Editorial

The promise and challenges of chimeric antigen receptor T cells in relapsed B-cell acute lymphoblastic leukemia

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Historically, surgery, chemotherapy and radiation therapy are the three traditional modalities of medical treatment for cancer patients. In recent years, cancer immunotherapy, which harnesses body's immune system to fight against cancer, has increasingly become a viable treatment option for cancer patients. A rapidly emerging cancer immunotherapy approach is called adoptive T cells transfer (ACT), which involves the isolation and reinfusion of tumor-reactive T lymphocytes into cancer patients (1). T cells used for adoptive immunotherapy are either from *ex vivo* expanded autologous tumor-infiltrating lymphocytes (TILs), or genetically engineered T cells.

In 1988, Rosenberg *et al.* from US National Cancer Institute (NCI) reported the first clinical study using ACT for the immunotherapy of patients with metastatic melanoma (2). In this study, T lymphocytes were isolated from cancer samples (TILs), expanded *ex vivo* in the presence of interleukin-2 (IL-2) and reinfused back into the same patient. Although objective responses were observed in 11 of 20 patients, the tumor regression was not durable and only lasted from 2 to more than 13 months because the transferred T cells failed to engraft and persist *in vivo*. There is accumulating evidence that preparative lymphodepletion can augment the efficacy of ACT by (I) depleting immunosuppressive regulatory T cells (Tregs) (3); (II) inducing immunogenic cell death (ICD) and enhancing antigen presentation (4); (III) depleting endogenous cells that compete for growth factors or cytokines (5). In 2002, Dudley demonstrated that lymphodepleting regimen, either chemotherapy or total body irradiation (TBI), prior to ACT led to persistent clonal repopulation of transferred T cells and increased tumor regression (6). Twenty of 93 patients with metastatic melanoma achieved complete responses after receiving the combinational therapy of TBI and ACT. Importantly, 19 of the 20 responses have ongoing complete regression for more than 3 years (7). However, the efficacy of TIL seems to be restricted to melanoma for unknown reasons. Other tumors, breast and colon cancer for instance, do contain T lymphocytes, however, these isolated TIL were tumor-promoting rather than tumor-suppressive (8,9). These findings largely limit the use of TIL for cancer immunotherapy in clinic.

There are two types of genetically modified T cells for adoptive transfer: tumor antigen-specific T cell receptor (TCR)-transduced T cells or chimeric antigen receptor (CAR)-transduced T cells. Tumor-reactive TCR can be isolated directly from the rare tumor-specific T cells in cancer patients (10) or from mouse immunized with human cancer antigens (11). Genes encoding desired TCRs were cloned into a retroviral or lentiviral vector, and transduced into T cells isolated from cancer patients. It was reported that adoptive transfer of T lymphocytes transduced with a retrovirus encoding TCRs that recognize a melanoma tumor antigen MART1 resulted in regression in patients with metastatic melanoma (12). Although many tumor antigen-specific TCRs have been identified, these TCRs are still major histocompatibility complex (MHC)-restricted and antigen presenting cells (APCs) are required to process and present the tumor antigen to TCR-transduced T cells. CARs are another approach to provide antigen specificity

to transduced T cells. CARs are hybrid receptors composed of an extracellular single-chain variable fragment (scFv) derived from an antibody that specifically recognizes a tumor antigen, an intracellular signal portion of the TCRs, and a costimulatory signaling domain such as CD28, 41BB, etc. Hence, CAR-transduced T cells combine the specificity of an antibody and the anti-tumor immunity of T cells. More importantly, CARs directly recognize and target antigen on tumor surface and avoid the limitations of MHC-restrictions (13,14).

CAR T cells therapy has achieved great success in hematologic malignancies, especially in the B-cell acute lymphoblastic leukemia (ALL) (15) and B cell lymphoma (16). Multiple clinical trials have shown that infusion of CD19 CAR T cells resulted in overall remission rates of 70% to 90% among children and adults with relapsed B-cell ALL, which are much higher than the response rates of standard chemotherapy (18% to 45%) (17-22). However, most of these clinical trials focused on the short-term clinical outcomes, the durability of remission in a large cohort and the factors associated with sustained remission remained unknown. In a recently published paper in *N Engl J Med*, Park *et al.* reported the long-term follow-up results from a phase 1 clinical trial involving adult patients with relapsed B-cell ALL who received CD19 CAR T cell therapy at Sloan Kettering Cancer Center (MSKCC) (23). A total of 53 patients were recruited. One of the 53 patients died from multi-organ failure and severe cytokine release syndrome on day 5 of treatment. Complete remission was observed in 44 of 53 patients (83%), which is consistent with previous studies (17-22). At a median follow-up of 29 months, the median event-free survival was 6.1 months, and median overall survival was 12.9 months. The authors further identified tumor burden before treatment as a useful clinical factor to predict the remission duration and survival. Patients with a lower tumor burden had a significantly longer event-free survival and overall survival than those with a higher tumor burden. They did not find a significant correlation between the persistence of CAR T cells and tumor remission as reported by other groups (21). In summary, these results suggested that although CD19 CAR T cells induced initial tumor remission, the antitumor was not durable and relapses occurred in majority of the patients. One possible explanation is that the residual tumor cells after initial remission in the patient with heavy tumor burden render CAR T cells dysfunctional, resulting in tumor relapse eventually. To overcome tumor-induced T cell tolerance, additional maintenance regimens are required. Immune-regulatory molecules known as immune checkpoints are crucial to maintain the immunological homeostasis and it has been known that some tumors use checkpoint systems to evade immune attack (24). In this landscape, the immune checkpoint blockades were developed to target the T cell regulatory pathways to augment antitumor immunity. The most widely studied immune checkpoint blockades are anti-CTLA-4, anti-PD-1, and anti-PD-L1 monoclonal antibodies. The CTLA4 blockade ipilimumab (Yervoy) is the first immune checkpoint blockade approved by the United States Food and Drug Administration (U.S. FDA) for advanced melanoma. Since 2016, five anti-PD-1 (pembrolizumab and nivolumab)/PD-L1 (atezolizumab, avelumab and durvalumab) monoclonal antibodies were approved for the treatment of patients with several types of cancer, including melanoma, non-small cell lung cancer, bladder cancer etc. (24). Further studies are required to explore if the combination of CD19 CAR T cells and immune checkpoint blockades will achieve durable antitumor immunity.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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