An Overview of Kidney Disease Following Hematopoietic Cell Transplantation

Minoru Ando

Abstract: Hematopoietic stem cell transplantation (SCT) recipients are exposed to a large amount of anti-cancer drugs, immunosuppressors, and irradiation during the peri-SCT period. Thus, they have to overcome serious adverse events related to unavoidable but toxic procedures, including organ disorders. In particular, acute kidney injury (AKI) is one of the most critical complications, because it influences the mortality of patients. A few patients who survive AKI may develop nephrotic syndrome, and precedent AKI is also closely associated with chronic and progressive loss of the renal function in post-SCT patients. These kidney diseases place a heavy burden on SCT patients, both medically and economically. Therefore, hematologists who evaluate SCT should be fully aware of the development of these kidney diseases after SCT. We herein review the common course of kidney disease development following allogeneic SCT to provide healthcare professionals with practical information on renal disease in SCT patients.

Key words: acute kidney injury, nephrotic syndrome, chronic kidney disease, stem cell engraftment, onco-nephrologist

Introduction

Hematopoietic stem cell transplantation (SCT) is a breakthrough curative treatment for refractory diseases, including hematopoietic malignances and autoimmune diseases, with roughly 50,000 procedures being performed annually worldwide (1). However, SCT therapy requires the administration of otherwise lethal doses of cytotoxic chemotherapy and immunosuppressors. Therefore, the management of serious adverse reactions and complications caused by these treatments is vital for success (1-4).

Among the complications associated with SCT, acute kidney injury (AKI) occurs frequently and is the most crucial to address, as it influences the prognosis of post-allogeneic SCT patients (5-8). Some survivors of AKI develop nephrotic syndrome within several years after allogeneic SCT (8-10), and some develop a gradual loss in the glomerular function, ultimately resulting in chronic kidney disease (CKD) (11-16). These kidney diseases place a heavy burden on SCT patients, both medically and economically (16). Therefore, hematologists evaluating SCT should be fully aware of the development of these kidney diseases after SCT. Furthermore, SCT requires cooperation by onco-nephrologists, who are experienced in the treatment of hematological malignancies and SCT procedures as well as facilitating the best treatment for renal disease in SCT recipients (17, 18).

This review describes the common course of kidney disease development following allogeneic SCT and provides information for healthcare professionals on the need for interventions by onco-nephrologists in the practice of SCT. The content of this review article was approved by the institutional committee on research ethics (approval number: 29-furyo-rin (B)-2).

Increasing number of SCT procedures and the survival rate of SCT patients

After SCT was initiated in the late 1950s in the US, treat-
SCT is divided into two types based on the preconditioning intensity-myeloablative and non-myeloablative (or reduced-intensity) SCT-and is also divided into two types based on the donor of the hematopoietic stem cells used—the patient’s own cells collected beforehand (autologous) and cells donated by a relative or others through a bone marrow bank (allogeneic). SCT is also classified into three types based on the hematopoietic stem cell source: bone marrow (BM), peripheral blood (PB), and cord blood (CB). Accordingly, a general description of SCT is myeloablative allogeneic PB stem cell transplantation (3, 7, 12). SCT is a breakthrough curative treatment mainly for hematological malignant cancers that has markedly improved the prognosis and quality of life of patients. However, SCT is also a highly toxic biological treatment that involves chemotherapy at a high dose, which is considered lethal, and total-body radiotherapy where necessary. Thus, patients are at risk of developing the serious adverse reactions and complications associated with these procedures.

The survival rate of patients markedly decreases to approximately 50% within 6 months after transplantation, regardless of the transplantation modality, and then slowly declines, plateauing at nearly 40% approximately 5 years after SCT, as shown in Fig. 2. Accordingly, the avoidance and management of factors associated with mortality are pivotal for improving the survival rates. In allogeneic but not autologous SCT, nephrologists have noted that the development of AKI early after SCT was closely associated with an increased mortality rate in the early phase (7, 8, 20, 21). Thus, hematologists committed to SCT need to obtain a clearer understanding of current concepts and diagnostic criteria for AKI, monitor changes in laboratory data related to kidney disease, and consult a nephrologist as soon as AKI is suspected.

### Time course of kidney disease development following allogeneic SCT

Allogeneic SCT patients frequently develop kidney disease in three stages following allogeneic SCT. Fig. 3 shows the time course of kidney disease development. AKI develops at a frequency of approximately 70% within 100 days after allogeneic transplantation and is an emergent condition that directly influences the prognosis of many transplant patients. Severe AKI develops in the period of bone marrow failure prior to the engraftment of transplanted stem cells within 30 days of the implementation of SCT in about 20%
of SCT recipients (20). Post-SCT AKI is more challenging to treat than normal AKI because patients are in a severely immunodeficient state and manifest complications of hemorrhagic tendencies, infections, and acute graft-versus-host disease (GVHD) in this period. Nearly 1% of patients who survive without AKI develop nephrotic syndrome, which is assumed to be associated with chronic GVHD, within several years of allogeneic SCT (10-12, 22). Some patients who survive AKI and nephrotic syndrome develop CKD (12-14, 20, 23), a few of whom (approximately 4%-5%) ultimately advance to end-stage renal disease (ESRD) requiring chronic blood purification therapy (23, 24). Subclinical or insidious kidney damage before and after SCT may be identified by microalbuminuria, proteinuria, and/or urinary tubular biomarkers. Further details on each kidney disease are described below.

AKI following allogeneic SCT

Since Zager et al. (5) defined post-SCT acute renal failure (ARF) in 1989, it has been conventionally classified into three grades based on elevations in the serum creatinine (Cr) concentration within 100 days after SCT. In the US, Schrier et al. (25) reported the frequency of post-SCT ARF and mortality of patients 6 months to 1 year after SCT according to SCT modalities, in which the incidence of ARF was 21%
in patients who received myeloablative autologous transplantation, 40% in those who received non-myeloablative allogeneic transplantation, and 69% in those who received myeloablative allogeneic transplantation, with mortality rates of 7%, 34%, and 58%, respectively. Ando et al. (7) examined the incidence of AKI based on the new concept of AKI using the Cr criteria defined by RIFLE and AKIN. The incidence of AKI that developed within 100 days after SCT was investigated in 249 patients who underwent SCT between August 2004 and December 2007. The overall incidences of AKI were 2%, 40%-48%, and 62-66% in patients treated with autologous, non-myeloablative allogeneic, and myeloablative allogeneic SCT, respectively, and the cumulative mortality rates of patients who developed AKI of either severity during the follow-up period of approximately 3 years were 11%-20%, 48%-50%, and 54%, respectively. Furthermore, the mortality rate increased as the severity of AKI increased, regardless of the transplantation modality.

AKI with a poor prognosis frequently develops prior to hematopoietic stem cell engraftment (approximately 7-30 days after transplantation). Shingai et al. (20) recently clarified the relationship between the incidence of “AKI before stem cell engraftment” (early AKI) and patient prognoses. According to the findings of their prospective study on the incidence of AKI and mortality rates in 106 patients who underwent allogeneic SCT, the incidence of early AKI was approximately 20%, and its cumulative survival rate was 50%-60%, showing a very poor survival even at 100 days after transplantation. This mortality rate was markedly higher than that (9%) in patients who developed AKI after engraftment (late AKI).

The causes of post-SCT AKI are complex; drugs used for preconditioning and prophylaxis for GVHD, infections including sepsis, circulatory failure, sinusoidal obstruction syndrome, and GVHD are concurrently involved (2, 3, 23). Furthermore, previous autopsy reports on SCT recipients (6, 26) have revealed no prominent histological changes in autopsied kidneys in most patients who developed severe AKI following SCT. Therefore, the renal function impairments were suggested to be mainly caused by hemodynamic rather than structural disorders.

Beyond our understanding of the precise pathophysiology of AKI, it is crucial, from a clinical perspective, to identify those patients predisposed to develop AKI following SCT, as it may help improve the prognosis of transplant recipients. The measurement of sensitive urinary tubular biomarkers represents a promising approach, as structural and/or functional tubular damage may initially emerge when renal and/or systemic stress occurs in the body. When the level of urinary liver-type fatty acid-binding protein (uL-FABP), a new biomarker of tubular ischemia or its injury, already exceeds the normal standard at baseline prior to the conditioning procedure, the risk of developing AKI increases by approximately 2.8-fold (27). In addition, increases in the level of urinary neutrophil gelatinase associated lipocalin (uNGAL) may augment the risk of AKI, and changes in the uNGAL concentrations at day +9 from baseline may be useful for predicting AKI in SCT recipients (28).

### Incidence of albuminuria, proteinuria, and nephrotic syndrome after allogeneic SCT

Garcia et al. (29) reported 2 nephrotic syndrome cases in 1988, showing that chronic GVHD developed in the kidneys following allogeneic SCT. Momoki et al. (22) surveyed the data of 1,175 patients who underwent allogeneic SCT over a 27-year period between January 1986 and December 2013. Nephrotic syndrome, which is considered to be associated with previous SCT, developed in 9 patients (frequency: 0.77%). The male-to-female ratio was 7:2, the mean age at the onset was 47.7±16.4 years old, the mean urinary protein amount was 6.5 (range: 3.8-13.6) g/day, and the mean time until the diagnosis of nephrotic syndrome was 24.8 (range: 15-35) months after SCT. The histological type based on a kidney biopsy was membranous nephropathy in 8 cases (89%) and minimal change type in 1 case. The stainability of IgG subclasses was IgG4 (9 cases) = IgG1 (9 cases) > IgG3 (4 cases) > IgG2 (2 cases). In previous studies on post-SCT nephrotic syndrome, the histological type was membranous nephropathy in more than 60% of cases of post-SCT nephrotic syndrome, followed by the minimal change type in 20%, and the subclass staining pattern of membranous nephropathy cases was similar (9, 10) to that described above.

Momoki et al. (22) also reported the clinical significance of incident proteinuria less than the nephrotic range (3.5 g/day). Proteinuria was prospectively investigated in all 693 allogeneic SCT recipients over 10 years between August 2004 and July 2014 and was monitored for ≥1 year after the implementation of allogeneic SCT. Within 1 year of transplantation, 1+ or more severe novel proteinuria persisted for ≥3 months in 57 patients (8.2%). The kidney function subsequently progressed to CKD (estimated glomerular filtration rate [eGFR] <60) during the follow-up period in 41 patients (72%), and 5 patients (8.8%) advanced to ESRD.

Morito et al. (30) quantitatively measured microalbuminuria immediately after allogeneic SCT in 31 patients. Microalbuminuria became positive (ACR ≥30 mg/g creatinine) within 1 month of SCT in 16 patients (52%), and the 1-year cumulative incidence of CKD was 62.5% in these patients (8.3% in microalbuminuria-negative cases). Accordingly, both studies suggested that the patients who develop proteinuria or albuminuria, even that in the subclinical range, are at an increased risk of future CKD.

### CKD among allogeneic SCT survivors and the strong relationship between CKD and prior AKI

Kidney disease progresses to CKD in some SCT patients who survive AKI or nephrotic syndrome. Hingorani et al. (3) reported that the cumulative incidence of CKD varied between 7% and 48% and developed between 6 months and 10 years after SCT. Risk factors for CKD include prior AKI, acute and chronic GVHD, an older age at SCT, a decrease...
in the GFR at baseline, hypertension, the use of calcineurin inhibitors, and exposure to total-body irradiation (TBI). However, CKD may be caused by a combination of these risk factors, including chronic GVHD, followed by chronic and persistent systemic inflammation, the long-term use of calcineurin inhibitors (contributing to thrombotic microangiopathy [TMA] in glomeruli), and prior exposure to TBI, which is relevant to vascular endothelium and tubular epithelium injury (31).

Ando et al. (23) examined 158 patients who survived for ≥3 years after allogeneic SCT between 1987 and 2003. The prevalence of CKD and its related factors were investigated in these patients. The CKD stage was ≥3 in 17% (27 cases [stage 3, 8; stage 4, 10; and stage 5, 9]). Regarding factors associated with CKD, the strongest relationship was noted with prior AKI (OR9.92). In addition, Shimoi et al. (32) prospectively examined the serum Cr concentrations in 77 patients who underwent allogeneic SCT and followed these patients for ≥10 years (median observation period: 14.4 [range: 10.5-20.2] years). The 10-year cumulative incidence of CKD (eGFR <60) was 34% (26 cases). A factor related to CKD was prior AKI in the transplantation period, and its influence increased as the AKIN stage of AKI became more severe (hazard ratios: stage 1, 3.27; stage 2, 6.98; stage 3, 14.8).

Other studies have reported that AKI is a risk factor for CKD and influences the prognosis of patients with successful SCT (long-term survivors) (2, 23, 33). A further increase in the incidence of post-SCT CKD is anticipated due to the aging of transplantation recipients. Indeed, the rate of SCT recipients ≥50 years of age was approximately 5% ten years ago but will exceed 30% with the expansion of non-myeloablative conditioning and the recent increase in the number of haploidentical SCT cases (34).

Regarding the treatment of post-SCT CKD, use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists seem promising, as their protective effects on the progression of post-SCT CKD have been shown in humans as well as in experimental models (35, 36).

Need for interventions by onco-nephrologists in the practice of SCT

Recent advances have been achieved in treatment techniques and the development of therapeutic drugs in SCT, and the annual number of SCT applications recently exceeded that of kidney transplantation in the US (1, 34). Although a further increase in the number of SCT applications is expected, several issues, including the prevalence of kidney disease, have yet to be resolved. In order to improve the prognosis of SCT recipients, cooperation among onco-nephrologists with experience in the treatment of hematological malignancies and SCT procedures as well as knowledge of the pathophysiology of kidney disease and the best treatments for kidney disease is necessary (17, 37). The management of pre- and post-SCT patients by onco-nephrologists includes the identification of patients at increased risk for AKI prior to SCT and early after SCT when only minor changes in the serum Cr and/or elevations in u-fABP and uNGAL levels are present, the application of interventions such as adjustment of drug dosing to avoid nephrotoxicity, the treatment of tumor- or treatment-related fluid and electrolytes abnormalities, and the early intervention with renal replacement therapy. In addition, a routine evaluation for the presence of albuminuria and/or proteinuria after SCT is pivotal for predicting the future burden of kidney disease, such as nephrotic syndrome and CKD, in SCT recipients.

Conclusions

AKI develops at a high frequency following allogeneic SCT and is generally induced by complex factors that are difficult to identify, potentially making such cases more intractable or lethal than AKI alone. Some long-term survivors develop nephrotic syndrome and advance to CKD or ESRD, which is likely associated with prior AKI. Hematologists who are committed to SCT should be fully aware of the development of these kidney diseases after SCT. Periodic monitoring for proteinuria and albuminuria after SCT is fundamental for identifying individuals at high risk of kidney disease. Furthermore, the professional management of post-SCT patients by onco-nephrologists is increasingly needed in order to improve the prognosis of SCT recipients.

The authors state that they have no Conflict of Interest (COI).

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References

1. Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: an update. J Am Soc Nephrol 16: 151-161, 2005.
2. Hingorani S. Renal complications of hematopoietic-cell transplantation. N Engl J Med 374: 2256-2267, 2016.
3. Bodge MN, Reddy S, Thompson MS, Savani BN. Preparative regimen dosing for hematopoietic stem cell transplantation in patients with chronic kidney disease: analysis of the literature and recommendations. Biol Blood Marrow Transplant 20: 908-919, 2014.
4. Miralbell R, Bieri S, Mermillod B, Helg C, Sancho G, Pastoors B,
Keller A, Kurtz JM, Chapuis B. Renal toxicity after allogeneic bone marrow transplantation: The combined effects of total-body irradiation and graft-versus-host disease. J Clin Oncol 14: 579-585, 1996.

Zager RA, O’Quigley J, Zager BK, Alpers CE, Shulman HM, Gamelin LM, Stewart P, Thomas ED. Acute renal failure following bone marrow transplantation: A retrospective study of 272 patients. Am J Kidney Dis 13: 210-216, 1989.

Parikh CR, McSweeney PA, Korul Darl, Eder T, Merouani A, Taylor J, Slat-Vasquez V, Shpall EJ, Jones RB, Bearman SI, Shrier RW. Renal dysfunction in allogeneic hematopoietic cell transplantation. Kidney Int 62: 566-573, 2002.

Ando M, Mori J, Ohashi K, Akiyama H, Morito T, Tsuchiya K, Nitta K, Sakamaki H. A comparative assessment of the RIFLE, AKIN and conventional criteria for acute kidney injury after hematopoietic SCT. Bone Marrow Transplantation 45: 1427-1434, 2010.

Mori J, Ohashi K, Yamaguchi T, Ando M, Hirashima Y, Kobayashi T, Kikihara K, Sakamaki H. Risk assessment for acute kidney injury after allogeneic hematopoietic stem cell transplantation based on acute kidney injury network criteria. Intern Med 51: 2105-2110, 2012.

Brukamp K, Doyle AM, Bloom RD, Bunin N, Tomaszewski JE, Cizman B. Nephrotic syndrome after hematopoietic cell transplantation: Do glomerular lesions represent renal graft-versus-host disease? Clin J Am Soc Nephrol 1: 685-694, 2006.

Terrier B, Delmas Y, Hummel A, Presne C, Glowacki F, Knebelmann B, Combe C, Lesavre P, Maillard N, Noel L-H, de Serre N P-M, Nusbaum S, Radford I, Buzyn A, Fakhouri F. Post-allogeneic hematopoietic stem cell transplantation membrane nephropathy: clinical presentation, outcome and pathogenic aspects. Nephrol Dial Transplant 22: 1369-1376, 2007.

Pilar F, Lourdes V, Dolores C, Pedro G-C, Lopez L, Jesus SM, Matias TJ. Chronic graft-versus-host disease of the kidney in patients with allogeneic hematopoietic stem cell transplant. Eur J Haematol 91: 129-134, 2013.

Ellis MJ, Parikh CR, Inrig JK, Kambay M, Patel UD. Chronic kidney disease after hematopoietic cell transplantation: A systematic review. Am J Transplantation 10: 2378-2390, 2008.

Choi M, Sun G-L, Kurian S, Carter A, Francisco L, Forman SJ, Bhatia S. Incidence and predictors of delayed chronic kidney disease after hematopoietic cell transplantation. Kidney Dis 3: 1691, 2012.

Singh N, McNeely J, Parikh S, Bhiinder A, Rovin BH, Shidham G. Kidney complication of hematopoietic cell transplantation. Am J Kidney Dis 61: 809-821, 2013.

Cohen EP. Renal failure after bone-marrow transplantation. Lancet 357: 6-7, 2001.

Cohen EP, Krzesinski J-M, Launay-Vacher V, Spranglers B. Onco-Nephrology: Core curriculum 2015. Am J Kidney Dis 66: 869-883, 2015.

Ando M. The need for ‘onco-nephrology’ is increasing in hematopoietic stem cell transplantation. Bone Marrow Transplantation 51: 767-768, 2016.

The Japanese data center for hematopoietic cell transplantation. http://www.jdchct.or.jp/en/data/slide/2016, accessed October 25, 2017.

Shingai N, Morito T, Najima Y, Kobayashi T, Doki N, Kikihara K, Ohashi K, Ando M. Early-onset acute kidney injury is a poor prognostic sign for allogeneic SCT recipients. Bone Marrow Transplantation 50: 1557-1562, 2015.

Imai H, Oyama Y, Miura AB, Endoh M, Sakai H. Hematopoietic cell transplantation-related nephropathy in Japan. Am J Kidney Dis 36: 474-480, 2000.

Momoki K, Yamaguchi T, Ohashi K, Ando M, Nitta K. Emergence of dipstick proteinuria predicts overt nephropathy in patients following stem cell transplantation. Nephron 135: 31-38, 2017.

Ando M, Ohashi K, Akiyama H, sakamaki H, Morito T, Tsuchiya K, Nitta K. Chronic kidney disease in long-term survivors of myeloablative allogeneic hematopoietic cell transplantation: prevalence and risk factors. Nephrol Dial transpl 25: 278-282, 2010.

Cohen EP. Significant increase in end-stage renal disease after hematopoietic stem cell transplantation. Bone Marrow Transplant 39: 571-572, 2007.

Schrier RW, Parikh CR. Comparison of renal injury in myeloablative autologous, myeloablative allogeneic and non-myeloablative allogeneic hematopoietic cell transplantation. Nephrol Dial transpl 20: 678-683, 2005.

Honda K, Ando M, Tsukokura M, Yamashita T, Akiyama H, sakamaki H. An autopsy case that manifested no convincing histological changes of severe renal failure after hematopoietic stem cell transplantation. CEN Case Rep 3: 34-39, 2014.

Shingai N, Morito T, Najima Y, Igarashi A, Kobayashi T, Doki N, Kikihara K, Ohashi K, Ando M. Urinary liver-type fatty acid-binding protein linked with increased risk of acute kidney injury after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 20: 2010-2014, 2014.

Taghizadeh-Gheibi M, Sarayani A, Ashouri A, Ataei S, Moslehi A, Hadjibabae M. Urine neutrophil gelatinase associated lipocalin as an early marker of acute kidney injury in hematopoietic stem cell transplantation patients. Ren Fail 37: 994-998, 2015.

Garcia GP, Arroyo HC, Gomez TA, et al. Renal involvement in chronic graft-versus-host disease: a report of two cases. Bone Marrow Transplant 3: 357-362, 1988.

Morito T, Ando M, Kobayashi T, et al. New-onset microalbuminuria following allogeneic myeloablative SCT is a sign of near-term decrease in renal function. Bone Marrow Transplant 48: 972-976, 2013.

Hingorani S. Chronic kidney disease in long-term survivors of hematopoietic cell transplantation: epidemiology, pathogenesis, and treatment. J Am Soc Nephrol 17: 1995-2005, 2006.

Shimoi T, Ando M, Munakata W, et al. The significant impact of acute kidney injury on CKD in patients who survived over 10 years after myeloablative allogeneic SCT. Bone Marrow Transplantation 48: 80-84, 2013.

Parikh CR, Coca SG. Acute renal failure in hematopoietic cell transplantation. Kidney Int 69: 430-435, 2006.

Humphreys BD. Renal complications of hematopoietic stem cell transplantation. In: Cancer and the kidney, edited by Cohen E, Oxford University Press 2010.

Ichida S, Okada K, Itoh M, Okada R, Katoh N, Kasai M, Yuzawa. Renal toxicity after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplantation 20: 1427-1434, 2013.

Moulder JE, Fish BL, Cohen EP, ACE inhibitors and All receptor antagonists in the treatment and prevention of bone marrow transplant nephropathy. Curr Pharm des 9: 737-749, 2003.

Berns JS, Rosser MH. Onco-nephrology: What the nephrologist needs to know about cancer and the kidney. Clin J Am Soc Nephrol 7: 1891, 2012.
