**Table 4** Posttransplant changes of possible parameters[a] influencing HRV

| | Baseline | Day 30 | Day 60 | Day 100 | *P* |
|---|---|---|---|---|---|
| Systolic blood pressure (mmHg) | 101 (97–117) | 116 (92–137) | 109 (91–136) | 111 (97–118) | 0.35 |
| Diastolic blood pressure (mmHg) | 60 (57–64) | 76 (62–87) | 68 (67–84) | 69 (68–74) | 0.03 |
| Heart rate (/min) | 79 (76–93) | 89 (76–120) | 85 (72–109) | 86 (84–88) | 0.08 |
| Body temperature (°C) | 36.5 (36.2–36.8) | 37.2 (36.8–38.2) | 36.8 (36.7–38.1) | 37.2 (37–37.5) | 0.04 |
| CsA trough (ng/ml) | 0 | 227 (193–277) | 237 (0–328) | 160 (0–378) | 0.07 |
| Hemoglobin (g/dl) | 8.8 (8.3–14.3) | 9.9 (7.7–14.2) | 9.4 (8–12.1) | 10.2 (7.9–10.9) | 0.55 |
| C-reactive protein (mg/dl) | 0.1 (0.01–0.21) | 0.2 (0.1–2.34) | 0.12 (0.1–1.99) | 0.25 (0.03–2.38) | 0.23 |

*CsA* cyclosporine

[a] Each data is the five patients' median value of the 3 days average data on or about the day HRV went

decline in kidney function due to renal toxicity caused by calcineurin inhibitors, antibiotics, antifungal drugs, or antiviral drugs and prompt adjustment of the dose of these drugs; and (3) transfusing at a slower rate than usual.

One study reported that prophylactic treatment with the ACE inhibitor enalapril not only prevented deterioration in left ventricular dysfunction prior to transplant, but also brought about an increase in LVEF in all patients [21]. Another study also demonstrated that early treatment with enalapril might prevent late cardiotoxicity due to high-dose chemotherapy in a randomized trial in 114 high-risk patients, identified by an increased troponin I value [22]. In our study, instead of receiving an ACE inhibitor, one patient (no. 5) started to receive an angiotensin receptor blocker before transplantation; she had no cardiac dysfunction after transplantation. Although the effectiveness of ACE inhibitors or angiotensin receptor blockers has not been sufficiently validated for preventing cardiac events in patients with pretransplant cardiac dysfunction, it may be useful to consider prophylactic administration of an ACE inhibitor or angiotensin receptor blocker.

In this case series, almost all patients had a temporary decrease in HRV posttransplant, and the patient with acute heart failure had an especially marked decrease prior to the onset of acute heart failure (Fig. 1, dashed line). Previous studies have reported a correlation between HRV and proinflammatory cytokines [23, 24], CsA [25], blood pressure [26], heart rate [27], anemia [28], and C-reactive protein [29, 30] as possible factors that influence changes in HRV after transplantation. In fact, the significant elevation of body temperature and diastolic blood pressure might have influenced the decrease in HRV. On time-domain analysis of HRV, a number of authors have identified a decreased SDNN value as a univariate risk factor for all-cause mortality, expressed as a dichotomized variable in the patients with chronic heart failure [31]. This review notes that an SDNN value of less than 44 ms was determined statistically to be the optimum cutoff point [32], and the value of 44 ms is similar to the value of <50 ms that best predicts mortality in myocardial infarction patients [7]. The predictive value of SDNN can be explained by the speculation that a reduction in the SDNN reflects the summed influence of abnormalities in sympathetic, parasympathetic and rennin–angiotensin activities, abnormal chemoreceptor function, changes in respiratory pattern, and physical inactivity in congestive heart failure [33].

Conversely, among the indicators used in frequency-domain analysis of HRV, a reduced LF value is reportedly highly predictive of sudden cardiac death in chronic heart failure [31]. Despite high levels of sympathetic activation, decreases in the LF value were often observed in patients with chronic heart failure, which may be secondary to abnormalities in central autonomic regulation and impairment of beta adrenergic receptor sensitivity [33]. Furthermore, a reduced LF value was reported as a marker of sympathetic overactivity, and it was concluded that a reduced short-term LF value during controlled breathing (<13 $ms^2$) is a powerful predictor of sudden death in patients with chronic heart failure [34]. In our case with acute heat failure, the LF value as well as the SDNN value temporarily but dramatically decreased to less than 44 ms and 13 $ms^2$, respectively, before the occurrence of acute heat failure, indicating that decreases in SDNN and/or LF values might be associated with the development of acute heat failure after transplantation. HF and r-MSSD are generally considered to be predominantly determined by the parasympathetic nervous system. In a rat study, it was reported that CsA induced a decrease in SDNN and r-MSSD values [25]. Therefore, in our study, CsA treatment after transplantation might play a role in the significant decrease in the HF value and the mild decrease in r-MSSD, by its suppression of parasympathetic activity.

This study has the following limitations: (1) the population is small and from a single institution; (2) lack of clarity about the causes for the decrease in HRV; and (3) we do not know the lower limit of cardiac function in patients still eligible for RIST. However, to our knowledge, there has been no prior report of comprehensive analyses of cardiac and autonomic nervous system function in patients with impaired cardiac function who underwent allo-HSCT.

In conclusion, RIST is relatively well tolerated in patients with pretransplant cardiac dysfunction, but apparent improvement of cardiac function cannot be expected except in cardiomyopathy induced by secondary hemochromatosis. We could not determine whether changes in autonomic function are associated with the development of cardiac events after transplant. Additional studies of a larger cohort are therefore required to confirm the usefulness of HRV for prediction of cardiac events after transplantation.

**Acknowledgments** This work was supported by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Science, Sports, and Culture, and a grant from the Japanese Ministry of Health, Welfare, and Labor.

## References

1. Sorror ML, Giralt S, Sandmaier BM, De Lima M, Shahjahan M, Maloney DG, Deeg HJ, Appelbaum FR, Storer B, Storb R (2007) Hematopoietic cell transplantation specific comorbidity index as an outcome predictor for patients with acute myeloid leukemia in first remission: combined FHCRC and MDACC experiences. Blood 110:4606–4613 doi:10.1182/blood-2007-06-096966
2. Sorror M, Storer B, Sandmaier BM, Maloney DG, Chauncey TR, Langston A, Maziarz RT, Pulsipher M, McSweeney PA, Storb R (2008) Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. Cancer 112:1992–2001
3. Ritchie DS, Seymour JF, Roberts AW, Szer J, Grigg AP (2001) Acute left ventricular failure following melphalan and fludarabine conditioning. Bone Marrow Transplant 28:101–103 doi:10.1038/sj.bmt.1703098
4. Kunisaki Y, Takase K, Miyamoto T, Fukata M, Nonami A, Kamezaki K, Kaji Y, Gondo H, Harada M, Nagafuji K (2007) Marked improvement of cardiac function early after non-myeloablative BMT in a heavily transfused patient with severe aplastic anemia and heart failure. Bone Marrow Transplant 40:593–595 doi:10.1038/sj.bmt.1705764
5. Nishio M, Endo T, Nakao S, Sato N, Koike T (2008) Reversible cardiomyopathy due to secondary hemochromatosis with multitransfusions for severe aplastic anemia after successful nonmyeloablative stem cell transplantation. Int J Cardiol 127:400–401
6. Abe Y, Matsushima T, Tachikawa Y, Nagasawa E, Nishimura J, Nawata H, Muta K (2005) Fludarabine-based conditioning used in successful bone marrow transplantation from an unrelated donor in a heavily transfused patient with severe aplastic anemia. Int J Hematol 81:81–82 doi:10.1532/IJH97.04134
7. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ (1987) Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 59:256–262 doi:10.1016/0002-9149(87)90795-8
8. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN (1992) Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 85:164–171
9. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ (1998) Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (autonomic tone and reflexes after myocardial infarction). Investigators. Lancet 351:478–484 doi:10.1016/S0140-6736(97)11144-8
10. Frenneaux MP (2004) Autonomic changes in patients with heart failure and in post-myocardial infarction patients. Heart 90:1248–1255 doi:10.1136/hrt.2003.026146
11. Guzzetti S, Cogliati C, Turiel M, Crema C, Lombardi F, Malliani A (1995) Sympathetic predominance followed by functional denervation in the progression of chronic heart failure. Eur Heart J 16:1100–1107
12. Furlan R, Piazza S, Dell'Orto S, Barbic F, Bianchi A, Mainardi L, Cerutti S, Pagani M, Malliani A (1998) Cardiac autonomic patterns preceding occasional vasovagal reactions in healthy humans. Circulation 98:1756–1761
13. Ajiki K, Murakawa Y, Yanagisawa-Miwa A, Usui M, Yamashita T, Oikawa N, Inoue H (1993) Autonomic nervous system activity in idiopathic dilated cardiomyopathy and in hypertrophic cardiomyopathy. Am J Cardiol 71:1316–1320 doi:10.1016/0002-9149(93)90547-P
14. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK (1998) Altered cardiovascular variability in obstructive sleep apnea. Circulation 98:1071–1077
15. Bernardi L, Ricordi L, Lazzari P, Soldá P, Calciati A, Ferrari MR, Vandea I, Finardi G, Fratino P (1992) Impaired circadian modulation of sympathovagal activity in diabetes. A possible explanation for altered temporal onset of cardiovascular disease. Circulation 86:1443–1452
16. Guzzetti S, Cogliati C, Broggi C, Carozzi C, Caldiroli D, Lombardi F, Malliani A (1994) Influences of neural mechanisms on heart period and arterial pressure variabilities in quadriplegic patients. Am J Physiol 266:1112–1120
17. Herait P, Poutignat N, Marty M, Bugat R (1992) Early assessment of a new anticancer drug analogue–are the historical comparisons obsolete? The French experience with pirarubicin. Eur J Cancer 28:1670–1676 doi:10.1016/0959-8049(92)90066-B
18. Kishi Y, Kami M, Miyakoshi S, Kanda Y, Murashige N, Teshima T, Kusumi E, Hara S, Matsumura T, Yuji K, Masuoka K, Wake A, Morinaga S, Kanemaru M, Hayashi T, Tanaka Y, Taniguchi S, Tokyo Stem Cell Transplant Consortium (2005) Early immune reaction after reduced-intensity cord-blood transplantation for adult patients. Transplantation 80:34–40 doi:10.1097/01.TP.0000163289.20406.86
19. Bazett HC (1920) An analysis of the time-relations of electrocardiograms. Heart 7:353–370
20. McKee PA, Castelli WP, McNamara PM, Kannel WB (1971) The natural history of congestive heart failure: the Framingham study. N Engl J Med 285:1441–1446
21. Kakavas PW, Ghalie R, Parrillo JE, Kaizer H, Barron JT (1995) Angiotensin converting enzyme inhibitors in bone marrow transplant recipients with depressed left ventricular function. Bone Marrow Transplant 156:859–861
22. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, Martinelli G, Veglia F, Fiorentini C, Cipolla CM (2006) Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 11423:2474–2481 doi:10.1161/CIRCULATIONAHA.106.635144
23. Straburzynska-Migaj E, Ochotny R, Wachowiak-Baszynska A, Straburzynska-Lupa A, Lesniewska K, Wiktorowicz K, Cieslinski A (2005) Cytokines and heart rate variability in patients with chronic heart failure. Kardiol Pol 63:478–485, discussion 486-7
24. Kunz-Ebrecht SR, Mohamed-Ali V, Feldman PJ, Kirschbaum C, Steptoe A (2003) Cortisol responses to mild psychological stress are inversely associated with proinflammatory cytokines. Brain Behav Immun 17:373–383 doi:10.1016/S0889-1591(03)00029-1
25. Omar AG, El-Mas MM (2004) Time-domain evaluation of cyclosporine interaction with hemodynamic variability in rats. Cardiovasc Drugs Ther 18:461–468 doi:10.1007/s10557-004-6223-1

26. Park SB, Lee BC, Jeong KS (2007) Standardized tests of heart rate variability for autonomic function tests in healthy Koreans. Int J Neurosci 117:1707–1717 doi:10.1080/00207450601050097
27. Agelink MW, Malessa R, Baumann B, Majewski T, Akila F, Zeit T, Ziegler D (2001) Standardized tests of heart rate variability: normal ranges obtained from 309 healthy humans, and effects of age, gender, and heart rate. Clin Auton Res 11:99–108 doi:10.1007/BF02322053
28. Gehi A, Ix J, Shlipak M, Pipkin SS, Whooley MA (2005) Relation of anemia to low heart rate variability in patients with coronary heart disease (from the Heart and Soul study). Am J Cardiol 95:1474–1477 doi:10.1016/j.amjcard.2005.02.017
29. Psychari SN, Apostolou TS, Iliodromitis EK, Kourakos P, Liakos G, Kremastinos DT (2007) Inverse relation of C-reactive protein levels to heart rate variability in patients after acute myocardial infarction. Hellenic J Cardiol 48:64–71
30. Kon H, Nagano M, Tanaka F, Satoh K, Segawa T, Nakamura M (2006) Association of decreased variation of R-R interval and elevated serum C-reactive protein level in a general population in Japan. Int Heart J 47:867–876 doi:10.1536/ihj.47.867
31. Sandercock GR, Brodie DA (2006) The role of heart rate variability in prognosis for different modes of death in chronic heart failure. Pacing Clin Electrophysiol 29:892–904 doi:10.1111/j.1540-8159.2006.00457.x
32. Aronson D, Mittleman MA, Burger AJ (2004) Measures of heart period variability as predictors of mortality in hospitalized patients with decompensated congestive heart failure. Am J Cardiol 93:59–63 doi:10.1016/j.amjcard.2003.09.013
33. Galinier M, Pathak A, Fourcade J, Androdias C, Curnier D, Varnous S, Boveda S, Massabuau P, Fauvel M, Senard JM, Bounhoure JP (2000) Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. Eur Heart J 21:475–482 doi:10.1053/euhj.1999.1875
34. La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O, Ferrari R, Franchini M, Gnemmi M, Opasich C, Riccardi PG, Traversi E, Cobelli F (2003) Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 107:565–570 doi:10.1161/01.CIR.0000047275.25795.17

# CNS Complications of Hematopoietic Stem Cell Transplantation

Tomokazu Nishiguchi[1,2]
Kunizo Mochizuki[1]
Miyuki Shakudo[3]
Tohru Takeshita[1]
Masayuki Hino[4]
Yuichi Inoue[1]

**OBJECTIVE.** With the worldwide increase in the use of hematopoietic stem cell transplantation (HSCT), a high level of diligence is required for radiologists to understand HSCT-related complications in the CNS. This article describes the clinical background of HSCT and complications that occur in a time-dependent manner through the course of HSCT and addresses pivotal issues in diagnostic imaging.

**CONCLUSION.** Acknowledging the realm of imaging manifestations and the underlying mechanism of HSCT will enhance diagnostic accuracy and optimize treatment decisions.

Hematopoietic stem cell transplantation (HSCT) is an accepted treatment option for various hematopoietic disorders, genetic disorders, inborn errors of metabolism, and autoimmune disorders. More than 20,000 transplantations are performed yearly, for a total of more than 230,000 transplantations to date, according to the annual report of the Center for International Blood and Marrow Transplant Research [1]. Complications in the posttransplantation period are mostly related to hematopoietic and immune system aplasia and to the alloreactivity of donor cells. Because preparative regimens destroy the recipient's immune and hematopoietic systems, immunologic recovery depends on engraftment and proliferation of the infused stem cells. The most common and clinically significant complications are infection, vascular disorders, therapy-induced cytotoxicity, graft-versus-host disease (GVHD), and recurrence of preexisting diseases. Early diagnosis is crucial to successful management and good prognosis, because CNS complications are potentially devastating. CT and MRI play an important role in early diagnosis, which maximizes the chance of prompt therapy for HSCT-related complications. To accurately interpret imaging manifestations both before and after transplantation, it is imperative to understand the clinical course and immunologic status of patients in terms of the timeline of events associated with transplantation.

The first HSCT was performed with allogeneic bone marrow by Thomas et al. [2] in 1957 to treat a patient with hematologic malignant disease after high-dose chemoradiation therapy. Since then, various terms have been used to describe the procedure, depending on the pretransplantation conditioning regimen (full- or reduced-intensity myeloablation), donor type (human leukocyte antigen [HLA]-identical twins, autologous or allogeneic), and the source of stem cells (bone marrow, peripheral blood cells, or cord blood cells). Improved therapeutic designs in HSCT with highly detailed matching between donor and recipient have improved clinical outcome. At the same time, however, clinical studies have shown CNS abnormalities in 11–59% of recipients, and autopsy studies have revealed neuropathologic abnormalities in more than 90% of patients who died after HSCT [3]. The frequency and diversity of neurologic complications largely depend on the degree and duration of myelosuppression, immunosuppression, and GVHD, which affect the immune reconstitution process of recipients [4]. CNS complications are frequently high-risk factors for transplantation-related morbidity and mortality [5]. Thus early recognition of these complications with imaging and appropriate management will allow early intervention with immunotherapy or additional chemotherapy to improve the chance of survival. Although a brief review of imaging features of CNS complications in children has been published [6], there is still a need for understanding the pathophysiologic mechanism of CNS complications before and after transplantation. This review summarizes the

**Keywords:** bone marrow transplantation, CNS, complications, hematopoietic stem cell transplantation, immune system, malignancy

DOI:10.2214/AJR.08.1787

Received September 6, 2008; accepted after revision October 9, 2008.

[1]Department of Radiology, Osaka City University Graduate School of Medicine, 1-4-3, Asahimachi, Abeno, Osaka, 545-8585 Japan. Address correspondence to T. Nishiguchi (tomokazu-n@med.osaka-cu.ac.jp).

[2]T & Co. Medical Imaging, Osaka, Japan.

[3]Department of Radiology, Osaka City General Hospital, Osaka, Japan.

[4]Department of Hematology, Osaka City University Graduate School of Medicine, Osaka, Japan.

**CME**
This article is available for CME credit.
See www.arrs.org for more information.

*AJR* 2009; 192:1003–1011

0361–803X/09/1924–1003

clinical aspects of HSCT-related CNS complications and provides clinical examples to illustrate the importance of accurate image interpretation.

## Normal Hematopoietic Stem Cell Condition

Hematopoietic stem cells (HSCs) give rise to all blood cell types, including trilineage myeloid cells (eosinophils, basophils, monocytes and macrophages, neutrophils, erythrocytes, and platelets) and lymphoid lineages (T cells, B cells, and natural killer cells). HSCs are found in the bone marrow and are mostly contained in the femur, hip, ribs, sternum, and other bones. HSCs also are found in umbilical cord blood and the placenta. In HSCT, stem cells are obtained directly by bone marrow aspiration or from the peripheral blood after administration of granulocyte colony–stimulating factor, which induces mobilization of stem cells from the bone marrow compartment.

## Types of HSCT

A diverse terminology has emerged to describe the type of HSCT based on the pretransplantation regimen (broadly categorized by the intensity of myeloablation, donor type, and source of stem cells) (Fig. 1). CNS complications have been found more frequently in allogeneic stem cell transplantation than in autologous or syngeneic stem cell transplantation. Reduced-intensity conditioning, in place of the combination of high-dose chemotherapy and total body irradiation, is used strategically for older patients and other patients at high risk. Owing to more rapid immune recovery, use of the reduced-intensity conditioning protocol has led to a reduction in therapy-related mortality after outpatient-based transplantation. However, a high incidence of relapse and delayed GVHD continues to be common. An infusion of harvested donor lymphocytes for induction of a graft-versus-malignancy effect is used in addition to HSCT and is associated with a higher survival rate.

## Recovery of Immune Function After HSCT

The duration and degree of myeloaplasia in HSCT recipients depend on the conditioning regimen in the pretransplantation period. Engraftment of infused donor cells generally occurs on the 15th–30th posttransplantation day. This engraftment period and the duration of graft survival are influenced mainly by the source of the graft, successful immunosuppression, and the HLA-matching rate. Immune reconstitution after successful engraftment takes at least 4 months, and complete recovery is achieved after 1 year (Fig. 2).

## Graft-Versus-Host Reaction

The acute and chronic forms of GVHD are partially overlapping but distinct major complications after allogeneic HSCT. Although the mechanism of acute GVHD, that is, alloreaction of donor T cells to host organs, is currently well understood, that of chronic GVHD is less well known. In chronic GVHD, two potential mechanisms—autologous reactivity of activated B cells and antibody-associated tissue injury—are suggested by the partial efficacy of rituximab and symptoms similar to those of autoimmune disease. Complications related to GVHD are more commonly seen in adult recipients than in pediatric patients. In long-term management of HSCT recipients, development of a therapeutic protocol that minimizes graft-versus-host reaction while inducing the least toxicity may offer the most benefit, creating the ideal balance of reduced morbidity, protection against opportunistic infection, and decreased risk of relapse [7].

## Complications

### *Infection*

In the initial posttransplantation period (0–30 days after HSCT), when patients are neutropenic, the primary risk is fungal and bacterial infection. HSCT recipients are most likely to have fungemia or bacteremia due to the long-term presence of an indwelling catheter, mucosal damage caused by high-dose chemoradiation therapy, inappropriate use of prophylactic antibiotics, and endemic or hygienic factors [8]. When GVHD occurs in the acute or subacute period after HSCT, additional immunosuppressive therapy for acute GVHD can cause profound, catastrophic depression of the immune system. The causative agents of early infection are mainly fungi (*Aspergillus* and *Candida* organisms),

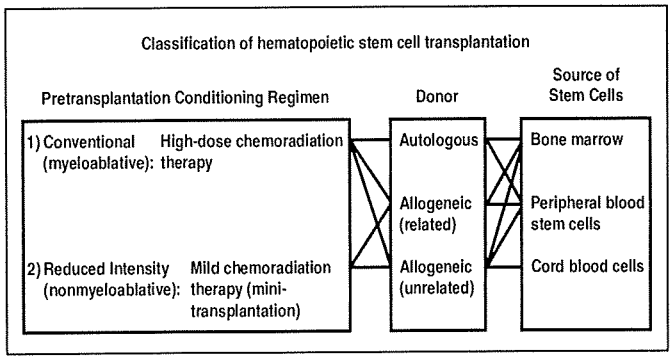



**Fig. 1**—Chart shows classification of hematopoietic stem cell transplantation.

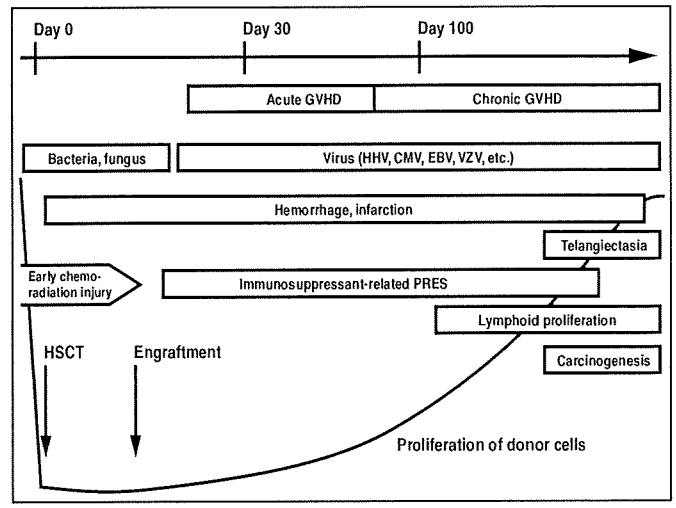



**Fig. 2**—Chart shows overview of specific CNS complications linked to timeline of transplantation. GVHD = graft-versus-host disease, HSCT = hematopoietic stem cell transplantation, HHV = human herpesvirus, CMV = cytomegalovirus, EBV = Epstein-Barr virus, VZV = varicella-zoster virus, PRES = posterior reversible encephalopathy syndrome.

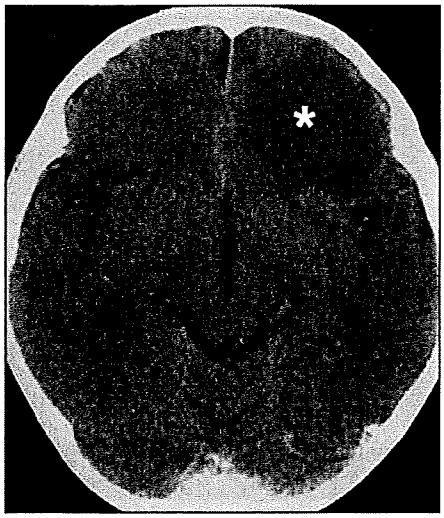


Fig. 3—9-year-old boy with brain abscess on 31st day after bone marrow transplantation. Patient underwent hematopoietic stem cell transplantation (HSCT) for acute myelocytic leukemia. Acute graft-versus-host disease occurred on 16th day after HSCT, and cyclosporine was administered. Serum WBC count was 11,800/μL with 2% lymphocytes (normal, 30–50%). Contrast-enhanced CT scan shows uniform low-attenuation area (*asterisk*) with subtle mass effect. No surrounding contrast enhancement is present. Deformation in left sylvian fissure is subtle for size of mass.

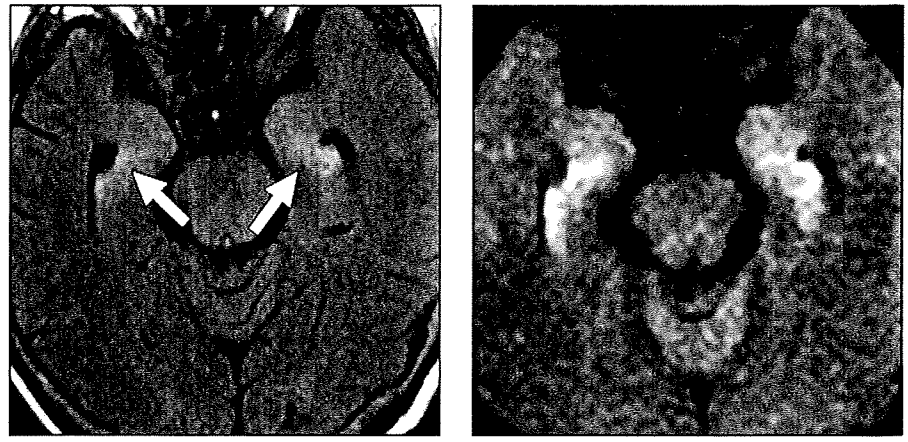


Fig. 4—57-year-old man with nonherpetic limbic encephalitis had short-term memory loss on 25th day after hematopoietic stem cell transplantation (HSCT). Abnormal signals on FLAIR MR images persisted through follow-up period.
**A,** FLAIR MR image obtained at presentation shows well-demarcated bilateral hyperintensity (*arrows*) in medial temporal lobes.
**B,** Diffusion-weighted image obtained at presentation shows robust hyperintensity corresponding to abnormal signal intensity on FLAIR image. No restricted water diffusion was visualized on apparent diffusion coefficient map (not shown).

gram-positive bacteria, and *Toxoplasma* organisms. The incidence of gram-negative bacterial and protozoan infections has decreased, but viral infections, cytomegalovirus in particular, have been reported to occur early in the course of HSCT [9]. The prevalence of these infections depends on the patient's immune status, although it can vary among populations and residential areas [10]. Cerebritis, ventriculitis, and meningitis due to hematogenous spread of pathogens to the brain are occasionally reported, and abscess formation sometimes occurs [11–13].

The imaging characteristics of cerebral infections are related to the immune status of recipients [4, 5]. As with brain abscesses in immunocompromised patients, encapsulation around the abscess cavity, which indicates the occurrence of sequential events involving neovascularization, inflammatory cell migration, and immune response, is not usually complete, and a mass effect or edema around the lesion caused by an inflammatory infiltrate of polymorphonuclear cells is relatively rare [14]. Therefore, brain abscess should be considered in the differential diagnosis when a low-density lesion is seen in the cerebral parenchyma, even if the lesion has minimal mass effect and negligible ring enhancement on contrast-enhanced CT or MR images (Fig. 3). It has been reported [15] that progressive vasogenic edema with mild ring enhancement, which develops after the increase in neutrophil count, may lead to cerebral herniation despite improved host defenses.

The risk of bacterial infection decreases after neutrophil recovery; however, recipients of HSCT remain at risk of infection with viruses and other opportunistic pathogens for several months because the full reconstitution of the immune system occurs more slowly. Cellular immunity (T-cell system) plays an especially important role in the regulation and mediation of the immune response in the subacute (30–100 days) to chronic (after 100 days) period [16]. Most posttransplantation infections in this period result from reactivation of latent herpes viruses, Epstein-Barr virus, and varicella-zoster virus [17]. Viral or virus-associated encephalitis is not an uncommon complication in the subacute period, and paraneoplastic limbic encephalitis is an occasional manifestation. Human herpes virus type 6 or 7 has been documented as one of the causative pathogens of limbic encephalitis in the hippocampal gyrus, amygdala, or both. Acute-onset mental alteration, drowsiness, and short-term memory loss are common clinical features.

MRI shows bilateral hyperintensity on T2-weighted and FLAIR images that is frequently detected in the limbic system (Fig. 4). It has been reported [18] that abnormal hyperintensity appears earlier on diffusion-weighted images than on T2-weighted and FLAIR images but that hyperintensity on T2-weighted and FLAIR images can persist. Temporomesial atrophy develops progressively in most cases. The pathologic–biophysical correlates of reduced water diffusivity include ischemic cytotoxic edema (with a failure of energy-dependent ion homeostasis), seizure-related excitotoxicity or hyperperfusion (glucose utilization exceeding oxygen delivery, leading to cellular lactate accumulation and osmotic shifting of extracellular and intracellular water), and acute myelin vacuolization [19]. Administration of acyclovir, which is widely used for prophylaxis of herpes simplex virus infection, is ineffective in cases of human herpes virus 6 or 7 and cytomegalovirus (herpes virus type 5) infection. For these pathogens, foscarnet or ganciclovir should be administered immediately.

Patients with chronic GVHD (more than 100 days after transplantation) are susceptible to late-onset infection due to not only immunoregulatory drugs but also long-term steroid therapy. Chronic GVHD seriously affects long-term survival, but it is less immediately life-threatening than acute GVHD [20]. Viral infections and reactivations of latent infections by varicella-zoster virus, Epstein-Barr virus, and other ubiquitous neurotropic viruses are still troublesome in this relatively late period.

### *Vascular Disorders*

Although recipients gradually recover from marked pancytopenia after successful engraftment, thrombocytopenia and fluctuation of the

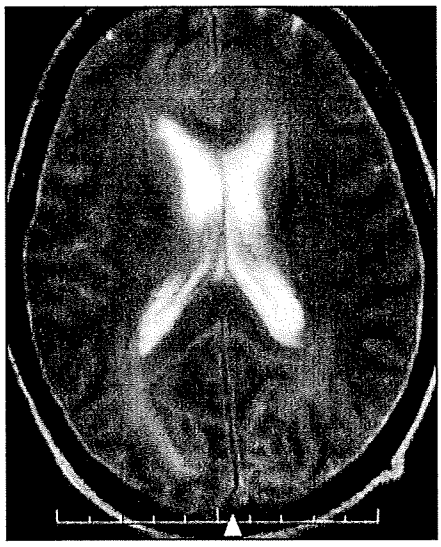


Fig. 5—55-year-old woman with venous sinus occlusion on 72nd day after hematopoietic stem cell transplantation (HSCT). T2-weighted MR image shows loss of flow void in superior sagittal sinus (*arrowhead*). Bilateral ill-defined diffuse hyperintensity is present in periventricular white matter, possibly indicating vasogenic edema due to venous congestion.

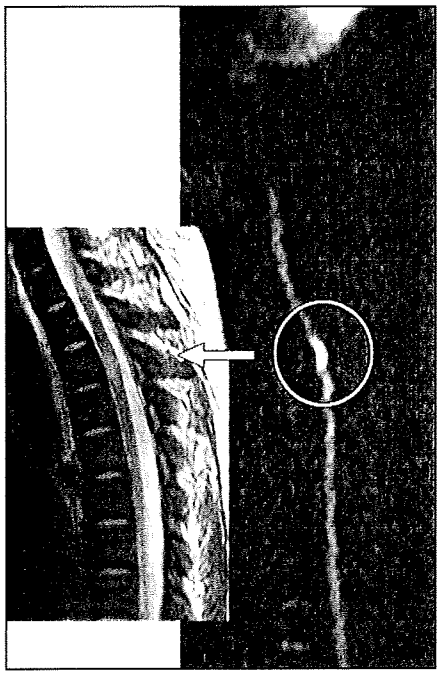
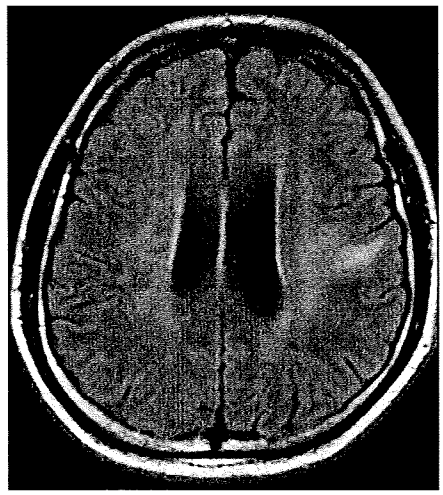
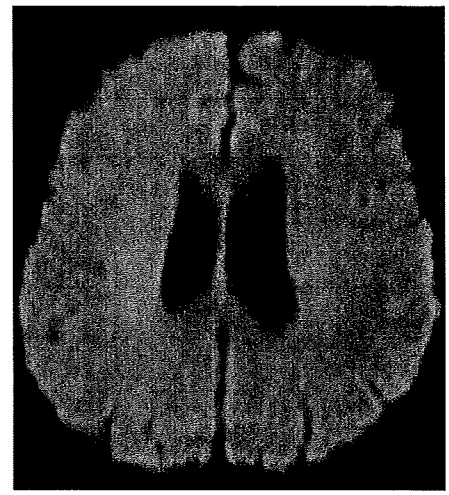


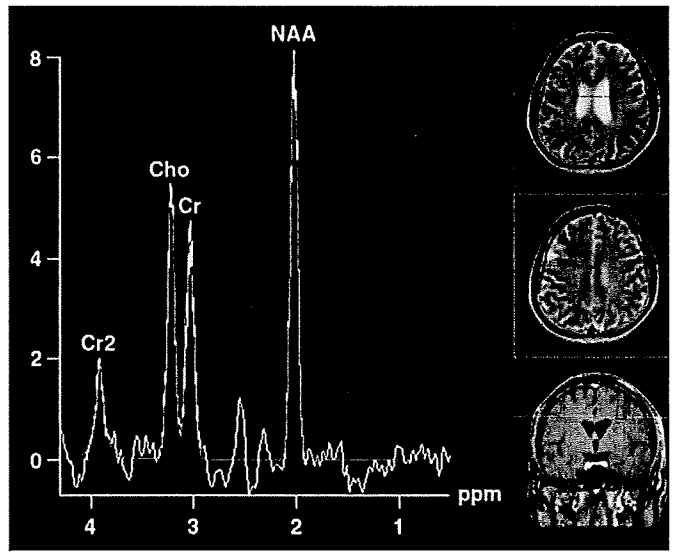
Fig. 6—31-year-old woman with spinal infarction presented with sudden-onset paralysis of right upper and lower extremities on 440th day after HSCT. MRI was performed 7 hours after onset. Sagittal diffusion-weighted image (b = 800) shows robust hyperintensity corresponding to abnormal signal intensity on T2-weighted image (*inset*). T2-weighted image shows ill-defined area of high signal intensity (*arrow*) in anterior part of spinal cord at T3 spinal level.



A



B




C

Fig. 7—35-year-old man with diffuse leukoencephalopathy 73 days after whole-brain chemoradiation therapy.
**A,** FLAIR MR image shows bilateral areas of ill-defined hyperintensity in deep white matter.
**B,** Diffusion-weighted image shows no areas of restricted water diffusion.
**C,** MR spectroscopic image (TE, 135) shows slight increase in choline-to-creatinine ratio. No lactate peak is evident.

coagulation system often occur in the relatively early posttransplantation recovery process. Intracranial hemorrhage is likely to occur in a variety of locations, including the subarachnoid space, subdural space, and brain parenchyma. The size of the lesions ranges from petechiae through focal subarachnoid bleeds to large hematoma, and one fifth of patients have more than one type of hemorrhage [21]. Coagulopathy resulting from disseminated intravascular coagulation and tumor-related tissue factors often causes thrombotic and embolic events in the cerebrovascular system [22]. These conditions are frequently associated with infection or underlying malignant disease. Arterial thrombosis and embolism most commonly are the result of nonbacterial and infective endocarditis [23]. Venous sinus thrombosis also can be caused by coagulopathy or direct infiltration of tumor and is a potential pitfall in image interpretation (Fig. 5). Spinal cord infarction is caused by the same mechanism, even though it is a rare disorder in the general population. Diffusion-weighted imaging is a novel technique for early diagnosis of spinal cord infarction (Fig. 6).

Most vascular complications in the late posttransplantation period are related to either chronic GVHD or tumor relapse. Transplantation-related microangiopathy generally occurs within 6 months after transplantation and is more frequently found, at the high incidence of 25–38%, in older patients who receive transplants from an unrelated donor [24]. The clinical findings include an increased schistocyte count due to endothelial injury; elevation of lactate dehydrogenase level, indicating microangiopathic hemolysis;

and anemia due to a decrease in hemoglobin level [25]. In HSCT recipients, the syndrome can range from asymptomatic to fulminant, and clinical and imaging manifestations occasionally are similar to those of hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura. The pathologic features of transplantation-related microangiopathy are intimal swelling and fibrinoid necrosis of the vessel walls of medium-sized to small arteries. This disorder is thought to be caused by immune-mediated systemic and focal endothelial damage related to chemoradiation therapy, immunosuppressive drugs, various pathogens, hemophagocytosis, and GVHD in combination with hypercytokinemia (cytokine storm) [24–26]. Transplantation-related microangiopathy can occur in conjunction with other neurotoxic processes. Reported imaging manifestations include a small, localized area of hyperintensity and diffuse extensive hyperintensity on T2-weighted and FLAIR MR images [26].

*Therapy-Induced Complications*

Therapy-induced cytotoxicity in HSCT recipients is caused by large-dose chemotherapy, radiation therapy, immunosuppressive therapy, and metabolic disturbances and generally occurs in the peritransplantation period. Therapy-induced cytotoxicity due to chemoradiation manifests itself as leukoencephalopathy in 6% of the pediatric age group. The finding on T2-weighted and FLAIR MR images is bilateral variable hyperintensity in the deep white matter of the cerebrum and brainstem (Fig. 7). Water molecule diffusion restriction on an apparent diffusion coefficient map varies depending on the nature and extent of damage relevant to the regimen. Most lesions disappear or become smaller as clinical symptoms subside. Progressive lesions, however, occasionally result in a chronic form of disseminated necrotizing leukoencephalopathy. It has been reported [27] that multifocal patterns on T2-weighted images may be an important early finding differentiating disseminated necrotizing leukoencephalopathy from mild leukoencephalopathy.

The histopathologic characteristics of disseminated necrotizing leukoencephalopathy are diffuse demyelination, gliosis, and coagulative necrosis caused by vascular damage. In contrast, mild leukoencephalopathy involves vasogenic edema and axonal degeneration as a result of the direct toxic effect of therapy. Therapy-induced leukoencephalopathy should be differentiated from other pathologically more critical diseases,

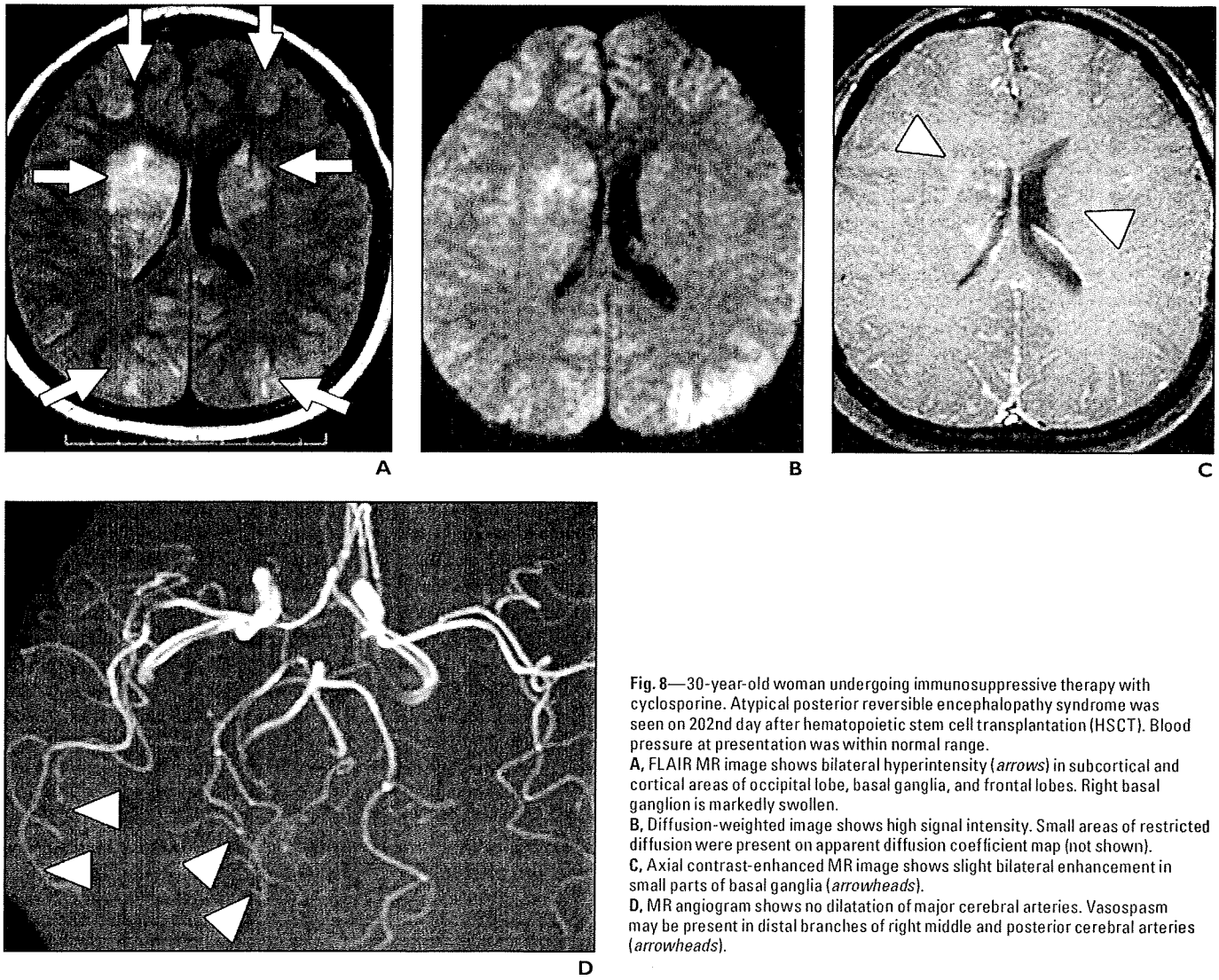


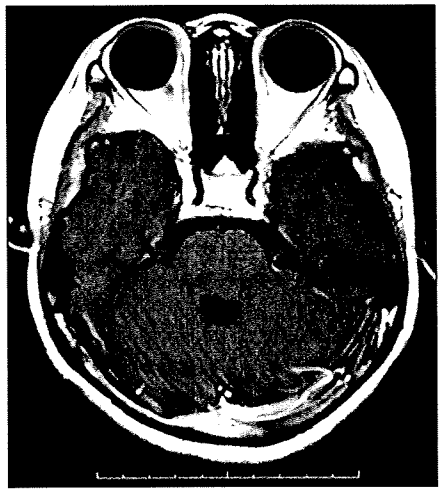

**Fig. 8**—30-year-old woman undergoing immunosuppressive therapy with cyclosporine. Atypical posterior reversible encephalopathy syndrome was seen on 202nd day after hematopoietic stem cell transplantation (HSCT). Blood pressure at presentation was within normal range.
**A**, FLAIR MR image shows bilateral hyperintensity (*arrows*) in subcortical and cortical areas of occipital lobe, basal ganglia, and frontal lobes. Right basal ganglion is markedly swollen.
**B**, Diffusion-weighted image shows high signal intensity. Small areas of restricted diffusion were present on apparent diffusion coefficient map (not shown).
**C**, Axial contrast-enhanced MR image shows slight bilateral enhancement in small parts of basal ganglia (*arrowheads*).
**D**, MR angiogram shows no dilatation of major cerebral arteries. Vasospasm may be present in distal branches of right middle and posterior cerebral arteries (*arrowheads*).

such as progressive multifocal leukoencephalopathy. Both lesions exhibit a variable lactate peak, high choline-to-creatinine ratio, and decreased *N*-acetyl aspartate–to–creatinine ratio on $^{1}$H MR spectroscopy [28, 29]. In therapy-induced encephalopathy, patients generally experience symptomatic remission within several weeks, facilitating differentiation from progressive multifocal leukoencephalopathy, which is fatal.

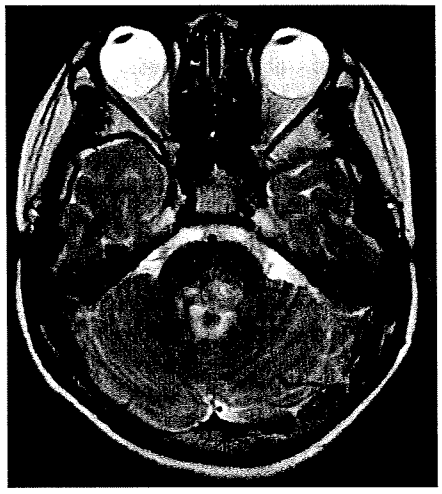
Cytotoxicity related to cyclosporine or FK-506, which predominantly appears in the cortical and subcortical areas in the posterior circulation territory, has been synonymous with posterior reversible encephalopathy syndrome (PRES) or reversible posterior leukoencephalopathy syndrome [30]. After transplantation, several PRES-related risk factors, such as postinfective sepsis, shock associated with multiple organ dysfunction, chemotherapy, and GVHD, coexist with cyclosporine or FK-506 toxicity. The pathophysiologic mechanism of PRES remains unsolved. A sudden increase in blood pressure (50 mm Hg from baseline), subsequent hyperperfusion, and autoregulation breakdown in the posterior circulation territory with less sympathetic innervation and vasogenic brain edema have been considered the chief mechanisms of PRES. Hypertension reaching the upper limits of autoregulation is not present in all patients, even though moderate-to-severe blood pressure elevation is found in most patients [31, 32]. Today, cyclosporine and FK-506 cytotoxicity is considered an aspect of widespread vasculopathy. Cyclosporine or FK-506, which is widely used for preventing graft rejection and GVHD after successful engraftment, carries a risk of endothelial damage with an incidence ranging from 1.6% to 10% [31, 33].

Direct endothelial cell damage may be responsible for the injury to the capillary bed that alters the blood–brain barrier. Capillary endothelial injury may alter microvasculature permeability, leading to vasogenic edema, first in the subcortical white matter and then in the gray matter, deep gray matter, and deep white matter. Increased microvascular permeability in turn results in release of vasoactive peptides such as endothelin and thromboxane, which cause vasospasm [34]. In such situations, sudden hypertension seems to act as a modulator of disease progression. According to Bartynski et al. [35], who analyzed the cases of 114 patients with PRES, the lesion was found in the superior frontal gyrus in 68% of cases, inferior temporal lobe in 40%, cerebellum in 30%, basal ganglia in 14%, and brainstem in 13%. It has been suggested that if autoregulatory local vasospasm is present in the arterioles or precapillaries, reduced blood flow should occur, particularly at the watershed zone. This mechanism may explain the minor ischemic changes in these cerebrovascular territories [36]. Lesion distribution does not always correspond to the bilateral posteroanterior gradient in HSCT recipients, and partial and asymmetric imaging patterns, including completely unilateral involvement, have been recognized [35, 37]. With predominantly or completely unilateral distribution, the differential diagnosis should include neoplasm, encephalitis, and leukoencephalopathy.

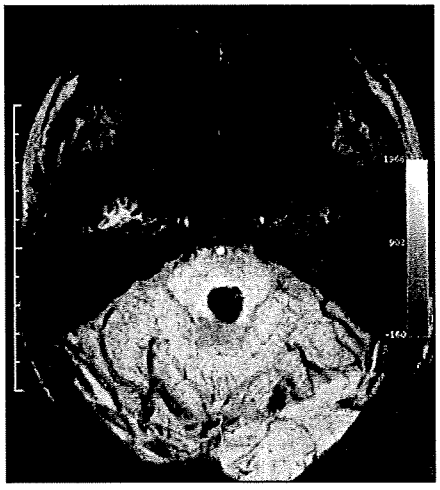
Clinically, cyclosporine and FK-506 cytotoxicity can affect HSCT recipients at any time after HSCT, most commonly in the first month after HSCT in association with immunosuppression therapy. Sudden mental alteration, headache, unconsciousness, and convulsions are the most common initial clinical manifestations. Blood levels of immunosuppressants do not appear to correlate with the severity of neurotoxicity, although neurologic improvement can be seen after discontinuation of the drug [29, 30]. The prognosis is mostly favorable without sequelae if the lesion is reversible. On T2-weighted and FLAIR MR images, hyperintensity in the subcortical and cortical regions of the bilateral parietooccipital lobes is typical. Subtle gray-matter enhancement on contrast-enhanced T1-weighted images can occur when the damage is severely prolonged (Fig. 8). Irreversible changes are observable in some parts of the lesion, reflecting intramyelinic or intracellular cytotoxic edema of varying degrees on apparent diffusion coefficient maps [38].



A



B



C

**Fig. 9**—22-year-old woman with radiation-induced cavernous malformation. Total-body irradiation therapy (30 Gy) for acute myeloid leukemia had been performed 10 years previously.
**A,** Axial contrast-enhanced T1-weighted MR image shows no apparent enhancement.
**B,** T2-weighted MR image shows focus of intermediate signal intensity in the pons. Evidence of slight peritumoral edema is present.
**C,** Susceptibility-weighted image shows bloomed focus suggesting hemorrhage in pons and in both sides of cerebral hemisphere (not shown).

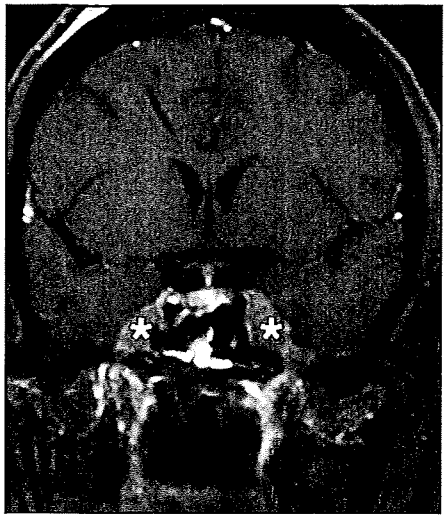


**Fig. 10**—24-year-old woman with CNS infiltration of malignant lymphoma. Coronal contrast-enhanced T1-weighted MR image shows bilateral masses in Meckel's cave (*asterisks*) and left foramen ovale.

As a late-onset complication, radiation-induced vascular injury such as telangiectasia (cavernoma formation) has been well recognized. Compared with conventional MRI, susceptibility-weighted imaging overwhelmingly depicts hemorrhagic foci and can contribute to the diagnosis (Fig. 9).

*Tumor and Tumor-Mimicking Lesions*

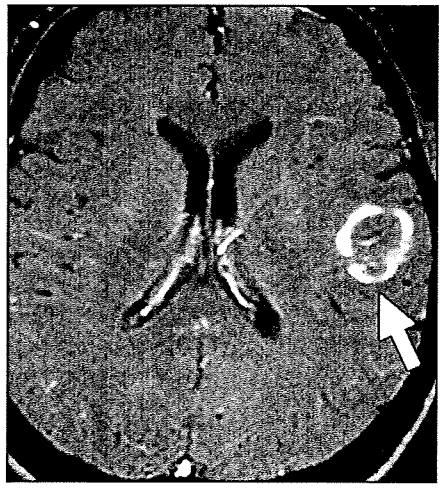
CNS relapse of underlying disease, especially in patients with leukemia or lymphoma, can occur depending on the initial treatment or depletion of the graft-versus-malignancy effect on the underlying disease (Fig. 10). An increased incidence of newly emerged cancer, mainly lymphoma and hematopoietic disorders, in the early follow-up period has been found among HSCT recipients. Patients treated for hematopoietic malignant disease, especially those who received high doses of total-body irradiation at a young age, are at high risk of development of a new solid malignant tumor 10 or more years later in life, the cumulative incidence being 2.2–6.7% [39]. In the CNS, tumors such as glioblastoma, astrocytoma, lymphoma, and meningioma can occur [22]. The clinical findings of relapse of leukemia or lymphoma can mimic the late neurologic sequelae of HSCT and should be carefully evaluated [40].

A tumefactive demyelinating lesion is an example of a tumor-mimicking lesion. This lesion is indistinguishable from a brain tumor in a single imaging analysis, especially when it occurs incidentally in the chronic phase after HSCT, during which an increased incidence of secondary malignant diseases is of great concern (Fig. 11). The tumefactive demyelinating lesion is thought to be a solitary lesion larger than 2 cm in diameter with imaging characteristics mimicking a neoplasm. Tumefactive demyelinating lesion affects young women with atypical clinical symptoms compared with those of conventional multiple sclerosis [41]. A good response to steroid therapy can be a clue to differentiation from neoplastic lymphoid infiltration, although this finding is not always definitive. Penetrating vessels, which are well depicted on susceptibility-weighted images, and the chemical composition of the demyelinating lesion, which is well depicted with proton MR spectroscopy, have been postulated to aid the differential diagnosis [42, 43]. Immune-mediated acute disseminated encephalomyelitis, Guillain-Barré syndrome, and chronic idiopathic demyelinating polyneuropathy have been reported [44–46] to occur in temporal relation to posttransplantation immunologic cross-reactions to a central or peripheral nerve protein, which can be triggered by various viral infections, reactivation of immunized pathogens, and chronic GVHD.

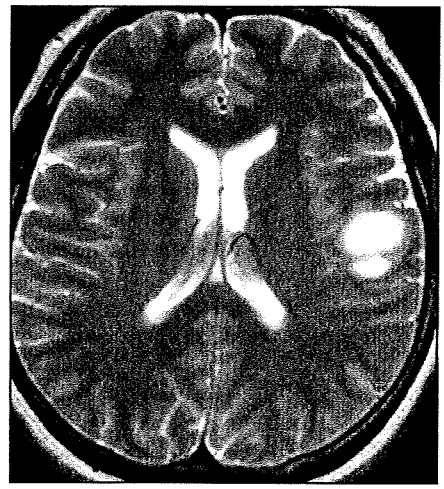
Progressive multifocal leukoencephalopathy can occur in immunocompromised patients. Although it is mostly found in HIV-positive populations and has been reported to be rare among HSCT recipients, this disorder should be considered in the differential diagnosis when an HSCT recipient has worsening of neurologic symptoms [47].

*Lymphoproliferative Disorders*

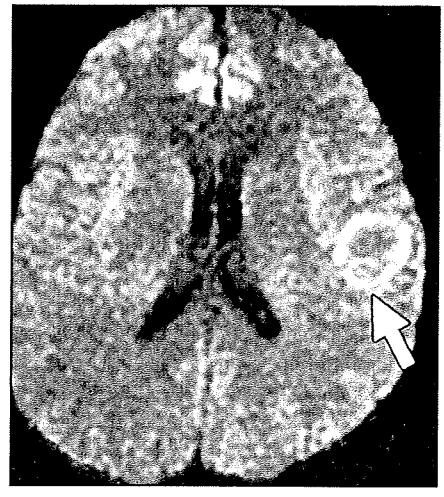
Latent viral infection or reactivation contributes to various abnormal immune reactions, including posttransplantation lymphoproliferative diseases. These diseases are a spectrum of unregulated proliferation of B cells ranging from polyclonal lymphoid hyperplasia to monoclonal malignant lymphoma. Epstein-



A



B



C

**Fig. 11**—31-year-old woman with tumefactive demyelinating lesion and clinically relapsed acute myeloid leukemia.
**A**, Axial contrast-enhanced T1-weighted MR image shows lesion has interrupted ring enhancement (*arrow*).
**B**, Axial T2-weighted MR image shows minimal mass effect and no perilesion edema.
**C**, Diffusion-weighted image (b = 1,000) depicts hyperintense rim suggesting increased extracellular space due to myelin vacuolization (*arrow*).

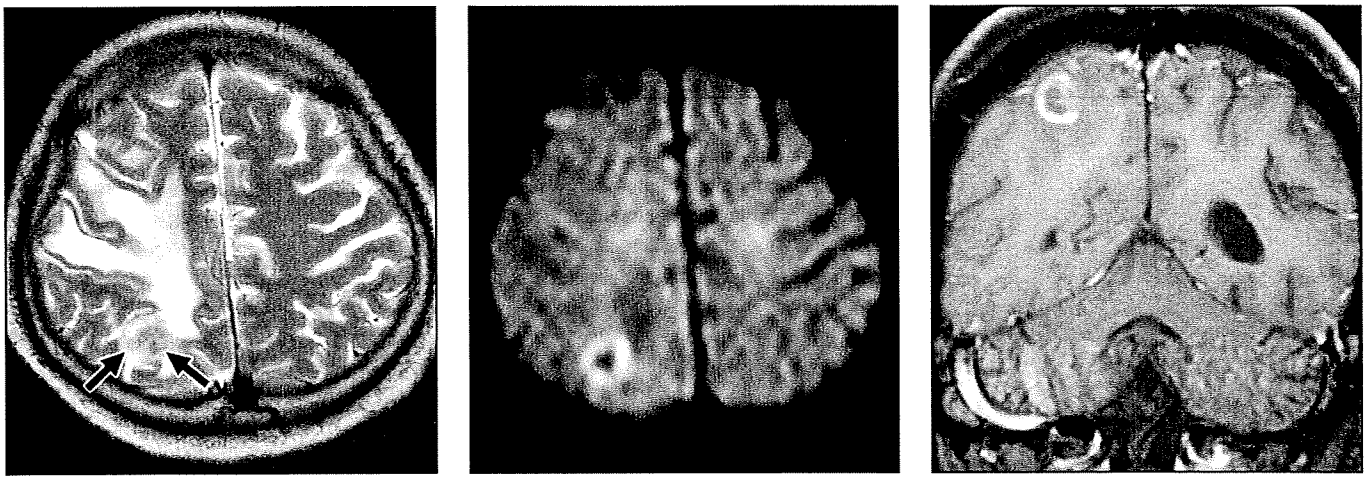


**Fig. 12**—32-year-old man with posttransplantation lymphoproliferative disorder on 180th day after hematopoietic stem cell transplantation (HSCT). (Courtesy of Ichihashi S, Kurashiki Chuo Hospital, Okayama, Japan)
**A**, Axial T2-weighted MR image shows mass (*arrows*) of low to intermediate signal intensity with prominent peritumoral edema.
**B**, Diffusion-weighted image shows restricted water diffusion suggestive of hypercellularity in mass.
**C**, Contrast-enhanced T1-weighted coronal image shows lesion with ringlike enhancement.

Barr virus–induced B-cell proliferation (85%) in combination with suppression of the T-cell system by immunosuppressive therapy is strongly related to the pathophysiologic mechanism [48]. The frequency is less than 2.0–7.4% of HSCT patients, and CNS involvement is rare (1–6%) with a reported incidence of 64% in the abdomen, 50% in the thorax, and 25% in the head and neck. Lymphoproliferative disorders generally occur 0.5–4 years after HSCT, in the first year in 60% of affected patients. The clinical symptoms of posttransplantation lymphoproliferative diseases are nonspecific, such as fever, malaise, and lymphadenopathy. It is difficult to differentiate the lesion from infection and tumor relapse in a single imaging assessment.

In general, CNS posttransplantation lymphoproliferative disease preferentially occurs in the cerebral subcortical white matter and periventricular white matter rather than in the cerebellum or brainstem. The lesion can be solitary or multifocal depending mostly on the immunologic status of the patient. The solitary mass is reported to be more common in nonimmunocompromised patients [49]. The imaging manifestations are ringlike enhancement after IV injection of contrast material, closely resembling that of CNS lymphoma in persons with AIDS-related conditions and in elderly persons. On T1-weighted, T2-weighted, and FLAIR MR images, the lesion has a slightly heterogeneous internal intensity, reflecting hypercellularity, hemorrhage, and necrosis [48, 50] (Fig. 12). Diffusion-weighted imaging cannot always be used to differentiate posttransplantation lymphoproliferative disease from CNS lymphoma, because necrosis is found in posttransplantation lymphoproliferative disease in 30–90% of cases [49]. The clinical history, immune status of the recipients, and response to therapy are important in diagnosis. Long survival is associated with accelerated reduction of immunosuppressive therapy and immune restoration by eradication of the Epstein-Barr virus.

## Conclusion

CT and MRI can show various CNS lesions in HSCT recipients. Dedicated imaging sequences and a comprehensive approach focusing on the patient's immune status, interval after treatment, and the pathophysiologic mechanisms of a spectrum of CNS complications will aid in achieving the correct diagnosis and prompt treatment. Radiologists can play a pivotal role in supporting proper treatment decisions and achieving better clinical prognoses in the era of advanced HSCT.

## Acknowledgments

We thank Dr. Craig Kolodziej for helpful comments on the manuscript, Haruko Asada for secretarial assistance, and Masato Kumon for technical support.

## References

1. Center for International Blood and Marrow Transplant Research. Progress report: January–December 2007. Milwaukee, WI: CIBMTR, 2008
2. Thomas ED, Lochte HL Jr, Lu WC, et al. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *N Engl J Med* 1957; 257:491–496
3. Weber C, Schaper J, Tibussaek D, et al. Diagnostic and therapeutic implications of neurological complications following paediatric haematopoietic stem cell transplantation. *Bone Marrow Transplant* 2008; 41:253–259
4. Graus F, Saiz A, Sierra J, et al. Neurologic complications of autologous and allogeneic bone marrow transplantation in patients with leukemia. *Neurology* 1996; 46:1004–1009
5. Uckan D, Cetin M, Yigitkanli I, et al. Life-threatening neurological complications after bone marrow transplantation in children. *Bone Marrow Transplant* 2005; 35:71–76
6. Yoshida S, Hayakawa K, Yamamoto A, et al. The central nervous system complications of bone marrow transplantation in children. *Eur Radiol* 2008; 18:2048–2059
7. Weisdorf D. GVHD: the nuts and bolts. *Hematology Am Soc Hematol Educ Program* 2007; 2007: 62–67
8. Ramphal R. Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. *Clin Infect Dis* 2004; 39:S25–S31
9. Saavedra S, Sanz GF, Jarque I, et al. Early infections in adult patients undergoing unrelated donor cord blood transplantation. *Bone Marrow Transplant* 2002; 30:937–943
10. Oliveira AL, de Souza M, Carvalho-Dias VM, et al. Epidemiology of bacteremia and factors

associated with multi-drug-resistant gram-negative bacteremia in hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2007; 39: 775–781

11. Miaux Y, Ribaud P, Williams M, et al. MR of cerebral aspergillosis in patients who have had bone marrow transplantation. *Am J Neuroradiol* 1995; 16:555–562
12. Ionita C, Wasay M, Balos L, et al. MR Imaging in toxoplasmosis encephalitis after bone marrow transplantation: paucity of enhancement despite fulminant disease. *Am J Neuroradiol* 2004; 25: 270–273
13. Fukui MB, Williams RL, Mudigonda S. CT and MR imaging features of pyogenic ventriculitis. *Am J Neuroradiol* 2001; 22:1510–1516
14. Dietrich U, Hettmann M, Maschke M, et al. Cerebral aspergillosis: comparison of radiological and neuropathologic findings in patients with bone marrow transplantation. *Eur Radiol* 2001; 11: 1242–1249
15. Yuh WT, Nguyen HD, Gao F, et al. Brain parenchymal infection in bone marrow transplantation patients: CT and MR findings. *AJR* 1994; 162: 425–430
16. Fujita Y, Rooney CM, Heslop HE. Adoptive cellular immunotherapy for viral disease. *Bone Marrow Transplant* 2008; 41:193–198
17. Bjorklund A, Aschan J, Labopin M, et al. Risk factors for fatal infectious complications developing late after allogeneic stem cell transplantation. *Bone Marrow Transplant* 2007; 40:1055–1062
18. Urbach H, Soeder BM, Jeub M, et al. Serial MRI of limbic encephalitis. *Neuroradiology* 2006; 48: 380–386
19. Seeley WW, Marty FM, Holmes TM, et al. Post-transplant acute limbic encephalitis. *Neurology* 2007; 69:156–165
20. Aschan J. Allogeneic haematopoietic stem cell transplantation: current status and future outlook. *Br Med Bull* 2006; 77–78:23–36
21. Bleggi-Torres LF, Werner B, Gasparetto EL, et al. Intracranial hemorrhage following bone marrow transplantation: an autopsy study of 58 patients. *Bone Marrow Transplant* 2002; 29:29–32
22. Guermazi A, Miaux Y, Lafitte F, et al. CT and MR imaging of central nervous system effects of therapy in patients treated for hematological malignancies. *Eur Radiol* 2003; 13:L202–L214
23. Levine DS, Navarro OM, Chaudry G, et al. Imaging the complications of bone marrow transplantation in children. *RadioGraphics* 2007; 27:307–324
24. Martinez MT, Bucher Ch, Stussi G, et al. Transplant-associated microangiopathy (TAM) in recipients of allogeneic hematopoietic stem cell transplants. *Bone Marrow Transplant* 2005; 36:993–1000
25. Batts ED, Lazarus HM. Diagnosis and treatment of transplantation-associated thrombotic microangiopathy: real progress or are we still waiting? *Bone Marrow Transplant* 2007; 40:709–719
26. Woodard P, Helton K, McDaniel H, et al. Encephalopathy in pediatric patients after allogeneic hematopoietic stem cell transplantation is associated with a poor prognosis. *Bone Marrow Transplant* 2004; 33:1151–1157
27. Oka M, Terae S, Kobayashi R, et al. MRI in methotrexate-related leukoencephalopathy: disseminated necrotising leukoencephalopathy in comparison with mild leukoencephalopathy. *Neuroradiology* 2003; 45:493–497
28. Raghavendra S, Chemmanam NT, Krishnamoorthy T, et al. Disseminated necrotizing leukoencephalopathy following low-dose oral methotrexate. *Eur J Neurol* 2007; 14:309–314
29. Chang L, Ernst T, Tornatore C, et al. Metabolite abnormalities in progressive multifocal leukoencephalopathy by proton magnetic resonance spectroscopy. *Neurology* 1997; 48:836–845
30. Hinchey J, Chaves C, Appignani B, et al. A posterior reversible leukoencephalopathy syndrome. *N Engl J Med* 1996; 334:494–500
31. Bartynski WS, Zeigler ZR, Shadduck RK, et al. Pretransplantation conditioning influence on the occurrence of cyclosporine or FK-506 neurotoxicity in allogeneic bone marrow transplantation. *Am J Neuroradiol* 2004; 25:261–269
32. Bartynski WS, Boardman JF, Zeigler ZR, et al. Posterior encephalopathy syndrome in infection, sepsis, and shock. *Am J Neuroradiol* 2006; 27:2179–2190
33. Siegal D, Keller A, Xu W, et al. Central nervous system complications after allogeneic hematopoietic stem cell transplantation: incidence, manifestations, and clinical significance. *Biol Blood Marrow Transplant* 2007; 13:1369–1379
34. Zwienenberg LM, Muizelaar JP. Clinical pathophysiology of traumatic brain injury. In: HR Winn, Youmans JR, eds. *Youmans neurological surgery*. 5th ed. Philadelphia, PA: Saunders; 2004:5039–5064
35. Bartynski WS, Boardman JF, Zeigler ZR, et al. Distinct imaging patterns and lesion distribution in posterior encephalopathy syndrome. *Am J Neuroradiol* 2007; 28:1320–1327
36. Bartynski WS, Boardman JF. Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. *Am J Neuroradiol* 2008; 29:447–455
37. McKinney AM, Short J, Truwit CL, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. *AJR* 2007; 189:904–912
38. Pande AR, Ando K, Ishikura R, et al. Clinicoradiological factors influencing the reversibility of posterior reversible encephalopathy syndrome: a multicenter study. *Radiat Med* 2006; 24:659–668
39. Curtis RE, Rowlings PA, Deeg HJ, et al. Solid cancers after bone marrow transplantation. *N Engl J Med* 1997; 336:897–904
40. Hollingsworth CL, Frush DP, Kurtzburg J, et al. Pediatric hematopoietic stem cell transplantation and the role of imaging. *Radiology* 2008; 248: 348–365
41. Given CA II, Stevens BS, Lee C. MRI appearance of tumefactive demyelinating lesions. *AJR* 2004; 182:195–199
42. Sasaki M, Kanbara Y, Shibata E, et al. Susceptibility-weighted imaging at 3-Tesla: clinical application in multiple sclerosis [in Japanese]. *Jpn J Magn Reson Med* 2006; 26:61–63
43. Cianfoni A, Niku S, Imbesi SG. Metabolite findings in tumefactive demyelinating lesions utilizing short echo time proton magnetic resonance spectroscopy. *Am J Neuroradiol* 2007; 28:272–277
44. Tomonari A, Tojo A, Adachi D, et al. Acute disseminated encephalomyelitis (ADEM) after allogeneic bone marrow transplantation for acute myeloid leukemia. *Ann Hematol* 2003; 82:37–40
45. Faraci M, Lanino E, Dini G, et al. Severe neurologic complications after hematopoietic stem cell transplantation in children. *Neurology* 2002; 59:1895–1904
46. Sostak P, Padovan CS, Yousry TA, et al. Prospective evaluation of neurological complications after allogeneic hematopoietic bone marrow transplantation. *Neurology* 2003; 60:842–848
47. Kharfan-Dabaja MA, Ayala E, Greene J, et al. Two cases of progressive multifocal leukoencephalopathy after allogeneic hematopoietic cell transplantation and a review of the literature. *Bone Marrow Transplant* 2007; 39:101–107
48. Pickhardt PJ, Siegel MJ, Hayashi RJ, et al. Post-transplantation lymphoproliferative disorder in children: clinical, histopathologic, and imaging features. *Radiology* 2000; 217:16–25
49. Castellano-Sanchez AA, Li S, Qian J. Primary central nervous system posttransplant lymphoproliferative disorders. *Am J Clin Pathol* 2004; 121:246–253
50. Pickhardt PJ, Wippold FJ II. Neuroimaging in posttransplant lymphoproliferative disorder. *AJR* 1999; 172:1117–1121

**FOR YOUR INFORMATION**

This article is available for CME credit. See www.arrs.org for more information.

Int J Hematol
DOI 10.1007/s12185-010-0543-7

ORIGINAL ARTICLE

# Heart rate variability during and after peripheral blood stem cell leukapheresis in autologous transplant patients and allogeneic transplant donors

Takahiko Nakane · Hirohisa Nakamae · Hideo Koh · Mika Nakamae · Ran Aimoto · Yoshiki Terada · Ki-Ryang Koh · Takahisa Yamane · Masayuki Hino

Received: 4 October 2009 / Revised: 22 January 2010 / Accepted: 14 February 2010


**Abstract** Side effects of varying severity are frequent in peripheral blood stem cell harvest (PBSCH). Life-threatening complications associated with PBSCH have also been reported. Heart rate variability (HRV), which reflects sympathovagal balance and autonomic cardiovascular control, has been a subject of intense interest in various diseases precipitating sudden death. Here, we prospectively assessed the impact of leukapheresis on HRV among autologous hematopoietic cell transplant patients and healthy donors. We found that HRV indicators, the standard deviation of normal-to-normal intervals (SDNN) value, the square root of the mean of the sum of squared differences between the adjacent normal-to-normal interval (r-MSSD) value, total frequency (TF), high frequency (HF) and low frequency (LF) powers decreased significantly to morbid levels during leukapheresis (all $P < 0.01$). Morbid changes in SDNN value, TF and LF powers were significantly sustained for 6–9 h after leukapheresis (all $P < 0.05$). Furthermore, TF and LF powers prior to leukapheresis were significantly lower in subjects with symptomatic hypotension than in the other subjects [3282 (3121–4427) vs. 6018 (4983–9816) $ms^2$, $P = 0.03$; 93 (42–144) vs. 237 (142–360) $ms^2$, $P = 0.03$, respectively]. Our results suggest that HRV analysis might be of use in evaluating and predicting the adverse effects of cardiovascular complications in PBSCH.

T. Nakane · H. Nakamae (✉) · H. Koh · M. Nakamae · R. Aimoto · Y. Terada · K.-R. Koh · T. Yamane · M. Hino
Department of Hematology, Graduate School of Medicine, Osaka City University, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan
e-mail: hirohisa@msic.med.osaka-cu.ac.jp

**Keywords** Peripheral blood stem cell (PBSC) harvest · Leukapheresis · Heart rate variability · Autologous hematopoietic cell transplant patients and PBSC donors

## 1 Introduction

Peripheral blood stem cell harvesting (PBSCH) has been widely used for rescue following high-dose chemotherapy, or as an alternative to bone marrow as a stem cell source for allogeneic hematopoietic cell transplantation. The most common side effects are associated with recombinant human granulocyte colony-stimulating factor (rhG-CSF) administration, securing peripheral venous access, or anticoagulation with acid-citrate-dextrose (ACD) solution. These adverse effects are usually transient, not severe and easily controlled with adequate treatment. Severe adverse events in PBSC donors, the majority of which are acute and transient, occur at an incidence of 0.6% [1]. However, although extremely rare, life-threatening complications relating to PBSC donation, including sudden death or transient cardiac arrest, have been reported [2–5]. In several sudden death cases following PBSCH, the underlying mechanisms that led to the occurrence of sudden death have not been clearly described or clarified.

In normal sinus rhythm, the heart rate varies from beat to beat. The impulse generated by the sinus node is affected by the automatic nervous system and various humoral factors. The cardiovascular signal variability of the R–R period (heart rate variability, HRV) is an established tool that can be used to assess autonomic control. HRV assessment enables the evaluation of dynamic changes in the automatic nervous system and humoral factors without an invasive procedure. Recent evidence shows that a decrease in HRV is strongly associated with sudden death



Journal : Large 12185 | Dispatch : 23-2-2010 | Pages : 7
Article No. : 543 | LE | TYPESET
MS Code : IJHM-D-09-00514 | CP | DISK

and/or a cardiac event after a myocardial infarction. The usefulness of HRV as a clinical tool has been explored in numerous conditions, such as ischemic sudden death, sustained ventricular tachycardia, myocardial infarction, congestive heart failure, vasovagal syncope, hypertrophic cardiomyopathy, obstructive sleep apnea, diabetic neuropathy and various neurological alterations [6–14]. Two types of analysis, time domain and frequency domain, are included in HRV analysis. In time domain analysis, acknowledged simple markers are the standard deviation of normal-to-normal intervals (SDNN) and the square root of the mean of the sum of squared differences between adjacent normal-to-normal intervals (r-MSSD). In frequency domain analysis, markers include TF, total frequency (0.0001–0.5 Hz); LF, low-frequency power (0.04–0.15 Hz); HF, high-frequency power (0.15–0.4 Hz); and LF/HF ratio. These HRV power spectrum analyses are used to investigate sympathovagal balance, autonomic cardiovascular control and/or target function impairment. The LF component, which is called perfusion rhythmicity, reflects the rennin–angiotensin system or angiokinetic activity. The HF component, called respiratory rhythmicity, reflects breathing variability. Thus, the LF/HF ratio and HF have been used as markers of sympathetic and parasympathetic activity, respectively [15]. The aim of this study was to assess HRV during or after leukapheresis in autologous transplant patients and healthy PBSC donors.

## 2 Subjects and methods

### 2.1 Baseline characteristics

In this study, we enrolled 29 subjects (22 allogeneic transplant donors and 7 autologous transplant patients; 10 males, 19 females; median age: 38 years; interquartile range (IQR): 27–53). Median age of the autologous transplant patients and healthy allogeneic donors was 56 (IQR: 33–62) and 35 (IQR: 27–50) years, respectively. Diagnoses of the 7 autologous transplant patients were non-Hodgkin's lymphoma (6 patients) and plasmacytoma (1 patient). All the autologous transplant patients had a history of previous chemotherapy including anthracycline. The median cumulative dose of anthracycline in the 7 autologous transplant patients was 245 mg/m$^2$ (IQR: 160–297).

The study was conducted in accordance with a protocol approved by the IRB at our institution. Written informed consent was obtained from each patient or healthy donor.

### 2.2 Peripheral blood collection procedure

Autologous PBSCH was performed during the recovery phase after chemotherapy and was supported by subcutaneous administration of 10 μg/kg/day of rhG-CSF. In allogeneic PBSCH from healthy donors, on the other hand, leukapheresis was initiated following the administration of 10 μg/kg/day of rhG-CSF for 4 days. Of the 29 leukapheresis, 18 were performed using a CS3000 Plus (Baxter, Tokyo, Japan), 4 using an Amicus™ Separator (Baxter, Tokyo, Japan) and 7 using a COBE Spectra (BCT Japan, Tokyo, Japan). In all 7 autologous harvest patients and 7 allogeneic harvest donors, central venous access via the femoral vein was secured.

### 2.3 HRV analysis

In all patients and donors, ambulatory ECG recording was performed for 24 h during the first leukapheresis day but also for 24 h prior to leukapheresis to obtain control data. As control data, we employed the values of HRV indicators obtained during the same time period as leukapheresis on another day before leukapheresis. The data obtained from the 24-h ambulatory ECG recording were stored in a computer. Beat-by-beat cardiac cycle data were obtained by off-line computer analysis methods. The maximum entropy spectral analysis method was used to calculate HRV (MemCalc/CHIRAM version 1, Suwatrust, Tokyo, Japan). This program can perform time domain and frequency domain analyses simultaneously, and is superior to the fast Fourier transform and autoregressive methods in terms of the reproducibility of the original time series. The analysis was automatically performed in short segments and then averaged. In the program, all extrasystolic beats and artifacts were eliminated. We used markers, including heart rate (HR), normal-to-normal intervals (NN), SDNN and r-MSSD in time domain analysis, and TF, LF, HF and LF/HF ratio in frequency domain analysis. The program represents the average values of all markers every 5 min. In the program, TF was defined as the frequency range from 0.0001 to 0.5 Hz and included HF, LF, very low frequency and ultra low frequency. Therefore, at least 3 h of data are needed for TF power measurement; however, since leukapheresis took less than 3 h in 3 of the 29 subjects, TF power during leukapheresis was used in only 26 subjects. We applied the average values of all markers during the leukapheresis periods to assess HRV during leukapheresis, and applied the average values of all markers every 3 h following leukapheresis to assess HRV after leukapheresis.

We compared HRV control data measured for 24 h before leukapheresis between autologous transplant patients and allogeneic transplant donors in all 29 subjects. Control data were available in 26 of the patients, obtained on the day before leukapheresis during the same time period as leukapheresis. We therefore compared HRV data obtained during leukapheresis with control data acquired during the same time period prior to leukapheresis in 26



Journal : Large 12185 | Dispatch : 23-2-2010 | Pages : 7
Article No. : 543 | LE | TYPESET
MS Code : IJHM-D-09-00514 | CP | DISK

evaluable subjects. Furthermore, to evaluate HRV changes after leukapheresis, we compared HRV data obtained during the nine-hour period after leukapheresis with control data obtained during the same time period prior to leukapheresis. This last comparison was possible in 24 subjects.

### 2.4 Statistical analysis

To evaluate the association between Hb levels just before leukapheresis and HRV indicators, we used Pearson's correlation coefficient. The Mann–Whitney $U$ test was employed to analyze differences in HRV value between autologous transplant patients and healthy donors. The Wilcoxon's rank test was used to compare differences between HRV values during leukapheresis, or transitional changes in HRV values following leukapheresis, with control data measured during the same time period as the measurements taken during or following leukapheresis. Repeated measurements of analysis of variance were used to evaluate the effect of factors [age (>60 or ≤60), sex, weight (>50 or ≤50 kg) and autologous transplant patients] on rate of change in HR and HRV values from before to during leukapheresis. All $P$ values less than 0.05 were considered significant.

## 3 Results

At HRV measurement, the median processed whole blood volume was 173 ml/kg (IQR: 140–196 ml/kg), the median leukapheresis time was 215 min (IQR: 188–248 min) and the median leukapheresis rate was 43 ml/min (IQR: 37–52 ml/min).

In all subjects, the r-MSSD value, TF, LF and HF powers at baseline showed a significant correlation with Hb levels before leukapheresis [Correlation coefficients: 0.61, 0.45, 0.58 and 0.45 (all $P < 0.05$), respectively]. In the autologous transplant patients, Hb levels before leukapheresis were significantly lower than in the healthy donors [(Median (IQR): 10.2 (9.4–11.5) vs. 13.5 (12.2–14.1) g/dl, respectively, $P = 0.0007$]. The r-MSSD value and LF power were significantly lower in the autologous transplant patients than in the healthy donors in the data for the 24 h prior to leukapheresis [Median (IQR); 21.8 (15.3–28.0) vs. 30.3 (26.1–39.4) ms, $P = 0.01$, 393 (205–416) vs. 603 (436–761) $ms^2$, $P = 0.03$, respectively] (Fig. 1).

In all the 26 evaluable subjects, SDNN, r-MSSD, TF, LF and HF values significantly and markedly decreased to morbid levels during leukapheresis (all $P < 0.001$) (Fig. 2). The HR and NN values and LF/HF ratio during leukapheresis did not change significantly compared with the control data. Similarly, among the allogeneic transplant donors, SDNN, r-MSSD, TF, LF and HF values decreased significantly (all $P < 0.05$) and the HR and NN values and LF/HF ratio did not change significantly during leukapheresis. When limited to the autologous transplant patients, HR became significantly elevated during leukapheresis [Median (IQR): 84.3 (77.4–88.4) vs. 93.4 (82.6–97.6) beats/min, respectively, $P = 0.03$]. NN, SDNN, r-MSSD, LF and HF values decreased significantly (all $P < 0.05$) and TF tended to decrease ($P = 0.07$) during leukapheresis. The LF/HF ratio did not change significantly during leukapheresis.

Advanced age (≤60) significantly affected HR elevation during leukapheresis in comparison to baseline (Mean ± SD: 76.4 ± 12.9 and 87.7 ± 9.4 beats/min, $P = 0.02$). However, the factors including age (>60 or ≤60), sex, weight (>50 or ≤50 kg) and autologous transplant did not significantly affect the degree of decrease in HRV values during leukapheresis from the baseline.

Furthermore, r-MSSD power improved almost to control levels 6–9 h following leukapheresis (Table 1). On the other hand, SDNN, TF and LF values did not normalize to control levels even 6–9 h following leukapheresis (all $P < 0.05$). Furthermore, HF also did not completely normalize to control levels even 6–9 h following leukapheresis; however, this was not statistically significant ($P = 0.22$).

Of the 29 harvest cases, symptomatic hypotension occurred during leukapheresis in 2 subjects and about 3 h after leukapheresis in 1 subject. All 3 subjects were female, their systolic blood pressure decreasing significantly from 108, 96 and 114 mmHg to 82, 72 and 76 mmHg, respectively. In a 47-year-old female, anginal chest pain and dyspnea occurred; in a 52-year-old female, nausea, blurry vision and chest oppression were evident; and another 52-year-old female experienced nausea and dizziness with hypotension. However, symptomatic hypotension immediately improved with saline infusion, tilting the patient head-down, or discontinuance of leukapheresis. Notably among the HRV indicators, in the three subjects with symptomatic hypotension, TF and LF powers were significantly lower prior to leukapheresis than those in the other subjects [3282 (3121–4427) vs. 6018 (4983–9816) $ms^2$, $P = 0.03$; 93 (42–144) vs. 237 (142–360) $ms^2$, $P = 0.03$, respectively].

## 4 Discussion

In the present study we detected that the time domain indicators including SDNN and r-MSSD, and the frequency domain indicators including TF, HF and LF markedly decreased during leukapheresis and that this decrease was sustained over several hours after leukapheresis.



Journal : Large 12185 Dispatch : 23-2-2010 Pages : 7
Article No. : 543 LE TYPESET
MS Code : IJHM-D-09-00514 CP DISK

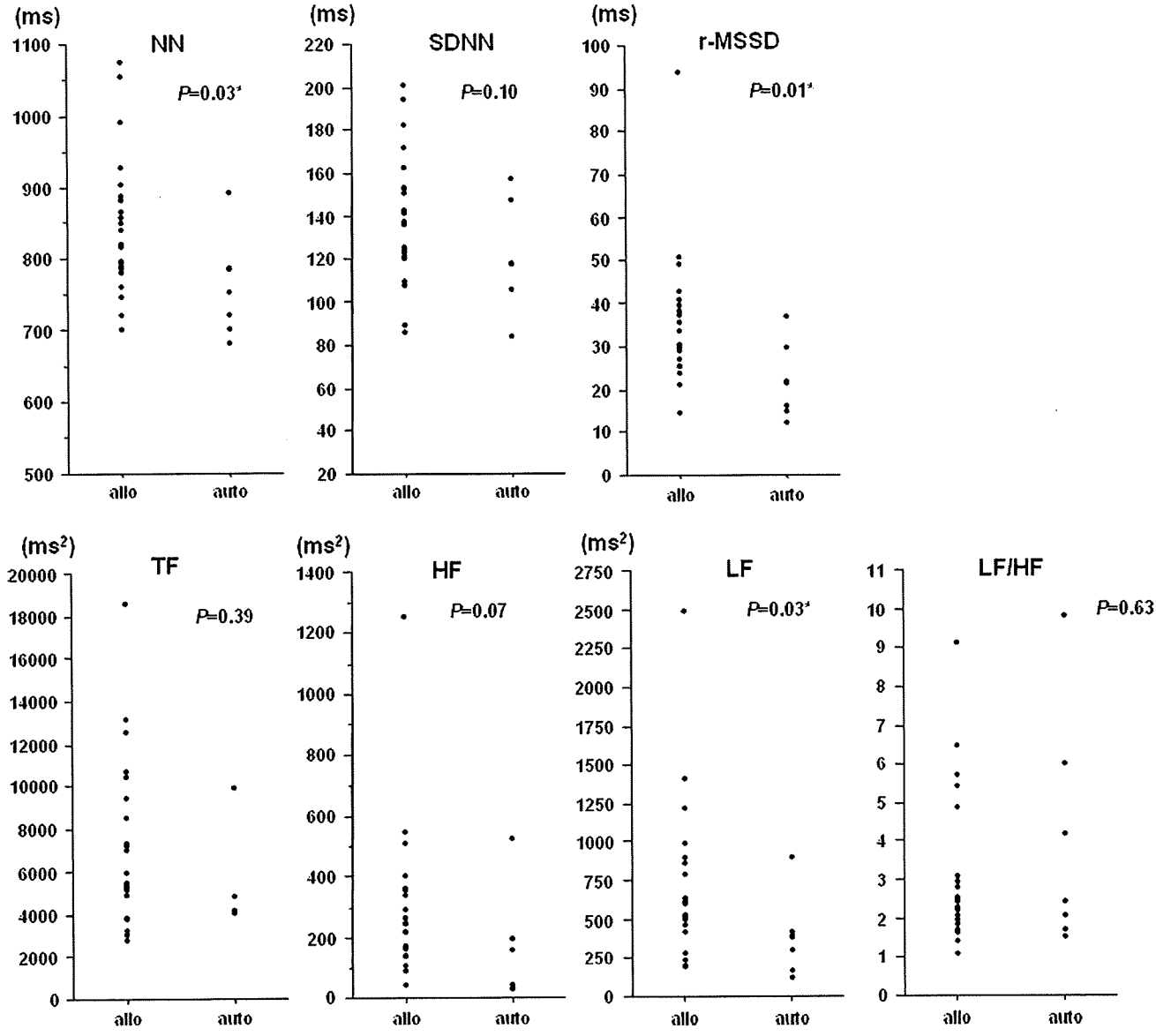



**Fig. 1** Comparison of heart rate variability (HRV) indicator values between autologous transplant patients and healthy donors. NN, r-MSSD and LF were significantly lower in the autologous hematopoietic cell transplant patients than in the healthy donors. *auto* autologous hematopoietic cell transplant patients, *allo* allogeneic hematopoietic cell transplant healthy donors, *NN* normal-to-normal intervals, *SDNN* standard deviation of normal-to-normal intervals, *r-MSSD* square root of mean of sum of squared differences between adjacent normal-to-normal intervals, *TF* total frequency, *HF* high frequency, *LF* low frequency

Interestingly, in subjects who had symptomatic hypotension, TF and LF powers at baseline were significantly lower than for subjects without adverse cardiovascular effects.

It is reported that in patients with chronic heart failure, those with an SDNN value of less than 44 ms are at risk of cardiac events and all-cause mortality [16]. Surprisingly, in the 6 (86%) out of the 7 autologous transplant patients and in 7 (32%) out of the 22 allogeneic transplant donors, the SDNN value decreased to less than 44 ms during leukapheresis. Additionally, in 2 out of the 3 subjects with symptomatic hypotension, SDNN values decreased to less than 44 ms during leukapheresis.

Although we cannot clearly explain the underlying mechanism of HRV alteration during leukapheresis, we speculate that such a major change in HRV indicators was induced by heightened sympathetic activity and parasympathetic withdrawal, mediated by a hemodynamical or neural effect of the leukapheresis procedure and/or other pathogenesis, including altered concentrations of electrolytes in serum and metabolic alkalosis [17]. Both r-MSSD and HF are known to reflect parasympathetic activity; thus the significant reduction in the r-MSSD value and HF power suggested parasympathetic activity was reduced during leukapheresis. It has been reported that



Journal : Large 12185 Dispatch : 23-2-2010 Pages : 7
Article No. : 543 LE TYPESET
MS Code : IJHM-D-09-00514 CP DISK

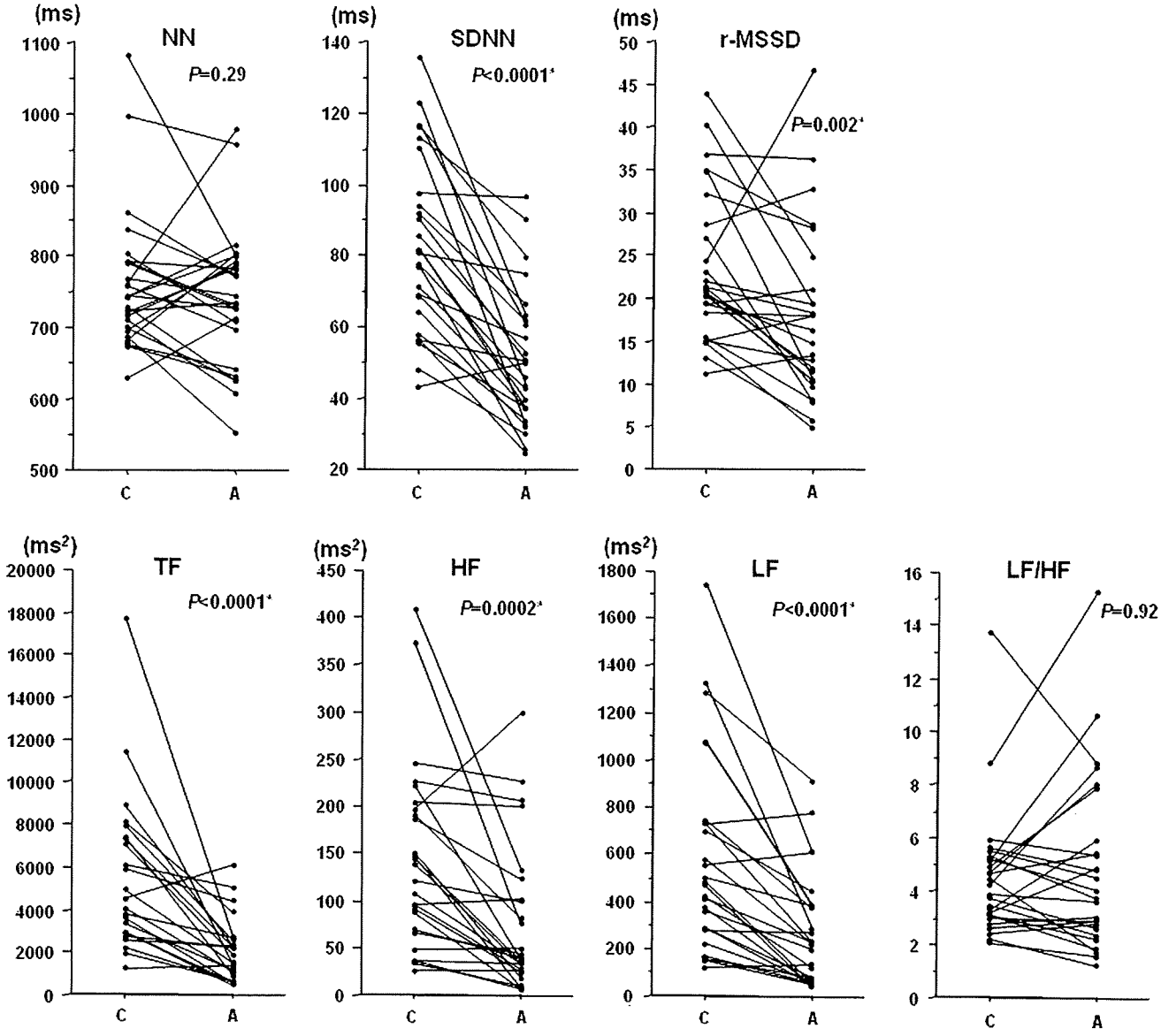



**Fig. 2** Comparison of control data and heart rate variability (HRV) indicator values during leukapheresis. Many HRV indicators decreased significantly during leukapheresis. *C* control HRV values, *A* HRV values during leukapheresis, *NN* normal-to-normal intervals, *SDNN* standard deviation of normal-to-normal intervals, *r-MSSD* square root of mean of sum of squared differences between adjacent normal-to-normal intervals, *TF* total frequency, *HF* high frequency, *LF* low frequency

parasympathetic withdrawal is seen in patients with congestive heart failure and parasympathetic withdrawal causes a decrease in HRV [18]. Therefore, we speculated that the suppression of parasympathetic activity might be causally related to critical cardiovascular complications in PBSCH.

In this study, LF power also significantly decreased during leukapheresis. In recent reports, reduced LF spectral power was also identified as a risk of all-cause mortality [19] and sudden cardiac death [20] in chronic heart failure. LF power is more complicated because it is jointly mediated by the sympathetic and parasympathetic nervous systems [21]. Reduced R–R interval variability and parasympathetic activity withdrawal might also be associated with reduced LF power.

In addition, citrate-based anticoagulants, such as the ACD solution used for leukapheresis, decrease the concentration of electrolytes in serum by chelation and cause hypocalcemia, hypomagnesemia [22] and intermittent hypotension [23] in leukapheresis. A previous report showed that electrolyte abnormalities mediated by citrate, such as hypocalcemia, may change HRV [24].

Life-threatening complications associated with PBSC donation reportedly occur after, rather than during, leukapheresis [2, 3]. Notably, our data showed that abnormal HRV indicators persisted 6–9 h after leukapheresis



Journal : Large 12185 Dispatch : 23-2-2010 Pages : 7
Article No. : 543 LE TYPESET
MS Code : IJHM-D-09-00514 CP DISK

**Table 1** Changes in HRV indicators following leukapheresis

| | 0–3 h [Median (IQR)] | | | 3–6 h [Median (IQR)] | | | 6–9 h [Median (IQR)] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Control | Post-leukapheresis | *P* | Control | Post-leukapheresis | *P* | Control | Post-leukapheresis | *P* |
| SDNN (ms) | 92 (74–110) | 75 (65–82) | 0.002* | 96 (82–110) | 69 (60–86) | 0.002* | 86 (74–103) | 75 (60–91) | 0.01* |
| r-MSSD (ms) | 26 (15–37) | 23 (13–31) | 0.002* | 30 (24–37) | 19 (12–34) | 0.001* | 33 (22–42) | 28 (15–42) | 0.34 |
| TF ($ms^2$) | 5996 (3861–10229) | 4291 (2925–5188) | 0.02* | 5723 (3408–8008) | 3772 (2760–6092) | 0.04* | 4909 (3647–7392) | 3097 (2556–5145) | 0.01* |
| HF ($ms^2$) | 157 (44–266) | 107 (27–196) | 0.02* | 215 (83–300) | 74 (28–235) | 0.002* | 277 (120–430) | 180 (46–417) | 0.22 |
| LF ($ms^2$) | 489 (382–751) | 471 (136–685) | 0.04* | 523 (340–846) | 287 (160–605) | 0.0008* | 688 (387–879) | 337 (190–579) | 0.0004* |
| LF/HF | 3.6 (2.9–5.1) | 4.0 (3.3–5.8) | 0.27 | 2.9 (2.3–4.5) | 3.1 (2.1–7.3) | 0.10 | 2.6 (1.5–5.5) | 2.3 (1.1–3.6) | 0.15 |

*IQR* interquartile range, *SDNN* standard deviation of normal-to-normal intervals, *r-MSSD* square root of mean of sum of squared differences between adjacent normal-to-normal intervals, *TF* total frequency, *HF* high frequency, *LF* low frequency

* $P < 0.05$

(Table 1). The altered concentration of electrolytes in serum, mediated by ACD solution or hypovolemia, which remained long after leukapheresis, might cause symptomatic hypotension and reduce HRV. Such pathologic conditions might, in extremely rare instances, lead to severe cardiovascular complications in a patient with latent cardiovascular diseases.

In the 3 subjects with symptomatic hypotension, tachycardia was not observed at the onset of hypotension (Subject 1: 82/46 mmHg, 72 beats/min; Subject 2: 72/42 mmHg, 66 beats/min; Subject 3: 76/48 mmHg, 60 beats/min). Vasovagal hypotension, which occasionally occurs during leukapheresis, is a neurally mediated reaction due to blood pressure decreases without compensatory tachycardia. In patients with vasovagal hypotension, bradycardia is therefore often observed. We therefore speculate that vasovagal reflex played a critical role in the development of symptomatic hypotension in these subjects.

Finally, some HRV indicators in the autologous transplant patients were significantly lower than those in healthy donors. In the present study, ages were higher and Hb levels before leukapheresis were lower in autologous transplant patients than in the healthy donors. Furthermore, all patients scheduled to receive an autologous transplant had a history of chemotherapy. Chemotherapy including anthracycline has been reported to reduce the values of HRV indicators [25]. Therefore, decreased values of some HRV indicators might have been caused by advanced age, anemia and/or the cumulative toxicity of chemotherapy, especially that caused by anthracycline drugs.

The major obstacle which precludes translating HRV analysis into clinical practice is that we can analyze HRV during leukapheresis only retrospectively. However, our data suggest that HRV prior to leukapheresis might have potential as a useful non-invasive tool for predicting autonomic or cardiovascular complications. Therefore, in the future, we need to examine the prognostic value of HRV for autonomic or cardiovascular complications in more detail by using a larger cohort.

**Acknowledgments** This work was supported by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Science, Sports and Culture, and a grant from the Japanese Ministry of Health, Welfare and Labor.

**Conflict of interest statement** All the authors declare no conflict of interest.

## References

1. Miller JP, Perry EH, Price TH, Bolan CD Jr, Karanes C, Boyd TM, et al. Recovery and safety profiles of marrow and PBSC donors: experience of the National Marrow Donor Program. Biol Blood Marrow Transplant. 2008;14:29–36.



Journal : Large 12185 | Dispatch : 23-2-2010 | Pages : 7
Article No. : 543 | LE | TYPESET
MS Code : IJHM-D-09-00514 | CP | DISK

2. Anderlini P, Korbling M, Dale D, Gratwohl A, Schmitz N, Stroncek D, et al. Allogeneic blood stem cell transplantation: considerations for donors. Blood. 1997;90:903–8.
3. Confer DL, Stroncek DF. Bone marrow and peripheral blood stem cells donors. In: Thomas ED, Blume KG, Forman SJ, editors. Hematopoietic cell transplantation. Massachusetts: Blackwell Science Inc.; 1998. p. 421–30.
4. Becker PS, Wagle M, Matous S, Swanson RS, Pihan G, Lowry PA, et al. Spontaneous splenic rupture following administration of granulocyte colony-stimulating factor (G-CSF): occurrence in an allogeneic donor of peripheral blood stem cells. Biol Blood Marrow Transplant. 1997;3:45–9.
5. Falzetti F, Aversa F, Minelli O, Tabilio A. Spontaneous rupture of spleen during peripheral blood stem-cell mobilisation in a healthy donor. Lancet. 1999;353:555.
6. Pozzati A, Pancaldi LG, Di Pasquale G, Pinelli G, Bugiardini R. Transient sympathovagal imbalance triggers "ischemic" sudden death in patients undergoing electrocardiographic Holter monitoring. J Am Coll Cardiol. 1996;27:847–52.
7. Hayashi H, Fujiki A, Tani M, Mizumaki K, Shimono M, Inoue H. Role of sympathovagal balance in the initiation of idiopathic ventricular tachycardia originating from right ventricular outflow tract. Pacing Clin Electrophysiol. 1997;20:2371–7.
8. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation. 1992;85:164–71.
9. Guzzetti S, Cogliati C, Turiel M, Crema C, Lombardi F, Malliani A. Sympathetic predominance followed by functional denervation in the progression of chronic heart failure. Eur Heart J. 1995;16:1100–7.
10. Furlan R, Piazza S, Dell'Orto S, Barbic F, Bianchi A, Mainardi L, et al. Cardiac autonomic patterns preceding occasional vasovagal reactions in healthy humans. Circulation. 1998;98:1756–61.
11. Ajiki K, Murakawa Y, Yanagisawa-Miwa A, Usui M, Yamashita T, Oikawa N, et al. Autonomic nervous system activity in idiopathic dilated cardiomyopathy and in hypertrophic cardiomyopathy. Am J Cardiol. 1993;71:1316–20.
12. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. Circulation. 1998;98:1071–7.
13. Bernardi L, Ricordi L, Lazzari P, Solda P, Calciati A, Ferrari MR, et al. Impaired circadian modulation of sympathovagal activity in diabetes. A possible explanation for altered temporal onset of cardiovascular disease. Circulation. 1992;86:1443–52.
14. Guzzetti S, Cogliati C, Broggi C, Carozzi C, Caldiroli D, Lombardi F, et al. Influences of neural mechanisms on heart period and arterial pressure variabilities in quadriplegic patients. Am J Physiol. 1994;266:H1112–20.
15. Malliani A, Montano N. Heart rate variability as a clinical tool. Ital Heart J. 2002;3:439–45.
16. Aronson D, Mittleman MA, Burger AJ. Measures of heart period variability as predictors of mortality in hospitalized patients with decompensated congestive heart failure. Am J Cardiol. 2004;93:59–63.
17. Perseghin P, Confalonieri G, Buscemi F, Dassi M, Pogliani E, Pioltelli P, et al. Electrolyte monitoring in patients undergoing peripheral blood stem cell collection. J Clin Apher. 1999;14:14–7.
18. Binkley PF, Nunziata E, Haas GJ, Nelson SD, Cody RJ. Parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure: demonstration in human subjects and verification in a paced canine model of ventricular failure. J Am Coll Cardiol. 1991;18:464–72.
19. Ponikowski P, Anker SD, Chua TP, Szelemej R, Piepoli M, Adamopoulos S, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1997;79:1645–50.
20. La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation. 2003;107:565–70.
21. Ori Z, Monir G, Weiss J, Sayhouni X, Singer DH. Heart rate variability. Frequency domain analysis. Cardiol Clin. 1992;10:499–537.
22. Callan MB, Appleman EH, Shofer FS, Mason NJ, Brainard BM, Groman RP. Clinical and clinicopathologic effects of plateletpheresis on healthy donor dogs. Transfusion. 2008;48:2214–21.
23. Drop LJ, Scheidegger D. Haemodynamic consequences of citrate infusion in the anaesthetized dog: comparison between two citrate solutions and the influence of beta blockade. Br J Anaesth. 1979;51:513–21.
24. Hagay ZJ, Mazor M, Leiberman JR, Piura B. The effect of maternal hypocalcemia on fetal heart rate baseline variability. Acta Obstet Gynecol Scand. 1986;65:513–5.
25. Postma A, Elzenga NJ, Haaksma J, Schasfoort-Van Leeuwen MJ, Kamps WA, et al. Cardiac status in bone tumor survivors up to nearly 19 years after treatment with doxorubicin: a longitudinal study. Med Pediatr Oncol. 2002;39:86–92.




Journal : Large 12185 | Dispatch : 23-2-2010 | Pages : 7
Article No. : 543 | LE | TYPESET
MS Code : IJHM-D-09-00514 | CP | DISK

Ann Hematol (2009) 88:581–588
DOI 10.1007/s00277-008-0641-2

ORIGINAL ARTICLE

# Myeloablative unrelated cord blood transplantation for acute leukemia patients between 50 and 55 years of age: single institutional retrospective comparison with patients younger than 50 years of age

**Takaaki Konuma · Satoshi Takahashi · Jun Ooi · Akira Tomonari · Nobuhiro Tsukada · Seiko Kato · Aki Sato · Fumihiko Monma · Senji Kasahara · Tokiko Nagamura-Inoue · Kaoru Uchimaru · Tohru Iseki · Arinobu Tojo · Takuhiro Yamaguchi · Shigetaka Asano**

Received: 20 May 2008 / Accepted: 4 November 2008 / Published online: 22 November 2008


**Abstract** Increasing recipient age is a well-known risk factor for graft-versus-host disease (GVHD) and treatment-related mortality (TRM) and has a negative impact on allogeneic hematopoietic stem cell transplantation. Since the incidence of severe GVHD after cord blood transplantation (CBT) is lower than that after transplants using bone marrow or mobilized peripheral blood grafts from adult cells, we should expect better outcomes from CBT in older patients. To evaluate the feasibility and efficacy of myeloablative unrelated CBT in patients aged between 50 and 55 years, we performed a retrospective comparison of 100 patients with acute leukemia who received cord blood grafts at our institution. Nineteen older patients (median age, 52; range, 50–55) and 81 younger patients (median, 36; range, 16–49) received a myeloablative conditioning regimen including 12 Gy of total body irradiation and chemotherapy. GVHD prophylaxis included cyclosporine with ($n$=96) or without ($n$=4) methotrexate. There were no significant differences in the incidences of grades II to IV acute GVHD, extensive-type chronic GVHD, TRM, and the probability of overall and disease-free survival between these groups. These results suggest that, in patients with acute leukemia, myeloablative CBT might be as safe and effective in patients aged between 50 and 55 years as in younger patients.

**Keywords** Cord blood transplantation · Older patient · Myeloablative conditioning · Acute leukemia

T. Konuma · S. Takahashi (✉) · J. Ooi · A. Tomonari · N. Tsukada · S. Kato · A. Sato · F. Monma · S. Kasahara · K. Uchimaru · T. Iseki · A. Tojo · S. Asano
Department of Hematology/Oncology,
The Institute of Medical Science, The University of Tokyo,
4-6-1, Shirokanedai, Minato-ku,
Tokyo 108-8639, Japan
e-mail: radius@ims.u-tokyo.ac.jp

T. Nagamura-Inoue
Department of Transfusion Medicine,
The Institute of Medical Science, The University of Tokyo,
Tokyo, Japan

T. Yamaguchi
Department of Clinical Trial Data Management,
The University of Tokyo,
Tokyo, Japan

## Introduction

Older recipient age has been reported to be associated with an increased incidence of morbidity and mortality following allogeneic hematopoietic stem cell transplantation (HSCT) after myeloablative conditioning [1–5]. Increasing recipient age is a well-known risk factor for severe graft-versus-host disease (GVHD) and treatment-related mortality (TRM) [1–7]. Moreover, older recipients generally receive transplants from older donors in the setting of allogeneic HSCT from related donors, and this might be associated with the increased risk of severe GVHD [8, 9].