Microreviews in Cell and Molecular Biology 2021

Multiple Myeloma: Immunotherapy Helping to end an Uncurable Disease

Author: Bret Marckx
Major: Chemical Engineering
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

Key Words:
Multiple myeloma, B cell maturation antigen, CD38, Daratumumab,

Multiple myeloma (MM) is a form of hematologic malignancy that affects the plasma cells and bone marrow in the body. MM is disease with no cure, but one that can be sent into complete remission. Relapsing almost always occurs in patients who achieve remission of MM initially. Traditional cancer treatments are common for MM as well as some specific immunotherapy options, however relapsed MM often becomes refractory and unresponsive to these immunotherapy treatments. New immunotherapy mechanisms such as B cell maturation antigen targeting and anti-CD38 antigens are showing promising results in studies as treatment methods. No single method has clearly shown to be the best way to treat MM and development of these methods and other new ones is ongoing. Treatment of MM is advancing rapidly, with the cure coming ever closer.

Introduction

Multiple myeloma (MM) is a form of hematologic malignancy and is the second most common form of malignant hematologic diseases (Fang & Hou, 2021). MM is a cancer affecting plasma cells in the blood stream and disrupts the proteins and antibodies they produce. The most common protein affected is monoclonal Immunoglobulin (M protein) which causes many of the non-bone related effects of the disease. However, these cells expand in the bone marrow they are produced in and often cause bone damage (Rajkumar & Kyle, 2013). Bone lesions, bone fractures, and bone pain mostly found in the pelvis and lower back are the primary symptoms corresponding to bone damage. Hypercalcemia, anemia, renal failure, and nerve or spinal cord compression are also common symptoms. Myeloma falls into three categories of increasing disease progression: monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and multiple myeloma. MGUS is asymptomatic and pre-malignant and is where all cases of MM develop from. SMM is also an asymptomatic and pre-malignant stage, but more advanced than MGUS that is not always progressed through

from MGUS to becoming MM. Diagnosis requires heightened levels of plasma cells in bone marrow. M protein levels outside of normal levels in urine and the presence of hypercalcemia or anemia can also be contributing factors to diagnosis. This disease is not curable, but remission is achievable. However, most patients will relapse in their lifetime (Fang & Hou, 2021).

Recent Progress

Treatment of MM is progressing rapidly towards increased remission rates and finding a permanent cure (Rajkumar & Kyle, 2013). The primary beneficiary of advancements in Multiple Myeloma (MM) treatment is immunotherapy. Earlier in the century, several drugs have emerged as effective treatment options such as bortezomib, lenalidomide, and thalidomide (Rajkumar & Kyle, 2013). These treatments commonly work for newly diagnosed MM, but relapsed MM can often be refractory to several of these treatments (Lokhorst et. al, 2015). The lack of response to treatment of relapsed MM has spurred research into more targeted therapies to directly attack MM cancer cells. When MM relapses, it can become "refractory to both proteasome inhibitors and immunomodulatory agents" which provides bad prognosis to patients (Lockhorst et al., 2015).

Several methods of this have been easy to pursue as MM plasma cells are easily differentiated from non-cancerous plasma cells. One such target is B-cell maturation antigen (BCMA) (Fang & Hou, 2013). BCMA is "type III transmembrane glycoprotein in the tumor necrosis factor receptors (TNFR) superfamily" (Fang & Hou, 2021). BCMA is a highly expressed antigen on MM cells that is not detectable on non-cancerous human cells. MM plasma cells require high levels of BCMA for survival. The heightened levels of BCMA are one way to differentiate MM B cells from healthy B cells. It is not known or expected that BCMA is required for non-malignant B cell homeostasis. The heightened protein levels which are necessary for survival of the cancer cells allows for selective and targeted immunotherapy treatment of the MM cells. Targeted immunotherapy devices include "BCMA-targeted vaccines, anti-BCMA antibodies and anti-BCMA CAR cells" (Fang & Hou, 2021). Vaccines have had mixed responses and research lines have stalled in some areas. Anti-BCMA antibodies have been shown to be successful, but antibody methods require additional treatments of other varieties. CAR T-cell treatments have advanced significantly recently and are looking very promising in treating MM and leading to remission. Phase one and two trials are underway for many BCMA CAR T-cell treatments (Fang & Hou, 2021).

BCMA vaccines are spit into two types: "BCMA-mRNA-loaded dendritic cell (DC) and BCMA-peptide specific cytotoxic T-cell (CTL) vaccines" (Fang & Hou, 2021). mRNA loaded DC vaccine inject the body with dendritic cells, a type of killer immune cell, that have been preloaded with mRNA specific to BCMA. The DC then can target MM cells that are overexpressing BCMA. BCMA-peptide specific CTL vaccines introduce to the body a cytotoxic T-cells, another type of killer immune cell, that have been trained to target specific peptides of BCMA and kill the cancer cells that are over expressing them.

Anti-BCMA antibodies treat cancer by attaching to the BCMA on cancer cells. These antibodies are attached to on their other end to a toxin. This toxin then causes cytotoxic behavior in the MM cells (Fang & Hou, 2021). The toxins attached to the anti-bodies can be toxic drugs or bacterial toxins. Another for of the antibody treatment is to produce bispecific antibodies. Bispecific antibodies attach to the BCMA on a MM cancer cell and attach to T-cells on the other

end allowing the T-cell to attack and kill the cancerous cell.

The final form of immunotherapy associated with BCMA involves the use CAR T-cells (Fang & Hou, 2021). CAR, or chimeric antigen receptors, are placed on T cells withdrawn from the patient. CARs are synthetic antigens which do not occur naturally but allow the specific targeting of cancer cells expressing BCMA by bodies immune system. CAR T cells are specifically engineered to target MM cells within the body by using the antigen placed on them to specifically attach the BCMA on cancer cells and stimulate the of the cancer cell by the T cell. CAR T cell therapy achieved mixed results in clinical trials. While the therapy is effective at eliminating MM cells, it does pose some toxicity to the body and neurologic toxicity occurred in many subjects (Fang & Hou, 2021). Other forms of toxicity also occurred, while almost have of patients achieved remission in one study.

Another common attribute of MM plasma cells is the over expression of CD38, "a 45-kD, type II transmembrane glycoprotein that associates with cell-surface receptors in lipid rafts, regulates cytoplasmic Ca^{2+} flux, and mediates signal transduction in lymphoid and myeloid cells" (Lokhorst et al., 2015). CD38 is almost always present on MM cells but is barley present on non-cancerous cells. The primary drug associated with this method is Daratumumab, which is an antibody that binds to CD38 and was studied by Lokhorst et al.

Daratumumab was studied for patients with relapsed multiple myeloma (RMM) by Lockhorst et al. These patients had RMM that was refractory to the common treatments of bortezomib and lenalidomide for most cases. These patients were given varying dosages of Daratumumab. Part one of the Lockhorst et al. study included dosing patients with increasing dosage from .005 mg Daratumumab per kg of body weight up to twenty-four mg per kg. Part two focused on separate schedules for both eight and sixteen mg per kg (Lokhorst, 2015). The primary focus of this study was to determine the safety of Daratumumab with a secondary focus on determining the efficacy of the drug as a treatment for RMM.

Pre-dosing of Daratumumab was done to prevent infusion reactions on full dosage. The eight mg per kg dosages were administered once a week for eight weeks and then every other week for 16 weeks. The sixteen mg per kg dosage schedules included a three week wash out period to collect pharmacokinetic data followed by seven weeks of infusion and then fourteen weeks of biweekly infusions. Both dosages then received a dose once a month until the disease progressed, or toxic events occurred at an unmanageable level (Lockhorst et al. 2015).

The result of the study was that Daratumumab has very manageable side effects for nearly all patients, and the safety was overall determined to be acceptable (Lokhorst et al., 2015). No patient had side effects so severe due to the infusions that treatment was stopped. Side effects were lesser across the board for the patients receiving the sixteen mg per kg as opposed to the patients receiving the eight mg per kg dosage. It was also shown that approximately one third of patients had a reaction to the drug that helped limit or treat their RMM at sixteen mg per kg and for the dosage increase study. Those that had a disease reaction to Daratumumab had plasma levels in their bone marrow decline or hold steady. When Daratumumab works, it helps significantly delay disease progression and can often help work RMM back towards remission.

Daratumumab when mixed with other drugs has shown extremely positive results. When combined with lenalidomide and dexamethasone, patients showed very high response rates that improved over time (Lokhorst et al., 2015). The method of

attacking the MM cells through CD38 has shown to kill cells that become resistant to other treatments which is why combining different methods can greatly improve reaction rates. Cells that become resistant to one method of treatment then are attacked by another method which prevents them from populating the body. The combination mechanism treatment is showing promising results at pushing MM and RMM towards remission.

Discussion

The efficacy of Daratumumab in RMM is still too low to be considered as a permanent part of the cure for multiple myeloma. However, the result of this study is still very positive as Daratumumab was shown to be a safe option for patients whose MM has become refractory to many other treatments. Daratumumab can be an option for patients with RMM that has been difficult to treat as its mechanisms of treatment are different than other treatments. Daratumumab does not work for everyone, but it is still an option that can be tried when many other options have been exhausted.

While Daratumumab may not be the drug of the future for multiple myeloma treatment, the anti-CD38 mechanism is a promising method for a cure to MM. Other the traditional treatments, including the use of lenalidomide and bortezomib, have been shown to become refractory to MM, but CD38 treatments have not shown such, possibly due to the primary testing being on patients with RMM as opposed to initial treatment of newly diagnosed MM. Further study and development of CD38 treatment mechanisms is very important to pursue as current results show that anti-CD38 antibodies can be effective at treating RMM that is otherwise untreatable. These mechanisms could become part of preliminary treatment for newly diagnosed MM.

Other methods such as BCMA targeting treatments have progressed dramatically in the years since the Lokhorst et al. study and may prove more successful at treating and preventing disease progression of MM. Multiple myeloma is a complex disease with no single, clear answer for treatment at this time. The more options patients have for treating, the better off they will be. Expanding the number of successful mechanisms of treatment means that more drug combinations will be available for doctors to be able to customize treatment for patients and improve outlook, survival, and remission rates. MM may never have a cure, having a set of drugs that can send any patients disease into remission is a goal of researchers, nonetheless. Advanced immunotherapy options are developing at a rapid pace for multiple myeloma, and currently appear to be the key to coming as close as possible to a cure for a disease that for the time being appears uncurable.

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