Not all T cells are created alike!

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Citation: Abecasis M. Not all T cells are created alike! (a comment on a report K. Beider). Cell Ther Transplant 2020; 9(4): 85-87.

Summary

The comment concerns discussion of results reported by K. Beider on the clinical response rates in patients with resistant/refractory lymphomas treated with CAR-T cells, and the factors predicting therapeutic success, in particular, distinct role of T cell ageing and their exhaustion phenotype as a reason for decreased response after adoptive cellular therapy. The patients who responded to treatment, had low levels of exhausted cells in blood and final CAR T cell product. Additional studies are needed to establish desirable attributes of CAR T cells, but the optimal characteristics might differ depending on the CAR construct and the malignancy being targeted.

Keywords

CAR-T cells, exhaustion phenotype, lymphoma, treatment.

Dear Editor,

I would like to comment a report by Dr. K. Beider "*Senescent/exhausted phenotype of CD 19 – targeted CAR-T cells and induction of immunoregulatory environment correlate with reduced response to CAR T cell therapy in relapsed/refractory B cell malignancies*" presented at the R. Gorbacheva Memorial Meeting in St. Petersburg at September 19, 2020 under *Focus on Lymphomas* (access: <https://rgmm.info/translycii/auditorya-5>).

The CD19-specific CAR T cells have shown significant antitumor activity in the treatment of high-risk relapsed and refractory leukemias and lymphomas and have revolutionized the treatment landscape for patients with advanced lymphoid malignancies. In 2018 two CAR T cell products were approved by the US and European regulatory authorities. Both Axicabtagene ciloleucel (Yescarta, Gilead/Kite) and tisagenlecleucel (Kymriah, Novartis) are now available for clinical use, based on the results of the ZUMA-1 (Yescarta) and JULIET (Kymriah) trials for refractory/relapsed relapsed/refractory aggressive B-cell lymphomas, and the ELIANA trial (Kymriah) for advanced acute lymphoblastic leukemia in patients up to 25 years of age.

Longer-term follow-up data from the lymphoma trials indicate durable responses for for the 40-60% of patients who

achieved a complete response. Studies to better identify predictors of response are needed in order to improve the risk-benefit balance and minimize unnecessary financial burden for individual patients and healthcare systems. This could eventually result in those predicted to respond poorly to chemotherapy but well to CAR T cells receiving them upfront. Among the more commonly cited impediments for effective CAR T cell therapy are loss or modulation of CD 19 expression by the target cells, lack of CAR T cell persistence, as well as product manufacturing failures. Adequate T cell manufacturing is an essential component of CAR T cell therapy. Quantitative and qualitative characteristics of the apheresis product can affect the ability to successfully produce an efficient T cell product. Even if T cell numbers are adequate the starting T cell phenotype can be an important determinant of subsequent clinical activity.

In her presentation Dr. Katia Beider discussed the factors that can preclude durable remissions following CAR T cell therapy with a special focus on the role of T cell senescence and exhaustion phenotype as a cause for reduced response after adoptive cell therapy in patients with relapsed/refractory B cell lymphomas. She presented data on 22 patients (86% with B cell non-Hodgkin's lymphomas) that were treated at Sheba Medical Center in Tel Hashomer (Israel) with an house-made CAR T cell construct composed of an

anti-CD19 single-chain Fv FMC63, CD28 co-stimulatory and CD3-zeta intracellular domain.

For each patient samples were collected after apheresis, but before lymphodepletion, from the CAR T cell infused product and on days 7, 14, 21, 30 and 60 after infusion. Clinical responses were evaluated at day 28, with 11 patients (50%) achieving complete response; 2 patients developed partial response (9%), and 9 patients (41%) had progressive disease. The manufactured product contained high-purity CD3 + T cells, composed with CD4+ and CD8+ T cells. The frequency of exhausted T cells, phenotypically defined as CD28 negative, with upregulation of CD57 and CD39 molecules, was analysed in the CAR T cell products. A significant increase of exhausted CD8 T cells was observed in the product infused in patients with progressive disease when compared to patients with clinical response.

The investigators then asked the question whether the exhausted T cells were already present in the peripheral blood of these patients, or developed following genetic transduction and *in vitro* expansion. Responding patients had very low levels of exhausted cells in the blood and the final product also had a very low frequency of these cells. In contrast, two groups were seen among the patients with progressive disease: patients who had increased numbers of exhausted T cells in their original pool, that did not change in the final product, and the patients that had low number of these cells in the initial product, but increased during the transduction and expansion procedures, showing that these cells can be induced during the manufacturing process.

Interestingly, the exhausted phenotype in CD8+ T cells was associated with an increase in memory phenotype acquisition in CAR T products; in contrast, naïve T cells were low in non-responders as compared to responders, suggesting that less differentiated phenotypes were associated with better responses.

They also showed an increased expression of the CCR7 chemokine on CD4+ and CD8+ CAR T cells from responding patients, with increased trafficking of these cells to lymphoid tissue. Finally, they studied the PD-1 expression in CD8+ cells in the CAR T product and found a significant correlation of an increased expression with the exhausted phenotype.

These results suggest that the starting T cell phenotype in the apheresis product and after expansion and transduction may influence the subsequent clinical activity of the CAR T cell product and elucidate in part the mechanisms of cell trafficking and efficacy.

The data also suggest that combining CAR T cell therapy with immune checkpoint inhibitors may improve the effectiveness of the treatment, and pre-clinical data support such a synergetic approach [1]. However, strategies that enhance the potency of these products run the risk of inadvertently worsening the already considerable toxic effects.

It would have been interesting to know whether these results have any correlation with the number of previous lines of chemotherapy given to patients before collecting the T cells, and the time from diagnosis to treatment since persistent

antigen exposure in cancer has been proposed to lead to cytotoxic T lymphocyte exhaustion.

These results were obtained in patients with B cell lymphomas and contrast with those in patients with B-ALL in whom standard parameters that define T cell potency, such as markers of T cell exhaustion, have been disappointing in terms of predicting clinical efficacy [2-5]. In patients with CLL, however, among whom response rates have been substantially lower than those in patients with ALL or lymphoma, product characteristics, such as enrichment for IL-6-STAT3 signatures, and elevated frequency of CD29+CD45RO-CD8+ T cells before CAR T cell generation, were able to identify a favourable response [6].

Additional data will be required to establish desirable attributes of CAR T cells, but the optimal characteristics might differ depending on the CAR construct and the malignancy being targeted.

Conflict of interest

None declared.

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Не все Т-клетки созданы одинаковыми (комментарий к докладу К. Байдер)

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Резюме

Статья-комментарий посвящена обсуждению результатов К.Байдер относительно частоты клинических ответов у пациентов с резистентными/рефрактерными лимфомами, леченых CAR-T-клетками, и факторов успешности этой терапии, в особенности – роли старения Т-клеток и фенотипа их «истощения» как причины снижения ответа после адоптивной клеточной терапии у больных. Больные, ответившие на лечение, имели низкие уровни «истощенных» клеток в крови и конечном CAR-T-клеточном продукте. Требуются дополнительные исследования для установления требуемых количеств CAR Т-клеток, но оптимальные параметры могут различаться в зависимости от генотипа CAR-конструкта и вида злокачественного заболевания.

Ключевые слова

CAR-T клетки, фенотип истощения, лимфомы, терапия.