Leukemia
https://doi.org/10.1038/s41375-019-0476-y

LETTER

Immunotherapy

Safety and feasibility of chimeric antigen receptor T cell therapy after allogeneic hematopoietic cell transplantation in relapsed/ refractory B cell non-Hodgkin lymphoma

Tania Jain[1] · Craig S. Sauter[1,2] · Gunjan L. Shah[1,2] · Molly A. Maloy[1] · Jason Chan[1] · Michael Scordo[1,2] · Scott T. Avecilla[3] · Yakup Batlevi[1] · Parastoo B. Dahi[1,2] · Connie W. Batlevi[2,4] · M. Lia Palomba[2,4] · Sergio A. Giralt[1,2] · Miguel-Angel Perales[1,2]

Received: 23 February 2019 / Revised: 9 April 2019 / Accepted: 11 April 2019

Introduction

Chimeric antigen receptor (CAR) T cell therapy is a paradigm shift in the management of B cell non-Hodgkin lymphomas (NHL). Two CAR T cell products, axicabtagene ciloleucel (axi-cel, Kite, Gilead) and tisagenlecleucel (Novartis), are now FDA approved based on significant responses in relapsed/ refractory B cell NHL [1, 2]. Neither of these pivotal trials included patients who had undergone a prior allogeneic hematopoietic cell transplantation (alloHCT). We hereby share our experience in four patients who received CAR T cell therapy with axi-cel, following lymphodepletion with fludarabine/cyclophosphamide, for relapsed NHL after alloHCT, where T cells were harvested from recipient following relapse.

Written informed consent for treatment was obtained, and approval for this retrospective review was obtained from the Institutional Review and Privacy Board. Details of CAR T cell therapy and alloHCT are outlined in Table 1 and timeline of events is illustrated in Fig. 1. All responses used Deauville criteria.

Case descriptions

Patient 1

A 33-year-old man was diagnosed with T cell rich B cell lymphoma Ann Arbor Stage 4B. He was treated with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) [progression of disease (POD)], rituximab, ifosfamide, carboplatin and etoposide (R-ICE) [complete response (CR)] and then alloHCT from a matched unrelated donor, 14 months after diagnosis [CR]. Post-alloHCT course was complicated by moderate chronic graft versus host disease (GVHD) managed with corticosteroids and tacrolimus. He relapsed 5 years later (off immunosuppression by then) with diffuse lymphadenopathy, and received rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (R-EPOCH) [partial response (PR)], followed by axi-cel. He developed grade 2 cytokine release syndrome (CRS) and grade 2 neurotoxicity (ASBMT consensus grading [3]). PR was noted on day +30, but POD at day +60; and he died day +108 after CAR T cell infusion. There was no reappearance of GVHD following CAR T cells.

Patient 2

A 45-year-old man was diagnosed with right submandibular diffuse large B cell lymphoma (DLBCL) Ann Arbor Stage 1A. He was treated with R-CHOP and local radiation [CR] followed by rituximab maintenance for 2 years. Late local

Supplementary information The online version of this article (https://doi.org/10.1038/s41375-019-0476-y) contains supplementary material, which is available to authorized users.

✉ Miguel-Angel Perales
peralesm@MSKCC.ORG

[1] Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

[2] Department of Medicine, Weill Cornell Medical College, New York, NY 10021, USA

[3] Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

[4] Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

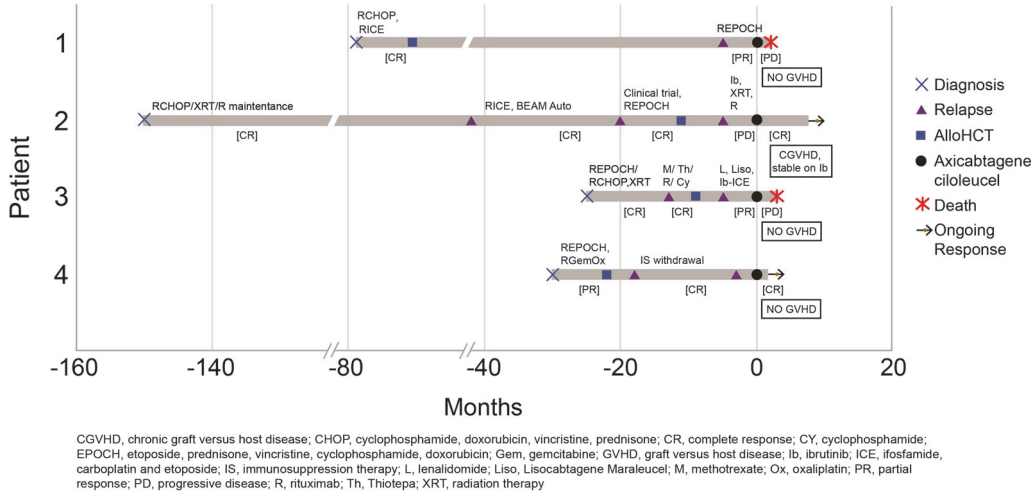
Published online: 21 May 2019

Table 1 Patient and treatment characteristics*

Patient	Age at CAR T/ Gender	Diagnosis	Donor type	Graft source	Conditioning regimen with alloHCT	GVHD prophylaxis/ GVHD at CAR T	Interval/ lines of therapy between alloHCT and CAR T (days)	Donor chimerism/ ALC at the time of mononuclear apheresis	CRS/ Neurotoxicity	Response at 1 month	B cell recovery	Status at last follow up
1	38/ M	T cell rich DLBCL	10/10 MUD	Peripheral blood	Flu, Cy, Thio, 400 cGy TBI	Tacrolimus, Methotrexate/ none	1,914/ one	T cell chimerism 100% donor/ 500	Grade 2 (tocilizumab)/ Grade 2 (dexamethasone)	PR	Not achieved until last follow up	Dead (106 days post CAR T) from disease
2	55/ M	Non-GCB DLBCL	MMRD (haploidentical from cousin)	Bone marrow	Flu Mel, Thiotepa	Post-transplant Cy, Tacrolimus, Mycophenolate/ chronic GVHD stable on ibrutinib	269/ two	Whole blood 100% donor (T cell subset chimerism not available)/ 600	None/ none	CR	B cell recovery at 9 months	Alive with CR (270 days post CAR T)
3	56/ M	Non-GCB DLBCL	10/10 MUD	Peripheral blood	Thio, Bu, Cy, Rituximab	Tacrolimus, Alemtuzumab/ none	291/ three	T cell chimerism 18% donor/ 300	None/ none	POD	Not achieved until last follow up	Dead (77 days post CAR T) from disease
4	66/ F	DLBCL (transformed from marginal zone)	9/10 MMUD	Peripheral blood	Flu, Mel	Tacrolimus, Methotrexate/ none	694/ none	Bone marrow (unsorted) 100% donor/ 1900	Grade 2 (tocilizumab)/ none	CR	Not available	Alive with CR (112 days post CAR T)

*All patients received Flu/ Cy lymphodepletion and axicabtagene ciloleucel (2×10^8 cells)

alloHCT allogeneic hematopoietic cell transplantation, *ALC* absolute lymphocyte count (reported in cells/ μL), *Bu* Busulfan, *CAR-T* chimeric antigen receptor T cell therapy, *CR* complete response, *CRS* cytokine release syndrome, *Cy* cyclophosphamide, *DLBCL* diffuse large B cell lymphoma, *F* female, *Flu* Fludarabine, *GCB* Germinal Center B cell like, *GVHD* graft versus host disease, *M* male, *Mel* melphalan, *MMRD* mismatched related donor, *MMUD* mismatched unrelated donor, *MUD* matched unrelated donor, *POD* progression of disease, *PR* partial response, *TBI* total body irradiation, *Thio* thiotepa



CGVHD, chronic graft versus host disease; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; CY, cyclophosphamide; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; Gem, gemcitabine; GVHD, graft versus host disease; Ib, ibrutinib; ICE, ifosfamide, carboplatin and etoposide; IS, immunosuppression therapy; L, lenalidomide; Liso, Lisocabtagene Maraleucel; M, methotrexate; Ox, oxaliplatin; PR, partial response; PD, progressive disease; R, rituximab; Th, Thiotepa; XRT, radiation therapy

Fig. 1 Timeline of events for all patients

relapse was noted 9 years after initial presentation, managed with high-dose therapy and autologous HCT [CR]. Over a year later, disease relapsed with diffuse lymphadenopathy treated with R-EPOCH [CR], followed by haploidentical alloHCT with post-transplantation cyclophosphamide. The course was complicated by stage 2 lower gastrointestinal GVHD and later, chronic GVHD of oral cavity, skin, joints, and liver; managed with systemic corticosteroids, tacrolimus, and later ibrutinib, with resolution of symptoms. Ibrutinib was started around the time of relapse, 6 months after alloHCT, with an aim to target both the disease and GVHD. PET imaging showed uptake in a lacrimal gland mass causing diplopia (radiated), and diffuse lymphadenopathy. He had systemic POD two months after initiation of ibrutinib and received rituximab [POD] as a bridge to axi-cel. Ibrutinib continued for 3 months until initiation of lymphodepleting chemotherapy. He did-not experience CRS or neurotoxicity. Ibrutinib was resumed two weeks post-CAR T cells due to fluctuations in transaminases, attributed to azole anti-fungal agents or GVHD. Day +30 imaging post-CAR T cells revealed CR (Supplementary Figure S1) and he remains disease-free 9 months post-treatment. Liver transaminases have normalized on ibrutinib and low dose tacrolimus. Other GVHD symptoms remain completely resolved.

Patient 3

A 56-year-old man was diagnosed with DLBCL, with a conglomerate mass in the abdomen, treated with R-EPOCH changed to R-CHOP followed by local radiation to the residual mass [CR]. CNS relapse, a year later, was treated with rituximab, methotrexate, cytarabine and thiotepa [CR]. This was followed by alloHCT from an unrelated donor, but he relapsed with a PET avid abdominal mass 4 months later. No GVHD was reported in this interval. He received lenalidomide [POD] followed by fludarabine/cyclophosphamide lymphodepletion with CD19 CAR T cells (Lisocabtagene Maraleucel) on clinical trial (NCT03483103) [POD]. He was then treated with ibrutinib with ICE [PR] followed by axi-cel within 2 months. Ibrutinib was given for over 1 month and discontinued prior to leukapheresis. No CRS or neurotoxicity was reported. Day +30 PET showed POD, and he died on day +77 post-treatment, due to sepsis in the setting of rapid POD. No GVHD was reported post-CAR T cells.

Patient 4

A 63-year-old woman was diagnosed with *myc*-rearranged DLBCL (transformed marginal zone lymphoma) with diffuse lymphadenopathy, splenomegaly and bone marrow involvement. She was treated with R-EPOCH [CR] but relapsed within 3 months with multiple PET avid subcutaneous nodules and inguinal lymphadenopathy; then treated with rituximab, gemcitabine and oxaliplatin [PR]. This was followed by unmodified mismatched unrelated donor alloHCT complicated by upper gastrointestinal GVHD, resolved with budesonide. Relapse was noted with another subcutaneous nodule four months later, that responded to withdrawal of immunosuppression without worsening GVHD. However, 15 months later, relapse was noted with subcutaneous nodules on bilateral upper extremities, treated with axi-cel nearly two years after alloHCT. This was complicated by grade 2 CRS but no new GVHD symptoms were reported. CR was noted at day +30 and she remains in remission four months post-CAR T cells.

Discussion

The question of safety of CAR T cells following prior alloHCT is clinically significant but remains under-studied so far. Herein we report our experience with recipient-derived CAR T cells in patients with relapsed DLBCL following alloHCT. While ours is the first report describing safety of recipient-derived (or "pseudo-donor-derived") CAR T cells post-alloHCT in DLBCL, there are reports of donor-derived CAR T cells administered in various hematological malignancies (Supplementary Table S1). Brudno et al. reported use of a single dose allogeneic CAR T cells derived from the patients' alloHCT donor [4]. Eight out of 20 patients responded, including two CRs, without any new onset acute GVHD despite 14 having had GVHD following alloHCT. In another study, 19 patients received planned adjuvant donor-derived CAR T cells after alloHCT, generated using sleeping beauty transposon [5]. Three patients developed acute GVHD. In a third report, donor-derived, virus-specific T cells engineered to express CD19-targeted CAR showed no GVHD in patients who relapsed post-alloHCT [6]. These data, along with our report, collectively suggest feasibility of CAR T cell therapy following alloHCT and that a prior alloHCT need not be considered an exclusion for CAR T cells after thorough assessment of risk factors. A recent report studying factors associated with durable remission after CAR T cell therapy for NHL, also included patients with prior alloHCT, but did-not discuss GVHD occurrence [7].

Interestingly, the four CAR constructs reported above demonstrating safety of CAR T cells post-alloHCT, including our series, used CD28 co-stimulation domain [4–6]. In a pre-clinical mouse model, Ghosh et al. showed that donor-derived CD19 CAR T cells co-stimulated by CD28 can exert anti-tumor effect without developing GVHD [8]. In contrast, another report from the NCI, showed leukemia responses with CD28 based donor-derived CD19 CAR T cells studied in immunocompetent murine models but also the potential for lethal GVHD, especially in presence of active leukemia [9]. How these translate into clinical findings in humans, remains to be studied. It should be noted that patients with B cell acute lymphoblastic leukemia with prior alloHCT were included in CD19 CAR T studies using constructs with 4-1BB or CD28 co-stimulation, without any evidence of development of GVHD [10–12].

Patient 2 in our series has an ongoing response, 9 months after CAR T cells in the setting of prior haploidentical alloHCT. This patient had also received ibrutinib to address chronic GVHD following alloHCT and showed stabilization of chronic GVHD. Although not seen in this patient, ibrutinib has been shown to induce disease response in 37% of patients with non-GCB subtype DLBCL, with higher responses in patients with concomitant *BCR* and *MYD88* mutations [13]. Additionally, he received ibrutinib until collection of mononuclear cells for CAR T cell production. This strategy, in vitro, has been shown to improve CAR T expansion in a chronic lymphocytic leukemia model, associated with decreased PD1 on T cells and decreased CD200 on B cells [14]. In xenograft models of mantle cell lymphoma also, combined treatment with ibrutinib and CD19 CAR T cells has shown more durable responses compared to CAR T alone [15]. Our patient has an ongoing response after CAR T cells while being on ibrutinib for chronic GVHD, with a prior progression on ibrutinib. Whether ibrutinib along with CAR T cells would augment efficacy or survival is currently being studied.

While this report is limited by a small sample size, our experience suggests that use of CAR T cells after alloHCT is generally safe and doesn't appear to worsen GVHD. Given the sample size, we are unable to analyze factors associated with response. When standard risk factors were analyzed in patients treated in ZUMA-1 trial, none were associated with response, including disease bulk [1]. However, we cannot exclude low T cell donor chimerism at the time of apheresis or immune rejection as a mechanism of failure for Patient 3 who received two CAR T cell constructs using the same scFv. Concerns about T cell function, persistence and exhaustion post-alloHCT, especially in the setting of immunosuppression therapy, remain to be addressed. Larger prospective studies will be needed to confirm these findings and careful monitoring should be pursued until more data becomes available.

Funding This research was supported in part by NIH/NCI Cancer Center Support Grant P30 CA008748. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Compliance with ethical standards

Conflict of interest CS—Consultant on advisory boards for: Juno Therapeutics, Sanofi-Genzyme, Spectrum Pharmaceuticals, Novartis, Precision Biosciences, Kite, a Gilead Company and GSK. Research funds for investigator-initiated trials from: Juno Therapeutics and Sanofi-Genzyme. GS—Research funding from Janssen and Amgen. MS—Consultancy: Angiocrine Bioscience, Inc., McKinsey & Company. Scott Avecilla—Honoraria for presenting a project in partnership with Abbott Laboratories. CB—Research funding from Epizyme, Novartis, Janssen, BMS, Miragen, Medimmune; Consultancy from Defined Health, GLG, Guidepoint Global; Honoraria from Dava Oncology. MLP—Advisory Board for Celgene, Consultant for Merck and Pharmacyclics. SG—Advisory Board for Amgen, Actinuum, Celgene, Johnson & Johnson, Jazz pharmaceutical, Takeda, Novartis, Kite, Spectrum Pharma; Research funding from Amgen, Actinuum, Celgene, Johnson & Johnson, Miltenyi, Takeda, Miguel-Angel Perales - Honoraria from Abbvie, Bellicum, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, and Takeda. He serves on DSMBs for Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. Research support for clinical trials from Incyte, Kite (Gilead) and Miltenyi Biotec.

References

1. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017; 377:2531–44.
2. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380:45–56.
3. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASBMT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;4:625–38.
4. Brudno JN, Somerville RP, Shi V, Rose JJ, Halverson DC, Fowler DH, et al. Allogeneic T cells that express an anti-CD19 chimeric antigen receptor induce remissions of B-cell malignancies that progress after allogeneic hematopoietic stem-cell transplantation without causing graft-versus-host disease. J Clin Oncol. 2016; 34:1112–21.
5. Kebriaei P, Singh H, Huls MH, Figliola MJ, Bassett R, Olivares S, et al. Phase I trials using sleeping beauty to generate CD19-specific CAR T cells. J Clin Invest. 2016;126:3363–76.
6. Cruz CR, Micklethwaite KP, Savoldo B, Ramos CA, Lam S, Ku S, et al. Infusion of donor-derived CD19-redirected virus-specific T cells for B-cell malignancies relapsed after allogeneic stem cell transplant: a phase 1 study. Blood. 2013;122:2965–73.
7. Hirayama AV, Gauthier J, Hay KA, Voutsinas JM, Wu Q, Gooley T, et al. The response to lymphodepletion impacts PFS in aggressive non-Hodgkin lymphoma patients treated with CD19 CAR-T cells. Blood. 2019;133:1876–87.
8. Ghosh A, Smith M, James SE, Davila ML, Velardi E, Argyropoulos KV, et al. Donor CD19 CAR T cells exert potent graft-versus-lymphoma activity with diminished graft-versus-host activity. Nat Med. 2017;23:242–9.
9. Jacoby E, Yang Y, Qin H, Chien CD, Kochenderfer JN, Fry TJ. Murine allogeneic CD19 CAR T cells harbor potent antileukemic activity but have the potential to mediate lethal GVHD. Blood. 2016;127:1361–70.
10. Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015;385:517–28.
11. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378:439–48.
12. Park JH, Riviere I, Gonen M, Wang X, Senechal B, Curran KJ, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. 2018;378:449–59.
13. Wilson WH, Young RM, Schmitz R, Yang Y, Pittaluga S, Wright G, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med. 2015;21:922–6.
14. Fraietta JA, Beckwith KA, Patel PR, Ruella M, Zheng Z, Barrett DM, et al. Ibrutinib enhances chimeric antigen receptor T-cell engraftment and efficacy in leukemia. Blood. 2016;127:1117–27.
15. Ruella M, Kenderian SS, Shestova O, Fraietta JA, Qayyum S, Zhang Q, et al. The addition of the BTK inhibitor ibrutinib to anti-CD19 chimeric antigen receptor T cells (CART19) improves responses against Mantle cell lymphoma. Clin Cancer Res. 2016;22:2684–96.