haematologica
Journal of the Ferrata Storti Foundation

Optimizing exposure: the case for dose-dense CAR T-cell administration

by Alberto Mussetti and Anna Sureda

Received: August 11, 2026.
Accepted: August 17, 2026.

Citation: Alberto Mussetti and Anna Sureda. Optimizing exposure: the case for dose-dense CAR T-cell administration.
Haematologica. 2026 Aug 27. doi: 10.3324/haematol.2026.301807 [Epub ahead of print]

Optimizing exposure: the case for dose-dense CAR T-cell administration

Alberto Mussetti[1], Anna Sureda[1,2]

1. *Clinical Hematology Department, Institut Català d'Oncologia-IDIBELL, Barcelona, Spain*
2. *Department of Medicine, Universitat de Barcelona, Barcelona, Spain*

COI notes: AM received research grants from Gilead Kite and honoraria for lectures from Novartis, Kite/Gilead; BMS, Novartis, Merck, Arog, Incyte. AS received honoraria for lectures / advisory boards from Takeda, MSD, Novartis, Gilead Kite, BMS / Celgene, GenMab, Abbvie, Roche, Sanofi, Pierre Fabre, Menarini, Therakos, Incyte and Research support from Takeda.

Author contributions and disclosures: AM has written the commentary; AM and AS have reviewed the final manuscript and approved the content.

Corresponding author:
Anna Sureda, MD, PhD
Institut Català d'Oncologia, Hospital Duran i Reynals, Gran Via de l'Hospitalet 199, 08908, L'Hospitalet de Llobregat, Barcelona (Spain); asureda@iconcologia.net

In this issue of *Haematologica*, Ortiz-Maldonado *et al.* reported intriguing results from a phase I/II trial (NCT01865617) evaluating a double infusion strategy using the academic anti-CD19 CAR T-cell product JCAR014.(1) Although conducted in a relatively small cohort, this "dose-dense" approach yielded encouraging clinical outcomes, particularly regarding durability of response. Indeed, the duration of response appears superior to that observed in a comparable cohort of patients treated with a single CAR T-cell infusion, raising important questions regarding the role of repeated CAR T-cell exposure in improving long-term disease control.

The concept of dose-dense therapy is not new in the treatment of large B-cell lymphomas. Historically, it emerged from attempts to improve outcomes by increasing chemotherapy intensity or shortening treatment intervals. This strategy has been explored in the frontline setting with regimens such as R-CHOP-14 and dose-adjusted R-EPOCH, as well as in the second line setting through high-dose chemotherapy followed by autologous stem cell transplantation.(2–4) Overall, these approaches have produced heterogeneous results. In frontline therapy, increased treatment intensity has generally translated into greater toxicity with limited or no overall survival benefit. More recently, improvements in efficacy have instead resulted from incorporating novel agents such as polatuzumab vedotin or the combination of tafasitamab and lenalidomide rather than from increasing chemotherapy dose intensity alone.(5,6) In contrast, in the relapsed/refractory setting, high-dose chemotherapy followed by autologous transplantation has demonstrated superior disease control and overall survival in selected patients, albeit at the expense of substantial toxicity. Unlike conventional chemotherapy, the efficacy of CAR T-cell therapy depends not only on the administered cell dose but also on complex biological factors including CAR T-cell expansion and persistence, tumor burden, antigen density, immune fitness, and characteristics of the CAR construct itself.(7,8) Consequently, whether increasing CAR T-cell exposure through repeated infusions can enhance efficacy is an important and still unanswered biological and clinical question.

In the present study, patients receiving the dose-dense strategy had a trend toward longer duration of response (8-year duration of response: 63% versus 27%, p=0.16). However, this encouraging finding should be interpreted in the context of the other efficacy endpoints, which did not significantly differ between groups. Eight-year

progression-free survival was 29% versus 16% (P=0.54), while 8-year overall survival was 63% versus 35% (P=0.19). Although these numerical differences seem to favor the double-infusion cohort, the small sample size precludes definitive conclusions regarding survival benefit.

Beyond efficacy, several observations provide novel insights into CAR T-cell biology. No patient receiving the dose-dense strategy developed grade ≥3 cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS), while the incidence of immune effector cell-associated hematotoxicity (ICAHT) was comparable between treatment groups. One possible explanation for this favorable safety profile could have been insufficient expansion of the second CAR T-cell infusion. However, the authors convincingly demonstrate that this was not the case. A distinct second expansion peak was observed following reinfusion, and remarkably, 41% of patients reached their maximum CAR T-cell expansion after the second infusion.

These findings are particularly noteworthy for two reasons. First, they suggest that clinically meaningful CAR T-cell expansion can occur even in the absence of repeat lymphodepleting chemotherapy. Second, they challenge the widely accepted association between CAR T-cell expansion and treatment-related toxicity established from studies evaluating a single infusion.(9) This dissociation between expansion and toxicity may indicate that the immunological context following an initial CAR T-cell infusion differs substantially from that of first exposure, although the mechanisms underlying this observation remain to be elucidated.

Another important finding concerns mechanisms of relapse. Patients treated with the dose-dense strategy exhibited a higher frequency of CD19 antigen loss at relapse (44% versus 11%). Furthermore, patients experiencing CD19-negative relapse had particularly poor outcomes, with a median overall survival of only 2 months compared with 5 months among patients retaining CD19 expression. This suggests that greater selective pressure exerted by repeated CAR T-cell exposure may increase the likelihood of antigen escape. Thus, while a dose-dense strategy may prolong remission in a subset of patients, it could also alter the biological characteristics of subsequent relapse, potentially limiting the efficacy of further CD19-directed therapies.

The key unanswered question therefore remains whether increasing cumulative CAR T-cell exposure ultimately translates into meaningful improvements in long-term survival. Ongoing prospective studies, including NCT05460533 evaluating tisagenlecleucel in acute lymphoblastic leukemia and NCT05794958 evaluating axicabtagene ciloleucel in B-cell non-Hodgkin lymphoma, are specifically designed to address this hypothesis in larger patient populations. Equally important is the question of reinfusion timing. In the present study, reinfusion was performed on day +14, a pragmatic choice based on anticipated recovery from lymphodepleting chemotherapy and resolution of early CRS and ICANS. However, the optimal timing of CAR T-cell reinfusion remains unknown. Existing evidence suggests that reinfusion at the time of relapse does not confer substantial clinical benefit.(10) The biological landscape between the initial infusion and eventual disease progression is dynamic and influenced by multiple variables, including immune reconstitution, CAR T-cell persistence, disease burden, minimal residual disease, and treatment-related complications. At present, no biomarker or combination of biomarkers reliably identifies patients most likely to benefit from reinfusion or determines the optimal timing for this intervention.

Finally, despite providing important proof-of-concept data and valuable biological insights, this study has several limitations that warrant careful consideration. The absence of matched patient populations limits the robustness of comparisons and increases the possibility of confounding. For example, dose-dense population had no bulky diseases, a factor associated to poorer outcomes in this setting. Also, the field of sequential CAR T-cell infusion is expanding and it should be tested if reinfusion of a same product is effective and superior to other reinfusion strategies such as sequential CD19 and CD20 CAR T-cell products.(11) Another point that goes beyond the scientific perspective of this strategy is the logistical and economic issues that could arise from a double infusion rather than a single one. Consequently, these findings should be regarded as hypothesis generating rather than practice-changing, as appropriately acknowledged by the authors.

Bibliography

1. Ortiz-Maldonado V, Liang EC, Huang JJ, et al. A novel dose-dense strategy for CD19-directed CAR T-cell therapy is associated with durable responses without increased toxicity in patients with B-cell non-Hodgkin lymphoma. Haematologica. xxx

2. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol.. 2008;9(2):105-116.

3. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma. N Engl J Med. 2013;368(15):1408-1416.

4. Gianni AM, Bregni M, Siena S, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. N Engl J Med. 1997;336(18):1290-1298.

5. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med. 2022;386(4):351-363.

6. Lenz G, Trněný M, Burke JM, et al. Tafasitamab plus lenalidomide and R-CHOP versus R-CHOP for first-line treatment of patients with high-risk diffuse large B-cell lymphoma (frontMIND): a global, phase 3, randomised, double-blind, placebo-controlled trial. Lancet. 2026;407(10547):2528-2541.

7. Locke FL, Rossi JM, Neelapu SS, et al. Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. Blood Adv. 2020;4(19):4898-4911.

8. Duell J, Leipold AM, Appenzeller S, et al. Sequential antigen loss and branching evolution in lymphoma after CD19- and CD20-targeted T-cell–redirecting therapy. Blood. 2024;143(8):685-696.

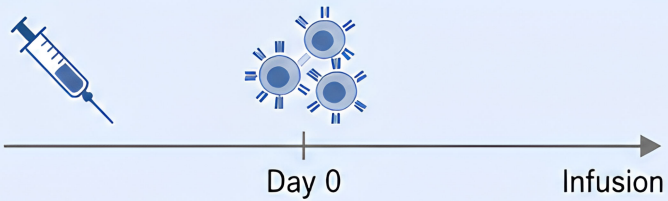
9. Boulch M, Cazaux M, Cuffel A, et al. A major role for CD4+ T cells in driving cytokine release syndrome during CAR T cell therapy. Cell Rep Med. 2023;4(9):101161.

10. Gauthier J, Bezerra ED, Hirayama AV, et al. Factors associated with outcomes after a second CD19-targeted CAR T-cell infusion for refractory B-cell malignancies. Blood. 2021;137(3):323-335.

11. Xue F, Liu R, Fu Z, et al. Sequential CD19-20 CAR T-cell therapy for refractory/relapsed diffuse large B-cell lymphoma. Cytotherapy. 2025;27(8):910-916.

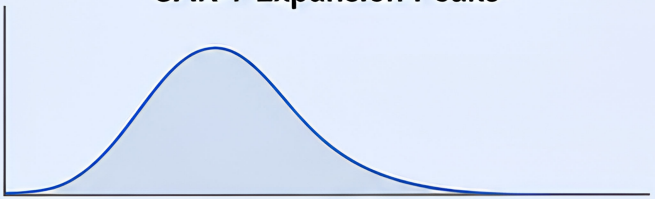
Figure 1. Single versus double anti-CD19 CAR T-cell infusion

STANDARD SINGLE INFUSION



8-Year Duration of Response

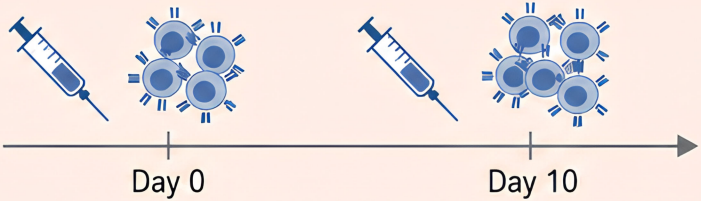
CAR T Expansion Peaks



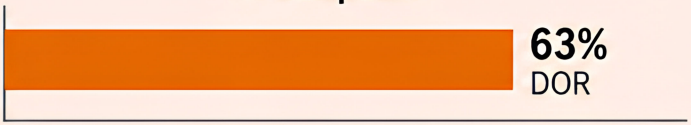
CD19-Negative Relapse Risk

11%
Antigen Loss

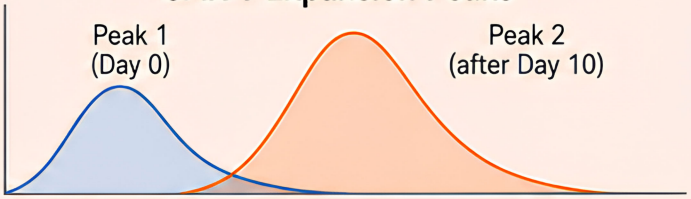
DOSE-DENSE STRATEGY



8-Year Duration of Response



CAR T Expansion Peaks



41% reach max expansion after second dose

Excellent Safety Profile on Reinfusion

Zero
Grade 3+ CRS
or ICANS

CD19-Negative Relapse Risk

44%
Antigen Loss