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LETTER

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First pediatric B-acute lymphoblastic leukemia patient treated with anti-CD19 chimeric antigen receptor T-cell therapy: Long-term remission or early cure?

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Dear Editor,

We read R. Awasthia *et al.*'s paper "*Kymriah® (tisagenlecleucel) – An overview of the clinical development journey of the first approved CAR-T therapy*"[1] with great interest. The authors describe the pathway of clinical evolution of tisagenlecleucel, the first autologous anti-CD19 chimeric antigen receptor (CAR) T-cell immunotherapy approved for the treatment of three relapsed/refractory (r/r) hematologic malignancies: pediatric and young adult B-acute lymphoblastic leukemia (B-ALL), diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL). We congratulate the authors for the qualitative description of this topic.

In Figure 1 of R. Awasthia et al.'s paper, the phrase "*First pediatric patient, Emily Whitehead, treated with CAR T therapy 10 years ago remains cancer-free*" is presented as Kymriah's achievement in 2022. Additionally, the first paragraph of the *Efficacy* section mentions "*... the first patient treated with tisagenlecleucel in a clinical trial for pediatric ALL recently celebrated 10 years in remission*." In both points, the authors argue that the young girl remains in long-term remission but not declared as cured. As the evidence around CAR T-cell therapies increases, the researchers feel more confident in believing that Emily is actually cured.[2] In light of the findings on long-lived functionally active CAR T-cells over a decade in two chronic lymphocytic leukemia (CLL) patients[3] and given the absence of relevant long-term data on Emily's case, her actual disease status remains unclear; was the B-ALL burden completely eradicated early soon after the CAR T-cell infusion, or some residual B-ALL cells remained over a decade and were being destroyed by potentially remaining anti-CD19 CAR T-cells?

Early complete disease remission (CR) in the child patient was associated with a persistent molecular remission. Analysis of minimal residual disease (MRD) by deep DNA sequencing of the total rearranged IGH gene locus revealed the malignant clone was undetected in the blood or marrow on day 180 post infusion.[4] If a residual leukemic clone was suppressed by remaining anti-CD19 CAR T-cells without relapsing for 11 consecutive years, the following questions are reasonably raised:

(1) During this period, have CAR T-cells been detected in the blood or marrow, contributing to the alleged long-term suppression of the remaining leukemic clone and even at undetectable MRD levels?
(2) How long B-cell aplasia lasted and has immunoglobulin replacement been administered?
(3) How unique could the cytotoxic potential of the hypothetical remaining few CAR T-cells be, so that for 11 consecutive years they suppress leukemia? Such a clinical course is not in keeping with the hitherto usual results, where prolonged CRs are rarely achieved and most patients relapse after months.[5,6]

To date, *Kymriah* has been administered to more than 7,000 r/r B-ALL, r/r DLBCL, and r/r FL patients in the real-world setting and in clinical trials.[1] In addition, more than 34,400 patients worldwide have received commercial CAR T-cell immunotherapies.[7] Although CAR T-cells are incredibly potent in killing tumor cells, to the best of our knowledge, only three cases have been published where the remission lasted (or lasts) more than 10 years: a) In 2010, anti-CD19 CAR T-cells were administered in 2 advanced, chemotherapy-resistant CLL patients – first patient Bill Ludwig 65 years old, and second patient Doug Olson 64 years old[3,8]; b) in 2012, third patient the 6-year-old girl with r/r pre-B-cell ALL, Emily Whitehead treated with the same product.[4] In the forthcoming years, as clinical trial and real-world data are expected to become available, more patients may be found as cancer-free after a decade follow-up.[3] Remarkably, the first and third patients were administered very high doses and both became gravely ill due to cytokine release syndrome grade 3/4 (Table 1). All three patients were leukemia-free for more than 10 years, and in January 2021, Bill Ludwig died due to COVID-19 infection.[9]

Both academics and biotechnologists are focused on manufacturing more potent and less toxic CAR T-cells.[10,11] Optimal *in vivo* clinical expansion and functional persistence are important determinants to ensure long-term therapeutic efficacy.[3,12] Current CAR T-cell products have been designed to combine robust *in vivo*

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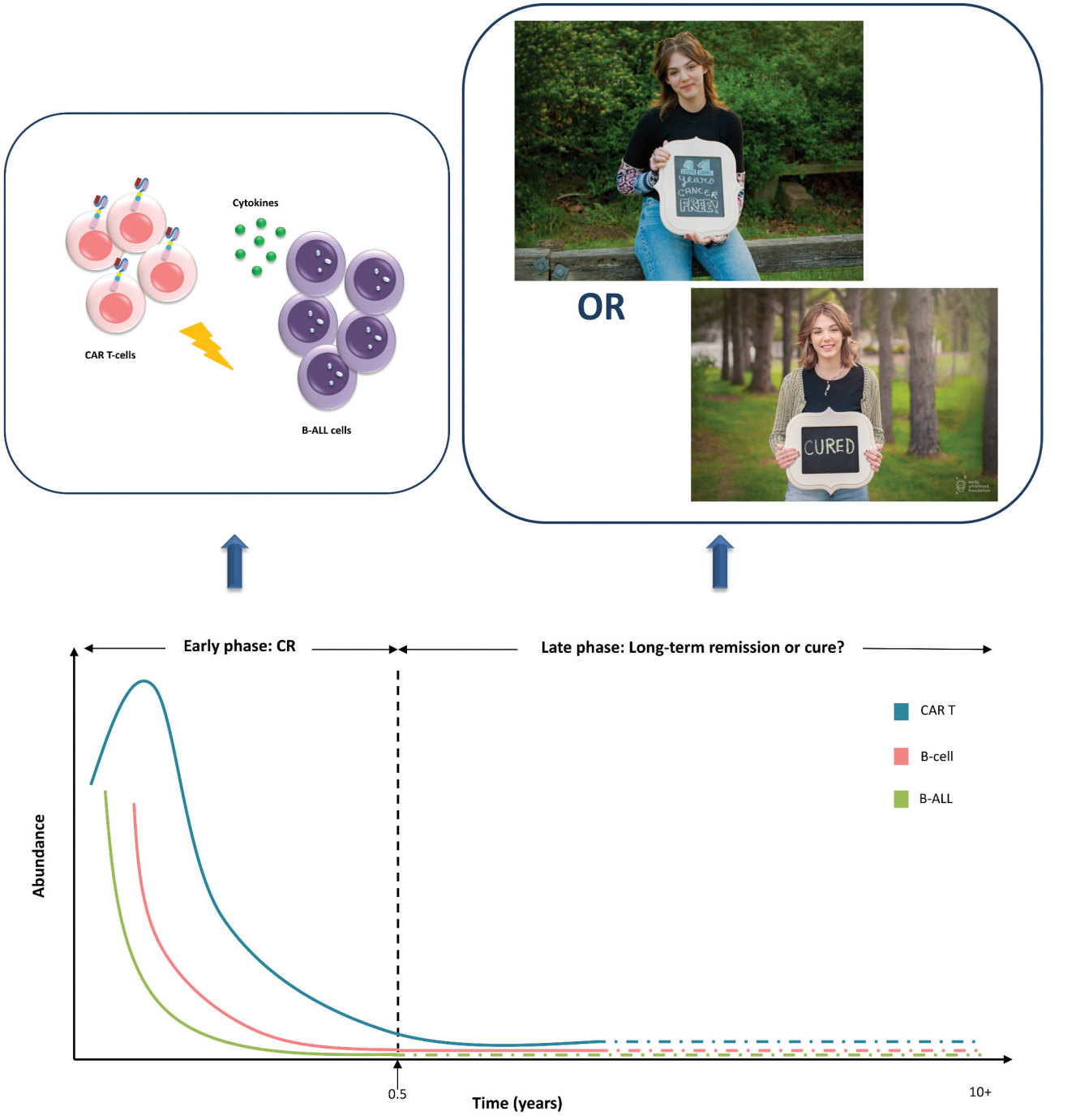

Figure 1. Long-term remission or cure? The leukemic clone was not detected in the blood or marrow by deep molecular sequencing on day 180 after CAR T-cell administration.[4] The actual B-ALL cell and CAR T-cell status of Emily remains unclear, on whether the malignant burden was completely eradicated soon after the CAR T-cell infusion, or whether some potentially remaining active CAR T-cells destroyed very few residual B-ALL cells. Emily Whitehead remains 11-year cancer-free celebrating a cure, with early disease eradication constituting a possible hypothesis. Photo credit: reproduction with permission from the Emily Whitehead Foundation. B-ALL: B-acute lymphoblastic leukemia, CR: Complete remission.

expansion with long-term persistence; however, it seems that such cell doses rarely offer prolonged disease remission or even cure, but they can increase patients' survival from months to a few years.[5] Because high-dose regimens have been associated with long-term remissions,[5] we speculate that they have the required ability to randomly eliminate the malignant clone early in the first months after infusion.[13] The over a decade disease-free duration of the first and third patients could be the outcome of the very high anti-CD19 CAR T-cell doses (Table 1).

Therefore, the following combination may represent a new therapeutic strategy:

(1) Very high CAR T-cell numbers infused in a split-dosing manner for safety reasons, with longer intervals between infusions.

Table 1. Patients characteristics and clinical outcome of two patients cancer-free for more than a decade post CAR T-cell therapy[3,4,8].

Characteristic	First Patient	Third Patient
Name	Bill Ludwig	Emily Whitehead
Sex	Male	Female
Age at infusion	65 years	7 years
Disease diagnosis	r/r CLL	r/r pre-B-cell ALL
Year of infusion	2010	2012
Total anti-CD19 CAR T-cell number (dose)	1.1×10^9 (1.6×10^7/kg)	1×10^8 (1.2×10^7/kg)
Method of administration	Split-dose	Split-dose in 3 consecutive days
Tumor burden before CAR T-cell infusion	High (1.7×10^{12} CLL cells in BM, approximately 1 kg of tumor load)	No data
Cell kinetics post infusion	10,000-fold expansion during 1st month	>1000 expansion compared to initial engraftment level
Best response	CR, molecular MRD negative	CR, molecular MRD negative
Best response achieved	At 1 month	At 6 months
Duration of best response	Ongoing for 11 years	Ongoing for 11 years
Cytokine release syndrome	Grade 3/4	Grade 4 (IL-6 levels increased >1000 times)
B-cell aplasia	Severe for 8 years	Severe

Abbreviations: ALL: acute lymphoblastic leukemia, BM: bone marrow, CAR: chimeric antigen receptor, CLL: chronic lymphocytic leukemia, r/r: relapsed/refractory, CR: complete remission, IL-6: interleukin-6, MRD: minimal residual disease.

(2) High CAR T-cell fitness to promote robust anti-leukemic capacity.
(3) Defined composition of CAR T-cell subpopulations in the infused product to help interpret the outcomes.[13]
(4) Short-term CAR T-cell persistence to minimize or avoid negative relapses, decrease long-term life-threatening infections and prevent potential secondary malignancies.[7,14]
(5) Effective control of the disease burden before the infusion.

In contrast, in current applied practice, both parameters of *in vivo* expansion and persistence are pursued to be augmented. However, the proposed strategy could increase the likelihood of early eradication of the malignancy by chance.

How could one convincingly answer the question *"have B-ALL cells been present for more than a decade in Emily's blood or marrow, or was she cured early after recovery from the IL-6 shock*?"[15] If Emily still has persisting CAR T-cells and tiny amounts of remaining B-ALL cells, obviously, the leukemic clone has been inactive for 11 years but there is no such evidence in the literature (Figure 1). In such a scenario, CAR T-cells are expected to disappear in approximately 14–15 years post infusion due to senescence,[13,16,17] eliminating also B-cell aplasia. If the B-ALL clone will not reappear, this can confirm the hypothesis of early cure. In the opposite scenario, if CAR T-cells have no longer been detected and B-cell aplasia has been gradually restored without leukemia reappearance, this constitutes an even stronger argument in favor of a potential early cure.

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DB and SB were involved in the conception and design; DB drafted the original paper; SB revised it critically for intellectual content, edited it, and designed the figure; DB and SB approved the final version to be published.

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