Commentary Article

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4SCAR2.0 Treating Refractory B Cell Lymphomas: An Advanced Technology Saves More Lives!

Cheng Jiao[1,2*], Liyuan Sheng[2,3] and Lung-Ji Chang [1,4]

[1] Shenzhen Geno-Immune Medical Institute, Shenzhen, 518000, China

[2] PKU-HKUST Shenzhen-Hong Kong Institutions, Shenzhen, 518057, China

[3] Peking University, Shenzhen Institute, Shenzhen Key Lab for Human Tissue Regenerate and Repair, Shenzhen, 518057, China

[4] University of Electronic Science and Technology of China, Sichuan, 611731, China

***Correspondingauthor:** Cheng Jiao, MD & PhD Shenzhen Geno-immune Medical Institute, PKU-HKUST Shenzhen-Hong Kong Institutions,2nd FL. 6 Yuexing 2nd Rd., Nanshan Dist. Shenzhen, Guangdong China 518000, Tel:+86182-0217-3776; E-mail: verajoe@mail.ru.

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Abstract

CAR-T cell therapy represents an innovative and effective therapy forpatientswithrefractory/relapsed Bcellmalignancies. However, many limitations remain with the currently approved CAR-T products, including antigen escape, CAR-T exhaustion *in vivo*, significant toxicity, and high cost, to name a few.

Keywords: CAR-T cell; Malignancies; lymphoma

Introduction

CAR-T cell therapy represents an innovative and effective treatment for patients with refractory/relapsed B cell malignancies. Remarkably, the anti-CD19 CAR-T cells treating B cell acute lymphoblastic leukemia (B-ALL) can achieve close to a 90% complete remission (CR) rate. However, many limitations remain with the currently approved CAR-T products, including target antigen escape, CAR-T exhaustion in vivo, significant toxicity and high cost, to name a few.

Based on an advanced 4th generation CAR design (4SCAR), our team in Shenzhen Geno Immune Medical Institute has demonstrated not only a significant improvement in efficacy, but also a high safety feature (low to no severe toxicity) by integrating multiple co-stimulatory signalling domains and an inducible suicide gene design. After years of clinical experiences, the 4SCAR19 T cell therapy has demonstrated a remission rate matching the 3rd generation CAR design but without severe side effects [1-12].

The ultimate goal for the 4SCAR2.0 therapy in treating highly refractory/relapsed B cell lymphomas (r/r BCLs) is to completely eradicate residual tumor cells, to prevent tumor antigen escape, and to prevent recurrence [13]. The novel regimen is designed to apply multiple CAR-T cell infusions to target different tumor antigens and to extend the in vivo CAR-T cell persistence. The 4SCAR2.0 regimen includes a primary and booster CAR-T infusions, and a consolidation infusion as needed. The number of infusions is based on patient's condition and tumor response. Through infusions of multi target 4SCAR-T cells, patients with r/r BCLs have obtained significant curative effect with little to no adverse reactions. Importantly, the 4SCAR2.0 is highly affordable due to the advanced technology improvement.

The key features to the success of the 4SCAR2.0 strategy are the followings

(1) **Preserving good quality of immune cells at an earlier time:** The collection of peripheral blood mononuclear cells (PBMCs) should be arranged prior to extensive chemotherapies, at the time of relapse and prior to re-induction chemotherapy. For examples, Patient 1 (**Figure 1A**) was not given any chemotherapy before a single apheresis blood cell collection for all of the CAR-T prepara- tions; Patient 2 (**Figure 1B**) collected PBMCs prior to a series of chemotherapies and auto transplantation and received 4SCAR-T infusions after achieved remission.

(2) **Precision tumor targeting multi CAR-T regimen.**The target an- tigens for the CAR-T cells were identified by immune staining of individual tumor specimens which were obtained at the time of initial diagnosis or relapses.

(3) **Extended in vivo protective CAR-T memory.** Through primary, booster and consolidation CAR-T infusions, the 4SCAR2.0 regimen can maintain the tumor targeting T cell reservoirs and ex- tend the CAR-T cell memory (**Figure 1**).

In summary, the 4SCAR2.0 regimen presents characteristics of low toxicity and high response rate, and still, is affordable for most patients; for example, the total treatment cost was less than 100,000 USD for the 5 CAR-T preparations for Patient 1 including two months of hospitalization costs.

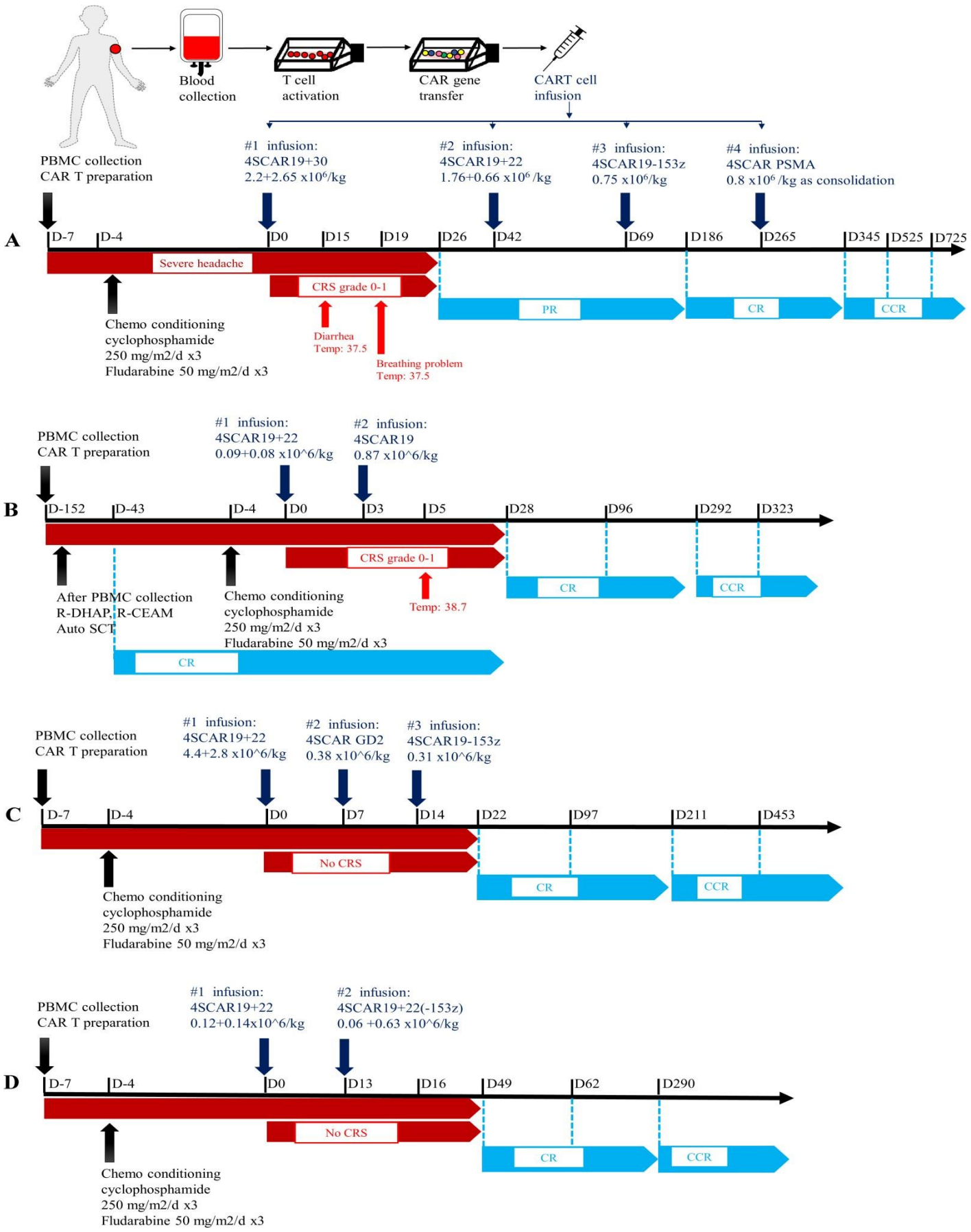

Figure 1 The timeline and key events of the 4SCAR2.0 therapy.
(A) The timeline and key events of multiple 4SCART therapy for Patient 1.
(B) The timeline and key events of multiple 4SCART therapy for Patient 2.
(C) The timeline and key events of multiple 4SCART therapy for Patient 3.
(D) The timeline and key events of multiple 4SCART therapy for Patient 4.

Conflict of Interest

There is no competing financial conflict of interests from all authors.

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