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Development of Early Neutropenic Fever, with or without Bacterial Infection, Is Still a Significant Complication after Reduced-Intensity Stem Cell Transplantation

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ABSTRACT

Little information is available on the clinical characteristics of infectious complications that occur in the early period after reduced-intensity stem cell transplantation (RIST). We retrospectively investigated the clinical features of neutropenic fever and infectious episodes within 30 days after RIST in 76 patients who had received fluoroquinolones as part of their antibacterial prophylaxis. Preparative regimens included cladribine 0.66 mg/kg or fludarabine 180 mg/m^2 plus busulfan 8 mg/kg. All but 1 patient survived 30 days after transplantation, and 75 patients (99%) became neutropenic within a median duration of 9 days. Neutropenic fever was observed in 29 patients (38%), and bacterial infection was confirmed in 15 (20%) of these, including bacteremia (n = 13), bacteremia plus pneumonia (n = 1), and urinary tract infection (n = 1). The causative organisms were gram-positive (n = 9) and gram-negative organisms (n = 7), with a mortality rate of 6%. Neither viral nor fungal infection was documented. Multivariate analysis showed that the presence of neutropenia at the initiation of preparative regimens was an independent risk factor for subsequent documented bacterial infections (P = .026; 95% confidence interval, 1.25-35.1). We conclude that neutropenic fever and bacteremia remain common complications in RIST.

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KEY WORDS

Reduced-intensity stem cell transplantation • Bacterial infection • Neutropenic fever

INTRODUCTION

Allogeneic stem cell transplantation (allo-SCT) is a promising strategy for patients with various malignant diseases that do not respond to conventional treatments. Although a graft-versus-tumor effect induced by allo-SCT [1-4] is beneficial in selected patient populations, increased regimen-related toxicity (RRT) and treatment-related mortality prevent the wider application of allo-SCT to older patients or those who have organ dysfunctions. Recently, a new strategy for transplantation by using a reduced-intensity or nonmyeloablative regimen has been developed to reduce RRT while preserving a graft-versus-tumor effect [5-7]. Although preliminary data seem attractive, widely acceptable regimens and indications for this strategy have not yet been established. At present, several preparative regimens have been reported in reduced-intensity SCT (RIST), with a wide variation in the intensity of immunosuppression and myeloablation [5,6,8,9].

Bacterial infection is a major cause of morbidity and mortality in neutropenic patients after cancer chemotherapy [10]. It has been reported that at least half of febrile neutropenic patients have an established or occult undiagnosed infection and that at least one fifth

of patients with neutrophil counts of $<0.1 \times 10^9$/L acquire bacteremia [10]. Because RIST provides early engraftment compared with conventional allo-SCT [6], it can be expected that the incidence of neutropenic fever and bacterial infections in the early period after transplantation may decrease after RIST. The incidence of bacterial infection during the early period has been reported to range from 0% to 15% [6,11-13]. However, all of these studies analyzed data from small numbers of patients who received different conditioning regimens or antimicrobial prophylaxis. Moreover, the definition of febrile neutropenia or bacterial infection was generally not clear. Thus, we retrospectively investigated the incidence of neutropenic fever and infectious episodes within 30 days of RIST from HLA-identical sibling donors and evaluated their clinical significance.

PATIENTS AND METHODS

Eligibility Criteria

From September 1999 to May 2002, 76 patients underwent RIST. It was thought that they would not be able to tolerate conventional myeloablative SCT because of age, organ dysfunction, or heavy prior treatment. Donor eligibility required an HLA-matched sibling donor determined by serologic typing for HLA-A and -B and molecular typing for HLA-DR.

Patient Characteristics

The patients' characteristics are shown in Table 1. We divided the risk of transplantation into 2 groups. The low-risk group included acute myeloid or lymphoid leukemia in first or second remission, malignant lymphoma in first or second remission, nonmalignant hematologic disorders, and solid tumors. The other patients were considered to have high-risk diseases, which indicates that patients had a smaller possibility of transplantation success in curing the underlying disease.

Preparative Regimens and Clinical Management

Twenty-three patients received cladribine 0.11 mg/kg on days −8 to −3 and busulfan 4 mg/kg on days −6 and −5 [7]. Fifty-three patients received fludarabine 30 mg/m^2 on days −8 to −3 and busulfan 4 mg/kg on days −6 and −5. Forty-one patients received additional rabbit antithymocyte globulin (ATG) 2.5 mg/kg for 2 or 4 consecutive days. Methylprednisolone 0.5 mg/kg was administered every 6 hours for 2 or 4 days in those who received ATG. Graft-versus-host disease (GVHD) prophylaxis was cyclosporine alone, which was started on day −1. Patients were treated in reverse isolation in a laminar airflow–equipped room. All of the patients received prophylaxis with trimethoprim/sulfamethoxazole or pentamidine against *Pneumocystis carinii* infection. Seventy-one patients received oral fluoroquinolones as antibacterial prophylaxis. These antibiotics were continued until engraftment or initiation of the empiric administration of intravenous antibiotics. The other 5 patients received intravenous administration of other antibiotics from the initiation of conditioning. The patients received fluconazole and acyclovir for fungal and herpes virus prophylaxis, respectively [14,15].

Granulocyte colony-stimulating factor was administered intravenously at 5 μg/kg/d from day 6 of transplantation until the patient's absolute neutrophil count became $>0.5 \times 10^9$/L for 2 consecutive days. Engraftment was defined as a white blood cell count of $>1.0 \times 10^9$/L with an absolute neutrophil count of $>0.5 \times 10^9$/L for 3 consecutive days and a platelet count of $>20 \times 10^9$/L, without transfusion. Acute and chronic GVHD were graded according to the consensus criteria [16,17]. When patients developed grade II to IV acute GVHD, we initiated methylprednisolone at 2 mg/kg/d in addition to cyclosporine.

Table 1. *Patient Characteristics*

Variable	Data
Age, y, median (range)	50 (4-67)
Sex (male/female)	51/25
Underlying disease	
Acute myeloblastic leukemia	20
Acute lymphoblastic leukemia	2
Chronic myelocytic leukemia	5
Myelodysplastic syndrome	9
Malignant lymphoma	16
Solid tumors*	18
Others	6
Risk of transplantation (high/low)†	31/45
Stem cells (blood/marrow)	76/0
Median number of transfused CD34† cells × 10^6 cells/kg, median (range)	3.8 (1.6-8.3)
Prophylactic antibiotics (fluoroquinolone/others)	71/5
Catheters (central/peripheral)	71/21‡

*All the patients with solid tumors had documented progressive lesions despite prior therapy.

†Risk of transplantation was divided into 2 groups: the low-risk group was defined as acute myeloid or lymphoid leukemia in first or second remission, malignant lymphoma in first or second remission, nonmalignant hematologic disorders, and solid tumors; the other patients were defined as having high-risk diseases.

‡Both peripheral and central lines were inserted in 16 patients.

Diagnosis and Definition of Infections

We defined neutropenia as peripheral neutrophil counts $<0.5 \times 10^9$/L and fever as a single axillar temperature of >38.3°C. Fever that occurred during neutropenia was defined as neutropenic fever and was treated as reported previously [10]. "Effective intrave-

nous antibiotics" was defined as a response evidenced by decreasing fever to <38°C within 72 hours of the initiation of antibiotics [10]. When febrile episodes occurred, we obtained more than 2 blood cultures after swabbing the skin or catheter hub with 10% povidone-iodine. When central venous catheters were placed, samples for blood culture were drawn through these lines. When these samples tested positive, we repeated blood sampling by vein puncture. When patients had received more than 0.5 mg/kg corticosteroid, we obtained more than 2 blood cultures in the same manner at least once a week [18]. Blood stream infection must have met at least 1 of the following criteria [19]. Bacteremia was defined as the condition described in criterion 2.

1. Criterion 1: patient has a recognized pathogen cultured from 1 or more blood cultures, and the organism cultured from blood is not related to an infection at another site.
2. Criterion 2: patient has at least 1 clinical symptom, such as temperature >38°C, chills, or hypotension (systolic blood pressure <90 mm Hg), and at least 1 of the following:
   a. Common skin contaminant such as diphtheroids, *Bacillus* species, *Propionibacterium* species, coagulase-negative staphylococci, or micrococci cultured from 2 or more blood cultures drawn on separate occasions.
   b. Common skin contaminant such as diphtheroids, *Bacillus* species, *Propionibacterium* species, coagulase-negative staphylococci, and micrococci cultured from at least 1 blood culture from a patient with an intravascular line, and the physicians have instituted appropriate antimicrobial therapy.

When febrile patients presented (1) an erythematous rash involving >25% of the body surface that was not clearly attributable to medication or (2) noncardiogenic pulmonary edema without an identifiable infectious etiology during early neutrophil recovery, the fever was diagnosed as engraftment syndrome [20]. Fevers associated with GVHD, administration of ATG, and primary malignancies were diagnosed on the basis of a clearly documented clinical history and physical examination, without a direct confirmation of infections as described previously.

End Points and Statistical Analysis

The aims of this study were to determine the incidence of neutropenia and neutropenic fever, to investigate the incidence and clinical features of bacterial infection early after RIST, and to identify their risk factors. A univariate analysis with the Fisher exact test and the Mann-Whitney test was performed to identify risk factors for neutropenic fever and bacteremia. These variables included age, primary disease and risk of transplantation, use of ATG, presence of neutropenia at day −11, nadir and duration of neutropenia, presence of a neutrophil count $<0.1 \times 10^9$/L at any time between day −11 and day 30 after RIST, use of corticosteroids except for prophylactic use during ATG administration, and diarrhea within 30 days after transplantation. The level of significance was set at $P < .05$. A multivariate analysis with a multiple logistic regression analysis was then added for the appropriate variables. Factors with a P value of <.25 in the univariate analysis, except for those that were considered to be strongly associated with another variables, were entered into the multiple logistic regression analysis. The overall survival of patients who developed a neutropenic fever was compared with that of patients without the presence of neutropenic fever by a Kaplan-Meier curve and the log-rank test. Similarly, the overall survival of patients who developed bacteremia within the first 30 days after RIST was compared with that of patients without bacteremia. P values <.05 were considered significant.

RESULTS

Neutropenia, Engraftment, and GVHD

Except for a patient who died of methicillin-resistant *Staphylococcus aureus* (MRSA) septicemia, all of the patients survived 30 days after RIST. Neutropenia was observed in 75 patients (99%), with a median duration of 9 days (range, 0-32 days). One patient developed primary graft failure, but the remaining 74 patients achieved sustained engraftment with a median time of 11 days after transplantation (range, 6-24 days). No patient required donor lymphocyte infusion to achieve complete donor chimerism. This was 20 days (range, 17-32 days) when only data for 10 patients who had neutropenia at the initiation of the preparative regimens were analyzed. In the remaining 66 patients, this value was 8 days (range, 0-18 days). A peripheral neutrophil count $<0.1 \times 10^9$/L was observed in 43 patients, with a duration of 1 day (range, 0-21 days).

Of the 74 patients with primary engraftment, 32 (43 %) developed grade II to IV acute GVHD on a median of day 51 (range, 13-90 days). Acute GVHD occurred within 30 days of transplantation in 8 patients.

Summary of Corticosteroid Use

Forty-one patients were given methylprednisolone while they were receiving ATG. Another 18 patients received corticosteroid within 30 days of transplantation for the treatment of engraftment syndrome (n = 6), acute GVHD (n = 5), tumor fever (n = 1), progression of Behçet disease (n = 1), brain edema due to brain metastasis of tumor (n = 1), serum disease due to ATG (n = 1), or other causes (n = 3).

Table 2. *Causes of Neutropenic Fever (n = 29)*

Variable	n
Defined causes	**20**
Bacteremia	**5**
Engraftment syndrome	**4**
ATG and tumor fever	**1**
ATG	**10**
Undefined causes	**9**

ATG indicates antithymocyte globulin.

Neutropenic Fever

Neutropenic fever developed in 29 (38%) of the 76 patients, with a time interval between the onset of neutropenia and fever of 7 days (range, 1-13 days). Defined causes of fever are shown in Table 2.

Six patients developed bacteremia during neutropenia. Febrile episodes occurred in 5 of these 6 patients, and the other patient developed a fever after neutrophil recovery. This patient was excluded from the cases of patients who had presented a neutropenic fever caused by bacteremia.

All of the 29 patients with neutropenic fever received empiric intravenous antibiotics, and 20 patients responded. Intravenous amphotericin B was added empirically to 3 patients. The probable causes of antibiotic-resistant fevers were as follows: refractory bacteremia (n = 4), engraftment syndrome (n = 2), use of ATG plus tumor fever (n = 1), and unknown (n = 2).

We found that the presence of neutropenic fever had no effect on ultimate mortality that included any cause of death within 30 and 100 days (Table 3). Additionally, the median follow-up duration was 13.7 months (range, 0.27-38.9 months), and the overall survival rate after a diagnosis of neutropenic fever was not significantly different between cases and controls (P = .80; log-rank test; Figure 1).

Bacterial Infection

Sites of bacterial infection were documented in 15 patients (20%) in the first 30 days (Table 4). Twelve of the 14 patients with bacteremia developed febrile episodes. All of the 12 febrile patients received intravenous antibiotics, and 6 responded to the empiric use of antibiotics. Five patients responded to the second or third lines of antibiotics, and 3 of these patients recovered from bacteremia after engraftment. The other patient died of MRSA septicemia on day 8. Two patients remained afebrile at the diagnosis of bacteremia. After a diagnosis was established, we initiated vancomycin and gentamicin in 1 patient, and the other continued to receive oral ciprofloxacin. These 2 patients improved after the removal of an inserted catheter or neutrophil recovery. One patient with pneumonia responded to empiric antibiotics. One patient with urinary tract infection showed no response to antibiotics and died of systemic infection after the concomitant use of steroids for acute GVHD on day 56. Thus, the mortality rate related to early bacterial infection after RIST was 1.3% (1/76) within 30 days after transplantation.

Gram-positive organisms were cultured in 9 patients. The pathogens are shown in Table 4. Eight patients were diagnosed as presenting BSI according to criterion 2a. In our study, all 8 patients presented ≥2 blood positive cultures drawn at different times. Gram-negative organisms were cultured from 7 pa-

Table 3. *Clinical Characteristics of Patients with Neutropenic Fever and Controls*

Variable	Patients with Neutropenic Fever (n = 29)	Controls (n = 47)	*P* Value*
Background			
Age, y, median (range)	**49 (14-67)**	**51 (4-65)**	**.97**
Primary diseases (hematologic malignancies/others)	**25/4**	**33/14**	**.17**
Use of antithymocyte globulin (yes/no)	**16/13**	**25/22**	**.99**
Neutropenia on day −11 (yes/no)	**7/22**	**3/44**	**.037†**
Number of nadir neutrophils, median (range)	**60 (0-360)**	**100 (0-560)**	**.006†**
Duration of neutropenia, (d), median (range)	**11 (5-26)**	**7 (0-32)**	**.0001†**
Presence of neutropenia 0.1 × 10^9/L‡ (yes/no)	**22/7**	**21/26**	**.0094†**
Risk of transplantation (high/low)	**17/12**	**14/33**	**.017†**
Diarrhea (yes/no)	**15/14**	**13/34**	**.05†**
Use of steroid (other than ATG) (yes/no)	**7/22**	**12/35**	**.99**
Outcome			
Documented bacterial infection within 30 days (yes/no)	**8/21**	**7/40**	**.24**
Mortality§			
Within 30 d	**1**	**0**	**.38**
Within 100 d	**4**	**5**	**.72**

*P values were calculated with univariate analyses by using the Fisher exact test and the Mann-Whitney test.

†Statistically significant.

‡Presence of a neutrophil count <0.1 × 10^9 at any time between day −11 and day 30 after RIST.

§The mortality includes any causes of death.

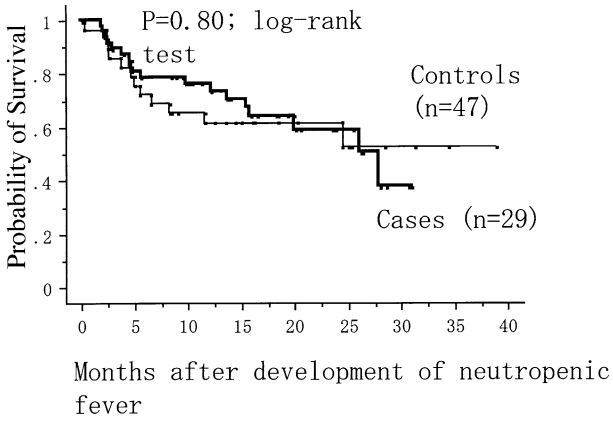

Figure 1. Overall survival after a diagnosis of neutropenic fever.

tients, and the pathogens are shown in Table 4. Four gram-negative strains indicative of multidrug resistance were observed in 4 patients: 3 isolates of *Stenotrophomonas maltophilia* and 1 isolate of *Pseudomonas aeruginosa*. All of these organisms were sensitive to fluoroquinolones. Three patients developed bacteremia caused by fluoroquinolone-sensitive organisms while they received prophylaxis.

Bacteremia developed during the neutropenic period in 8 of the 14 patients. Of these 8 patients, 6 were febrile at the diagnosis of bacteremia, and 1 responded to the empiric administration of antibiotics. Among the other 6 patients who developed bacteremia after neutrophil recovery, all were febrile, and 5 responded to antibiotics. In the 4 patients with catheter-associated bacteremia, the fever subsided after removal of the inserted catheters with the use of appropriate antibiotics. Causative organisms were as follows: *Bacillus* species (n = 1), *Staphylococcus epidermidis* (n = 2), and *Serratia* species (n = 1).

We found that the presence of bacterial infection within the first 30 days after RIST had no effect on ultimate mortality, which included any cause of death within 30 and 100 days (Table 5). The overall survival rate after the diagnosis of bacteremia was not significantly different between patients with bacterial infection and controls (P = .79; log-rank test) with a median follow-up duration of 13.7 months (range, 0.27-38.9 months; Figure 2).

Other Infectious Complications

Cytomegalovirus antigenemia developed in 12 patients within 30 days after transplantation, and all were successfully treated with preemptive ganciclovir. None of the patients developed invasive fungal infections within 30 days after transplantation.

Diarrhea was observed in 5 and 28 patients, respectively, during neutropenia and within 30 days after transplantation. The estimated primary causes of diarrhea were acute GVHD (n = 5), RRT (n = 5), and engraftment syndrome (n = 5). *Clostridium difficile* toxin A was positive in 5 patients, but no suspected diagnosis was made in the remaining 8 patients. There was no significant association between bacterial infections and diarrhea (P = .77).

Risk Factors for Neutropenic Fever

The patients' characteristics were compared between those with and without neutropenic fever. Significant risk factors for neutropenic fever by univariate analysis are shown in Table 3. Multivariate analysis showed that presence of a neutrophil count $<0.1 \times 10^9$/L at any time between day −11 and day 30 after RIST (P = .026; 95% confidence interval [CI], 1.20-16.15), duration of neutropenia (P = .019; 95% CI, 1.02-1.24), and diarrhea (P = .016; 95% CI, 1.33-15.14) were independent risk factors for neutropenic fever (Table 6).

Risk Factors of Documented Bacterial Infections

The patients' characteristics were compared between those with and without bacterial infections (Table 5). None of the variables was a significant risk factor in the univariate analysis. However, a multivariate analysis with logistic regression showed that the presence of neutropenia at the beginning of preparative regimens (P = .026; 95% CI, 1.25-35.1) was the sole independent risk factor for bacterial infections (Table 6).

DISCUSSION

During the first few months after transplantation, hematopoietic SCT (HSCT) recipients carry obvious

Table 4. *Bacterial Infections (n = 15)*

Variable	n
Clinical presentation	**15***
Bacteremia	**13***
Bacteremia and pneumonia	**1***
Urinary tract infection	**1***
Gram-positive organisms	**9***
Staphylococcus epidermidis	**5†**
***Bacillus* species**	**3†**
MRSA	**1†**
S. captis	**1†**
Gram-positive rods	**1†**
Gram-negative organisms	**7***
***Acinetobacter* species**	**3†**
***Serratia* species**	**3†**
Stenotrophomonas maltophilia	**3†**
Pseudomonas aeruginosa	**2†**
***Klebsiella* species**	**1†**
Escherichia coli	**1†**
***Gardnerella* species**	**1†**

*Number of patients.
†Number of positive cultures.

Table 5. *Clinical Characteristics of Patients with Bacterial Infections and Controls*

Variable	Patients with Bacterial Infections (n = 15)	Controls (n = 61)	*P* Value*
Background			
Age, y, median (range)	53 (16-67)	48 (4-65)	.31
Primary diseases (hematologic malignancies/others)	13/2	45/16	.50
Use of antithymocyte globulin (yes/no)	7/8	34/27	.57
Neutropenia on day −11 (yes/no)	4/11	6/55	.10
Number of nadir neutrophils, median (range)	100 (0-360)	80 (0-560)	.65
Duration of neutropenia, d, median (range)	9 (2-23)	9 (0-32)	.37
Presence of neutropenia 0.1 × 10^9/L (yes/no)†	7/8	36/25	.40
Risk of transplantation (high/low)	7/8	24/37	.77
Diarrhea (yes/no)	6/9	22/39	.77
Use of steroid (other than ATG) (yes/no)	6/9	13/48	.18
Central catheters (yes/no)	15/0	56/5	.58
Peripheral catheters (yes/no)	5/10	16/45	.75
Outcome			
Mortality‡			
Within 30 d	1	0	.38
Within 100 d	2	7	.99

*P values were calculated with univariate analyses by using the Fisher exact test and the Mann-Whitney test.
†Presence of a neutrophil count $<0.1 \times 10^9$ at any time between day −11 and day 30 after RIST.
‡The mortality includes any causes of death.

risks for infections [21]. Most physicians believe that RIST is associated with less infection because reduced-intensity preparative regimens are less myeloablative, leading to a shorter duration of neutropenia and less damage to mucosal barriers. However, no detailed data are currently available to confirm this.

Slavin et al. [6] reported that 25 of 26 recipients of similar fludarabine/busulfan-based regimens developed neutropenia $<0.5 \times 10^9$/L, and 8 had neutropenia below 0.1×10^9/L. Considering that life-threatening bacterial infection occurs most often at neutrophil counts $<0.1 \times 10^9$/L in the setting of conventional allogeneic HSCT [22], RIST might pose a risk for infections. In our study, neutropenia $<0.5 \times 10^9$/L was observed in essentially all patients, with a median duration of 9 days, and neutropenia $<0.1 \times 10^9$/L was observed in 56% of the patients, with a median duration of 1 day. Thus, neutropenia is still a significant problem in our RIST procedure.

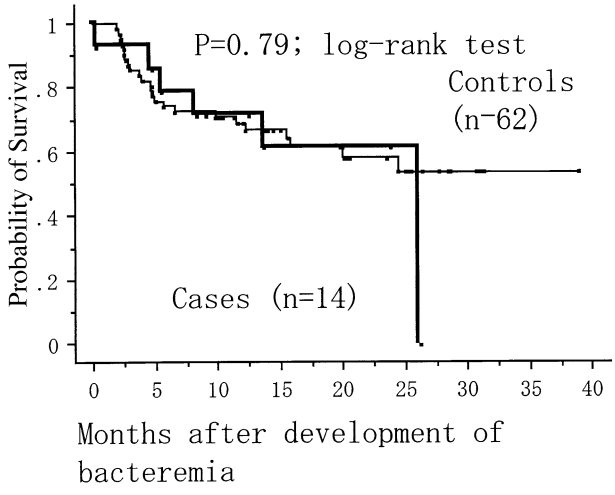

Figure 2. Overall survival after a diagnosis of bacteremia.

Although it is widely believed that infection is the primary cause of febrile neutropenia, a variety of noninfectious causes such as drugs, primary diseases, GVHD, and cytokine dysregulation associated with engraftment can cause a febrile episode during the neutropenic period. All of these disorders require individualized approaches. In our study, approximately 40% of the recipients undergoing RIST developed febrile neutropenia, which remains a significant problem after RIST, although this is far less than the reported incidence of 90% after conventional alloge-

Table 6. *Multivariate Analysis of Risk Factors for Neutropenic Fever and Bacterial Infection*

Variable	Neutropenic Fever (n = 29)	Bacterial Infections (n = 15)
Age	—	.116 (.99-1.08)
Neutropenia on day −11	—	.026 (1.25-35.1)†
Duration of neutropenia	.019 (1.02-1.24)†	—
Presence of neutropenia 0.1 × 10^9/L‡	.026 (1.20-16.15)†	.071 (.068-1.117)
Risk of transplantation	.088 (.86-8.79)	—
Diarrhea	.016 (1.33-15.14)†	—

Data are P value (95% confidence interval).
*Factors with a P value of <.25 in the univariate analysis, except for those that were considered to be strongly associated with another variable, were entered into the multiple logistic regression analysis.
†Statistically significant.
‡Presence of a neutrophil count $<0.1 \times 10^9$/L at any time between day −11 and day 30 after RIST.

neic HSCT [23]. We found that neutropenic fever could be attributed to noninfectious causes in 16 of the 29 patients with febrile neutropenia. Fifteen patients (20%) had confirmed evidence of documented infection within a month after transplantation. Thus, we also confirmed that the risk of bacterial infection was predominant in the early period after RIST, as reported by Junghanss et al. [11]. They reported that 9% and 27% of RIST recipients developed bacteremia within 30 and 100 days of transplantation, respectively, and that neutropenia, which was defined as an absolute neutrophil count $<0.1 \times 10^9$/L, was observed within a median of 0 days (range, 0-11 days) [11]. They concluded that neutropenia was an independent risk factor for early bacterial infection. Although there were considerable differences in the transplantation procedures between their study and ours, the results still suggested that bacterial infection is a significant early complication after RIST. The higher prevalence of bacterial infections in our study population reflected that our preparative regimen was more myeloablative compared with the regimen used by Junghanss et al. [11].

In this study, causative gram-positive bacteria included *S. epidermidis* (n = 5), *Bacillus* species (n = 3), and MRSA (n = 1). Wisplinghoff et al. [24] reported that secondary BSI most often originated from intravenous catheters and occurred in 24% of patients with a neutrophil count $<1.0 \times 10^9$/L. The high incidence of *S. epidermidis* infection suggests that skin damage due to an indwelling central venous catheter could be the main portal of entry in recipients of RIST, as well as in conventional HSCT [25]. Because regimen-related toxicities are mild in RIST and most recipients can continue oral intake during conditioning and subsequent transplantation [26], it may be useful to avoid placing central lines in recipients of RIST.

Gram-negative bacteria are the most virulent bacterial pathogens in neutropenia. In this study, 7 patients developed gram-negative bacteremia, and all of these patients recovered with neutrophil recovery, intravenous administration of antibiotics, or both. Four patients had diarrhea at the diagnosis of bacteremia, but the remaining 3 showed no evidence of gastrointestinal damage. Although gram-negative bacteria usually invade the bloodstream through damaged gastrointestinal mucosa, skin breakdown and venous catheters might also be possible routes of entry in RIST recipients. Another important finding of this study was that some causative gram-negative bacteria were resistant to multidrugs. Three patients did not respond to empiric antibiotic therapy. Causative organisms in these 3 patients were *Stenotrophomonas maltophilia*, *Serratia* species, *Escherichia coli*, *P. aeruginosa*, and *Acinetobacter* species.

We used fluoroquinolones as prophylactic antibiotics in RIST, as well as conventional HSCT. It has been reported that although antibacterial prophylaxis with fluoroquinolones has reduced the frequency of gram-negative bacteremia, it has not contributed to the reduction of infection-related mortality [27]. Moreover, the evolution of resistance to fluoroquinolones in coagulase-negative staphylococci and *E. coli* has been reported [28]. On the basis of these findings, the Centers for Disease Control and Prevention guidelines recommended that the routine use of antibiotic prophylaxis should be avoided [29]. We analyzed risk factors for documented bacterial infection to establish a suitable individualized management of infectious complications according to the risk factors. Our data suggest that the duration of neutropenia and the presence of neutropenia at the beginning of preparative regimens are independent risk factors for neutropenic fever and bacterial infection, respectively, by multivariate analysis (Table 6). Risk of transplantation was not an independent risk factor on multivariate analysis. However, considering that risk of transplantation and neutropenia were closely associated, we can safely say that high-risk patients have a high probability for developing bacteremia and neutropenic fevers. These findings suggest that routine prophylaxis should be individualized according to the risk of early bacterial infection.

Our study has several limitations. First, this is a retrospective study, and the rate of febrile episodes could be influenced by the variable use of antipyretic agents. Second, we could not compare the rate of neutropenic fever and bacterial infections with controls receiving myeloablative SCT. Third, a central venous catheter was inserted in 93% of the patients; therefore, we could not evaluate the contribution of catheter use to the development of bacteremia. Therefore, further studies are needed to evaluate the rate of neutropenic fever and bacterial infections in patients without the use of a central venous catheter.

In conclusion, we found that bacterial infection is still a significant problem after RIST, as well as conventional allogeneic HSCT. Our data demonstrated that the treatment of bacterial infections within the early period after RIST requires individualized management according to the defined risk. It may be beneficial to avoid the routine use of a central venous catheter in recipients of RIST, which could reduce the incidence of early gram-positive bacteremia, although this should be confirmed in a future prospective study.

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