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Review

Preparative Regimen Dosing for Hematopoietic Stem Cell Transplantation in Patients with Chronic Kidney Disease: Analysis of the Literature and Recommendations

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A B S T R A C T

Hematopoietic stem cell transplantation (HSCT) is a potentially life-saving therapy that has traditionally been associated with high treatment-related mortality due to direct regimen toxicity and a high incidence of graft-versus-host disease. Historically, pre-existing renal insufficiency has been considered an exclusion criterion for transplantation. The advent of nonmyeloablative conditioning regimens as a less toxic modality for treatment has made HSCT more accessible to elderly patients and patients with comorbidities, such as renal impairment. However, there is no clear standard for how to dose preparative regimens for patients with chronic renal impairment who undergo HSCT. This article serves as a review of the current literature to provide dosing recommendations for commonly used preparative agents in the setting of chronic kidney disease, with the aim of providing optimal dosing for this patient population.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is considered to be a life-saving therapy for patients with certain malignant and nonmalignant disease states. It has been well documented in the literature that renal injury is a common complication of HSCT and leads to increased morbidity and mortality [1-4]. Patients with pre-existing chronic kidney disease (CKD) are frequently not considered to be candidates for HSCT and are, therefore, not offered this potentially life-saving therapy. Additionally, major risk scoring indices include renal insufficiency as a risk factor for post-transplantation mortality [5,6].

There have been various reports in the literature describing successful autologous and allogeneic HSCT for patients with CKD, including patients with end-stage renal disease (ESRD) requiring dialysis. However, the literature consists of mostly case reports and small case series, and there is no clear consensus on optimal dosing for preparative regimens before transplantation. When selecting a preparative regimen for patients with CKD who undergo transplantation, there is always a risk for unintentional overdosing or underdosing, based on variable pharmacokinetics in this patient population. Underdosing may lead to graft rejection or suboptimal disease control, whereas overdosing may lead to multiorgan toxicity [7].

METHODS

A thorough review of the MEDLINE library database with review of supporting references of included and excluded articles was performed. The literature search was limited to articles published in English with human participants (Appendix 1). MESH headings and key words searched were renal insufficiency, chronic; kidney failure, chronic; bone marrow transplantation; and hematopoietic stem cell transplantation.

RESULTS

It was found that the available literature provides insufficient information to draw evidence-based conclusions (level I or II) upon how to optimally dose a HSCT preparative regimen in a patient with baseline renal impairment. This was due to the largely retrospective nature of the reports, limited information regarding creatinine clearance and dialysis schedules for patients who were hemodialysis dependent, and lack of pharmacokinetic reporting for the majority of cases. The available data are supportive of HSCT in patients with renal insufficiency, but the data are insufficient to provide optimal dosing regimens for patients with renal impairment. This is especially true in pediatric patients because of the differences in pharmacokinetic parameters and more limited reported data.

Because of the limitations encountered during this review, and the inability to develop level I or II recommendations, it was decided to instead provide a summary of the published literature. The research question of what preparative regimen may yield the best outcomes for these patients has evolved into a guideline to provide a basis for future studies of these patients. With that intent, the following information on preparative regimens in HSCT patients is reported to set a basis for regimen selection, especially aimed

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Table 1
Dosing Recommendation for Agents in Hematopoietic Stem Cell Transplantation

Agent	Suggested Dosing	Additional Information
Alemtuzumab	Unmodified	This agent has not been studied in the setting of renal impairment. Available literature suggests no adjustment is required in the setting of insufficiency.
Antithymocyte globulin (equine)	Unmodified	This agent has not been specifically studied in the setting of renal impairment; however, elimination does not appear to be influenced by renal function.
Antithymocyte globulin (rabbit)	Unmodified	This agent has not been specifically studied in the setting of renal impairment; however, elimination does not appear to be influenced by renal function.
Busulfan	Unmodified	Renal excretion plays a minor role in elimination for patients who receive this agent, even in the setting of dialysis.
Clofarabine	Avoid use in adults > 60 yr with creatinine clearance <60 mL/min (NCCN AML guidelines)[8] Fifty percent dosage adjustment with CrCl 30 to 60 mL/min[9]	Primarily excreted by the kidney, with 60% of the drug being excreted unchanged by both tubular secretion and glomerular filtration, with a half-life of 4-6 h in most cases. Administration may be possible for patients on hemodialysis.
Cyclophosphamide	Unmodified in the setting of mild renal impairment. Consider dosage reduction in the setting of moderate to severe renal impairment. Moderately dialyzable (20%-50%); for patients who are dialysis dependent, administer dose after hemodialysis.	Increased myocardial toxicity observed in CKD patients. Pharmacokinetic studies have demonstrated decreased clearance with renal insufficiency.
Fludarabine	20%-25% dose reduction in the setting of mild-to-moderate renal impairment. 50% dosage adjustment in the setting of severe renal impairment or in the setting of hemodialysis.	Sixty percent of the active metabolite 2-fluoro-ara-A (F-ARA-A) is cleared renally.
Melphalan	100-140 mg/m^2 for patients with renal impairment and those who are dialysis dependent	Melphalan is apparently not removed by dialysis, but the short half-life in water may contribute to the lack of detectable levels in the dialysate. Sixty percent is bound to plasma proteins, primarily albumin. Prolonged mucositis has been observed with standard doses in CKD patients.
Rituximab	Unmodified	This agent has not been studied in the setting of renal impairment. Available literature suggests no adjustment is required in the setting of insufficiency.
Thiotepa	Unmodified in the setting of mild-to-moderate renal impairment.	Cleared through liver metabolism and not affected by renal function. May be contraindicated in the setting of severe renal dysfunction.

NCCN indicates National Comprehensive Cancer Network; AML, acute myelogenous leukemia; CKD, chronic kidney disease; CrCl, creatinine clearance.

at supporting the study of drug dosing in patients with baseline impaired renal function. In Appendix 2, the data available for dosing in patients with baseline renal impairment will be reported, in addition to general population results and sufficient supporting information, such that the medical provider can assess the applicability to their respective patient populations.

CONCLUSIONS

High-dose chemotherapy followed by HSCT is becoming more widely utilized in patients with comorbidities, including those with renal insufficiency. It is often assumed that pharmacokinetics and pharmacodynamics of preparative regimen agents are significantly altered in the setting of renal insufficiency; however, this review suggests that HSCT can be safely performed in patients with baseline renal impairment. Based upon this literature review, recommendations for dosing chemotherapeutic agents in HSCT conditioning regimens are provided (Table 1). Please note the standardized definitions to support clarity in providing dosing information. Furthermore, to support patient care, we suggest future research that pertains to the dosing of antineoplastics or toxicity assessment in conditioning regimens for HSCT be required to report patient baseline renal impairment and assess patient outcome and toxicity with reference to these parameters.

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Appendix 1
Renal Impairment Overviews and Recommendations

Reference	Basis	Comments	Outcomes	Recommendation
[10]	Prospective study to evaluate the relationship between Mel pharmacokinetics and renal function in 20 patients with multiple myeloma. All patients received 200 mg/m^2 Mel divided into 2 daily doses of 100 mg/m^2 i.v. on 2 consecutive days, followed by peripheral blood stem cells.	Six patients had severe renal insufficiency (CrCl <40 mL/min), including 5 patients on chronic hemodialysis.	Mel pharmacokinetics, performed after the first dose of 100 mg/m^2, was not adversely affected by impaired renal function. Renal insufficiency did not have an apparent negative impact on stem cell collections or adversely affect post-transplantation engraftment, transfusion requirements, incidence of severe mucositis, or overall survival. It was associated with longer durations of fever ($P = .0005$) and hospitalization ($P = .004$).	Renal failure does not require dose reduction of Mel in auto transplantation.
[11]	Report of 6 patients with multiple myeloma and chronic renal insufficiency, including 4 on dialysis, who received high-dose BuCy, followed by auto stem cell transplantation. No dose adjustments were made for renal failure in the BuCy prep regimen. Bu was given at 1 mg/kg PO every 6 h for 16 doses and Cy was given at 60 mg/kg/d i.v. × 2 d.	Chronic renal insufficiency defined as serum creatinine >3.0 mg/dL. All patients on dialysis had renal biopsies; 2 demonstrated light chain deposition disease and the other 2 demonstrated myeloma cast nephropathy. Patients requiring renal replacement therapy were dialyzed before the first dose of Cy and again at 24 and 48 h after completion of the second dose.	Patterns of engraftment and toxicities were not apparently different from those seen in myeloma patients with normal renal function. There was 1 toxicity-related death, 1 patient died from disease progression 6 mo after transplantation, and the remaining 4 are alive and free of myeloma progression 6-39 mo after HDT.	BuCy is an acceptable preparative regimen in patients with multiple myeloma and CKD.
[12]	Case report of a 31-yr-old patient with CML who developed malignant nephrosclerosis with renal failure. He underwent an allo-HSCT in first chronic phase CML with a preparative regimen consisting of TBI with a total dose of 13.5 Gy from d −6 to −4 and Cy 60 mg/kg once daily i.v. on d −3 and −2. The pharmacokinetics of Cy on hemodialysis were studied. Clinical parameters were compared with those of a patient with normal renal function who also received an unrelated HSCT as treatment for CML in first chronic phase.	Hemodialysis was performed 6 h after each Cy dose over a period of 6 h. The patient also received bladder irrigation and a continuous i.v. infusion of mesna 60 mg/kg/24 h on d −3 and −2. GVHD prophylaxis consisted of cyclosporine and prednisone. Patient B also received methotrexate 15 mg/kg on d +1 and 10 mg/kg on d +3 and +6.	Drug-related toxicity was similar in both patients. Both patients developed grade II mucositis, grade II gastrointestinal toxicity, and only mild hepatic dysfunction. No difference was seen in time to engraftment. Peak Cy concentration on d 1 was 303.0 μmoL/L for patient A and 397.7 μmoL/L for patient B.	Cy/TBI is a suitable conditioning regimen for allo-HSCT in patients with renal failure on hemodialysis.
[13]	A patient with pre-existing ESRD underwent successful matched related donor allo bone marrow transplantation using conditioning with high-dose Cy (60 mg/kg/d × 2) and TBI (165 cGy twice daily × 4 d)	Six-h hemodialysis sessions were performed before CY infusion and again 14 h after the end of each of the 2-h CY infusions on d −6 and −5. Regular 4-h hemodialysis sessions were resumed on d −4, then 3 times weekly until hospital discharge. Systemic clearance in this patient was 38.4 mL/min, compared with the normal range of 51-100 mL/min in patients with normal renal function.	The patient's clinical course was uncomplicated. There were no acute cardiac effects detected or hemorrhagic cystitis. He did develop CMV infection on d +46 with positive blood and urine cultures, which was cleared following a 14-d course of ganciclovir therapy. He developed mild chronic GVHD 6 mo after transplantation after discontinuation of prophylactive prednisone.	Cy/TBI is a feasible preparative regimen for patients with ESRD.
[14]	Report of 6 patients with multiple myeloma and moderate-to-severe renal insufficiency who were treated with auto stem cell transplantation. Preparative regimens included Bu 12 mg/kg + Mel 120 mg/m^2 (4 patients) or a single dose of Mel 80 mg/^{2} alone for a patient with CrCl <20 mL/h and the patient on hemodialysis.	Impaired renal function was defined by CrCl <40 mL/h. Five patients had renal failure at the time of diagnosis (median, CrCl 27 mL/h; range 5-34 mL/h). Renal biopsy revealed a picture of myeloma-cast nephropathy in 3 patients or light-chain deposition in 2 patients. One patient had severe renal insufficiency, which required hemodialysis 3 times per wk. The patient on hemodialysis who received Mel 80 mg/m^2 had hemodialysis performed 2 h after Mel infusion.	Engraftment occurred in all patients after transplantation. Three patients experienced grade 3-4 mucositis and 1 patient experienced veno-occlusive disease. Renal function either improved or remained stable throughout the transplantation period.	Bu and Mel are acceptable preparative agents for patients with moderate-to-severe renal insufficiency.
[15]	Case report detailing the impact of hemodialysis on the clearance of Bu in a patient with chronic renal failure undergoing auto peripheral stem cell transplantation.	The patient received 5 test doses (.17 mg/kg) and 14 therapeutic doses (.60-1.0 mg/kg) of oral Bu given every 6 h over 5 d, followed by 2 daily infusions of Cy (100 and 50 mg/kg). Bu doses were administered at the start of a 4-h hemodialysis session.	The extraction ratio for Bu across the dialyzer was .530 ± .026 at a blood flow of 400 mL/min, which corresponds to a hemodialysis clearance of 2.23 ± .56 mL/min/kg. A 4-h hemodialysis session enhanced the apparent oral clearance of Bu by 65%.	Plasma Bu concentration monitoring is warranted in patients undergoing hemodialysis.

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Appendix 1
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Reference	Basis	Comments	Outcomes	Recommendation
[16]	Report of 81 multiple myeloma patients with renal failure at the time of auto HSCT, including 38 patients on dialysis. Sixty patients (27 on dialysis) received Mel 200 mg/m^2 (Mel-200) given as 100 mg/m^2 for 2 d. Due to excessive toxicity, the subsequent 21 patients (11 on dialysis) received Mel 140 mg/m^2. Thirty-one patients, including 11 on dialysis, completed tandem auto-HSCT.	Renal failure was defined as creatinine >176.8 μmoL/L. Patients on dialysis who received Mel were dialyzed before Mel infusions and again 24-48 h after stem cell infusion. Renal failure patients tend to have a low serum albumin, which may affect Mel pharmacokinetics, as 60% of the drug is bound to plasma proteins, primarily albumin.	Median times to neutrophil and platelet engraftment were 11 and 41 d, respectively. Nonhematologic toxicities included mucositis, pneumonitis, dysrhythmias, and encephalopathy. At a median follow-up of 31 mo, 30 patients had died. Complete remission was achieved in 21 patients after first HSCT and 31 patients after tandem HSCT. Dialysis dependence and Mel dose did not affect event-free or overall survival.	Mel 140 mg/m^2 had an acceptable toxicity and appears equally effective when compared with Mel-200. Renal failure patients with low albumin and higher TRM may do better with even lower doses of Mel (70-100 mg/m^2)
[17]	Case report of a 4.5-yr-old boy with FA and CKD who underwent successful allo-HSCT. His conditioning regimen consisted of Cy 20 mg/kg + TAI 500 cGY.	GVHD prophylaxis consisted of Cy.	The patient successfully engrafted and did not develop GVHD. His kidney function did continue to decline to dialysis dependence 2 y after bone marrow transplantation. Three and one half years after his HSCT, the patient received a renal transplant and his serum creatinine normalized.	CY/TAI is an acceptable preparative regimen for patients with CKD.
[18]	Case report detailing the course of a 27-yr-old man with AA and renal insufficiency requiring dialysis who underwent allo-HSCT. The patient had ESRD, which predated his bone marrow failure by 15 yr. The patient's preparative regimen consisted of Mel 60 mg/m^2, ATG (equine) 15 mg/kg × 3 d, and TLI 4.0 Gy in 2 fractions for 1 d.	Before transplantation, serum levels of creatinine and BUN were 990 μmoL/L and 43.5 μmoL/L. The patient was dialyzed before Mel administration and again 24 and 72 h after administration. GVHD prophylaxis consisted of cyclosporine and prednisolone.	The patient's clinical course was uncomplicated. He experienced rapid engraftment and pharmacokinetic parameters of Mel were not significantly altered. The patient developed grade I mucositis and did not develop veno-occlusive disease. Pharmacokinetic parameters for Mel were C_{max} 5.3 mg/L, elimination $t_{1/2}$ of 98.1 min, AUC 7.65 mg h/L, Vc 6.3 l/m^2, Vd_{ss} 15.6 l/m^2, CL_s .126 L/min m^2.	Mel can be safely used in patients with renal failure requiring dialysis.
[19]	Prospective study of 22 patients with varying levels of renal function who received a single i.v. dose of Flu (25 mg/m^2) followed 1 wk later by 5 (1 per d) doses that were adjusted according to 3 predefined CrCl levels.	Sixty percent of Flu's primary metabolite (F-ara-A) is eliminated renally.	Total F-ara-A clearance correlates with CrCl and F-ara-A exposure levels and patient toxicity profiles were similar across treatment groups.	Flu is an acceptable preparative agent for patients with renal insufficiency with dose adjustment.
[20]	Analysis of 59 dialysis-dependent patients who received high-dose Mel before auto transplantation. The first 27 patients received Mel 200 mg/m^2 as a single agent 2 d before transplantation. The dose was subsequently reduced to 140 mg/m^2 (n = 32) because of significant toxicity.	37 patients had been on dialysis ≤ 6 mo. Stem cell transplantation was preceded by dialysis 24-36 h after Mel.	Five-year event-free and overall survival rate of all patients after HSCT were 24% and 36%, respectively. Of 54 patients who were evaluable for renal function improvement, 13 became dialysis independent at a median of 4 mo after HSCT (range, 1-16). Twenty-three patients received a second auto-HSCT; of women, 4 died of TRM during the 6 mo after second HSCT.	Mel 140 mg/m^2 is less toxic than 200 mg/m^2.
[21]	Report of a patient with anuric acute renal failure who received Flu 40 mg/m^2 twice daily for 3 consecutive days.	The patient underwent 3 consecutive extended (daily) dialysis sessions, which removed a considerable amount of the drug.	The average dialysis clearance was 33.85 mL/min, which is about 25% of the clearance of a patient without renal failure. No toxic side effects were observed.	Flu treatment may be considered in dialysis patients if dose reduction and adequate removal by hemodialysis are provided.
[22]	Trial of 137 patients who received high-dose chemotherapy with auto transplantation at a single center. Patients were divided into 3 groups based on estimated CrCl. Group A had normal renal function both at diagnosis and at transplantation (n = 78), group B had normal renal function at transplantation (n = 30), and group C had renal failure both at diagnosis and at transplantation (n = 29). The majority of patients received Mel 200 mg/m^2. Eleven patients received Mel 100 mg/m^2 for 2 d, and 3 patients received Mel 140 mg/m^2 for 1 d.	Renal failure was defined as CrCl <60 mL/min. Estimated CrCl was calculated based on the CG formula. Eight of the 29 patients in group C were on hemodialysis at the time of transplantation.	There were no differences in the number of stem cells harvested, time to engraftment, or response to transplantation between the groups. Ten of the patients in group C had normalization of renal function after transplantation. Significantly longer hospitalization, increased use of blood products, and increased number of infections were seen in group C compared with groups A and B. TRM was 17% in group C compared with 0% and 1% in groups B and A, respectively. Four of the 8 patients on dialysis at the time of transplantation died from TRM.	High-dose chemotherapy is feasible in multiple myeloma patients with renal failure. Reduction to 140 mg/m^2 or 100 mg/m^2 for 2 d are potential approaches to patients with renal impairment.

[23]	Evaluated the toxicity and survival of dialysis-dependent patients who underwent HDT supported by auto stem-cell transplantation with Mel 100 mg/m^2 compared with those without renal insufficiency (Mel 200 mg/m^2) in a matched pairs analysis of 34 patients.	Renal failure requiring dialysis occurred a median of 4.5 mo (range, 1-8) before HSCT.	No significant differences were observed between hematologic toxicity, TRM, or disease response. Dialysis patients showed comparable event-free and overall survival. They required significantly extended intravenous antibiotic treatment and longer hospitalization. Two patients recovered from dialysis dependency 5 and 6 mo after ASCT.	Recommend a reduced dosage of Mel (100 mg/m^2), which appears to be equally effective and less toxic, in patients on chronic dialysis.
[24]	Report of 4 pediatric patients with normalized GFR <60 mL/min/1.73 m^2. These patients received auto-HSCT preparative therapy for advanced and recurrent solid tumors with escalating Mel, ranging from 135-180 mg/m^2, thiotepa 200 mg/m^2 for 3 d, and vincristine 1 mg/m^2 × 2 doses.	Two patients had Wilms' tumor and 2 patients had neuroblastoma.	None of the patients developed acute renal failure, excess toxicities, or delayed engraftment.	It is feasible and safe to perform HSCT in pediatric patients with low GFR using Mel- and thiotepa-based preparative regimens.
[25]	Case report of 2 adult sickle cell patients who underwent Flu-based nonmyeloablative stem cell transplantation from HLA-identical matched siblings. One patient had ESRD and 1 did not. Pharmacokinetics of the Flu metabolite F-Ara-A was studied in the patient with ESRD and 2 additional patients with normal renal function. Conditioning consisted of 200 cGy TBI followed by Flu 24 mg/m^2 and Cy 500 mg/m^2 both given daily for 4 d and alemtuzumab 100 mg given in divided doses over 5 d for the patient with ESRD.	Nearly identical Flu drug exposure to patients with normal renal function was achieved with a 20% dose reduction followed by daily dialysis for six h, 12 h after each Flu dose. Severe neurotoxicity is the primary concern in this patient population due to potential for high levels of F-ara-A.	Both patients achieved full donor erythroid chimerism, have normal blood counts, and are on no immunosuppressive medications. Neither patient developed acute GVHD or chronic GVHD. Four months after transplantation, the patient with ESRD developed symptomatic heart failure with moderate left ventricular dilation, a small pericardial effusion, and an ejection fraction of 35%. Cy toxicity was likely the primary cause of the patient's cardiac pathology; however, cardiac iron deposition may have been a contributing factor.	Flu-based nonmyeloablative stem cell transplantation is feasible for patients, even in the setting of ESRD.
[26]	Report of 3 cases of severe AA with significant renal impairment from databases at 2 tertiary care centers. Patient 1 received a preparative regimen of Cy 87.5 mg/kg and ATG with a modified Cy dose for creatinine clearance. Patient 2 received a conditioning regimen of Flu 30 mg/d × 4 d (reduced 50%), Cy 300 mg/m^2 × 4 d, and alemtuzumab 75 mg. Patient 3 received a conditioning regimen of Flu 30 mg/d × 4 d (reduced 50%), CY 10 mg/kg × 4 d, and alemtuzumab 60 mg.	Two patients had end-stage renal impairment secondary to immunoglobulin A nephropathy before the diagnosis of AA. The other patient developed cyclosporine-induced nephrotoxicity related to prior immunosuppressive therapy. Patient 1 had a more significant degree of renal impairment (CrCl 11 mL/min at BMT) compared to patients 2 (CrCl 43 mL/min) and 3 (CrCl 20 mL/min) and was dialysis dependent before transplantation. Patients 2 and 3 used a calcinuerin-free GVHD prophylaxis regimen.	Patient 1 experienced significant regimen-related toxicity and died of multiorgan failure 7 mo after transplantation. Patients 2 and 3 did not develop any acute or chronic GVHD and were off all immunosuppressants by 12 and 9 mo after transplantation, respectively.	These cases suggest that BMT is feasible in patients with severe AA and significant renal impairment when a minimally intensive conditioning regimen is utilized.
[27]	Case report of a 5-yr-old girl with FA and a pretransplantation creatinine clearance of 22 mL/min who underwent allo HSCT. The conditioning regimen utilized was Flu 15 mg/m^2 for 3 d and TAI 4 Gy once.	GVHD prophylaxis consisted of mycophenolate mofetil and prednisone.	The post-transplantation period was uncomplicated. She did not develop mucositis, acute GVHD, or infection. Her renal function remained stable and she engrafted on d +37.	Flu/TAI is an acceptable preparative regimen for patients with impaired renal function.
[28]	Report of 13 patients with a GFR <60 mL/min/1.73 m^2 (range, 35-59) as a single comorbidity before HSCT. All patients received nonmyeloablative HSCT with Flu (30 mg/m^2/d for 3 d) followed by TBI at 200 cGY or TBI of 200 cGY alone given in the tandem auto and allo HSCT. ATG (rabbit) was given to recipients of a matched unrelated donor or a single HLA-antigen mismatched family donor HSCT.	Patients received GVHD prophylaxis consisting of mycophenolate mofetil and cyclosporine. Serum creatinine was noted at the day of HSCT and renal function was assessed with the simplified MDRD Study prediction equation at the day of HSCT.	Seven patients (54%) experienced improvement or stabilization to a GFR ≥60 mL/min/1.73 m^2 at last follow-up. Four patients (31%) developed CKD stage 3 (GFR <60 mL/min/1.73 m^2) compared with 3 patients (12%) in the control group ($P = .039$). There was no difference in survival between cases and controls, as well as no differences in complications after HSCT, cyclosporine dose, and trough levels.	Nonmyeloablative HSCT can be safely offered to patients with mildly reduced renal function.

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Appendix 1
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Reference	Basis	Comments	Outcomes	Recommendation
[29]	Report on 8 yr of experience with a conditioning regimen of Flu 30 mg/m^2 daily for 3 d, Cy 750 mg/m^2 daily for 3 d, and rituximab 375 mg/m^2 for 1 d plus 1000 mg/m^2 for 3 d before allo-HSCT.	Included 47 patients who received HLA −matched hematopoietic cells from related (n = 45) or unrelated (n = 2) donors. Tacrolimus and methotrexate were used for GVHD prophylaxis. Patients with serum creatinine ≥ 1.6 mg/dL were excluded.	All patients achieved CR with only 2 relapses. Median follow-up was 60 mo (range, 19-94). Estimated survival and progression-free survival rates were 85% and 83%, respectively. Optimal dose of rituximab not clearly defined.	Effective nonmyeloablative regimen should be explored in patients with renal impairment due to reduced TRM observed in patients with normal renal function.
[30]	Study of 141 patients with AML (n = 131) or MDS (n = 10) who underwent allo transplantation with Flu/Mel-based regimens. Flu dose consisted of 25-30 mg/m^2 for 4-5 d and Mel dose was 100-180 mg/m^2. ATG was added for recipients of unrelated or mismatched-related donor HCT. The influence of the estimated GFR measured before transplantation on outcomes was analyzed.	GFR was estimated by both the CG and the MDRD equations using the creatinine value obtained before starting chemotherapy. Most of the patients with renal function impairment had it for at least 1 mo before transplantation. For the subgroup with baseline <60 (MDRD), the median GFR was 56 (range, 39-77) and one half had a GFR < 60. By the CG method, patients with baseline GFR < 60 had a median GFR of 56 (range, 23-106); 75% had a GFR < 60 1 mo before transplantation.	Estimated GFR was ≥ 90 for 45 (32%), 60-89 for 78 (55%), and < 60 for 18 (13%) patients by CG and GFR was ≥ 90 for 45 (32%), 60-89 for 66 (47%), and < 60 for 10 (7%) of patients by MDRD. There were no differences in overall survival and NRM in the 3 groups by any GFR estimation method. The median GFR remained stable in the survivors belonging to the subgroup of patients with a baseline GFR < 60 at 100 d and 1 yr after transplantation.	Mild-to-moderate decrease in GFR was not associated with an increase in NRM. Flu/Mel is not markedly nephrotoxic and conclusions found in this trial may not apply to other conditioning regimens.
[31]	Case report of a 69-yr-old dialysis patient who underwent auto HSCT after conditioning with adjusted doses of Flu 6 mg/m^2/d for 4 d and Mel 100 mg/m^2 on the fifth day.	The patient had a low performance status going into transplantation. A reduction of about 75% and one third of the doses of Flu and Mel respectively, were given.	After 16 mo, the patient was alive and in CR with no changes in dialysis requirement.	Flu/Mel is feasible in patients with dialysis-dependent renal failure
[32]	Case report of a 2-yr-old girl with confirmed FA and chronic renal failure, who underwent a matched-related donor stem cell transplantation. She received a conditioning regimen of Cy 3.75 mg/kg/d i.v. for 4 d, Flu 15 mg/m^2/d i.v. for 3 d, and rabbit ATG 5 mg/kg/d i.v. for 4 d.	At the time of transplantation, the patient's estimated calculated CrCl was 17 mL/min per 1.73 m^2. The CrCl based on 24-h urine collection was 12 mL/min per 1.73 m^2.	The patient engrafted on d +14 and had platelet engraftment on d +65. Chimerism studies on d +28 showed 100% donor myeloid and lymphoid engraftment. Her renal laboratory profile remained within the same pre-SCT range.	Flu and Cy are acceptable preparative agents for patients with renal insufficiency.
[33]	Case report of a 61-yr-old man with ESRD who had been on hemodialysis for 5 yr and underwent allo-HSCT from a mismatched unrelated donor. The conditioning regimen used was Flu 15 mg/m^2/d for 5 d, Mel 50 mg/m^2/d for 2 d, and TBI (400 cGy). ATG 1.25 mg/kg/d for 2 d was given before transplantation for prophylaxis of acute GVHD.	During the conditioning regimen, daily hemodialysis was performed for volume control. Tacrolimus and mycophenolate mofetil were used for GVHD prophylaxis.	The patient engrafted successfully at d 12 after transplantation. Donor chimerism at d 29 revealed 100% donor cells. The patient developed sinusoidal obstruction syndrome on d 12 and bilirubin increased to 8.1 mg/dL. He also developed grade III gut GVHD on d 15, which resolved with methylprednisolone treatment.	Dose-adjusted Flu, Mel, and TBI are sufficient and tolerable preparative regimens for allo-HSCT in patients with ESRD requiring hemodialysis.
[34]	Case report of a 22-yr-old patient with refractory ALL and ESRD requiring dialysis who was treated with clofarabine 40 mg/m^2/d for 5 d and cytarabine 20 mg/m^2/d subcutaneous for 7 d.	Clofarabine was administered concurrently with CCVHD from d 1 to 5. Plasma and dialysate specimens were collected for determination of clofarabine levels at h0, h3, h7, and h24. After chemotherapy, intermittent dialysis was resumed at 3 sessions per week.	The average peak of clofarabine was 2.72 ± .81 μM. There was no accumulation between d 1 and 5. The average dialysis clearance was 1.39 ± .26 L/h/m^2, which is about 15% of the clearance in patients without renal failure. Drug removal appeared to be mainly due to hemofiltration.	Clofarabine administration is possible in the setting of ESRD, but may carry significant risk.
[35]	Prospective study that enrolled 19 patients eligible for auto-HSCT with a CrCl ≤60 mL/min/1.73 m^2. Patients were given palifermin on d −5 through −3 and again on d +1 through +3 at a dose of 60 mcg/kg/d. Mel was dose escalated until dose-limiting toxicity was reached.	Mel dose was calculated using ABW except when the ABW was > 40% above the IBW, and then adjusted body weight was used. Median CrCl was 42.8 mL/min (range, 29-60). Thirteen patients had stage 3 CKD, 1 patient had stage 4 CKD, and 1 patient had stage 2 CKD.	Mel was given in doses up to and including 200 mg/m^2. Three patients were enrolled at dose level 4, 200 mg/m^2, and 1 death occurred due to multiorgan failure as a result of multiple grade 4 toxicities and grade 3 infections. Another patient in level 4 developed grade 3 dose-limiting toxicities and dose escalation was stopped. No dose-limiting toxicities were observed at dose level 3, 180 mg/m^2. The overall incidence of oral mucositis ≥ 3 was 53%. Two of 4 patients who received 180 mg/m^2 showed complete response at 1 yr.	Mel can be safely and effectively increased up to 180 mg/m^2 in patients with CrCl ≤60 mL/min. Oral mucositis may be controlled with palifermin.

[36]	Phase I-II study that included 10 patients in the phase I portion and 72 patients in the phase II portion. Clofarabine 40 mg/m^2 for 5 d, Mel 140 mg/m^2, and alemtuzumab 20 mg/d for 5 d was adopted as the preparative regimen before allo-HSCT for the phase II portion.	Median GFR at admission was 96 mg/mL/1.73 m^2 (range, 25-120). After the first 24 patients were treated at the phase II level, the clofarabine dose was reduced to 30 mg/m^2 and the infusion was lengthened from 1 to 3 h; however, these modifications did not appear to reduce renal toxicity. Renal deterioration often occurred early, after 1 or 2 doses of clofarabine and alemtuzumab and before administration of Mel.	Grade 3-5 renal toxicity was observed in 5 of 24 patients treated at the initial phase II level (clofarabine 40 mg/m^2 $\times$ 5 and Mel 140 mg/m^2). Overall, 16 of 74 patients treated at the phase II doses experienced grade 3-5 renal toxicity. Grade 1-2 elevations of creatinine were observed in an additional 20 patients treated at this dose level. There was a significant correlation between baseline GFR and renal toxicity.	Clofarabine potentially has intrinsic nephrotoxicity, at least in susceptible patients, such as patients with impaired baseline renal function and/or older adults.
[37]	Report of 5 patients with profound renal impairment, including 3 on dialysis, who underwent HSCT. The preparative regimen utilized consisted of Flu 24-30 mg/m^2/d for 5 d, Mel 100 mg/m^2, and alemtuzumab 20 mg/d for 5 d.	Doses of Mel were reduced 25% to 100 mg/m^2 and Flu was reduced by 20% in 3 of the 5 patients. Estimated GFR based on the modified MDRD for the 2 patients who were not dialysis dependent was 30 mL/min and 28 mL/min before transplantation.	Frequent neurologic complications were observed, which were attributable to tacrolimus, prompting early discontinuation of tacrolimus in 4 of 5 patients and contributing to death in 2 of 5 patients. Renal function remained stable in nondialysis patients and 1 patient on hemodialysis became dialysis independent 6 mo after HCT. One patient developed PRES months after transplantation without exposure to calcineurin inhibitors, possibly as a late result of neurotoxicity from Flu.	Flu dosing may need to be minimized or avoided in patients with renal impairment to reduce the potential for neurologic toxicity.
[38]	Prospective trial that included 26 patients with recurrent CD20$^+$ B cell lymphoid malignancies who received Flu 30 mg/m^2 daily for 4 d, Cy 750 mg/m^2 daily for 3 d, and rituximab 375 mg/m^2 on d -13, -6, $+1$, and $+8$ as a preparative regimen before allo-HSCT. Patients receiving unrelated donor allo-HSCT also received intravenous rabbit ATG, total dosage of 5-7.5 mg/kg daily for 3 d.	GVHD prophylaxis consisted of tacrolimus and i.v. mini-methotrexate (5 mg/m^2 with or without leucovorin on d $+1$, $+3$, and $+6$). Ten patients had chronic lymphocytic leukemia, 7 had mantle cell lymphoma, 3 had diffuse large B cell lymphoma, 3 had follicular lymphoma, and 3 had transformed lymphoma.	The conditioning regimen was well tolerated with no patients developing grade III or IV mucositis and none requiring intravenous parenteral nutrition support. All patients engrafted and survived 100 d after transplantation. Maximum acute GVHD occurred in 8 patients and chronic GVHD occurred in 6 patients.	Data supports the effectiveness of standard rituximab dosing for allo-HSCT. Flu/Cy/rituximab is an effective preparative regimen for patients with B cell lymphoid malignancies. This regimen appears to be safe, with a low incidence of acute GVHD and NRM.
[39]	Retrospective analysis of the effect of mildly reduced renal function based on CrCl on outcome after allo HSCT. Patients were classified into group 0 (n = 440, $\geq$90 mL/min/1.73 m^2), group 1 (n = 56, 60-89 mL/min/1.73 m^2), or group 2 (n = 11, 30-59 mL/min/1.73 m^2).	67 patients were considered to have mild impairment, whereas only 2 had a serum creatinine $>$ 1.2 mg/dL. In patients in whom the CrCl was measured more than once before HSCT, the average values were used. CrCl was calculated from a serum sample and 24-h urine sample, and corrected by the actual body surface area. CrCl was also measured using the CKD-EPI formula.	Engraftment was achieved in 92.5, 92.5, and 100% of the patients in groups 0, 1, and 2, respectively, $P = .67$. There was no difference between groups in overall survival. The incidence of NRM was higher in group 2, although the differences were not statistically significant (23.7, 28.2, and 47.2% at 3 yr, $P = .20$).	Patients with mildly reduced CrCl do not have worse outcomes with HSCT.

AA indicates aplastic anemia; ABW, actual body weight; ALL, acute lymphoblastic leukemia; allo, allogeneic; AML, acute myeloid leukemia; ATG, antithymocyte globulin; auto, autologous; AUC, area under the curve; BMT, bone marrow transplantation; Bu, busulfan; CCVHD, continuous veno-venous hemodialysis; CG, Cockcroft-Gault; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology collaboration; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; CR, complete remission; CrCl, creatinine clearance; CY, cyclophosphamide; d, day; ESRD, end-stage renal disease; FA, Fanconi anemia; F-ARA-A, 2-fluoro-ara-A; Flu, fludarabine; GFR, glomerular filtration rate; GVHD, graft-versus-host disease; HDT, high-dose therapy; HSCT, hematopoietic stem cell transplantation; IBW, ideal body weight; MDRD, modification of diet in renal disease; MDS, myelodysplastic syndrome; Mel, melphalan; NRM, nonrelapse morality; PO, per oral; PRES, posterior reversible encephalopathy syndrome; TAI, thoracoabdominal irradiation; TBI, total body irradiation; TLI, total lymph node irradiation; TRM, treatment-related mortality.

Appendix 2
Chemotherapy Evidence Table

Reference	Agent	Basis	Doses Utilized	Comments
[25]	Alemtuzumab	Report of an adult sickle cell patient who required dialysis. He received Flu, Cy, and alemtuzumab as a preparative regimen before allo-HSCT. The patient received daily dialysis for 6 h, 12 h after each Flu dose.	100 mg given in divided doses over 5 d	Robust immune recovery was observed in this patient.
[26]	Alemtuzumab	Report of a severe AA patient with renal impairment (CrCl 43 mL/min) who received Flu, low-dose CY, and alemtuzumab as a preparative regimen before allo-HSCT.	75 mg	No dosage adjustment was utilized.
[26]	Alemtuzumab	Report of a dialysis-dependent patient with severe AA who received Flu, low-dose CY, and alemtuzumab as a preparative regimen before allo-HSCT.	60 mg	No dosage adjustment was utilized.
[37]	Alemtuzumab	Report of 5 patients with profound renal impairment who received a preparative regimen consisting of Flu/Mel/ATG before allo-HSCT. Three patients were dialysis dependent. The 2 patients who were not dialysis dependent had an estimated GFR based on the modified MDRD of 30 mL/min and 28 mL/min before transplantation.	20 mg/d for 5 d	Three patients were dialysis-dependent. Creatinine values for the remaining 2 patients before transplantation were 1.8 mg/dL and 2.0 mg/dL.
[18]	ATG (equine)	Case report of a 27-yr-old patient with AA requiring dialysis who received Mel, ATG, and TLI as a preparative regimen before allo-HSCT. The patient was dialyzed before Mel administration and again 24 and 72 h after administration.	15 mg/kg/d for 3 d	Excretion not influenced by renal impairment.
[28]	ATG (rabbit)	Report of 4 patients with GFR <60 mL/min/1.73 m^2 who received Flu/TBI/ATG as a preparative regimen before allo-HSCT.	2 mg/kg/d for 4 d	ATG was given before Flu was infused.
[32]	ATG (rabbit)	Report of a 2-yr-old patient with FA who received Flu/CY/ATG was a preparative regimen before allo-HSCT. Before transplantation, the patient's estimated CrCl was 17 mL/min/1.73 m^2.	5 mg/kg/d for 4 d	Standard FA conditioning regimen consisted of CY 5 mg/kg/d i.v. for 4 d, Flu 30 mg/m^2/d i.v. for 5 d, and ATG 5 mg/kg/d i.v. for 4 d.
[33]	ATG	Report of a 61-yr-old patient with ESRD on hemodialysis for 5 yr who received Flu/Mel/TBI/ATG as a preparative regimen before allo-HSCT. The patient received daily hemodialysis during the conditioning regimen.	1.24 mg/kg/d for 2 d	Unclear whether equine or rabbit ATG was utilized.
[15]	Bu	Case report detailing the impact of hemodialysis on the clearance of Bu in a patient with chronic renal failure undergoing auto peripheral stem cell transplantation. Bu doses were administered at the start of a 4-h hemodialysis session.	.6-1.0 mg/kg every 6 h for 5 d for patients on dialysis undergoing auto HSCT.	This patient received oral Bu.
[11]	Bu	Report of 6 patients, with multiple myeloma and chronic renal insufficiency (serum creatinine >3.0 mg/dL), including 4 patients on dialysis, who received high-dose Bu and Cy followed by auto-HSCT. Patients who were dialysis-dependent were dialyzed before the first dose of Cy and again at 24 and 48 h after completion of the second dose.	1 mg/kg PO every 6 h for 16 doses	Oral formulation only.
[14]	Bu	Report of 6 multiple myeloma patients who received Bu/Mel before auto-HSCT. Five of the 6 patients had renal failure with a median CrCl of 27 mL/h, range 5-34 mL/h. One patient was dialysis dependent requiring dialysis 3 times per wk. Hemodialysis was performed 2 h after melphalan infusion.	12 mg/kg	Unclear what the schedule or formulation of Bu was.
[34]	Clofarabine	Case report of an ALL patient with ESRD, requiring dialysis, who received clofarabine with CVVHD. Clofarabine was administered concurrently with CCVHD from d 1 to d 5.	40 mg/m^2/d for 4 d	Clearance was reduced compared with patients without renal impairment, but the patient did not experience major toxicity.
[36]	Clofarabine	Phase II trial that included 72 patients received clofarabine, Mel, and alemtuzumab before allo-HSCT. Median GFR at admission was 96 mg/mL/1.73 m^2 (range, 25-120).	30-40 mg/m^2/d for 4 d	Significant renal toxicity occurred, particularly in elderly patients and patients with baseline impaired renal function.
[11]	Cy	Report of 6 patients with multiple myeloma and chronic renal insufficiency (serum creatinine >3.0 mg/dL), including 4 patients on dialysis, who received high-dose Bu and Cy followed by auto-HSCT. Patients who were dialysis dependent were dialyzed before the first Cy dose and again at 24 and 48 h after completion of the second dose.	60 mg/kg/d for 2 d	Patients requiring renal replacement therapy were dialyzed before the first dose of Cy and again at 24 and 48 h after completion of the second dose.

[12]	Cy	Case report of a 31-yr-old CML patient with chronic renal failure, dialysis-dependent, who received CY/TBI as a preparative regimen before allo-HSCT. Hemodialysis was performed six h after each Cy dose over a period of 6 h. The patient also received bladder irrigation and a continuous i.v. infusion of mesna 60 mg/kg/24 h on d −3 and −2.	60 mg/kg/d for 2 d	Hemodialysis was performed 6 h after each CY infusion over a period of 6 h.
[13]	Cy	Case report of a patient with ESRD on hemodialysis who received CY/TBI as a preparative regimen before allo-HSCT. Six-h hemodialysis sessions were performed before CY infusion and again 14 h after the end of each of the 2-h CY infusions on d −6 and −5. Regular 4-h hemodialysis sessions were resumed on d −4, then 3 times each wk until hospital discharge.	60 mg/kg/d for 2 d	ABW was used for calculating CY dose. Hemodialysis was performed before CY and again 14 h after the end of each 2-h CY infusion.
[17]	Cy	Case report of a 4.5-yr-old boy with FA who received CY/TAI as a preparative regimen before allo-HSCT. The patient's serum creatinine before transplantation was 278 μM.	20 mg/kg	Unclear whether this was a single dose.
[25]	Cy	Report of an adult sickle-cell patient who required dialysis. He received Flu, Cy, and alemtuzumab as a preparative regimen before allo-HSCT. The patient was dialyzed daily for six h, 12 h after each Flu dose.	500 mg/m^2 given daily for 4 d	The patient developed symptomatic heart failure 4 mo after transplantation, which may have been due to Cy toxicity.
[26]	Cy	Report of a severe AA patient who was dialysis dependent and received CY/ATG as a preparative regimen before allo-HSCT. The patient's CrCl was 11 mL/min at time of BMT.	87.5 mg/kg	Usual dose 200 mg/kg, reduced for creatinine clearance.
[26]	Cy	Report of a severe AA patient who received Flu, low-dose CY, and alemtuzumab as a preparative regimen before allo-HSCT. The patient's CrCl was 43 mL/min at time of BMT.	300 mg/m^2	No dosage adjustment was utilized.
[26]	Cy	Report of a severe AA patient who received Flu, low-dose CY, and alemtuzumab as a preparative regimen before allo-HSCT. The patient's CrCl was 20 mL/min at time of BMT.	10 mg/kg given daily for 4 d	No dosage adjustment was utilized.
[32]	Cy	Report of a 2-yr-old patient with FAwho received Flu/CY/ATG was a preparative regimen before allo-HSCT. The patient's CrCl was CrCl was 17 mL/min/1.73 m^2 at the time of transplantation.	3.75 mg/kg/d for 4 d	Standard FA conditioning regimen consisted of CY 5 mg/kg/d i.v. for 4 d, Flu 30 mg/m^2/d i.v. for 5 d, and ATG 5 mg/kg/d i.v. for 4 d.
[25]	Flu	Report of an adult sickle-cell patient who required dialysis. He received Flu, Cy, and alemtuzumab as a preparative regimen before allo-HSCT. The patient received a 20% dose reduction and dosing was followed by daily dialysis for six h, 12 h after each Flu dose.	24 mg/m^2 given daily for 4 d	Flu was dose-reduced by 20%. Nearly identical Flu drug exposure to patients with normal renal function was achieved. Dialysis was performed for six h, 12 h after each Flu dose.
[26]	Flu	Report of 2 severe AA patients who received Flu, low-dose CY, and alemtuzumab as a preparative regimen before allo-HSCT. Patient 1 had a CrCl of 43 mL/min, while the second patient had a CrCl of 20 mL/min at time of BMT.	30 mg/d given daily for 4 d	50% dosage reduction was utilized for both patients.
[28]	Flu	Report of 13 patients with GFR <60 mL/min/1.73 m^2 who were not dialysis-dependent and received Flu/TBI or Flu/TBI/ATG as a preparative regimen before allo-HSCT.	30 mg/m^2 daily for 3 d	These patients had only mildly reduced renal function compared with controls, estimated GFR range, 35-59 mL/min/1.73 m^2.
[27]	Flu	Report of a 5-yr-old patient with FA and renal impairment (CrCl 22 mL/min) who received Flu/TAI as a preparative regimen before allo-HSCT.	15 mg/m^2 daily for 3 d	Creatinine clearance was 22 mL/min before transplantation.
[30]	Flu	Study of 141 patients with reduced GFR who received Flu/Mel or Flu/Mel/ATG preparative regimens before allo-HSCT. A subgroup of patients had baseline GFR <60 mL/min. This subgroup had a median GFR of 56 (range, 39-77).	25-30 mg/m^2 for 4-5 d	Unclear how the Flu dose was selected given the range reported.
[31]	Flu	Case report of a patient with non-Hodgkin lymphoma who was dialysis dependent and received Flu/Mel as a preparative regimen before auto-HSCT.	6 mg/m^2/d for 4 d	75% dosage reduction was utilized. Dialysis schedule during preparative regimen administration not reported.

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Appendix 2
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Reference	Agent	Basis	Doses Utilized	Comments
[32]	Flu	Report of a 2-yr-old patient with FA who received Flu/CY/ATG was a preparative regimen before allo-HSCT. The patient's CrCl was CrCl was 17 mL/min/1.73 m^2 at the time of transplantation.	15 mg/kg/d i.v. for 3 d	Standard FA conditioning regimen consisted of CY 5 mg/kg/d i.v. for 4 d, Flu 30 mg/m^2/d i.v. for 5 d, and ATG 5 mg/kg/d i.v. for 4 d.
[33]	Flu	Report of a 61-yr-old patient with ESRD, on dialysis for 5 yr, who received Flu/Mel/TBI/ATG as a preparative regimen before allo-HSCT. During the preparative regimen, the patient received daily hemodialysis for volume control.	15 mg/m^2/d for 5 d	Represents a 50% dosage reduction.
[37]	Flu	Report of 5 patients with profound renal impairment, including 3 on dialysis, who received a preparative regimen consisting of Flu/Mel/ATG before allo-HSCT. Estimated GFR based on the modified MDRD for the 2 patients who were not dialysis dependent was 30 mL/min and 28 mL/min before transplantation.	24-30 mg/m^2/d for 5 d	Flu was reduced by 20% for the 3 patients receiving dialysis. Dialysis schedules during preparative regimen dosing not reported.
[24]	Mel	Report of 4 pediatric patients with decreased nGFR (<60 mL/min/1.73 m^2) who received dose-escalating Mel, thiotepa, and vincristine as a preparative regimen before auto-HSCT.	135-180 mg/m^2	Patients 1 and 2 received Mel 150 mg/m^2, patient 3 received Mel 180 mg/m^2, and patient 4 received Mel 135 mg/m^2.
[14]	Mel	Report of 4 multiple myeloma patients who received Bu/Mel before auto-HSCT. Impaired renal function was defined as CrCl <40 mL/h. Median CrCl was 27 mL/h, range, 5-34 mL/h.	120 mg/m^2	Patients who received this dose had a CrCl ranging from 28-34 mL/hr.
[14]	Mel	Report of 2 patients with severe renal impairment (CrCl ≤20 mL/hr), including 1 patient on hemodialysis, who received a single dose of 80 mg/m^2 before auto-HSCT.	80 mg/m^2	Outcomes were similar to 4 other multiple myeloma patients who received Mel 120 mg/m^2 + Bu 12 mg/kg. Dialysis schedule during Mel administration not reported.
[10]	Mel	Prospective pharmacokinetic analysis of 20 multiple myeloma patients who received this regimen. Six patients had severe renal insufficiency (CrCl <40 mL/min), including 5 patients on chronic hemodialysis.	100 mg/m^2 given for 2 d	Other studies have shown this regimen to be too toxic in patients with renal impairment. Dialysis schedule during Mel administration not reported.
[16]	Mel	Prospective study of 81 multiple myeloma patients with renal failure (defined as creatinine >176.8 μmoL/L) who underwent HSCT. Patients on dialysis who received Mel were dialyzed before the dose and again 24-48 h after stem cell infusion.	140 mg/m^2 70-100 mg/m^2 for patients with low serum albumin or high risk of TRM	Initial dosing was 100 mg/m^2 given for 2 d, but this regimen was found to be too toxic.
[20]	Mel	Prospective study of 59 dialysis-dependent patients who underwent auto-HSCT. Dialysis was performed 24-36 h after Mel dosing.	140 mg/m^2	Dose was reduced from 200 mg/m^2 because of excessive toxicity.
[22]	Mel	Prospective trial of 137 multiple myeloma patients who received HDT followed by auto stem cell transplantation. Twenty-nine patients had renal failure (CrCl <60 mL/min) including 8 patients who were hemodialysis dependent.	Reduce the dose from 200 mg/m^2 to either 140 mg/m^2 or 100 mg/m^2 for 2 d.	Does not detail their criteria for dose modification in their patient population. Dialysis schedule during Mel administration not reported.
[23]	Mel	Matched-pairs analysis that included 17 patients with multiple myeloma and light-chain amyloidosis on chronic dialysis.	100 mg/m^2	This reduced dose appears to be equally effective to 200 mg/m^2 administered to patients with normal renal function. Dialysis schedule not reported.
[30]	Mel	Study of 141 patients with reduced GFR who received Flu/Mel or Flu/Mel/ATG preparative regimens before allo-HSCT. A subgroup of patients had baseline GFR <60 mL/min. This subgroup had a median GFR of 56 (range, 39-77).	100, 140, or 180 mg/m^2 total dose	Unclear how the Mel dose was selected, given the range of dosages.
[31]	Mel	Case report of a patient with non-Hodgkin lymphoma who was dialysis dependent and received Flu/Mel as a preparative regimen before auto-HSCT.	100 mg/m^2	A dosage reduction of approximately 33% was utilized. Dialysis schedule during preparative regimen administration not reported.
[35]	Mel	Phase I dose-escalation study of 19 patients with renal impairment who were not dialysis dependent. Median CrCl was 42.8 mL/min (range, 29-60 mL/min).	180 mg/m^2 with palifermin	Dose-limiting toxicities were observed at 200 mg/m^2.

[33]	Mel	Report of a 61-yr-old dialysis-dependent patient with ESRD who received Flu/Mel/TBI/ATG as a preparative regimen before allo-HSCT. During the conditioning regimen, daily hemodialysis was performed for volume control.	50 mg/m^2/d for 2 d	Represents a 50% dosage reduction.
[37]	Mel	Report of 5 patients with profound renal impairment, including 3 patients who were dialysis dependent, who received a preparative regimen consisting of Flu/Mel/ATG before allo-HSCT. Estimated GFR based on the MDRD for the 2 patients who were not dialysis dependent was 30 mL/min and 28 mL/min before transplantation.	100 mg/m^2	Represents a dosage reduction of 25%.
[38]	Rituximab	Prospective study of 26 patients with B cell lymphoid malignancies who received FCR as a preparative regimen before allo-HSCT.	375 mg/m^2 for 3 d	Standard rituximab dosing is efficacious in this setting. CrCl not reported.
[29]	Rituximab	Retrospective review of 47 patients who received FCR as a preparative regimen before allo-HSCT. Patients with serum creatinine $\geq$ 1.6 mg/dL were excluded.	375 mg/m^2 for 1 d plus 1000 mg/m^2 for 3 d	Optimal rituximab dosing not clearly defined from this trial.
[24]	Thiotepa	Report of 4 pediatric patients with reduced nGFR ($<$60 mL/min/1.73 m^2), not dialysis dependent, who received Mel, thiotepa, and vincristine as a preparative regimen before auto-HSCT.	200 mg/m^2 for 3 d	Patients ranged in age from 21 mo to 5 yr.

AA indicates aplastic anemia; ABW, actual body weight; ALL, acute lymphoblastic leukemia; Allo, allogeneic; ATG, antithymocyte globulin; auto, autologous; BMT, bone marrow transplantation; Bu, busulfan; CCVHD, continuous veno-venous hemodialysis; CML, chronic myelogenous leukemia; CrCl, creatinine clearance; CY, cyclophosphamide; d, day; ESRD, end-stage renal disease; FA, Fanconi anemia; F-ARA-A, 2-fluoro-ara-A; fludarabine, cyclophosphamide, rituximab (FCR); Flu, fludarabine; GFR, glomerular filtration rate; HDT, high-dose therapy; HSCT, hematopoietic stem cell transplantation; MDRD, modification of diet in renal disease; Mel, melphalan; PO, per oral, PRES, posterior reversible encephalopathy syndrome; TAI, thoracoabdominal irradiation; TBI, total body irradiation; TLI, total lymph node irradiation; TRM, treatment-related mortality.