ASCO 2018 Focused on the CAR-T Safety Problem

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Abstract

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CAR-T therapy is very different from traditional drugs. First, the therapy requires the isolation of T cells from the patient's body. The T cell is modified *in vitro* using a chimeric antigen receptor (CAR) to specifically recognize cancer cells, and then the transformed T cells are expanded and returned to the patient's body.

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In January 2018, Celgene acquired Juno Therapeutics for about US$9 billion. Juno Therapeutics is one of the pioneer companies in the development of immune cell therapy and has deployed a wide range of innovative CAR-T projects.

At the ASCO annual meeting, Celgene released the latest clinical data of JCAR017. JCAR017 showed

greater competition in the treatment of lymphomas than Kymriah and Yescarta. f Moreover, JCAR017 has a relatively low safety risk, that is, the probability of occurrence of cytokine release syndrome CRS and neurotoxicity (two common side effects) is relatively low and more than half of clinical patients do not have CRS or neurotoxicity.

For 102 evaluable patients (including multiple dose levels), the overall response rate and complete response rate of JCAR017 reached 40% and 34%, respectively. Of these, 49% of the 37 patients with relapsed or refractory B-cell non-Hodgkin's lymphoma responded to JCAR017 for the 6-month response index. Overall, the patient's complete response rate reached 46%.

These safety data bring great confidence for Celgene. to verify the feasibility of using JCAR017 as an outpatient treatment. In addition to liso-cel, bb2121, the Celgene and Bluebird's CAR-T cooperation project also attracted attention at ASCO annual meeting. Bb2121 is suitable for multiple myeloma. In patients receiving cell therapy, the average progression-free survival was 11.8 months. Of the 22 patients receiving over 150 million CAR-T cell injections, 95.5% had a response with an average duration of 10.8 months.

In terms of safety, CRS immune responses occurred in 63% of 43 patients. Chief researcher Noopur Raje emphasized that these patients are not severely affected and that the median duration of CRS is 6 days. In addition, CAR-T is also a hot topic in academia. Many scientists have been troubled by its side effects. About one-third of patients will have CRS (typical symptoms include varying degrees of flu-like symptoms, fever, nausea, muscle pain, severe ICU-level care).

On May 28th, two articles were published in *Nature,* revealing a new approach to combating cytokine release syndrome.

In the study titled 'Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells,' scientists from the University of San Rafael, Italy used mice as the model and simulated the occurrence of CRS. They screened a key molecule responsible for the CRS response, IL-1 (mainly derived from macrophages, which is associated with inflammation). Based on this finding, they further found a drug called anakinra, which could prevent CRS and neurotoxicity by inhibiting IL-1 molecules.

In another study completed by scientists at the Sloan Kettering Cancer Center in the United States, they also found IL-1 based on different mouse models and confirmed that the severity of the CRS reaction is not mediated by cytokine mediates secreted by T cells but is associated with interleukins IL-6, IL-1, and nitric oxide (NO) produced by macrophages. What's different is that they did not block IL-1. Instead, but blocked the CRS by adding a suppressor gene to the CAR-T cells.

Although these two studies were performed on animal models, they provide great clues for improving the safety of CAR-T, opening up new avenues for safer and more effective cell therapy.

Author Bio

As a global company, Creative Biolabs has more than 200 talented and well-trained scientists located in different continents working closely with partners from the entire world to develop and produce medicines of tomorrow. Specifically, we are the established leading expert in TCR technology and CAR T&NK cell

immune therapy development, as we offer the one-stop custom services that cover the entire new drug development pipeline. Additionally, we also offer an exclusive line of ready-to-use TCR and CAR T&NK cell construction products, such as virus packaging, purification, expansion and titer determination kits. Furthermore, we have built up a unique unparalleled CAR construction and production platform for all four CAR T generations.