Apamistamab-Based Lymphodepleting Regimen Before CAR T-Cell Therapy May Prevent Cytokine Release Syndrome

EMERGING THERAPIES

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Wayne Kuznar

Orlando, FL—A new CD45-targeting antibody radiation-conjugate, iodine-131 (I-131) apamistamab, may be a less toxic alternative to today's standard practice of chemotherapy-based lymphodepletion regimens before initiation of adoptive cell therapy, according to results presented at ASH 2019.

The use of I-131 apamistamab before chimeric antigen receptor (CAR) T-cell therapy may enable lymphodepletion through a single-dose outpatient administration compared with chemotherapy-based lymphodepletion regimens that require multiple infusions in an inpatient setting over several days.

Adverse events associated with the current chemotherapy-based lymphodepletion regimen of fludarabine plus a cyclophosphamide include cytokine release syndrome and neurotoxicity.

"There is good rationale to use apamistamab before you infuse CAR T-cells. When you add the lymphocytes from the outside for a therapeutic reason, these lymphocytes grow much better if the host immune system lymphocytes have been depleted. At the same time, there is more toxicity from a CAR-T procedure if it is given with lymphodepletion," said Rajneesh Nath, MD, hematology/medical oncology specialist, Banner M.D. Anderson Cancer Center, Gilbert, AZ.

"When we used a test dose of apamistamab to see the biodistribution of this drug, we noticed that the lymphocyte count in the blood was dropping. The lymphocyte count dropped enough so that this could be used as lymphodepleting chemotherapy. Lymphocytes remain depleted in the time frame when we need to infuse the CAR T-cells," Dr Nath noted.

The SIERRA Study

In the pivotal phase 3 SIERRA clinical trial presented at the meeting, an 85% reduction in lymphocytes was observed at the postdosimetry infusion time point, a 67% decrease at day 1 post–dosimetric infusion, followed by a 43% decrease 1 week later, just before I-131 apamistamab therapeutic infusion, in patients with relapsed or refractory acute myeloid leukemia (AML) compared with pre–dosimetric infusion, he said.

In addition to the 85% reduction in lymphocytes at the postdosimetry infusion, a 35% reduction in peripheral leukemic blasts was found at the postdosimetry infusion, suggesting a rapid antileukemic effect with single-agent I-131 apamistamab.

These data suggest that this method of lymphodepletion is specifically targeted to CD45-positive immune cells, which, according to Dr Nath and colleagues, could have an antitumor effect. Furthermore, they noted in their poster, it “can be administered in an outpatient setting.”

I-131 apamistamab targets CD45, an antigen expressed on the surface of many cells that are relevant to CAR T-cell therapy, including lymphocytes, macrophages, and regulatory T-cells. A preponderance of these cells has been associated with a lack of durable response to CAR T-cell therapy, as well as the adverse event of cytokine release syndrome and other neurologic events.

In the SIERRA study, before administration of a therapeutic dosage of I-131 apamistamab in patients with AML, dosimetry using a tracer amount of I-131 apamistamab was performed in the outpatient to calculate a patient-specific therapeutic infusion dose.

Blood samples from 56 evaluable patients demonstrated a significant but transient reduction in lymphocytes and white blood cells compared with pre–dosimetry infusion levels, at approximately one-tenth of the targeted lymphodepletion dose of I-131 apamistamab.

There was no significant change in the levels of platelets, red blood cells, and neutrophils preinfusion versus postdosimetry infusion.

“Based on the clearance of iodine-131 apamistamab, an adoptive-cell therapy such as CAR T could be administered around 6 days postlymphodepletion, with a 75 mCi dosage,” said Dr Nath. Based on the SIERRA study, a nonmyeloablative dosage of 75 mCi has been proposed as a starting dose, in combination with a CAR T-cell therapy.

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