patients who were candidates for such myeloablative conditioning, survival and relapse were not significantly different after CBT and rBMT/PBSCT.

Whether an older sibling donor or unrelated donor should be chosen as an optimal donor is an important question in allo-HSCT for older patients. There have been some clinical comparisons of allo-HSCT from older sibling donors and unrelated donors in older patients [16-18]. A European Group for Blood and Marrow Transplantation analysis by Kröger et al. [16] reported on comparisons of allo-HSCT from older sibling donors and young unrelated donors in 719 patients older than 50 years with MDS. They showed that recipients from young unrelated donors had improved survival compared with those from older sibling donors among older patients with MDS. A single-institute analysis by Ayuk et al. [17] showed similar outcomes from older sibling donors compared with young unrelated donors among older patients with AML in CR. On the other hand, Alousi et al. [18] of the Center for International Blood and Marrow Transplantation also performed a similar study in 2172 patients older than 50 years with leukemia or lymphoma. In contrast, their data showed that the risks of overall mortality, relapse, and TRM were lower after allo-HSCT from older sibling donors compared with those from young unrelated donors. However, comparative clinical outcomes of CBT and BMT/PBSCT from older related donors after myeloablative conditioning have yet to be clarified. Our data showed comparable outcomes for CBT and BMT/PBSCT from older related donors after myeloablative conditioning in relatively older patients when cord blood was selected as a primary unrelated donor source.

In comparison with other sources of allo-HSCT, the lower risk of GVHD without compromised graft-versus-leukemia effects is one of the most important advantages of CBT. In our study, the incidences of severe aGVHD and cGVHD were not significantly different after CBT and rBMT/PBSCT. Relapse was also similar between CBT and rBMT/PBSCT recipients. However, TRM was significantly lower after CBT compared with that after rBMT/PBSCT. GVHD-associated mortality was a common cause of late death after rBMT/PBSCT compared with CBT. Newell et al. [19] reported a shorter duration and a higher response of cGVHD to systemic immunosuppressive treatment in CBT recipients than in BMT/PBSCT recipients, suggesting that a longer duration of systemic immunosuppressive treatment for cGVHD might have contributed to higher infection-related late mortality after rBMT/PBSCT compared with CBT. In fact, we previously reported that the termination of immunosuppressive treatment for rBMT/PBSCT recipients was slower than those for CBT recipients [10]. These effects might have contributed to higher TRM after rBMT/PBSCT compared with CBT in our study. In addition, the absence of risk for donors may also be one of the most attractive advantages of CBT for older patients. Older patients generally have older donors as well when they have an HLA-compatible sibling. Because older donors are more likely to have organ dysfunction or comorbidity, older patients hardly ever find healthy sibling donors. These problems could be overcome with the advantages of CBT, especially in older patients.

Myeloablative conditioning regimens for allo-HSCT have been restricted to younger patients and those without comorbidities, because TRM occurs more frequently among older patients and those with serious comorbidities. RIC regimens have recently been expanded for use with graft sources not only from bone marrow or mobilized peripheral blood but also from cord blood. Although the risk of graft failure after CBT has been reported to be higher after RIC compared with myeloablative conditioning [20], several reports showed similar survival with acceptable engraftment between CBT and other graft sources from related and unrelated adult donors after RIC [21,22]. Further studies are warranted to establish optimal RIC regimens for CBT.

In conclusion, our data showed that CBT had almost equivalent results compared with rBMT/PBSCT after myeloablative conditioning for relatively older patients. However, these results should be interpreted with caution because this study was a retrospective single-institute analysis that included a heterogeneous population and a relatively small number of patients. In addition, although our study was performed in patients older than 45 years of age, it should be noted that most patients were younger than 55 years of age. This is because the patients in our cohort received myeloablative conditioning, which often excludes even older patients. As such, our results cannot be extended to patients older than 60 years of age until another similar study is performed using RIC in those older than 55 years. Although these findings should be confirmed in larger prospective studies, CBT could be as safe and effective as BMT/PBSCT from older related donors after myeloablative conditioning for relatively older patients when it is used as a primary unrelated stem cell source.

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Does the Hematopoietic Cell Transplantation Specific Comorbidity Index (HCT-CI) Predict Transplantation Outcomes? A Prospective Multicenter Validation Study of the Kanto Study Group for Cell Therapy

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A B S T R A C T

Recent advances in allogeneic hematopoietic stem cell transplantation have led to increasing use of this modality in older patients who tend to have been more heavily pretreated and have more comorbidities. Thus, the evaluation of comorbidity is of increasing importance to more precisely assess the benefits and risks of the transplantation procedure. Researchers from Seattle developed the hematopoietic cell transplantation–specific comorbidity index (HCT-CI), which was associated with the risk of mortality in several retrospective studies. However, its clinical utility has not been extensively documented in prospective studies. The aim of the present study was to evaluate the utility of the HCT-CI prospectively in a multicenter setting. Overall survival (OS) and nonrelapse mortality (NRM) at 2 years were 59% and 20%, respectively (n = 243). We found that the HCT-CI in its original scale failed to predict OS and NRM in this set of patients. Thus, we applied a flexible HCT-CI risk scoring system (restratifying scores from 0 to 3 to indicate low risk, and scores of 4 or higher as high-risk). The flexible HCT-CI was found to predict 2-year NRM and OS better than the original HCT-CI (NRM: $P = .01$, OS: $P = .003$). In subgroup analysis, we evaluated the usefulness of the original HCT-CI for patients excluding those who received cord blood transplantation (n = 186). Both 2-year OS and 2-year NRM were not significantly different according to the original HCT-CI ($P = .304$, $P = .996$), but with the flexible HCT-CI, there were significant differences in 2-year OS and 2-year NRM ($P = .005$ and $P = .005$, respectively). Multivariate analysis identified age >50, performance status (PS) <90, donor type (HLA-mismatched/unrelated donor), and the flexible HCT-CI ≥4 as significant predictors for worse OS at 2 years. However, the flexible HCT-CI did not remain a significant predictor for NRM at 2 years in multivariate analysis, whereas age, PS, and donor type did. The HCT-CI did not consistently predict both NRM and OS, but it still can be a useful tool in combination with other

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factors, such as PS and age. Furthermore, the HCT-CI, although potentially useful for capturing pretransplantation comorbidity and risk assessment, may need further validation before its adoption for routine clinical use.

INTRODUCTION

Understanding the impact of specific pretransplantation variables on the risk of mortality, especially nonrelapse mortality (NRM), after allogeneic hematopoietic stem cell transplantation (HSCT) is of the utmost importance for deciding which patients will benefit most from this high-risk procedure. In 2005, Sorror et al. developed and validated the most popular HSCT-specific index, the hematopoietic cell transplantation–specific comorbidity index (HCT-CI), intended to quantify the impact of a patient's pretransplantation comorbidities on post-transplantation outcome [1].

Since its creation, various studies have attempted to validate the HCT-CI in different disease-specific settings [2-13]. Its ability to predict survival and NRM has differed between studies, and its ability has not been confirmed in all of them. Furthermore, it has not been fully validated in prospective multicenter studies and its predictive value remains to be elucidated in the Japanese population.

Therefore, the primary aim of the present study was to independently validate the HCT-CI calibration and discrimination in a multicenter prospective study setting. As a secondary aim, we evaluated its usefulness in Japanese patients.

METHODS

Patients

Per protocol, we considered only first transplantations performed using peripheral blood stem cells, bone marrow, or cord blood cells on patients ≥ 16 years old for malignant or nonmalignant hematologic disease as eligible for analysis. Written informed consent was obtained from all patients before registration. The study was approved by the institutional review board of each participating center and was conducted in accordance with the Declaration of Helsinki.

Table 1
Patient and Disease Characteristics

Characteristic	Value
Total patients	243
Age at transplantation, median (range), yr	45.3 (16-74)
Diagnoses	
AML	102
ALL	45
MDS	39
Lymphoma	20
CML	9
AA	9
ATL	8
MF	6
MM	5
Disease risk	
High	139
Intermediate	104
Remission status at transplantation	
High	37
Low	206
Conditioning regimens	
MAC	166
RIC	77
Donors	
Related	68
Unrelated	175
Hematopoietic cell source	
BM	156
CBT	57
PB	30

AML indicates acute myeloid leukemia; ALL, acute lymphoid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; AA, aplastic anemia; ATL, adult T cell leukemia; MF, myelofibrosis; MM, multiple myeloma; BM, bone marrow; CBT, cord blood; PB, peripheral blood.
Data presented are n unless otherwise indicated.

Comorbidity Scoring System

Pretransplantation comorbidities were scored according to the original HCT-CI before conditioning started in all patients, who were then followed for 2 years or until relapse or death, if earlier than 2 years after transplantation. Of the 244 patients, complete clinical data allowing assessment of HCT-CI were available in 243. One patient with incomplete information was excluded from the analysis. Although the original HCT-CI uses a definition of pulmonary dysfunction based on subjective symptoms or the results of respiratory function testing, we modified it to use only the results of the latter, to define pulmonary dysfunction more precisely and eliminate bias between facilities in diagnosing pulmonary comorbidity. The respiratory function test was performed in all patients but 1. According to the original HCT-CI, patients were divided into 3 groups: low (score = 0), intermediate (1 and 2), and high (≥3), as previously reported.

Transplantation

According to the European Group for Blood and Marrow Transplantation (EBMT) criteria [14], we considered regimens with a total busulfan dose >8 mg/kg, cyclophosphamide dose >120 mg/kg (or >60 mg/kg, if in combination with other drugs), or total body irradiation >6 Gy as myeloablative conditioning (MAC). Reduced-intensity conditioning (RIC) regimens were fludarabine-based with or without low-dose total body irradiation (4 Gy).

Disease Risk and Remission Status at Transplantation

As described by Sorror et al. [1], we categorized disease risk as low or high. Low-risk diseases were defined as chronic myeloid leukemia in first or second chronic phase, aplastic anemia, acute leukemia in first or second complete remission, myelodysplastic syndrome in refractory anemia or refractory anemia with ring sideroblasts, and chemosensitive lymphoma or multiple myeloma. All other conditions were classified as high-risk diseases.

Statistical Methods

The primary endpoints for this analysis were the cumulative incidence of NRM and OS 2 years after allogeneic HSCT. Probabilities of NRM and OS were calculated using the Kaplan-Meier method, and the log-rank test was used for univariate comparisons. The Cox regression model was used for multivariate analysis to identify prognostic factors among variables that included age, performance status (PS), disease risk, remission status at the time of HSCT, donor type, and the HCT-CI. Stepwise selection algorithm was applied for model selection using as criteria $P = .10$ for variable entry. Relative risk with 95% confidence interval and P value were determined from these analyses. All P values were 2-sided, with the type 1 error rate fixed at .05. Statistical analyses were performed with SAS software version 8.2 (SAS institute, Cary, NC).

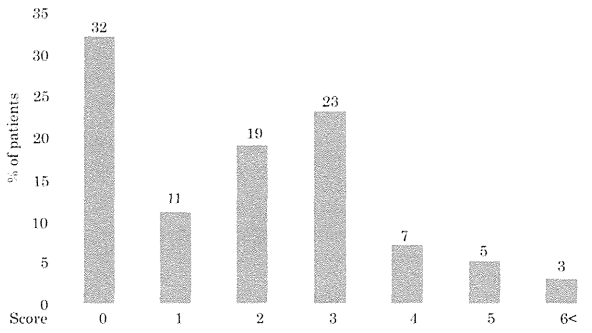

Figure 1. Distribution of HCT-CI. The distribution of HCT-CI scores is found to be essentially the same in Japanese patients as reported in the original study.

Table 2
Prevalence of Comorbidities

Comorbidity	Prevalence
Pulmonary (mild)	67 (27.5)
Pulmonary (severe)	59 (24.2)
Hepatic (mild)	35 (14.4)
Infection	22 (9.0)
Psychiatric	11 (4.5)
Diabetes	8 (3.2)
Hepatic (moderate/severe)	6 (2.4)
Solid tumor	6 (2.4)

Data presented are n (%).
Compared with the original report, our study cohort has a larger proportion of patients with pulmonary comorbidity.

RESULTS

Patient Characteristics

In this study, 243 consecutive patients with a variety of hematological disorders who underwent allogeneic HSCT from 2007 to 2009 in 14 facilities of the Kanto Study Group for Cell Therapy in Japan were enrolled. Diagnosis and other details of the patients are summarized in Table 1. The median age at transplantation was 45.3 years (range, 16 to 74 years). A total of 166 patients received MAC and 77 received RIC. The stem cell sources included bone marrow (n = 156), peripheral blood (n = 30), and cord blood (n = 57). Sixty-eight patients received a transplant from a related donor and 175 from an unrelated donor. The most frequent diagnosis was myeloid malignancies (acute myeloid leukemia/myelodysplastic syndrome; 58.2%), followed by acute lymphoblastic leukemia (18.4%) and non-Hodgkin lymphoma (10.7%).

HCT-CI

The distribution of HCT-CI scores was found to be essentially the same in Japanese patients as reported in the original study (Figure 1). The distribution of the comorbidities represented in the HCT-CI score is shown in Table 2. The most frequent comorbidities were mild or severe pulmonary comorbidities (51.9%), followed by mild hepatic comorbidity (14.6%) and active infections (9.3%). The other comorbidities observed in this cohort included psychiatric problems (4.8%),

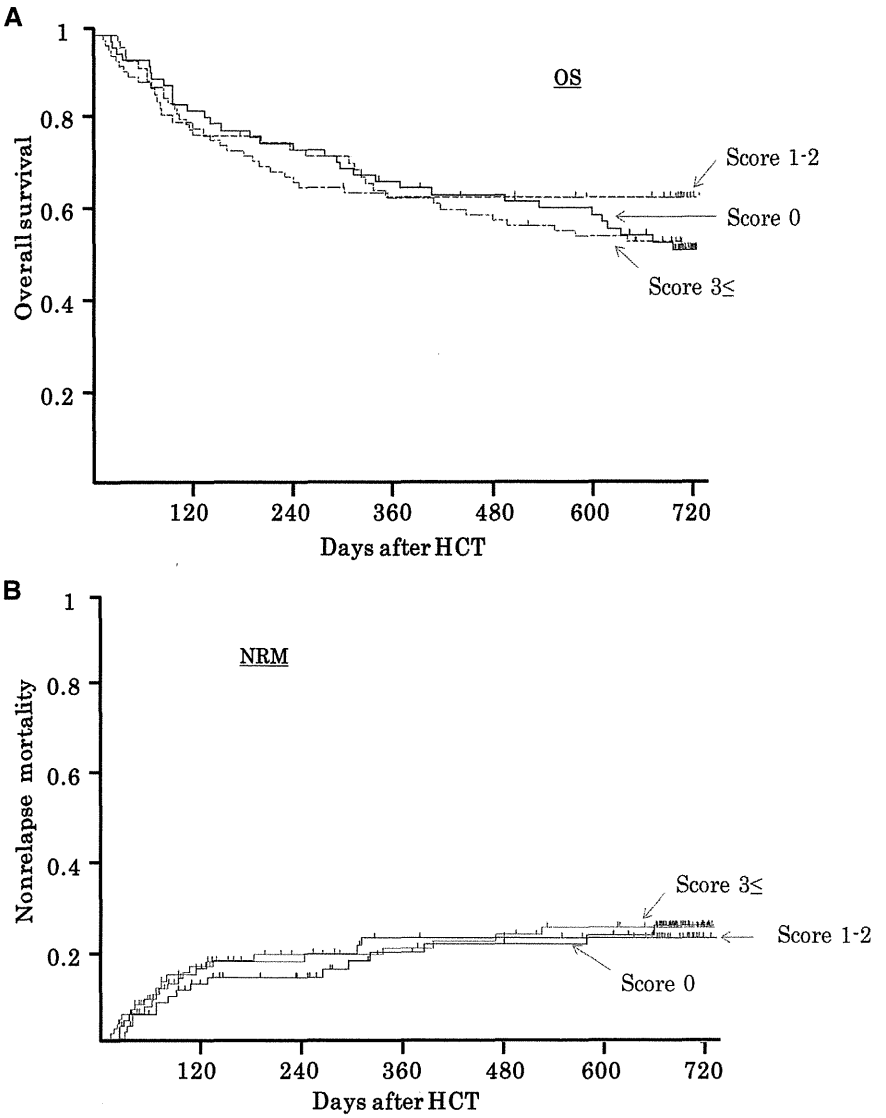

Figure 2. Two-year OS/NRM using the original HCT-CI scoring system. (A) Shows OS ($P = .44$) and (B) NRM ($P = .96$). The original HCT-CI scoring system fails to predict OS and NRM at 2 years in our cohort.

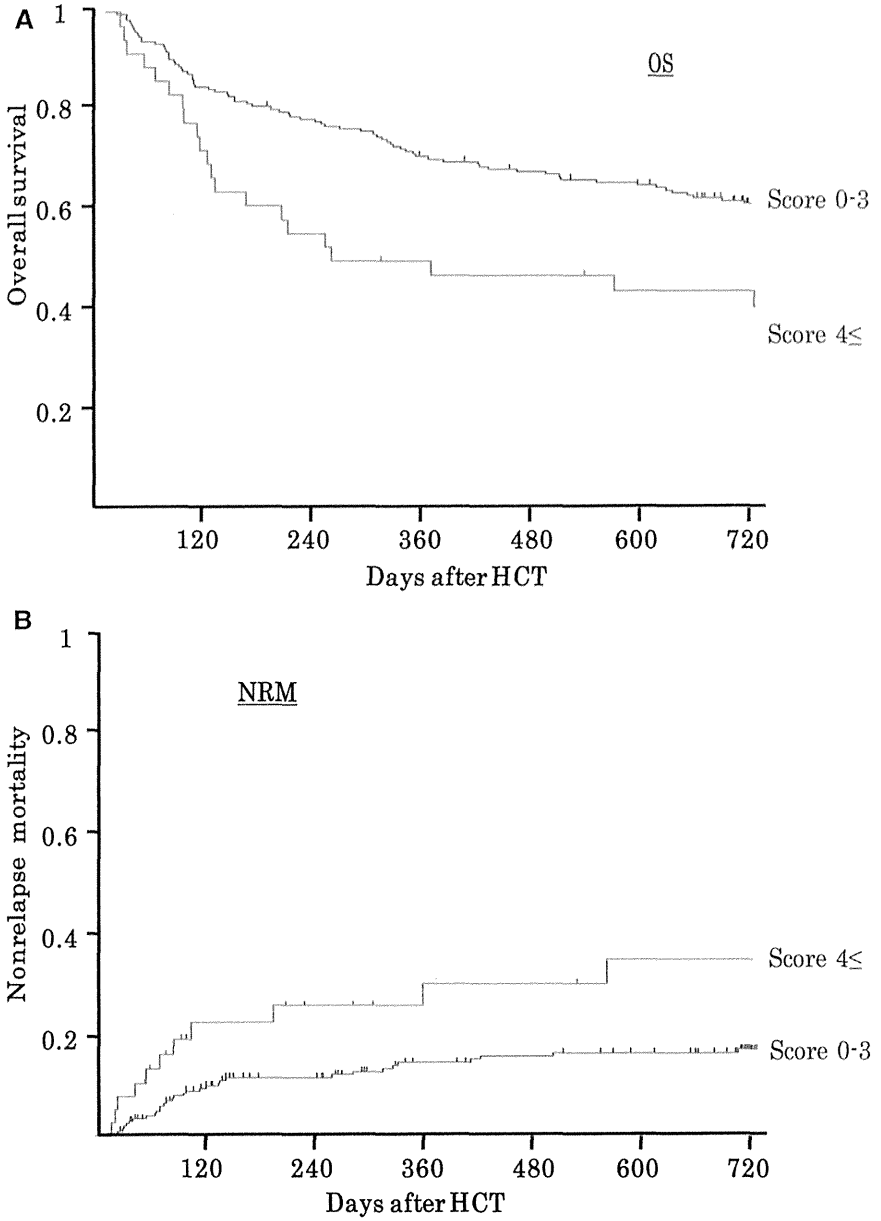

Figure 3. Two-year OS/NRM using the flexible HCT-CI scoring system. (A) Shows OS ($P = .003$) and (B) shows NRM ($P = .01$). The flexible HCT-CI has a better predictive capacity for NRM and OS at 2 years than the original HCT-CI.

diabetes (3.6%), moderate to severe hepatic dysfunction (2.8%), and solid tumors (2.8%). The original HCT-CI scoring system failed to predict OS ($P = .44$) and NRM ($P = .96$) at 2 years in our cohort (Figure 2). When outcome was plotted according to the number of individual HCT-CI scores, 2 risk groups emerged. We, therefore, applied the flexible HCT-CI risk scoring system (scores of 0 to 3 were restratified as low risk and scores ≥4 as high-risk). Thus, we grouped our patients into 2 risk categories (low and high). The distribution of the flexible HCT-CI did not differ significantly for age at the time of transplantation (younger versus older than 50 years), source of transplanted stem cells (bone marrow versus peripheral blood versus cord blood), or conditioning regimen (MAC versus RIC). The superior predictive capacity of the flexible HCT-CI for NRM ($P = .01$) and OS at 2 years ($P = .003$) compared with the original HCT-CI was confirmed (Figure 3).

Comparing the prognostic value of the original HCT-CI with the flexible HCT-CI using the Cox regression model and likelihood ratio test, there was a significantly higher predictive power for both NRM (likelihood ratio test: 5.12, $P < .001$) and OS at 2 years (likelihood ratio test: 7.00, $P < .001$) using the flexible HCT-CI.

Outcome and Cause of Death

The OS and NRM of all patients were 59% and 20% at 2 years, respectively. The most common cause of NRM was infection. Although the distribution of the HCT-CI was not associated with any causes of NRM, patients with a score ≥ 3 were more likely to die from infection (data not shown).

Multivariate Analysis

Multivariate analysis identified age (>50) ($P = .01$, hazard ratio [HR], 1.80), PS (<90) ($P = .002$; HR, 2.57), donor type

Table 3
Multivariate Analysis

Factor	Two-Year OS		Two-Year NRM	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age				
≤50	1		1	
>50	1.80 (1.14-2.84)	.01	2.17 (1.14-4.12)	.017
Sex				
M	1		1	
F	.91 (.60-1.36)	.65	.82 (.46-1.45)	.5
PS				
≥90	1		1	
<90	2.57 (1.38-4.79)	.002	4.60 (2.12-9.99)	.0001
Disease risk				
Low	1		1	
High	1.25 (.81-1.93)	.3	.92 (.50-1.69)	.8
Conditioning				
MAC	1		1	
RIC	.70 (.43-1.13)	.14	.61 (.31-1.18)	.1448
Donor type				
MRD	1		1	
Not	1.82 (1.08-3.06)	.02	2.80 (1.18-6.64)	.0189
HCT-CI score				
0-3	1		1	
≥4	1.82 (1.10-3.01)	.019	1.65 (.81-3.36)	.165

Multivariate analysis identified age (>50), PS (<90), donor type (HLA-mismatched/unrelated donor), and flexible HCT-CI score (≥4) as significant predictors for worse OS at 2 years. However, flexible HCT-CI score does not remain a significant predictor for NRM at 2 years, whereas age, PS, and donor type did remained as significant predictors.
95% CI indicates 95% confidence interval; MRD, HLA-matched related donor.

(HLA-mismatched/unrelated donor) ($P = .02$; HR, 1.82), and the flexible HCT-CI score (≥4) ($P = .019$; HR, 1.82) as significant predictors of worse OS at 2 years (Table 3). However, the flexible HCT-CI was not a significant predictor of NRM at 2 years, in contrast to age ($P = .017$; HR, 2.17), PS ($P = .0001$; HR, 4.60) and donor type ($P = .0189$; HR, 2.80).

Subgroup Analysis

As Sorror's original study excluded cord blood transplantations, we evaluated the usefulness of the original HCT-CI for patients excluding cord blood recipients (n = 186). Both 2-year OS and 2-year NRM were not significant different according to the original HCT-CI ($P = .304$, $P = .996$, respectively), but with the flexible HCT-CI, there were significant differences in 2-year OS and 2-year NRM ($P = .005$ and $P = .005$, respectively) (Figure 4).

DISCUSSION

We originally planned to independently validate the HCT-CI, a widely used prognostic tool originally proposed in 2005, the usefulness of which has been subsequently reported only in studies based on limited, retrospective, and mostly single-center patient series. For this study, we prospectively enrolled unselected patients consecutively undergoing allogeneic HSCT in Japan and evaluated the predictive ability of the HCT-CI for NRM and OS, applying the same selection criteria originally used by Sorror et al.

We found no predictive value for OS and NRM using the original HCT-CI. We then applied a flexible HCT-CI risk scoring system (restratifying those with a score of 0 to 3 as low risk and those with a score ≥ 4 as high risk). We found that this flexible HCT-CI did have predictive capacity for NRM and OS at 2 years. Furthermore, multivariate analysis identified age (>50), PS (<90), donor type (HLA-mismatched/unrelated donor), and the flexible HCT-CI (≥4) as significant predictors of worse OS at 2 years. However, the flexible HCT-CI did not appear to be a significant predictor for NRM at 2 years, whereas age, PS, and donor type were significant predictors. Compared with the original report, our study cohort had a larger prevalence of pulmonary comorbidity (51.9% versus 33%). We assume that the sensitivity of detecting this in our study was higher than in the original study because we used respiratory function testing to capture pulmonary comorbidity. We think it is very useful to evaluate the respiratory function in this way, to determine pulmonary comorbidity more accurately. However, this may result in a requirement to modify scoring because of the higher sensitivity of respiratory function testing when applied as the only criterion of pulmonary dysfunction. Renal dysfunction is defined by creatinine levels, but these are gender sensitive and also vary between facilities. Creatinine levels > 1.2 mg/dL (the reference value in the original definition) indicate that the glomerular filtration rate has already decreased significantly. Therefore, creatinine levels do not reflect renal dysfunction correctly. We would like to propose the use of creatinine clearance instead. In our cohort, the score distribution was almost the same as in the original study, but the frequencies of comorbidities were different. Some comorbidities, such as obesity, occur less frequently in Japan than in Western countries. Racial differences are evident in the distribution of the particular comorbidity in scale. We may have to re-examine the distribution of the score and reconsider certain items for a more appropriate Japanese scale.

About 85% of patients were included in the score from 0 to 3 group. Patients in this group had similar outcomes, regardless of any differences in the score, possibly because of a strong influence of the high prevalence of pulmonary comorbidity. More than 50% of patients were assessed as having pulmonary dysfunction; undoubtedly, some cases were included where pulmonary dysfunction did not directly affect the prognosis. Barba et al. reported that 85% of patients were considered to be suffering from pulmonary comorbidity in their cohort [15]. They found no predictive value of the original score, and, therefore, used a different risk group stratification. With the aim of including a sufficient number of patients in each risk group, they decided to use a modified HCT-CI, in which patients were classified into low (score 0 to 3), intermediate (4 and 5), and high risk (≥6). They suggest that modified HCT-CI has better predictive capacity for 2-year NRM than the original HCT-CI. There are a few reports employing modified-risk group stratification because the original cut-off points failed to yield any significant differences [16,17]. That is, if the frequency of the comorbidity is different from the original study, the original cut-off points may no longer be applicable. Because the prevalence of comorbidity depends on the patient's background, the cut-off points may need to be changed according to the characteristics of the patient population.

Considering regional and racial differences in the prevalence and severity of comorbidities, the HCT-CI tool required validation in non-Western countries, as well. Three retrospective Japanese studies on the HCT-CI were previously reported. Maruyama et al. assessed 132 transplantation patients with non–complete remission. A higher HCT-CI score was associated with increased risk of NRM and poor OS. That study was valuable in that it demonstrated that the HCT-CI could be applicable in Japan [18]. Kataoka et al. investigated the usefulness of the HCT-CI with 187 patients who underwent transplantation. They classified patients into 2 groups, according to disease risk. The HCT-CI was associated

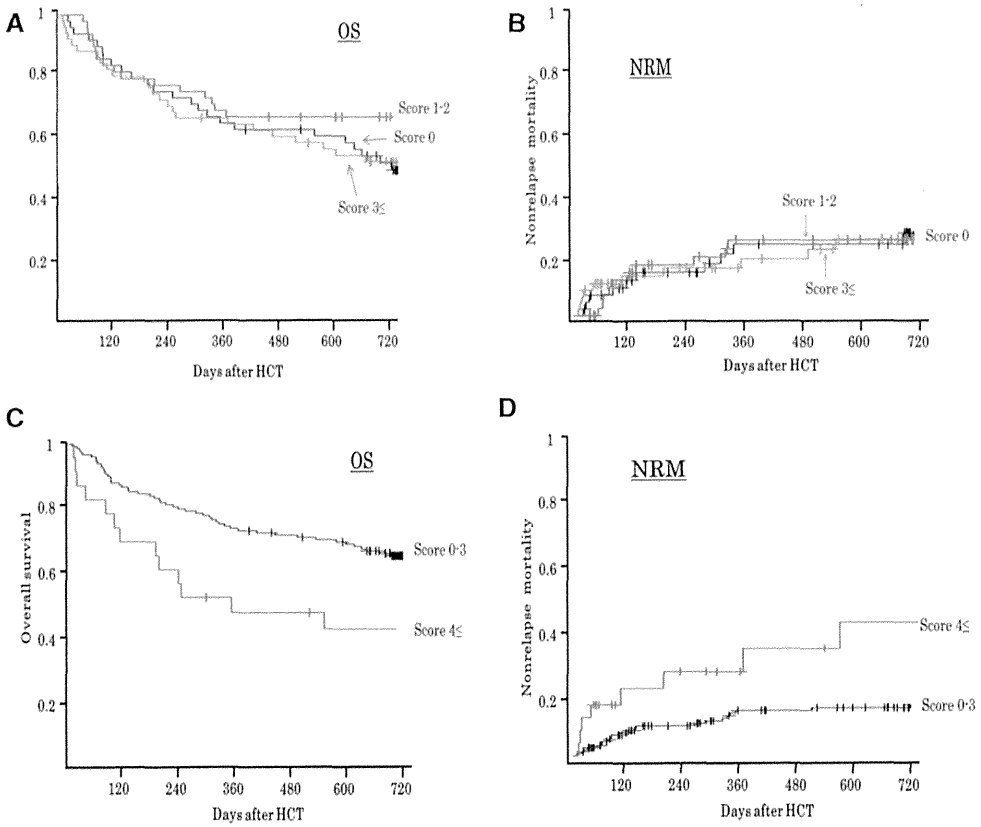

Figure 4. Two-year OS/NRM in patients excluding cord blood recipients. (A) Shows OS by the original HCT-CI ($P = .304$). (B) Shows NRM by the original HCT-CI ($P = .996$). (C) Shows OS by the flexible HCT-CI ($P = .005$). (D) Shows NRM by the flexible HCT-CI ($P = .005$). The flexible HCT-CI has a better predictive capacity for NRM and OS at 2 years than the original HCT-CI in patients excluding cord blood recipients.

with OS and NRM at 3 years in low-risk patients but not in high-risk patients. Regarding the prevalence of comorbidity, hepatic dysfunction was most common (42%), followed by pulmonary dysfunction (35%) [19]. Takasaki et al. examined 71 transplantation patients over 50 years of age. A high HCT-CI (≥3) was significantly associated with worse OS and NRM at 5 years. In that study, the most frequent comorbidity was pulmonary comorbidity (39%), followed by infection (23%) [20]. More recently, 2 large prospective studies were carried out to assess the usefulness of this scale [21,22]. In agreement with previous reports, the HCT-CI was 1 of several significant prognostic factors, but it was not consistently predictive. According to our multivariate analysis, the HCT-CI may be a useful predictive tool in combination with other factors, such as PS and age.

Our study has the typical limitation of a small sample size and relatively short duration of follow-up. Statistical power is low because of our small sample size. We cannot deny that significant differences did not become apparent because of the low power. Hence, it is difficult to draw any definitive conclusions. Nevertheless, the observed data demonstrate that the HCT-CI is useful for assessing the role of comorbidity information in clinical risk-adapted decision-making for HSCT candidates.

In conclusion, the HCT-CI is a simple novel tool that considers the presence or absence of pretransplantation comorbidities to predict the risk of death from transplantation-related complications. It has the potential for widespread applicability, both in clinical practice and in clinical trials in Western countries. However, some investigators have already shown that the HCT-CI may not useful for all the different possible allogeneic HSCT settings, such as different disease types, transplantation procedures, and donors, as well as the patient's risk profile [6-30]. Thus, a possible weakness of all current models may be related to their not having the same impact in different patient and transplantation populations. The HCT-CI, although a useful tool for capturing pretransplantation comorbidity and risk assessment, needs to be further validated before adopting it for routine clinical use.

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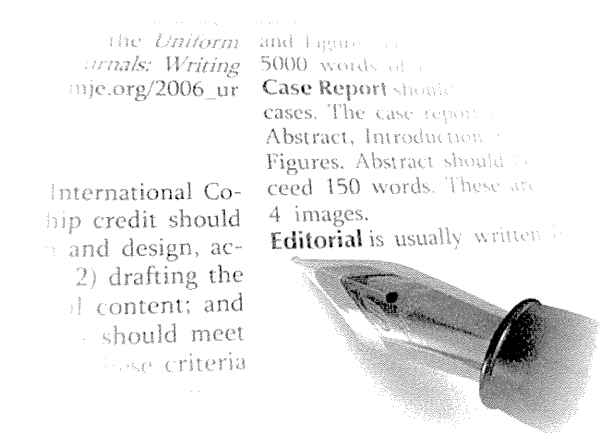

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Editorial

Here comes the cord

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Hematopoietic stem cell transplantation has been established as a lifesaving therapy for leukemias or other hematopoietic malignancies since more than a half century ago [1]. Human leukocyte antigen (HLA)-matched sibling is the preferred donor for the better clinical outcomes, whiles, even patients without suitable family donor could also receive the benefits from unrelated donor registries or cord blood (CB) banks. International collaboration has also been well-improved in this field. Nowadays, almost all patients who need allogeneic transplantation are able to find adequate donors.

Advantages to use CB unit are the quick availability, lower risk of severe graft-versus-host disease (GVHD) even though HLA between recipients and CB grafts is mismatched in most cases, and no risk for CB donors medically and mentally. Since the first patient received the CB from his HLA-matched sister to treat Fanconi Anemia successfully in 1988 [2], many CB banks have been established and the numbers of transplants using unrelated CB units dramatically increased. There are approximately 621,000 CB units in the database of Bone Marrow Donors Worldwide (BMDW: http://www.bmdw.org/). Recently, more than 3,000 CB transplantation (CBT)s are carried out annually all over the world: one third in Europe, one third in North America and another one third in Asia (mostly in Japan). Pediatric patients were major users in early period, however, CBT are gradually adopted in adults in this decade. For example, we are performing more than 1,200 transplantations using single CB unit annually in Japan, and more than 80% are adult patients with hematology malignancies, and a half of the recipients are older than 50 years. The major reason of this increment in the world is the improved clinical outcomes. Recently, for example, Eapen and colleagues [3] compared results of 165 single CBT for adult patients, 888 peripheral blood stem cell transplant (PBSCT) patients, and 472 bone marrow transplant (BMT) patients. Transplant-related mortality was higher for the CBT patients, but chronic GVHD were lower. Leukemia-free survival was comparable among CBT, fully matched, and mismatched PBSCT/BMT patients [3]. These findings have contributed to increase the CBT activity among the international transplant societies and have gradually improved the reliability of this transplant strategy.

There is still limitation in CBT such as delayed engraftment and poor immune cell reconstitution [4]. The quality assurance of CB unit is also key issue for the reliability of CBT among the patients, their families, and transplant physicians. Cell dose is the most significant parameters for engraftment capacity of CB unit and also for survival results after CBT. Especially, CD34-positive cell number indicates the hematopoietic stem or progenitor cell function. However, the diversity of technical difference between CB banks has been evoked and it is necessary that we adjust that standard. Efforts are being intensified by the Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee - International Society for Cellular Therapy and European Group for Blood and Marrow Transplantation (FACT-JACIE), the American Association

of Blood Banks (AABB), and CB banks all over the world. Because the importance of cell dose is critical, researchers are focusing on CB expansion strategies and some of them are under laboratory and clinical assessment.

Under the situation described as above, CBT is definitely contributing to improving the life prognosis of patients with hematological malignancies. On the other hand, the utilized percentage of donated CB units all over the world is 6.3% reported by World Marrow Donor Association (WMDA), however it was reported as 1.2% in Korea. In this issue of **Blood Research**, Choi *et al.* [5] has analyzed the reasons by the questionnaire survey using "Audience Response System" for 67 board-certified transplant physicians at the annual meeting of the Korean Society of Blood and Marrow Transplantation. According to ordinary expectations, Korean physicians are now not positive for choose CB units as stem cell source for transplantation, because of the fears for poor clinical results and for unsatisfied quality of CB units from domestic CB banks. However, some Korean transplant specialists and CB bank persons have continued to proceed with great efforts for achieving the satisfied clinical outcomes with CBT and for obtaining good enough quality of CB units. They have already known the education is also important to improve the reliabilities for the strategy. Please just remember the time when you started BMT or PBSCT, or even transplant with haplo just a couple of years ago. Nothing gains without going forward. Here comes the time of CBT.

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ASBMT American Society for Blood and Marrow Transplantation

Choreito Formula for BK Virus–associated Hemorrhagic Cystitis after Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Therapy for BK virus (BKV)–associated hemorrhagic cystitis (BKV-HC) is limited after hematopoietic stem cell transplantation (HSCT). We examined whether choreito, a formula from Japanese traditional Kampo medicine, is effective for treating BKV-HC. Among children who underwent allogeneic HSCT between October 2006 and March 2014, 14 were diagnosed with BKV-HC (median, 36 days; range, 14 to 330 days) after HSCT, and 6 consecutive children received pharmaceutical-grade choreito extract granules. The hematuria grade before treatment was significantly higher in the choreito group than in the nonchoreito group ($P = .018$). The duration from therapy to complete resolution was significantly shorter in the choreito group (median, 9 days; range, 4 to 17 days) than in the nonchoreito group (median, 17 days; range, 15 to 66 days; $P = .037$). In 11 children with macroscopic hematuria, the duration from treatment to resolution of macroscopic hematuria was significantly shorter in the choreito group than in the nonchoreito group (median, 2 days versus 11 days; $P = .0043$). The BKV load in urine was significantly decreased 1 month after choreito administration. No adverse effects related to choreito administration were observed. Choreito may be a safe and considerably promising therapy for the hemostasis of BKV-HC after HSCT.

INTRODUCTION

Hemorrhagic cystitis (HC) is a severe complication in patients undergoing hematopoietic stem cell transplantation (HSCT), resulting in significant morbidity, such as nephropathy and renal failure, prolonged hospitalization, and prolonged blood transfusion requirement [1,2]. Effects on mortality have also been reported in children undergoing HSCT [3]. Early-onset HC occurs within 1 week after HSCT and is mostly a symptom of regimen-related toxicity. Late-onset HC usually occurs after engraftment and is associated with viral infections, including those caused by the human polyomavirus BK (BKV), polyomavirus JC, adenovirus (AdV), and cytomegalovirus (CMV) [4]. BKV is the most frequent cause of late-onset HC and affects 5.3% to 21.2% of children undergoing HSCT [5-9]. BKV viruria is detected by real-time quantitative PCR (RT-PCR) in all patients with BKV-HC. A BKV load of more than 10^6 copies/mL in urine may be associated with a high risk of developing HC after HSCT [5]. However, asymptomatic BK viruria is detected in 50% to 100% of patients after HSCT [5,7,10], implicating that the presence of BKV viruria alone does not explain the pathogenesis of HC. High BKV viremia ($\geq 10^3$ copies/mL) is a better predictor of BKV-HC after HSCT, with a reported specificity of 93% [8]. Children with high BKV viremia ($\geq 10^4$ copies/mL) are at a higher risk of developing severe HC [6].

The standard treatment for BKV-HC has not been established [2]. Supportive therapy is provided to patients with mild BKV-HC, including intravenous hydration, bladder irrigation, and symptomatic relief treatment, such as the use of analgesics. Patients with severe BKV-HC require additional therapy. The current first line BKV-oriented therapy is intravenous cidofovir; however, its efficacy remains controversial [2]. Alternative strategies include intravesical instillation of cidofovir [2,7], hyperbaric oxygen therapy [11], leflunomide, and fluoroquinolone [12]; however, their effect is limited [13]. Invasive intervention such as vascular embolization or cystectomy may be necessary in uncontrollable HC.

Choreito is a formula derived from Japanese traditional Kampo medicine. The indication for choreito in the context of

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Kampo medicine is "dampness-heat" in the lower abdomen, the characteristic symptoms of which include dysuria, heat in the lower abdomen, and thirst. All these symptoms may be caused by inflammation and blood clots in the bladder. Based on this indication, choreito has been administered to patients with acute simple cystitis and urolithiasis, and its effectiveness has been confirmed [14]. Recently, choreito was successfully used to treat massive gross hematuria with clot retention in the bladder in a child with refractory acute lymphoblastic leukemia [14]. At present, choreito is covered by the national health insurance and is widely used for genitourinary symptoms in Japan.

Symptoms leading to the traditional use of choreito appear to overlap with symptoms associated with BKV-HC; indeed, some children receive choreito for HC. In this study, we retrospectively analyzed BKV-HC in children undergoing HSCT and evaluated the efficacy of choreito treatment.

PATIENTS AND METHODS

Definition

HC was defined as microscopic (blood in urine graded 1+ or more) or macroscopic hematuria combined with dysuria, pollakisuria, urinary urgency, and/or the sensation of residual urine in the absence of bacteria in urine as observed by culture [9]. *BKV-HC* was defined as the association of HC with BKV viruria and/or viremia. HC was graded according to the widely used criteria [15]. Grade I is defined as microscopic hematuria, grade II as macrohematuria, grade III as macroscopic hematuria with clots, and grade IV as macroscopic hematuria with renal or bladder dysfunction. The onset of BKV-HC was defined as the first day when patients presented with urinary symptoms, and *complete resolution* (CR) of HC was defined as blood in urine (− or ± for hemoglobin) and disappearance of dysuria, pollakisuria, urinary urgency, and the sensation of residual urine related to HC.

Patient Inclusion Criteria of BKV-HC and Choreito Administration

Among the children (≤18 years old) who received allogeneic HSCT between October 2006 and March 2014 in Nagoya University Hospital, 14 were diagnosed with BKV-HC and included in the study. Their medical records were retrospectively analyzed. Patient characteristics are listed in Table 1. Intravenous fluids corresponding to 2.5 to 3.0 L/m^2/day with forced alkalinized diuresis were administered during conditioning, and patients treated with cyclophosphamide received prophylactic mesna for the prevention of HC. All the patients received acyclovir for herpes prophylaxis and weekly intravenous immunoglobulin for viral prophylaxis. Tacrolimus was intravenously administered for graft-versus-host disease (GVHD) prophylaxis in patients receiving HSCT from an unrelated donor. Cases of engraftment syndrome and GVHD were treated by methylprednisolone, followed by salvage therapies in nonresponding patients. Six children with BKV-HC diagnosed after March 2013 received a pharmaceutical-grade medicine, choreito extract granules (Tsumura & Co., Tokyo, Japan) with a dose of .2 g/kg per os daily in 3 divided doses (maximum, 7.5 g/day). Cidofovir and choreito were administered at the onset of macroscopic hematuria. Because it is not currently approved for clinical use in Japan, cidofovir was administered only to those who provided written informed consent.

Quantification of BKV DNA

Children undergoing HSCT were weekly monitored for plasma CMV, human herpesvirus 6, and Epstein-Barr virus, and those who met the criteria for HC underwent additional viral workup, including analysis for BKV, polyomavirus JC, and AdV. For 2 patients with BKV diagnosed before December 2009, BKV had been detected in urine by qualitative PCR. This qualitative PCR could not detect BKV in patients without HC. After January 2010, viruses were monitored by multiplex RT-PCR for quantification of DNA from BKV, polyomavirus JC, and AdV, as described previously [16]. In April 2010, BKV RT-PCR was used to screen all 30 hospitalized children with various hemato-oncological diseases who had neither HC-related symptoms nor abnormal urinalysis. All patients provided informed consent for viral PCR workup in accordance with the Declaration of Helsinki. This retrospective analysis was approved by the ethics committee of Nagoya University Graduate School of Medicine.

Statistical Analysis

Statistical analysis was performed using the Fisher's exact test for categorical variables and the Mann-Whitney's U test for continuous variables. The Wilcoxon signed-rank test was used for paired samples. Odds ratios with confidence intervals were estimated by the logistic regression. A probability (P) value <.05 was considered to indicate statistical significance. All statistical analyses were conducted using JMP Pro 11.0.0 (SAS Institute Inc., Cary, NC).

RESULTS

BKV Screening in Hemato-oncological Patients without Genitourinary Symptoms

All children with hemato-oncological disorders hospitalized in the same ward were screened for BKV viruria for the purpose of surveillance. BKV viruria was detected in 5 (17%) of 30 hospitalized children with various hemato-oncological diseases who had neither HC-related symptoms nor abnormal urinalysis. The median urine BKV load in children with asymptomatic viruria was 1.3×10^6 copies/mL (range, 3.5×10^3 to 2.0×10^9 copies/mL), which was significantly lower than that in children with BKV-HC (median, 5.4×10^{10} copies/mL; range, 8.3×10^7 to 1.5×10^{11} copies/mL; $P = .0021$).

Patient Characteristics of Cases with BKV-HC after HSCT

Table 1 summarizes the patient characteristics of 14 children who underwent HSCT and later developed BKV-HC. In patients 1 and 2, BKV was detected in urine by qualitative

Table 1
Patient Demographics of BKV-HC after HSCT

UPN	Choreito Treatment	Age, yr	Sex	Diagnosis	Clinical Status	Preconditioning Regimen	Stem Cell Source	GVHD Prophylaxis
1	No	15.3	M	AA	Non CR	CY + ATG + TBI 5 Gy	UR-BM	FK + sMTX
2	No	16.0	M	AA	Non CR	FLU + CY + Campath + TBI 3 Gy	UR-BM	FK + sMTX
3	No	12.3	M	B-ALL	CR1	MEL + TBI 12 Gy	UR-BM	FK + sMTX
4	No	11.8	M	CML	CyCR	FLU + MEL + TBI 3 Gy	UR-BM	FK + sMTX
5	No	7.1	F	T-ALL	CR2	FLU + MEL + ATG + TBI 12 Gy	Haplo	FK + sMTX
6	No	5.7	M	NB	CR1	FLU + MEL + TBI 2 Gy	UR-CB	FK + sMTX
7	No	15.4	M	CMML	Non CR	FLU + MEL + ATG + TBI 5 Gy	Haplo	FK + sMTX
8	No	7.8	M	B-ALL	CR2	MEL + ATG + TBI 12 Gy	UR-BM	FK + sMTX
9	Yes	14.3	M	AA	Non CR	FLU + MEL + ATG + TBI 3 Gy	Haplo	FK + sMTX
10	Yes	5.4	M	MDS	Non CR	FLU + MEL + ATG + TBI 5 Gy	Haplo	FK + sMTX
11	Yes	10.1	F	AA	Non CR	FLU + MEL + ATG + TBI 5 Gy	Haplo	FK + sMTX
12	Yes	12.2	F	CMML	Non CR	FLU + MEL + ATG + TBI 5 Gy	Haplo	FK + sMTX
13	Yes	6.8	M	B-ALL	CR2	MEL + TBI 12 Gy	UR-BM	FK + sMTX
14	Yes	7.5	M	MDS	Non CR	FLU + MEL + ATG + TBI 5 Gy	Haplo	FK + sMTX

UPN indicates unique patient number; M, male; AA, aplastic anemia; Cy, cyclophosphamide; ATG, antithymocyte globulin; TBI, total body irradiation; UR, unrelated; BM, bone marrow; FK, tacrolimus; sMTX, short course of methotrexate; FLU, fludarabine; Campath, alemtuzumab; ALL, acute lymphoblastic leukemia; MEL, melphalan; CML, chronic myelogenous leukemia; CyCR, cytological complete remission; F, female; Haplo, haploidentical transplant; NB, neuroblastoma; CB, cord blood; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome.

PCR; therefore, other agents including preconditioning could have contributed to HC. Six of the 14 children received choreito because of BKV-HC. All patients were older than 5 years (median, 11 years; range, 5.4 to 16 years). Antithymoglobulin or alemtuzumab was administered to 10 of 14 children (71%) as a preconditioning. Notably, all the children received total body irradiation with various doses.

Children were diagnosed with BKV-HC at a median 36 days (range, 14 to 330 days) (Table 2) after HSCT. Six of 14 patients (43%) had grade II to IV acute GVHD, and 11 of 14 (79%) received steroids for treatment of engraftment syndrome and/or acute GVHD before being diagnosed with BKV-HC. Three children with acute GVHD grade III or IV received intensified immunosuppressive treatment for steroid-resistant GVHD; 1 received infliximab and the other 2 received infliximab, basiliximab, and mesenchymal stem cells. All 3 responded well to additional therapy for acute GVHD. Concomitant AdV viruria was detected in 2 of 14 children (14%), and 12 of 14 children (86%) developed CMV and/or Epstein-Barr virus infection after HSCT. AdV titers in the urine were 2.6×10^8 copies/mL in patient 3 and 1.8×10^8 copies/mL in patient 7 at the time of diagnosis. CMV viruria was not detected in any of these 14 children when BKV-HC was diagnosed. Six children were receiving gancyclovir and/or foscarnet for CMV reactivation at the time of BKV-HC diagnosis.

Treatment for BKV Cystitis with Choreito

Six of 14 children with BKV-HC diagnosed after October 2013 received choreito (Tables 1 to 3). All 6 fulfilled the Kampo indication for receiving choreito ("lower energizer dampness-heat" in patients 9, 11, 12, 13, and 14, and "heat binding in the lower energizer" in patient 10). Patient characteristics, including age at HSCT, sex, underlying disease, engraftment syndrome, acute GVHD frequency and grade, immunosuppressive treatment, absolute lymphocyte count, antiviral therapy, duration of steroid use before the diagnosis of BKV-HC, and duration from HSCT to the onset of BKV-HC, did not differ significantly between the choreito group and the nonchoreito group (Tables 1 and 2). However, the hematuria grade at the time of diagnosis of BKV-HC was significantly higher in the choreito group than in the nonchoreito group ($P = .018$) (Table 2). Choreito was administered over a median of 5 days after the onset of symptoms related to BKV-HC (range, 2 to 16 days), and this interval was not statistically different from that of other treatments (median, 4 days; range, 1 to 23 days; $P = .43$) (Table 3). The urine BKV load before treatment amounted to a median of 2.6×10^{10} copies/mL (range, 1.3×10^9 to 6.3×10^{10} copies/mL) in children receiving choreito, which was not statistically different from that in those not receiving choreito (median, 3.4×10^{10} copies/mL; range, 8.3×10^7 to 1.3×10^{11} copies/mL; $P = .67$) (Table 3). Similarly, the BKV load in whole blood before treatment was not statistically different between the choreito and nonchoreito groups ($P = .24$, Table 3).

In all 14 children with BKV-HC, the duration from the start of therapy to CR as defined by disappearance of dysuria, pollakisuria, urinary urgency, and the sensation of residual urine was significantly shorter in the choreito group (median, 9 days; range, 4 to 17 days) than in the nonchoreito group (median, 17 days; range, 15 to 66 days; $P = .037$) (Table 3, Figure 1A): the odds ratio of choreito versus nonchoreito was .63 (95% confidence interval, .22 to .93; $P = .0031$). With regard to 11 children with HC graded ≥ II at the beginning of therapy, the administration of choreito

Table 2
Clinical Characteristics of Patients with BKV Cystitis

UPN	Engraftment Syndrome	Acute GVHD		ALC at the Diagnosis of BKV-HC ($\times 10^9$/L)	Steroid Use (d before BKV-HC)	Other Immunosuppressants	Onset of BKV-HC (d from SCT)	Hematuria (Grade)	Viruria (Urine log copy/mL)	CMV (Whole Blood log copy/mL)	Viral Infections	Antiviral Therapy at BKV-HC
		Stage	Grade									
1	+	-	-	4.7	14	-	35	II	BKV	0.0	CMV, EBV	GCV
2	-	skin 3	II	.3	24	-	65	II	BKV	3.1	CMV	PFA
3	+	-	-	.8	10	-	36	III	BKV (9.2), AdV (8.4)	0.0	CMV	PFA
4	+	skin 3	II	1	90	-	330	II	BKV (7.9)	0.0	CMV, EBV	PFA
5	+	skin 2, gut 1	II	.2	-	-	14	II	BKV (10.8)	2.6	CMV	-
6	-	skin 2, gut 3	III	1	10	INX	45	I	BKV (10.9)	0.0	-	-
7	-	skin 3, gut 2	III	.6	67	INX, BSX, MSC	86	I	BKV (11.1), AdV (8.3)	3.0	CMV, EBV	-
8	+	-	-	2	2	-	27	II	BKV (10.0)	3.2	CMV	-
9	-	-	-	.2	-	-	16	III	BKV (9.1)	2.9	EBV	-
10	+	skin 2, liver 4, gut 2	IV	.8	12	INX, BSX, MSC	25	III	BKV (9.2)	0.0	-	-
11	+	-	-	1.8	30	-	48	III	BKV (9.5)	0.0	CMV, EBV	GCV + PFA
12	+	-	-	.2	45	-	67	III	BKV (10.8)	2.7	CMV	GCV
13	-	-	-	1.3	-	-	21	III	BKV (10.7)	0.0	CMV	-
14	+	-	-	.5	6	-	26	I	BKV (10.7)	0.0	EBV	-

ALC indicates absolute lymphocyte count; SCT, stem cell transplanation; EBV, Epstein-Barr virus; GCV, gancyclovir; PFA, foscarnet; INX, infliximab; BSX, basiliximab; MSC, mesenchymal stem cell transplantation.

Table 3
Summary of Treatment for Patients with BKV Cystitis

UPN	Duration from Onset to Tx, d	Primary Tx for BKV	Hematuria Grade at Tx	Hematuria Grade ≤I (d from Tx)	CR (d from Tx)	Urine BKV Load before Tx (log copy/mL)	Plasma BKV Load before Tx (log copy/mL)	Urine BKV Load 1 mo after Tx (log copy/mL)	Plasma BKV Load 1 mo after Tx (log copy/mL)	Possible Complications
1	7	Cidofovir (5 mg/kg qwk ×2), hydration	II	11	17	N/A	N/A	N/A	N/A	None
2	4	Bladder irrigation, hydration	II	16	55	N/A	N/A	N/A	N/A	None
3	14	Cidofovir (1 mg/kg qwk ×2), hydration	III	28	66	9.2	0.0	6.5	3.8	Renal failure
4	4	Hydration	II	10	15	7.9	0.0	N/A	N/A	None
5	2	Hydration	II	5	16	10.8	0.0	N/A	N/A	None
6	1	Hydration	I	N/A	15	10.9	3.0	10.5	3.6	None
7	1	Hydration	I	N/A	15	11.1	0.0	N/A	N/A	None
8	23	Hydration	II	8	23	10.0	0.0	N/A	N/A	None
9	16	Choreito, cidofovir (1 mg/kg qwk ×11), hydration	III	4	6	9.1	4.0	8.7	4.6	None
10	5	Choreito	III	2	4	9.2	3.1	8.3	4.0	None
11	2	Choreito	III	2	16	9.5	0.0	7.8	0.0	None
12	4	Choreito	III	3	17	10.8	0.0	8.2	5.8	None
13	5	Choreito	III	2	7	10.7	5.0	4.4	0.0	None
14	16	Choreito	I	N/A	11	10.7	2.1	10.5	3.2	None

Tx indicates treatment; qwk, every week; N/A, not applicable or available.

significantly shortened the duration from the onset to BKV-HC grade ≤ I (median, 2 days; range, 2 to 4 days) in comparison with that in the nonchoreito group (median, 11 days; range, 5 to 28 days; $P = .0043$) (Table 3, Figure 1B). The duration from start of therapy to CR was also significantly shorter in the choreito group (median, 7 days; range, 4 to 17 days) than in the nonchoreito group (median, 20 days; range, 15 to 66 days; $P = .048$) (Table 3, Figure 1C): here, the odds ratio of choreito versus nonchoreito was .66 (95% confidence interval, .14 to .95; $P = .0058$).

Sequential Analysis of BKV Load after Choreito Treatment

BKV-HC–related symptoms improved significantly earlier in children receiving choreito, and we studied whether these earlier improvements were related to the clearance of BKV. The BKV load in urine and whole blood was monitored after the diagnosis of BKV-HC in children receiving choreito. The urine BKV load generally decreased over time. The median urine BKV load was 1.7×10^8 copies/mL (range, 2.6×10^4 to 3.1×10^{10} copies/mL) 1 month after BKV-HC diagnosis when all children had achieved CR, and they experienced a statistically significant decrease in BKV load since the time of diagnosis ($P = .031$; Wilcoxon signed-rank test for paired samples) (Table 3, Figure 2A). At the time of CR, only 1 of 6 children had a urine BKV load lower than 1.3×10^6 copies/mL, which was the median urine BKV load in children with asymptomatic viruria. The BKV load in whole blood appeared stable during the course of BKV-HC, and no significant decrease was observed a month after diagnosis ($P = .44$) (Table 3, Figure 2B).

All 6 children eventually finished taking choreito, and relapse of HC was not observed, except for in 1 patient who experienced relapse twice (patient 9). This patient was diagnosed with idiopathic aplastic anemia and received a bone marrow transplant from an unrelated donor; however, the graft was rejected and he underwent haplo-identical HSCT as the second HSCT. Because he developed chronic GVHD, he was administered prednisolone, which was increased during the exacerbation of chronic GVHD and which may have contributed to the prolonged elevation of the BKV load. Every time the patient had a relapse of BKV-HC, he was administered choreito, and his genitourinary symptoms resolved within a few days (Supplemental Figure 1).

Safety and Tolerability of Treatment

All children were able to take choreito per os. Notably, there were no adverse effects due to choreito intake, and renal function impairment was not observed in children receiving choreito (Table 3). The reported adverse effects of choreito include drug allergy and mild gastric discomfort [14], which were not observed in any of the children. In the nonchoreito group, 1 patient (patient 3) who received cidofovir for BKV infection developed impaired renal function, possibly resulting from renal toxicity of cidofovir and post-renal acute kidney injury due to clot retention.

DISCUSSION

Unlike its effect in immunocompetent patients, HC is life threatening in immunocompromised patients with hemato-oncological disease, particularly among patients undergoing HSCT [17]. To our knowledge, prospective studies of the treatment for BKV-HC are not available, and there are no standard treatment guidelines for post-HSCT HC. Treatment modalities are limited, particularly in children, partly owing to few reports on children receiving pharmaceutical and

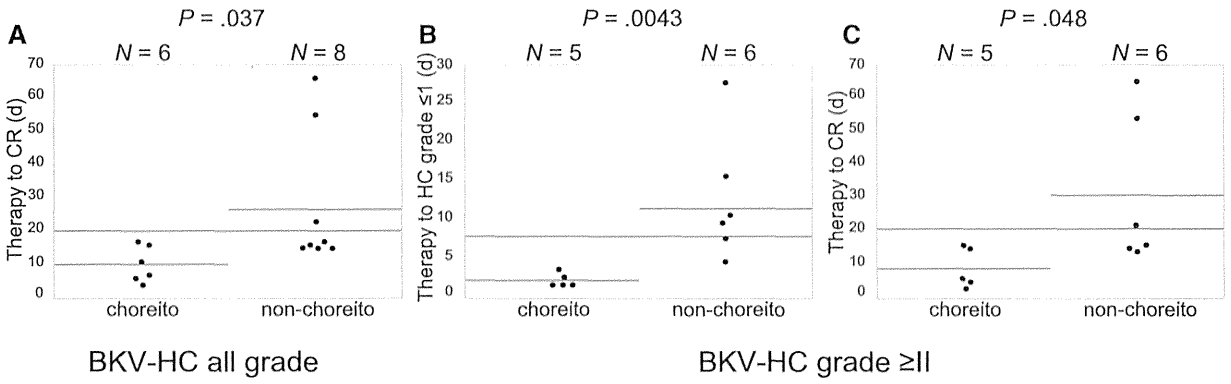

Figure 1. Comparison of choreito and nonchoreito treatment for BK virus-associated hemorrhagic cystitis (BKV-HC). The duration from the beginning of therapy to complete resolution (CR), as defined by the absence of dysuria, pollakisuria, urinary urgency, or the sensation of residual urine, was shorter in the choreito group (median, 9 days; range, 4 to 17 days) than in the nonchoreito group (median, 17 days; range, 15 to 66 days; $P = .037$) (A). When comparing children with HC graded ≥ II, the administration of choreito significantly shortened the duration from the onset to BKV-HC grade ≤ I (median, 2 days; range, 2 to 4 days) in comparison with that in the nonchoreito group (median, 11 days; range, 5 to 28 days) (B). The duration from start of therapy to CR was also significantly shorter in the choreito group (median, 7 days; range, 4 to 17 days) than in the nonchoreito group (median, 20 days; range, 15 to 66 days; $P = .048$) (C).

surgical treatments [4,18-20]. Intravenous hydration with forced diuresis is conducted; however, this is supportive treatment only without reliable efficacy.

At present, cidofovir is the only commercially available antiviral agent against BKV, and its efficacy for BKV-HC has been investigated only in retrospective studies [19-21]. In the report from the European Group for Blood and Marrow Transplantation, intravenous or intravesical cidofovir was administered to 62 patients with BKV-HC [21]. Of the 62 patients, 41 (66%) achieved CR and 8 (13%) had partial response after cidofovir treatment; however, no improvement or deterioration was observed in 12 patients (19%). CR is related to clearance of BK viremia in patients with BK viremia detected at the beginning of treatment, and the median time to clearance is 37 days (range, 7 to 102 days). Of 57 patients receiving intravenous cidofovir, 17 (30%) experienced renal toxicity. In a pediatric cohort, 19 children received cidofovir for BKV-HC grade ≥ II [19]. Macroscopic hematuria resolved in 15 (79%) after a median of 22 days (range, 9 to 63 days). In 1 patient, HC progressed to grade IV during cidofovir treatment. Notably, the baseline creatinine level appeared to be elevated after treatment. Another pediatric cohort included 12 children with BKV-HC treated by intravenous and/or intravesical cidofovir [20]. The median duration of symptoms was 25 days (range, 9 to 73 days) and no persistent nephrotoxicity was observed. Compared with cidofovir treatment, children treated with choreito treatment in our study experienced no impairment of renal function; all patients with BKV-HC achieved CR and BKV-HC resolved earlier.

Hyperbaric oxygen therapy is another alternative treatment for BKV-HC [11,22]. A retrospective study included 16 patients with BKV-HC grade ≥ II (5 patients under 19 years of age), 15 (94%) of whom achieved CR after a median of 17 days (range, 4 to 116 days) [11]. In a pediatric cohort of 10 children with BKV-HC grade ≥ II, 9 (90%) achieved CR after a median of 15 days (range, 10 to 37 days), including spontaneous resolution [22]. Hyperbaric oxygen is generally well tolerated; however, it requires a high-cost facility and adverse effects have been reported, including ruptured tympanum.

Other alternative therapies include leflunomide and fluoroquinolone antibiotics [12]; however, experience is limited, even in adults [13]. Few reports of leflunomide use in the setting of HSCT are available and its safety has not been

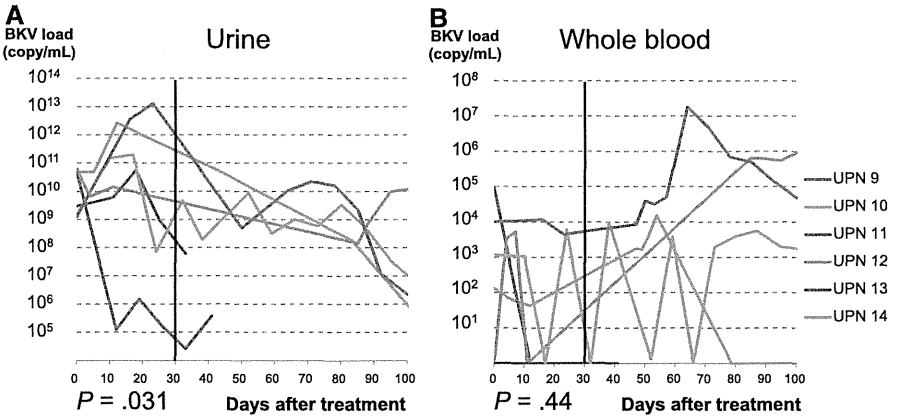

Figure 2. BK virus (BKV) load after choreito treatment. The BKV load before treatment amounted to a median of 2.6×10^{10} copies/mL in urine (range, 1.3×10^{9} to 6.3×10^{10} copies/mL) and a median of 6.5×10^{2} copies/mL in whole blood (range, 0 to 9.0×10^{4} copies/mL). The median urine BKV load was 1.7×10^{8} copies/mL (range, 2.6×10^{4} to 3.1×10^{10} copies/mL) 1 month after BKV-HC diagnosis, and the BKV load had significantly decreased since the time of diagnosis (Wilcoxon signed-rank test, $P = .031$) (A). The BKV load in whole blood appeared stable during the course of BKV-HC, and no significant decrease was observed a month after diagnosis (Wilcoxon signed-rank test, $P = .44$) (B).

confirmed in children. Fluoroquinolones are historically contraindicated in children because they cause arthrotoxicity in juvenile animals and are associated with reversible musculoskeletal events in both children and adults; therefore, they are not recommended in the absence of convincing evidence.

Choreito is a formula stemming from Japanese traditional (Kampo) medicine, originally developed from traditional Chinese medicine; it was the orthodox medicine in Japan until the 19th century, when modern Western medicine took over [14]. Nevertheless, some Kampo formulae are still officially registered in the Japanese Pharmacopoeia. Although Kampo extracts are crude drugs derived from plants, animals, and minerals, their quality is strictly controlled in accordance with the Japanese Pharmacopoeia by quantitative analysis of marker components using high-performance liquid chromatography. Kampo formulae are classified as dietary supplements outside Japan and are approved for marketing by the Food and Drug Administration in the United States.

Choreito is a crude product from *Polyporus umbellatus* sclerotium, *Wolfiporia extensa* sclerotium, *Alisma orientale* rhizome, aluminum silicate hydrate with silicon dioxide, and glue. Ergone isolated from *P. umbellatus* prevented early renal injury in a rat model of nephropathy [23] and may play a central role in the effect exerted by choreito. Pollakisuria was ameliorated in 93% of patients who received choreito for lower urinary tract symptoms in an open-label, single-arm study of 30 patients [24]. Choreito was also administered to patients with urolithiasis for enhancing the evacuation of stones after extracorporeal shock wave lithotripsy [25]. In these studies, no severe adverse effects were observed, suggesting high safety of choreito.

Considering the wide range of indications in genitourinary disorders, choreito may protect epithelial cells irrespective of the type of pathogens and thereby be an effective treatment option for the hemostasis of HC. Although the precise pathogenesis of BKV-HC remains unclear, urothelial cells infected with BKV in vitro detached without causing local cell lysis, which may be associated with the denudation of the damaged mucosa in patients with BKV-HC [26]. Choreito may protect urothelial cells from detaching, which may result in a significant reduction of the BKV load in urine, although the whole blood BKV load appears unchanged and the BKV burden itself is not reduced. Notably, unlike other antiviral agents or surgical interventions, no adverse effects were observed during choreito administration, although the mechanism of action of choreito remains unclear; hence, its safety cannot be easily predicted.

Our study has some limitations. The small number of study subjects in this single-center retrospective analysis may result in bias. Five of 8 subjects in the nonchoreito group had grade II to III GVHD, whereas 1 out of 6 subjects in the choreito group had grade IV GVHD. This difference in GVHD frequency could have been a contributing factor for the difference in HC severity and BKV clearance, although it was not statistically different ($P = .14$) among the 2 groups, possibly because of the small sample size. Children with concomitant AdV viruria were included only in the nonchoreito group, which may explain the longer time before CR in the nonchoreito group. In the present study, HC was significantly more severe in the choreito group than the nonchoreito group. This difference may represent the difference in preconditioning and donor sources: the choreito group included more cases of haplo-identical HSCT, which may have resulted in intensified immunosuppression. More severe HC correlates with a longer duration of HC [2]. Nevertheless, the duration of HC was significantly shorter in the choreito group, which exemplifies its effectiveness. Although the urine BKV load had significantly decreased 1 month after choreito treatment examined by the paired samples, this decrease could not be compared with that of the nonchoreito group because of a lack of paired samples in most of the patients in the nonchoreito group. Thus, the impact of choreito treatment on the urine BV virus load should be investigated in a prospective study where the BKV load is sequentially followed for every study subject.

In conclusion, choreito may be a safe and effective therapy for the hemostasis of late-onset BKV-HC following HSCT, although it may not decrease the BKV burden. Although its precise mechanism of hemostasis remains unclear, choreito may be administered as the first-line treatment for post-HSCT HC. Prospective, randomized studies are warranted to confirm the efficacy of choreito in the treatment of BKV-HC. Fundamental research aiming to identify the active ingredients and mechanisms of action is also essential.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2014.10.018.

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Bloodstream Infection after Stem Cell Transplantation in Children with Idiopathic Aplastic Anemia

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Childhood

A B S T R A C T

Bloodstream infection (BSI) is the most common infectious complication of hematopoietic stem cell transplantation (HSCT) and can cause substantial morbidity and mortality. Identification of risk factors for BSI might be helpful in efforts to reduce transplantation-related death. This study analyzed the incidence of BSI and risk factors for BSI after HSCT in pediatric patients with aplastic anemia (AA). BSI occurred in 39 of the 351 patients with AA (11.1%). Onset of BSI occurred at a median of 8 days after HSCT (range, 0 to 92 days). The 5-year overall survival rate was lower in patients with BSI than in patients without BSI (63.32% ± 7.90% versus 93.35% ± 1.44%; $P < .0001$). Univariate analysis identified the following variables as associated with BSI: history of immunosuppressive therapy with antithymocyte globulin (ATG), transplantation from an unrelated donor, frequent blood transfusion before transplantation, major or major plus minor ABO type mismatch, graft-versus-host disease prophylaxis with tacrolimus and without cyclosporine, and long interval from diagnosis to transplantation. Among these factors, long interval from diagnosis to transplantation was the sole statistically significant risk factor for BSI on multivariate analysis. In patients who underwent HSCT from a related donor, age ≥14 years at transplantation was risk factor for BSI. In contrast, history of immunosuppressive therapy with ATG, frequent blood transfusion before HSCT, graft failure, and major or major plus minor ABO type mismatch were risk factors for BSI in patients who underwent HSCT from an unrelated donor. Because the overall 5-year survival rate without BSI was >90%, even in patients who were received a transplant from an unrelated donor, control of BSI is very important for successful HSCT in pediatric patients with AA.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is first-line therapy for severe aplastic anemia (AA). HSCT from an HLA-matched sibling donor is an established standard therapy for children with severe AA and is associated with high survival rates [1]. Outcomes of HSCT from an unrelated donor have gradually improved [2,3].

Bloodstream infection (BSI) is the most common infectious complication of HSCT and causes substantial morbidity and mortality [4,5]. Identification of risk factors for BSI may aid efforts to reduce transplantation-related deaths. We previously identified AA as a common risk factor for BSI in a retrospective multicenter study [6]. In the present study, we analyzed the incidence of BSI and risk factors for BSI after

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HSCT in pediatric patients with AA using the Transplant Registry Unified Management Program (TRUMP) system of the Japanese Society of Stem Cell Transplantation.

PATIENTS AND METHODS

Between 1980 and 2011, 1098 patients age ≤19 years who underwent HSCT for AA (excluding hereditary bone marrow failure, paroxysmal nocturnal hemoglobinemia, and secondary AA) were registered with the TRUMP system of the Japanese Society of Stem Cell Transplantation. Of these 1098 patients, 516 who underwent HSCT before 2000 were excluded from this analysis, owing to the drastic changes in infection control practices promulgated by the Japanese Society of Stem Cell Transplantation in 2000, including antibiotics and antifungal drugs and guidelines for infection management in the early post-transplantation period. Of the remaining 582 patients, 231 were excluded due to insufficient data; thus, our study group comprised 351 pediatric patients with AA who underwent HSCT, including 193 males and 158 females, with a median age of 11 years (range, 0 to 19 years).

Diagnosis and assessment of severity of disease were established according to published criteria [7]. Severity of AA at initial diagnosis was as follows: very severe, n = 84; severe, n = 137; nonsevere, n = 130. Severity of AA at HSCT was as follows: very severe, n = 122; severe, n = 166; nonsevere, n = 63. The median interval from diagnosis to transplantation was 337 days (range, 9 to 5261 days). Two hundred and seventy-eight patients had received some specific treatment for AA before transplantation, including steroids (n = 171), antithymocyte globulin (ATG; n = 210), cyclosporine (CsA; n = 244), and granulocyte colony-stimulating factor (n = 141). Stem cell source was bone marrow in 315 patients, peripheral blood in 12 patients, bone marrow plus peripheral blood in 1 patient, and cord blood in 23 patients. One hundred seventy-three patients had a related donor, 1 patient had a syngeneic donor, and 177 patients had an unrelated donor.

The conditioning regimen included ATG for 240 patients, cyclophosphamide for 317, fludarabine for 244, melphalan for 39, total body irradiation for 145, thoracoabdominal irradiation for 49, and total lymphoid irradiation for 70 patients. Graft-versus-host disease (GVHD) prophylaxis, defined as planed administration of immunosuppressive drugs before evidence of acute GVHD, included steroids in 17 patients, CsA in 160, tacrolimus in 191, and methotrexate in 319.

Twenty-four patients underwent a second HSCT, 3 patients underwent a third HSCT, and 1 patient underwent a fourth HSCT. Twenty-one patients had a bacterial or fungal infection at the time of transplantation. In patients with multiple HSCTs, each transplantation was analyzed separately.

BSI was defined as isolation of 1 or more recognized bacterial or fungal pathogens from 1 or more blood cultures and at least 1 of the following signs and symptoms within 24 hours of collection of a positive blood culture: fever (>38°C), chills or rigors, or hypotension. We classified ABO compatibility as minor (eg, from an type O donor to a type A, B, or AB recipient), major (eg, from a type A, AB, or B donor to an type O recipient), and major and minor (eg, type A donor to type B recipient). We defined an HLA match donor as a 6/6 HLA-A, -B, and -DR antigen match between recipient and donor, using low-resolution typing. The median duration of follow-up was 39 months. Data collected as of October 2012 were analyzed.

In univariate analysis, the chi square test and Fisher's exact test were used to assess risk factors for BSI. Multivariate stepwise regression was performed to explore the independent effects of variables that demonstrated a significant influence in univariate analysis ($P < .10$). Overall survival was analyzed using the Kaplan-Meier method, with differences compared using the log-rank test. Statistical analyses were performed using SPSS 11.0 for Windows release 11.0.1J (SPSS Japan, Tokyo, Japan).

RESULTS

Assessment of BSI in All 351 Patients Who Underwent HSCT

BSI occurred in 39 of the 351 patients with AA (11.1%). Onset of BSI occurred at a median of 8 days after transplantation (range, 0 to 92 days). The bacteria that were isolated are summarized in Table 1. *Staphylococcus* spp were detected in 11 patients, and *Streptococcus* spp were detected in 7 patients. Gram-positive cocci were detected in 20 patients (51.3%); gram-positive bacilli, in 5 patients (12.8%); gram-negative bacilli, in 11 patients (28.2%); and *Candida* spp, in 3 patients (7.7%). The 5-year overall survival rate was lower in patients with BSI compared with patients without BSI (65.32% ± 7.90% versus 93.35% ± 1.44%; $P < .0001$) (Figure 1). The cause of death was directly associated with BSI in 5 of the 13 patients with BSI who died.

Table 1
Organisms Isolated from Blood Cultures of Patients with AA Who Underwent HSCT

Organism	n
Staphylococcus	11
Staphylococcus epidermidis	8
Staphylococcus haemoliticus	1
Coagulase-negative staphylococci	1
Staphylococcus sp	1
Streptococcus	7
Streptococcus mitis	4
Streptococcus viridans	1
α-streptococci	1
Streptococcus sp	1
Micrococcus	1
Enterococcus	1
Bacillus	4
Gram-positive rods	1
Escherichia coli	1
Enterobacter cloacae	2
Acinetobacter	1
Pseudomonas aeruginosa	4
Stenotrophomonas maltophilia	3
Candida	3

We performed univariate and multivariate analyses to identify risk factors for BSI in the patients with AA (Table 2). Variables associated with BSI on univariate analysis included (1) history of immunosuppressive therapy with ATG, (2) transplantation from an unrelated donor, (3) frequent blood transfusions before HSCT, (4) major or major plus minor ABO mismatch, (5) tacrolimus as acute GVHD prophylaxis with use of CsA, and (6) extended interval from diagnosis of AA to HSCT. Infectious complications at the time of HSCT were not associated with BSI after transplantation. Multivariate analysis identified extended interval from diagnosis to HSCT (>300 days) as the sole statistically significant risk factor for BSI (Table 3).

Assessment of BSI in 158 Patients Who Underwent First HSCT from a Related Donor

BSI occurred in 11 of 158 patients with AA who underwent first HSCT from a related donor (7.0%). The 5-year overall survival rate was lower in patients with complicated BSI compared with patients without BSI (81.82% ±

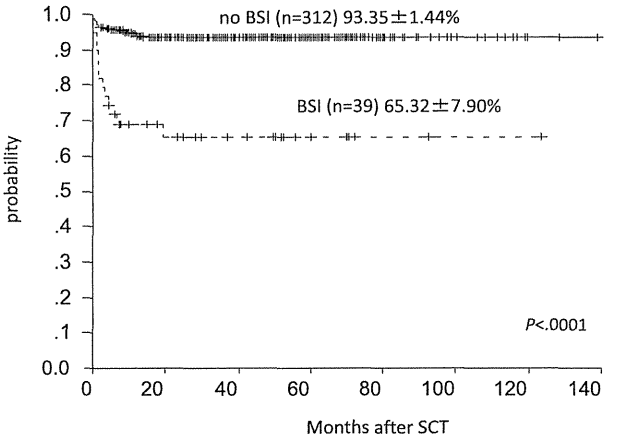

Figure 1. Kaplan-Meier estimate of overall survival for patients with BSI (n = 40; 63.68% ± 7.87%) and patients without BSI (n = 311; 93.65% ± 1.41%); $P < .0001$.