Highlights from AACR 2019

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Advancements in Adoptive Cell Therapies

Despite the recent CAR-T approvals in select hematologic malignancies and the remarkable expansion of CAR-T clinical trials for a wide range of heme and solid tumors—many challenges remain. The chief among them are identifying tumor-restricted antigens to minimize on-target, off-tumor toxicities, enhancing tumor-killing effect, improving T-cell persistence and developing strategies to ameliorate CAR-T associated toxicities, such as cytokine release syndrome (CRS) and CAR-T-related encephalopathy syndrome. At AACR 2019, an array of presentations described innovative technological solutions to address these challenges. The highlights were (1) early activity of novel CAR-Ts in the clinic, (2) approaches to address two of the main challenges faced by adoptive cellular therapies in the clinic – loss of targeted antigen and exhaustion of CAR-T cells, and (3) interesting CAR design strategies for improved efficacy and safety from the "bench."

Early clinical results of CAR-Ts:

Early promising data was presented on Mesothelin-targeted CAR-T cells in malignant pleural mesothelioma, Her2-targeted CAR-T cells in advanced sarcomas, and CD19/CD22 bispecific CAR in B-cell malignancies

a. A Phase I study reported that the humanized mesothelin targeted CAR (iCasM28z CAR), when intrapleurally administered as a single dose followed by PD-1 checkpoint blockade, resulted in durable responses (72% response rate) in 15 mesothelioma patients. No CRS or neurotoxicity was observed in any patient. The hypothesis is that the mesothelin-targeted CAR-T-cell therapy transforms the tumor microenvironment (TME) to a more "immune hot" signature, thus making the tumors more susceptible to PD-1 blockade. A clinical trial specifically analyzing the combination of CAR-T cells and anti-PD-1/L1 agent is planned to start later in 2019.[1]

b. Another Phase I study (HEROS) evaluated autologous HER2-targeted CAR-T cells in patients with advanced HER2+ sarcomas, after lymphodepleting chemotherapy. These cells additionally express CD-28, which make the T cells persist longer when stimulated. Two of the 10 patients treated on the protocol, experienced long-term complete responses (CRs) and 3 patients had stable disease. Although a majority of patients treated developed CRS, these events were resolved within 5 days by supportive care. This study uses a CD-28 modified, Her2-targted CAR and follows an earlier trial which analyzed the efficacy/safety of just the Her2-targeting component and achieved an mOS of 10.3 months in 19 patients.[2]

Combating antigen escape and T-cell exhaustion that drive tumor resistance:

Antigen low relapses limit the long-term durability of response following CAR therapies.

a. Although CD19-targeted CAR Ts have received approvals in some heme malignancies, relapses with loss or diminished surface expression of CD19 are increasingly recognized as a cause of treatment failure. CD22-targeted CAR-T cells are poised to address leukemia resistant to anti-CD19 immunotherapy, demonstrating that resistance to immunotherapy via antigen loss can be overcome by treatment with CAR-T cells targeting an alternative antigen, opening the way to dual targeted CAR therapies. CD19/CD22 bispecific CAR-T cells have begun to show efficacy along with a good safety profile in relapsed/refractory B-cell malignancies. One CR and 2 PRs were noted in 5 DLBCL patients treated and 5 CRs and 1 PR among 7 B-ALL patients treated.[3,4]

T-cell exhaustion occurs commonly in CAR-T cells and is a major factor limiting success, especially in solid tumors.

b. In one study, c-Jun overexpression in the engineered CAR-T cells demonstrates increased efficacy in controlling even low-antigen disease in in vivo preclinical models. Additionally, transcription factors belonging to the bZIP/IRF family were identified as key components contributing to the T cell exhaustive signature using whole genome analyses. New CAR-T cell designs focused on including modulation of bZIP/IRF-motif proteins (such as c-Jun) can potentially enhance treatment efficacy while resisting CAR-T cell exhaustion.[5]

CAR-T Cell Design/Engineering Strategies:

Improved therapeutic T cells have multiple sensors that recognize combinations of tumor antigens, allowing the cells to assess their environment and make more precise decisions on when to activate.

a. Universal Immune Receptor using SpyCatcher enables covalent attachment of targeting ligands (SpyTag) to the T-cell surface receptors and allows for dose-dependent cytokine secretion and specific lysis of antigen-expressing tumor cells. In a preclinical study, cell populations that expressed both Her2 and EGFR were demonstrated to be specifically selected using this technology. Although early in development, an array of different antigens (e.g., Her2, EGFR, EpCAM, and CD20) can be recognized by Spy-T cells, either simultaneously or sequentially, thus broadening the possibility of response against tumors with heterogenous antigen expression.[6]

b. Combining induced pluripotent stem cells (iPSC) and genome editing technologies, iCAR-T cells have been designed such that tumor-targeted T cells can arise from a single clone of iPSC. This technology could achieve 100% accuracy in the genome editing of the target using CRISPR technology, without off-target effects. One study disrupts the diacylglycerol kinase proteins (DGKα and DGKζ) and demonstrates enhanced persistence and improved anti-tumor activity of iCAR-T cells in in vivo tumor models. DGKs are membrane-bound kinases that modulate multiple pathways including ERK, VEGF, c-Met, mTOR, and others. In immune cells, DGK inhibition boosts T-cell activation by increasing Ras/Erk pathway activity, which, in turn, drives IL-2 receptor expression and T-cell proliferation.[7]

1. Prasad Adusumilli, AACR 2019, A phase I clinical trial of malignant pleural disease treated with regionally delivered autologous mesothelin-targeted CAR T cells: Safety and efficacy.
2. Shoba Navai, AACR 2019, Administration of HER2-CAR T cells after lymphodepletion safely improves T cell expansion and induces clinical responses in patients with advanced sarcomas.
3. Crystal Mackall, AACR 2019, Next-generation CAR-T cells designed to overcome tumor resistance.
4. Kendarian Saad, AACR 2019, CAR-T cells in the clinic: Strategies to enhance efficacy and reduce toxicity.
5. Crystal Mackall, AACR 2019, Next-generation CAR-T cells designed to overcome tumor resistance.
6. Nicholas Minutolo, AACR 2019, Dose control of CAR-like T cell activity through post-translational covalent loading of ligands to a universal immune receptor.
7. Tatsuki Ueda, AACR 2019, Enhanced effector responses of regenerated CAR-T cells derived from genome edited iPSCs.

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