Table 1 Baseline data of each country/region

Country/region	*Population (× 1000)* [a]	*Category of income* [b]	*Donor program*	*CB bank*	*First HSCT in this study*
China	1 330 000	Lower middle	Yes	Yes	1987
Hong Kong	7019	High	Yes	Yes	1990
Iran	65 875	Lower middle	Yes	Yes	1991
Japan	127 288	High	Yes	Yes	Before 1986
Korea	48 379	High	Yes	Yes	Before 1986
Malaysia	25 274	Upper middle	Yes	Yes	1987
Singapore	4608	High	Yes	Yes	Before 1986
Taiwan	22 921	Lower middle	Yes	Yes	Before 1986
Vietnam	86 117	Low	No	Yes	1995
Total	1 717 481				

[a]Data obtained from the US census office (http://www.census.gov), updated June 2008.
[b]The World Bank's definition (http://www.worldbank.org).

and Vietnam) were collected according to each disease indication, donor type and stem cell source, using a simple survey sheet. The data were submitted to the APBMT data center through the national/regional registries in Japan, Korea, Malaysia and Taiwan. In Japan, the data were collected by paper forms or using a new electronic registration system, *TRUMP* (Transplant Registry Unified Management Program), as previously reported.[3,22] In Hong Kong, Iran, Singapore and Vietnam, the APBMT data center contacted the major transplant centers in each country/region. It was estimated by each APBMT regional coordinator that 80–100% of all transplants performed between 1986 and 2006 were captured in each country/region except for mainland China. In mainland China, where there are more than 50 transplant centers,[5] data from only 12 centers could be collected. The information on population and the World Bank's income category based on the Gross National Income per capita were collected from the following websites (http://www.census.gov and http://www.worldbank.org, respectively). According to the criteria set by the World Bank, each country's economic status was classified as low income, middle income (subdivided into lower middle and upper middle) or high income (Table 1). The list of the participating centers is shown in the Appendix according to the countries/regions.

Results

Number of transplants

Transplant data of 58 113 HSCTs from 432 teams in nine countries/regions were submitted to the APBMT Data Center. The number of participating transplant teams, the reported numbers of HSCTs between 1986 and 2006 and the reported numbers of performed HSCTs in 2006 are shown in Table 2. The information on population, the World Bank's income category and the availability of donor programs and cord blood (CB) banks in each country/region are also shown in Table 1. The largest number of transplants was performed in Japan with a total of 38 523 transplants, followed by Korea with 9570.

Allogeneic vs autologous HSCTs

The total reported number of HSCTs in the study period is increasing in all countries/regions, except for Vietnam. As shown in Table 2, the number of HSCTs performed per 10 million people was higher in the countries/regions with higher incomes (Japan, Korea, Singapore and Hong Kong) than in those with middle/low incomes. The number of HSCTs performed in the nine countries/regions in 2006 was 6418, which has doubled in the past 10 years ($n = 2734$ in 1996). The number of allogeneic HSCT has been consistently increasing in this study period, but the increase in autologous HSCT has slowed down since 1998 (Figure 1a). Of 6418 HSCTs performed in 2006, 3992 (62%) were allogeneic and 2416 (38%) were autologous. In most countries/regions, the number of allogeneic HSCT was larger than autologous HSCT (Figure 1b).

Related vs unrelated donors

As shown in Figure 1a, the total number of HSCTs from unrelated donors in the nine countries/regions has been increasing in the study period and exceeded the number of HSCTs from related donors in 2006. The number of related HSCTs has stabilized since 2002. However, the proportion of related and unrelated HSCTs differed among countries/regions. Recently, the number of unrelated HSCTs was higher than or equal to that of related HSCTs in Japan, Korea and Singapore (Figure 1b). In other countries/regions the proportion of related HSCTs was higher. In Iran and Vietnam, only a few unrelated HSCTs were performed.

Trends of HSCTs in each country/region

The trends of autologous and allogeneic HSCTs in each country/region are shown in Figure 2. Autologous transplant was increasing in all Asian countries (Figure 2a). An increase in the number of related HSCTs has been observed in China and Iran since 2000, although it was only recently stabilized in other countries (Figure 2b). Unrelated HSCTs were increasing in most of the countries except for Iran and Vietnam in the study period (Figure 2c).

Table 2 Numbers of institutes and transplants in each country/region

Country/region	*Institutes*		*No. of reported HSCTs*				
	No.	*Per 100 million population*	*2006*	*Per 10 million population*	*Ratio of 2006/1996*	*Total from 1986 to 2006*	*Median no. of HSCTs/year*
China	12	1[a]	352	3[a]	9.8	2220	39.5
Hong Kong	3	43	142	202	1.7	1684	100
Iran	2	3	325	49	10.2	1699	45.5
Japan	355	279	3834	301	1.9	38 523	1992
Korea	37	76	1338	277	3.4	9570	388
Malaysia	9	36	124	49	4.4	1174	31.5
Singapore	3	65	73	158	1.6	839	42
Taiwan	9	39	225	98	1.8	2351	114
Vietnam	2	2	5	1	—	53	4
Total	432	25 (108)[b]	6418	37 (157)[b]	2.3	58 113	

Abbreviations: HSCT = hematopoietic SCT; NE = not evaluable.
[a]Among more than 50 institutes in China, data from 12 institutes were included in this study.
[b]Numbers in parentheses are those excluding China.

Stem cell source

The stem cell source of autologous HSCT has changed from BM to PBSC, and 95% of autologous HSCTs were PBSC transplantations (PBSCTs) in 2006. For related HSCT, a shift of stem cell source from BM to PBSC was also observed, and the number of PBSCTs has exceeded that of BMTs since 2001 (Figure 3a). In 2006, the number of PBSCTs was higher than that of BMTs in most countries/regions, except for China, Hong Kong and Japan (Figure 3b). In China, transplants of both BM and PBSC from a haplo-identical familial donor, which was designated as other stem cell source in this survey, were recently performed in large numbers.[23] In Hong Kong and Japan, the numbers of BMTs and PBSCTs were almost equal in 2006.

For unrelated HSCTs, all types of stem cell sources (BM, PBSC and CB) have been continuously increasing in the study period (Figure 3a). In 2006, the annual number of unrelated BMTs, unrelated PBSCTs and cord blood transplantations (CBTs) were 1087, 229 and 701, respectively. However, as shown in Figure 3b, the proportion of each stem cell source varied among countries/regions. In China and Taiwan, a large proportion of the unrelated HSCTs performed were PBSCTs. In contrast, almost no unrelated PBSCTs were performed in Japan. In Iran and Vietnam, where only a few unrelated HSCTs have been performed, all unrelated HSCTs were CBTs. The recent increase in CBT was most prominent in Japan, where 593 CBTs were performed in 2006.

Disease indication

The diseases requiring HSCTs in each country/region between 1986 and 2006 are depicted in Figure 4. The most common indication for HSCT was hematological malignancy in all countries/regions (72–94% of all HSCTs). The proportions of solid tumors ranged between 0% in Vietnam to 11% in Japan. Among non-malignant diseases, hemoglobinopathy was one of the most common diseases in Asian countries/regions, except for China, Korea and Japan, where no or very few transplants for this disorder were reported.

The number of HSCTs for most types of hematological malignancies, including acute myeloid leukemia, acute lymphoblastic leukemia and malignant lymphoma, has been increasing in most Asian countries/regions in the study period. However, CML showed a different trend (Figure 5). The number of transplants for CML has decreased since 2000, excluding China and Iran. The proportion of CML out of the total HSCTs was almost stable in Iran and Malaysia from 10 to 20%. The ratio was decreasing in Hong Kong, Japan, Korea, Singapore and Taiwan. HSCTs for solid tumors also showed a unique trend. In Japan, the number had been increasing until 1998 ($n = 169$ in 1998) and then it decreased ($n = 41$ in 2006).[24] In Korea, it also decreased after 1999. In other countries/regions, the number of HSCTs for solid tumors was low and stable.

Discussion

This survey showed that the number of HSCTs performed has been increasing in most Asian countries/regions over the past two decades, although several differences exist in donor selection, transplant procedures and disease indications among countries/regions. HSCT is expensive for all countries. The significant effect of the economic strength of individual countries on HSCT activity was reported by Gratwohl *et al.*[25] Our results are consistent with their findings. The most significant increases in the past 10 years were observed in Iran and China, which have middle incomes. Even in countries/regions of the high-income group (Hong Kong, Japan, Korea and Singapore) the number of HSCTs performed has been consistently increasing in the study period and is not likely to reach a plateau any time soon. This suggests that the demand for HSCTs has not been fulfilled in any of these countries. The improving likelihood of finding an HLA matched donor because of expanding donor pools; the development of reduced-intensity conditioning regimens, which has broadened the indication of HSCT to older patients; and the increased list of disease

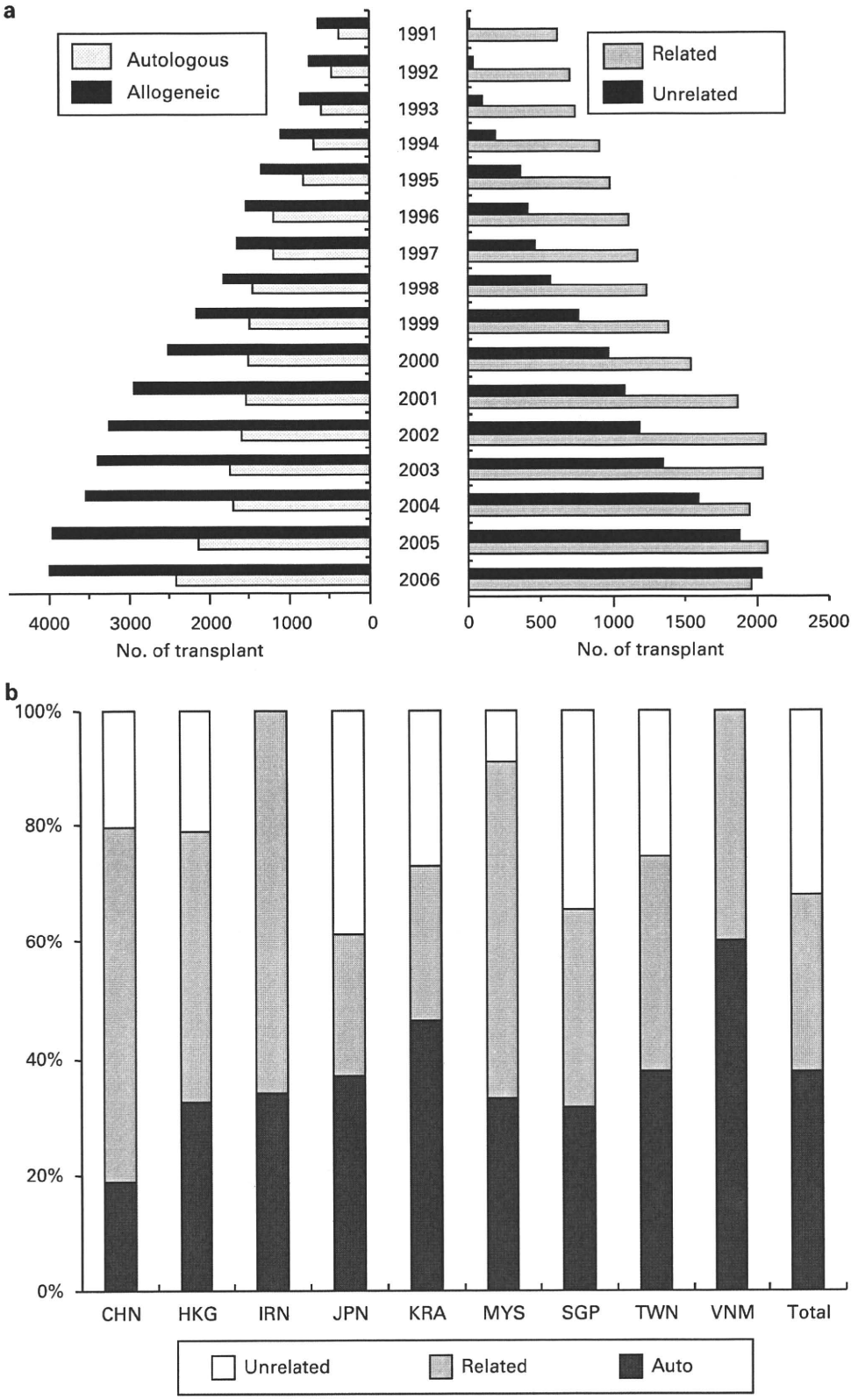

Figure 1 Activity of hematopoietic SCT (HSCT) in nine Asian countries/regions. (**a**) Trends of the total numbers of autologous HSCTs and allogeneic HSCTs from related and unrelated donors in nine countries/regions are shown. (**b**) The proportions of autologous and allogeneic HSCTs from related and unrelated donors in 2006 in each country/region are shown. CHN, mainland China; HKG, Hong Kong; IRN, Iran; JPN, Japan; KRA, Korea; SGP, Singapore; TWN, Taiwan; VNM, Vietnam.

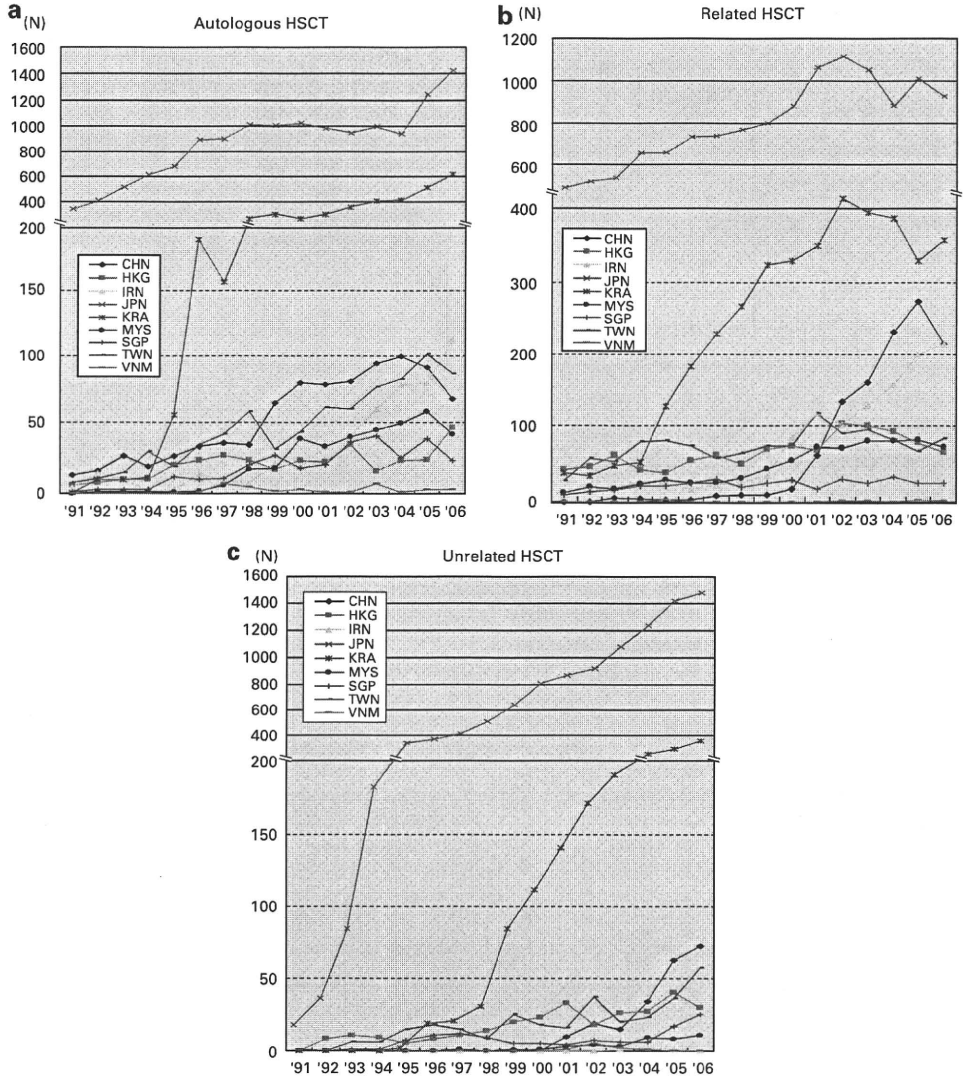

Figure 2 Trends of hematopoietic SCT (HSCT). Numbers of autologous (**a**) and allogeneic HSCTs from related (**b**) and unrelated donors (**c**) in each year are plotted. See legend to Figure 1 for abbreviations.

indications for HSCT may lead to further increases in the numbers of HSCTs performed.

The high proportion of allogeneic HSCTs compared with autologous HSCTs in most Asian countries/regions (62% in 2006) was in contrast to a report from Europe (39% in 2006).[26] However, our results need careful interpretation because of possible reporting bias. The capture rate of autologous HSCTs might be lower than that of allogeneic HSCTs, because some smaller centers, which perform only autologous HSCTs, could not be sufficiently included in this survey.

A notable finding in this study was that there were marked differences in donor and stem cell selections among Asian countries/regions. First of all, the proportion of unrelated HSCTs among allogeneic HSCTs was quite different (62% to <1%). In most of the countries/regions, except for Iran and Vietnam, the number of unrelated HSCTs has been increasing in the study period. This might partially depend on the size of donor pools and the activity of each donor program. A dramatic increase in the number of unrelated HSCTs performed in China was observed after the China Marrow Donor Program started servicing the public in 2001, resulting in the rapid expansion of the donor pool, which is currently the largest among the nine Asian countries/regions (more than 0.7 million donors).[5] Unrelated HSCT activity is associated with economic strength.[27] Because of the cost of searching for donors, coordination and shipment of the product, unrelated HSCT is more expensive than related HSCT. In this report, the number of unrelated HSCTs was higher in countries with higher incomes, which is consistent with a report from Europe.[27] The high use of unrelated HSCTs in Japan was, in part, dependent on the limited HLA diversity of Japanese population because of the historical isolation of island country, and low incidence of GVHD.[28]

Another interesting finding in this study is the difference of stem cell source for both unrelated and related HSCTs. For related HSCTs in 2006, the proportion of PBSCTs was higher than that of BMTs in many countries/regions, which was consistent with reports from Europe.[4,26] However,

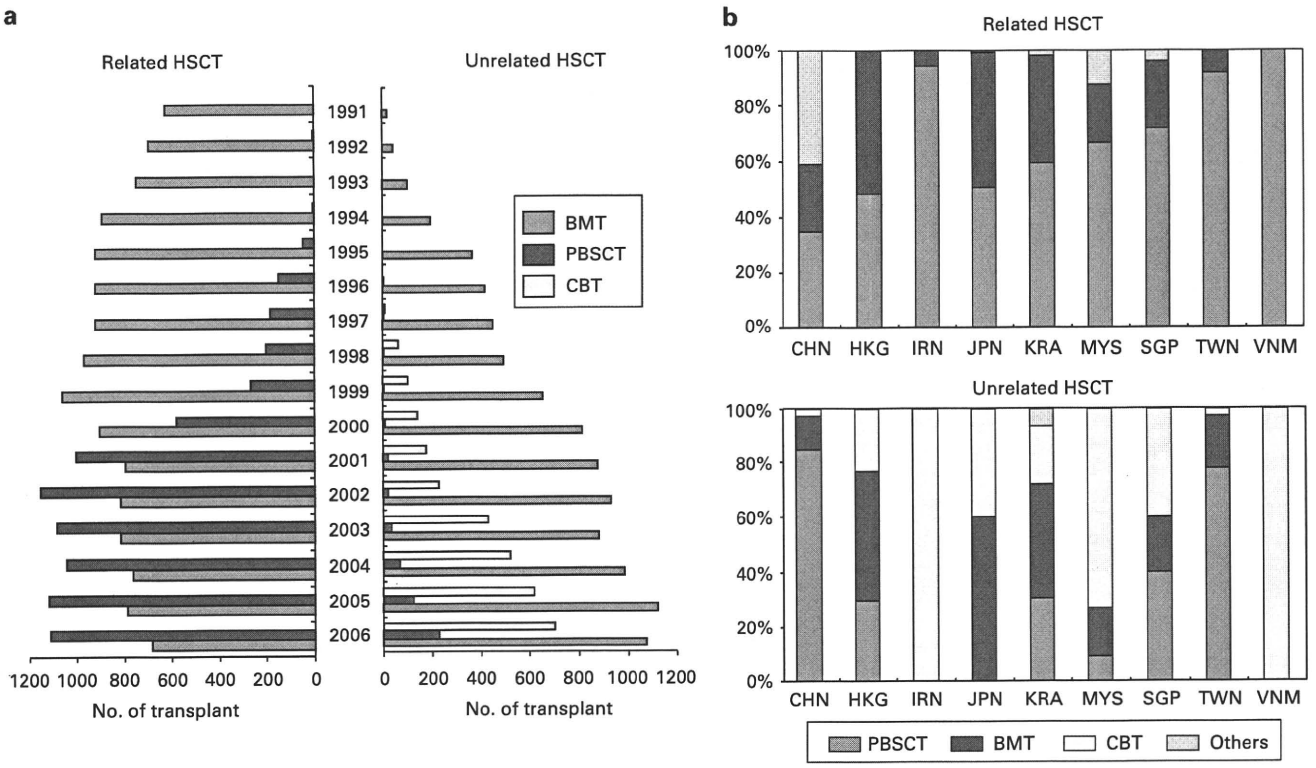

Figure 3 Stem cell sources of hematopoietic SCT (HSCT). (**a**) Trends of the total number of stem cell sources for allogeneic HSCTs from related and unrelated donors in nine Asian countries/regions. CBT, cord blood transplantation. (**b**) The proportion of each stem cell source for allogeneic HSCT from related and unrelated donors in 2006 in each country/region. The data from Iran and Vietnam for allogeneic HSCTs from unrelated donors indicate all transplants between 1986 and 2006 because of the low numbers of HSCTs from unrelated donors in these two countries. See legend to Figure 1 for abbreviations.

China showed the unique use of transplants involving combined BM and PBSC from haplo-identical donors, which made up a large proportion of the related HSCTs.[5,23] This procedure was intensively studied because of the decreasing family size in China.[5] The stem cell source of unrelated HSCTs largely depended on the policy of the donor program of each country. The Japan Marrow Donor Program provided only BM, but the China Marrow Donor Program provided only PBSCs. It is noteworthy that CBT made up 35% of unrelated HSCTs in 2006, which was larger than that reported by the European Group for Blood and Marrow Transplantation (EBMT).[27] CB banks have been established, and unrelated CBT has been performed in all countries/regions. CB seems to be an important stem cell source in Asian countries/regions.

There was a marked difference in disease indications for HSCTs among APBMT countries/regions. Disease prevalence might be one of the factors that influence the activity of HSCT. Thalassemia is common in South and Southeast Asia, but rare in Northeast Asia. A high proportion of HSCTs for this disorder was noted in the former region. The numbers of HSCTs performed for most diseases are increasing in the study period, but those for CML and solid tumors were exceptions. Gratwohl *et al.*[29] also reported marked differences in the trends of HSCTs for CML among European countries, reflecting the economic strength of each country. The dramatic decrease of HSCTs for CML since 1999 after the introduction of imatinib, which was observed in Asian countries/regions with high incomes and some with middle incomes, was similar to the phenomenon observed in European countries with high incomes.[29] Interestingly, a marked increase in the number of HSCTs for CML has been observed even after 2004 in mainland China and Iran. Imatinib is an expensive agent, which needs to be given to patients for a long period. The consideration of cost effectiveness between these two highly expensive treatments, imatinib and HSCT, by health-care providers in each country may have a great effect on the trends among countries/regions.[30] The number of HSCTs for solid tumors has remained low in most Asian countries/regions. In Japan, there was an increase in the number of autologous HSCTs performed for solid tumors, especially for breast cancer, in the 1990s because of expectations of its positive effectiveness on the outcome of patients. However, the disappointing results of several randomized clinical trials called into question its benefits and resulted in decreases in the number of HSCTs performed for breast cancer as well as other solid tumors.[31–34] This trend is similar to that observed in European countries.[35]

Although this simple survey was able to provide reasonably comprehensive information about the current state of HSCT in Asia, further efforts should be made to establish a registry system to obtain information from all centers and Asian countries/regions that are missing from this study. It is also important to be aware that there are some countries where very few HSCTs are currently performed because of several factors, such as financial restrictions, lack of a

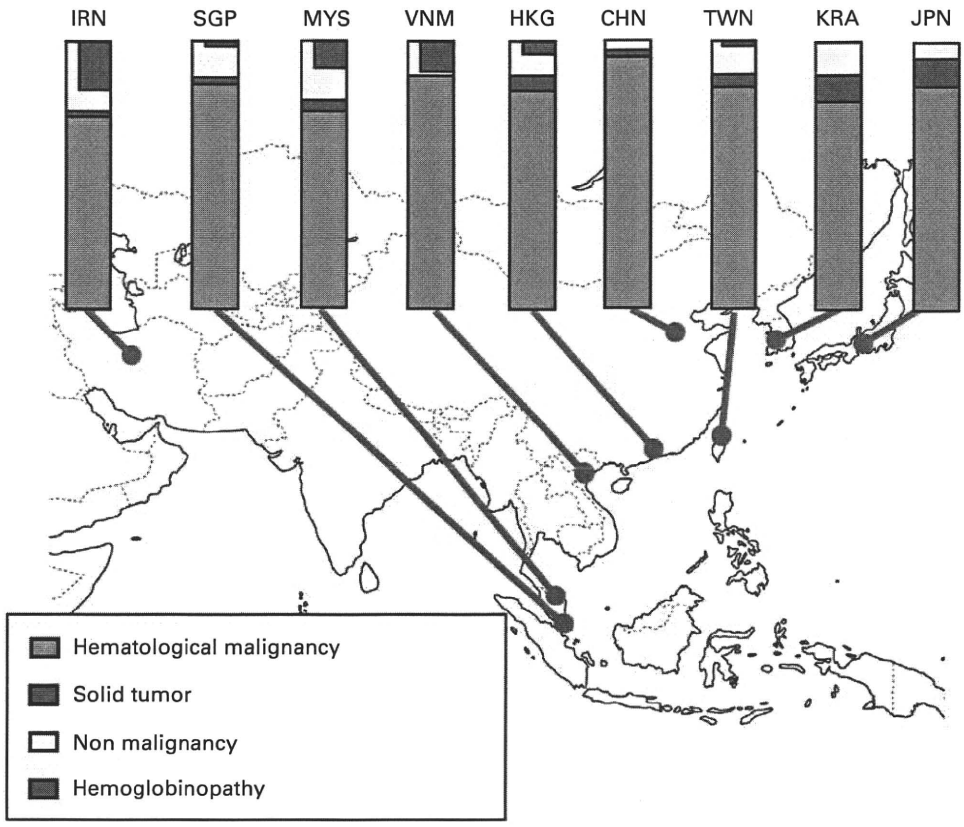

Figure 4 Disease indications of hematopoietic SCT (HSCT). Proportions of each category of disease indication in each country/region are shown.

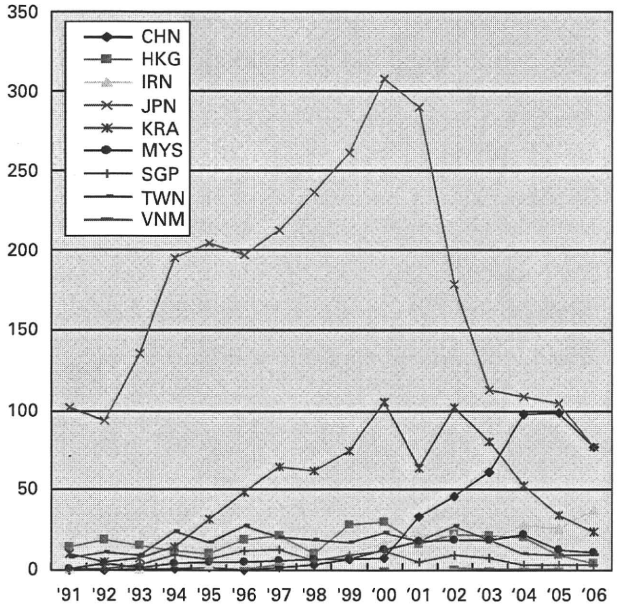

Figure 5 Trends of HSCTs for chronic myelogenous leukemia (CML) in each country/region. The number of transplants for CML has decreased since 2000, excluding China and Iran. See legend to Figure 1 for abbreviations.

national health insurance system and governmental support and an inability to develop local transplant centers.[7,11]

A similar survey has been annually reported by the EBMT since 1990 to illustrate the trends of HSCT in European countries in an elegant way.[4,25–27,29,35–37] Although this study elucidated several differences, such as the proportion of allogeneic and autologous HSCTs between Europe and Asia, there were many similarities in the trends of HSCTs in both regions. This suggests that similar clinical decisions have been made globally in the practice of HSCT, probably because of the rapid spread of information about the technology and the outcome of HSCT. A global transplant activity survey has been recently planned by the EBMT, the Centre for International Blood and Marrow Transplant Research and the APBMT, among others, under the umbrella of the Worldwide Network of BMT (http://wbmt.org), which may clarify the global trends of HSCT and provide fundamental information to facilitate international cooperative studies for further improvement of this treatment procedure.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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Appendix

Regional coordinators and the contributing centers are listed according to their countries/regions.

China (mainland)
Coordinator: Dao Pei Lu
Centers: Nanjing Drum Tower Hospital, The Third Affiliated Hospital Sun Yat-sen University, Peking University First Hospital, Jiangsu Institute of Hematology: The First Affiliated Hospital of Soochow University, Xinqiao Hospital, Union Hospital Fujian Medical University, Union Hospital Tongji Medical College of Huazhong University of Science and Technology, Harbin Hematology and Oncology Research Institution, Cancer Hospital Chinese Academy of Medical Science, Beijing Daopei Hospital, Nanfang Hospital Southern Medical University, The Military General Hospital of Beijing.

Hong Kong
Coordinator: Albert KW Lie
Centers: Queen Mary Hospital, The University of Hong Kong, Prince of Wales Hospital, The Chinese University of Hong Kong.

Iran
Coordinator: Ardeshir Ghavamzadeh
Centers: Teheran University of Medical Science: Transplant Research Center, Shiraz University of Medical Sciences.

Japan (National Registry)
Coordinators: Ayami Yoshimi, Yoshiko Atsuta, Ritsuro Suzuki, and Yoshihisa Kodera, supported by the Japan Society for Hematopoietic Cell Transplantation, the Japan Society of Pediatric Hematology, Japan Marrow Donor Program, and Japan Cord Blood Bank Network
Centers: National Hospital Organization Nishigunma National Hospital, Aichi Cancer Center Hospital, Aichi Medical University Hospital, Aiseikai Yamashina Hospital, Akashi Municipal Hospital, Akita University School of Medicine, Anjo Kosei Hospital, Aomori Prefectural Central Hospital, Asahikawa City Hospital 1, Asahikawa Medical College Hospital, Asahikawa Red Cross Hospital, Chiba Aoba Municipal Hospital, Chiba Children's Hospital, Chiba University Hospital, Children's Medical Center, Osaka City General Hospital, Chugoku Rosai General Hospital, Dokkyo Medical University School of Medicine, Ehime Prefectural Central Hospital, Ehime University Graduate School of Medicine, Faculty of Medicine Hospital Tokyo Medical and Dental University, Faculty of Medicine, Saga University, Faculty of Medicine, Kagawa University, Fuchu Hospital, Fujita Health University School of Medicine, Fukaya Red Cross Hospital, Fukuoka University School of Medicine, Fukushima Medical University School of Medicine, Gifu Municipal Hospital, Gifu University Graduate School of Medicine, Gunma Children's Medical Center, Gunma University Graduate School of Medicine, Hakodate Municipal Hospital, Hamamatsu Medical Center, Hamamatsu University School of Medicine, Hamanomachi Hospital, Higashi Sapporo Hospital, Hirosaki University Hospital, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima University Hospital, Hirosima-Nishi Medical Center, Hitachi General Hospital, Hokkaido Medical Center for Child Health and Rehabilitation, Hokkaido University Hospital, Hyogo Cancer Center, Hyogo Children's Hospital, Hyogo College of Medicine, Ibaraki Children's Hospital, Iizuka Hospital, Imamura Bun-in Hospital, International Medical Center of Japan, Ishikawa Prefectural Central Hospital, Iwaki Kyoritsu General Hospital, Iwate Medical University, Iwate Medical University School of Medicine, Iwate Prefectural Kitakami Hospital, Japanese Red Cross Nagasaki Genbaku Hospital, Japanese Red Cross Nagoya First Hospital, Japanese Red Cross Narita Hospital, Japanese Red Cross Society Wakayama Medical Center, Japanese Red Cross Medical Center, Jichi Medical University Hospital, Jikei University school of Medicine, Jikei University Kashiwa Hospital, Juntendo University School of Medicine, Kagawa National Children's Hospital, Kagawa University, Kagoshima City Hospital, Kagoshima University Medical and Dental Hospital, Kameda General Hospital, Kanagawa Cancer Center, Kanagawa Children's Medical Center, Kanazawa Medical University, Kanazawa University Hospital, Kansai Medical University, Kansai Medical University Hirakata Hospital, Kawasaki Medical School, Keio University School of Medicine, Kin-ikyo Sapporo Hospital, Kinki University School of Medicine, Kishiwada City Hospital, Kita-Fukushima Medical Center, KKR Suifu Hospital, Kobe Central Hospital of Insurance, Kobe City Medical Center General Hospital, Kobe University Graduate School of Medicine, Kochi Health Sciences Center, Kochi Medical School, Kochi University, Kochi University, Kokura Memorial Hospital, Komaki City Hospital, Konan Kosei Hospital, Kouseiren Takaoka Hospital, Kumamoto University School of Medicine, Kurashiki Central Hospital, Kurobe City Hospital, Kurume University School of Medicine, Kyorin University School of Medicine, Kyoto City Hospital, Kyoto First Red Cross Hospital, Kyoto Katsura Hospital, Kyoto Prefectural University of Medicine, Kyoto University Hospital, Kyushu Kosei-Nenkin Hospital, Kyushu University Hospital, Kyushu University Hospital at Beppu, Maebashi Red Cross Hospital, Matsudo City Hospital, Matsushita Memorial Hospital, Matsuyama Red Cross Hospital, Matsuzaka General Hospital, Meitetsu Hospital, Mie University Hospital, Mitoyo General Hospital, Miyagi Cancer Center, Miyagi Children's Hospital, Miyazaki prefectural Miyazaki Hospital, Nagano Children's Hospital, Nagano Red Cross Hospital, Nagaoka Red Cross Hospital, Nagasaki University Graduate School of Biomedical Sciences, Nagoya City University Hospital, Nagoya Daini Red Cross Hospital, Nagoya University Graduate School of Medicine, Nagoya Memorial Hospital, Nakadoori General Hospital, Nara Medical University, National Cancer Center Hospital, National Cancer Center Hospital East, National Center for Child Health and Development, National Defense Medical College Hospital, National Hospital Organization Kyusyu Medical Center, National Hospital Organization Okayama Medical Center, National Hospital Organization Hokkaido Cancer Center, National Hospital Organization Kure Medical Center, National Hospital Organization Mito Medical Center, National Hospital Organization Okayama Medical Center, National Hospital Organization Osaka Minami Medical Center, National Hospital Organization Osaka National Hospital, National Hospital Organization Tokyo Medical Center, National Hospital Organization, Kagoshima Medical Center, National Hospital Organization Nagoya Medical Center, National Hospital Organization Shikoku Cancer Center, National Hospital Organization Kumamoto Medical Center, National Hospital Organization Minami-Okayama Medical Center, National Hospital Organization Nagasaki Medical Center, National Kyushu Cancer Center, Nihon University Itabashi Hospital, Niigata Cancer Center, Niigata University Medical and Dental Hospital, Nippon Medical School, NTT Kanto Medical Center, NTT West Osaka Hospital, Oita Prefectural Hospital, Oita University Faculty of Medicine, Oita University Hospital, Oita Kouseiren Tsurumi Hospital, Okayama Rosai Hospital, Okayama University Hospital, Okazaki City Hospital, Okinawa Prefectural Nanbu Medical Center and Children's Medical Center, Osaka City General Hospital, Osaka City

University Graduate School of Medicine, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka Medical Center For Cancer and Cardiovascular Diseases, Osaka Medical College Hospital, Osaka Red Cross Hospital, Osaka University Hospital, Our Lady of Snow Medical Juridical Corporation St Mary's Hospital, The Institute of Medical Science: The University of Tokyo, Rinku General Medical Center Izumisano Municipal Hospital, Ryukyu University Hospital, Saga Prefectural Hospital Koseikan, Saga University, Saiseikai Maebashi Hospital, Saitama Children's Medical Center, Saitama Medical Center: Saitama Medical University, Saitama Medical Center: Jichi Medical University, Saitama Medical University Hospital, Saitama Medical University Hospital, Saitama Medical University International Medical Center, Sakai Hospital Kinki University School of Medicine, Saku Central Hospital, Sapporo City General Hospital, Sapporo Hokuyu Hospital, Sapporo Medical University Hospital, Sasebo City General Hospital, Seirei Hamamatsu General Hospital, Shiga Medical Center for Children, Shiga University of Medical Science, Shimane Prefectural Central Hospital, Shimane University Faculty of Medicine, Shimonoseki Kosei General Hospital, Shinshu University School of Medicine, Shizuoka Children's Hospital, Shizuoka City Hospital, Shizuoka General Hospital, Shizuoka Red Cross Hospital, Shizuoka Saiseikai General Hospital, Showa University Fujigaoka Hospital, Showa University School of Medicine, Social Insurance Chukyo Hospital, Social Insurance Kyoto Hospital, St Marianna University School of Medicine Yokohama City Seibu Hospital, St Luke's International Hospital, St Mariannna University School of Medicine, Sumitomo Hospital, Suzuka General Hospital, Suzuka Kaisei Hospital, Takamatsu Red Cross Hospital, Takanohara Central Hospital, Teikyo University School of Medicine, Teikyo University School of Medicine Mizonokuchi Hospital, Teine Keijinkai Hospital, Tenri Hospital, The Institute of Medical Science: The University of Tokyo, The Tazuke Kofukai Medical Research Institute Kitano Hospital, Tochigi Cancer Center, Toho University Omori Medical Center, Tohoku University Hospital, Tokai University School of Medicine, Tokushima Red Cross Hospital, Tokushima University Hospital, Tokuyama Central Hospital, Tokyo Medical University Hospital, Tokyo Metropolitan Bokutoh Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center-Komagome Hospital, Tokyo Metropolitan Fuchu Hospital, Tokyo Metropolitan Geriatric Hospital, Tokyo Metropolitan Kiyose Children's Hospital, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo Women's Medical University Hospital, Toranomon Hospital, Tottori Prefectural Central Hospital, Tottori University Faculty of Medicine, Toyama Prefectural Central Hospital, Toyohashi Municipal Hospital, Toyota Memorial Hospital, Tsuchiura Kyodo General Hospital, Tsukuba Memorial Hospital, Tsukuba University Hospital, University of Fukui Hospital, University of Miyazaki Hospital, University of Occupational and Environmental Health Japan, University of the Ryukyus Hospital, University of Tokyo Hospital, University of Toyama, University of Tsukuba, University of Yamanashi Faculty of Medicine, Wakayama Medical University, Yamagata University School of Medicine, Yamanashi Prefectural Central Hospital, Yokohama City University Hospital.

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ORIGINAL ARTICLE

A comparative assessment of the RIFLE, AKIN and conventional criteria for acute kidney injury after hematopoietic SCT

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An observational cohort study was conducted to compare the performance of the RIFLE (risk, injury, failure, loss and end-stage kidney disease), AKIN (acute kidney injury network) and conventional graded criteria to identify acute kidney injury (AKI) following SCT and to predict long-term mortality in 141 myeloablative allogeneic SCT (m-allo), 60 non-myeloablative allogeneic SCT (nm-allo) and 48 autologous SCT (auto) cases. The AKIN criteria had less ability to identify patients as having the lowest category, stage 1 (analogous to RIFLE risk): 33% (37%) in m-allo, 23% (32%) in nm-allo and 8.3% (16.7%) in auto. Cox regression showed that categories higher than the intermediate stage were independent predictors of mortality in all three definitions. The areas under receiver operating characteristic curves showed that both definition systems had similar and significant ability to predict mortality (0.643–0.649 in m-allo and 0.734–0.766 in nm-allo, respectively). These abilities of the conventional graded criteria were comparable with those of the RIFLE criteria. The RIFLE criteria have greater sensitivity than the AKIN criteria to identify patients with AKI and therefore are more favorable as a uniform definition system for post-SCT AKI. However, the RIFLE criteria do not improve on the clinical relevance of the conventional graded criteria.

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Keywords: acute kidney injury; allogeneic myeloablative transplant; allogeneic nonmyeloablative transplant; autologous transplant; long-term mortality

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Introduction

Acute kidney injury (AKI) is a common early complication after hematopoietic SCT.[1,2] Recent reports have also shown that AKI associated with SCT results in poor long-term survival of affected patients.[3,4] At present, there are three major SCT modalities that include autologous SCT (auto), myeloablative allogeneic SCT (m-allo) and non-myeloablative allogeneic SCT (nm-allo), with selection depending on stem cell sources and preconditioning procedures. AKI is a common complication of all these SCT modalities, although the incidence, severity and impact on mortality differ between the three modalities. Schrier *et al.*[5] showed the frequency of AKI increased significantly from auto (21%) to nm-allo (40%) to m-allo (69%), and that the increased incidence of AKI correlated with a parallel increase in mortality 6–12 months after SCT from 7 to 34 to 58%, respectively. However, the clinical validity of such epidemiological data needs to be re-examined from the viewpoint of the contemporary paradigm for AKI, as these earlier studies were conducted according to conventional, but likely arbitrary definition systems, used at that time.

The lack of consensus concerning the quantitative definition of AKI has hindered clinical research as it confounds comparisons between studies. Thus, the Acute Dialysis Quality Initiative (ADQI) group has proposed a new graded definition for AKI, called the RIFLE criteria (risk, injury, failure, loss of kidney function, end-stage kidney disease), to establish a uniform standard for diagnosing and classifying AKI.[6] More recently, the acute kidney injury network (AKIN) proposed new diagnostic criteria and a three-staging system for AKI modified from RIFLE, with the aim of increasing the sensitivity of the classifications.[7] These criteria have now been evaluated in a number of clinical studies of critically ill patients with AKI and have been shown to be able to identify and classify the severity of AKI and monitor progression of the disorder, in addition to being a predictive index of in-hospital mortality.[8–10] It is possible that these new AKI criteria may have great utility in standardizing the definitions for establishing inclusion criteria and outcomes for post-SCT AKI. However, it is unknown currently whether discernible advantages exist between RIFLE, AKIN and the conventional graded criteria for classifying post-HCT AKI introduced by Parikh *et al.*[5,11,12]

The objectives of this study were (1) to determine the current incidence of post-SCT AKI according to the two new definition systems, and (2) to compare the performance of the RIFLE, AKIN and the conventional graded criteria for identifying AKI and predicting long-term all-cause mortality associated with post-SCT AKI in the three major SCT modalities

Patients and methods

The subjects were 249 Japanese patients (mean age, 41.7 ± 12.5 years; 157 males) who received SCT between August 2004 and December 2007 in the Department of Hematology at Tokyo Metropolitan Cancer Center Komagome Hospital. This cohort comprised 141 myeloablative allogeneic SCTs (m-allo), 60 non-myeloablative allogeneic SCTs (nm-allo) and 48 myeloablative autologous SCTs (auto). Candidates for allogeneic myeloablative SCT were screened for the presence of pre-existing comorbidities and deemed suitable for the procedure on the basis of normal kidney morphology and a 24 h timed urine creatinine (Cr) clearance $\geqslant$80 ml/min and albuminuria $\leqslant$300 mg/gCr. Patients older than $\geqslant$50 years or with other comorbidities such as hypertension, diabetes and hepatic dysfunction were excluded from the study. Patients who were not eligible for myeloablative SCT were considered for non-myeloablative SCT. Patients gave their written consent and were treated according to protocols approved by the institutional Ethics Committee.

The study was an observational cohort study. Preparative therapy was performed according to the primary disease and type of transplant. In general, patients with lymphoid malignancy were conditioned using a TBI (12 Gy)-containing regimen that included administration of cytarabine (8 g/m^2) and CY (120 mg/kg). Selective kidney shielding blocks were used during TBI and this reduced the renal dose to 10 Gy.[13] Conversely, patients with myeloid malignancy were conditioned using a non-TBI-containing regimen that included administration of BU (16 mg/kg) and CY (120 mg/kg). The plasma concentrations of BU were not monitored. TLI (7 Gy) was included in the BU/CY regimens in cases of mismatched or unrelated transplantation. Patients with severe aplastic anemia were also conditioned using a TLI-containing regimen. The preparative regimen for the non-myeloablative procedure consisted of CY (120 mg/kg) and fludarabine (125 mg/m^2). The GVHD prophylaxis regimen typically comprised a short course of MTX and CYA (CSP) or tacrolimus (FK). FK was used in cases involving either unrelated or mismatched transplantation. MTX was administered at 10 mg/m^2 i.v. on day +1 and at 7 mg/m^2/day on days +3, +6 and +11. Continuous i.v. infusion of CSP and FK was started on day −1 at dosages of 3 mg/kg/day and 0.03 mg/kg/day, respectively. The target blood concentrations were 450–550 ng/ml for CSP and 10–20 ng/ml for FK, with the dosage of both drugs being adjusted according to renal function and the grade of acute GVHD. If no GVHD was present, both drugs were administered orally approximately 2 months after SCT, followed by tapering of the dosages between 3 and 6 months. Acute and chronic GVHD were diagnosed and graded according to previously established criteria.[14,15] Tosulfloxacin and fluconazol were administered orally for 14 days before SCT. Trimethoprim–sulfamethoxazole (TMP 240 mg, SMX 1200 mg; 3 times per week) was also used to prevent pneumocystis pneumonia. CMV infection was monitored weekly by CMV antigenemia. Positive antigenemia, defined as >1 cell/65 000 cells, was treated using ganciclovir twice daily until negative CMV antigenemia was obtained.

Definition of post-SCT AKI

AKI was defined and classified into three categories according to two current AKI definitions, the RIFLE and AKIN criteria and also by the conventional graded system introduced by Parikh *et al.*,[11,12] hereafter denoted as 'the Grading criteria'. A comparison of these AKI definitions is shown in Table 1. AKI within the first 100 days after SCT was defined based on serum creatinine (Cr) and/or estimated glomerular filtration rate (eGFR) criteria proposed by each of the AKI definitions. The RIFLE criteria was determined on the basis of the most abnormal value of either Cr or eGFR criteria. Urine output criteria included in the RIFLE and AKIN definitions were not used, as we were unable to obtain accurate records of urine output from all the patients. The serum concentration of Cr was measured by an enzymatic method using an isotope-dilution mass spectrometry-traceable calibrator (N-assay L Creatinine Kit, Nittoubo Medical Co., Tokyo, Japan). eGFR was calculated by the modification of diet in renal disease formula, as modified by the Japanese Society of Nephrology: $\text{eGFR (ml/min/1.73m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female).[16] 'Severe AKI' was defined as greater than the intermediate category, such as injury in RIFLE, $\geqslant$stage 2 in AKIN and $\geqslant$grade 2 in the Grading criteria.

Statistical analysis

Data are shown as the mean ± s.d. Comparisons between more than three groups were performed using analysis of variance for continuous variables and the χ^2-test for categorical variables. Patient follow-up was undertaken on 31 December 2007. All-cause mortality was determined at 1000 days following SCT. Cumulative survival curves were prepared by the Kaplan–Meier method and the log-rank test was used to analyze differences between the curves. Cox regression analysis was used to determine the association of each AKI category with mortality, followed by calculation of adjusted hazard ratio (HR) and 95% confidence intervals. The multivariate models incorporated a forward selection stepwise method using variables with a P-value of <0.20 in the univariate analyses. JMP version 7 (SAS Institute Japan, Cary, CA, USA) was used for all the statistical analyses. Values of $P<0.05$ were considered statistically significant.

Results

Demographics and baseline characteristics of patients following SCT

The baseline characteristics of the 141 m-allo patients, 60 nm-allo patients and 48 auto patients are summarized in Table 2. The age of the patients at the time of SCT was

Table 1 A comparison of post-SCT AKI[a] definition and classification according to serum Cr levels in the RIFLE, AKIN and grading criteria

(A) RIFLE	
Risk	Increase in serum Cr $\geqslant$1.5 × baseline or decrease in GFR $\geqslant$25%
Injury	Increase in serum Cr $\geqslant$2.0 × baseline or decrease in GFR $\geqslant$50%
Failure	Increase in serum Cr $\geqslant$3.0 × baseline or decrease in GFR $\geqslant$75% or an absolute serum Cr $\geqslant$4.0 mg/dl (354 μmol/l) with an acute rise of at least 0.5 mg/dl (44 μmol/l)
Loss	Persistent AKI >4 weeks
ESKD	ESKD >3 months
(B) AKIN	
Stage 1	Increase in serum Cr $\geqslant$0.3 mg/dl (26.5 μmol/l) or increase to 150–199% (1.5–1.9-fold) from baseline
Stage 2	Increase in serum Cr to 200–299% (>2.0–2.9 fold) from baseline
Stage 3	Increase in serum Cr to $\geqslant$300% ($\geqslant$3-fold) from baseline or serum Cr $\geqslant$4.0 mg/dl (354 μmol/l) with an acute rise of at least 0.5 mg/dl (44 μmol/l).
(C) Grading	
Grade 0	Decrease in GFR <25% of baseline
Grade 1	Increase in serum Cr<2-fold from baseline with a decrease in GFR >25% but <50% of baseline
Grade 2	Increase in serum Cr $\geqslant$2-fold from baseline but not requiring dialysis
Grade 3	Increase in serum Cr $\geqslant$2-fold from baseline and need for dialysis

Abbreviations: GFR = glomerular filtration rate; RIFLE = risk, injury, failure, loss of kidney function, and end-stage kidney disease; AKIN = acute kidney injury network; Cr = creatinine; AKI = acute kidney injury; ESKD = end-stage kidney disease.
[a]Post-SCT AKI is defined within the first 100 days after SCT.

Table 2 Demographics and baseline characteristics of the patients following SCT

Variable	*M-allo (n = 141)*	*Nm-allo (n = 60)*	*Auto (n = 48)*
Age (years)	38.3 ± 10.8	42.9 ± 13.8†	50.4 ± 11.6*
Gender (M/F)	87/54	35/25	35/13
Baseline Cr μg/l	64.2 ± 17.6	66.3 ± 19.9	66.8 ± 17.3
Diagnosis			
ALL	37 (26.2%)	2 (3.3%)	0 (0%)
ANLL	53 (37.6%)	26 (43.3%)	5 (10.4%)*
CML	13 (9.2%)	5 (1.7%)	0 (0%)
MDS	23 (16.3%)	10 (16.7%)	0 (0%)
MM	3 (3.1%)	2 (2.5%)	29 (60.4%)*
AA	1 (0.7%)	12 (6.5%)	0 (0%)
NHL	5 (3.5%)	1 (1.7%)	11 (22.9%)*
Others	6 (4.3%)	3 (5%)	3 (6.3%)
Stem cell source			
BM	102 (72.3%)	42 (71.6%)	0 (0%)
PB	23 (16.3%)	12 (17.4%)	48 (100%)*
CB	16 (11.4%)	6 (11.0%)	0 (0%)
Related donor	53 (37.6%)	16 (26.7%)	—
Acute GVHD			
Grade 0–1	94 (66.7%)	37 (61.7%)	—
Grade $\geqslant$2	47 (33.3%)	23 (38.3%)	—
Chronic GVHD	18 (12.8%)	10 (16.7%)	—
Relapse	38 (27.0%)	12 (24.9%)	—

Abbreviations: M-allo = myeloablative allogeneic transplantation; Nm-allo = non-myeloablative allogeneic transplantation; Auto = autologous transplantation; Cr = serum creatinine before transplant; ALL = acute lymphocytic leukemia; ANLL = acute non-lymphocytic leukemia; CML = chronic myelocytic leukemia; MDS = myelodysplastic syndrome; MM = multiple myeloma; AA = aplastic anemia; CB = umbilical cord blood stem cell.
Asterisk (*) indicates a significant difference between the auto and other SCT modalities. Mark (†) indicates a significant difference between the m-allo and nm-allo groups.

significantly higher in the auto group than in the other two SCT modalities. There was also a significant difference in age between the m-allo and the nm-allo groups. The auto transplant group had the lowest proportion of acute non-lymphocytic leukemia and the highest proportion of multiple myeloma and peripheral blood SCT compared with the other two modalities. There were no significant differences in gender proportion, baseline Cr level, ratio of related donors, frequency of acute and chronic GVHD and frequency of relapse between the three modalities.

Incidence of AKI classified according to the RIFLE, AKIN and grading criteria

A comparison of the incidence data of post-SCT AKI according to the three different criteria is shown in Table 3. The current incidence of any AKI ranged between 62 and 66% in m-allo, between 40 and 48% in nm-allo and between 10 and 19% in auto transplants. We found small differences in the number of patients classified as having AKI between the AKIN and the other two criteria. The AKIN criteria had the lowest ability to identify patients with AKI of the three criteria for all three SCT modalities, because of reduced sensitivity to identify the lowest category of AKI. Only two patients were classified into stage 1 of AKIN, based on a rapid increase in serum Cr $\geqslant$0.3 mg per 100 ml in the 48 h period after SCT. However, the ability to identify severe AKI ($\geqslant$injury or $\geqslant$stage 2 or $\geqslant$grade 2) was identical between the three criteria (29% in m-allo, 17% in nm-allo and 2% in auto). The sensitivity of the RIFLE criteria was comparable with that of the grading criteria. Two patients in the m-allo group and three patients in the nm-allo group were classified into stage 3 of AKIN as they were receiving dialysis treatment.

Mortality of AKI classified according to the RIFLE, AKIN and grading criteria

Mortality according to the three different criteria is shown in Table 4. The mortality of patients with any AKI category was approximately 54% in m-allo, 48–50% in nm-allo and 11–20% in auto transplants. Mortality increased in parallel with increases in AKI category, with mortality for

Table 3 Incidence of AKI classified according to the RIFLE, AKIN and grading criteria

RIFLE	*No. (%)*	*AKIN*	*No. (%)*	*Grading*	*No. (%)*
M-allo (n = 141)					
None	48 (34.0)	None	54 (38.3)	Grade 0	48 (34.0)
Risk	52 (36.9)	Stage 1	46 (32.6)	Grade 1	52 (36.9)
Injury	21 (14.9)	Stage 2	21 (14.9)	Grade 2	38 (27.0)
Failure	20 (14.2)	Stage 3	20 (14.2)	Grade 3	3 (2.1)
Any category[a]	93 (66.0)	Any stage	87 (61.7)	Any grade	93 (66.0)
Severe AKI[b]	41 (29.1)	Severe AKI	41 (29.1)	Severe AKI	41 (29.1)
Nm-allo (n = 60)					
None	31 (51.7)	None	36 (60.0)	Grade 0	31 (51.7)
Risk	19 (31.7)	Stage 1	14 (23.3)	Grade 1	19 (31.7)
Injury	5 (8.3)	Stage 2	5 (8.3)	Grade 2	7 (11.7)
Failure	5 (8.3)	Stage 3	5 (8.3)	Grade 3	3 (5.0)
Any category	29 (48.3)	Any stage	24 (40.0)	Any grade	29 (48.3)
Severe AKI	10 (16.7)	Severe AKI	10 (16.7)	Severe AKI	10 (16.7)
Auto (n = 48)					
None	39 (81.3)	None	43 (89.6)	Grade 0	39 (81.3)
Risk	8 (16.7)	Stage 1	4 (8.3)	Grade 1	8 (16.7)
Injury	1 (2.1)	Stage 2	1 (2.1)	Grade 2	1 (2.1)
Failure	0 (0)	Stage 3	0 (0)	Grade 3	0 (0)
Any category	9 (18.8)	Any stage	5 (10.4)	Any grade	9 (18.8)
Severe AKI	1 (2.1)	Severe AKI	1 (2.1)	Severe AKI	1 (2.1)

Abbreviations: RIFLE = risk, injury, failure, loss of kidney function, and end-stage kidney disease; AKIN = acute kidney injury network; M-allo = myeloablative allogeneic transplantation; Nm-allo = non-myeloablative allogeneic transplantation; Auto = autologous transplantation.
[a]Any category includes AKI ⩾risk or ⩾stage 1 or ⩾grade 1.
[b]Severe AKI is denoted as AKI ⩾injury or ⩾stage 2 or ⩾grade 2.

Table 4 Mortality[a] of AKI classified according to the RIFLE, AKIN and grading criteria

RIFLE	*No. (%)*	*AKIN*	*No. (%)*	*Grading*	*No. (%)*
M-allo (n = 141)					
None	48 (34.0)	None	54 (38.3)	Grade 0	48 (34.0)
Risk	52 (36.9)	Stage 1	46 (32.6)	Grade 1	52 (36.9)
Injury	21 (14.9)	Stage 2	21 (14.9)	Grade 2	38 (27.0)
Failure	20 (14.2)	Stage 3	20 (14.2)	Grade 3	3 (2.1)
Any category[a]	93 (66.0)	Any stage	87 (61.7)	Any grade	93 (66.0)
Severe AKI[b]	41 (29.1)	Severe AKI	41 (29.1)	Severe AKI	41 (29.1)
Nm-allo (n = 60)					
None	31 (51.7)	None	36 (60.0)	Grade 0	31 (51.7)
Risk	19 (31.7)	Stage 1	14 (23.3)	Grade 1	19 (31.7)
Injury	5 (8.3)	Stage 2	5 (8.3)	Grade 2	7 (11.7)
Failure	5 (8.3)	Stage 3	5 (8.3)	Grade 3	3 (5.0)
Any category	29 (48.3)	Any stage	24 (40.0)	Any grade	29 (48.3)
Severe AKI	10 (16.7)	Severe AKI	10 (16.7)	Severe AKI	10 (16.7)
Auto (n = 48)					
None	39 (81.3)	None	43 (89.6)	Grade 0	39 (81.3)
Risk	8 (16.7)	Stage 1	4 (8.3)	Grade 1	8 (16.7)
Injury	1 (2.1)	Stage 2	1 (2.1)	Grade 2	1 (2.1)
Failure	0 (0)	Stage 3	0 (0)	Grade 3	0 (0)
Any category	9 (18.8)	Any stage	5 (10.4)	Any grade	9 (18.8)
Severe AKI	1 (2.1)	Severe AKI	1 (2.1)	Severe AKI	1 (2.1)

Abbreviations: RIFLE = risk, injury, failure, loss of kidney function, and end-stage kidney disease; AKIN = acute kidney injury network; M-allo = myeloablative allogeneic transplantation; Nm-allo = non-myeloablative allogeneic transplantation; Auto = autologous transplantation.
[a]Mortality was determined 1000 days after transplantation.
[b]Any category includes AKI ⩾risk or ⩾stage 1 or ⩾grade 1.

the highest category in the RIFLE and AKIN criteria increasing markedly in m-allo transplants and fatally in nm-allo transplants. The difference in mortality between AKI and no AKI according to the RIFLE criteria was marked and was especially apparent in the nm-allo group (48 versus 16%) compared with the m-allo group (54 versus 35%). This difference was not applicable to the auto group. Three patients in the m-allo group and three patients in the nm-allo group who required dialysis treatment died within 100 days of SCT. The Kaplan–Meier curves stratified by the RIFLE classification are shown in Figures (a), (b) and (c) and show clear differences in long-term survival between

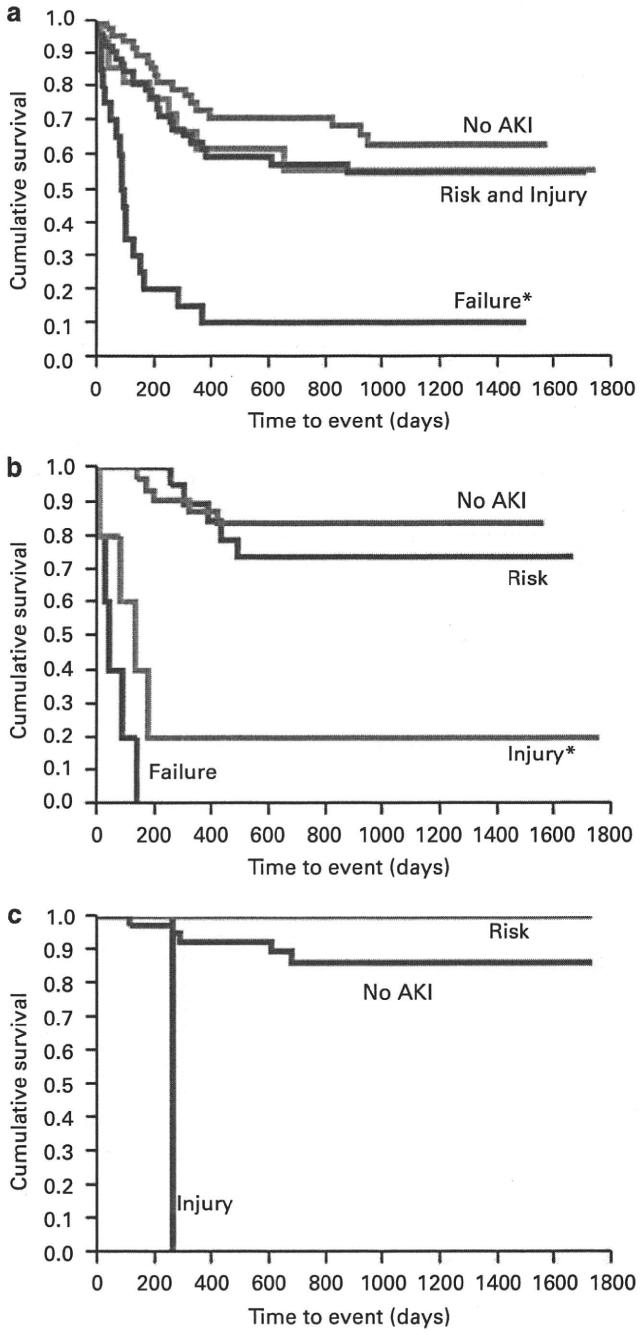

Figure 1 (**a**), (**b**) and (**c**) show cumulative survival curves after m-allo, nm-allo and auto transplants, stratified according to the RIFLE categories. The *x* axis represents the number of days post-hematopoietic cell transplantation (HCT) and the *y* axis represents cumulative survival. (**a**): myeloablative allo-SCT ($n=141$), (**b**): nonmyeloablative allo-SCT ($n=60$), (**c**): auto-SCT ($n=48$). *Indicates log-rank test, $P<0.0001$.

the various categories. The difference between curves 1000 days after SCT were significant for failure in m-allo transplants and for injury in nm-allo transplants, compared with no AKI (log-rank, $P<0.0001$). Similar curves of comparable significance were obtained when other criteria were used for stratification (data not shown).

Adjusted association of each AKI category with mortality and discriminative ability of each classification in allogeneic SCT

Cox regression analysis, adjusted for age at SCT, baseline serum Cr, gender (male), absence or presence of acute GVHD ⩾grade 2 and chronic GVHD, an unrelated donor and relapse of underlying diseases, showed that each category (⩾injury, ⩾stage 2 and ⩾grade 2) independently predicted mortality in both of the m-allo and nm-allo groups (Table 5). A large stepwise increment in hazard ratio for mortality was observed with increases in AKI category for all three classification systems. The discriminative ability for mortality was almost comparable in the three definitions. In the m-allo group, the AuROC curve was 0.649 ($P=0.0005$) with the RIFLE criteria, 0.643 ($P=0.0007$) with the AKIN criteria and 0.629 ($P=0.0058$) with the grading criteria. In the nm-allo group, the corresponding AuROC values were 0.766 ($P=0.0006$) with the RIFLE criteria, 0.734 ($P=0.0008$) with the AKIN criteria and 0.765 ($P=0.0006$) with the grading criteria (Table 5).

Discussion

The present study obtained the most recent data regarding the incidence and mortality of AKI following SCT, according to two new and one conventional AKI definition systems. Compared with the RIFLE and grading criteria, the AKIN criteria had the disadvantage of relatively poor sensitivity to identify the lowest category of AKI in any type of transplantation modality. All three criteria were found to have comparable utility for stratifying post-SCT patients with AKI according to mortality risk.

Our study showed that the current incidence of post-SCT AKI was, at most, 66% in m-allo, 48% in nm-allo and 19% in auto transplants and that mortality was, at most, 54% in m-allo, 50% in nm-allo and 20% in auto transplants. The incidence rates for each of the allogeneic types were markedly higher than those of auto transplants, a finding that is comparable with those reported in previous studies.[1,2,5] The current incidence rates were considerably lower than those reported previously by Parikh *et al.* and Caliskan *et al.* using the grading criteria within the first 100 days after SCT (91–92% in m-allo, 90% in nm-allo and 52–57% in auto).[2,11,12,17] In contrast, the present mortality rate was almost the same as previous estimations using the grading criteria (56–58% in m-allo transplants and 43% in nm-allo transplants, but no reference mortality in auto transplants alone).[2,4,11,18] Most recently, Lopes *et al.* showed the incidence of AKI (40%) and 3-year mortality (48.8%) according to the AKIN criteria in m-allo, and the incidence (53.6%) and 5-year mortality (58.4%) in reduced intensity conditioning SCT according to the RIFLE criteria.[3,19] Compared with our results, the incidences and mortality rates reported were lower in m-allo transplants and higher in RIC transplants. However, there were the following differences between the two studies: their cohort of m-allo transplants included 35.8% of myeloablative auto transplants and the length of the follow-up periods was longer than in our study. Unfortunately, this earlier study

Table 5 Adjusted association of each AKI category with mortality[a] and discriminative ability of each classification in allogeneic transplantation

AKI category	*Adjusted HR*[b] *(95% CI)*	P-*value*	*AuROC*	P-*value*
Myeloablative (n = 141)				
RIFLE			0.649	0.0005
Failure	8.802 (4.720–16.467)	<0.0001		
Injury	2.590 (1.252–5.151)	0.0114		
Risk	1.639 (0.939–2.897)	0.0822		
None (reference)	1.00			
AKIN			0.643	0.0007
AKIN stage 3	7.950 (4.359–14.413)	<0.0001		
AKIN stage 2	2.332 (1.149–4.503)	0.0202		
AKIN stage 1	1.409 (0.800–2.460)	0.2319		
None (reference)	1.00			
Grading			0.629	0.0058
Grade 3	10.04 (3.226–26.160)	0.0004		
Grade 2	4.333 (2.494–7.652)	<0.0001		
Grade 1	1.670 (0.956–2.952)	0.0715		
Grade 0 (reference)	1.00			
Non-myeloablative (n = 60)				
RIFLE			0.766	0.0006
Failure	123.9 (16.74–1228)	<0.0001		
Injury	34.51 (4.813–277.4)	0.0005		
Risk	1.246 (0.298–3.428)	0.7589		
None (reference)	1.00			
AKIN			0.734	0.0008
AKIN stage 3	110.3 (16.07–1036)	<0.0001		
AKIN stage 2	28.20 (4.277–202.4)	0.0007		
AKIN stage 1	0.822 (0.157–9.041)	0.7950		
None (reference)	1.00			
Grading			0.765	0.0006
Grade 3	609.3 (48.81–11813)	<0.0001		
Grade 2	52.85 (8.859–399.9)	<0.0001		
Grade 1	1.316 (0.310–5.843)	0.7059		
Grade 0 (reference)	1.00			

Abbreviations: AKI = acute kidney injury; HR = hazard ratio; RIFLE = risk, injury, failure, loss of kidney function, and end-stage kidney disease; AKIN = acute kidney injury network; AuROC = the area under the receiver operator characteristic curve for long-term mortality.
[a]Mortality was determined 1000 days after transplantation.
[b]Adjusted for age, acute GVHD, chronic GVHD, unrelated donors, relapse and stem cell sources.

did not include a comparative assessment of their data with the grading criteria. Further epidemiological studies on post-SCT AKI according to the new AKI criteria are needed to estimate the recent incidence and mortality of AKI following SCT.

The Kaplan–Meier curves showed that the separation between the 'risk' and 'injury' curves in the m-allo group appeared to be obscure, compared with that seen in the nm-allo group. In addition, Cox regression analysis indicated that the HR of 'injury' for long-term mortality was significant but rather lower in the m-allo group (HR; 2.59) than in the nm-allo group (HR; 34.5). These differences suggest that the nm-allo group may be more vulnerable for exposure to the 'intermediate' level of AKI in the long term than the m-allo group. There was a significant difference in age at the time of SCT between the m-allo and nm-allo groups (38.3 versus 42.9 years). The older age of the nm-allo group may therefore have contributed to their higher risk of mortality after they were exposed to the 'intermediate' level of AKI.

The sensitivity of the AKIN criteria to identify patients with the lowest category of AKI was less than the other two criteria for all three transplant modalities. The AKIN criteria require at least two Cr values within a 48 h period rather than referring to a baseline Cr value in Stage 1. A rapid, small increase ($\geqslant$0.3 mg per 100 ml) in serum Cr within 48 h could be under-recognized and often overlooked in the context of SCT. In fact, the 48 h time frame definition was not available in almost all post-SCT patients as we were not able to measure serum Cr frequently during the 100 days after SCT. This is most likely associated with the lower sensitivity of the AKIN criteria to identify stage-1 AKI, possibly leading to misclassification of AKI stages. In addition, Cox regression analysis showed that each of the categories higher than the intermediate stage were significant independent predictors of mortality in all three AKI definition systems. The AuROC curves for mortality showed equal significance for all the AKI definition systems. These results show that the RIFLE and AKIN classifications have almost the same predictive utility for mortality in patients with post-SCT AKI, but that they do not substantially improve the ability of the grading criteria to predict mortality in the context of SCT. Taken together, our results suggest that the RIFLE criteria are more favorable than the AKIN criteria as a uniform identification system for post-SCT AKI, and that clinical significance of previous epidemiological data according to the grading criteria remain valid today.

This study has some limitations. Firstly, we were not able to use urine output criteria in the new AKI criteria. When

applying these new definitions to post-SCT AKI, it proved difficult to obtain accurate records of urine output in every patient throughout the SCT period. In addition, the volume status of patients during the acute period of SCT may have varied widely according to infusion therapy, whereas urinary tract obstruction sometimes occurred because of hemorrhagic cystitis induced by local adenoviral infections or as a side effect of administration of high dose of CY. These conditions may have resulted in a biased assessment of the true burden of post-SCT AKI using the two new criteria. The difficulties in practicing the urine output criteria are inherent in the assessment of the new AKI criteria especially in the setting of SCT. Secondly, we used serum Cr level and Cr-based estimates of GFR according to previous literature.[1,2] However, a challenge in the study of AKI in the post-SCT population is that serum Cr is a less effective measure of GFR in the setting of co-morbid illness. Cr-based estimates of GFR above 60 ml/min/1.73 m^2 are considered imprecise even in the general population.[16] Thirdly, although non-relapse mortality would add important information to this study, the current data set was not adequate to perform statistical analysis for non-relapse mortality in all types of SCT in accordance with that described in previous studies.[2,3] Finally, this was a single-center study on a relatively small cohort of SCT patients.

In summary, the variability in incidence of AKI following SCT most likely reflects the lack of a standard definition for post-SCT kidney disease, differences in the types of transplants investigated and variability in the length of the follow-up periods. It is, therefore, worthwhile to establish a uniform standard for diagnosing and classifying post-SCT AKI in comparative studies and carrying out robust epidemiological investigations internationally. The RIFLE criteria have shown promise as a uniform standard to identify and classify post-SCT patients with various degrees of AKI and to predict the mortality of these patients. However, this definition system does not substantially exceed the abilities of the conventional grading criteria. The incidence of AKI that we observed appears to be lower than that reported in previous studies, although the mortality of patients with higher categories of AKI still remains high in m-allo and nm-allo transplants. Emerging evidence suggests that even minor changes in serum Cr are associated with increased mortality.[7–10] Despite the significant progress made in understanding the biology and mechanism of AKI in animal models, application of this knowledge into improved management and outcomes for patients has been limited. However, immediate fluid therapy for potential circulatory deficits, avoidance and minimizing the use of nephrotoxic agents and dosage adjustment of medication according to kidney function are sometimes effective for preventing worsening of the early stages of AKI.[20] Transplant physicians and nephrologists need to work together in the treatment of patients receiving SCT to identify early renal disease and also to examine small changes in serum creatinine concentration or promising new urinary biomarkers.[6,21] Further efforts will be required to decrease the frequency of life-threatening AKI, with initial focus on m-allo and nm-allo transplants.

Conflict of interest

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Phase II study of tacrolimus and methotrexate for prophylaxis of acute graft-versus-host disease after HLA-A, B, and DRB1 genotypically mismatched unrelated bone marrow transplantation among Japanese patients

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Abstract Bone marrow transplantation from unrelated donors (UR-BMT) has been considered to be effective for patients with hematological malignancies who have no suitable related donor. However, disparities of HLA between a recipient and a donor increase the risk of severe acute graft-versus-host disease (GVHD). We evaluated GVHD prophylaxis using tacrolimus and methotrexate for HLA-A, B, or DRB1 genotypically mismatched UR-BMT. Fifty-five patients were enrolled in this study. The incidence of grade III to IV acute GVHD was 23.6% for all patients. No significant difference in the incidence of grade III to IV acute GVHD was observed between HLA-A or B 1 locus mismatch transplantation (18.8%) and HLA-DRB1 1 locus mismatch transplantation (16.7%) ($P = 0.96$). The incidence of chronic GVHD was 71.7%. Disease-free survival at 5 years was 53.2% for patients with standard risk disease and 24.5% for patients with high-risk disease. Patients with chronic GVHD exhibited better disease-free survival than those without chronic GVHD (53.2 vs. 30.9%, $P = 0.011$). Twenty patients (36.4%) had a relapse of leukemia and 14 of them died of recurrent leukemia. This study indicates tacrolimus and methotrexate can lower the risk of severe acute GVHD after HLA-A, B, or DRB1 genotypically 1 locus mismatched UR-BMT.

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Keywords Tacrolimus · GVHD prophylaxis · HLA mismatched UR-BMT

1 Introduction

Acute graft-versus-host disease (GVHD) is one of the most common causes of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT) [1, 2]. Although bone marrow transplantation from unrelated donors (UR-BMT) has been established as an effective treatment for patients with hematological malignancies who have no suitable related donor, the control of GVHD is indispensable to successful outcome after UR-BMT [3–5].

Tacrolimus has been shown to be more potent as an immunosuppressant than cyclosporine since its discovery in 1984 [6]. It was initially demonstrated to be effective for the treatment and prevention of rejection in solid-organ transplantations [7, 8]. Tacrolimus was also reported to be effective in the treatment and prevention of GVHD after allogeneic BMT [9–12].

In several clinical studies containing UR-BMT, the incidence of grade II to IV acute GVHD was 21–56% in patients who received tacrolimus and methotrexate for the prevention of acute GVHD[13–17]. Multicenter randomized studies have shown that tacrolimus is more effective in preventing GVHD than cyclosporine, which has been used commonly for GVHD prophylaxis [16, 17]. Despite the lower rate of GVHD, tacrolimus has exhibited no survival benefits, compared with cyclosporine [16, 17]. In these clinical studies, most patients received stem cells from an HLA matched unrelated donor. The risk of GVHD after HLA-mismatched UR-BMT is higher than after HLA-matched UR-BMT because immunological events such as GVHD are affected by the HLA disparity between a patient and a donor [18–21]. We conducted a phase II study to evaluate tacrolimus and methotrexate for the prevention of GVHD in recipients of marrow transplants from an HLA-A, B, or DRB1 genotypically mismatched unrelated donors.

2 Materials and methods

2.1 Patients

From August 1999 to August 2001, 55 patients were enrolled in this study at 27 transplantation centers in Japan. The study was approved by the institutional review board at each center and all patients gave written informed consent for participation in the study. Eligible patients had leukemia or myelodysplastic syndrome (MDS), and had an HLA-A, B, or DRB1 genotypically mismatched unrelated donor. Patients were required to be between the ages of 16 and 50 years old, to have an Eastern Cooperative Oncology Group performance status of 0, 1 or 2, and to have adequate hepatic function (total bilirubin less than 1.5 mg/dl and transaminase $\leqq 2 \times$ upper normal limit), renal function (serum creatinine less than 1.2 mg/dl and estimated creatinine clearance greater than 60 ml/min), cardiac function (ejection fraction greater than 50%) and pulmonary function (arterial oxygen pressure greater than 70 mmHg). Patients were ineligible if they fulfilled one of the following exclusion criteria: (1) a previous transplantation, (2) use of T cell-depleted marrow, (3) use of anti-thymocyte globulin (ATG) for preparative regimen, (4) any history of severe cardiac disease, pancreatitis, diabetes mellitus, hyperkalemia or hypertension necessitating medication, (5) any infection including hepatitis B and hepatitis C, human immunodeficiency virus or syphilis, and (6) pregnant or lactating women.

2.2 Study design

The primary endpoint of this study was the incidence of grade III to IV acute GVHD. The secondary endpoints were the incidence of chronic GVHD, survival, disease-free survival, relapse and complications. Sample size was derived to ensure that the 95% confidential interval (CI) of the point estimation of the incidence of grade III–IV acute GVHD, which was set to be 15%, did not exceed 10%. The historical incidence in case of cyclosporine was 30% [18].

2.3 Treatment protocol

Patients received bone marrow from an HLA-A, B, or DRB1 genotypically mismatched unrelated donor on day 0, following myeloablative chemoradiotherapy. Preparative regimens and supportive care were assigned according to each institutional protocol at the clinical sites.

All patients received tacrolimus and methotrexate for GVHD prophylaxis. Tacrolimus was administered by 24-h continuous intravenous infusion at a dose of 0.03 mg/kg beginning on day-1. When patients were able to tolerate oral intake, the route of administration was switched from intravenous to oral at the ratio of 1:3 in two divided doses per day based on the intravenous dose at the time of conversion.

Methotrexate was given at 10 mg/m^2 intravenously on day +1 and 7 mg/m^2 on days +3 and +6.

Whole blood level of tacrolimus was measured twice a week during the first 4 weeks posttransplantation and weekly thereafter by EIA method. The target blood level was determined as 15 ng/ml and the dose was adjusted so as not to exceed 20 ng/ml. Unless patients had evidence of GVHD after day 50, the tacrolimus dose was tapered by 10% every 2 weeks. If the serum creatinine increased to

levels above 1.5 × upper normal limit, tacrolimus was temporarily withheld. When the serum creatinine lowered to levels below 1.5 × upper normal limit, tacrolimus was resumed at the dose of 25% reduction.

In principle, patients who developed grade II to IV acute GVHD were treated initially with prednisolone or methylprednisolone at the dose of 1–2 mg/kg. When acute GVHD was not controlled, secondary treatment was assigned according to treatment protocols at each site.

2.4 Assessment of GVHD

Acute GVHD was diagnosed and graded by clinicians at each institution according to the consensus criteria [22]. The clinical and laboratory parameters used to assess the grade of acute GVHD included the percentage of body surface area with skin rash, the volume of diarrhea, total bilirubin, and Karnofsky's performance status. Chronic GVHD was categorized as limited type or extensive type [23]. Tissue biopsy samples were obtained to confirm the diagnosis of GVHD as much as possible. The response of treatment for acute GVHD was evaluated based on previously described criteria [24].

2.5 Statistics

Standard risk disease was defined as acute leukemia in first complete remission, chronic myelogeneous leukemia (CML) in first chronic phase and MDS classified as refractory anemia, whereas high-risk disease was defined as a more advanced status than standard risk disease. The time to develop acute GVHD was determined from the date of transplantation. Patients who did not develop acute GVHD were censored at the date of their last contact, death or relapse, whichever occurred first. Overall survival was calculated from the date of transplantation to the date of death. Disease-free survival was calculated from the date of transplantation to the date of death or relapse, whichever occurred first. Patients alive at the date of last contact were censored. The Kaplan–Meier method was used to estimate the incidences of GVHD, survival, and relapse. *P* values of less than 0.05 were regarded as statistically significant. The grade of adverse events was assessed according to National Cancer Institute Common Toxicity Criteria version 2.0.

3 Results

3.1 Patient characteristics

Fifty-five patients were enrolled in the study between August 1999 and August 2001. Patients characteristics are summarized in Table 1. All patients received bone marrow from an HLA-A, B, or DRB1 genotypically mismatched unrelated donor. In 50 patients, there were no HLA-A, B or DR serological disparities. Five patients underwent an HLA-DR serological 1 locus mismatched transplantation. Four of them received bone marrow matched for broad specificities at HLA-DR loci, and the other one received bone marrow matched in GVHD direction and mismatched in rejection direction. The median follow-up period for surviving patients was 1,629 days.

Table 1 Patients characteristics

No. of patients	55
Median patient age, years (range)	33 (16–50)
Median donor age, years (range)	33 (20–51)
Sex (donor/recipient), *n* (%)	
Male/male	21
Male/female	14
Female/male	15
Female/female	5
HLA disparity, *n* (%)	
Class I DNA 1 locus mismatch	16 (29.1%)
Class II DNA 1 locus mismatch	24 (43.6%)
≧DNA 2 loci mismatch	10 (18.2%)
Class II serological 1 locus mismatch	5 (9.1%)
Diagnosis, *n* (%)	
Acute myelogeneous leukemia	19 (34.5%)
Acute lymphoblastic leukemia	10 (18.2%)
Chronic myelogeneous leukemia	20 (36.4%)
Myelodysplastic syndrome	6 (10.9%)
Disease status, *n* (%)	
Standard risk disease[a]	24 (43.6%)
High-risk disease[b]	31 (56.4%)
Preconditioning, *n* (%)	
TBI regimen	52
Non-TBI regimen	3

TBI total body irradiation

[a] Acute leukemia in first complete remission, chronic myelogenous leukemia in first chronic phase and myeloid displastic syndrome in refractory anemia

[b] More advanced status than standard risk leukemia

3.2 Adverse events

Nephrotoxicity occurred in 20 patients (36.4%) within 100 days post-transplantion. Most of them developed grade 2 or less, and only two patients developed grade 3 or 4 nephrotoxicity. Grade 3 or 4 hepatotoxicity developed in six patients (10.9%). Veno-occlusive disease occurred in three (5.5%) patients. Eight patients (14.5%) had a neurological adverse event. Twenty-nine patients had at least one documented infection during the first 100 days.