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Allogeneic Hematopoietic Cell Transplant for Patients with End Stage Renal Disease Requiring Dialysis – a Single Institution Experience

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Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative treatment for a number of benign and malignant hematologic disorders; however, it is also associated with treatment-related complications.¹ The advent of reduced-intensity (RIC) and nonmyeloablative (NMA) conditioning regimens has made allogeneic HCT a viable option for patients who might otherwise have been ineligible because of medical comorbidities.² Patients with hematologic malignancies are at increased risk of developing renal insufficiency either because of the disease pathophysiology (e.g. myeloma) or as a result of adverse effects from treatment with multiple lines of cytotoxic chemotherapy agents.³ Unlike autologous HSCT, the published data regarding the feasibility and outcomes of allo-HCT for patients with chronic kidney disease (CKD) and especially for those with end-stage renal disease (ESRD) requiring renal replacement therapy is limited. This paucity of data may lead to the unnecessary exclusion of patients on hemodialysis or peritoneal dialysis from allogeneic-HCT as a treatment option. Herein, we report the outcomes of patients with hematologic malignancies who were transplanted while on renal replacement therapy (RRT) at our institution. In this retrospective study, we used our institutional database at Fred Hutchinson Cancer Research Center (FHCRC) and reviewed all patients who received a RIC or NMA allo-HSCT from 1997 to 2014. For this report we included the patients who were on either hemodialysis or peritoneal dialysis at the time of transplant at the FHCRC. Clinical data were extracted from electronic medical records directly. The study is approved by the FHCRC IRB. We identified 6 patients who were transplanted at the FHCRC between 1997

and 2014 while on dialysis. Their median age was 43.5 (range 13 – 52 years) and 50% of patients were female (n=3). (Table-1) Multiple myeloma was the most common etiology for ESRD in 3 patients followed by polycystic kidney disease (PCKD) in 2 and hemolytic-uremic syndrome (HUS) secondary to E.coli infection in 1. The median duration of receiving RRT before HSCT was 14 months (range: 6 – 48 months). Five patients were on hemodialysis (HD) and 1 was on peritoneal dialysis (PD). Primary hematologic disorders included multiple myeloma (n=3), follicular lymphoma (n=1), myelodysplastic syndrome (MDS) (n=1) and Wiskott-Aldrich syndrome (n=1). Four of the 6 patients had previously undergone an autologous HCT. Three patients received their peripheral stem cell grafts from HLA-matched-related donors. For these patients, conditioning included 2 Gy total-body irradiation (TBI) at a rate of 0.07–0.10 Gy/minute from a linear accelerator on the day of HCT (day 0). Two patients had peripheral stem cell grafts from HLA-matched-unrelated donors after conditioning with fludarabine (30 mg/m²/day days -4 to -2) in addition to 2 Gy TBI (day 0). Fludarabine was given at full dose in one patient who was on HD at the time of transplant consult but not at the time of conditioning. In the other patient, the dose was reduced by 25% and the drug was given after HD in each day of administration. One patient received an HLA-haploidentical bone marrow transplant. The conditioning protocol included full-dose cyclophosphamide (14.5 mg/kg/day on days -6 and -5), fludarabine dose reduced by 50% (to 15 mg/m²/day on days -6 to -2) and 2-Gy TBI (day -1). Both cyclophosphamide and fludarabine were given after dialysis on each treatment day. Patients with HLA-matched related or unrelated grafts (n=5; 83%) received cyclosporine and mycophenolate mofetil (MMF) for GVHD prophylaxis. Cyclosporine dose was adjusted to achieve a therapeutic level between 120–360 ng/mL as tolerated by toxicity. MMF was given at the standard dose. The GVHD prophylaxis regimen for the patient who received an HLA-haploidentical transplant included a single dose of cyclophosphamide 50 mg/kg on day 3 after HCT, which was given with 25% dose reduction (37.5 mg/kg) after dialysis. In addition, the patient received tacrolimus (starting day +4) and MMF. Tacrolimus dosing was adjusted to achieve blood level between 5–15 ng/ml. After median follow-up of 15.5 months (range: 9.6 – 84.6), one patient was alive with no evidence of recurrence of multiple myeloma 24 months after HLA haploidentical transplant. Five patients (83%) died between 9.6 to 84.5 (median 12.2 months) months after transplant. One patient died at 9.6 months from tumor lysis syndrome after disease relapse. The remaining patients died from etiologies other than relapse: one died at 10.7 months from CMV pneumonia, one at 12.3 months from cerebral hemorrhage secondary to fungal infection, one from uncontrolled bleeding during cardiac surgery for aortic aneurism. Bleeding in this patient was not related to renal failure. One patient died at 84.7 months from sepsis. We did not observe any of the known serious complications of calcineurin inhibitors like posterior reversible encephalopathy syndrome (PRES) or thrombotic microangiopathy (TMA) in our patients. Six patients who were on either hemodialysis or peritoneal dialysis while undergoing allogeneic HCT for advanced blood disorders did not experience adverse short-term or long-term events related to their end-stage renal disease or renal replacement therapy. While meticulous clinical monitoring and dosing adjustment for both conditioning regimen and post-transplant GVHD medications is necessary in these patients, they should not be routinely excluded from allogeneic HCT solely because they are on renal replacement therapy. In a recent comprehensive review, Bodge and colleagues ⁴ discussed the recommendations for optimal

adjustments of preparative regimens in patients with different stages of chronic kidney disease. Experience is limited in regards to allogeneic-HCT for end-stage renal disease patients requiring dialysis and clinical practices have been quite variable.⁵⁻⁷ Fludarabine-based regimens in combination with low dose TBI are commonly used for NMA allogeneic - HCTs. It has been shown that approximately 60% of the active metabolite of fludarabine is eliminated by the kidneys and therefore appropriate dose adjustment needs to be implemented in patients with renal failure.⁸ In addition, data on dialysate concentration and pharmacokinetics of the principal metabolite of fludarabine, 2-fluoro-ara-A (2F-Ara-A) suggests that fludarabine is adequately removed by hemodialysis and can be used in dialysis patients with dose adjustment.⁹ We administered dose-adjusted fludarabine after dialysis and consistent with our approach, other groups have reported use of fludarabine with 20% dose reduction in dialysis patients.⁶⁻⁷ In one report, 4 of 5 patients with different degrees of renal failure developed severe neurologic toxicities including 2 deaths when transplanted after conditioning with fludarabine-based regimens.⁷ Of note, in their report, the only patient without neurotoxicity was one of the 2 dialysis dependent patients who in fact received full dose fludarabine (30 mg/m² for 5 days). Calcineurin inhibitors and/or late effect of fludarabine were reported as possible etiologies for neurotoxicity and significant dose reduction or even omission of fludarabine from conditioning regimens for patient with renal failure was suggested by the authors. As reported above, we did not observe any neurologic adverse events in our patients and are reluctant to agree with their recommendations in the absence of stronger evidence for neurotoxicity by fludarabine. Cyclophosphamide and its metabolites are also cleared by the kidneys and only partially removed by dialysis. There are no universally recognized guidelines for dosing of cyclophosphamide in patients with renal impairment and in those on dialysis. Optimal dose adjustment remains controversial for cyclophosphamide. It is in general recommended that cyclophosphamide doses be reduced by 25-50% in patients with severe renal impairment (GFR <10 mL/min) and some authors suggest a supplemental dose after dialysis.¹⁰⁻¹² As a result, in published case reports of dialysis patients undergoing allogeneic-HCT with cyclophosphamide containing regimens the approach is variable and inconsistent. In addition, timing of the first dialysis after cyclophosphamide has been variable ranging from 6 to 14 hours.¹³⁻¹⁴ In our patients, the lower doses (14.5 mg/kg/day on each of 2 successive days) of cyclophosphamide in the conditioning regimen were not changed; however, the higher dose (50 mg/kg) cyclophosphamide scheduled for day 3 after transplant used as GVHD prophylaxis was reduced by 25%. In both instances, the drug was given after dialysis. Dialysis does not appreciably alter the pharmacokinetics of cyclosporine, tacrolimus, or MMF.¹⁰ For calcineurin inhibitors dosing was done according to trough levels which resulted in less frequent administration of drugs. We have demonstrated the ability to successfully transplant patients on dialysis and suggest that dialysis should not be an exclusion criterion. The current report only includes patients with history of end-stage kidney disease who were established dialysis patients at the time of referral to our transplant center. Systematic review of national registries is needed in order to address the feasibility and safety of allogeneic-HCT in ESRD patients requiring dialysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical information on individual cases

Table 1

ID	Age (years)	Sex	Diagnosis	Etiology of Renal Failure	Type of Dialysis	Duration of Dialysis before Transplant (months)	Type of Transplant	Prior Auto-SCT	Conditioning Regimen	Immunosuppression	Survival after Transplant (months)	Etiology of Death
1	42	F	Multiple Myeloma	Myeloma Kidney	HD	12	MRD-BM	Yes	2GyTBI	MMF/CSP	9.6	TLS secondary to relapse
2	52	F	Follicular Lymphoma	HUS	HD	48	MRD -PBSC	Yes	2GyTBI	MMF/CSP	82.2	Bleeding during open heart surgery
3	41	M	MDS/MPN	PCKD	HD	6	MURD – PBSC	No	Flu/2GyTBI	MMF/CSP	84.7	Sepsis
4	13	M	WAS	PCKD	HD	16	MURD – PBSC	No	Flu(75% [*])/2GyTBI	MMF/CSP	12.3	Cerebral hemorrhage
5	50	M	Multiple Myeloma	Myeloma Kidney	PD	10	MRD – PBSC	Yes	2GyTBI	MMF/CSP	10.7	CMV pneumonia
6	45	F	Multiple Myeloma	Myeloma Kidney	HD	24	Haploidentical-BM	Yes	Flu(50% [*])/Cy/2GyTBI	Cy(75% [*])/MMF/TAC	24 (alive)	N/A

^{*} Indicates the percentage of the drug given after dose adjustment for the renal failure.

BM = bone marrow; CSP=Cyclosporine; Cy=Cyclophosphamide; F=female; Flu=Fludarabine; HD= Hemodialysis; HUS=Hemolytic uremic syndrome; M=male; MMF= Mycophenolate mofetil; MRD= matched-related donor; MURD= matched unrelated donor; PBSC= peripheral blood stem cell; PCKD= polycystic kidney disease; PD=Peritoneal dialysis; TAC=Tacrolimus; TBI=total body irradiation; TLS=tumor lysis syndrome; WAS= Wiskott–Aldrich syndrome