



Delayed kidney transplantation after HLA-haploidentical hematopoietic cell transplantation in a young woman with myelodysplastic syndrome with renal failure

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ABSTRACT

Patients with end-stage renal disease (ESRD) are often excluded from potentially curative allogeneic hematopoietic cell transplantation (alloHCT). Our institution pioneered simultaneous living donor kidney transplantation in patients undergoing alloHCT from the same donor for hematologic malignancies. Herein, we present the case of a 31-year-old woman diagnosed with myelodysplastic syndrome who developed ESRD during cytoreductive induction therapy. She achieved disease control, then successfully underwent a human leukocyte antigen (HLA)-haploidentical alloHCT while on hemodialysis. After rapidly tapering off graft-versus-host disease prophylaxis, fourteen months from her alloHCT she received a kidney transplant from her same haploidentical sibling donor, which obviated the need for further systemic immunosuppression.

1. Introduction

Allogeneic hematopoietic cell transplantation (alloHCT) is the mainstay of treatment for high risk myelodysplastic syndromes (MDS) – and represents the only curative therapy[1]. There is limited data if long-term outcomes are improved when cytoreductive therapy is given prior to alloHCT[2]. Generally, patients with high risk features are treated with chemotherapy or hypomethylating agents to reduce malignant clonal burden. There are several downsides to this approach, namely accrual of toxicity, as well as inherently poor response rates and thereby risk of disease progression.

Herein, we present the case of a young woman with MDS who developed end-stage renal disease (ESRD) during induction. Patients on dialysis are often excluded from alloHCT due to an unacceptable risk of non-relapse mortality (NRM)[3,4]. Our institution pioneered simultaneous living donor kidney and hematopoietic cell transplantation in patients with hematologic malignancies, including for human leukocyte antigen (HLA)-haploidentical pairs, however logistical challenges during the COVID-19 pandemic temporarily limited the implementation of this approach[5]. Remarkably, this patient achieved disease control and subsequently underwent HLA-haploidentical alloHCT while on

hemodialysis. Fourteen months later, she received a kidney from her same sibling donor, obviating the need for further systemic immunosuppression. This case highlights the feasibility of (1) HLA-haploidentical alloHCT in patients with ESRD and (2) delayed kidney transplantation in this context.

2. Case description

A 31-year-old woman (G5P4A1) presented with one month of progressive fatigue and exertional dyspnea in Cameroon. Her complete blood count showed severe macrocytic anemia and mild thrombocytopenia. A bone marrow biopsy and aspirate performed during medical evacuation revealed 75% cellularity, trilineage dysplasia and 13% blasts, consistent with MDS with excess blasts type 2. Cytogenetic analysis demonstrated 46,XX with t(3;3)(q21;q26.2), a poor-risk abnormality affecting *MECOM/EVI1*. Next-generation DNA sequencing was performed for *IDH1/2*, which were both wild-type. Taken together, her MDS was deemed very high risk by the Revised International Prognostic Scoring System.

After relocation to Wisconsin, specimens for HLA typing were obtained, and cytoreduction commenced with decitabine (20 mg/m², days

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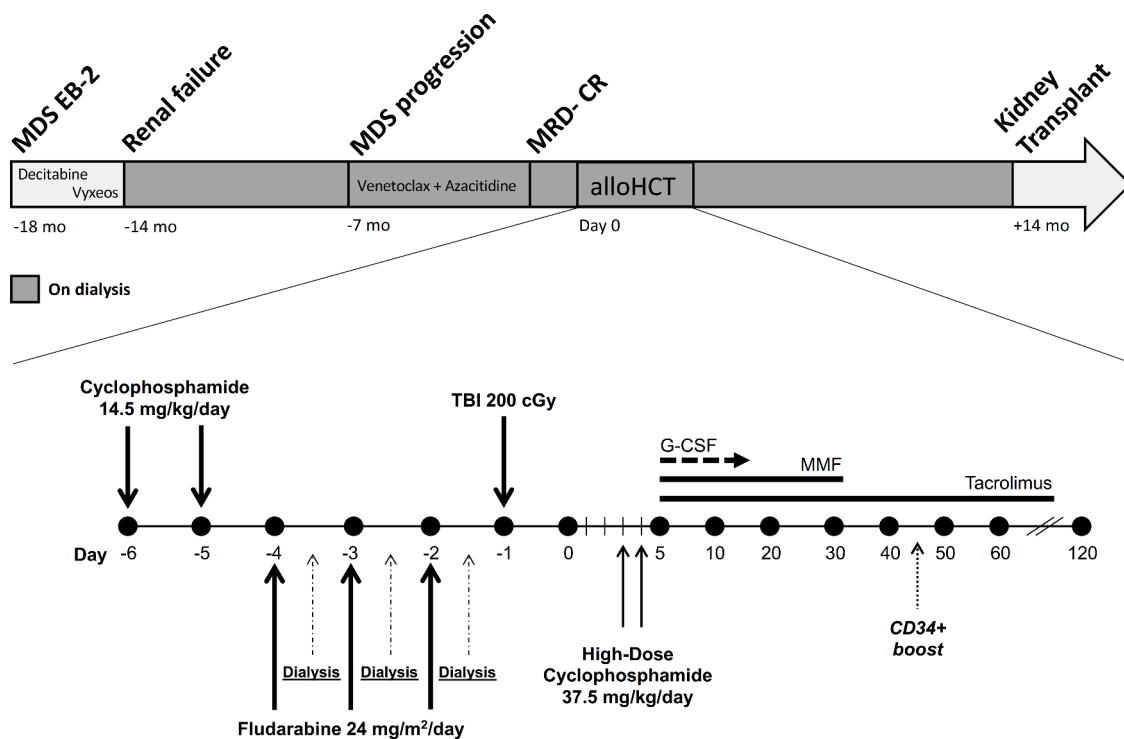


Fig. 1. Schema depicting treatment course from diagnosis to kidney transplant for the patient. MDS, myelodysplastic syndrome; vyxeos, liposomal daunorubicin and cytarabine; alloHCT, allogeneic hematopoietic cell transplant; MRD-, measurable residual disease-negative; CR, complete remission; TBI, total body irradiation; cGy, centiGray; MMF, mycophenolate mofetil.

1–10). There was no initial response, so liposomal daunorubicin and cytarabine was initiated (Vyxeos, 100 units/m², days 1, 3, 5). Shortly thereafter, she was hospitalized with neutropenic fever, acute kidney injury and nephrotic syndrome. Kidney biopsy was initially deferred due to severe thrombocytopenia. Hypoxemic respiratory failure ensued secondary to hypervolemia, so hemodialysis was initiated along with corticosteroids. A repeat bone marrow aspirate showed 6% blasts. Due to persistent renal dysfunction and laboratory evidence of hemolysis, her kidney was biopsied, which revealed severe thrombotic microangiopathy. ADAMTS13 activity was normal; eculizumab was initiated for presumed atypical hemolytic uremic syndrome (aHUS). However, no hematologic or renal response was observed after six doses of eculizumab. She transitioned to plasmapheresis, which improved hemolysis parameters, but remained with persistent ESRD. Genetic testing did not identify any variants to explain aHUS. However, functional assays revealed low Factor B (19.7 mg/dL, reference range 22–50 mg/dL), low Factor H (134 mg/L, reference range 180–420 mg/L) and a Factor B autoantibody of unknown significance. She was maintained on supportive care, including plasmapheresis tapered over six months, and transitioned to peritoneal dialysis.

A bone marrow aspirate several months later showed 18% blasts consistent with progression toward acute myeloid leukemia. She was subsequently treated with azacitidine (75 mg/m², days 1–5, monthly) and after one cycle, venetoclax was added (100 mg daily). She was considered for concomitant alloHCT and kidney transplantation in Boston via telemedicine consultation[5], but was deferred due to the COVID-19 pandemic and her refractory hematological malignancy. She remained on azacitidine and venetoclax. A bone marrow aspirate five months later showed normal hematopoiesis, normal cytogenetics and was without evidence of measurable residual disease by flow cytometry (University of Washington, <0.1%).

She proceeded to a non-myeloablative HLA-haploidentical related donor transplant from her sister 18 months from the original date of diagnosis. Conditioning commenced with cyclophosphamide (14.5 mg/kg/day, days –6 and –5), fludarabine (reduced to 24 mg/m²/day, days

–4, –3, –2), and total-body irradiation (200 cGy, day –1), with additional hemodialysis after each dose of fludarabine as previously described[5]. On day 0, 6.12×10^6 CD34⁺ cells/kg were given with a T cell replete peripheral blood stem cell graft. Graft-versus-host disease (GVHD) prophylaxis incorporated post-transplant cyclophosphamide (PTCy, reduced to 37.5 mg/kg, days +3 and +4), mycophenolate mofetil (MMF) (starting day +5) and tacrolimus (starting day +5) (Fig. 1). The transplant was ABO matched (A+/A+) and both donor and recipient were cytomegalovirus seronegative. MMF was stopped on day +30. On day +35, the patient was 100% donor in CD3⁺ and CD33⁺ fractions. Neutrophil engraftment occurred on day +36. An additional 4.2×10^6 CD34⁺ cells/kg were transfused on day +45 (Miltenyi Biotec) to aid hematopoietic recovery. Platelet engraftment occurred on day +50. The remainder of her post-transplant course was uneventful. Tacrolimus was rapidly tapered starting day +60 due to high-risk biology and stopped by day +105. She had no evidence of acute or chronic GVHD and remained on peritoneal dialysis throughout.

Fourteen months after alloHCT, a bone marrow aspirate showed normal hematopoiesis without dysplasia, with 100% donor chimerism in all lineages. Repeat functional assays showed no evidence of complement dysregulation or autoantibodies. She relocated to Boston and subsequently received a kidney transplant from her same HCT donor sister. Surgery was uncomplicated and she immediately had robust urine output. For immunosuppression, she only received intravenous methylprednisolone peri-operatively, then tapered off corticosteroids within one week. Her creatinine normalized and she remains without evidence of kidney rejection, chronic GVHD, aHUS or MDS relapse now three months after kidney transplantation.

3. Discussion

Historically, ESRD has excluded patients from alloHCT[6,7]. Renal dysfunction independently predicts for poor post-transplant outcomes [8]. A recent retrospective study detailed the outcomes of 46 patients from 35 centers who were on hemodialysis at the time of alloHCT. The

1-year probability of overall survival was 20%, with a dismal 67% probability of NRM[3].

A central issue is the safe administration of conditioning in the setting of dialysis. Fludarabine presents a challenge because 60% of its primary metabolite is renally cleared[4]. Our group demonstrated through pharmacokinetic sampling that fludarabine neurotoxicity is avoidable with dose reductions, longer (~6 h) dialysis sessions occurring 6–12 h after each administration, and use of a larger dialyzer[5].

Generally, PTCy is considered safe to administer in the setting of renal failure, but both cyclophosphamide and several of its metabolites are renally cleared to some extent[9]. This likely contributed to delayed engraftment and the need for additional donor cells here, despite a 25% dose reduction. Similarly, MMF and its metabolites are renally cleared and could have contributed to delayed engraftment[10].

Due to logistical challenges during the COVID-19 pandemic as well as refractory MDS, this patient was unable to undergo initial concomitant alloHCT and kidney transplant, which we recently adapted to include PTCy for haploidentical transplants[5]. With all kidney transplants, the risk of recurrent renal injury must be thoroughly considered as this is a major cause of graft failure. The insults that precipitated aHUS here were thought to be medications and/or infection during induction, and thus had resolved prior to kidney transplantation. As was expected, she accepted the kidney from her same donor without needing further systemic immunosuppression.

This case highlights several important issues, namely the need for further research on the adaptation of alloHCT protocols for patients with ESRD, as well as investigating the use of concomitant transplantation to engender immune tolerance.

CRediT authorship contribution statement

Kevin C. Miller: Resources, Writing – original draft. **Aric C. Hall:** Resources, Writing – review & editing. **Abraham Cohen-Bucay:** Resources, Writing – review & editing. **Yi-Bin Chen:** Resources, Writing – review & editing.

Declaration of Competing Interest

K.C.M., A.C.H. and A.C.B. declare no competing financial interests. Y-B.C. has performed consultancy for Daiichi, Equilibrium, Actinium, Celularity, and Incyte.

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References

- [1] U. Platzbecker, Treatment of MDS, *Blood* 133 (10) (2019) 1096.
- [2] E.P. Alessandrino, M.G. Della Porta, C. Pascutto, et al., Should cytoreductive treatment be performed before transplantation in patients with high-risk myelodysplastic syndrome? *J. Clin. Oncol* 31 (21) (2013) 2761.
- [3] N. Farhadfar, A. Dias, T. Wang, et al., Impact of pretransplantation renal dysfunction on outcomes after allogeneic hematopoietic cell transplantation, *Transplant. Cell Ther* 27 (5) (2021) 410.
- [4] M. Shadman, S. Hingorani, S.A. Lanum, et al., Allogeneic hematopoietic cell transplant for patients with end stage renal disease requiring dialysis - a single institution experience, *Leuk. Lymphoma* 58 (3) (2017) 740.
- [5] Y.-B. Chen, N. Elias, E. Heher, et al., Haploidentical hematopoietic cell and kidney transplantation for hematological malignancies and end-stage renal failure, *Blood* 134 (2) (2019) 211.
- [6] E.C. Heher, T.R. Spitzer, Hematopoietic stem cell transplantation in patients with chronic kidney disease, *Semin. Nephrol.* 30 (6) (2010) 602.
- [7] M.N. Bodge, S. Reddy, M.S. Thompson, et al., Preparative regimen dosing for hematopoietic stem cell transplantation in patients with chronic kidney disease: analysis of the literature and recommendations, *Biol. Blood Marrow Transplant* 20 (7) (2014) 908.
- [8] M.L. Sorror, M.B. Maris, R. Storb, et al., Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT, *Blood* 106 (8) (2005) 2912.
- [9] S. Ren, T.F. Kalthorn, G.B. McDonald, et al., Pharmacokinetics of cyclophosphamide and its metabolites in bone marrow transplantation patients, *Clin. Pharmacol. Ther* 64 (3) (1998) 289.
- [10] K. Yoshimura, I. Yano, T. Yamamoto, et al., Population pharmacokinetics and pharmacodynamics of mycophenolic acid using the prospective data in patients undergoing hematopoietic stem cell transplantation, *Bone Marrow Transplant* 53 (1) (2018) 44.