Urvi A. Shah says cost will be a major factor in the availability of some immunotherapies.

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Immunotherapies target multiple myeloma

Treatments that help the immune system to fight multiple myeloma are emerging fast, but the number of people who relapse remains high. **By Dalmeet Singh Chawla**

In 2015, the US Food and Drug Administration (FDA) approved the first immunotherapies for multiple myeloma, a cancer that forms in white blood cells called plasma cells in bone marrow. According to Muzaffar Qazilbash, a stem-cell-transplant physician at the University of Texas MD Anderson Cancer Center in Houston, this class of therapy, which use a person's own immune system to fight cancer, is one of the main reasons there has been such "tremendous progress" in the treatment of multiple myeloma over the past few years. The treatments bring hope of long-term remission, with less risk of complications than previous therapies, he says.

Plasma cells are a crucial part of the immune system, but in multiple myeloma, they become cancerous and grow uncontrolled, outnumbering other blood cells and limiting the body's ability to make healthy blood cells. Most therapies so far haven't been able to guarantee long-term survival. An allogeneic stem-cell transplant — which involves giving people high doses of chemotherapy to kill cancer cells, followed by a transplant of stem cells from a healthy donor so that the person can continue to produce blood cells — is the treatment that most often lengthens the period of time a person is in remission. Around 20% of people who receive the therapy have no trace of the cancer left afterwards, but the mortality rate is alarmingly high, with people over the age of 65 and those with comorbidities most at risk. Allogenic stem-cell transplants, therefore, are usually only offered to people at high risk and with a poor long-term prognosis. And even then, most people are unable to have them because of age or medical restrictions. So researchers are continuing to hunt for safer therapies.

In the past decade or so, the focus has shifted away from harsh systemic treatments, such as chemotherapy, to more targeted ones, such as immunotherapy. Hearn Jay Cho, a haematologist at the Icahn School of Medicine at Mount Sinai in New York, says immunotherapy is fundamentally different from chemotherapy because it's much more targeted and tailored. "It's like you're conducting an orchestra, you're not dropping a bomb."

Progress so far

The first immunotherapies approved for people with multiple myeloma were the monoclonal antibodies daratumumab and elotuzumab. Daratumumab targets CD38, a protein that's highly expressed on the surface of myeloma cells. Whereas elotuzumab targets SLAM-7, which is expressed on both normal and malignant plasma cells. "This was the beginning of the immunotherapy era for multiple myeloma," Qazilbash says. A third monoclonal antibody, isatuximab, was approved for relapsed refractory multiple myeloma in March 2020.

CD38-targeting antibodies have surprisingly few side effects, given that the protein is also expressed in the brain, kidneys and the pancreas, says Niels van de Donk, a haematologist at the VU University Medical Center in Amsterdam. "The toxicity profile is very mild," he says. "Patients tolerate it very well."

Since their approval, daratumumab and elotuzumab have been used all over the world, Qazilbash says. Daratumumab is often the first choice, he adds, describing it as a "blockbuster drug". Although it was initially tested in people who had no other treatment options, it has since been shown to be effective in those who are newly diagnosed, says van de Donk. "That's an important advance," he says, because there are a limited number of options for these people. Most immunotherapies are aimed at those who have already been through several rounds of treatment.

Elotuzumab is approved for use in combination with other drugs, most commonly the immunomodulatory drugs lenalidomide, pomalidomide and thalidomide, which enhance the immune system's ability to fight cancerous cells through little-understood mechanisms. As well as proteasome inhibitors such as bortezomib, which block or slow down the proteasomes that break down proteins in both healthy and cancerous cells.

Another class of immunotherapies take aim at a different target: the B-cell maturation antigen (BCMA), which is usually found on the surface of myeloma cells but, importantly, not on healthy cells. That location specificity makes BCMA a good target for more powerful

therapies that might otherwise cause serious side effects, says van de Donk.

The most promising of these BCMA-targeted therapies includes chimeric antigen receptor T-cell (CAR-T) therapy, says Qazilbash. The therapy involves extracting a person's own T cells, and genetically engineering them to express anti-myeloma antibodies on their surface that bind to BCMA. The engineered cells are then reinfused back into the individual.

Early studies have shown that CAR-T therapy can be highly effective. The biotechnology firm Bluebird Bio in Cambridge, Massachusetts, and global pharmaceutical firm Bristol Myers Squibb announced last year that CAR-T therapy reduced the disease burden in 83% of people who had already been through at least three lines of therapy. And mid-trial results announced in May by the pharmaceutical giant Janssen showed that 86% of people with myeloma who were given CAR-T therapy had a complete response. The response levels are unprecedented, says Qazilbash. Cho says the "remarkable upfront response rates" for CAR-T therapies in phase I studies have mostly stood up in phase II trials, as well.

Still, CAR-T therapy does have its drawbacks. Around 10% of people experience severe toxicity, Qazilbash says, including life-threatening hypoxia or shortness of breath that is severe enough to require support from a mechanical ventilator. Although most side-effects are milder, he adds, such as fever, nausea, fatigue and headache that tend to last only a few days.

Cost will be a major factor that determines the availability of CAR-T therapy, says Urvi A. Shah, a haematologic oncologist at the Memorial Sloan Kettering Cancer Center in New York. CAR-T therapy is expensive — it is estimated to cost between US$370,000 and $475,000 per dose. And people can relapse, so one dose might not be enough.

Despite encouraging results, CAR-T therapy hasn't been shown to eliminate multiple myeloma entirely. "You would expect that an expensive treatment like this would potentially be curative," Qazilbash says, "but so far, there is no evidence for that."

Other options

Although CAR-T therapy has received the lion's share of media attention, it is not the only immunotherapy showing promise. Researchers are also excited about antibody-drug conjugates (ADCs), in which antibodies are used as a guide to deliver drugs to cancerous cells and destroy them.

One such drug, belantamab mafodotin, which targets BCMA, was approved by the FDA in August. According to results of a trial that involved 97 people who had already received

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Haematologist Niels van de Donk.

multiple therapies, 31% responded, at least partially. The median progression-free survival in this trial was 12 months (S. Lonial *et al. Lancet Oncol.* **21**, 207–221; 2020). The treatment can have side effects, including blurry vision and corneal irritation, but, says Shah, "if we can manage the toxicities, then these drugs become inherently more attractive".

One big advantage of drugs such as belantamab mafodotin is that they are active even in people in whom the cancer has returned after treatment or a period of remission, says Cho. They provide another option for people who have already received chemotherapy and different forms of immunotherapy.

ADCs are also cheap, easy to manufacture and easier to administer than CAR-T therapy is. They also don't cause cytokine-release syndrome, a systemic inflammatory response that is triggered by certain infections and drugs, such as CAR-T and other T-cell therapies, and some monoclonal-antibody treatments.

Another antibody-based therapy targeting multiple myeloma involves bispecific antibodies, which bind to both the BCMA antigen and to the CD3 protein on the surface of T cells. This binding activates T cells, bringing them close to tumours so that they can kill them. But so far, the response rate for people with multiple myeloma has been lower than that of CAR-T therapy.

AMG 420, developed by US biopharmceutical company Amgen, is the most advanced bispecific antibody. In a phase I study in 42 people testing the safety of the product, the drug led to a lower tumour burden in half of the participants, who had already received various therapies for multiple myeloma (M. S. Topp *et al. J. Clin. Oncol.* **37**, 8007; 2019).

One key benefit of bispecific antibodies is that there's no need for conditional chemotherapy before the treatment. By contrast, people receiving CAR-T cells must first be given a type of chemotherapy that depletes lymphocytes to give the CAR-T cells the best chance of fighting the cancer.

Unlike CAR-T cells, bispecific antibodies don't need to be manufactured specifically for each individual — they are off-the-shelf agents that can be used right away. Bispecific antibodies, however, do share some of the side effects that dog CAR-T cell therapy, including cytokine release syndrome and neurotoxicities.

Not all immunotherapies have been a success for multiple myeloma. Initially, researchers and drug companies were enthusiastic about checkpoint inhibitor therapy — another form of cancer immunotherapy that has shown promise in other types of cancer. The protein PD-L1 on myeloma cells can interact with the protein PD-1 on T cells to stop these cells from signalling to the immune system that it should attack tumours. Blocking that interaction can, therefore, potentially prevent the cancerous cells from eluding the immune system.

A number of pharmaceutical companies who already had drugs that target PD-1 or PD-L1 for other cancers launched trials testing the treatment in people with multiple myeloma. In some trials, pembrolizumab (a monoclonal antibody that targets PD-1) was given in combination with pomalidomide and lenalidomide to people with multiple myeloma. But in 2017, the FDA suspended the trials after a significantly higher number of people receiving pembrolizumab died for reasons that were unclear than in the control groups.

Of the therapies that do prove to be effective against multiple myeloma, "it's going to be a bit of a horse race", says Cho. But he suspects that, in the long term, bispecific antibodies will win, because these agents don't require customized manufacturing and, therefore, can be more readily deployed.

"The beauty of our current situation is that we have a broad range of active agents with different targets and different activities that may be beneficial at different points in the cycle of generating the anti-tumour immune response," Cho says. With the right combinations, he says, we should be able to find effective treatments for most people.

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