CD38/CD3 targeting shows a bright future for multiple myeloma immunotherapy

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There are a variety of diseases and malignancies that stem from blood cells. One of the most prevalent of these malignancies is Multiple Myeloma (MM) which originates from plasma cells. Over the past 20 years, patients have seen significant improvements in the treatment of MM but there has still yet to be a cure found. MM patient survival, measured by the median overall survival (MOS), has increased from 2 years to 5-6 years following the introduction of immunomodulatory drugs and proteasome inhibitors which have all been significant advancements in the field of MM treatment. Since 2012, multiple different treatments and therapies have been introduced such as new drugs, and CAR-T cell therapies which helps the immune system target MM cells. As of now, CD38/CD3 proteins related to MM, have been heavily targeted and researched and provide the answer to finally bridging the gap to find a potential cure for MM (1,2,3,4).

In Multiple Myeloma immunotherapy, targeting CD38 is widely sought after because CD38 has such a high expression and multiple mechanisms of action. Plasma cells generally express CD38 but myeloma cells express it highly. CD38 is an extracellular enzyme that works as a metabolic sensor by recognizing the increased concentrations of NAD+ in bone marrow microenvironments and it acts as a catalyst in the cleavage of NAD+ into cyclic adenosine diphosphate ribose (cADPR). Furthermore, it can also act as a catalyst in the production of NAADP by cation exchange catalyzing NADP. It also acts as a second messenger which induces the release of intracellular Ca2+ ions and it increases in synthesis of Adenosine in the bone marrow microenvironment. As CD38 participates in myeloma cell growth and enables immune escape, CD38 is an attractive target for myeloma therapy (1,2).

CD38 is a novel multifunctional glycoprotein involved in interacting with CD31 as an adhesion molecule. CD38 also can play a role as a receptor for certain ligands. It is an ectoenzyme that catalyzes the extracellular conversion of NAD+ to the immunosuppressive factor adenosine making it a metabolic sensor. CD38 is involved in the alternative axis of extracellular production of the immunosuppressive factor adenosine through working with CD73 and CD203a which is mediated by CD39. Several anti-CD38 monoclonal antibodies have been developed for targeting multiple myeloma because CD38 is highly expressed in multiple myeloma, although it is widely expressed in the bone marrow microenvironment too. There are multiple factors that impact the efficacy of anti-CD38 monoclonal antibodies such as the expression level of CD38 on the surface of multiple myeloma and the immune-microenvironment cells. Several drugs such as lenalidomide, panobinostat, the all-trans retinoic acid, and the DNA methyltransferase inhibitors have been reported to increase the expression of CD38 which means CD38 could possibly modulate. This increases the expression on multiple myeloma cells and is the step before potentiating the clinical efficacy of the anti-CD38 monoclonal antibodies. CD38 has been vastly used to design clinical trials with the combination of anti-CD38 monoclonal antibodies and the drugs mentioned previously (1,2).

Daratumumab, an anti-cancer monoclonal antibody medication, is the first one of its kind that targets CD38 and has shown good therapeutic efficacy for multiple myeloma. It has shown potential both with normal standard-of-care regimens and also when used by itself. Unfortunately, as a result of FcγR-dependent decreasing CD38 expression on MM cells, with inhibition of complement-dependent cytotoxicity (CDC), antibody-dependent cell mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) mechanisms, a number of patients experience relapses (1,2,4).

Bispecific T-cell engagers (BiTEs) help to recognize specific antigens that are being displayed on the surface of tumour cells. They also simultaneously activate T cell function by targeting CD3E&CD3D or CD3E&CD3G molecules on T cells. BiTEs are bispecific antibodies which activate T cells and exert T cell-mediated cytotoxicity which kill tumour cells directly (1).

As of right now, three different BiTEs are being used to target CD38/CD3 in an attempt to treat MM but all of them are still in the early stages of clinical trials. However, recently, AMG424, an anti-CD38 bispecific antibody was used in experiments and there is a high possibility that MM cells were eliminated as a result of the antibody through the promotion of T-cell cytotoxicity on cells in the immune system (2).

Based on BiTEs research and designs, scientists have begun to develop an innovative CD38/CD3 antibody to try and counter MM. This antibody is known as the Bi38-3 and it recognizes only CD38 on MM cells and uses that information to receive a signal and bind to CD3 on T cells in the immune system. Fortunately, it has been shown that the antibody only triggers T-cell-mediated killing of MM cells with highly expressed CD38 with very minimal to no side effects in hematopoietic progenitors, B, T or NK cells which these cells can express intermediate levels of CD38. MM cell death induced by Bi38-3 in very low concentrations (0.1 ng/ml) does not affect Foxp3+ regulatory T cells. Overall, it has shown promising results for the future of MM treatment (2).

There was a study conducted that shows that Bi38-3 may be one of the best options for targeting CD38/CD3 compared to other antibodies. In MM cells that are resistant to standard treatments, it has been found that Bi38-3 can efficiently trigger the killing of MM cells to fight against the disease. Following daratumumab therapy, Bi38-3 is also expected to help kill MM cells in relapsed patients because it is able to recognize specific epitopes on CD38 antibodies that lack the Fc Region. Further investigations are still needed regarding Bi38-3 applications in clinical trials for MM patients. In conclusion, further immunotherapy research for MM will produce a successful treatment for curing MM patients (2).

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