Advances in CAR T-Cell Therapies

Gene therapies, especially chimeric antigen receptor (CAR) T-cell therapies, experienced significant growth in 2017. The CAR T-cell therapies are among the most clinically important of the adoptive cell transfer therapies. In August, the FDA approved tisagenlecleucel for patients aged < 26 years with acute or relapsed lymphoblastic leukemia (ALL). In October, the FDA approved axicabtagene ciloleucel for treatment of adult patients nonresponsive to, or relapsed from treatment of, certain types of large B-cell lymphoma. And in November, the FDA granted breakthrough therapy designation to Celgene and Bluebird Bio for the bb2121 anti-B-cell maturation antigen (BCMA) CAR T-cell therapy for relapsed and refractory multiple myeloma (MM).

Chimeric antigen receptor T-cells circumvent the human major histocompatibility complex that T-cell receptors must navigate, shifting cell-based therapy away from identification of existing cells and toward creating T-cell products through genetic engineering. This broadens the potential for CAR T-cell applications and allows for rapid manufacture of tumor and patient-specific agents.[1] Both Novartis' Kymriah and Kite Pharma's Yescarta are derived from investigations into anti-CD19 CAR therapy, which has been the most heavily researched of the CARs due to its links with B-cell malignancies, expression in most tumor cells, and absence from vital tissues.[2] Studied in relation to a number of cancers, CD19 has not shown much success in either MM or solid tumor cancers.

Targeting the right antigen for myeloma is complicated: first because common MM antigens—CD38, CD56, CD138—also are expressed on essential normal cells, and second, because myeloma cells are synonymous with heterogeneity. The FDA based its designation of bb2121, or BCMA CAR T-cell therapy, on preliminary data from an ongoing phase 1 CRB-401 trial that, as of December 2017, concluded that 94% of 21 patients with MM treated with the highest doses showed complete or partial remissions and high rates of progression-free survival.[3] The trial also showed that cytokine-release toxicity (CRS), although severe in some patients, was generally reversible and short lived.

Multiple myeloma BCMA is only one of several CAR targets under consideration for MM treatment; others include CD138, CD38, signaling lymphocyte-activating molecule 7, and κ light chain. However, B-cell maturation antigen is attractive to researchers because BCMA–specific CAR-expressing T lymphocytes recognize and kill B-cell maturation antigen–expressing tumor cells. Also, BCMA acts as a receptor for both a proliferation-inducing ligand and as a B-cell–activating factor and is a member of the tumor necrosis factor receptor superfamily, playing a key role in plasma cell survival. B-cell maturation antigen is expressed in most, if not all, myeloma cells but not in epithelial tissues. Finally, integration of CAR-Ts with other myeloma therapies is an important area of future research.[4]

Most of the 23 trials looking at CAR T-cell therapy for MM are in the U.S. or China, and several deal jointly with MM, leukemia, and lymphoma. The THINK (THerapeutic Immunotherapy with NKR-2) multinational open-label phase 1 study stands alone in assessing the safety and clinical activity of multiple administrations of autologous NKR-2 cells in 7 refractory cancers, including 5 solid tumors (colorectal, ovarian, bladder, triple-negative breast and pancreatic cancers) and 2 hematologic tumors (acute myeloid leukemia and MM). Unlike traditional CAR T-cell therapy, which targets only 1 tumor antigen, NK cell receptors enable a single receptor to recognize multiple tumor antigens.

Despite challenges of toxicity, costs, and restricted availability for immunotherapies, CAR T-cell therapies seem to offer great possibilities of groundbreaking treatments and possible cures for formerly hard to treat cancers, including MM.[5]

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