MAJOR ARTICLE

Low Mannose-Binding Lectin Concentration Is Associated with Severe Infection in Patients with Hematological Cancer Who Are Undergoing Chemotherapy

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Background. Mannose-binding lectin (MBL) is a serum lectin involved in innate immune response. Low serum MBL concentration may constitute a risk factor for infection in patients receiving myelosuppressive chemotherapy.

Methods. We conducted a prospective, observational study that assessed MBL concentration as a risk factor for infection in patients with hematological malignancy who were hospitalized to undergo at least 1 chemotherapy cycle. MBL deficiency was defined using an algorithm that considered the serum MBL concentration and the MBL genotype. The primary end point was the ratio of duration of febrile neutropenia to the duration of neutropenia. Secondary end points included the incidence of severe infection (e.g., sepsis, pneumonia, bacteremia, and invasive fungal infection). Logistic regression analysis was conducted, and Fisher's exact test was used to analyze binary outcomes, and Kaplan-Meier estimates and log rank tests were used for time-to-event variables.

Results. We analyzed 255 patients who received 569 cycles of chemotherapy. The median duration of neutropenia per cycle was 7 days (interquartile range, 0–13 days). Sixty-two patients (24%) were found to have MBL deficiency. Febrile neutropenia occurred at least once in 200 patients. No difference in the primary outcome was seen. The incidence of severe infection was higher among MBL-deficient patients than among non–MBL-deficient patients (1.96 vs. 1.34 cases per 100 days for analysis of all patients [$P = .008$] and 1.85 vs. 0.94 cases per 100 days excluding patients with acute leukemia [$P < .001$]).

Conclusions. MBL deficiency does not predispose adults with hematological cancer to more-frequent or more-prolonged febrile episodes during myelosuppressive chemotherapy, but MBL-deficient patients have a greater number of severe infections and experience their first severe infection earlier, compared with nondeficient patients.

Mannose-binding lectin (MBL) is a serum protein important in the innate immunity system [1, 2]. MBL initiates the complement cascade [3] through the binding of cellular membrane constituent sugars present on the surface of pathogens. Serum MBL concentrations vary between individuals by a factor up to a 1000, ranging from <5 to >5000 ng/mL, because of genetic mutations within the gene and its promoters [4, 5]. In the literature, the incidence of the O/O genotype ranges from 3% to 16%, depending on the ethnic group studied [6].

We tested the hypothesis, generated by previous studies [7–10], that patients with hematological cancer who are MBL deficient have a higher risk of developing infectious complications when receiving myelosuppressive chemotherapy than do non–MBL-deficient patients.

METHODS

Patients

Adult patients (age, >16 years) with hematological malignancy who were undergoing chemotherapy were

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Table 1. Characteristics of the 569 eligible chemotherapy cycles.

Characteristic	All cycles	Cycles for MBL-deficient patients	Cycles for non–MBL–deficient patients
No. (%) of fully eligible cycles[a]	569	136 (23)	433 (76)
Duration of neutropenia per cycle, median days (IQR)	7 (0–13)	6 (0–13)	7 (0–13)
No. (%) of cycles involving growth factors [95% CI]	359 (63) [59–67]	82 (60)	277 (64)
No. (%) of cycles involving prophylactic antimicrobial use [95% CI]			
All	386 (68) [64–72]	92 (68)	294 (68)
Antibacterials[b]	229 (40) [36–44]	50 (37)	179 (41)
Antivirals[c]	274 (48) [44–52]	66 (49)	208 (48)
Antifungals[d]	266 (47) [43–51]	62 (46)	204 (47)
No. (%) of cycles involving a cytarabine-containing regimen [95% CI]	237 (42) [38–46]	50	187
Reason for chemotherapy, no. (%) of cycles [95% CI]			
Transplantation			
All	168 (30) [26–33]	43 (32) [24–40]	125 (29) [25–33]
Autograft	129	34	95
Allograft	25	6	19
Leukemia			
Induction	38	8	30
Consolidation, intensification, or other	109	16	93
Reinduction	19	2	17
Reason other than leukemia			
First-line	88	23	65
Subsequent line	315	87	228

NOTE. IQR, interquartile range; MBL, mannose-binding lectin.

[a] There were 587 registered cycles (139 among MBL-deficient patients and 448 among non–MBL-deficient patients). Of those, 18 had a restricted eligibility (3 among MBL-deficient patients and 15 among non–MBL-deficient patients); these 18 cycles were included in all analyses that considered cumulative cycles. The reason for restricted eligibility was ongoing fever or receipt of antibiotic treatment for a previously registered cycle. There was no significant difference in the distribution of MBL deficiency for the cycles of restricted eligibility, compared with fully eligible cycles.

[b] Ciprofloxacin, 227 cycles; trimethoprim-sulfamethoxazole, 47 cycles; various agents for the rest.

[c] In all cases, the agent used was acyclovir.

[d] Fluconazole, 209 cycles; itraconazole, 125 cycles; amphotericin B aerosols, 75 cycles; nystatin, 2 cycles; and voriconazole, 2 cycles.

eligible. Patients must have been afebrile and not receiving antimicrobial treatment for an ongoing infection at the time of enrollment in the study. The study was conducted at 3 university hospitals. All patients who were scheduled to undergo myelosuppressive chemotherapy for hematological malignancies were sequentially offered enrollment in the study. Patients could have received prior chemotherapy before enrollment. Written informed consent was obtained from all participants. The study protocol was approved by each institution's ethics committee.

Definitions

Neutropenia was defined as an absolute neutrophil count of <500 cells/mL. The duration of neutropenia was measured from the first occurrence of a neutrophil count of <500 cells/mL until permanent recovery (neutrophil counts, ⩾500 cells/mL). Fever was defined as a temperature of ⩾38.5°C recorded on at least 1 occasion or as a temperature of ⩾38°C noted on ⩾2 occasions during a 12-h period. Febrile neutropenia was defined as fever that occurred during neutropenia, regardless of what may have been the cause of the fever. For patients who experienced fever, the date of defervescence was defined as the first day in a 5-day period in which the patient's temperature was <38°C. Severe infection was defined as the presence of pneumonia, septicemia, invasive fungal infection, or sepsis. Sepsis was considered to be present when ⩾2 of the following criteria were present: temperature, >38°C or <36°C; heart rate, >110 beats/min; respiratory rate, >20 breaths/min; or partial pressure of carbon dioxide, <32 mm Hg. Sepsis had to be associated with a microbiologically or clinically documented infection. Mucositis of grade 3 or 4 that occurred during fever of unknown origin was considered to represent a documented infection. Pneumonia had to be documented by the presence of a pulmonary infiltrate noted on a chest radiograph or chest CT. Septicemia was defined as the presence of clinical signs or symptoms of infection accompanied by a microbiologically documented clinical infection and by the isolation of a bacterium or fungus in a blood specimen, with the exception of some pathogens (e.g., *Staphylococcus epidermidis*). These pathogens were considered to be contaminant pathogens when they

Table 2. Distribution of the genotypes and mean concentrations of mannose-binding lectin (MBL).

	Genotype distribution for 187 patients with available measurements		MBL concentration among 167 patients	
Genotype	No. of patients	Frequency, %	No. of patients	Mean MBL concentration, ng/mL (95% CI)
YA/YA	58	31	51	3731 (3312–4150)
XA/YA	54	29	46	2508 (2128–2888)
YA/O	37	20	35	743 (544–943)
XA/XA	15	8	13	1131 (634–1627)
XA/O	12	6	11	317 (0–720)
O/O	11	6	…	…
Total	187	100	…	…
Missing	68	…	…	…
Total	255	…	…	…

NOTE. Three point mutations in exon 1 of the *MBL2* gene are strongly associated with low MBL concentrations. These 3 structural variants are named B, C, and D for mutations on codons 54, 57, and 52 respectively. The normal allele is called A; other variants are called O.

occurred in only 1 culture bottle with positive results only or in patients for whom 1 blood specimen was used in 2 culture bottles; thus, they were not relevant in the definition of septicemia. A minimum of 2 positive results for culture bottles that included 2 different blood specimen sets were to be taken into account. Invasive fungal infections were classified as probable or proven on the basis of European Organization for Research and Treatment of Cancer–Mycosis Study Group criteria [11].

End Points

The ratio of the duration of febrile neutropenia (calculated as the number of febrile neutropenic days) to the duration of neutropenia (calculated as the number of neutropenic days) was the primary end point. This end point covers the most important determinant of initiation of or change in treatment for patients undergoing myelosuppressive therapy. It also takes into account the fact that the duration of neutropenia influences the frequency, severity, and outcome of infection [12]. It is sometimes difficult to determine the precise cause of fever in the context of chemotherapy and neutropenia; therefore, all reported days of fever were taken into consideration, even if the fever was finally determined to be unrelated to an infectious problem in our classification of documentation of infection.

The secondary end points included the time to a first event and the following events: occurrence of fever (including all causes of fever), clinically or microbiologically documented infectious episodes occurring during neutropenia, severe infections (as defined above), septicemia, and documented bacteremia, independent of the presence or absence of neutropenia.

Observation Period

Patients were enrolled during the period from December 2001 through December 2003. Patients were observed from the first day of each cycle of chemotherapy administration after enrollment until recovery from neutropenia. The maximum duration of follow-up was 45 days for patients with protracted neutropenia.

Laboratory Tests

All analyses were performed blindly by NatImmune (Copenhagen, Denmark). Clinicians were blinded to all results of the analyses.

MBL plasma concentration. Plasma samples were obtained for assessment of the mbl2 genotype and/or to determine the plasma MBL level; samples had to be obtained on day 1 of chemotherapy or during the 3 days preceding chemotherapy. MBL concentration was measured using a time-resolved immunofluorometric assay [13].

Genotyping. MBL genotyping was performed as described elsewhere [14, 15] using a real-time PCR assay on a LightCycler (Roche Applied Sciences). This assay detects a single-nucleotide polymorphism by monitoring the temperature-dependent hybridization of probes to single-stranded DNA. Detection of the hybridization was performed using fluorescence resonance energy transfer.

Assessment of MBL deficiency. MBL concentration was always determined in the absence of fever or infection before chemotherapy. When possible, the MBL concentration was determined before the first cycle of chemotherapy. However, for a few patients, the MBL concentration was determined prior to a subsequent cycle of chemotherapy or after the completion of chemotherapy. MBL deficiency was defined as an MBL concentration of <500 ng/mL [10].

Statistical Analysis

Descriptive analysis was performed using frequency tabulations for categorical variables and summary parameters for continuous variables. Analysis of variance was performed for serum MBL levels on the basis of genotype.

For assessment of the risk of infection in relation to MBL status, analyses were performed using the patient as the analysis unit (with 2 end points: counts of events per 100 days of follow-up and time to the first event) or the first chemotherapy cycle as an analysis unit. Several statistical models were used to fit the data and to compare the groups of MBL-deficient and non–MBL-deficient patients (the Mann-Whitney *U* test was used for comparing the ratio of febrile neutropenic days to neutropenic days, and the χ^2 test or Fisher's exact test was used for comparing binary variables). Counts of events were analyzed using Poisson regression models, and time-to-event variables were analyzed using both Kaplan-Meier estimates and Cox re-

Table 3. Characteristics of mannose-binding lectin (MBL)–deficient and non–MBL-deficient patients.

Characteristic	MBL-deficient patients	Non–MBL-deficient patients
No. of eligible patients	62	193
Age, median years (range)	55 (20–77)	52 (19–80)
No. (%) of male patients	40 (64)	112 (58)
Median time from diagnosis to registration (range)	168 days (0–16 years)	201 days (0–18 years)
No. (%) of registered chemotherapy cycles per patient		
1	34 (55)	98 (51)
2	12 (19)	38 (20)
3	5 (8)	24 (12)
4	3 (5)	9 (5)
5	3 (5)	11 (6)
>5	5 (8)	13 (7)
Underlying cancer, proportion (%) of patients		
Acute leukemia	16/62 (26)	62/193 (32)
Myeloma	16/62 (26)	39/193 (20)
High-grade lymphoma	10/62 (16)	31/193 (16)
Intermediate-grade lymphoma	10/62 (16)	13/193 (7)
Hodgkin disease	2/62 (3)	14/193 (7)
Chronic leukemia	4/62 (6)	11/193 (6)
Myelodysplasic syndrome	4/62 (6)	11/193 (6)
Low-grade lymphoma	0/62 (0)	9/193 (5)
Leukemia not otherwise specified	0/62 (0)	2/193 (1)
Polycythemia vera	0/62 (0)	1/193 (<1)
Duration of neutropenia per patient, median days (IQR)	9 (5–16)	9 (5–15)

NOTE. A total of 255 patients were eligible from among the 282 enrolled patients. IQR, interquartile range.

[a] Data are for 587 cycles.

gression models. Regression coefficients were estimated using the maximum likelihood method and are reported with 95% CIs. All reported *P* values are 2-tailed and nominal. For correcting for multiplicity (i.e., febrile neutropenia and documented and severe infections analyzed in terms of counts of events and time to the first event with 2 subgroups), we applied Bonferroni's conservative method; therefore, $P < .004$ should be used to define significance, to keep the overall risk of at least 1 false-positive result to 5%. Secondary analysis was restricted to the period of neutropenia throughout all cycles for each patient and for subgroup analysis that excluded patients with acute leukemia.

RESULTS

Characteristics of patients and chemotherapy cycles. Two hundred eighty-two patients, who underwent a total of 688 cycles of chemotherapy, were enrolled in the study. On the 255 eligible patients, the following assessments were possible: 210 patients were evaluated on the basis of an adequate serum sample at the first eligible cycle, 25 patients were evaluated on the basis of an adequate serum sample at a subsequent eligible cycle, 16 patients were assessed for genotype only (15 patients with the A/A or A/O genotype were classified as non–MBL deficient, and 1 patient with the O/O genotype was classified as MBL deficient), and 4 patients were assessed using all available plasma MBL levels.

Overall, 62 (24%) of 255 patients were determined to be MBL deficient. The median number of available plasma MBL levels for the 255 eligible patients was 9 (range, 0–57). Of the 187 patients with available genotypes, 23 (12%) had XA/O or O/O genotypes (table 1).

Of 688 cycles of chemotherapy administered to 282 sequential patients, 53 cycles were unassessable (i.e., no serum, genotype, or outcome information was available), and 48 were ineligible. Reasons for ineligibility were as follows: for 43 cycles, the patients had ongoing fever or were receiving ongoing antibiotic therapy for a previous infection at the time of enrollment (these 43 episodes involved 36 patients, 31 of whom had acute leukemia), 4 cycles involved patients who were eligible for the study but who did not consent to participate, and 1 cycle involved a patient who received an injection of contaminated stem cells and was thus considered to have a baseline infection. There were 569 fully eligible cycles, and 18 cycles had to be included in the analysis despite the occurrence of baseline infection or fever because they involved patients who were already included in the study. Therefore, 587 cycles involving

Table 4. Univariate analysis of incidence of infectious complication.

Variable	MBL Status		RR (95% CI)[a]	*P*
	MBL-deficient patients (*n* = 62)	Non–MBL-deficient patients (*n* = 193)		
All patients (*n* = 255)				
Documented infection				
No. of events	117	353	…	
Rate of event per 100 days	3.30	2.80	1.17 (0.96–1.45)	.12
Severe infection				
No. of events	69	166	…	
Rate of event per 100 days	1.96	1.34	1.46 (1.11–1.94)	.008
Septicemia[b]				
No. of events	27	88	…	
Rate of event per 100 days	0.77	0.71	1.08 (0.70–1.66)	.73
Sepsis[b]				
No. of events	30	77	…	
Rate of event per 100 days	0.85	0.56	1.37 (0.90–2.09)	.14
Pneumonia				
No. of events	25	49	…	
Rate of event per 100 days	0.71	0.39	1.80 (1.11–2.91)	.02
Patients with nonacute leukemia (*n* = 177)				
No. of patients	46	131	…	
Documented infection				
No. of events	85	171	…	
Rate of event per 100 days	3.11	2.21	1.40 (1.08–1.82)	.009
Severe infection				
No. of events	50	72	…	
Rate of event per 100 days	1.85	0.94	1.97 (1.37–2.83)	<.001
Septicemia[b]				
No. of events	19	27	…	
Rate of event per 100 days	0.70	0.35	2.00 (1.11–3.59)	.02
Sepsis[b]				
No. of events	21	33	…	
Rate of event per 100 days	0.78	0.50	1.80 (1.04–3.12)	.03
Pneumonia				
No. of events	17	26	…	
Rate of event per 100 days	0.63	0.34	1.85 (1.01–3.42)	<.05
All patients, considering only the period of neutropenia during follow-up (*n* = 241)				
No. of patients	60	181	…	
Documented infection				
No. of events	93	276	…	
Rate of event per 100 days	7.15	6.51	1.10 (0.87–1.39)	.43
Severe infection				
No. of events	58	146	…	
Rate of event per 100 days	4.46	3.44	1.30 (0.96–1.76)	.10
Patients with nonacute leukemia, considering only the period of neutropenia during follow-up (*n* = 165)				
No. of patients	44	121	…	
Severe infection				
No. of events	39	60	…	
Rate of event per 100 days	4.99	2.96	1.69 (1.13–2.53)	.01

NOTE. MBL, mannose-binding lectin; RR, relative risk.

[a] RR is for the estimated increase in the rate of events in MBL-deficient patients.

[b] Defined in the Definitions subsection of Methods.

Table 5. Time to the development of the first infectious complication.

Group, outcome	Time to the development of the first infectious complication, median days		HR (95% CI)	P[a]
	MBL-deficient patients	Non–MBL-deficient patients		
All patients (n = 255)				
Fever	11	12	1.15 (0.84–1.58)	.36
Febrile neutropenia	12	13	1.12 (0.81–1.54)	.49
Severe infection				
All	**20**	**54**	**1.50 (1.04–2.16)**	**.03**
Bacteremia	74	93	1.34 (0.85–2.13)	.20
Sepsis	121	NR	1.39 (0.85–2.26)	.19
Pneumonia	118	162	1.51 (0.89–2.56)	.13
Excluding patients with acute leukemia (n = 177)				
Fever	12	12	1.15 (0.79–1.68)	.47
Febrile neutropenia	12	13	1.08 (0.73–1.60)	.69
Severe infection				
All	**21**	**84**	**1.79 (1.14–2.80)**	**.01**
Bacteremia	**90**	**190**	**2.08 (1.13–3.85)**	**.02**
Sepsis	**165**	NR	**1.81 (0.98–3.34)**	**.05**
Pneumonia	131	NR	1.44 (0.73–2.83)	.29

NOTE. Statistically significant variables are shown in boldface font. HR, hazard ratio; MBL, mannose-binding lectin; NR, number of events was insufficient to calculate a median value.

[a] Determined using the log rank test.

255 patients were analyzed. A total of 168 intensification cycles (30% of fully eligible cycles; 95% CI, 26%–33% of fully eligible cycles) were performed in preparation for transplantation, as follows: autologous stem cell transplantations, 129 cycles; allograft transplantations, 25 cycles; and minitransplantations, 13 cycles (1 transplantation was ultimately not performed).

Follow-up of the patient was not completed until recovery from neutropenia for 16 of 136 cycles in the MBL-deficient group versus 53 of 433 cycles in the non–MBL-deficient group ($P = 1$); this was most commonly the reason when patients without fever or infection were discharged from the hospital with neutropenia, when a new chemotherapy cycle was started, or when the patient died. Baseline characteristics were similar for patients and cycles for the MBL-deficient and non–MBL-deficient groups (tables 2 and 3).

Influence of MBL concentration on infection. The primary end point (i.e., the ratio of the number of febrile neutropenic days to the number of neutropenic days) was similar in MBL-deficient patients and non–MBL-deficient patients. The count of severe infections was found to be higher in MBL-deficient patients (table 4), and those severe infections developed earlier in MBL-deficient patients (table 5); in patients without acute leukemia, these associations were stronger. The rate of documented infection was not statistically different when the entire population was considered. Univariate analysis of the time to the first severe infection for the entire patient population ($n = 255$) revealed a shorter time to the first severe infection for MBL-deficient patients than for non–MBL-deficient patients (20 vs. 54 days; hazard ratio, 1.5; $P = .01$, determined by log rank test) (figure 1*A*).

Multivariate analyses were performed to adjust for factors known to affect the risk of infection. These factors were as follows: (1) use of antibiotic prophylaxis, administration of growth factors, or both; (2) diagnosis of a hematologic malignancy other than myeloma and lymphoma (e.g., acute leukemia and other diagnoses); and (3) diabetes. Only factors that were found to be significant in a univariate analysis were included in the multivariate model.

Multivariate analysis was performed to determine the rate of severe infection, the rate of documented infection, and the time to first severe infection (these were the 3 outcomes that had a significant result on univariate analysis and that were thought to be most relevant to infection in cases of neutropenia). For the 3 outcomes in the multivariate analysis, an increased risk was present in MBL-deficient patients, compared with non–MBL-deficient patients (table 6).

Analysis on the first cycles only. We restricted the analysis to the first cycle of chemotherapy included for each of the 255 patients. The median duration of follow-up for the first cycle was 25 days (range, 0–45 days; interquartile range, 17–37 days).

In the overall per-patient analysis, there were 141 patients who developed at least 1 severe infection. Of these patients,

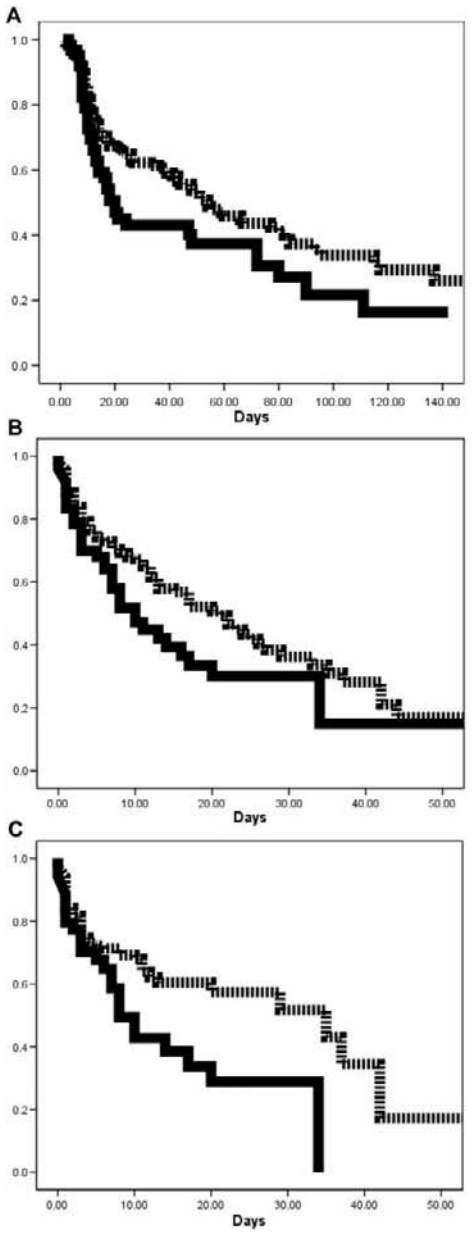

Figure 1. Kaplan-Meier estimates of time to first severe infection among patients with mannose-binding lectin (MBL) deficiency. Severe infection was defined as pneumonia, invasive fungal infection, septicemia, and/or sepsis associated with an infection. *A,* Analysis of all 255 patients for time to first severe infection, showing a shorter time to event for MBL-deficient patients than for non–MBL-deficient patients (median, 20 vs. 54 days; hazard ratio, 1.50; 95% CI, 1.04–2.16; $P = .01$, by log rank analysis). *B,* Analysis of all 241 patients having developed neutropenia for time to first severe infection, showing that the time to first severe infection during neutropenia was shorter in MBL-deficient patients than in non–MBL-deficient patients (median, of 10 vs. 21 days ; $P = .05$). Sixty patients were MBL deficient, and 127 patients developed at least 1 severe infection during neutropenia. *C,* Analysis excluding 165 patients with acute myeloid leukemia for time to first severe infection, showing that the time to first severe infection during neutropenia was shorter in 44 MBL-deficient patients than in 121 non–MBL-deficient patients (median, 35 vs. 8 days; $P = .01$).

104 developed this first severe infection during the follow-up period for the first cycle. Analysis of the influence of MBL deficiency on the time to severe infection revealed that the 75th percentile for time to infection development during follow-up was 10 days among MBL-deficient patients, whereas it was 12 days for non–MBL-deficient patients (hazard ratio, 1.52; 95% CI, 1.00–2.31; $P = .05$). The number of severe infections was not significantly linked to the MBL deficiency status (relative risk, 1.38; 95% CI, 0.96–2.00; $P = .08$). On bivariate analysis, the results were similar after adjustment for antibiotic prophylaxis (adjusted hazard ratio, 1.53; 95% CI, 1.00–2.33; $P = .05$, by stratified log rank test) and administration of growth factors (adjusted hazard ratio, 1.55; 95% CI, 1.02–2.36; $P = .04$, by stratified log rank test).

MBL concentration, neutropenia, and infectious complications. Analysis was performed by looking at the incidence of severe infections that occurred during neutropenia. Fourteen patients who never developed neutropenia were excluded from this analysis. Among the remaining 241 patients, 60 were MBL deficient. One hundred twenty-seven patients developed at least 1 severe infection during the period of neutropenia.

The rate of severe infection was higher in the analysis that examined the period of neutropenia than in the analysis that examined the total duration of follow-up. The rate of severe infection was similar in MBL-deficient and non–MBL-deficient patients when analyzing the entire population. When we excluded patients with acute leukemia, the rate of severe infection in MBL-deficient patients was higher than the rate in non-MBL-deficient patients ($P < .05$) (table 4).

The time to the first severe infection during neutropenia was shorter in MBL-deficient patients than in non–MBL-deficient patients (10 vs. 21 days; $P = .05$) in the entire population (figure 1*B*). The time to the first severe infection in 165 neutropenic patients who did not have leukemia (44 of whom were MBL deficient) was shorter in MBL-deficient patients than in non–MBL-deficient patients (8 vs. 35 days; $P = .01$) (figure 1*C*).

DISCUSSION

The present study did not reveal a difference in the primary outcome (i.e., the effect of the duration of febrile neutropenia on the number of days of neutropenia). However, a higher risk of severe infection was noted for patients with hematological malignancies who were receiving chemotherapy and who had low MBL concentrations, compared with patients with a normal MBL concentration. These severe infections occurred earlier in patients who were MBL-deficient.

A recent retrospective study suggested that a microbiologically confirmed systemic or disseminated infection is more common among patients with cancer who have a MBL defi-

Table 6. Multivariate analysis of the number of infectious complications and the time to severe infection.

Variable, covariate	Adjusted risk (95% CI)[a]	Adjusted HR (95% CI)	*P*
Documented infection			
MBL deficiency	1.30 (1.05–1.61)	…	.02
Use of growth factors alone	1.73 (1.18–1.79)	…	<.001
Acute leukemia	1.73 (1.41–2.13)	…	<.001
Leukemia other than acute leukemia and myeloma/lymphoma	1.40 (1.04–1.87)	…	.03
Absence of diabetes	0.74 (0.57–0.97)	…	.03
Severe infection			
MBL deficiency	1.70 (1.28–2.27)	…	<.001
Use of growth factors alone	2.06 (1.41–3.03)	…	<.001
Acute leukemia	1.89 (1.44–2.48)	…	<.001
Absence of diabetes	0.60 (0.42–0.85)	…	.005
Time to severe infection			
MBL deficiency	…	1.77 (1.22–2.57)	.003
Use of growth factors alone	…	2.77 (1.69–4.54)	<.001
No acute leukemia	…	0.49 (0.35–0.71)	<.001

NOTE. HR, hazard ratio; MBL, mannose-binding lectin.

[a] Estimated increase in the rate among MBL-deficient patients.

ciency and who are undergoing high-dose chemotherapy and autologous peripheral blood stem cell transplantation [16]. These results are similar to the conclusions of our study.

Various end points have been used to investigate the infection risk in patients with hematological malignancies who are undergoing chemotherapy. Studies that measured the incidence of fever as an end point did not find an association with MBL deficiency [17, 18], which is consistent with the results of the present study, in which febrile episodes and their duration did not vary on the basis of MBL status. However, one study of children with malignancies did find an association between the duration of febrile neutropenic episodes and MBL deficiency [19]. Fifty-five percent of the subjects in that study had acute lymphocytic leukemia, and 9% had neuroblastoma; this differs from the population evaluated in the present study

In 2001, a retrospective study of 54 adult patients who received treatment for hematological cancer, including a few cases of acute leukemia (13%), suggested that there was a greater number of MBL-deficient patients among subjects with major infections (13 of 16) than among those with minor infections (11 of 38) [10]. Kilpatrick et al. [18] found no relationship between MBL levels and chemotherapy-related infection. In that retrospective study, 128 adult patients who underwent chemotherapy for hematological cancer were evaluated. These patients had similar types of diseases and received similar treatments, as did patients in the present study. The population was divided into 4 clinical subgroups on the basis of type of infection and fever and into 4 categories on the basis of MBL concentration. When all 4 subgroups were analyzed together, no significant association was found between MBL concentration and chemotherapy-related infection. The frequency of patients with a very low level of MBL deficiency (MBL level, <100 μg/L, as determined by ELISA) was higher among subjects with major infection (e.g., pneumonia and/or bacteremia) than among subjects who showed no sign of infection. Although the data are not directly comparable (i.e., the cutoff values and methodologies are different), these results differ from the results of the study by Peterslund et al. [10], who found a strong association between MBL concentration and chemotherapy-related infection when a higher MBL cutoff value (<500 μg/L, as determined by time-resolved immunofluorometric assay) was used.

Both studies evaluated a small number of patients. None of the studies adjusted for potential confounding risks for infection, such as the use of granulocyte colony-stimulating factor or antibiotic prophylaxis, as was done in the present study.

The results of the studies discussed above, despite their limitations, are compatible with our findings: MBL concentration influences the risk of infection, but the magnitude of the risk decreases in the context of prolonged neutropenia. This is consistent with the results of the study by Bergmann et al. [20].

Two factors should be considered when evaluating the association between MBL concentration and the risk of infection in patients with acute leukemia. First, the duration of neutropenia was longer in patients with acute leukemia than in other patients (14.5 vs. 5 days; $P < .001$). Second, there may have been an enrollment bias, because patients with acute leukemia and an ongoing fever or infection were excluded at the study's start. Severe immunosuppression in patients with acute myelocytic leukemia who are undergoing chemotherapy may reduce

the ability to demonstrate the protective effects of MBL in these patients. Indeed, few functional scavenger cells are present in patients with acute leukemia, which may reduce the impact of the opsonization deficit that results from MBL deficiency.

The present study is, to our knowledge, the largest study to have evaluated the risk of infectious complications associated with MBL deficiency to have been published to date, and our results should be added to the growing evidence that a low MBL concentration increases the risk of severe infection in patients undergoing chemotherapy. In conclusion, the significantly increased risk of severe infection in MBL-deficient patients found in this study is relevant and strongly supports the evaluation of the use of MBL replacement therapy for this population.

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