

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Advances in the Development of Vaccines and Other Immunotherapies for Multiple Myeloma



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H&O What types of immune-based therapies are in development for multiple myeloma?

DA Immunotherapy is an important area in multiple myeloma, and this field encompasses several types of treatment. Antibody therapy has become part of the standard of care. Antibody therapies approved by the US Food and Drug Administration (FDA) include elotuzumab (Empliciti, Bristol-Myers Squibb) and daratumumab (Darzalex, Janssen). Data clearly show that targeting of surface proteins is associated with significant response rates. These response rates are often augmented when antibody therapies are used in conjunction with other therapies. For example, the combinations of daratumumab plus an immunomodulatory imide drug (IMiD) or a proteasome inhibitor have shown substantial activity in early stages of relapsed disease. These combinations can lead to deep remissions, a significant time to progression, and, in some patients, a negative level of minimal residual disease (MRD). Among patients with later-stage disease, responses are still evident, but shorter. This area is under investigation. There is interest in understanding the mechanism of action, including how much is a direct cytotoxic effect related to the binding of the antibody, and how much relates to recruitment of other immune effector cells.

Another exciting area is cell therapy, particularly engineering of T cells. The FDA has approved chimeric antigen receptor (CAR) T-cell therapies targeting CD19 for the treatment of certain types of lymphoma and acute

lymphoblastic leukemia. CAR T-cell therapies have shown strong activity in these settings. In multiple myeloma, studies are exploring CAR T-cell agents that target the B-cell maturation antigen (BCMA), as well as other

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antigens. BCMA is commonly expressed on plasma cells, both malignant and nonmalignant. It is an encouraging target because it is differentially expressed on plasma cells. Several companies are developing CAR T-cell therapies. In a recent study published in the *New England Journal of Medicine* of patients with advanced multiple myeloma, a therapy known as bb2121 was associated with very high response rates, and many of the patients achieved negative minimal residual disease status. Importantly, the time to disease progression was nearly a year. The median number of treatment cycles was 7 or 8. The study reported deep responses—particularly in patients with very advanced disease—and a median progression-free survival of nearly a year. Although these responses were encouraging to see

in patients with advanced disease, their long-term durability remains uncertain. A significant number of patients appear to relapse with the current strategy. The primary modes of resistance are thought to be antigen escape owing to the emergence of antigen-negative variants, a lack of persistence of the CAR owing to immunogenicity, and the reestablishment of T-cell tolerance by the tumor microenvironment.

There is also the question of when to administer a CAR T-cell therapy. The initial studies often enrolled patients with fairly late-stage disease. Some of the newer trials, however, are administering CAR T-cell therapy earlier in the disease course and focusing on patients with higher-risk disease. Durable responses may be easier to achieve in patients with less-advanced disease. However, it is not yet known whether CAR T-cell expansion will be effective in low-volume disease.

Bispecific T-cell engager (BiTE) antibodies are another type of immunotherapy under investigation. These antibodies co-localize T cells with myeloma cells via binding to 2 areas: a myeloma protein, such as BCMA, and a T cell through CD3. Initial studies are promising, and suggest that it is possible to generate responses in multiple myeloma. However, the follow-up for these studies is still relatively short.

Antibody drug conjugates are antibodies linked to a cytotoxic agent. These drugs have been associated with some interesting responses in multiple myeloma. Researchers are still evaluating the durability of the responses, as well as the associated toxicities.

Vaccines are another promising area of research.

H&O What has your research of vaccines shown?

DA The process of engineering T cells involves removing cells from a patient, activating them, and then administering them back to the patient, almost like a drug. In contrast, vaccines try to stimulate a T-cell response inside the patient, *in vivo*. There have been several different strategies. The approach developed by our group has been to create hybridomas that fuse patient-derived whole tumor cells with the patient's own dendritic cells. The hybridoma expresses a broad array of tumor antigens, including neoantigens from the patient's tumor, and it may be able to capture the different subclones of that tumor, putting them in proximity to the costimulatory signals from the dendritic cell. In a phase 2 study of patients with multiple myeloma who had undergone transplant, administration of a vaccine significantly increased the rate of patients who ultimately achieved a complete remission. The results of this study led to a large randomized trial we are conducting in collaboration with the Blood and Marrow Transplant Clinical

Trials Network (BMT CTN) cooperative group. This randomized trial will evaluate a vaccine administered in conjunction with lenalidomide (Revlimid, Celgene) maintenance. A control arm will consist of lenalido-

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mide maintenance alone. The study involves 17 sites nationwide. We taught each participating center how to manufacture the vaccine in an open-source format. There is central review of site production. The study has already enrolled more than 200 patients. The primary endpoint of the study is to assess the number of patients in complete remission at 1 year. Secondary endpoints include a detailed assessment of immunologic response, as well as measurement of progression-free survival.

H&O What are the typical components of vaccines for multiple myeloma?

DA In multiple myeloma, the goal of a vaccine is to induce a response by targeting a tumor cell, typically through the recognition of an individual antigen or multiple ones. Examples of shared antigens include NY-ESO and WT1. The term “neoantigen” refers to a foreign antigen arising from a mutational event that is unique to a patient. A potential advantage to neoantigens is that they may be associated with a more robust response because they are foreign. Some, however, may not be recognized by the T-cell repertoire. Another strategy is to target the entire cell. The idea behind hybridomas created from whole patient tumors and dendritic cells is to let the patient's immune system determine which targets are most meaningful and stimulatory.

For a vaccine to be effective, antigen presentation must occur in the context of co-stimulation, which is required to activate T-cell responses. This can be done through the use of immunoadjuvants or by recruiting immunostimulatory cells, such as *in vivo* dendritic cells, to the vaccine bed. It is also possible to generate dendritic cells *ex vivo*, by culturing progenitor cells with a particular formula of cytokines.

An additional strategy that is currently being pursued is the incorporation of immunomodulatory agents that could positively impact the tumor microenvironment and prevent the re-establishment of tolerance. Potential agents would include IMiDs, checkpoint inhibitors, hypomethylating agents, and other novel drugs that demonstrate immune modulation.

Researchers are trying to determine whether all 3 of these components are always necessary, or whether only 1 or 2 might be adequate in certain settings.

H&O What are the advantages to this type of vaccine?

DA The advantage to using patient-derived tumor cells and dendritic cells in a vaccine is that it creates a broad array of targets—including both neoantigens and shared antigens—and lets the biology select the most relevant one. The dendritic cell partner provides the critical costimulation. We first confirmed the feasibility of this concept in preclinical models. We then completed a phase 1 study in patients with multiple myeloma, which showed that the vaccine generated immune responses and was safe in general. The phase 2 trial showed a near doubling of the complete response rate in patients who received the vaccine after transplant. That was without the addition of maintenance therapy. We are now evaluating the vaccine in a randomized trial performed through the cooperative group. This trial is the first to evaluate a personalized cell therapy through a collaborative approach in the academic setting.

H&O What are the challenges in developing a vaccine for multiple myeloma?

DA The biggest challenge is that the immune system in patients with multiple myeloma likely has significant deficiencies, even early after diagnosis. The patient's T cells and other immune effector cells may be somewhat sluggish in their response. It is therefore necessary to account for the tumor microenvironment and the native difficulty in generating a response.

Another challenge is understanding the best targets and how they may differ among patients. A personalized cell vaccine has the advantage that it can hit multiple targets, but it raises the logistical hurdle of working with patient-derived material. These therapies pose challenges compared with off-the-shelf approaches. The experience with CAR T cells and the data from our national trial, however, show that these types of strategies are feasible.

The quality of the response is important. The response must be clinically meaningful, as well as durable. Durability relates to the persistence of the immune effector cells. It

is necessary to ensure that the myeloma does not create a tolerant environment that ultimately defeats the vaccine.

Another challenge in all of immunotherapy is posed by the nature of the disease. It may be difficult for a vaccine that relies on immune system T cells to catch up kinetically to diseases that are more advanced and rapidly proliferative. Immunotherapy may be most effective in diseases that have a slow enough cadence to allow the immune system a chance to work.

H&O What are the goals when using a vaccine in patients with multiple myeloma?

DA The primary goal is to generate an immune response that can effectively target the disease and potentially lead to remission. In patients with residual disease after standard therapy who are likely to relapse, a vaccine might be able to prevent or delay the relapse. Ideally, there is the potential that a highly potent vaccine could be used for prevention, eradicating the clone in patients with smoldering myeloma, premyleloma, or monoclonal gammopathy.

H&O Are there any other clinical trial data for the use of vaccines in multiple myeloma?

DA There are several other studies. Several peptide strategies have been studied in smoldering disease. In the post-transplant setting, a study is evaluating a vaccine using Langerin dendritic cells, with RNA materials serving as the antigen. Final results are forthcoming.

H&O How might vaccines be incorporated into the treatment course?

DA Their role will ultimately depend on their efficacy. Most likely, vaccines will be used as a second step. There are several effective biologic therapies that are associated with good rates of response and remission. There is hope that vaccines, by inducing an immune response, might be able to prolong a remission or make it permanent. A vaccine may be able to prevent early evolution of disease from a smoldering or premyleloma state to myeloma.

It is possible that vaccines will be used in combination with other therapies, such as CAR T cells, even in patients with more active disease. In general, much research in this field is directed toward understanding each patient's unique immunologic milieu. Ultimately, a combinatorial strategy may be needed. CAR T cells have a very high level of potency, but the durability of responses may be compromised by tolerization of the T cells or the time spent in the immune environment. Vaccines may be able to stimulate the immune system and prevent the CAR T cells from being extinguished. Our group is

leading a large project, sponsored by the Multiple Myeloma Research Foundation and with researchers throughout the United States and Europe, investigating the strategy of combining vaccines and CAR T-cell therapy. It is hoped that this combination will help broaden the response, as well as create a more durable presence of CAR T cells and other tumor-specific T cells. Another potential combination involves checkpoint inhibitors, which are not highly efficacious as monotherapy in multiple myeloma. There have been some safety concerns when they were combined with IMiDs. However, trials are evaluating checkpoint inhibitors with CAR T cells or vaccines. Our group is also leading a study of the potential synergy between vaccination and checkpoint inhibitors in patients with more-advanced disease.

H&O Have your studies of vaccines provided any surprising insights?

DA We saw that it is possible to generate what appear to be tumor-activated T cells that were durable, even in patients with relatively advanced disease. This observation has also been made in patients with acute leukemia. The critical question is how to create a scenario in which those cells are most effective and lead to clinically meaningful results. Further study is needed.

H&O Does your research of vaccines have implications for other types of malignancies?

DA Our model is not restricted to multiple myeloma. The idea of using a hybridoma is also being explored in acute leukemia. Our group led a study of patients with acute myeloid leukemia who received this type of personalized, dendritic cell tumor fusion vaccine. Enrolled patients had achieved remission after standard chemotherapy. They were not transplant candidates, and their median age was older than 60 years. More than 70% of the initial cohort remained in remission at a median follow-up of nearly 5 years. This exciting result led to an ongoing randomized trial.

H&O What is next for the use of vaccines in hematologic malignancies?

DA Studies have demonstrated that it is possible to generate immune responses. In some settings, these immune responses might be quite meaningful on their own. It will be necessary to understand which immune environments are most susceptible to the vaccine alone, and which require combinatorial strategies—whether with CAR T-cell therapy, antibodies, IMiDs, or checkpoint inhibitors—to achieve the most durable effects.

Disclosure

Dr Avigan has received research support from Celgene and Pharmacyclics. He is a member of the advisory boards of Celgene, Juno, Partners Tx, Karyopharm, BMS, and Aviv MedTech Ltd. He is a consultant for Janssen, Parexel, and Takeda.

Suggested Readings

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