Glimpsing the future: New immune-based therapies for multiple myeloma.

Over the last year, the U.S. FDA approved a flurry of new drugs for use in multiple myeloma, a cancer that affects the bone marrow. Those drugs, seven in total, represent a near doubling of the drugs approved throughout the last 12 years to treat the disease.

“There’s now a very good understanding of the mechanisms we need to target to interrupt multiple myeloma cell growth, survival, and resistance,” explains Kenneth Anderson, director of the Jerome Lipper Multiple Myeloma Center and the LeBow Institute for Myeloma Therapeutics at Dana-Farber Cancer Institute.

Compared to other cancers, multiple myeloma is quite complex genetically. As the disease progresses, its genetic complexity continues to evolve, making patients highly prone to drug resistance and disease relapse. To address these challenges, therapeutic approaches in multiple myeloma now increasingly rely not on single agents, but on combinations of targeted agents.

One of the fastest-growing therapeutic areas in multiple myeloma — and in other cancers — is immune-based therapy. “This is the future of multiple myeloma therapy,” says Anderson. “Immunity is very potent, selective, and adaptable, so it just may be able to overcome the various genetic changes that myeloma cells undergo in order to resist current treatments.”

Anderson likens these immune therapies to a team, with each member playing an important role in multiple myeloma treatment. One of the newest potential team recruits is the so-called immune checkpoint inhibitors. The drugs, often in the form of antibodies, block normal proteins found on the surface of tumor cells and their counterparts on immune cells. These proteins, including PD-1 and PD-L1, can enable cancers to avoid and curtail an immune attack. By blocking them, as with PD-1-specific drugs such as pembrolizumab and nivolumab, it becomes possible to rev up patients’ immune systems and deploy them in a fight directed at their own tumors. Indeed, checkpoint inhibitors have shown early promise in patients with other forms of cancer, such as advanced melanoma and Hodgkin lymphoma.

There is an additional layer to how these drugs might work in multiple myeloma. Cells found within the tumor microenvironment, specifically plasmacytoid dendritic cells and myeloid derived suppressor cells, also express PD-L1. So PD-L1 blockade could interfere with the functions of these accessory cells, which include promoting tumor cell growth, survival, and drug resistance, as well as suppressing the immune response. Checkpoint inhibitors are now in early stage clinical trials for use in multiple myeloma in combination with other immunomodulatory drugs (such lenalidomide, a thalidomide derivative). Hopes are high that they will become major players on the cancer’s “immune team.”

Remarkably, there could be other new team members on the horizon, too:

- Both peptide-based and cell-based vaccines are now being tested in two different cohorts of multiple myeloma patients — those with early stage (or “smoldering”) disease and those who received an autologous stem cell transplant.
- A new selective inhibitor against histone deacetylase (HDAC) 6 is now undergoing clinical testing in multiple myeloma, both alone and in combination with other immune-based treatments.
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- Cellular therapies, such as chimeric antigen receptor (CAR) T-cells, are also being evaluated for use in multiple myeloma. T-cells are first harvested from patients, genetically programed to react against a target on myeloma cells — the target now being tested is B-cell maturation antigen (BCMA) — then expanded and transfused back into the patients.

“The holy grail is to get a memory immune response in patients against their own multiple myeloma, and that has been a long sought after goal,” says Anderson. “With a combination of immune approaches, that may be achievable.”