Long Term Renal Survival in Patients undergoing T-Cell Depleted vs Conventional Hematopoietic Stem Cell Transplants

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Abstract

Calcineurin inhibitor-sparing T cell depleted (TCD) hematopoietic stem cell transplants HSCTs are presumed less nephrotoxic than conventional HSCTs. We evaluated incidence and risk factors for kidney failure and chronic kidney disease (CKD) in 231 TCD and 212 conventional HSCT recipients. Kidney failure required a median glomerular filtration rate (GFR) <60 mL/min/1.73 m² for ≥100 days anytime after 180 days post-HSCT. Two year cumulative incidence (CI) of kidney failure was 42% in the conventional vs. 31% in the TCD group (p=0.005). TCD, age, acute kidney injury and number of toxic CNI levels all impacted on kidney failure, which was associated with increased all-cause mortality (hazard ratio 2.86 (95% CI: 1.88–4.36), p <0.001). Renal recovery occurred in 28% of kidney failure patients, while the remaining patients were defined to have chronic kidney disease (CKD). In those with baseline GFR>60 mL/min/1.73 m² only exposure to nephrotoxic medications was associated with CKD (p=0.033). In the myeloablative conditioning subgroup only total body irradiation was associated with CKD (p=0.013). Of all patients, five (1.13%) required dialysis. These results confirm an impact of TCD on kidney failure but not CKD for which other risk factors such as radiation or nephrotoxic drug exposure may play a role.

Keywords

T-cell depleted hematopoietic stem cell transplantation; chronic kidney disease; acute kidney injury; total body irradiation; nephrotoxicity
INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is widely used in the treatment of hematologic disorders with approximately 50,000 transplants performed worldwide yearly (1). Long-term survival after HSCT has improved and as the number of survivors continues to increase, special interest has focused on transplant-related health issues impacting quality of life and healthcare costs (2, 3).

Kidney failure and ultimately chronic kidney disease (CKD) are long-term complications of HSCT (4–9). While it may develop as a consequence of acute kidney injury (AKI), it has also been associated with older age, lower pre-treatment glomerular filtration rate (GFR), female gender, total body irradiation (TBI), fludarabine in the conditioning regimen, graft versus host disease (GVHD), calcineurin inhibitor (CNI) exposure, and a variety of other factors (4–8).

In appropriately selected patients, T-cell depleted (TCD) HSCT has similar overall survival and disease free survival as those with conventional HSCTs (10–12). TCD can obviate the need for CNIs and thus potentially decrease the risk of renal impairment (13). We previously analyzed the incidence of kidney failure in patients receiving allogeneic TCD grafts who were never exposed to CNI and found a 2-year cumulative incidence (CI) rate of 29.2% in TBI naïve patients and 48.8% in patients conditioned with TBI (total dose of 1375cGy) (8). In multivariate analysis, age at transplant, and TBI were associated with higher CKD rates. In the current study, we directly compare renal function after HSCT in both TCD and conventional HSCT recipients to evaluate whether CNI-free TCD HSCT offers less renal toxicity.

PATIENTS AND METHODS

Patients

Patients receiving a HSCT at Memorial Sloan Kettering Cancer Center (MSKCC) between January 1, 2005 and December 31, 2010 were eligible for inclusion in this study. Those who died, relapsed, had a second transplant <180 days post transplant, were <18 years of age, or had a prior allogeneic HSCT transplant were excluded. The day +180 landmark was utilized to allow comparison with previously published studies on CKD in HSCT patients (4, 5, 14) and because the focus of the study was on long term survivors and their renal outcomes. Patients were followed for up to 24 months after transplant unless lost to follow up or death occurred prior to that. All serum creatinine (SCr) values obtained >180 days after the transplant were included in patient assessments. Baseline and follow up demographic, clinical, and laboratory data were extracted from existing patient databases. Data collection and analysis were performed with approval of the Institutional Review Board of MSKCC.

Renal function assessment

Renal function was determined by calculating GFR using the Modified Diet in Renal Disease equation (15). Kidney failure was defined as a median GFR < 60 ml/min/1.73m² for ≥100 days according to Kidney Disease –Improving Global Outcomes initiative (KDIGO) guidelines (16). At least 3 SCr values in any 100 consecutive days were required for the
diagnosis. CKD following the initial kidney failure incident event was defined as having a median GFR<60 ml/min/1.73m$^2$ among remaining GFR measurements with at least 3 GFR measurements required.

SCr measurements in the first 6 months after HSCT were excluded to avoid misclassifying acute kidney injury (AKI) as CKD (17). Early AKI as a risk factor for CKD was characterized by an increase in SCr>2.0 times baseline value during the first 3 months after HSCT, according to the definition of Stage 2 or higher AKI by KDIGO guidelines (18).

Preparative regimens, donors and grafts

The majority of patients, who underwent TCD HSCT, received 1 of 2 conditioning regimens. An ‘all chemotherapy’ regimen consisted of busulphan, melphalan and fludarabine with antithymocyte globulin (ATG) over 9 days as previously described (19) or hyperfractionated TBI (HFTBI) with fractions of 125 cGy over 4 days to a total dose of 1375 cGy, followed by thiotepa and fludarabine or cyclophosphamide. The kidneys were not shielded. The majority of these received ATG (10, 20, 21). In the conventional group, which included volunteer donor and double cord blood (DUCB) grafts, 16% of the patients received regimens which included 1320–1375cGy of TBI plus chemotherapy, 53% received regimens that included 200–400 cGy of TBI plus chemotherapy, and 12% received busulfan-based chemotherapy regimens. A small number of patients in both the TCD and conventional groups received combination chemotherapy regimens which included a variety of agents: fludarabine, clofarabine, melphalan, cyclophosphamide and others. Only patients in remission or with low volume disease (most often myeloid disease) were offered TCD HSCTs. Patients with lymphoid disease in need of a graft vs lymphoma effect were more likely to receive a reduced intensity conventional (RIC) or nonmyeloablative (NMA) transplant.

Stem cell sources were cord blood, matched and mismatched, related or unrelated volunteer donors recruited via the National Marrow Donor Program. Selection of CD34+ stem cells was accomplished using the ISOLEX 300i Magnetic Cell Separator, followed by sheep red blood cell (sRBC)-rosette depletion of T cells or by CD34+ selection using the Miltenyi CliniMACs automated system. These methods achieved an approximate 3–5 log$10$ depletion of CD3+ cells (22). TCD of bone marrow (BM) was performed as previously described (23). Fifty seven patients received DUCB transplants using cords selected as previously described (24). Patients with TCD grafts received no additional GVHD prophylaxis. Those transplanted with conventional volunteer donor grafts received prophylaxis with tacrolimus plus methotrexate or tacrolimus plus sirolimus +/- methotrexate. Cyclosporine and mycophenolate were used with DUCB grafts. Targeted tacrolimus trough level was 5–10 ng/ml and for cyclosporine 250–350 ng/ml. Toxic levels were considered to be >500 ng/ml for cyclosporine and >15ng/ml for tacrolimus. There was no institutional standard for tapering CNI. Tapers were based on individual protocol recommendations or status of disease at transplant, and degree of match with the donor.

Supportive care

Patients were managed clinically according to MSKCC standard guidelines and as previously described (21). First line treatment for GVHD, when it occurred, was topical
steroids (including budesonide) or systemic steroids. During the peri-transplant period, patients received several potentially nephrotoxic medications including cidofovir, amikacin, liposomal amphotericin, and foscarnet. Toxic exposure was defined as >1 day administration of cidofovir and >5 days of amikacin, liposomal amphotericin, or foscarnet (25–28).

**Biostatistics**

Descriptive statistics were used to summarize patient and treatment characteristics by transplant type (conventional and TCD). Differences across groups were assessed using either Wilcoxon rank-sum tests or Fisher’s exact tests as appropriate. The time-to-kidney failure development was calculated from a 6 month post-transplant landmark to the minimum of the kidney failure date, date of death, relapse, second HSCT or last follow-up as applicable. Cumulative incidence (CI) functions were used to estimate the incidence of kidney failure by patient and treatment characteristics. Death, second HSCT, and relapse were considered competing events for this analysis. Univariate and multivariate analysis of factors associated with the risk of kidney failure were estimated using cause-specific Cox proportional hazards regression. Separately for patients with a pre-transplant GFR above and below 60 ml/min/1.73m$^2$, the univariate analysis of kidney failure risk included type of transplant and conditioning, age, previous AKI, and use of nephrotoxic drugs. The multivariate analysis included all factors in the univariate analysis due to the expected clinical importance. A subset analysis was conducted to examine the potential association of TBI > 1000 cGy with the risk of kidney failure among patients who received TCD or conventional myeloablative transplants. The increased risk of any-cause mortality for patients developing kidney failure was evaluated using Cox regression with a time-dependent covariate.

CKD was explored by determining whether the median of remaining GFR measurements following the incident event was < 60 ml/min/1.73m$^2$. To be eligible for this subanalysis, patients were required to have at least 3 GFR measurements following the initial kidney failure event. Univariate and multivariate logistic regression was used to estimate the association between CKD and characteristics of the patient and treatment. The clinical factors included in the univariate and multivariate regression are the same as the previous model; however, due to the sample size, the analysis was only conducted among patients with GFR ≥60 ml/min/1.73m$^2$. Statistical tests were two-sided and considered statistically significant at the 0.05 level. All analyses were conducted using the R statistical program (29).

**RESULTS**

This analysis includes 69% of the transplants performed during the 6 year study period who met the criteria outlined in the patient and methods section. Two hundred and thirty-one patients in the TCD group and 212 patients in the conventional group met the criteria for inclusion in the analysis. Baseline characteristics of the study group are listed in Table 1. Patients in the TCD group were significantly older (p<0.001), had predominantly myeloid disease (p=0.001), lower median baseline GFR (p=0.02), higher incidence of abnormal baseline kidney function (GFR < 60 ml/min/1.73m$^2$; p=0.04), received a TBI-containing...
conditioning (p<0.001), and had greater exposure to nephrotoxins (p<0.001) but lower incidence of post-HSCT AKI (p<0.001). All patients in the TCD group received myeloablative conditioning versus only 30.6% in the conventional group. The median follow-up for surviving patients in the TCD group was 39.2 months and for the conventional group 38.9 months. Table 2 describes the patients who were excluded from the study cohort.

Development of Kidney Failure

One hundred fifty-eight patients (36%) developed kidney failure, 70 in the TCD and 88 in the conventional group. The 2 year CI of kidney failure was 42% (95% CI: 35–48%) in the conventional vs. 31% (95% CI: 25–37%) in the TCD group (p=0.005) (Fig.1 A). When only patients with initial GFR ≥60 ml/min/1.73m$^2$ were analyzed, the CI was 38% (95% CI: 31–45%) and 24% (95% CI: 18–30%), respectively (p=0.001) (Fig. 1 B). The majority of patients who developed kidney failure did so within 18 months post-HSCT.

Univariate and multivariate analyses for risk factors associated with developing kidney failure, according to baseline GFR, are presented in Table 3A. The univariate association between kidney failure risk and HSCT conditioning was significant both for patients with baseline GFR ≥60 ml/min/1.73m$^2$ (p=0.001) and GFR<60 ml/min/1.73m$^2$ (p=0.013). This association appeared to be derived from an increased risk of kidney failure among those receiving a RIC or NMA HSCT compared to a TCD HSCT. Older age, and AKI were also associated with an increased risk of kidney failure for patients with GFR ≥60 ml/min/1.73m$^2$ in univariate analysis. In a multivariate model for patients with GFR ≥60 ml/min/1.73m$^2$, all 3 factors remained significant. Exposure to nephrotoxic medications did not affect the risk of developing kidney failure in either group. The small number of patients with baseline GFR<60 ml/min/1.73m$^2$ precluded a multivariate model.

To investigate the risk of kidney failure for patients receiving TBI, a second model analyzed risk factors only among recipients of myeloablative TCD and myeloablative conventional HSCTs with baseline GFR ≥60 ml/min/1.73m$^2$ group (Table 3B). Risk factors in these patients are shown in Table 4. Patients in the TCD group were older (p<0.001), and had a lower median baseline GFR (p=0.001), but received TBI at a similar rate as the conventional group. The risk of kidney failure was significantly different for TCD and conventional myeloablative HSCT in the multivariate model only. TBI, older age and exposure to nephrotoxins were associated with a risk of developing kidney failure as well.

Toxic CNI levels in the conventional group impacted the incidence of kidney failure. When the number of toxic CNI levels in the first 180 days after the transplant was evaluated continuously as a predicative factor for the risk of kidney failure in patients with baseline GFR ≥60 ml/min/1.73m$^2$, the HR for the entire group was 1.111 (95% CI 1.02–1.21), p=0.012).

Developing kidney failure increased patients’ risk of any-cause mortality with hazard ratio (HR) of 2.86 (95% CI: 1.88–4.36), p-value <0.001. Similarly, in patients with baseline GFR ≥60 ml/min/1.73m$^2$ all-cause mortality HR was 2.51 (1.60–3.68) p < 0.001. The HR remained significant (2.15 [1.34–3.46], p=0.002) for patients with baseline GFR ≥60
ml/min/1.73m² when adjusted for age, use of nephrotoxic drugs, TCD vs conventional graft, and AKI.

**Development of CKD**

One hundred fifty-eight patients fulfilled the criteria for a diagnosis of kidney failure. CKD following the initial kidney failure incident event was defined as having a median GFR<60 ml/min/1.73m² among remaining GFR measurements with at least 3 GFR measurements required throughout the remainder of follow-up. Three patients had too few measurements and were removed. Among the 155 kidney failure patients, 111 (72%) developed CKD and 44 (28%) recovered renal function. Therefore CKD represents 25% of the total study population. Patients who received a TCD or conventional HSCT who developed kidney failure were equally likely to have CKD (71% and 74%, respectively). CKD was more likely in patients with a pre-transplant GFR<60 ml/min/1.73m² (86%) versus a GFR ≥60 ml/min/1.73m² (66%) (p=0.02).

Univariate and multivariate analyses for CKD are summarized in Table 5 for patients with pre-transplant GFR ≥60 ml/min/1.73m². (No additional models were fit for patients with pre-transplant GFR <60 ml/min/1.73m² due to the small sample size.) Only use of nephrotoxic drugs was significantly associated with CKD (Table 5A). For the subgroup that received myeloablative conditioning (Table 5B), TBI use was associated with higher odds of CKD (p=0.013). The association remained significant after adjusting for transplant type (Table 5B). No additional multivariate model was considered due to sample size. The number of toxic CNI levels evaluated continuously for patients with GFR ≥60 ml/min/1.73m² did not significantly increase the odds of sustained CKD incidence with OR 1.10 (95% CI: 0.91–1.37; p=0.34).

Five of the 111 patients who developed CKD, progressed to end stage renal disease (ESRD) and required dialysis - 3 TCD and 2 conventional HSCTs. Four of these ESRD patients died from post-HSCT complications, and 1 is alive on maintenance dialysis. One of the deceased patients had biopsy proven BK nephritis; biopsies were not obtained for the others.

**DISCUSSION**

The premise of this study was that TCD HSCT patients are not exposed to the nephrotoxic effects of CNIs and therefore theoretically should have better renal outcomes than conventional HSCT patients. Little data exists to confirm this in the HSCT literature. In this study we compared post-transplant kidney function in these two populations from a single institution, analyzing a number of risk factors for kidney disease.

The incidence of kidney failure in HSCT patients has been reported to vary between 4.4% and 49% (30). The wide variation is likely in part due to the use of different definitions of kidney dysfunction. This study used the standard criteria of the KDIGO working expert opinion group (GFR <60 ml/min/1.73m² in excess of 3 months duration) for defining chronic renal dysfunction (16). The rate of developing kidney failure for the entire study group (36%) was at the higher end of the previously reported spectrum and markedly higher than 4.3% in the general population. The CI of kidney failure in the TCD HSCT group as a
whole and in the subgroup of patients with baseline GFR $\geq 60$ ml/min/1.73m$^2$ was significantly lower than that for the similar conventional HSCT groups. Furthermore, in patients with baseline GFR $\geq 60$ ml/min/1.73m$^2$, the HR of kidney failure was also higher for the conventional group in both univariate and multivariate analysis, which included a variety of known risk factors for kidney failure. Other factors such as age, AKI as well as the number of toxic levels of CNIs also predicted for kidney failure in univariate and multivariate analysis, suggesting a number of possible contributors. Because all TCD HSCT patients received ablative conditioning, we compared their risk of kidney failure to that of patients undergoing conventional myeloablative HSCTs, all with GFR $\geq 60$ ml.min/1.73m$^2$. Although there was no difference in univariate analysis, when adjusted for age and TBI exposure, in multivariate analysis TCD HSCT appeared to offer better renal outcome. These findings are particularly important since we also show that the development of kidney failure was associated with an increased risk of any-cause mortality, similar to the general population, where kidney disease is associated with increased risk of cardiovascular disease and any-cause mortality (31).

This study was focused on long-term effects of HSCT on kidney function. Despite using a standard definition of chronic renal disease (16) and establishing the landmark analysis beginning at 6 months (to avoid misdiagnosis of AKI), 28% of patients, who initially met the criteria, ultimately recovered renal function. Those who did not recover were classified as the CKD group and represent 25% of the entire study cohort. These results are similar to those previously reported by Touzot et al. with 22% of patients with kidney dysfunction eventually improving (30). No specific cause for improvement could be identified in the current study and those who recovered were equally divided between the TCD and conventional groups. A number of factors besides a natural recovery may have contributed: 1) Patients undergoing HSCT can have a significant decrease in muscle mass and thus decreased rate of creatinine synthesis. This could lead to decreased SCr and an increase in estimated GFR without a real improvement in renal function; 2) Poor nutrition associated with HSCT may result in decreased creatinine intake and decreased SCr giving the appearance of recovery.

Of the 443 patients included in our study, only 5 (0.8%) developed ESRD. Although significantly higher than the general population, this result is similar to that previously reported in HSCT survivors (32, 33). As expected dialysis requirement after HSCT appears to be associated with very poor prognosis as evident from our study and previous reports (34).

In the analysis of risk factors for CKD, only exposure to nephrotoxic drugs, but not the number of toxic levels of CNI, was significantly predictive for patients with kidney failure who had baseline GFR $\geq 60$ ml/min/1.73m$^2$. TCD did not influence the risk of CKD. In the myeloablative subgroup, only high dose TBI was associated with an increased risk of CKD in both univariate and multivariate analysis even after adjusting for the type of transplant they received. The influence of TBI is in agreement with the findings of our previous study in TCD HSCT (8) and consistent with other literature reports as well (6–8). The results in this group argue a lesser effect of CNI toxic levels and TCD, than factors such as exposure to nephrotoxic drugs and to TBI, or even other variables that were not evaluated here. Based
in part on our prior work, our institution has reduced the use of high dose TBI in preparatory regimens. Future analysis may determine if such practice change resulted in decreased CKD.

Due to the retrospective nature of the study there were unique features and biases to the cohorts that impacted on the analysis. First, all TCD HSCT patients received myeloablative conditioning while only 30.6% of the conventional group did. This precluded the direct analysis of risk factors based on individual conditioning intensities in the entire cohort. Second, patients with baseline GFR<60 ml/min/1.73m$^2$ were preferentially offered TCD HSCTs, whenever appropriate for their disease, to avoid CNI use, possibly resulting in a biased distribution of healthier individuals with better baseline kidney function into the conventional group. Third, TCD vs. the conventional HSCT patients were significantly older particularly in the group receiving myeloablative conditioning. This is a significant disparity as age has been associated with worse kidney outcomes in HSCT patients.

In summary, the renal toxicity from all forms of HSCT can be significant; affecting almost 40% of patients in this study, with 25% ultimately developing CKD and associated with increased any-cause mortality. Incidence plateaus at around 18 months Several of the risk factors studied including type of graft and number of toxic levels of CNIs early post transplant impacted on development of kidney failure in patients with normal baseline renal function, but not on CKD, where nephrotoxic drug exposure played a more significant role. These results in patients who developed kidney failure support the hypothesis of a negative impact of CNI, but as shown by the results for patients with CKD, other factors likely predominate. In the subset of patients with baseline abnormal GFR, TCD appears to reduce the risk of developing kidney failure but a greater sample size would be needed to confirm this and better understand the pathophysiology. With the availability of new methods of transplant including TCD and the increasing number of older adults undergoing HSCT, studies on individual toxicities of HSCT and methods of preventing them will likely gain greater attention.

Acknowledgments

This work is supported in part by MSK Cancer Center Support Grant/Core Grant (P30 CA008748).

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Figure 1.
Cumulative Incidence of Kidney Failure among (A) All HSCT‡ (TCD* vs. Conventional) Patients and among (B) Patients with Baseline Pre-transplant GFR** ≥60 ml/min/1.73m².
## Table 1

### Study Population Demographics

|                           | TCD\(^a\) (n=231) | CONV (n=212) | P-value |
|---------------------------|-------------------|--------------|---------|
| **Age, Median (Range)**   | 54.6 (18–72)      | 49.8 (18–69) | <0.001  |
| **Gender**                |                   |              | 0.49    |
| **Female**                | 101               | 85           |         |
| **Male**                  | 130               | 127          |         |
| **Diagnosis**             |                   |              | <0.001  |
| **AML\(^a\)/ALL\(^b\)/Other Acute** | 134   | 56           |         |
| **CLL\(^c\)/NHL\(^d\)/HD\(^e\)**  | 13    | 126          |         |
| **Chronic Myelogenous Leukemia** | 10   | 2            |         |
| **Multiple Myeloma**      | 20                | 2            |         |
| **MDS\(^f\)/MPD\(^g\)**  | 51                | 17           |         |
| **Other**                 | 3                 | 9            |         |
| **Donor Match**           |                   |              | 0.11    |
| **Matched Related Donor** | 94                | 69           |         |
| **Matched Unrelated Donor** | 73    | 69           |         |
| **Mismatched Related Donor** | 4     | 1            |         |
| **Mismatched Unrelated Donor** | 60   | 73           |         |
| **Conditioning Intensity**|                   |              | <0.001  |
| **Myeloablative**         | 231               | 65           |         |
| **Reduced intensity**     | 0                 | 49           |         |
| **Nonmyeloablative**      | 0                 | 98           |         |
| **Baseline GFR\(^h\), ml/min/1.73m\(^2\)** | 70.8 (33.7–158.9) | 75.4 (37.4–202.2) | 0.02    |
| **Median (Range)**        |                   |              |         |
| **Baseline GFR, ml/min/1.73m\(^2\)** |                 |              | 0.04    |
| \(≥60\)                  | 187               | 187          |         |
| \(<60\)                  | 44                | 25           |         |
| **Total Body Irradiation >1000cGy** | 89    | 34           | <0.001  |
| **GFR \(≥60\) ml/min/1.73m\(^2\)** | 78/187 | 33/187 | <0.001  |

**Legend:**

\(^a\) T-cell depleted,

\(^b\) acute myelogenous leukemia,

\(^c\) acute lymphocytic leukemia,

\(^d\) chronic lymphocytic leukemia,

\(^e\) non-Hodgkin’s lymphoma,

\(^f\) Hodgkin’s lymphoma,
f. myelodysplastic syndrome.

g. myeloproliferative syndrome.

h. glomerular filtration rate.
Table 2
All Transplants 2005–2010 – Outcomes for Patients Excluded Prior To 6 Month Landmark

|                          | TCD† | Conventional |
|--------------------------|------|--------------|
| # of pts in each group   | 300  | 304          |
| Relapse/POD‡ < 6 months  | 16   | 30           |
| 2nd HSCT < 6 months      | 2    | 1            |
| Deaths < 6 months        | 51   | 60           |

| Cause of death          | TCD† | Conventional |
|-------------------------|------|--------------|
| GvHD**                  | 2    | 21           |
| Infection               | 17   | 6            |
| Relapse                 | 12   | 9            |
| Other                   | 20   | 24           |
| Study Group             | 231  | 212          |

Legend:
* Hematopoietic stem cell transplant;
† T-cell depleted;
‡ Progression of disease;
** graft vs host disease.
### Table 3

**Risk Factors for Incident Kidney Failure Event**

|                      | Total # of Pts | Kidney Failure | Univariate HR 95% CI | p-value | Multivariate HR 95% CI | p-value |
|----------------------|----------------|----------------|-----------------------|---------|------------------------|---------|
| **Pts with Pre-Transplant GFR < 60** |                |                |                       |         |                        |         |
|                      | 69             | 43             |                       |         |                        |         |
| Transplant and Conditioning |                |                |                       |         |                        |         |
| TCD myeloablative    | 44             | 26             | (reference)           |         |                        |         |
| Conventional myeloablative | 4             | 1              | ---                   |         |                        |         |
| reduced-intensity    | 6              | 6              | ---                   |         |                        |         |
| non-myeloablative    | 15             | 10             | 3.15 (1.28–7.77)      |         |                        |         |
| Age (per 10 years)   | 60 (21–71)     | 59 (34–71)     | 1.15 (0.83–1.59)      | 0.412   | 1.30 (1.1–1.53)        | 0.002   |
| AKI                  | 6              | 2              | 0.41 (0.1–1.72)       | 0.224   |                        |         |
| Nephrotoxic drug     | 21             | 13             | 1.84 (0.96–3.54)      | 0.068   |                        |         |
| **Pts with Pre-Transplant GFR ≥ 60** | 374            | 115            |                       |         |                        |         |
| Transplant and Conditioning |                |                |                       |         |                        |         |
| TCD myeloablative    | 187            | 44             | (reference)           |         | (reference)            |         |
| Conventional myeloablative | 61             | 19             | 1.42 (0.83–2.43)      | 1.27 (0.7–2.32) |
| reduced-intensity    | 43             | 21             | 2.89 (1.72–4.87)      | 2.4 (1.39–4.15) |
| non-myeloablative    | 83             | 31             | 1.73 (1.1–2.75)       | 1.66 (1.02–2.71) |
| Age (per 10 years)   | 51 (18–72)     | 52 (18–68)     | 1.17 (1–1.37)         | 0.045   | 1.30 (1.1–1.53)        | 0.002   |
| AKI                  | 78             | 37             | 2.42 (1.63–3.58)      | <0.001  | 2.32 (1.49–3.61)       | <0.001  |
| Nephrotoxic drug     | 149            | 47             | 1.20 (0.82–1.75)      | 0.351   | 1.40 (0.94–2.09)       | 0.100   |
| Variable                                      | Univariate         | Multivariate        |
|-----------------------------------------------|--------------------|---------------------|
|                                               | HR 95% CI          | p-value             |
|                                               |                    | HR 95% CI           | p-value             |
| **Myeloablative Transplants with Pre-Transplant GFR ≥ 60** |                    |                     |
| Transplant and Conditioning                   | 0.188              | 0.006               |
| TCD myeloablative                            | 187 44 (reference) |                     |
| Conventional myeloablative                   | 61 19 1.44 (0.84–2.46) 2.31 (1.27–4.21) |                     |
| TBI** > 1000                                 | 111 32 1.28 (0.78–2.1) 0.326 2.22 (1.2–4.12) 0.011 |                     |
| Age (per 10 years)                           | 50 (18–72) 53 (18–68) 1.18 (0.96–1.45) 0.117 1.63 (1.23–2.16) < 0.001 |                     |
| Nephrotoxic drug                             | 118 33 1.34 (0.82–2.2) 0.249 1.5 (0.91–2.49) 0.112 |                     |

**Legend:**
- ‡glomerular filtration rate
- *T-cell depleted
- **acute kidney injury
- ** total body irradiation
## Table 4
Demographics of Patients with Myeloablative Conditioning and Baseline Glomerular Filtration Rate ≥60 ml/min/1.73 m²

| TCD\(^*\) (n=187) [%] | CONV (n=61) [%] | P- value: |
|------------------------|-----------------|-----------|
| **Age, Median (Range)** | 53.2 (18–72) | 36.1 (22–64) | < 0.001 |
| **Gender** | . | . | 0.88 |
| Female | 74 [40] | 23 [38] |
| Male | 113 [60] | 38 [62] |
| **Diagnosis** | . | . | 0.01 |
| **AML\(^a\)/ALL\(^b\)/Other Acute** | 107 [57] | 38 [62] |
| **CLL\(^c\)/NHL\(^d\)/HD\(^e\)** | 12 [6] | 11 [18] |
| **CML\(^f\)** | 9 [5] | 2 [3] |
| **Multiple Myeloma** | 17 [9] | 0 |
| **MDS\(^g\)/MPD\(^h\)** | 40 [21] | 10 [16] |
| **Other** | 2 [1] | 0 |
| **Donor Match** | . | . | 0.37 |
| **Matched Related Donor** | 7 [39] | 17 [28] |
| **Matched Unrelated Donor** | 62 [33] | 22 [36] |
| **Mismatched Related Donor** | 4 [2] | 1 [2] |
| **Mismatched Unrelated Donor** | 48 [26] | 21 [34] |
| **Baseline GFR\(^i\), ml/min/1.73 m² Median (Range)** | 76.0 (60.1–158.9) | 82.3 (60.5–186.8) | **0.001** |
| **Total Body Irradiation >1000cGy** | 78 [42] | 33 [54] | **0.103** |
| **Acute Kidney Injury** | 15 [8] | 27 [44] | <0.001 |

**Legend:**

\(^*\) T-cell depleted,  
\(^a\) acute myelogenous leukemia,  
\(^b\) acute lymphocytic leukemia,  
\(^c\) chronic lymphocytic leukemia,  
\(^d\) non-Hodgkin’s lymphoma,  
\(^e\) Hodgkin’s disease,  
\(^f\) chronic myelogenous leukemia,  
\(^g\) myelodysplastic syndrome,  
\(^h\) myeloproliferative syndrome,  
\(^i\) glomerular filtration rate.
## Table 5

### Risk Factors for Chronic Kidney Disease

|                         | Pts with Pre-Transplant GFR ≥ 60 |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
|-------------------------|----------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                         | # of CKD Failure Pts.             | Univariate       | Multivariate     |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
|                         |                                  | OR 95% CI        | p-value          | OR 95% CI        | p-value          |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| *Pts with Pre-Transplant GFR ≥ 60* | 112                              | 74               |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| Transplant and Conditioning |                              |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| TCD myeloablative       | 42                              | 26               | (reference)      | (reference)      |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| Conventional myeloablative | 18                              | 12               | 1.23 (0.39–4.13) | 1.6 (0.38–7.28) |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| reduced-intensity       | 21                              | 14               | 1.23 (0.42–3.85) | 1.76 (0.53–6.34) |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| non-myeloablative       | 31                              | 22               | 1.5 (0.56–4.18)  | 2.18 (0.75–6.71) |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| Age (per 10 years)      | 52 (19–68)                      | 52 (19–68)       | 0.89 (0.62–1.27) | 0.531            | 0.93 (0.6–1.42)  | 0.729            |                  |                  |                  |                  |                  |                  |                  |                  |
| AKI**                   | 36                              | 22               | 0.73 (0.32–1.68) | 0.446            | 0.54 (0.21–1.39) | 0.199            |                  |                  |                  |                  |                  |                  |                  |                  |
| Nephrotoxic drug        | 42                              | 33               | 2.59 (1.11–6.51) | 0.033            | 3.1 (1.26–8.3)   | 0.018            |                  |                  |                  |                  |                  |                  |                  |                  |

### 5B

|                         | Myeloablative Transplants with Pre-Transplant GFR ≥ 60 |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
|-------------------------|--------------------------------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                         | # of CKD Failure Pts.                                  | Univariate       | Multivariate     |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
|                         |                                  | OR 95% CI        | p-value          | OR 95% CI        | p-value          |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| *Myeloablative Transplants with Pre-Transplant GFR ≥ 60* | 60                                  | 38               |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| Transplant and Conditioning |                              |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| TCD myeloablative       | 42                              | 26               | (reference)      | (reference)      |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| Conventional myeloablative | 18                              | 12               | 1.23 (0.39–4.13) | 0.82 (0.22–2.99) |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| TBI** > 1000            | 32                              | 25               | 4.12 (1.39–13.28) | 0.013            | 4.33 (1.4–14.86) | 0.014            |                  |                  |                  |                  |                  |                  |                  |                  |
| Age (per 10 years)      | 0.89 (0.58–1.34)                       | 0.589            |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
|          | Univariate       |               | Multivariate  |               |
|----------|------------------|---------------|---------------|---------------|
|          | HR 95% CI        | p-value       | HR 95% CI     | p-value       |
| AKI      | 0.63 (0.2–1.96)  | 0.415         |               |               |
| Nephrotoxic drug | 2.65 (0.9–8.34) | 0.083         |               |               |

Legend:

† chronic kidney disease,
‡ glomerular filtration rate,
* T-cell depleted,
** acute kidney injury,
*** total body irradiation.