Monoclonal Antibodies in Multiple Myeloma Come of Age

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Multiple myeloma is a cancer of plasma cells that has an estimated incidence of 26,850 new patients in 2015 in the United States. In the past few years, dramatic progress has been made in the treatment of this disease. New classes of drugs, including proteasome inhibitors (e.g., bortezomib and carfilzomib) and immunomodulatory agents (e.g., lenalidomide and pomalidomide), have improved response rates and survival significantly, and it now appears that immunotherapy is likely to lead to even greater advances.

Results regarding the use of daratumumab, an antibody directed against CD38, in patients with relapsed, refractory multiple myeloma are now reported in the *Journal.* Earlier this year, a phase 3 trial that targeted signaling lymphocytic activation molecule F7 (SLAMF7) with a monoclonal antibody, elotuzumab, showed encouraging results. The latest data provide convincing evidence that targeting CD38 is very effective in the treatment of advanced multiple myeloma. We may finally be at the threshold of having several monoclonal antibody–based treatments approved for the treatment of myeloma.

Daratumumab is a human IgG1 antibody that targets CD38, a 46-kD type II transmembrane glycoprotein that is abundantly expressed on malignant plasma cells. This antibody was granted a breakthrough-therapy designation by the Food and Drug Administration for patients who had received three prior lines of therapy including an immunomodulatory agent and a proteasome inhibitor. Patients who have disease that is refractory to these agents have a particularly poor prognosis. In such patients, the median overall survival is 9 months and the median event-free survival is 5 months. Moreover, myeloma, like other cancers, is genetically heterogeneous, with clones and subclones evolving over time and under the influence of treatment. The efficacy of monoclonal antibodies in late stages of disease is an important advance. Since these monoclonal antibodies are directed toward cell-surface proteins that are not usually subject to genetic variability, they are likely to be unaffected by the genetic risk of the underlying tumor.

Monoclonal antibodies have been engineered to improve efficacy by augmenting their ability to fix complement or mediate cell killing or by conjugating them with a drug, toxin, or radioisotope. In the context of multiple myeloma, antibodies directed against interleukin-6, B-cell activating factor, CD138, dickkopf 1 (DKK1), receptor activator of nuclear factor-κB ligand (RANKL), and more recently, SLAMF7 are among those in clinical development. However, none of these antibodies have shown activity as a single agent in patients with myeloma.

By contrast, daratumumab has shown impressive single-agent activity in a very heavily pretreated patient population. In this phase 1–2 study, patients had received a median of four previous lines of treatment, and 79% of the patients had disease that was refractory to their most recent therapy, including proteasome inhibitors and immunomodulators. The majority of patients (76%) had also undergone autologous stem-cell transplantation. In the cohort that was treated with daratumumab at a dose of 16 mg per kilogram of body weight, the overall response rate was 36%, including two patients with a complete response and two with a very good partial response; 65% of the patients with a
The response did not have disease progression at 12 months. The main side effect of the antibody was infusion-related reactions, typically at the time of the first infusion.

The single-agent activity of daratumumab, including complete responses, in this patient population is surprising and very encouraging. These results are probably due to its pleiotropic mechanisms of action against myeloma (Fig. 1).

Immune-based approaches in the treatment of myeloma are currently being actively pursued. These have included designer-specific cellular
therapies such as chimeric antigen receptor T cells, bone marrow–infiltrating lymphocytes, and dendritic cell–fusion vaccines, to name a few. The introduction of monoclonal antibodies into the arsenal against myeloma is game-changing in multiple myeloma treatment. These agents have the advantage of an immune-based approach without the need for patient-specific cell manipulation. Their limited toxicity allows for easy combining with existing therapies. Already, daratumumab is being combined with immunomodulators and proteasome inhibitors in clinical trials across the spectrum of plasma-cell disorders. Another agent, SAR650984, a humanized IgG1 monoclonal antibody, also targets CD38 and has shown clinical activity as monotherapy and in combination therapy in patients with myeloma.

Even with this enthusiasm, unanswered questions remain. How do tumors escape the effects of daratumumab? Can daratumumab, like rituximab in the treatment of lymphoma, be active in many phases of treatment, such as in induction, consolidation, and maintenance therapies? Can daratumumab resistance be predicted? As we begin to tackle the complexity of these questions, it is reassuring to know that we have yet one more treatment option that will contribute in an important way to improvement in outcomes in patients with myeloma.

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