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The Cancer Cell Therapy Showdown: CAR-Ts Versus CAR-NKs

by Ayisha Sharma

Will CAR-NK cell therapies overshadow traditional CAR-T options for the treatment of some cancers? While preliminary data for CAR-NKs point to enhanced safety and solid tumor penetration, oncologists and executives discuss the pros and cons of these two approaches to cell therapy.

In 2017, the US Food and Drug Administration approved *Novartis AG*'s Kymriah for the treatment of patients with acute lymphocytic leukaemia (ALL). The decision marked a sea change – Kymriah became the first of several chimeric antigen receptor (CAR) T-cell therapies to enter the cancer market.

CAR-T cell treatment involves taking T-cells from patients' blood, enhancing them in the lab by adding a gene for a CAR and returning them to the patient to boost their immune response. The therapies improved survival in patients with poor prognosis and helped usher in a new age of precision immuno-oncology.

Now, a new kind of CAR cell therapy is emerging that could offer significant improvements, based on the use of natural killer (NK) cells. Thanks to allogeneic manufacturing processes and off-the-shelf administration, CAR-NK cell therapies could prove more attractive to payers than CAR-T cell therapies.

However, economic differences are just the tip of the iceberg and the two mechanisms are likely to have distinct risk-benefit profiles, target diseases and settings of administration, among other features but could also prove complementary in some settings. The distinctions ultimately boil down the main difference between T-cells and NK cells in the human body: T-cells form part of the adaptive immune system whereas NK cells are part of the innate immune system.

Target Specificity A Major Differentiator

Katy Rezvani, of the MD Anderson Cancer Centre, Houston, TX, said: "NK cells are part of the

body's first line of defence against viruses or transformed cells," adding their germline encoded receptors ensure they can recognize cells that are abnormal or stressed. While these cells target anything that appears foreign, "T-cells are more antigen-driven," Tania Jain, director, Adult CAR-T Cell Therapy Program, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, explained.

Indeed, all FDA-approved CAR-T cell therapies to date target one of two antigens on a B-cell – CD19 or B-cell maturation antigen (BCMA). "T-cells have difficulty penetrating into the solid tumor micro-environment compared with liquid tumors because solid tumors are more complex – there are a lot more cells present such as macrophages that suppress the T-cells," noted Justin Darrah, Hematology-Oncology, Samuel Oschin Cancer Center, Los Angeles, CA.

There have been attempts to infuse T-cells into solid tumor lesions to enable them to reach the micro-environment but these have seen little success. By contrast, preclinical research suggests NK cells have enhanced penetration into solid tumors.

One firm exploring this avenue is Monrovia, CA-based *CytoImmune Therapeutics, LLC*, whose lead candidate, CYTO-102, is in Phase I development for the treatment of non-small-cell lung cancer. "CYTO-102 is essentially an engineered NK cell but without a CAR element," said CytoImmune CEO Christina Coughlin.

Using the firm's TRACK-NK Platform, CYTO-102' s tumor targeting is enhanced with triple cytokine induction. The firm claims CYTO-102 is differentiated because it has high levels of cycling CD16 on the cell surface and secretes high levels of interleukin-15 (IL-15) and interferon gamma. "We plan to develop this candidate in combination with tumor-targeted biologics," Coughlin said, adding CD16 expression is important because it enables the candidate to detect monoclonal antibodies on the cancer cell surface and kill cancer cells via antibody-dependent cellular cytotoxicity (ADCC). Moreover, the CD16 cycling means one CYTO-102 cell can kill many times, in effect turning it into a "serial killer."

As for IL-15 and interferon gamma, "those two cytokines together are the ones that call in the T-cells," Coughlin said. CYTO-102 is thus designed to traffic to the tumor, recognize the antibody through receptor-ligand killing, function through ADCC and attract the T-cells, the CEO explained. The US firm has an in-house manufacturing facility in Toa Baja, Puerto Rico, with adequate capacity for all of its planned trials.

Unlike CYTO-102, many of the 13 anticancer CAR-NK cell therapy assets in the pipeline are in clinical development for blood cancers, according to the Citeline database Pharmaprojects (see table). Noteworthy examples include *Nkarta, Inc.*'s co-lead candidates, NKX101 and NKX019, which are in Phase I development for the treatment of relapsed/refractory acute myeloid leukemia (r/r AML) or myelodysplastic syndromes (MDS) and B-cell malignancies, respectively.

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Whereas most CAR-NK cell therapies utilize umbilical cord blood or induced pluripotent stem cells (IPSCs) as a source of the NK cells, NKX101 is derived from healthy donor blood. With ISPCs, "the cells have to go through a series of complicated genetic manipulations and chemical treatments to sort of 'force' them to become an NK cell, whereas we are starting with actual NK cells," said chief medical officer David Shook.

Last April, Nkarta released data from 21 patients with r/r AML or MDS enrolled in its Phase I trial of NKX101. The data showed that three of five AML patients attained a complete response (CR) with hematological recovery and the remaining two attained CR with minimal residual disease negativity. Across all dose cohorts, eight of 17 AML patients had an overall response, although none of the MDS patients had responded at the time. (Also see "*Nkarta Unveils Early But Promising Data For CAR-NK Therapies In AML, NHL*" - Scrip, 25 Apr, 2022.)

Similarly, the lead candidate in the CAR-NK cell therapy pipeline is in development for CD19+ hematological malignancies. Born of a collaboration forged between *Takeda Pharmaceutical Co. Ltd.* and MD Anderson Cancer Center back in 2019, TAK-007 is under investigation in a 242-participant Phase II trial for the treatment of relapsed or refractory B-cell non-Hodgkin's lymphoma (r/r NHL).

Topline data from a previous Phase I/IIa trial released back in 2020 showed 73% of nine evaluable r/r NHL patients at the time responded to treatment with TAK-007, including seven who attained CR and had and no evidence of disease at a median follow-up of 13.8 months. (Also see "*Strong Early Promise For Takeda 'Off The Shelf' CAR-NK Therapy* " - Scrip, 10 Feb, 2020.)

Early Safety Significantly Surpasses CAR-Ts

Furthermore, none of the patients in both Takeda's Phase I/IIa trial of TAK-007 and Nkarta's Phase I trial of NKX101 experienced cytokine release syndrome (CRS) or neurological toxicities, both of which are crucial safety concerns commonly seen with CAR-T cell therapies.

The label for *Kite Pharma, Inc.*'s Yescarta (axicabtagene ciloleucel) notes a 93% all-grade rate of CRS and an 87% all-grade rate of neurological toxicities in patients with large B-cell lymphoma population. Meanwhile, the label for Kymriah (tisagenlecleucel) notes a 77% all-grade rate of CRS and a 71% all-grade rate of neurological toxicities in patients with ALL.

The reason for the preliminary enhanced safety seen with CAR-NK cell therapies is not entirely clear, Rezvani said, although she posited it could be related to the different cytokine profiles of NK cells and T-cells. "CRS appears to be driven by IL-6 and other inflammatory cytokines produced by the myeloid cells of CAR T-cell therapies, but NK cells interact differently with cells

of the myeloid compartment," she explained.

"Toxicities with CAR-T cell therapies are certainly not trivial but we have gotten better at treating them," Jain said. Events are often managed with a combination of supportive care, tocilizumab and steroids. Jain explained that with adoption of these strategies, she had seen fewer grade 3 or higher events of CRS in the real world. While higher-grade neurological toxicities are still seen, she noted that early intervention with steroids and novel agents to address toxicities early could help in the future.

However, Darrah said that while management strategies have improved since the advent of CAR-T cell therapies, the side effects are still present, even if at a lower grade. "These patients still need much closer monitoring, they oftentimes still need in-patient treatment. Even if you're able to start in the outpatient setting, if someone starts developing fevers or confusion, a lot of the time that will trigger hospital admission despite early intervention."

CAR-NKs Could Offer Key Bridging Strategy

Ultimately, Jain said, "the question is how much do these toxicities worry us so as to potentially change the field entirely from using a product that we know works to something that may have lower toxicity but at the expense of potentially lower efficacy, which is linked to the poor persistence of NK cells." She was referring to the fact that infused T-cells can proliferate in the body unlike infused NK cells, leading to anticipated differences in treatment longevity.

On the flip side, the safety profile of CAR-T cell therapies means "they are often tied to large treatment centres because patients have to stay close to hospital to have access to an ICU," Shook highlighted. "NK cell therapies can be delivered in an outpatient setting without the risk of high-grader CRS and neurotoxicity meaning we can put the power of cellular therapy in the hands of more physicians and ultimately more patients because it can be accessed on a more localized basis."

Overall, both CAR-NK cell therapies and CAR-T cell therapies will play an important role in the treatment of cancer. The anticipated shorter longevity means CAR-NK cell therapies could be used to induce short-term remission to bridge patients through to potentially curative allogeneic stem cell transplant or other investigational consolidation approaches, Jain said.

However, Rezvani said there are not enough data on response durations with CAR-NK cell therapies, adding it is too early to determine their place in the treatment paradigm.