PALLIATIVE CARE CASE OF THE MONTH

"CAR-T Therapy: What is it and who does it help?"

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Case: Mr. M is a 73 year-old male with a history of follicular lymphoma subsequently transformed to diffuse large B cell lymphoma (DLBCL) with neurolymphomatosis. He presented with severe neuropathic arm pain worsened with movement and light touch. His pain was refractory to opioids and amitryptyline. Palliative care was consulted for management of his severe pain. He was awaiting chimeric antigen receptor T-cell therapy (CAR-T) for his lymphoma. This case prompted the questions: How does CAR-T work and what is the likelihood of cure or symptom reduction after this treatment?

Discussion:

Overview

CAR-T is a relatively new and promising cancer treatment using autologous genetically modified T-cells, which express chimeric antigen receptors (CARs or CAR-T cells) specific to the patient's malignancy. The antigen, specifically CD19, is targeted in acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphomas (DLBCL).

In 2017, the FDA approved CAR-T therapy for acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL). The two approved CAR-T therapies include tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta). Tisagenlecleucel and axicabtagene ciloleucel are autologous T cell immunotherapies directed at CD19. Tisagenlecleucel is currently approved for treatment of relapsed or refractory ALL and relapsed or refractory DLBCL. Axicabtagene ciloleucel (Yescarta) is approved for treatment of relapsed or refractory DLBCL.

The Process

To be eligible for CAR-T, patients must have refractory disease or their second or later relapse. Patients with central nervous system lymphoma are not eligible for this treatment. Prior to apheresis, patients must meet certain parameters including greater than three months from their last stem cell transplant and limited use of steroids, due to T cell suppression.

Creation of CAR-T cells takes a minimum of two weeks and is based on the rate of cellular reproduction. First, patients undergo apheresis in order to isolate white blood cells. Then, the blood sample is sent to a processing facility where the T cells are isolated. The CAR gene is attached to the patient's T cells using an inactivated virus, which introduces the genetic material into the host cell's genome. The CAR protein is expressed on the cell wall as a transmembrane protein. The cell population is then expanded, or grown, to produce enough cells for treatment. The product is then frozen and shipped to the receiving facility for infusion.

Once the infusion product is ready, patients present to the hospital to undergo three days of lymphodepleting chemotherapy to deplete regulatory T cells. Two days after the last dose of chemotherapy, patients receive CAR-T therapy. Similar to blood product administration, patients receive premedication with acetaminophen and diphenhydramine to attenuate potential reactions to the infusion. Due to the potential for serious complications, patients are monitored closely in the hospital following the CAR-T infusion. Interestingly, after infusion, CAR-T cells continue to proliferate in the patient's blood stream for approximately two weeks with some evidence of continued proliferation at one year. CAR-T cells then identify malignant cells and create an immune response resulting in tumor cell death.

Outcomes

In the ZUMA-1 trial, 52% of patients with B cell lymphoma who received axicabtagene ciloleucel (Yescarta) achieved complete remission, with a median response time of 1 month. Partial response was obtained in 27% of patients. At 15-month follow-up, 40% of all treated patients maintained complete response. Overall survival at 18 months was 52%. The JULIET trial evaluated the use of tisagenlecleucel for B-cell lymphoma and demonstrated a 40% complete remission with a 13% partial remission. Tisagenlecleucel, which is FDA approved for treatment of refractory ALL demonstrated a 90% complete remission rate at one month with a six month survival rate of 78%. Patient reported outcomes continue to be collected by the Center for International Blood and Marrow Transplantation Research (CIBMTR) from patients who have received CAR-T therapy. Data regarding quality of life, pain control, and symptom management after CAR-T therapy have not yet been reported.

Complications

Significant complications of CAR-T include cytokine release syndrome (90%), neutropenia (78%), anemia (43%), and thrombocytopenia (38%). Cytokine release syndrome (CRS) presents as a systemic inflammatory response and may be life threatening. Symptoms of CRS may range from mild flu-like symptoms to multi-organ dysfunction. CRS occurs approximately two days after infusion. Most occurrences of CRS are low-grade; about 13% experience more severe symptoms. Neurologic complications can also occur. These include neurologic dysfunction including encephalopathy, aphasia, and difficulty with executive function and attention. Treatment for these events may include glucocorticoid treatment or tocilizumab, depending on the severity of symptoms. Most complications of treatment resolve within approximately two to three weeks after infusion.

Discussion Continued

Cost

In addition to being time-intensive, CAR-T therapy is expensive. The cost of a single infusion of CAR-T can be between $373,000 - $475,000, and this does not include hospital stays, management of complications, and additional costs. The total cost of treatment may be over $800,000 per patient. In 2019, Centers for Medicare & Medicaid Services began covering CAR-T therapy if provided for FDA approved indications.

Summary and Future Directions

CAR-T is a novel targeted cancer treatment for patients with refractory ALL or DLBCL. It is a time-intensive and expensive treatment with promising success rates for patients who would otherwise have limited or no further cancer directed treatment options. Future indications for CAR-T will depend on detection of unique surface proteins expressed on malignant cells. CAR-T shows promise for other hematologic malignancies, including multiple myeloma. Solid tumor malignancies such as pancreatic, lung, ovarian, and mesothelioma remain ongoing areas of evaluation.

Conclusion: Mr. M received CAR-T infusion. His course was complicated by mild cytokine release syndrome and neurotoxicity which later resolved. Follow up PET/CT showed non-significant increase in lymphadenopathy. He did well for approximately four months post-infusion. At five months post-infusion, he experienced progression of cutaneous lymphoma and was transitioned to hospice.

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