DOI: 10.18203/issn.2456-3994.IntJMolImmunoOncol20170057

Putting viruses to work in CAR therapies

Sir,

You hear a lot about focus on "Personalized Medicine" and rightly so. Cancer care has moved from radical surgeries to nonspecific chemotherapies to targeted therapies. Critical question of why some residual cancer cells remain unkilled, dormant, and invisible to immune systems is now the new focus. At the end of the day, the difference between the patient who gets cured after surgery, chemotherapy, and event-targeted therapies and who relapses with a small quantum of intrepid cancer cells is whether the dendritic cell–T-cell complex could find and eliminate residual minimal tumor load.

A very significant chapter in these battles has opened up with the chimeric antigen receptor (CAR) therapy.

A good number of B-cell neoplasms express CD19. The idea was to create a CAR and then modify T-cells to express CARs. The next step was an adaptive transfer of CAR T-cells with anti-CD19 faculties.

In the groundbreaking study reported in NEJM, a group of 30 patients (adult and pediatric) with refractory acute lymphatic leukemia (ALL) received CAR T-therapy (CTL019) and 27 of this entered remission. These were transplant failures, blinatumomab failures, and considered end stage.[1] A subsequent study of 16 adults with refractory ALL produced 88% response rate, which was converted to long-term remission by autologous bone marrow transplants.[2]

The CAR T-technology has shown continued promise, and this year, at the American Society of Hematology at San Diego last week, several encouraging abstracts were presented. The pantheon of B-cell neoplasms is large and includes ALL, chronic lymphocytic leukemia, non-Hodgkin lymphoma, and myelomas. How applicable this technology will be in each of these remains to be seen.

The issue of side effects such as severe "cytokine storm" leading to hyperferritinemia, hypotension, capillary leak, and disseminated intravascular coagulation was ameliorated using anti-interleukin 6 molecule tocilizumab. Unfortunately, indiscriminate use of this compound could lead to inadequate T-cell proliferation due to "cytokine feedback loop." Hence, its use was curtailed to severe cytokine release syndrome.

Here is also an issue of cost. Lentivirus system is costly. Other approaches using transposon or RNA transfection are being explored.

Can this apply to other liquid cancers? Can it extend to solid tumors where PD -1 and PDL-1 inhibitors and CTL4 downregulators are playing the inner field?

Molecular biology as the template for weaponizing anticancer therapeutics is attempting to cross the last frontier. Why do some cancer cells persist, remain dormant, start the drum beats, and grow in a second shower of metastasis and eventually end the life of the patient? Immune failure to "see" these cells, target, and eradicate them is the focus of CAR T and other strategies.

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How to cite this article: Mehta DG. Putting viruses to work in car therapies. Int J Mol Immuno Oncol 2017;2:25-26.

Source of Support: Nil. **Conflict of Interest:** None declared.

Reply to the Letter to the Editor

Reply to - Putting viruses to work in CAR therapies

It is an exciting time for immunotherapy in cancer. Two new approaches have emerged over the last few years: One involving the inhibition of immune checkpoints (CTLA-1 and PD-1) and the other using chimeric antigen receptor (CAR) T cells in a revolutionary therapy involving the re-engineering of T cells collected from a patient. Different laboratories have used different vectors (retroviruses or lentiviruses) for the transduction of the CAR and costimulatory molecule(s) into T cells. The altered T cells that express CARs on their surface have been under investigation and development in research laboratories since the 1980s, with modifications made over time to optimize specificity and lower the side effects. The re-engineered CAR T cells are expanded in the laboratory and frozen, after which they are infused into the patient from whom they originated. Once the CAR T cells re-enter the patient, they proliferate and can target the tumor antigen recognized by the CAR. Apart from the immediate benefit of CARs attacking tumors cells, there is possibly a long-term benefit as they may protect against cancer recurrence owing to their ability to remain in the body for a long time. Initial results from clinical trials of CD19 CAR T cells to target ALL are clearly promising. In addition, other non-CD19 tumors are being explored for CAR T cell treatment, including cancers of the pancreas and brain. For example, CARTmeso cells recently developed at the University of Pennsylvania are T cells that target mesothelin, by expressing a chimeric receptor against mesothelin fused to a costimulatory molecule 4-1BB. These CARTmeso cells have been proposed for targeting mesothelin overexpressing cancers including pancreatic, mesothelioma, ovarian, triple-negative breast cancer, and ovarian cancer. There is much to look out for in the months to come.

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