Support Care Cancer (2016) 24:187–194
DOI 10.1007/s00520-015-2762-1

ORIGINAL ARTICLE

Pre-treatment blood inflammatory markers as predictors of systemic infection during induction chemotherapy: results of an exploratory study in patients with acute myeloid leukemia

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Received: 1 May 2014 / Accepted: 30 April 2015 / Published online: 19 May 2015

Abstract
Purpose The purpose of this study is to evaluate the role of C-reactive protein (CRP) and ferritin blood levels in predicting the incidence of systemic infection among adult patients with acute myeloid leukemia (AML) treated with induction chemotherapy.
Methods Adult patients with newly diagnosed AML who were initially treated with conventional 3+7 induction chemotherapy within 5 days of their diagnosis were included. Patients with previous cytotoxic chemotherapy <3 years, acute promyelocytic leukemia diagnosis, human immunodeficiency virus infection, or significant systemic infection at the time of diagnosis were excluded. Patients were treated with an institutional policy of substantial identity with negligible differences regarding supportive care.
Results Among 110 patients (median age 54.5 years), 39 infectious events in 38 patients were reported, along with 21 episodes of infectious treatment-related mortality (TRM; 19.1 %). Elevated pre-treatment CRP (p=0.032) and ferritin (p=0.002) were related to the incidence of systemic infection. The degree of increase of blood CRP and ferritin level was correlated with the extent of leukocytosis. However, patients with elevated inflammatory markers above normal range had increased risk of infection irrespective of whether they had leukocytosis or not, suggesting that expansion of leukemic blast is another factor affecting the elevation of the markers independent to infection propensity and therefore the magnitude of the elevation does not quantitatively predict the risk of infection.
Conclusions Modest elevation of baseline blood inflammatory markers above the normal range could be an indicator for predicting the incidence of systemic infection in patients with AML.

Keywords Acute myeloid leukemia · Induction chemotherapy · C-reactive protein · Ferritin · Infection

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Introduction

Acute myeloid leukemia (AML), one of the most common hematologic malignancies, is characterized by the clonal expansion of myeloid precursor cells in the peripheral blood and bone marrow [1]. Younger patients, usually defined as younger than 60 years of age, and some older patients who have a good performance status (PS) are initially treated with remission induction therapy [2]. The induction therapy is a dose-intense chemotherapy consisting of idarubicin or daunorubicin in combination with cytarabine. This backbone has not changed in over 30 years [1–3].

For patients with AML, induction chemotherapy is a dynamic and sometimes dangerous procedure. There are many risk factors associated with serious morbidity and even mortality. Complications can occur during the debulking of the tumor burden. There is a significant bleeding tendency due to thrombocytopenia. Most importantly, infectious

complications result from the immune-compromised status. Previous large series have reported treatment-related mortality (TRM) of induction chemotherapy of 12–24 % in patients with newly diagnosed AML [4–7]. Despite the best supportive care, such as prophylactic use of antimicrobial agents and administration of granulocyte colony-stimulating factor (G-CSF), most cases of TRM are due to infectious causes, and they remain major obstacles in the ultimate achievement of cure in patients with AML. In addition, serious systemic infection during induction chemotherapy, despite patient survival, may result in a decline of PS of the patient and may also induce poor survival by preventing the patient from proceeding to consolidative therapy in time.

Blood inflammatory markers such as C-reactive protein (CRP) and serum ferritin have predictive value for the incidence of systemic infection in patients who underwent hematopoietic stem cell transplantation (HSCT) [8, 9]. However, their roles in patients with newly diagnosed hematologic malignancy, i.e., who required treatment for significant tumor burden, have not yet been studied.

The purpose of the current study is to evaluate the role of two representative blood inflammatory markers, CRP and ferritin, in predicting the incidence of systemic infection and infectious TRM among adult patients with newly diagnosed AML who were treated with current standard induction chemotherapy.

Materials and methods

Patients

The inclusion criteria for the current study were (1) age >20 years, (2) AML diagnosis according to the 2008 World Health Organization classification at a single institution, Gachon University Gil Medical Center (GUGMC), and (3) initial treatment with induction chemotherapy within 5 days after diagnosis of AML. Patients who had already been exposed to other chemotherapy or radiotherapy due to myelodysplastic syndrome (MDS) or any other tumors within 3 years, were diagnosed as AML with t(15;17)(q22:q12); PML-RARα, had human immunodeficiency viral infection, or were treated with other than the standard induction therapy were excluded. Patients who had been suffering from significant systemic infection at the time of diagnosis and underwent treatment for infectious disease before induction chemotherapy were excluded from the analysis.

Systemic infection was defined as an infection in which the pathogen is distributed throughout the human body rather than concentrated in localized areas. An infectious event was considered systemic if it combined the systemic inflammatory response syndrome (SIRS) [10]. Patients were excluded if they had SIRS and at least one of the following two factors: (1) obvious clinical symptom of infection and (2) any microbiological or serologic evidence of infection.

The current study was reviewed and approved by the institutional review board of the GUGMC (Approval Number: GCIRB2013-322). Informed consent was waived by the review board, considering the lack of actual intervention for the analyzed patients and the retrospective study design.

Induction chemotherapy and prophylactic measures

Induction chemotherapy was composed of continuous intravenous infusion of cytarabine 100 mg/m^2/day for seven consecutive days with intravenous administration of idarubicin 12 mg/m^2/day (or daunorubicin 90 mg/m^2/day) for three consecutive days.

Prophylactic oral ciprofloxacin was prescribed for those who had no fever before initiation of chemotherapy. If a patient had a body temperature ≥38.0 °C before induction therapy, although the patient did not have significant symptoms or sign of systemic bacterial infection other than fever, intravenous cefepime was initiated. One of three azoles (fluconazole, itraconazole, or posaconazole) was selected for use as a prophylactic oral antifungal agent. Prophylactic antimicrobial drugs were used from the first day of induction therapy to the day of absolute neutrophil (ANC) >1000/μL for three consecutive days. Either filgrastim 300 μg/day or lenograsim 250 μg/day was applied intravenously to patients after the neutrophil nadir was achieved with the disappearance of leukemic blasts in peripheral blood. Antiviral and antipneumocystis prophylaxis was not provided. For the monitoring of mold disease, blood aspergillus antigen and chest X-ray were evaluated twice a week.

A 7-French non-tunneled subclavian central venous catheter was inserted into patients before initiation of chemotherapy. Induction therapy was administered with reverse isolation in single laminar airflow rooms with a high-efficiency particulate air (HEPA) filter. Patients received a low bacterial diet during the period of ANC <500/μL.

Systemic infection during induction chemotherapy

Any episode of systemic infection reported before the third consecutive day of ANC >1000/μL was analyzed. Indication of blood cultures and interpretation of the culture results were as described previously [8]. Systemic bacterial infection denotes systemic infection with relevant culture-proven bacterial growth. Systemic fungal infection was defined as systemic infection with any fungemia or deep tissue infection by mold or yeast proven with culture or highly suggestive according to histo- or cytochemical evidence, imaging reports, or antigen positivity.

Statistical analysis

An exploratory retrospective study was conducted by reviewing the electronic medical charts and laboratory data of included patients. The pre-treatment blood levels of CRP and ferritin within 2 days before the start of induction therapy were dichotomized and their relationship to systemic infection was analyzed. The cutoff value of normal CRP was 0.5 mg/dL, as in our previous study [8], and the upper limit of normal range (ULN) of the institutional laboratory. Serum ferritin level was considered elevated if the value was >290 ng/mL according to the institutional cutoff value. Fisher's exact test or the chi-square test was used as appropriate to estimate the relationship between two dichotomous variables. Among risk factors for systemic infection with a $p<0.1$ in the chi-square or Fisher's exact test, multiple binary logistic regression tests were performed as multivariable analysis. Correlation between two continuous variables was analyzed according to the Pearson's correlation coefficient. Both the non-parametric Mann-Whitney *U* test and the independent samples *t* test were used for the comparison of means between two groups. All values were two sided and statistical significance was accepted at the level of $p<0.05$.

Results

Patient characteristics

One hundred and fifty-eight consecutive patients were diagnosed with AML and treated from February 2006 to July 2013. A total of 110 patients (median age 54.5 years, range 20–80) satisfied the inclusion criteria and 48 patients were excluded. Twenty-three patients received palliative therapy only. Thirteen patients were diagnosed as AML with t(15;17)(q22:q12); PML-RARα. Twelve patients were excluded because they had significant systemic infection at the time of AML diagnosis. Among those 12 patients, seven died in a month without a chance to recover from the infection. Only five recovered after appropriate antimicrobial therapy and later received induction chemotherapy (not included in the current study). All 12 patients had elevated pre-treatment CRP and ferritin.

Serum CRP within the 2 days before the start of induction chemotherapy was evaluated in every included patient. Data on baseline serum ferritin was acquired from 79 out of the 110 patients (71.8 %). Thirty-one patients were excluded from the analysis of serum ferritin for either red cell transfusion before blood sampling ($n=16$) or unchecked serum ferritin within 2 days before the start of induction chemotherapy ($n=15$). Those 31 patients belonged to none of two groups (ferritin >290 vs. ≤290 ng/dL) and were excluded from analyses. A detailed summary of patient characteristics is shown in Table 1.

Table 1 Patient characteristics

	No.
Age, years	
Median (range)	54.5 (20–80)
≥60	46 (41.8 %)
≥65	35 (31.8 %)
Gender	
Male	59 (53.6 %)
Female	51 (46.4 %)
ECOG performance status	
0 or 1	79 (71.8 %)
≥2	31 (28.2 %)
Cytogenetic risk	
Better	15 (13.6 %)
Intermediate	60 (54.5 %)
Poor	35 (31.8 %)
Hemoglobin (g/dL)	
Median, range	8.2 (28–13.6)
White blood cell ($\times10^3/\mu L$)	
Median, range	11.1 (0.7–44.3)
Platelet (/μL)	
Median, range	5,6000 (4000–964,000)
Blasts in peripheral blood (%)	
Median, range	42.0 (0–98.0)
Blasts in bone marrow (%)	
Median, range	65.5 (14.8–99.0)
C-reactive protein (mg/dL)	
Median (range)	3.8 (0.01–27.64)
≤0.5	17 (15.5 %)
>0.5	93 (84.5 %)
Erythrocyte sedimentation rate (mm/h)	
Median (range)	26.5 (2–120)
≤20	43 (39.1 %)
>20	61 (55.5 %)
Not checked	6 (5.5 %)
Ferritin (ng/mL)	
Median (range)	658.6 (47.3–7184.7)
≤290	16 (14.5 %)
>290	63 (57.3 %)
Not checked	31 (28.2 %)
Serum albumin (g/dL)	
Median (range)	3.5 (2.3–4.4)
≥3.5	62 (56.4 %)
<3.5	48 (43.6 %)

ECOG Eastern Cooperative Oncology Group

Infectious episodes and mortalities during induction chemotherapy

Fifty-nine out of 110 included patients (53.6 %; ciprofloxacin prophylaxis) were absolutely afebrile before the initiation of induction chemotherapy. The other 51 patients (46.4 %;

cefepime prophylaxis) reported fever (≥38.0 °C) at least once but had no SIRS. Thirty-nine events of systemic infection were reported in 38 patients (38.5 %) because one patient had both Gram-negative bacteremia and invasive pulmonary aspergillosis. Nineteen patients had Gram-negative bacteremia, six patients had Gram-positive bacteremia, six patients had mold infection, two patients had yeast infection, and one patient had systemic viral infection (enteroviral pneumonia). In addition, five patients experienced definite systemic infection despite a lack of microbiological evidence (four patients with pneumonia and one patient with enterocolitis) during the period of induction chemotherapy. The suspected ports of entry were pulmonary (n=15), gastrointestinal (n=13), central venous catheter related (n=6), sinonasal (n=1), perianal (n=1), and unknown (n=3).

Twenty-two patients experienced TRM. Of these, 21 were considered induction deaths due to infectious cause (21/110=19.1 %). One patient died of cerebral hemorrhage. During the median follow-up period of 33.9 months, the median overall survival (OS) was 13.0 months (95 % confidence interval 8.1–17.8). Pre-treatment blood level of CRP and ferritin was not related to the OS of the patients (p=0.246 and p=0.630, respectively).

Relation of elevation of inflammatory markers to the incidence of systemic infection/induction death

Elevation of serum CRP (p=0.032) and ferritin (p=0.002) was related to the incidence of systemic infection (Table 2). Elevation of CRP was also related to infectious TRM (p=0.029), whereas elevation of ferritin was not (p=0.119; Table 2). There was no difference in the incidence of systemic infection (p=0.578) or infectious TRM (p=0.271) according to the type of antibacterial prophylaxis.

Because older age and poorer PS were also related to increased incidence of systemic infection, we evaluated the relation of the inflammatory markers to age and PS. Elevation of CRP and ferritin were not related to age < or ≥60 years (p=0.259 for CRP and p=0.696 for ferritin, respectively). They showed a borderline relationship with poorer PS (p=0.087 and p=0.065, respectively) by chi-square test. In multivariate analysis, serum ferritin was an independent risk factor affecting the incidence of systemic infection, although CRP failed to reach statistical significance despite a trend with the odds ratio of 3.31 (Table 3). Multivariate analysis for infectious TRM was not conducted because (1) there was a technical impossibility in conducting a binary logistic regression test with a CRP elevation variable due to the finding that no patient with a CRP ≤0.5 mg/dL experienced systemic infection and (2) of a small patient number of infectious TRM (n=21).

Table 2 Relationship of baseline characteristics to incidence of systemic infection and induction death due to infectious causes

Parameters	Incidence of systemic infection		Incidence of induction death due infection	
	No	Yes	No	Yes
Age				
<60 years	47	17	56	8
≥60 years	25	21	33	13
	p=0.038		p=0.038	
Gender				
Male	34	25	46	13
Female	38	13	43	8
	p=0.063		p=0.398	
WBC ($\times 10^3/\mu L$)				
<10	32	19	39	12
≥10	40	19	50	9
	p=0.578		p=0.271	
<100	60	33	76	17
≥100	12	5	13	4
	p=0.628		p=0.613	
ECOG performance status				
0 or 1	63	15	73	5
≥2	9	23	16	16
	p<0.001		p<0.001	
Diabetes mellitus				
No	61	34	76	19
Yes	11	4	13	2
	p=0.490		p=0.542	
C-reactive protein (mg/dL)				
≤0.5	15	2	17	0
>0.5	57	36	72	21
	p=0.032		p=0.029	
ESR (mm/h)				
≤20	29	14	36	7
>20	41	20	47	14
	p=0.980		p=0.404	
Ferritin (ng/mL)				
≤290	15	1	15	1
>290	32	31	48	15
	p=0.002		p=0.119	
Serum albumin (g/dL)				
<3.5	30	18	37	11
≥3.5	42	20	52	10
	p=0.566		p=0.369	
Antibacterial prophylaxis				
Ciprofloxacin	40	19	50	9
Cefepime	32	19	39	12
	p=0.578		p=0.271	

ECOG Eastern Cooperative Oncology Group, *ESR* erythrocyte sedimentation ratio

Table 3 Multivariate analysis of potential risk factors for the incidence of systemic infection

Risk factors with $p<0.1$ in univariate analysis	Odds ratio (95 % confidence interval)	p value
With C-reactive protein (CRP)		
Age ≥60 years	0.99 (0.35–2.77)	0.989
Male gender	1.97 (0.74–4.90)	0.194
ECOG performance status ≥2	9.77 (3.35–28.48)	<0.001
CRP >0.5 mg/dL	3.31 (0.62–17.67)	0.161
With ferritin		
Age ≥60 years	0.95 (0.28–3.25)	0.932
ECOG PS ≥2	13.60 (3.48–53.25)	<0.001
Ferritin >290 ng/dL	13.14 (1.36–126.71)	0.026

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Relationship of blood inflammatory markers to leukemic tumor burden

Because blood inflammatory markers can be influenced by the expansion of myeloblasts, we estimated the relationship of CRP and ferritin with the peripheral blood white blood cell (WBC) count. Both pre-treatment CRP and ferritin levels were correlated with WBC count (Fig. 1). However, WBC elevation itself was not related to the incidence of systemic infection or infectious TRM (Tables 2 and 4). Fewer incidences of systemic infection were observed in patients with inflammatory markers within normal range, whether they had higher ($\geq 10\times10^3/\mu L$) or lower ($<10\times10^3/\mu L$) WBC counts (Table 4).

Discussion

In the current study, elevation of blood CRP or ferritin above normal range was significantly related to the incidence of systemic infection. However, magnitude of the elevation of the inflammatory markers is not proportional to the probability of systemic infection. For example, suppose that there are two patients and their baseline CRP levels are 5.0 and 25.0 mg/dL, respectively. Both of them had an elevated CRP level and may have increased risk of systemic infection, compared to those who have a normal blood CRP level. However, it is not expected that the patient with a CRP level of 25.0 mg/dL has a higher probability of systemic infection compared to the patient with a CRP level of 5.0 mg/dL: the magnitude of the elevation of blood inflammatory markers is proportional to the degree of leukocytosis due to leukemic myeloblasts in the analyzed patients (Fig. 1). However, patients with elevated inflammatory markers had increased risk of systemic infection irrespective of whether they had leukocytosis or not (Tables 2 and 4). Taken together, we prudently assume that although elevation of the blood inflammatory markers above normal range is a predictor of systemic infection, the magnitude of the elevation does not quantitatively predict the risk of infection and expansion of leukemic WBC is a factor affecting elevation of the inflammatory markers independent to infection propensity.

Despite low specificity, thanks to its high sensitivity and rapid kinetics of metabolism [11], the clinical application of CRP has been studied extensively. It has been accepted in some areas of medicine, including in the prediction of vascular

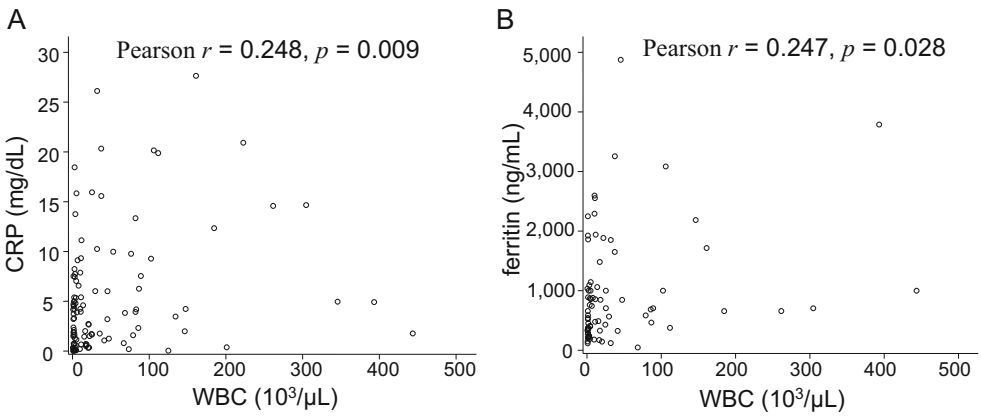

Fig. 1 Correlation of baseline blood **a** C-reactive protein and **b** ferritin levels to white blood cell count among the analyzed patients (according to the Pearson's correlation coefficient)

Table 4 Incidence of systemic infection according to elevation of white blood cell count and inflammatory markers

	Number of patients without systemic infection	Number of patients with systemic infection
WBC $<10\times10^3/\mu L$ and CRP ≤0.5 mg/dL	11	1
WBC $\geq10\times10^3/\mu L$ and CRP ≤0.5 mg/dL	4	1
WBC $<10\times10^3/\mu L$ and CRP >0.5 mg/dL	21	18
WBC $\geq10\times10^3/\mu L$ and CRP >0.5 mg/dL	36	18
WBC $<10\times10^3/\mu L$ and ferritin ≤290 ng/mL	11	1
WBC $\geq10\times10^3/\mu L$ and ferritin ≤290 ng/mL	4	0
WBC $<10\times10^3/\mu L$ and ferritin >290 ng/mL	12	16
WBC $\geq10\times10^3/\mu L$ and ferritin >290 ng/mL	19	14

diseases [12, 13], and in the field of oncology, anticipating inferior survival in advanced cancers [14]. Likewise, serum ferritin, an acute phase reactant [15], is an indicator of iron overload after repetitive packed red cell transfusion [16] and a biomarker of poor prognosis in patients with several hematologic malignancies [17–19]. However, the prognostic implication of these inflammatory markers in patients with acute leukemia seems inappropriate because the treatment of acute leukemia consists of the administration of high-dose chemotherapy and, in selected patients, HSCT. Each induction and consolidative therapy can be considered an individual treatment procedure, and multifactorial components contribute to overall prognosis of patients with acute leukemia. Instead, inspired by previous studies conducted among patients who underwent HSCT [8, 9], we evaluated and observed similar roles for CRP and ferritin at the first gateway of AML treatment, induction chemotherapy.

Precise selection of patients who can tolerate dose-intensive chemotherapy is one of the most important decision points in the treatment of patients with AML. In particular, it is of pivotal importance among those with age ≥60 years to avoid TRM for frail patients but not to lose the opportunity for cure by high-dose chemotherapy for biologically younger patients. Checking pre-treatment blood levels of CRP or ferritin might be helpful for the decision of physicians. In addition, even after the decision to administer high-dose chemotherapy, there are several options to be decided, such as dose of cytarabine and the administration of a conventional vs. augmented dose of anthracycline. Considering the results of our study, a physician could have more confidence in administering a higher dose of cytotoxic chemotherapeutic agents if a patient had blood inflammatory markers within normal range along with good PS.

The actual mechanism of the modest elevation of CRP or ferritin in the pre-treatment stage of patients with AML who are vulnerable to systemic infection is uncertain. One possible explanation is that non-infectious comorbid medical conditions may induce modest elevation of CRP and ferritin [12, 20, 21]. Although patients with active infection were excluded from the current study, we did not exclude all patients with any detailed comorbidities or non-infectious inflammatory conditions, such as rheumatologic disease, because our interest was to investigate the predictive role of inflammatory markers in overall general patients who can tolerate intensive induction chemotherapy, not limited to patients absolutely healthy except for being diagnosed with AML. Patients with comorbidities or non-infectious inflammatory conditions can be more vulnerable to systemic infection during induction chemotherapy. Considering that more than 40 % of analyzed patients in this study were aged ≥60 years, comorbidities might have an impact on the elevation of blood inflammatory markers and subsequently on the incidence of systemic infection and infectious TRM. Although multivariate analysis showed that serum ferritin was independent of ECOG PS in predicting the incidence of systemic infection (Table 3), this possibility needs to be defined in future larger scale prospective studies.

Mild-degree CRP elevations are observed in several non-inflammatory medical conditions including obesity, chronic fatigue, and depression, and such elevations are not considered to be specific for inflammation [22]. A minimal acute phase response occurs in many non-inflammatory conditions, and the cytokines responsible for the acute phase response [15] have functions unrelated to inflammation [22, 23]. Previous studies have suggested that the modest elevation of acute phase proteins can be a marker of older biological rather than chronological age [22, 24]. Due to the limited number of patients in this study, we cannot be conclusive regarding the question: Is the modest elevation of blood inflammatory markers a predictor that is independent from older age and PS, or is it a chemical marker reflecting the frailty of a patient? Whatever the answer, we can cautiously assume that normal blood levels of the markers of acute phase response in a patient indicates that the patient has a relatively more intact immune system for the prevention of systemic inflammatory response after the invasion of microorganisms prompted by either the disease itself or chemotherapy-driven bone marrow suppression.

The current study is limited by its retrospective nature with relatively limited numbers of analyzed patients. Measuring

pre-treatment CRP and ferritin is not a standard practice, and the results should not be overestimated until a properly designed prospective trial with the correct sample size proves the potential role of those markers.

The definition of systemic infection could be regarded as subjective, although we set criteria to separate clinically meaningful infectious events from insignificant symptoms or signs. One might argue that the applied cutoff values of CRP and ferritin were arbitrary, rather than evidence based. At first, we considered using a cutoff value calculated by a receiver operating characteristic (ROC) curve. However, we decided to use the conventionally designated ULN (in our institution, 0.5 mg/dL for CRP and 290 ng/mL for ferritin) instead, because we thought that the genuine role of the markers would be exaggerated because a cutoff value attained by ROC curve is an artificially calculated value to maximize the predictive role. The majority of previous studies [7, 8, 18, 25–27] also used the conventional ULN, which does not differ substantially among the institutions, as a cutoff. We believe that using the ULN as a cutoff might be more conservative and does not invalidate the main idea of the predictive value of blood CRP and ferritin level for the prediction of systemic infection. We used an isolated determination of CRP and ferritin before induction chemotherapy. Because technical mistakes in laboratory studies are not unusual, confirmation of the results in a second determination would be a better approach in future studies.

In conclusion, modest elevation of blood level of CRP and ferritin above normal range showed an association with the probability of systemic infection in patients with AML who underwent dose-intensive induction chemotherapy. The role of these cheap and easily testable blood markers could be more clearly defined in future prospective studies.

Sources of support This study was supported in part by Grants-in-Aid from Jeil Pharmaceutical Co., Ltd, Seoul, Korea. The company was not involved in any stage of the study (concept, design, conduct, or interpretation) or authorship.

Conflict of interest Dr. Jae Hoon Lee has received research funding from Jeil Pharmaceutical. The other authors have no conflicts of interests. We have full control of all primary data and would allow the journal to review the data if requested.

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