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IMMUNOTHERAPY FOR WALDENSTROM MACROGLOBULINEMIA

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Waldenstrom macroglobulinemia (WM) is a cancer of lymphocytes and plasma cells. These cells are part of the body's immune system, and when lymphocytes and plasma cells have become malignant, the immune system is still able to partially regulate their growth. Immune cells and cancer cells interact, and this interaction plays a role in controlling the progression of WM. It is usual that B-cells, plasma cells, and immune cells, such as T-cells and macrophages, interact in the bone marrow, lymph nodes, and spleen. Immunotherapy is a way to utilize this interaction and enable the immune system to more actively target cancer cells.

There are three major ways through which immunotherapy attempts to achieve this: first, by helping the immune system target the cancer cells; second, by reactivating immune cells that are suppressed; or third, by bypassing the barriers that suppress the immune system.

STRATEGY 1 – TARGETING CANCER CELLS

A common way to allow the immune system to more effectively visualize and target the cancer cells is to activate the immune system by the presence of a monoclonal antibody bound to the outside of the malignant cell.

Treatments such as rituximab (Rituxan) target CD20, a protein on the outside of B-cells, including malignant B-cells. When rituximab attaches to CD20 on a WM cell, immune cells are activated and kill the antibody-coated WM cell. The immune cells that participate in this process include macrophages and monocytes, as well as natural killer (NK) cells and T-cells that kill cells with antibodies on their surface. This process is called antibody-dependent cytotoxicity, meaning that antibody stuck to the cell targets the cell for destruction by the immune system.

Rituximab is now part of standard therapy for WM and is used either alone or in combination with chemotherapy. Rituximab is also commonly used as maintenance treatment after initial chemotherapy. This strategy of targeting cancer cells by using antibodies is being improved by the development of new antibodies that target CD20 or that target other proteins on the surface of

cancer cells. New anti-CD20 antibodies in use in B-cell malignancies include ofatumumab (Arzerra) and obinutuzumab (Gazyva).

STRATEGY 2 – REJUVENATING A SUPPRESSED IMMUNE SYSTEM

The immune system in WM is not normal. Cancer cells make many immunologically active proteins (cytokines are an example) that suppress the function of immune cells. Also, immune cells can become worn out and eventually exhausted by continually responding to cancer cells. Suppressed or exhausted immune cells are unable to effectively kill cancer cells.

This second immunotherapy strategy involves treatment approaches to reinvigorate immune cells that have become suppressed or exhausted. This type of treatment is typically called immune checkpoint blockade (or immune checkpoint inhibitor) and uses antibodies to block the signals that switch the immune system off.

Immune checkpoint blockade is now widely used in the management of cancer patients. The exhausted and suppressed immune cells often have receptors on their surface, among them a receptor called PD-1. Signals through PD-1 cause the cell to become suppressed. PD-1 normally is important in maintaining self-tolerance, preventing autoimmunity, and protecting tissues from immune collateral damage. Unfortunately, PD-1 can be “hijacked” by cancer cells, in effect “hiding” them from the immune system cells. An antibody that blocks signaling through PD-1 allows the immune cells to “wake up” and “see” the cancer cells, thereby more effectively targeting them.

Treatments that block PD-1 include antibodies such as nivolumab (Opdivo) and pembrolizumab (Keytruda). Nivolumab and pembrolizumab have shown promising efficacy in other lymphomas and are just now being introduced into treatments for WM. Results with these PD-1 inhibitors in WM are eagerly awaited.

STRATEGY 3 – OVERCOMING IMMUNOLOGICAL BARRIERS WITH CAR T-CELLS

The immune system often struggles to directly attack cancer cells. This is because the cancer cells are somewhat “invisible” to the immune system since they lack proteins on their surface that identify them as “foreign.” Also, as mentioned above, proteins produced by cancer cells often significantly suppress the immune system. A third strategy to overcome the immune suppression and to target the malignant cell more effectively is to put an artificial “docking site” into the patient’s T-cells.

This “docking site” allows immune cells to directly bind to cancer cells even when they lack proteins that label them as “foreign,” and therefore enables immune cells to kill the cancer cells more efficiently. A CAR (chimeric antigen receptor) T-cell is a T-cell that has had an artificial receptor (or artificial “docking site”) introduced into it. This receptor includes an automatic activating protein as well so that the T-cell becomes activated when the receptor binds.

These CAR T-cells typically target CD19 (a protein on B-cells) and will bind directly to any cell that has CD19 on the cell surface. The T-cells are automatically activated when they attach to cancer cells, and these activated T-cells kill the malignant B-cells. This treatment involves taking

a patient's T-cells from his or her peripheral blood, growing them in the lab to increase their numbers, and introducing the chimeric receptor into the T-cells. The CAR T-cells are then reinfused into the patient, where they recognize and attack the cancer cells.

So far, CAR T-cell treatment has proved very promising in B-cell malignancies, but it has only been tested in a few patients with WM. This treatment also has significant risks. A cytokine release syndrome (fevers, chills, low blood pressure, possible heart and breathing issues), as well as neurological toxicity (confusion, speaking problems, unresponsiveness), sometimes results but resolves with appropriate support. Interestingly, these toxicities are often seen in patients who have the best clinical results. Because of these potential side effects, CAR T-cell therapy needs to be given in centers with significant expertise in this area.

LOOKING TO THE FUTURE

All told, the future for immunotherapy is very promising, and these novel treatment strategies are currently being tested in clinical trials. At this point, multiple approaches to reactivate and target the immune system are being explored, and we will need to wait and see which will be most successful. In the near future, we anticipate that these treatments will be useful either alone or in combination with other treatment approaches for patients with WM. We anticipate that activating the immune system to directly target B-cells and plasma cells will result in improved treatments for WM patients.

TERMS TO KNOW

Immunotherapy – treatments that use the immune system to fight cancer.

Antibody – an immune molecule that attaches to cells, bacteria, or viruses that the body sees as foreign (man-made versions include rituximab).

Immune checkpoint inhibitors – antibodies that block signaling by molecules (such as PD-1) that suppress immune cells (examples are nivolumab and pembrolizumab).

Receptor – a protein on the cell surface that receives messages from outside the cell (e.g. CD19, CD20, and PD-1).

Chimeric antigen receptor (CAR) – artificial receptor put into T-cells to cause them to interact with cancer cells.

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