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Opinion

Clinical Progress of Immunotherapy for Cancer

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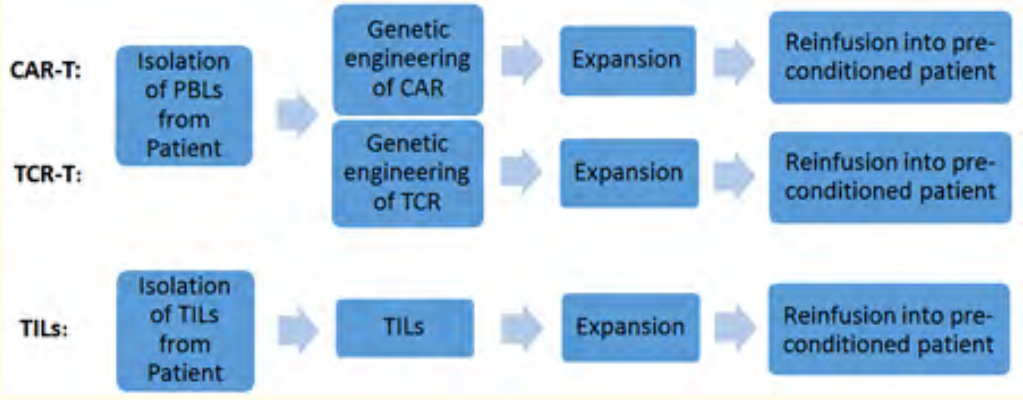
Cancer Immunotherapy, including Adoptive T cell (ACT) therapy, immune checkpoint (mainly PD-1, PD-L1, and CTLA-4) inhibition therapy, and the combination, has been successfully developed in the last few years, as exciting new treatments for cancer, especially for B cell leukemias and lymphomas [1-3]. Apart from the traditional surgery, chemotherapy, and radiotherapy, Cancer Immunotherapy is becoming the fourth treatment method for cancer.

ACT therapy, mainly including Chimeric Antigen Receptor T-cell (CAR-T) therapy, Tumor-Infiltrating Lymphocytes (TIL) therapy, and T cell Receptor engineered T cells (TCR-T) therapy, recognizing and destroying tumor cells by harnessing and enhancing the innate power of the immune system, is the most promising new cancer treatment approach. The general process of ACT Cancer Immunotherapy is shown in the flowchart below.



Flowchart: *General process of ACT Cancer Immunotherapy.*
PBLs: Peripheral Blood Lymphocytes

This article summarized and discussed the current progress of Cancer Immunotherapy mainly basing on the recently reported clinical data (including 2 latest case reports published on *New England Journal of Medicine* on Dec 8th and Dec 29th, 2016), and information got back from the 58th *American Society of Hematology (ASH) annual meeting* held on December 3-6, 2016 at San Diego, USA.

The most encouraging and proof-of-principle evidences about ACT inducing regression of tumors including leukemia, lymphoma, melanoma, and metastatic colorectal cancer are described below.

CAR-T therapy

By engineering chimeric antigen receptors (CARs) on the surface of T cells, enables the redirection of T cell specifically targeting tumor cells expressing the antigen. Till now, anti-CD19 CAR-T (CART19) cells treatment for CD19+ B cell malignancies, is the most successful example of immunotherapy from the reported clinical trials. These CD19+ B cell malignancies include non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL). Among the anti-CD19 CAR-T cell products, the hottest are: KTE-C19 developed by NCI and Kite Pharm; CTL019 and CTL119 developed by University of Pennsylvania and Novartis; JCAR014, 015, and 017 developed by Juno Therapeutics.

KTE-C19

The construct of KTE-C19 was initially established at National Cancer Institute (NCI) and later developed by Kite Pharm [4-6]. At NCI, the application of this CART19 on 27 Diffuse large B-cell lymphoma (DLBCL)/Primary Mediastinal B-cell Lymphoma (PMBCL) patients, led to 70% overall response (ORR) and 48% complete response (CR); on 7 CLL patients, 86% ORR and 57% CR; on 6 indolent NHL patients, 100% ORR and 66% CR; on 1 Mantle cell lymphoma (MCL) patients, 100% ORR and 100% CR (presented on *American Association of Cancer Research, AACR*, 2016).

4 KTE-C19 clinical trials have been registered. Initial results from the multicenter phase 1-2 ZUMA-1 trial (NCT02348216): 4 of the 6 DLBCL/PMBCL patients showed CR, 1 patient PR, 1 patient stable disease (SD)[7]. Interim results of ZUMA-1 presented on the 58th *ASH annual meeting* showed, 6 PMBCL/Transformed Follicular Lymphoma (TFL) patients received KTE-C19 had 100% ORR [8]. Since the anti-CD19 scFv of KTE-C19 is murine, to reduce risks of immunization-mediated clearance of CAR-T cells in patients, Kite Pharm designed a novel fully humanized Anti-CD19 CAR (HuCAR-19). Infusion of HuCAR-19 to 11 lymphoma patients led to 86% ORR [9] (presented on 58th *ASH annual meeting*). Preliminary results for ZUMA-3 (NCT02614066), and ZUMA-4 (NCT02625480) on adult and pediatric patients with Relapsed/Refractory ALL (R/R ALL) treated with KTE-C19 showed all 5 patients got MRD-remission [10] (presented on 58th *ASH annual meeting*).

CTL019 and CTL119

Results from a pilot trial showed 57% of the 14 CTL019 treated CLL patients had ORR, 29% had CR; for MCL patients, 50% (1/2) ORR [11]. Preliminary 3 month response analysis showed, for DLBCL patients, CTL019 treatment led to 54% (7/13) ORR; for Follicular Lymphoma (FL) patients, 100% (7/7) ORR [12]. For 14 R/R FL patients, 79% (11/14) ORR occurred at 3 month after infusion of CTL019, the other 3 patients got Partial Response (PR), 50% (7/14) CR; at 6 month, 2 of the 3 PR patients converted to CR [13] (presented on 58th *ASH annual meeting*). For 35 pediatric and young adult R/R ALL patients, 29 patients were infused with CTL019, 6 withdrew prior to infusion (2 manufacturing failures, 4 deaths due to disease progression or intracranial hemorrhage, organ failure, or pneumonia separately). Interim analysis showed ORR in all infused patients was 69% (20/29) patients showed CR [14] (presented on 58th *ASH annual meeting*). Besides the efficacy, CTL019 showed expansion in both peripheral blood (PB) and bone marrow (BM), homed to tumor sites, released cytokines to kill tumor cells, and even can persist for 4 years in certain patients [15,16].

CTL119, a humanized version of CTL019, was designed with a human scFv peptide. Preliminary results with CTL119 on 6 ALL patients who failed with CTL019 before, showed 50% CR [17]. The latest report showed 1 month after CTL119 infusion, 87% (26/30) R/R ALL patients achieved CR; among the 11 patients who failed with CTL019 previously, 64% (7/11) patients achieved CR 1 month after infusion of CTL119 [18] (presented on 58th *ASH annual meeting*).

JCAR014, 015, and 017

One clinical trial applying JCAR014 on 18 adult R/R DLBCL, 6 R/R MCL, 6 R/R CLL patients who had previously received ibrutinib (a Bruton Tyrosine Kinase inhibitor causing PR in CLL patients), showed average of 67% ORR [19]. The latest presentation showed the ORR for 18 CLL patients was 76% (8 PR, 5 CR), 1 month after JCAR014 infusion [20] (presented on 58th *ASH annual meeting*).When applying JCAR014 on 29 adult R/R B-ALL patients, led to 93% CR [21]. JCAR014 treatment combined with anti-PD-L1 antibody (durvalumab) has been designed and registered for R/R NHL patients (NCT02706405).

Applying JCAR015 on 38 R/R B-ALL patients, led to 87% CR, and 58% of 6-month OS [22,23]. Despite the efficacy shown with JCAR015, the phase II ROCKET trial of JCAR015 was halted twice due to patient deaths. The trial led to deaths in this July relating to addition using of fludarabine to the pre-conditioning regimen, argued by Juno Therapeutics, and was allowed to resume by U.S. Food and Drug Administration (FDA). However, another 2 deaths occurred recently relating to cerebral edema, which might because of rapid proliferation of CAR-T cells in the body.

Testing JCAR017 on 37 R/R adult ALL patients, led to 91% CR (presented on AACR 2015). For DLBCL patients, JCAR017 treatment led to 82% (9/11) OR, 73% (8/11) CR, 9% (1/11) PR and 18% (2/11) PD at one month after infusion [24] (presented on 58th *ASH annual meeting*).

Multiple CAR-T products are competing for commercialization; part of the above popular ones will likely get approval from FDA in the upcoming 1 or 2 years [25].

One striking news of CAR-T therapy just reported CAR-T treatment successfully regressed solid tumor on a patient with glioblastoma. It is a case report published on the *New England Journal of Medicine* on Dec 29th, 2016. The 50-year-old man with recurrent multifocal glioblastoma was given multiple infusion of CAT-T cells genetically modified with tumor associated antigen interleukin-13 receptor alpha 2 (IL13Ra2), and later showed regression of all intracranial and spinal tumors until 7.5 months after initiation of the infusion. Unfortunately, the disease recurred at 4 new locations 228 days after initial CAR-T infusion, might due to decreased expression of IL13Ra2 [26]. Still, this is the first time proving recurrent multifocal glioblastoma can be regressed even though transiently. And it is a real meaningful try, for the first time proving CAR-T therapy can regress solid tumors.

TIL and TCR-T therapy

The infusion of tumor-infiltrating lymphocytes (TILs) has already shown efficacy in treating metastatic melanoma, its underling mechanism is these lymphocytes contain T cell receptors specifically recognizing the tumor specific non-synonymous mutations. Currently, TILs therapy had led to durable CR in 20 - 25% of metastatic melanoma patients [27,28].

A recent case report published on the *New England Journal of Medicine* on Dec 8th, 2016, showed autologous TILs killed the tumor cells of one KRAS G12D mutation metastatic colorectal cancer patient. After TILs infusion, all seven metastatic lung nodules regressed, with only one progressed (this one was surgically removed). So far, this is the first study proving by administering TILs can effectively mediate antitumor immune response against KRAS G12D mutated cancers [27]. Thus, this case indicate the possibility of T cell receptor (TCR) gene therapy (TCR-T) for cancers expressing this common mutation.

The first clinical trial applying TCR-T was on metastatic melanoma patients. The T cells was genetically modified with a TCR directed against the melanoma antigen recognized by T cells (MART1), and infused to 31 patients, finally 4 patients got measurable regression [29,30]. Later clinical trials with TCRs against glycoprotein 100 (gp100), cancer testes antigen (NYESO-1), and melanoma-associated antigen 3 (MAGE-A3), demonstrated significant and prolonged regression on melanoma or sarcoma patients. Among the 16 gp100 specific

melanoma patients, 1 patient achieved CR, 2 achieved PR; for the 17 NYESO-1 melanoma and sarcoma patients, 2 achieved CR, 7 achieved PR; for the 9 MAGE-A3 specific melanoma and synovial sarcoma patients, 1 achieved 1 CR, 4 achieved PR [31-34]. These earlier TCR-T therapies showed overall feasibility and potential as treatments for different cancers, even though not exciting enough yet.

Conflict of Interest

There is no conflict.

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