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Original Article

Pretransplant serum ferritin and C-reactive protein as predictive factors for early bacterial infection after allogeneic hematopoietic cell transplantation

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Short title: Risk factors for bacterial infection after HCT

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Abstract

Although fluoroquinolones or other antibiotics are commonly used to prevent bacterial infections after hematopoietic cell transplantation (HCT), due to the growing presence of multidrug-resistant microorganisms, it is important to identify patients who are more likely to benefit from antibacterial prophylaxis. To evaluate risk factors for early bacterial infection after allogeneic HCT, we retrospectively analyzed clinical data for 112 consecutive adult patients with hematologic malignancies who received transplants without any antibacterial prophylaxis. The cumulative incidence of bacterial infection at 30 days after transplantation was 16%. Among various pre-transplant factors, only high serum ferritin (>700 ng/mL, 47 patients) and high C-reactive protein (CRP) (>0.3 mg/dL, 28 patients) levels were significantly associated with the development of bacterial infection in a multivariate analysis (hazard ratio [95% confidence interval]: ferritin, 4.00 [1.32–12.17]; CRP, 3.64 [1.44–9.20]). In addition, septic shock and sepsis with organ failure were exclusively observed in patients who had high ferritin and/or high CRP levels. These results suggest that pretransplant serum ferritin and CRP levels can be useful markers for predicting the risk of early bacterial infection after allogeneic HCT. It may be prudent to limit antibacterial prophylaxis to patients with predefined risk factors to ensure the safety of HCT with the use of fewer antibiotics.

Keywords: antibacterial prophylaxis, fluoroquinolone, bacterial infection, allogeneic hematopoietic cell transplantation.

Introduction

Bacterial infection is an important cause of mortality and morbidity after autologous or allogeneic hematopoietic cell transplantation (HCT).[1, 2] When neutropenic patients who receive cytotoxic chemotherapy are compared to HCT recipients, the risk of severe bacterial infection appears to be considerably higher in the latter because high-dose chemotherapy and/or total-body irradiation (TBI) may cause severe mucosal damage that facilitates massive bacterial translocation under profound post-transplant immunosuppression. Therefore, the use of oral fluoroquinolones (FQs) or other antibiotics as antibacterial prophylaxis is strongly considered for HCT recipients, although significant variations have been reported among transplant centers and countries.[3-5]

Recently, the widespread emergence of FQ-resistant or multidrug-resistant microorganisms in hematology-oncology units has been suggested to compromise the effectiveness of routine antibacterial prophylaxis with FQs in patients undergoing cytotoxic chemotherapy or HCT.[6-14] In our center, the isolation rate of FQ-resistant gram-negative bacilli was high (57.1%) during a period when FQs were routinely administered as antibacterial prophylactic agents; in particular, among isolated *Enterobacteriaceae* strains, 66.7%, 33.3%, and 22.2% were resistant to levofloxacin, piperacillin, and ceftazidime, respectively.[8] In an attempt to reduce the emergence of antibiotic-resistant microorganisms, we stopped using any antibacterial prophylaxis in both autologous and allogeneic HCT recipients in 2004,[8] and found that this discontinuation of FQ prophylaxis, even in the setting of myeloablative allogeneic HCT, did not significantly affect early mortality after transplantation.[15]

Another approach to balance the safety of HCT with judicious antibiotic use would be to limit the use of antibacterial prophylaxis to HCT recipients who are at high risk of bacterial infection, since a delay in antibiotic treatment may lead to serious complications after infectious episodes in such patients if prophylactic antibiotics are not administered. To identify the pretransplant characteristics of patients who are more likely to be susceptible to bacterial infection after allogeneic HCT, we conducted a single-center retrospective study with the clinical data of 112 consecutive allogeneic transplants for hematologic malignancies that were performed without antibacterial prophylaxis. As a potential biomarker for predicting bacterial infection, high levels of pretransplant ferritin levels have recently been shown to be associated with an increased incidence of bloodstream infection, as well as decreased overall survival and increased early mortality.[16] In addition, elevated pretransplant serum CRP levels have been shown to be associated with an increased incidence of bacterial infection in the setting of chemotherapy for acute myeloid leukemia[17] and allogeneic transplantation.[18] Sato et al. reported that pretreatment serum CRP levels of greater than 0.26 mg/dL were useful for predicting the incidence of documented infection in patients who received their first consolidation chemotherapy for acute myeloid leukemia.[17] Since these biomarkers are easy to measure and may be useful in clinical practice, in the present study we explored the association between bacterial infection and these biomarkers as well as various patient characteristics.

Subjects and methods

Study population

The medical records of 137 consecutive adult patients with hematologic malignancies who underwent T-cell replete allogeneic HCT from September 2004 to March 2009 at Kyoto University Hospital were reviewed. Patients who had active infections prior to the transplantation procedure (n = 23) and those who had a recent history of autologous or allogeneic HCT within 1 year (n = 2) were excluded; thus, a total of 112 patients were included in the analysis, without any duplication of subjects. Patients were considered to have standard-risk disease if they received a transplant without prior chemotherapy or in complete remission, while those who received a transplant in any other status were considered to have high-risk disease. This study was approved by the Ethics Committee of Kyoto University Graduate School and the Faculty of Medicine. Written informed consent for the transplantation protocol was obtained from all of the patients.

Prophylaxis, monitoring, and diagnosis of infection

A central venous catheter was inserted in the subclavian vein prior to the beginning of the conditioning regimens for all patients. Each patient was isolated in a single room equipped with a high-efficiency particulate air filter system from a day before the transplantation until at least 4 weeks after transplantation. Each patient was then maintained on a low-microbial diet and asked to take strict control measures under the supervision of the ward staff to prevent the acquisition of nosocomial pathogens. No bacterial prophylaxis was prescribed for these patients according to our institutional protocols.[8] Intravenous antibiotics with

anti-pseudomonal activity were promptly administered in response to episodes of febrile neutropenia or suspected bacterial infections. Trimethoprim-sulfamethoxazole (trimethoprim; 160 mg/day, three times a week) was administered as prophylactic therapy for *Pneumocystis jiroveci* pneumonia from the day of admission until the day of transplantation, and this prophylaxis was reinitiated after the day of neutrophil engraftment. All patients received 200 or 400 mg of fluconazole and 400-1000 mg of acyclovir per day as prophylactic agents from the conditioning period until 30 days after transplantation. Prophylactic fluconazole and acyclovir were usually continued when patients were receiving steroid therapy for acute or chronic graft-versus-host disease. For each febrile episode, 1 or 2 sets of blood samples were cultured, and cultures of specimens other than blood specimens and imaging examinations to search for the focus of infection were performed according to the clinician's judgment. Microbiologically documented infections included the presence of bloodstream bacterial infection or any other bacterial infection. Bloodstream bacterial infection was diagnosed when at least 1 of the following criteria was met: (1) the culture of blood obtained during a febrile episode tested positive at least once for bacterial organisms other than common skin contaminants, (2) the culture of blood obtained during a febrile episode tested positive for the same common skin contaminant in independent analysis conducted within an interval of 72 h, and (3) the blood culture tested positive at least once for a common skin contaminant, and the patient was diagnosed with septicemia with hypotension (systolic blood pressure, <90 mm Hg) and disseminated intravascular coagulation. Infections other than bloodstream infection were diagnosed when the following criteria were met: (1) sputum, urine, or stool samples were found to contain pathogenic bacteria on at least 2 occasions, and (2) the patient showed

symptoms of infection corresponding to those specimens. Septic shock and sepsis with organ failure were defined as severe infection.

Measurement of serum biomarkers (serum ferritin and C-reactive proteins)

Both serum ferritin and CRP levels were measured using peripheral blood samples obtained just prior to the start of the conditioning regimen. The serum ferritin concentration was measured by an immunoenzymometric assay (AIA-PACK FER, Tosoh Corporation, Tokyo, Japan) (normal range; ≤150 ng/mL), and the serum CRP concentration was measured by a latex agglutination assay (N-Assay LA CRP-S, Nittobo, Tokyo, Japan) (normal range; ≤0.2 mg/dL), according to the respective manufacturer's instructions.

Statistical analysis

The primary endpoint was the cumulative incidence of documented bacterial infections during the first 30 days after transplantation. Overall survival and treatment-related mortality were also analyzed as secondary endpoints. To eliminate the effect of a competing risk, the cumulative incidence was assessed using methods described elsewhere.[19] In the analysis of the cumulative incidence of bacterial infections and treatment-related mortality, a competing event was defined as death without an event of interest. The overall survival was estimated using the Kaplan-Meier method. We applied Fine and Gray's proportional-hazards model for the sub-distribution of a competing risk to analyze the cumulative incidence of bacterial infection and treatment-related mortality, and the Cox proportional-hazards model for that of overall survival.[20] Factors with *P* values of less than 0.10 in the univariate analysis were

included in the multivariate analysis. Factors evaluated in the analysis included the recipient's age (≤50 or >50), recipient's sex (female or male), diagnosis (myeloid or lymphoid malignancies), disease status at transplant (standard risk or high risk), duration from diagnosis to transplant (≤1 or >1 year), duration from the last pretransplant cytotoxic chemotherapy to conditioning of transplant (no history of prior chemotherapy or >2, or ≤2 months), number of courses of prior cytotoxic chemotherapy (≤5 or >5), source of stem cells (related bone marrow or peripheral blood, unrelated bone marrow, or unrelated cord blood), conditioning regimen (conventional or reduced-intensity regimen), use of granulocyte colony-stimulating factor (G-CSF) (yes or no), serum ferritin levels (≤700 ng/mL, >700 ng/mL, or unknown), and serum CRP levels (≤0.3 mg/dL or >0.3 mg/dL). We assessed the interaction between ferritin and CRP levels, using interaction terms between a ferritin category with scores of 0 (ferritin ≤700 ng/mL) and 1 (ferritin >700 ng/mL) and a CRP category with scores of 0 (CRP ≤0.3 mg/dL) and 1 (CRP >0.3 mg/dL). The cutoff point for the ferritin levels was the median value and that for the CRP levels was the higher tertile value. The correlation between ferritin and CRP levels was also tested by Pearson's correlation coefficient. *P* values of less than 0.05 were considered statistically significant. All analyses were conducted using Stata software version 11 (StataCorp., College Station, TX, USA).

Results

Patient characteristics

The patient characteristics are shown in Table 1. The median age of the patients was 47 years (range, 18–66 years). The primary diseases in these patients were as follows: acute myeloid leukemia in 46 patients, acute lymphoblastic leukemia in 11, myelodysplastic syndrome in 16, chronic myelogenous leukemia in 4, non-Hodgkin lymphoma in 19, adult T-cell leukemia/lymphoma in 10, myeloproliferative disorder in 4, and plasma-cell myeloma in 2. Sixty-six patients (58.9%) had standard-risk disease. The source of stem cells used for HCT was related bone marrow or peripheral blood in 40 patients (35.7%), unrelated bone marrow in 52 (46.4%), and unrelated cord blood in 20 (17.9%). A conventional myeloablative regimen was used in 54 patients (48.2%), and G-CSF was used after HCT in 57 patients (50.9%). The number of patients with pretransplant serum ferritin levels of ≤700 ng/mL, >700 ng/mL, and unavailable were 49, 47, and 16, respectively, and the number of those with pretransplant serum CRP levels of ≤0.3 mg/dL and >0.3 mg/dL were 84 and 28, respectively.

Documented bacterial infections

A total of 19 episodes of bacterial infections were documented during the first 30 days after HCT; these included 18 episodes of bloodstream infections and 1 of pneumonia. No patient had more than 1 episode of bacterial infection within 30 days after HCT. The bacterial organisms associated with the documented infections are listed in Table 2. The detected bacterial organisms were mainly gram-negative bacilli (n = 16, 84.2%), 15 of which (93.6%) were sensitive to FQs.

The cumulative incidence of bacterial infections was 16% (95% confidence interval [CI], 10%–24%). Among confounding factors that were potentially associated with bacterial infection, only high pretransplant serum ferritin (>700 ng/mL vs. ≤700 ng/mL) and high CRP (>0.3 mg/dL vs. ≤0.3 mg/dL) levels were significantly associated with the development of bacterial infection in the multivariate analysis (hazard ratio [95% CI]: ferritin, 3.97 [1.35–11.69], *P* = 0.012; CRP, 3.63 [1.45–9.10], *P* = 0.006) (Table 3). Even when serum ferritin and CRP levels were treated as continuous variables, their impact remained significant. Although there was no correlation between ferritin and CRP levels (P=0.062), we analyzed the impact of high ferritin levels in subgroups of patients with either high (>0.3 mg/dL) or low CRP levels (≤0.3 mg/dL), to exclude the effect of inflammation on ferritin levels. We obtained almost consistent results in both groups (hazard ratio [95% CI]: CRP >0.3 mg/dL, 3.67 [0.87-15.63], *P* = 0.078; CRP ≤0.3 mg/dL, 4.12 [0.86-19.64], *P* = 0.076). Further, no interaction was observed between the ferritin and CRP categories (*P* = 0.949). Next, we re-evaluated the risk of bacterial infection with the combination of these 2 risk factors (ferritin and CRP levels). Figure 1 shows the cumulative incidence of bacterial infection for patients divided into 3 risk groups according to this model. The cumulative incidences of bacterial infections were 5.3% (95% CI; 1.0–15.7%) in patients without any risk factors (n = 39), 20.5% (95% CI; 10.1–33.3%) in those with 1 factor (n = 44), and 53.8% (95% CI; 24.8–76.0%) in those with 2 factors (n = 13). The hazard ratios for 1 and 2 risk factors relative to no risk factors in the multivariate analysis were 4.04 (95% CI, 0.88–18.62) and 14.68 (3.02–71.30), respectively. Among patients with bacterial infections, septic shock

or organ failure was observed in 1 patient with 2 risk factors and 4 patients with 1 risk factor, but not in any patients with no risk factors.

Overall survival and treatment-related mortality

Next, we evaluated the impact of the ferritin and CRP levels on other endpoints in 96 patients for whom data on ferritin levels were available (Figures 2 and 3). The median duration of follow-up was 23 months (range, 2.2-54.9). With regard to overall survival, only a high ferritin level (hazard ratio [95% CI]: 2.47 [1.19–5.11], $P = 0.015$) and a duration of less than 2 months from the last cytotoxic chemotherapy to the conditioning of transplant (hazard ratio [95% CI]: 2.16 [1.10–4.26], $P = 0.026$) were significant variables in the multivariate analysis. The causes of death are shown in Table 4. Interestingly, 7 patients among those with high ferritin levels died within 100 days (causes of death: acute graft-versus-host diseases, n = 2; infection, n = 3; hepatic veno-occlusive disease, n = 1; organ failure, n = 1), while none of the patients with low ferritin levels died. With regard to treatment-related mortality, only ferritin and CRP levels were adversely associated with higher treatment-related mortality in the multivariate analysis (hazard ratio [95% CI]: ferritin, 5.21 [1.41–19.30], $P = 0.013$; CRP, 5.76 [1.70–19.48], $P = 0.005$).

Discussion

In our cohort of 112 patients with hematologic malignancies who underwent allogeneic HCT without antibacterial prophylaxis, we found that only high serum ferritin and high CRP levels prior to transplantation were significant risk factors for the post-transplant development of bacterial infection; patients with high ferritin levels and those with high CRP levels had an almost 4-fold higher risk of bacterial infection than those with low ferritin levels or those with low CRP levels. In addition, while severe complications associated with bacterial infection were observed in 5 patients with high ferritin levels and/or high CRP levels, none were seen in patients with low ferritin and low CRP levels. These results suggest that pretransplant serum ferritin and CRP levels may be useful markers for predicting the risk of early bacterial complications after allogeneic HCT.

An association between iron overload and bacterial or fungal infection has been shown in hereditary and secondary hemochromatosis.[21, 22] With regard to HCT, Pullarkat et al. reported that ferritin levels of ≥1000 ng/mL were associated with a 2-fold higher risk of bloodstream infection compared to patients with ferritin levels of <1000 ng/mL in myeloablative HCT.[16] In agreement with their finding, in the present study, ferritin levels of >700 ng/mL were associated with a 4-fold increased risk compared to the risk in patients with levels of ≤700 ng/mL. An increase in plasma non-transferrin-bound iron (NTBI) is considered to play an important role in the adverse effect of iron overload on bacterial infection. Under normal conditions, toxic reactions due to the production of NTBI are prevented by circulating transferrin, which forms a compound with Fe^{3+}.[23] However, plasma

NTBI increases to a measurable level in patients with iron overload because transferrin is almost saturated with Fe^{3+}.[24] The inhibition of iron utilization in erythrocytes by chemotherapeutic agents and irradiation further increases NTBI levels.[25] Hydroxyl radical reactions by NTBI exacerbate mucosal damage caused by chemotherapeutic agents and irradiation, which allows bacterial organisms to enter through the circulation.[26] In addition, iron is an important nutrient for the proliferation of bacteria and fungi.[27] In the HCT setting, the ability of NTBI to induce the proliferation of *Staphylococcus epidermidis* has been demonstrated in an in vitro study using the serum of patients undergoing HCT.[28]

In addition to the adverse impact of iron overload on early infection-related complications, several studies have suggested that high ferritin levels are adversely associated with overall survival and treatment-related mortality.[16, 29-31] In agreement with these studies, our results demonstrated that high ferritin levels are associated with a 2.5-fold increased risk of overall mortality and a 5-fold increased risk of higher treatment-related mortality, compared with low ferritin levels. These studies collectively suggest that iron overload is an important and strong prognostic factor in various clinical outcomes of allogeneic HCT.

Recently, an association between iron chelation therapy and longer overall survival was demonstrated in patients with MDS or severe anemia requiring multiple blood transfusions,[32, 33] and adequate iron chelation therapy is recommended for such patients.[34] The administration of oral iron chelating agents such as deferasirox may be an attractive treatment for iron-overloaded patients compared to deferoxamine, which requires subcutaneous or

intravenous administration. However, the optimal dosage and timing for the administration of deferasirox in allogeneic HCT should be carefully determined in future studies because its renal and gastrointestinal side effects may exacerbate complications of HCT.

At present, only one report has referred to the association between pretransplant CRP levels and transplant outcomes.[18] In that report, pretransplant CRP levels had a marginally significant association with infection within 100 days after reduced-intensity HCT, while other confounding factors, including age, disease status, hematopoietic cell transplantation-specific comorbidity index (HCT-CI), and performance status, had no association; this result is consistent with our present findings. One possible explanation of these findings is that the slightly elevated CRP levels might have reflected minute inflammation, which may represent the presence of latent bacterial infection with negative clinical signs and negative results in pretransplant screening tests, such as X-ray or CT scans. Undetectable bacterial organisms colonized under bacteriostatic conditions before transplant might have rapidly proliferated in the post-transplant neutropenic and immunosuppressive state. Therefore, even if no bacterial infection is detected before transplant in screening tests, latent bacterial infection should be considered in patients with high CRP levels. With regard to treatment-related mortality, an elevated pretransplant CRP level was found to be a significant risk factor in our study, consistent with a previous report.[18] The reason for the worse treatment-related mortality in patients with elevated pretransplant CRP levels remains unclear and needs to be clarified in future studies.

To ensure the safety of allogeneic HCT with the limited use of antibacterial agents, the selective prophylactic administration of antibacterial agents such as FQs only to patients at high risk of bacterial infection may be effective. In the present study, gram-negative bacilli that were highly sensitive to FQs (93.6%) were the main bacterial organisms isolated, which suggests that these infections may have been prevented by the prophylactic administration of FQs in our center. However, this approach may be effective only if most of the bacterial isolates at the transplant center were sufficiently sensitive to these prophylactic antibiotics. In future studies, it would be worthwhile to evaluate whether the incidence of early bacterial infection can be reduced by the prophylactic administration of antibiotics in patients with predefined risk factors such as high ferritin levels or high CRP levels. Iron chelation therapy before HCT is another intriguing strategy that is worthy of future evaluation.

The present study had several limitations. The retrospective study design, small sample size, and heterogeneous background of diseases and transplantation procedures may have biased the results. In addition, HCT-CI, including the performance status, was not evaluated in this cohort due to a lack of adequate information. Further, the impact of serum ferritin levels on the outcomes should be interpreted with caution. Although we consistently determined that high ferritin levels have an adverse impact on early bacterial infection regardless of CRP levels, serum ferritin levels can be affected by conditions associated with other diseases.[35] In a future study, it may be worthwhile to quantify iron overload by other methods, such as magnetic resonance imaging of the liver,[36] and to re-analyze the effect of iron content on the outcome.

In conclusion, the present results suggest that pretransplant serum ferritin and CRP levels, which can be easily measured in various centers, may be useful markers for predicting the risk of early bacterial complications after allogeneic HCT. However, larger prospective studies are warranted to validate our findings and further research is needed to identify other biomarkers that may be associated with the development of post-transplant bacterial complications.

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Conflict of interest

The authors have no conflict of interest to declare.

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TABLES

Table 1 Patient characteristics

Category	Patients	
	n = 112	
Age, years		
Median (range)	47	(18-66)
Sex, n (%)		
Male	49	(43.8)
Female	63	(56.3)
Diagnosis, n (%)		
Acute myeloid leukemia	46	(41.1)
Acute lymphoblastic leukemia	11	(9.8)
Myelodysplastic syndrome	16	(14.3)
Chronic myelogenous leukemia	4	(3.6)
Non-Hodgkin lymphoma	19	(17.0)
Adult T-cell leukemia/lymphoma	10	(8.9)
Myeloproliferative disorder	4	(3.6)
Plasma-cell myeloma	2	(1.8)
Disease status at transplant, n (%)		
Standard risk	66	(58.9)
High risk	46	(41.1)
Source of stem cells, n (%)		
Related bone marrow or peripheral blood	40	(35.7)
Unrelated bone marrow	52	(46.4)
Unrelated cord blood	20	(17.9)
Conditioning regimen, n (%)		
Conventional-intensity regimen	54	(48.2)
BU/CY	10	
TBI/CY based regimen	44	
Reduced-intensity regimen	58	(51.8)
Flu/BU +- TBI	23	
Flu/Mel +- TBI	34	
Flu/TT	1	
Use of G-CSF, n (%)		

Yes	57	(50.9)
No	55	(49.1)
Duration from diagnosis to transplant, n (%)		
≤1 year	57	(50.9)
>1 year	55	(49.1)
Duration from the last pretransplant cytotoxic chemotherapy to conditioning of transplant, n (%)		
No history of prior cytotoxic chemotherapy or >2 months	68	(60.7)
≤2 months	44	(39.3)
Number of courses of prior cytotoxic chemotherapy, n (%)		
≤5 courses	60	(53.6)
>5 courses	52	(46.4)
Pretransplant serum ferritin level (ng/mL)		
Median (range)	694.6	(34.7-12079.1)
Pretransplant serum CRP level (mg/dL)		
Median (range)	0.1	(0.0-4.6)

Abbreviations: BU = busulfan; CY = cyclophosphamide; TBI = total-body irradiation; Flu = fludarabine; Mel = melphalan; TT = thiotepa, G-CSF = granulocyte colony-stimulating factor.

Table 2 Documented bacterial organisms within 30 days after transplantation

Category	Bacterial isolates
Gram-positive cocci (n)	*Enterococcus faecium* (2)
	Streptococcus epidermidis (1)
Gram-negative bacilli (n)	*Klebsiella pneumoniae* (5)
	Escherichia coli (4)
	Pseudomonas aeruginosa (2)
	Klebsiella oxytoca (1)
	Enterobacter cloacae (1)
	Capnocytophaga species (1)
	Prevotella intermedia (1)
	Bacteroides thetaiotaomicron (1)

P. aeruginosa was detected in the sputum of one patient with pneumonia. Other organisms were detected in blood culture bottles.

Table 3 Univariate and multivariate analyses of factors that are potentially associated with documented bacterial infection

Category	Number	Univariate Analysis		Multivariate Analysis	
		hazard ratio (95% CI)	*P* value	hazard ratio (95% CI)	*P* value
Age, years					
≤ 50	10/64	1.00	Reference		
>50	9/48	1.27 (0.51-3.17)	0.608		
Sex					
Female	9/49	1.00	Reference		
Male	10/63	0.80 (0.32-2.00)	0.632		
Diagnosis					
Myeloid malignancies	13/72	1.00	Reference		
Lymphoid malignancies	6/40	0.86 (0.33-2.26)	0.766		
Disease status at transplant					
Standard risk	11/66	1.00	Reference		
High risk	8/46	1.13 (0.45-2.84)	0.795		
Source of stem cells					
Related bone marrow or peripheral blood	6/40	1.00	Reference		
Unrelated bone marrow	8/52	0.88 (0.30-2.59)	0.816		
Unrelated cord blood	5/20	1.84 (0.56-6.05)	0.318		
Conditioning regimen					
Conventional-intensity regimen	8/54	1.00	Reference		
Reduced-intensity regimen	11/58	1.48 (0.57-3.79)	0.419		

Use of G-CSF					
No	10/55	1.00	Reference		
Yes	9/57	0.98 (0.39-2.45)	0.966		
Duration from diagnosis to transplant					
≤1 year	9/57	1.00	Reference		
>1 year	10/55	1.33 (0.53-3.34)	0.550		
Duration from the last pretransplant cytotoxic chemotherapy to conditioning of transplant					
No history of prior cytotoxic chemotherapy or >2 months	13/68	1.00	Reference		
≤2 months	6/44	0.76 (0.29-2.03)	0.589		
Number of courses of prior cytotoxic chemotherapy					
≤5 courses	9/60	1.00	Reference		
>5 courses	10/52	1.44 (0.57-3.64)	0.441		
Serum ferritin level					
≤700 ng/mL	5/49	1.00	Reference	1.00	Reference
>700 ng/mL	14/47	4.04 (1.35-12.05)	0.012	3.97 (1.35-11.69)	0.012
Not available	0/16	-	-	-	-
Serum CRP level					
≤0.3 mg/dL	10/84	1.00	Reference	1.00	Reference
>0.3 mg/dL	9/28	3.38 (1.36-8.39)	0.009	3.63 (1.45-9.10)	0.006

Abbreviations: CI = confidence intervals; G-CSF = granulocyte colony-stimulating factor.

Table 4 Causes of death

Category	Low ferritin group (≤700 ng/mL) (n = 49)	High ferritin group (>700 ng/mL) (n = 47)
Within 100 days after transplant		
Infection	0	2 (29%)
Organ failure	0	2 (29%)
Graft-versus-host disease	0	2 (29%)
Hepatic veno-occlusive disease	0	1 (14%)
Total	0	7
More than 100 days after transplant		
Relapse	9 (82%)	12 (75%)
Infection	1 (9%)	2 (13%)
Organ failure	1 (9%)	0
Idiopathic pneumonia syndrome	0	1 (6%)
Bleeding	0	1 (6%)
Total	11	16

FIGURE LEGENDS

Figure 1

Cumulative incidence of documented bacterial infection within 30 days after transplantation. A) Solid black line, patients with low ferritin levels (≤700 ng/mL) (n = 49); gray line, patients with high ferritin levels (>700 ng/mL) (n = 47), B) Solid black line, patients with low CRP levels (≤0.3 mg/dL) (n = 84); gray line, patients with high CRP levels (>0.3 mg/dL) (n = 28), C) Solid black line, patients with low ferritin (≤700 ng/mL) and low CRP levels (≤0.3 mg/dL) (n = 39); gray line, patients with low ferritin and high CRP levels (>0.3 mg/dL) or high ferritin (>700 ng/mL) and low CRP levels (n = 44); dotted black line, patients with high ferritin and high CRP levels (n = 13).

Figure 2

Kaplan-Meier estimate of overall survival after transplantation. A) Solid black line, patients with low ferritin levels (≤700 ng/mL) (n = 49); gray line, patients with high ferritin levels (>700 ng/mL) (n = 47), B) Solid black line, patients with low CRP levels (≤0.3 mg/dL) (n = 73); gray line, patients with high CRP levels (>0.3 mg/dL) (n = 23).

Figure 3

Cumulative incidence of treatment-related mortality after transplantation. A) Solid black line, patients with low ferritin levels (≤700 ng/mL) (n = 49); gray line, patients with high ferritin levels (>700 ng/mL) (n = 47), B) Solid black line, patients with low CRP levels (≤0.3 mg/dL) (n = 73); gray line, patients with high CRP levels (>0.3 mg/dL) (n = 23).

Figure 1

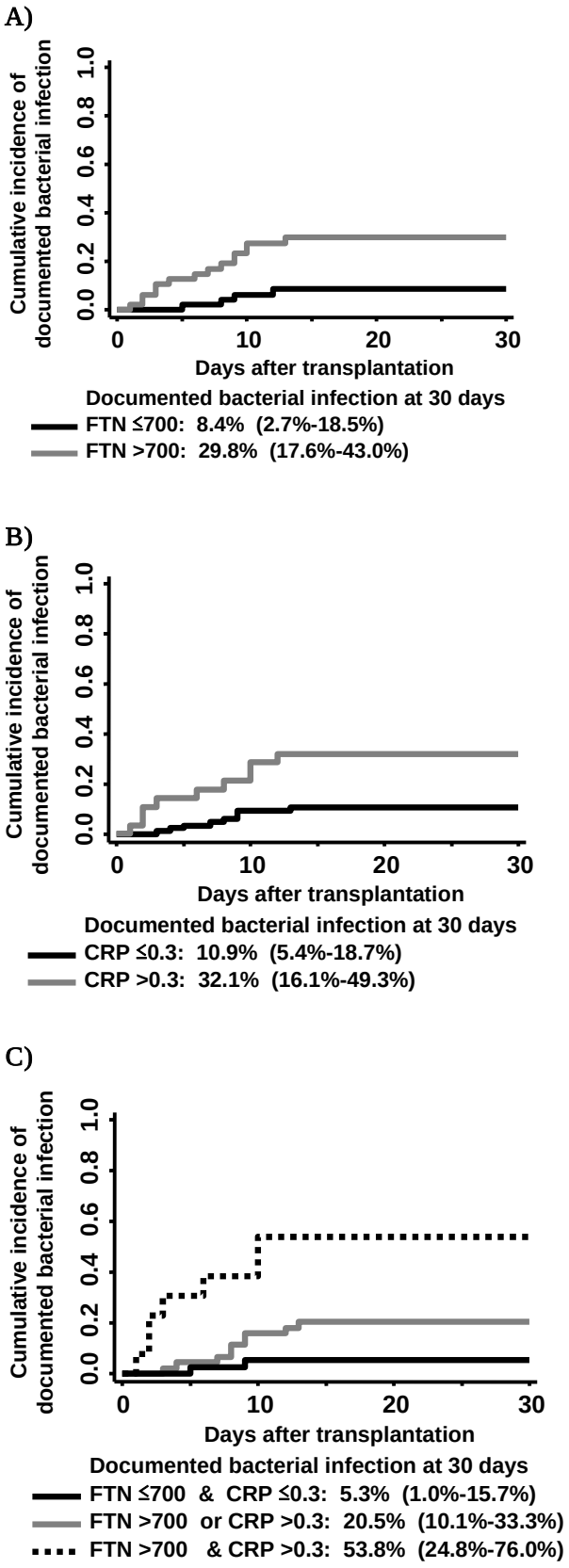
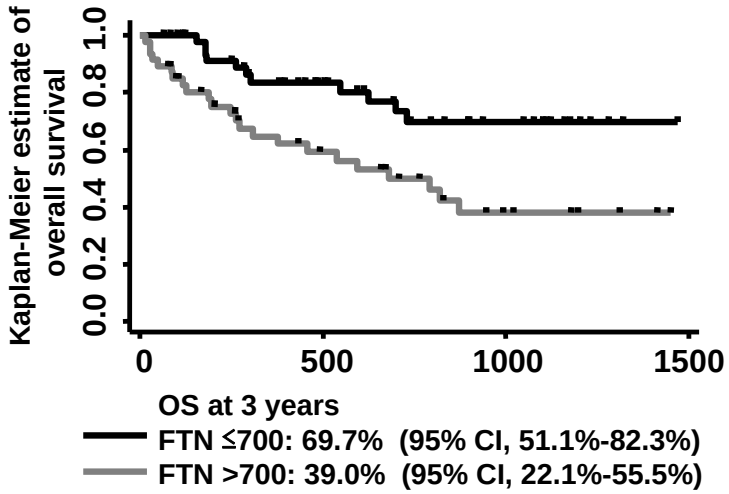

A)
Cumulative incidence of documented bacterial infection
0.0 0.2 0.4 0.6 0.8 1.0
0 10 20 30
Days after transplantation
Documented bacterial infection at 30 days
FTN ≤700: 8.4% (2.7%-18.5%)
FTN >700: 29.8% (17.6%-43.0%)
B)
Cumulative incidence of documented bacterial infection
0.0 0.2 0.4 0.6 0.8 1.0
0 10 20 30
Days after transplantation
Documented bacterial infection at 30 days
CRP ≤0.3: 10.9% (5.4%-18.7%)
CRP >0.3: 32.1% (16.1%-49.3%)
C)
Cumulative incidence of documented bacterial infection
0.0 0.2 0.4 0.6 0.8 1.0
0 10 20 30
Days after transplantation
Documented bacterial infection at 30 days
FTN ≤700 & CRP ≤0.3: 5.3% (1.0%-15.7%)
FTN >700 or CRP >0.3: 20.5% (10.1%-33.3%)
FTN >700 & CRP >0.3: 53.8% (24.8%-76.0%)

Figure 2

A)


Kaplan-Meier estimate of overall survival
0.0 0.2 0.4 0.6 0.8 1.0
0
500
1000
1500
OS at 3 years
FTN ≤700: 69.7% (95% CI, 51.1%-82.3%)
FTN >700: 39.0% (95% CI, 22.1%-55.5%)

B)

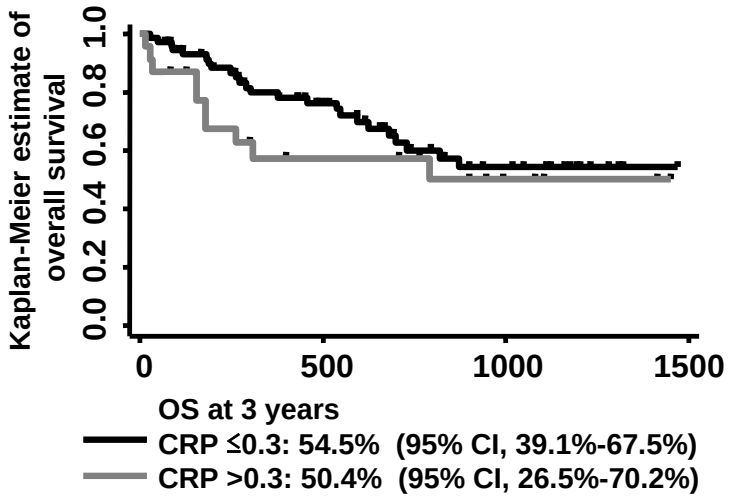
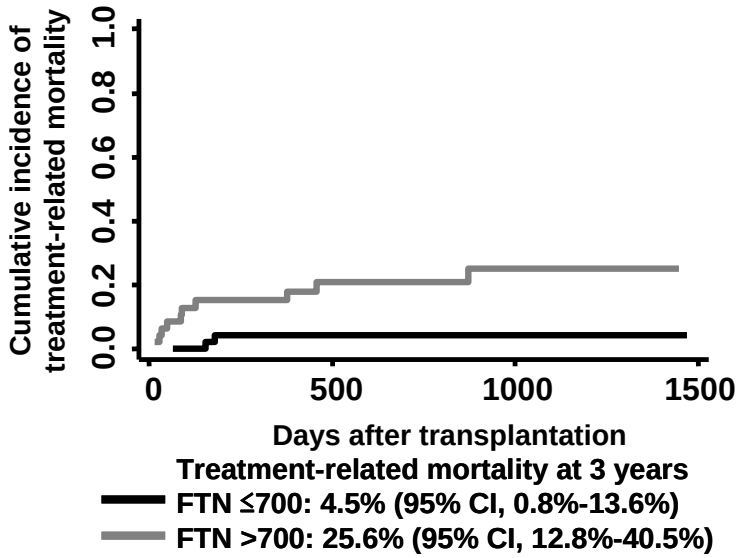
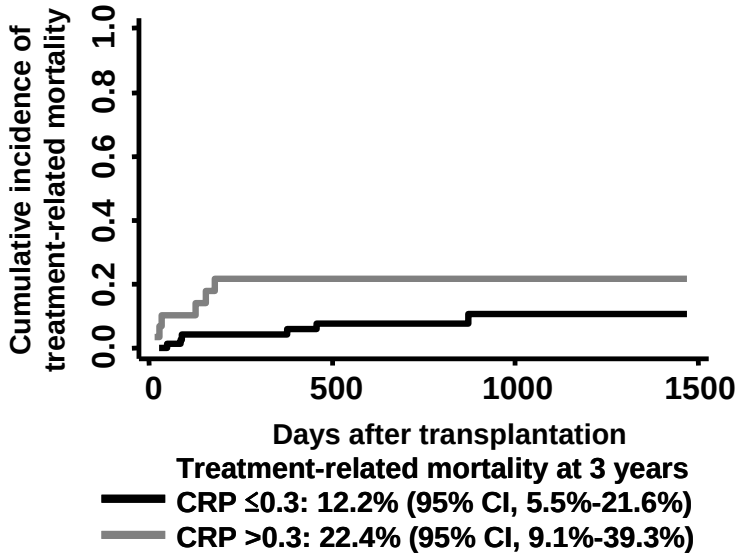

Kaplan-Meier estimate of overall survival
0.0 0.2 0.4 0.6 0.8 1.0
0
500
1000
1500
OS at 3 years
CRP ≤0.3: 54.5% (95% CI, 39.1%-67.5%)
CRP >0.3: 50.4% (95% CI, 26.5%-70.2%)

Figure 3

A)


Cumulative incidence of treatment-related mortality
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
Days after transplantation
Treatment-related mortality at 3 years
FTN ≤700: 4.5% (95% CI, 0.8%-13.6%)
FTN >700: 25.6% (95% CI, 12.8%-40.5%)

B)


Cumulative incidence of treatment-related mortality
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
Days after transplantation
Treatment-related mortality at 3 years
CRP ≤0.3: 12.2% (95% CI, 5.5%-21.6%)
CRP >0.3: 22.4% (95% CI, 9.1%-39.3%)