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LETTER TO THE EDITOR

Acute kidney injury in critically ill allo-HSCT recipients

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We read with great interest the study by Benz *et al.*[1] on risk factors and outcomes of patients admitted to the intensive care unit (ICU) after allogeneic hematopoietic SCT (allo-HSCT). They found that acute GVHD and HLA mismatch were associated with ICU admission. They also reported poor outcomes after ICU admission (case fatality rate 64%), mostly related to the extent of organ dysfunction. On the basis of our experience,[2] we would like to draw attention to the clinical relevance of acute kidney injury (AKI) in allo-HSCT recipients, a feature not addressed by Benz *et al.* Indeed, allo-HSCT recipients are known to be at high risk for AKI as they often are exposed to combinations of various nonspecific insults (sepsis, nephrotoxic drugs, contrast agents, dehydration, kidney infiltration by the malignancy, anemia). In addition, they can develop specific causes of AKI over time such as tumor lysis syndrome, engraftment syndrome, veno-occlusive disease (VOD) and thrombotic microangiopathy (TMA).[3]

In our center, of 647 allo-HSCT performed over five years (January 2007 to December 2011), we report on 75 patients (11.6%) who were admitted to the ICU. Time between HSCT and ICU admission was 149 (interquartile range (IQR), 29–594) days. The median age was 43 (IQR, 28–57) years and 53 (70%) were male. The main indications for allo-HSCT were ALL (20, 26.6%), AML (14, 18.6%) and lymphoma (12, 16%). The transplant procedure was performed mostly with a reduced-intensity regimen (44, 59%), graft source was PBSC (52, 71%) and the donor was unrelated (30, 41%) or a matched sibling (28, 37%).

The main reasons for ICU referral were: respiratory failure (62%), shock (42%) and AKI (28%). At ICU admission, 57 (76%) patients received immunosuppressive drugs to treat or prevent GVHD (CsA ± MTX ± steroids). Fifteen (20%) patients had acute GVHD grade II–IV and 26 (35%) had chronic GVHD. Throughout the ICU stay, 33 (44%) patients required vasopressors, 24 (32%) mechanical ventilation and 3 (4%) renal replacement therapy (RRT). Infections were documented in 37 (49%) patients with the following distribution: bacteria (27, 73%), fungi (11, 30% including 9 cases of probable invasive aspergillosis) and viruses (7, including 4 CMV reactivation). The median ICU and hospital lengths of stay were 3 (IQR, 2–6) days and 32 (IQR, 14–57) days. The overall ICU and hospital mortality were 19% and 46%, respectively.

INCIDENCE AND CAUSES OF AKI

According to the KDIGO criteria,[4] 49 (65%) patients had AKI, of whom 39% were in stage 1, 28% in stage 2 and 33% in stage 3. There was a decreased AKI incidence throughout the study period (75% of AKI in the 2007–2009 period vs 52% in the 2009–2011 period ($P = 0.05$)), which is in line with earlier reports.[5] Almost all the patients in our center (72, 96%) had exposure to a median of 3 (IQR, 2 to 4) nephrotoxic drugs. The drugs involved were: aminoglycosides (71%), CsA (63%), vancomycin (61%), diuretics (30%), acyclovir (20%), contrast agents (15%), renin–angiotensin–aldosterone system inhibitors (15%), liposomal amphotericin B (12%), foscarnet (11%) and i.v. Ig (7%). In the ICU setting, the main causes of AKI reported in our study were dominated by sepsis (75%) and circulatory shock (44%). Specific causes of AKI were scarcely reported: engraftment syndrome (8%), VOD (2.6%) and TMA (2.6%).

RISK FACTORS FOR AKI

By univariate analysis, the two factors associated with AKI were circulatory shock (odds ratio (OR): 4.09, 95% confidence interval (CI): 1.4–11.9, $P = 0.01$) and chronic GVHD (OR: 3.15, 95% CI: 1.02–9.73, $P = 0.04$). In contrast, age, donor relation, conditioning regimen, TBI, stem cell source, CsA, number of nephrotoxic drugs and acute GVHD were not associated with AKI. Regarding acute GVHD, it is conceivable that the absence of statistical association with AKI could be explained by our ICU admission policy that selects patients with no or controlled GVHD. Indeed, in the study by Benz *et al.*, 61% of ICU patients had acute GVHD grade II–IV as compared with 20% in our study. When ICU admission is required in patients with acute GVHD uncontrolled by high-dose steroids, we and others published very low survival rates.[6,7]

IMPACT OF AKI ON OUTCOME

AKI adversely affects survival, gradually with the severity (Figure 1). This effect is remarkable from stage 1, which is associated with a hospital mortality of 47%. Not surprisingly, AKI stage 3 was associated with a poor prognosis, with only 19% of patients being alive at hospital discharge. RRT was scarcely implemented (three patients) during the study period. This policy was influenced by our experience over the period 2004–2011, where among the 56 patients treated by this procedure in our ICU, hospital mortality rate reached 95% with a median survival time of 14 (IQR, 7–32) days. Another situation with a poor prognosis was the association of AKI with liver dysfunction (defined by a serum bilirubin leve l > 68 μmol/L). Hospital mortality was 100% among the 11 patients from the present study who met these criteria. These were predominantly patients with acute GVHD grade II–IV or VOD (82%).

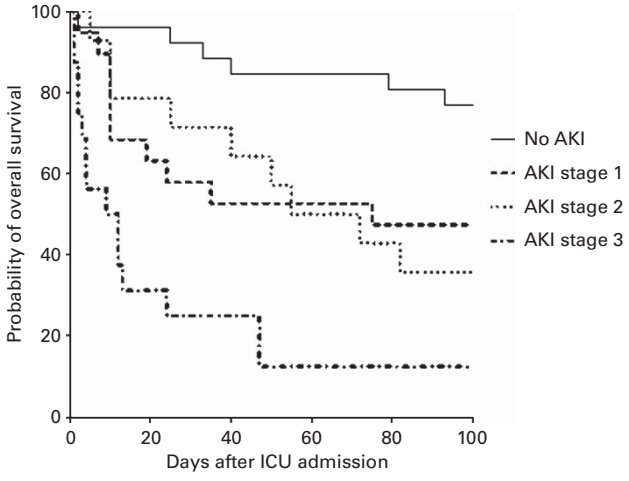

Figure 1. Probability of survival stratified according to the KDIGO categories of AKI. The x axis represents the number of days post ICU admission and the y axis represents cumulative survival.

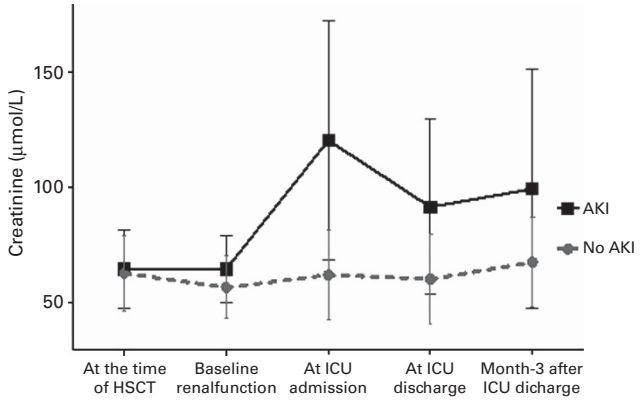

Figure 2. Change in renal function over time stratified according to AKI. Serum creatinine values (mean ± s.d.) during five time periods.

RENAL RECOVERY

All 17 patients who experienced AKI and were alive 3 months after ICU discharge did not recover their pre-ICU renal function. As shown in Figure 2, an analysis of this subgroup showed a rise in serum creatinine from 67 µmol/L (IQR, 59–76) at baseline to 100 µmol/L (IQR, 69–130) at 3 months ($P = 0.03$). Clinical importance of small changes in kidney function has been advocated.[8] Nephrologists should be involved early in the management of these patients at risk for later development of chronic kidney disease (CKD).[9]

In conclusion, AKI is a frequent complication in allo-HSCT recipients admitted to the ICU. Survival decreases with AKI severity. The incomplete renal recovery suggests that patients who have had AKI are at increased risk of subsequent CKD. Improvement in GVHD management and careful attention to the hemodynamic status might improve ICU outcome. Collaborative studies that involve a multidisciplinary approach toward kidney protection are warranted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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