A New Treatment Strategy for Multiple Myeloma with Monoclonal Antibodies

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Abstract

The approval of the first two monoclonal antibodies in the treatment of patients with relapsed and refractory multiple myeloma was a watershed moment for the multiple myeloma community in 2015. Despite early setbacks, monoclonal antibodies targeting CD38 (daratumumab) and signalling lymphocytic activation molecule F7 (SLAMF7) (elotuzumab) for patients with multiple myeloma became available in the same year for patients with multiple myeloma. Phase 3 clinical trials of combination treatments containing daratumumab or elotuzumab, in particular, have shown efficacy as well as a low safety profile. These monoclonal antibodies for multiple myeloma can kill target cells through antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, antibody-dependent phagocytosis, and direct signalling cascade blocking. Furthermore, their immunomodulatory activities may inhibit the immunosuppressive bone marrow microenvironment while also restoring immune effector cell activity. We focus on monoclonal antibodies that have shown clinical efficacy or have potential preclinical anti-multiple myeloma actions that warrant further clinical development in our study. We review the mechanisms underlying these monoclonal antibodies' anti-myeloma activities *in vitro* and *in vivo*, as well as pertinent preclinical and clinical findings. Monoclonal antibody-based immunotherapies have already changed the therapy landscape for multiple myeloma and will continue to do so.

Keywords: Multiple myeloma • Monoclonal antibody • Immunomodulatory • Bone marrow • Immunotherapy

Introduction

Multiple myeloma is the second most prevalent hematologic cancer, defined by the growth of malignant plasma cells in the bone marrow and an excess of immunoglobulin synthesis [1,2]. The development of novel therapeutic agents such as the proteasome inhibitors bortezomib [3], carfilzomib [4,5], and ixazomib [6] or immunomodulatory drugs (IMiDs) such as thalidomide [7], lenalidomide [8,], and pomalidomide [9,10] has improved the clinical outcome of patients with multiple myeloma in recent decades. In newly diagnosed patients, the response rate and extent, progression-free survival, and overall survival have all increased dramatically since the introduction of these innovative medicines into myeloma therapy methods. Due to its characteristic pattern of remission and return, it remains a chronic and incurable disease in the majority of instances. Patients with refractory illness or who relapse following treatment with proteasome inhibitors and IMiDs have a very bad prognosis. As a result, alternative methods aimed at diverse mechanisms are urgently needed to overcome drug resistance and reduce disease relapse. Multiple myeloma's origin and evolution have been connected to distinct immune system deficiencies as our understanding of the disease's biology have improved. Malignant plasma cells have higher levels of programmed cell death ligand 1 (PD-L1) and lower levels of tumour antigens and Human Leukocyte Antigen (HLA) molecules, which have been associated with deficiencies in dendritic cell antigen-presenting capacity and immunological tolerance, respectively. In addition, the bone marrow microenvironment in multiple myeloma has been demonstrated to be immunosuppressive, offering a haven for malignant plasma cells to proliferate, migrate, survive, and acquire drug resistance. Secreted inflammatory cytokines have been shown to promote the proliferation of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs), Tumour-Associated Macrophages (TAMs), and regulatory T-cells in previous studies (Treg). Bone marrow stromal cells, Osteoclasts (OCs), and plasmacytoid Dendritic Cells (pDC), as well as cytokines such as interleukin-6 (IL-6), Macrophage Colony-Stimulating Factor (M-CSF), interleukin-10 (IL-10), tumour necrosis factor-beta, C-C Motif Chemokine Ligand 2 (CCL2), and vascular endothelial growth factor (VE These findings imply that an effective anti-myeloma treatment will need not only targeting the malignant plasma cell but also restoring the anti-tumour responses of immune effector cells by disrupting inhibitory signals on effector cells and blocking tumour evasion. When compared to targeted small compounds, monoclonal antibody-based treatments that provide additional effector cell-mediated tumour killing mechanisms are effective cancer therapy options. Monoclonal antibodies can kill cancer cells by targeting specific surface antigens through a variety of effector-dependent and effector-independent ways. Until now, therapeutic monoclonal antibodies based on IgG1 have been engineered to cause effector-mediated tumour cell lysis, such as Antibody-Dependent Cellular Cytotoxicity (ADCC), Complement-Dependent Cytotoxicity (CDC), and/or Antibody-Dependent Phagocytosis (ADPC). Therapeutic antibodies, which are dependent on target antigens, can also hinder cell development, trigger apoptosis, or deliver a medication, radiation, or cytotoxic substance by blocking receptors. In addition, the Fc region of antibodies is vital in facilitating the death of cancer cells by activating particular immune cells (NK cells or cytotoxic T cells). The development of the anti-CD20 monoclonal antibody rituximab for the treatment of haematological malignancies was a watershed moment that opened up new avenues for targeted cancer immunotherapies. Because of the effectiveness of rituximab in treating B-cell lymphomas, researchers have been looking for new monoclonal antibodies to treat myeloma. Because only a tiny number of myeloma patients express CD20, rituximab is ineffective in most cases. In late 2015, the Food and Drug Administration (FDA) approved two monoclonal antibodies targeting CD38 (daratumumab) and SLAMF7 (elotuzumab) to treat patients with relapsed and refractory multiple myeloma after demonstrating promising preclinical and clinical activities. CD38 is a 46-kDa type II transmembrane glycoprotein with a short N-terminal cytoplasmic tail (20 aa) and a large extracellular domain (256 aa) found on the surface of immune system cells. When lymphocytes are activated, the intensity of CD38 expression increases, and it is detected in the majority of hematopoietic linage cells. It's found on a lot of lymphoid and myeloid cells, although it's not present in most mature resting lymphocytes. It promotes the synthesis of secondary messengers that influence Ca2+ mobilisation. The regulation of calcium homeostasis in CD38-expressing lymphocytes has been connected to CD38's biological activity. Furthermore, CD38 serves many but distinct biological functions as a bifunctional enzyme that synthesises and hydrolyzes cyclic ADP-ribose as well as a signal-transducing surface receptor. CD38-/- mice are healthy and free of histological or pathological defects. Nicotinamide adenine dinucleotide (NAD)+, the substrate for its ecto-enzyme activity (ADP-ribosyl cyclase), and CD31/PECAM are natural ligands for CD38. In lymphocytes, the binding of CD31/PECAM and CD38 causes tyrosine phosphorylation and downstream signalling events that control proliferation and cytokine release. Previous research on CD38 and multiple myeloma have demonstrated that this glycoprotein is expressed abundantly and uniformly in terminally differentiated normal and malignant plasma cells. Due to its high expression in a number of haematological malignancies, such as multiple myeloma, B- and T-Acute Lymphoblastic Leukaemia (ALL), Non-Hodgkin lymphoma (NHL), Acute myeloid leukaemia (AML), and Chronic Lymphocytic Leukemia (CLL), a role for CD38 in the pathophysiology has been proposed (CLL). Due to its participation in the generation of immunosuppressive adenosine, a recent study revealed that CD38 enzymatic activity may be linked to immunosuppression in patients with multiple myeloma (ADO).

Daratumumab, a human IgG1-kappa monoclonal antibody, was the first naked CD38 monoclonal antibody to be further developed for clinical application after preclinical investigations with cell lines and animal models revealed potential anti-myeloma effectiveness. Daratumumab (previously HumaxCD38) has been shown in preclinical tests to kill CD38-expressing lymphoma and myeloma cells by CDC, ADCC, ADCP, and induction of apoptosis after Fc receptor-mediated crosslinking with anti-human IgG1 secondary antibody. The mechanism of CDC cytotoxicity generated by daratumumab was not seen in other CD38-expressing cells such as human NK cells, B and T cells, activated T cells, or monocytes. When compared to malignant plasma cells from multiple myeloma patients, CD38 expression on the cell membrane of these cells is comparatively modest. Increased expression of complement regulating proteins on the surface membrane of these cells or the requirement for a certain threshold amount of antigen expression to activate CDC is two possible explanations for this therapeutic indicator. Daratumumab-mediated ADCC was observed in these cells as well as primary tumour cells, in contrast to CDC. Another study found that pretreatment of mononuclear effector cells taken from healthy peripheral blood donors with lenalidomide dramatically increased ADCC, which was linked to lenalidomide activation of NK effector cells. Daratumumab also showed substantial anticancer activity in immune-deficient mice with CD38-expressing xenografts, suggesting that daratumumab may mediate non-immune mediated anti-tumour effects in vivo. Daratumumab treatment rapidly depleted CD38 high-expressing immunosuppressive regulatory T cells (Treg) and B cells (Breg), as well as myeloid-derived suppressor cells, according to a recent correlative study using flow cytometry on bone marrow and peripheral blood samples from clinical trial participants (MDSC). Immune effector cells such as helper and cytotoxic T cells, on the other hand, increased in number. CD38 levels vary significantly among hematopoietic lineage cell subpopulations. When compared to normal T, B, NK, and monocytes, it is discovered to be expressed at much higher levels in Treg, Breg, and MDSCs. Daratumumab decreases these major immune inhibitory cellular components immediately, alleviating their suppressive immunological function and enhancing effector cell-induced tumour cell lysis, according to this study. Daratumumab monotherapy was given to strongly pretreated patients with relapsed or refractory multiple myeloma in phase 1-2 investigation (with a median of 5.5 lines of prior therapy, 75 percent refractory to lenalidomide and bortezomib). In the dose-escalation phase, 32 individuals were enrolled. Daratumumab was given at doses ranging from 0.005 to 24 mg/kg once a week for eight weeks. The maximum dose that could be tolerated was not attained. Daratumumab was given to 72 individuals in the expansion phase at doses of 8 mg/kg or 16 mg/kg. Patients who received 16 mg/kg of daratumumab had a higher overall response rate (36%) and a longer median progression-free survival (5.6 *vs*. 2.4 months) than those who got 8 mg/kg. The most common reported side effects in the dose-expansion group were infusion-related responses, which occurred in 71% of patients and were predominantly grade 1 or 2. Neutropenia was the most common hematologic side event, occurring in 12 percent of patients in the 16 mg/kg group. The results of this tiny clinical study showed that monotherapy with this medication had significant activity in patients who had no other treatment alternatives, leading to FDA approval in 2015. Daratumumab at 16 mg/kg was given to 106 individuals with multiple myeloma refractory to proteasome inhibitors and IMiDs (with a median of 5 lines of prior treatment) in the phase 2 SIRIUS investigation. Overall, 29.2 percent of people responded. The median progression-free survival was 3.7 months and the time to response was 1.0 month. Overall survival at 12 months was 64.8 percent, and median overall survival was 17.5 months. Infusion-related events were reported in 42% of patients, with the majority of these being grade 1 or 2. Anaemia (24 percent), thrombocytopenia (19 percent), and neutropenia (14 percent) were the most common grade 3 or 4 side events (12 percent). The findings of two phase 3 trials on combination studies have been released. 498 individuals with relapsed or refractory multiple myeloma (one prior line of therapy) were treated with bortezomib plus dexamethasone with or without daratumumab in the CASTOR study. Daratumumab's addition to the treatment regimen enhanced the overall response rate (82.9 percent *vs*. 63.2 percent, p 0.001), 12-month progression-free survival (60.7 percent *vs*. 26.9%), and median progression-free survival (not reached *vs*. 7.2 months, p 0.001). Thrombocytopenia (45.3%), anaemia (14.4%), and neutropenia (14.4%) were the most prevalent grade 3 or 4 adverse events recorded in the daratumumab group (12.8 percent). Infusion-related events were reported in 45.3 percent of daratumumab individuals.

Conclusion

Monoclonal antibodies that target specific multiple myeloma antigens are a significant step forward in the development of successful immunotherapies for patients with multiple myeloma. Monoclonal antibodies can produce immunomodulatory effects on immune cells in the bone marrow microenvironment by decreasing the function and number of immunosuppressive cells and restoring the tumour-killing activities of immune effector cells, in addition to various mechanisms mediated *via* FcR-expressing effector cells (ADCC, CDC, or ADCP). Such unique immunomodulatory effects may lead to deeper clinical responses and greater efficacy, as seen in recent large phase 3 clinical trials with daratumumab. Previous clinical trials have shown that monoclonal antibodies are an effective treatment option for patients with relapsed and refractory multiple myeloma who have been highly pretreated. These antibodies will dramatically enhance the prognosis when used alone or in combination with other anti-myeloma medicines, immune checkpoint inhibition, and vaccination techniques. Monoclonal antibodies are also good partners to combine with various anti-myeloma treatments in the search for better and more durable responses in patients with all stages of the disease, particularly in early disease when the immune cells are still functional. Monoclonal antibodies that have already been licenced for the treatment of relapsed and refractory myeloma are being thoroughly explored for their potential function as frontline therapies. Studies are currently underway and will be conducted in the future to determine which combinations are most effective at various stages of the disease. We should expect a revolution of the therapy landscape and an improvement in patient outcomes as novel monoclonal antibodies continue to be developed at a rapid pace.

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