Sustained Remission of Relapsed Diffuse Large B-cell Lymphoma After Safe Administration of CD19-directed CAR T-cells in a Patient With Chronic Intestinal and Pulmonary GvHD

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We report the case of a patient with relapsed diffuse large B-cell lymphoma (DLBCL) treated with CD19-directed chimeric antigen receptor (CAR) T-cells in the presence of active intestinal and pulmonary chronic graft-versus-host disease (cGvHD) after allogeneic stem cell transplantation (allo-SCT). In the course after lymphodepleting (LD) therapy and infusion of CAR T-cells lymphoma remission as well as remission of cGvHD was achieved.

A 43-year-old male patient was diagnosed with follicular lymphoma grade 1–2, Ann Arbor stage IV, in 2012. Treatment with 6 cycles of bendamustine-rituximab (BR) was initiated in August 2012 due to dropping blood counts and symptomatic splenomegaly, which resulted in a complete response and was followed by rituximab maintenance. He relapsed beginning of 2014 and was retreated with BR resulting in stable disease but progressed shortly after completion of 4 cycles. Histologically, transformation to DLBCL was diagnosed.

After several lines of salvage chemoimmunotherapy, complete response was obtained and the patient underwent allo-SCT with a matched unrelated male donor in April 2015 after conditioning with fludarabine and cyclophosphamide (25 and 250 mg/m², respectively, q3d). On day+3 after CAR T-cell infusion, he developed cytokine release syndrome (grade I, mild hyperthermia) not requiring further intervention which lasted for 6 days. No infectious complications were noted with grade 3 or 4 toxicities.

On March 15, 2021, the patient received CD19-targeting CAR T-cell treatment (tisagenlecleucel, 6.2 x 10^6 CAR T-cells/kg body weight) after LD chemotherapy with fludarabine and cyclophosphamide (25 and 250 mg/m², respectively, q3d). On day+3 after CAR T-cell infusion, he developed cytokine release syndrome (grade I, mild hyperthermia) not requiring further intervention which lasted for 6 days. No infectious complications were noted with grade 3 or 4 toxicities.

Chimerism analysis continued to show 100% donor cells in the patient’s peripheral blood. A prompt leukapheresis collection with cryoconservation was planned and the patient was maintained for another week until admission for CAR T-cell treatment. Respiratory symptoms improved substantially but diarrhea remained with about 5 stools/d and abdominal cramps. Ruxolitinib treatment was stopped after 3 weeks. Steroids were maintained for another week until admission for CAR T-cell treatment. Clinically, intestinal cGvHD was still present before CAR T-cell administration in line with the results of positron emission tomography (PET/CT)–morphological changes were observed. Chronic pulmonary GvHD (cGvHD) was diagnosed and histologically confirmed by bronchoscopy accompanied by the onset of ocular cGvHD. Symptoms improved after systemic as well as topical steroid treatment and CSA was reinitiated. The patient was then treated in a different clinic for about 1.5 years. CSA was stopped there in March 2019.

In January 2021, the patient presented with histologically confirmed DLBCL relapse (spleen, lesion of the left upper thigh) after allogeneic hematopoietic stem cell transplantation (HSCT) and concomitant dry cough as well as diarrhea (6–8 watery stools/day) representing symptoms of pulmonary and intestinal cGvHD. Therefore, endoscopy was performed and intestinal cGvHD without evident lymphomatous infiltration could be confirmed histologically (Lerner grade I without fibrosis, aggregates of small CD20+ B-cells were detected). Chimerism analysis continued to show 100% donor cells in the patient’s peripheral blood. A prompt leukapheresis collection with cryoconservation was planned and the patient was put on steroids and ruxolitinib afterward to improve symptoms as effective as possible before the scheduled CAR T-cell treatment. Respiratory symptoms improved substantially but diarrhea remained with about 5 stools/d and abdominal cramps. Ruxolitinib treatment was stopped after 3 weeks. Steroids were maintained for another week until admission for CAR T-cell treatment. Clinically, intestinal cGvHD was still present before CAR T-cell administration in line with the results of positron emission tomography (PET/CT)–morphological changes were observed. Chronic pulmonary GvHD (cGvHD) was diagnosed and histologically confirmed by bronchoscopy accompanied by the onset of ocular cGvHD. Symptoms improved after systemic as well as topical steroid treatment and CSA was reinitiated. The patient was then treated in a different clinic for about 1.5 years. CSA was stopped there in March 2019.

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3 neutropenia present from d+1 to d+5 after CAR T-cell infusion not requiring administration of growth factors. Peak CAR T-cell expansion was on d+9 with 75,600 cp/Mio white blood cells as measured by quantitative polymerase chain reaction. B-cells are not detectable since LD and CAR T-cell treatment.

PET/CT imaging 3 months after treatment not only demonstrated complete metabolic response of the lymphoma manifestations but also decreased glucose metabolism of the intestinal tract suggesting resolution of cGvHD (Figure 1B). Diarrhea symptoms had completely resolved during the hospital stay. The patient continues to be in complete metabolic response of the
lymphoma without any clinical signs of the previous pulmonary and intestinal GvHD.

To the best of our knowledge, this is the first report on safe administration of CD19-directed CAR T-cells in a lymphoma patient with active GvHD resulting in sustained remission of lymphoma and cGvHD. Previous allogeneic HSCT (JULIET/ZUMA-1 trials1,2) or active GvHD after previous allo-SCT (Transcend 001 NHL trial1) were considered exclusion criteria for the respective CAR T-cell trials due to the possible risk of GvHD induction, GvHD worsening or the initiation of other uncontrolled inflammatory responses. GvHD has been described as a potential complication after post-allo-SCT CAR T-cell therapy.4 Cordeiro et al5 recently described late complications as a potential complication after post-allo-SCT CAR T-cell therapy.5 Cordeiro et al5 recently described late complications after CAR T-cell treatment starting or persisting beyond day+90 after CAR T infusion. Three of 15 patients (20%) after allo-SCT were reported to have developed GvHD after CAR T-cell treatment. One patient with no history of GvHD developed late acute GvHD of the gastrointestinal tract, liver, and skin, which resolved after systemic steroid treatment. Two patients, including one with history of acute GvHD after transplantation, developed cGvHD requiring multiple lines of therapy. GvHD developed 1.9–3.2 months after CAR T-cell infusion.6 The group also reported other possible immune-related effects in 7 of 86 patients such as lymphocytic alveolitis, spongiosis and psoriasiform dermatitis, eosinophilic pneumonia, pneumonitis, and collagenous colitis. The median time of symptom onset was 234 days after CAR T-cell infusion (range, 67–1099 days).7 Our patient suffered from active cGvHD at the time of LD conditioning naturally comes along with immunosuppressive therapy for acute intestinal GvHD. It also reflected symptom improvement of the patient described herein. However, further analyses are needed to validate the role of PET/CT in monitoring treatment for intestinal GvHD.

LD conditioning naturally comes along with immunosuppressive properties potentially contributing to GvHD regression in combination with the short rituximab and steroid pretreatment. However, sustained remission of cGvHD in this context is noteworthy and not characteristic of known cGvHD dynamics. CD19-directed CAR T-cell therapy induces profound and continuous B-cell aplasia. Potential involvement of B-cells in the pathophysiology of especially cGvHD has been described.8 Moreover, rapid remission of refractory systemic lupus erythematosus, a B-cell driven autoimmune disease, by CD19-targeted CAR T-cells was recently demonstrated.8 Both of the 2 mechanisms can be discussed to explain the clinical response observed and we are not able to formally prove our hypothesis of a CAR T-cell impact on the described GvH reactions.

However, our report demonstrates that CD19-directed CAR T-cell treatment can successfully and safely be performed in patients with relapse after allo-SCT and active GvHD. Our patient continues to be in complete metabolic response of the lymphoma without any signs of GvHD 12 months after CAR T-cell administration. Tisagenlecleucel CAR T-cells are continuing to persist in the patient’s peripheral blood and the B-cell count is still completely suppressed. This case report adds to the experience on CAR T-cell treatment strategies and may help to define criteria to identify suitable patients. In addition, our data may further support the concept of using allogeneic CAR T-cells derived from the original stem cell donor to treat relapse after allo-SCT.

AUTHOR CONTRIBUTIONS

NK participated in research design, data analysis, and writing of the paper. PG participated in data analysis and writing of the paper. C-AV participated in data analysis and writing of the paper. CK participated in research design and writing of the paper. MH participated in research design and writing of the paper. CS participated in research design and writing of the paper. PB participated in research design and writing of the paper. UH participated in research design, data analysis, and writing of the paper.

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NK received research funding and travel support from Gilead Sciences, Inc.; honoraria from AstraZeneca; and travel support from Janssen and Celgene. PG received travel support from Novartis, Gilead Sciences. MH has provided consultancy, is a member of the speakers’ bureau and received honoraria, and research funding from Roche; AbbVie; Gilead Sciences, Inc.; Janssen; Celgene; and AstraZeneca. CS received honoraria from BMS/Celgene, Gilead Sciences, Janssen, Novartis. PB received honoraria fro BMS/Celgene, Gilead Sciences, Janssen, Miltenyi Biotech, Novartis. UH received honoraria from BMS/Celgene, Gilead Sciences, Janssen, Miltenyi Biotech, Novartis.

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