Kidney Medicine

Chimeric Antigen Receptor (CAR) T-Cell Therapy Use in Patients with Multiple Myeloma and Kidney Failure on Maintenance Hemodialysis: A Report of 2 Cases

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Chimeric antigen receptor (CAR) T-cell therapy against B-cell maturation antigen is a new treatment modality for relapsed or refractory multiple myeloma (MM). Patients with kidney failure and MM were excluded from the pivotal CAR T-cell therapy clinical trials: KaRMMa (idecabtagene vicleucel) and CARTITUDE (ciltacabtagene autocleucel). The safety and efficacy of CAR T-cell therapy in patients with relapsed or refractory MM and kidney failure are limited to a few case reports using idecabtagene vicleucel. Here, we report the first 2 cases of ciltacabtagene autoleucel use in patients with kidney failure on maintenance hemodialysis and relapsed or refractory MM. Both patients achieved a hematologic response following ciltacabtagene autoleucel administration without serious adverse events. These findings suggest that ciltacabtagene autoleucel may be safe and effective in patients with relapsed or refractory MM and kidney failure. In this report, we review the available literature regarding the use of CAR T-cell therapy in patients with MM and kidney failure. We also discuss the modification of the lymphodepletion regimen in the kidney failure setting.

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INTRODUCTION

Chimeric antigen receptor (CAR) T-cell against B-cell maturation antigen represents a new treatment modality for relapsed or refractory multiple myeloma (RRMM). Refractory myeloma refers to myeloma that is nonresponsive to primary or salvage therapy or progresses within 60 days of the last therapy; relapsed myeloma refers to previously treated myeloma that progresses and requires the initiation of salvage therapy.[1] In clinical trials, idecabtagene vicleucel (ide-cel) and ciltacabtagene autocleucel (cilta-cel) led to deep and durable responses in patients with RRMM,[2,3] and recent randomized controlled trials further demonstrated their benefits in disease response and progression-free survival when compared with standard therapy.[4,5] However, these pivotal trials excluded patients with kidney failure (KF); hence, data on the safety and efficacy of CAR T-cell therapy in KF are scarce.[6–9] We report 2 cases of cilta-cel administration in patients with RRMM and KF on maintenance hemodialysis (HD).

CASE REPORT

Two patients treated with CAR T-cell therapy for MM in the setting of KF were identified at Memorial Sloan Kettering Cancer Center, New York. Demographic, clinical, laboratory, and follow-up data were obtained from a retrospective review of the electronic medical records. Approval from the institutional review board was not required because the study was a retrospective review of clinical records involving only 2 patients. Informed consent was obtained from both patients.

Case 1

A 50-year-old woman was diagnosed with kappa free light chain (FLC) international staging system stage III MM with high-risk cytogenetics del(1p) and del(17p) 8 years previously. She initially presented with an acute kidney injury requiring urgent HD. The kidney biopsy showed light chain cast nephropathy. She remained dialysis-dependent despite achieving a very good partial response with a sizeable reduction in serum FLC after cyclophosphamide-bortezomib-dexamethasone induction and autologous hematopoietic stem cell transplantation. Subsequently, she had several MM relapses, for which she received lenalidomide-bortezomib-dexamethasone, daratumumab-lenalidomide-dexamethasone, and carfilzomib-pomalidomide-dexamethasone, with very good partial response following each regimen. After 2.5 years on carfilzomib-pomalidomide-dexamethasone, she developed progression of the disease, with serum kappa FLC 368 mg/L and κ/λ ratio of 20. A decision was made to administer cilta-cel for relapsed MM.

Because of the underlying KF, the lymphodepletion and HD prescriptions were modified. Cyclophosphamide 300 mg/m^2 (standard dose) and fludarabine 15 mg/m^2 (50% dose reduction) were administered on days −5, −4, and −3, and HD was performed ∼12 hours after each fludarabine dose. On day −3, the patient's dialysis arteriovenous graft infiltrated during cannulation, requiring urgent HD catheter insertion. Each HD session lasted 6 hours, using a high-flux dialyzer (Optiflux F160Nre) and blood flow rates of 300-350 mL/min. Cilta-cel was administered uneventfully on day 0, and the patient received a standard 4-hour HD on day +1, more than 24 hours after the cilta-cel infusion.

The patient did not develop cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, or fludarabine-related neurotoxicity. Her absolute neutrophil count reached a nadir of 0.7 × 10^9/L on day +4 and then normalized by day +10 without intervention. She received 1 unit of packed red blood cells for a hemoglobin of 6.8 g/dL on day −1, then remained transfusion-free, with hemoglobin returning to a baseline level of 9.4 g/dL on day +40. The platelet count stayed above 100 ×10^9/L. The serum κ FLC decreased from 141 mg/L to 0.8 mg/L, the κ/λ ratio decreased from 19.29 to 0.42 and remained low on her latest follow-up on day +64. Bone marrow examination on day +28 showed no immunohistochemical or immunophenotypic evidence of disease, consistent with measurable residual disease and a negative complete hematologic response.

Case 2

A 70-year-old man with a history of hypertension, polycythemia vera, KF, and κ FLC international staging system stage III MM with a high-risk cytogenetics del (17p) was referred to our center. He was diagnosed with MM and biopsy-proven MM-related kidney disease 14 years previously. Initially, he received bortezomib-dexamethasone with a good hematologic response. Eight years later, he had progression of the disease, and despite carfilzomib-dexamethasone therapy, he developed KF, requiring maintenance HD. He subsequently received carfilzomib-lenalidomide-dexamethasone, followed by daratumumab-bortezomib-dexamethasone, and had been on maintenance daratumumab-bortezomib for 3 years. On referral to our center, restaging investigations noted a serum M-spike of 0.74 g/dL, κ FLC 168 mg/L, and κ/λ ratio of 8.26. The bone marrow biopsy showed 20%-25% plasma cells, of which 97.6% were abnormal. A decision was made to administer cilta-cel for cytoreduction of MM to achieve kidney transplant eligibility.

Fludarabine was omitted from the lymphodepletion regimen, and the patient received cyclophosphamide 300 mg/m^2 (standard dose) on days −5, −4, and −3. He received HD on days −6, −3, −1, and +1. Each HD session lasted 4 hours, using a high-flux dialyzer (Optiflux F160Nre) and a blood flow rate of 400 mL/min. The HD sessions on days −1 and +1 were at least 24 hours apart from the cilta-cel infusion. He developed grade 1 cytokine release syndrome with fevers on days +6, +8, and +9, which subsided after tocilizumab on day +6 and dexamethasone on days +8 and +9. He did not develop immune effector cell-associated neurotoxicity syndrome. The absolute neutrophil count dropped below 0.5 × 10^9/L on day +9 and normalized without intervention by day +17. He remained transfusion-free with his lowest hemoglobin and platelet count at 8.8 g/dL and 95 × 10^9/L on day +10, respectively. The disease restaging on day +28 showed a serum M-spike 0.38 g/dL, κ FLC of 5 mg/L, and a κ/λ ratio of 0.78, and the bone marrow biopsy was negative for plasma cell neoplasm by both immunohistochemistry and flow cytometry. These results constitute a serologic very good partial response but absent measurable residual disease in the bone marrow. On day +90, the serum M-spike trended down to 0.18 g/dL, and the κ/λ ratio remained normal at 0.93.

DISCUSSION

Here, we report 2 cases of cilta-cel use in patients with RRMM and KF on maintenance HD, representing all such patients in our center to date, with both patients demonstrating satisfactory short-term safety and favorable efficacy outcomes. Current data regarding the use of CAR T-cell therapy in patients with RRMM and KF are limited. The KarMMa-3 and CARTITUDE-4 trials required subjects to have a serum creatinine clearance of ≥45 mL/min and an estimated glomerular filtration rate of ≥40 mL/min/1.73m^2, respectively.[4,5] However, up to 50% of patients with MM present with decreased kidney function, and some progress to KF despite treatment.[10] A recent retrospective study suggested that ide-cel achieved similar response rates and survival outcomes in patients with MM with a serum creatinine clearance of <50 mL/min when compared with those with normal kidney function; however, only 1 patient in this cohort was dialysis-dependent.[8]

Both ide-cel and cilta-cel require lymphodepletion, commonly with fludarabine and cyclophosphamide, before CAR T-cell infusion. Cyclophosphamide is primarily metabolized by the liver. Although some believe cyclophosphamide has clinically insignificant renal clearance,[11] others demonstrated decreased cyclophosphamide clearance in patients with poor kidney function.[12,13] This explains the variability in cyclophosphamide dosing in patients with KF receiving CAR T-cell therapy (Table 1).[6-10,14]

A primary concern with CAR T-cell therapy in patients with KF is the risk of fludarabine-associated neurotoxicity. Fludarabine neurotoxicity can present with headaches, confusion, pyramidal tract dysfunction, focal neurologic deficits, seizures, and can be fatal.[15] The reported onset of fludarabine neurotoxicity was approximately a month after fludarabine initiation.[15,16] Risk factors for fludarabine neurotoxicity include poor kidney function, old age, cumulative fludarabine exposure, and underlying central nervous system disease. Fludarabine and its metabolites are primarily cleared through the kidneys; hence, their accumulation increases the risk of neurotoxicity in patients with KF. Pharmacokinetic studies of fludarabine in patients with KF are limited to a few case reports.[16-18] Fludarabine dose adjustments for patients with KF vary widely across institutions.[6,8]

Drug clearance on HD depends on factors including HD session duration, dialyzer clearance, and the blood and dialysate flow rates. Chen et al[16] illustrated the effect of HD prescription on the pharmacokinetics of fludarabine in patients with KF undergoing combined hematopoietic cell

Table 1. Summary of Published Cases of CAR T-Cell Therapy in Patients With Kidney Failure Receiving Hemodialysis

	Hunter et al[7] Case 1	Hunter et al[7] Case 2	Wood et al[6] Case 1	Wood et al[6] Case 2	Wasch et al[9]	Sidana et al[8]	Present Report Case 1	Present Report Case 2
Product	Axi-cel	Liso-cel	Tisa-cel	Brexu-cel	Ide-cel	Ide-cel	Cilta-cel	Cilta-cel
LD prescription								
Schedule	Days −5, −4, and −3	Days −5, −4, and −3	Days −5, −4, and −3	Days −5, −4, and −3	Days −5, −4, and −3	Days −5, −4, and −3	Days −5, −4, and −3	Days −5, −4, and −3
Cyclophosphamide dose (%)[a]	300 mg/m^2 (60%)	300 mg/m^2 (100%)	500 mg/m^2 (200%)	Days −5, −3: 500 mg/m^2 (100%) Day −4: 375 mg/m^2 (75%)[b]	300 mg/m^2 (100%)	300 mg/m^2 (100%)	300 mg/m^2 (100%)	300 mg/m^2 (100%)
Fludarabine dose (%)[a]	20 mg/m^2 (66.7%)	20 mg/m^2 (66.7%)	12.5 mg/m^2 (50%)	15 mg/m^2 (50%)	Not administered	24 mg/m^2 (80%)	15 mg/m^2 (50%)	Not administered
HD prescription								
Schedule	Days −5, −4, −3	Days −5, −4, −3	Days −5, −3	Days −5, −3		Days −5, −4	Days −5, −4, −3	Day −3
During lymphodepletion	12 h after chemotherapy	12 h after chemotherapy	12 h after chemotherapy	12 h after chemotherapy	ND	12 h before chemotherapy	10.5-15 h after chemotherapy	Between second and third dose chemotherapy
Subsequent sessions	ND	ND	Day 0: ended <2 h from cell infusion	Day 0: ended <2 h from cell infusion	ND	ND	Day +1: started >24 h after cell infusion	Day −1: ended >24 h from cell infusion Day +1: started >24 h after cell infusion
Duration of each HD session	ND	ND	ND	ND	ND	ND	Days −5, −4, −3: 6 h Day +1: 4 h	4 h
Dialyzer	ND	ND	ND	ND	ND	ND	Optiflux F160NRe	Optiflux F160NRe
BFR (mL/min)	ND	ND	ND	ND	ND	ND	300-350	400
CRS (grade)	1	Nil	1	2	1	ND	1	Nil
ICANS (grade)	2	Nil	4	Nil	Nil	ND	Nil	Nil

Abbreviations: Axi-cel, axicabtagene ciloleucel; Liso-cel, lisocabtagene maraleucel; Tisa-cel, tisagenlecleucel; Brexu-cel, brexucabtagene autoleucel, Ide-cel, idecabtagene vicleucel; Cilta-cel, ciltacabtagene autoleucel; LD, lymphodepletion; HD, hemodialysis; ND, not described; BFR, blood flow rate; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.
[a]Percentage dose of Food and Drug Administration-approved standard lymphodepletion dose, given to patients daily on days −5, −4, and −3.
[b]Mesna at 20% of daily cyclophosphamide given.

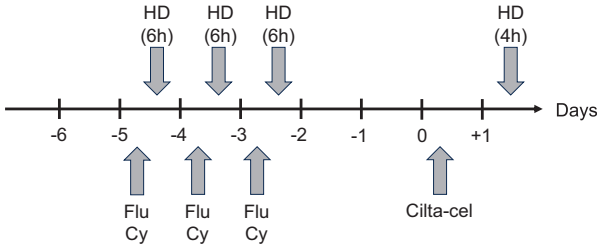

Figure 1. Lymphodepletion and hemodialysis schedule of case 1.

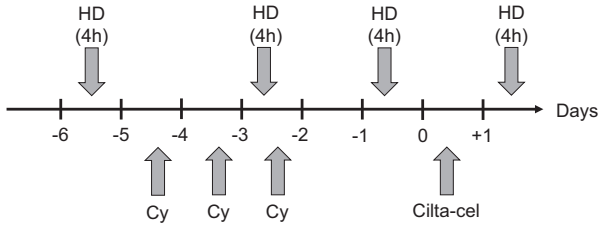

Figure 2. Lymphodepletion and hemodialysis schedule of case 2. HD, hemodialysis; Flu, fludarabine; Cy, cyclophosphamide; Cilta-cel, ciltacabtagene autoleucel.

and kidney transplantation. In this case series, 1 patient developed presumed fludarabine neurotoxicity at 1 month following fludarabine exposure. This patient received fludarabine 24 mg/m^2 daily for 5 days, with a standard HD of 6-12 hours after each dose. This event of fludarabine-related neurotoxicity led the investigators to modify the lymphodepletion and HD protocols. The subsequent 3 patients received fludarabine 24 mg/m^2 daily for only 3 days, with extended 6-hour HD using a high-flux dialyzer following each fludarabine dose. Pharmacokinetic analyses demonstrated that the areas under the curve in the latter 3 patients were similar to those in patients with normal kidney function receiving standard fludarabine dose. Therefore, fludarabine dosing and HD prescription require modification in patients with KF. However, clinical practice varies significantly as fludarabine dosing and HD schedules are not standardized (Table 1).[6-9] Furthermore, in most published reports, details of HD prescription following fludarabine administration are not reported.

In our case report, the fludarabine dose was reduced by 50% for case 1 to mitigate the risk of fludarabine neurotoxicity. Three doses of fludarabine were administered, as described by Wood et al[6], followed by a 6-hour HD after each fludarabine dose (Figs 1 and 2).[6] In case 2, fludarabine was not administered, based on previous reports of cyclophosphamide-only lymphodepletion regimen.[9,19] The decision whether to administer fludarabine was made by the primary oncologist. Standard dose cyclophosphamide was administered to both patients. Case 1 did not develop fludarabine neurotoxicity, and neither patient had prolonged cytopenia. Case 1 developed an arteriovenous graft infiltration necessitating urgent HD catheter insertion, highlighting the challenges associated with intensive HD treatments following fludarabine administration.

In conclusion, cilta-cel administration appears to be safe and efficacious in the short term in patients with RRMM and KF. The optimal lymphodepletion and HD regimens for CAR T-cell therapy in patients with MM and KF remain to be defined. The lack of therapeutic drug monitoring and information regarding long-term outcomes, such as delayed onset parkinsonism or survival data following CAR T-cell therapy, are limitations of this report. Further studies on pharmacokinetics and the safety and efficacy of B-cell maturation antigen-targeting CAR T-cell therapy in patients with KF and MM are needed.

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