.

## DRUG TREATMENT

Traditionally, conventional chemotherapeutic drugs kill cells indiscriminately, resulting in collateral damage to normal healthy tissues. Myeloma is considered incurable as we are unable to eradicate all the cancer cells in the body. After treatment, the residual cancer cells will regrow and result in another relapse. Barely twenty years ago, the prognosis of a patient diagnosed with multiple myeloma was only about 4-5 years. The only effective way to improve the chance of survival by 1-2 years was with high-dose chemotherapy followed by a stem cell transplantation. This procedure carries definite mortality risks and hence, only younger myeloma patients are able to withstand this intensive therapy. Back then, the disease was regarded as a terminal cancer due to the limitation on life expectancy after a patient is being diagnosed.

Now the drug approach to cancer is more targeted, and for incurable blood cancers like myeloma, the intention is to prolong the remission and delay the onset of relapse with the least amount of side effects. With more novel drugs coming on-stream, there is a big paradigm shift in how some blood cancers are being treated today. Predicated on our improved understanding of the disease biology, the focus now is not hitting the disease hard, but hitting it smart with new drugs in the armamentarium. Although there is still no cure for multiple myeloma, patients are benefiting from the significantly improved treatment options that have emerged in the past decade which improve survival rate, and decrease pain and complications, such that myeloma is now more akin

to a chronic disease (where patients can survive for 10 years or more) than a terminal cancer. Importantly, older patients now have a chance to defy the natural history of multiple myeloma as newer targeted drugs are better tolerated and have better side effect profiles.

## ADVANCES IN MULTIPLE MYELOMA THERAPY

The development of the proteasome inhibitor, bortezomib in the past decade represented a major advancement in multiple myeloma therapy. This was predicated on the discovery of the proteasome, the "garbage bin" of the cell. Disrupting this with a proteasome inhibitor results in excessive accumulation of waste products in the cell which would eventually lead to cell death. Myeloma cells are most susceptible to proteasome inhibition. The success of bortezomib led to the development of the next-generation proteasome inhibitor called carfilzomib which is more potent than bortezomib. This drug was approved by the FDA in 2012 and it plays an important role in salvaging patients when the disease relapses.

Immunomodulatory drugs like thalidomide, lenalidomide and the next-generation pomalidomide have also resulted in significant improvement outcomes for multiple myeloma patients. They are highly effective in stimulating the patient's immune system to fight the myeloma cells. Results from various clinical trials demonstrate that having these 2 classes of drugs in the myeloma armamentarium doubles the survival rate of many patients. Their introduction has tremendously lowered the reliance on conventional chemotherapy to treat the disease.

The latest excitement in the field of myeloma therapeutics is the advent of immunotherapy. This modality harnesses the body's immune system to effect cancer cell killing. Antibodies are substances produced by the immune system to fight off viruses, bacteria and other foreign substances. Myeloma researchers have found ways to produce synthetic antibodies in the laboratory, and these antibodies can help enhance the patient's own immune system response and target myeloma cells. One such monoclonal antibody, daratumumab was initially approved for the treatment of relapsed multiple myeloma in 2015. Due to its impressive effect in eradicating myeloma cells, it was recently approved as the frontline standard of care for multiple myeloma. When daratumumab is combined with a proteasome inhibitor and/or immunomodulatory agent in the frontline, the remission duration achieved can be as long as what a stem cell transplantation can accord.

Cellular immunotherapy is the latest modality to be approved recently in the treatment of myeloma. Chimeric antigen receptor therapy (CAR-T) involves extracting a patient's T cells which are the immune system's "defender cells" responsible for finding and eliminating abnormal cells throughout the body. These T cells are then modified to recognize multiple myeloma cells as dangerous intruders and reintroduced into the patient's body to help fight the cancer. Data from clinical trials have shown spectacular results with the use of CAR-T in patients who have failed all standards of care.

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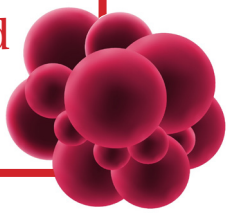

Treatment for multiple myeloma is now always tailored to the specific stage of the disease as well as the patient's age, kidney function, overall health status, and other needs. Often, treatment involves a combination of various novel pharmacologic agents alluded above.

## FUTURE OF MULTIPLE MYELOMA TREATMENT

Over the past 2 decades, our understanding of the biology of multiple myeloma has led to the discovery of highly effective anti-myeloma agents that have revolutionized the way we treat the disease. Elderly patients are no longer precluded from effective therapies, and are able to enjoy a good quality of life even with the diagnosis of multiple myeloma. Work is currently underway to further improve upon the success of these recent drug discoveries such that one day, the cure of multiple myeloma could be a reality. PRIME


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