ORIGINAL PAPER

Nagoya J. Med. Sci. **79**. 17 ~ 26, 2017
doi:10.18999/nagjms.79.1.17

Retrospective survey and evaluation of first-line antibiotics for chemotherapy-induced febrile neutropenia in patients with acute myeloid leukemia

Naoki Mukoyama[1,2], Marie Nakashima[3], Koichi Miyamura[3], Akira Yoshimi[1], Yukihiro Noda[1] and Kazuhiro Mori[2]

[1]*Division of Clinical Sciences and Neuropsychopharmacology, Faculty and Graduate School of Pharmacy, Meijo University, Nagoya, Japan*
[2]*Department of Pharmacy, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan*
[3]*Department of Hematology, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan*

ABSTRUCT

Patients with acute leukemia are susceptible to chemotherapy-induced severe myelosuppression, and therefore are at a high risk for febrile neutropenia (FN). In such cases, the use of broad-spectrum antibiotics such as fourth-generation cephalosporins and carbapenems is recommended as first-line antimicrobial treatment; however, the effectiveness of these agents in patients with acute myeloid leukemia (AML) has not been investigated in detail. We retrospectively examined and evaluated the effectiveness of first-line antibiotic treatment regimens for chemotherapy-induced FN in patients with AML in Japanese Red Cross Nagoya Daiichi Hospital. The evaluated first-line treatment regimens were as follows: cefozopran (CZOP) + amikacin (AMK) in 38 cases, cefepime (CFPM) alone in 2 cases, CFPM + AMK in 2 cases, piperacillin (PIPC) + AMK in 2 cases, and CZOP alone in 1 case. Additionally, prophylactic antifungal agents were administered in all cases. Markedly effective, effective, moderately effective, and ineffective responses occurred in 31.1%, 8.9%, 8.9%, and 51.1%, respectively, of the treated cases. The response rate, defined as the combination of markedly effective and effective outcomes, was 40.0%. In 11 cases, impairment of renal functions were observed, and they were associated with combination treatments including AMK; nine of these were associated with a glycopeptide. The combination of CZOP with AMK (84.4%) was the most commonly used first-line treatment for FN in patients with AML; carbapenem or tazobactam/PIPC has never been used for treatment of such cases. Our findings demonstrate that fourth-generation cephems will be an effective first-line treatment for FN in patients with AML in our hospital.

Key Words: febrile neutropenia, acute myeloid leukemia, first-line antibiotics

INTRODUCTION

Since chemotherapy for hematopoietic cancers is typically associated with severe neutropenia, the management of febrile neutropenia (FN) is very important for patients receiving

Received: November 22, 2016; accepted: December 5, 2016

Corresponding author: Kazuhiro Mori

Department of Pharmacy, Japanese Red Cross Nagoya Daiichi Hospital, 3-35 Michishita-cho, Nakamura-ku, Nagoya 453-8511, Japan

Phone: +81-52-481-5111, FAX: +81-52- 482-7733, Email: koresupo758@gmail.com

chemotherapy. In such cases, the aberrant blood counts caused by the underlying disease are exacerbated by the myelosuppressive effects of treatments with high-dose anticancer agents. The resultant inhibition of immune responses causes rapid deterioration of patient health, and has negative impact on patient outcomes. In many cases of chemotherapy-induced infections, it is difficult to identify the causative microorganisms. Nevertheless, gram-negative bacilli, including *Pseudomonas aeruginosa*, have been often isolated from patients, and are known to be associated with severe clinical symptoms, including endotoxin shock.[1)]

The effectiveness of third- and fourth-generation cephalosporins and carbapenems as agents for empirical antibiotic therapy for hematological cancer-associated FN has been extensively described in clinical studies, and in treatment guidelines.[2,3)] One report suggests that it is desirable to deal with the high risk for FN in patients with acute leukemia, even if they are not deemed to be at a high risk as indicated by their Multinational Association for Supportive Care in Cancer Risk Index scores, while they receive remission-induction therapy or consolidation therapy for their leukemia.[4)] Although there are many reports describing first-line treatments for FN in patients with hematopoietic cancers, there are no detailed reports describing the effectiveness of these treatments in patients with acute myeloid leukemia (AML). We retrospectively examined and evaluated the effectiveness of first-line antibiotic treatment regimens for chemotherapy-induced FN in patients with AML, in Japanese Red Cross Nagoya Daiichi Hospital.

MATERIALS AND METHODS

Subjects

This study evaluated 45 cases in 30 patients with AML who received antibiotic therapy for FN after undergoing chemotherapy (including induction and consolidation therapies) between April 2015 and March 2016, in Department of Hematology Japanese Red Cross Nagoya Daiichi Hospital.

The major exclusion criteria for the present study were acute promylocytic leukemia (APL) and the patients, who had already used antimicrobial when they had an onset of FN.

Study parameters

We retrospectively surveyed patient medical records and evaluated the following parameters: patient age, gender, body temperature at the times of initiation of antibiotic agents, serum albumin levels, white blood cell counts, neutrophil counts, C-reactive protein levels, serum creatinine levels, blood cultures, anticancer treatment regimens, first-line antibiotic treatment regimens, changes to the antibiotic treatment regimens, and treatment with granulocyte-colony stimulating factor, prophylactic use of antifungal agents. An increase in serum creatinine levels by greater than 50% from baseline or 0.5 mg/dL was defined as an impairment of renal functions.[5,6)]

FN in patients was defined as the possession of neutrophil counts that were either lower than 500/μL, or less than 1000/μL and predicted to further decrease to below 500/μL, at an axillary temperature ≥37.5°C.[3)]

Response criteria

Response criteria were as follows: (1) Markedly effective: normal body temperature restored within 4 days of treatment administration and maintained for a minimum of 3 days, with improvements in clinical symptoms and laboratory findings; (2) Effective: a reduction in

fever within 4 days of administration and the restoration of normal body temperature within 7 days, with improvements in clinical symptoms and laboratory findings; (3) Moderately effective: a reduction in fever within 4 days of administration that continued through the seventh day, with improvements in clinical symptoms and laboratory findings; (4) Ineffective: no reduction in fever was observed within 7 days, and clinical symptoms and laboratory findings associated with infections remaining unchanged or worsening.[7] This includes cases where no reduction in fever was observed within 3 days of administration, and the treatment regimen was altered.

Markedly effective and effective responses were defined as successful treatments in cases completed and successed by first-line treatment, and moderate effective and ineffective responses were defined as unsuccessful treatments in others including additional treated with glycopeptides.

Statistical analyses

Statistical significance between the two groups was determined using Student's t-test or Fisher's exact test. Univariate logistic regression analysis was performed to assess the independent contribution of the risk factors to unsuccessful outcomes by first-line antibiotic agents. $P < 0.05$ was considered statistically significant.

Ethical considerations

This study was approved by the Ethics Review Committee of Japanese Red Cross Nagoya Daiichi Hospital (No. 2016-074) and followed the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the good clinical practice guidelines.

RESULTS

Patient characteristics and treatment

The characteristics of the 30 patients studied, who had an average age of 51.3 years, are listed in Table 1. In total, 45 cases of infection occurred among 30 patients. Average C-reactive protein levels, neutrophil counts, and body temperature at initiation of antibiotic treatment were 3.07 mg/dL, 35.9/μL, and 38.6°C, respectively.

In 14 cases, infections were confirmed by two sets of blood cultures and by indication of therapeutic start in the medical records. First-line treatment regimens evaluated in this study were as follows: cefozopran (CZOP) + amikacin (AMK) in 38 cases (84.4%), cefepime (CFPM) alone in 2 cases (4.4%), CFPM + AMK in 2 cases (4.4%), piperacillin (PIPC) + AMK in 2 cases (4.4%), and CZOP alone in 1 case (2.2%). Prophylactic antifungal agents were administered in all cases.

Clinical outcomes

Impairment of renal functions was confirmed in 11 cases (24.4%) (Table 1). All of these cases had received combination treatments which included AMK, and 9 of these cases had a glycopeptide [vancomycin (VCM) or teicoplanin (TEIC)] included in their treatment regimens (Table 1). Glycopeptides or granulocyte colony-stimulating factor (G-CSF) were used in accordance with the Infectious Diseases Society of America (IDSA) and National Comprehensive Cancer Network (NCCN) guidelines in cases who had gram-positive cocci in blood cultures or had severe mucositis.

The clinical outcomes of treatments are shown in Table 2. The markedly effective,

Table 1 Clinical characteristics of patients

Patients: 30	
Age	51.3 ± 17.5
Gender	Male 21, Female 9
Cases: 45 [( ): number of cases]	
Body temperature	38.6 ± 0.8
CRP levels	3.07 ± 3.64
Neutrophil count	35.9 ± 72.2
First-line antibiotic treatment regimen	CZOP + AMK (38)
	CZOP (1)
	CFPM + AMK (2)
	CFPM (2)
	PIPC + AMK (2)
Therapeutic regimen	Induction and re-induction
	IDR + Ara-C100 (4)
	DNR + Ara-C100 (8)
	MEC (4)
	CAG (3)
	HAM (1)
	Consolidation
	High dose Ara-C (2 g/m^2) (6)
	MIT + Ara-C200 (10)
	DNR + Ara-C200 (6)
	ACR + Ara-C200 (1)
	A tripleV (2)
Impairment of renal functions (11 cases)	Additional VCM combination (7)
	Additional TEIC combination (2)
	Additional AMK combination (11)

The results were obtained from 45 cases in 30 patients. CZOP: cefozopran, AMK: amikacin, CFPM: cefepime, PIPC: piperacillin, IDR: idarubicin, HDAra-C: high dose cytarabine, Ara-C100: cytarabine 100 mg/m^2, Ara-C200: cytarabine 200 mg/m^2, DNR: daunorubicin, MIT: mitoxantrone, ACR: aclarbicin, A tripleV: cytarabine + etoposide + vincristine + vindesine, MEC: mitoxantrone + cytarabine + etoposide, CAG: cytarabine + aclarbicin + granulocyte colony-stimulating factor (G-CSF), HAM: mitoxantrone + High dose Ara-C, CRP: C-reactive protein, VCM: vancomycin, TEIC: teicoplanin.

effective, moderately effective, and ineffective responses occurred in 31.1%, 8.9%, 8.9%, and 51.1%, respectively, of the treated cases. The cumulative success rate of treatment (combination of markedly effective and effective responses) was 40.0% (Table 2).

As shown in Table 3, there were no significant differences in patient age, gender, serum albumin levels, or neutrophil counts at the initiation of antibiotic treatments, and the duration for attainment of neutrophil counts <500 or <100, treatment phase, first-line antibiotic treatment regimens, and therapeutic regimens between the successfully and unsuccessfully treated cases. However, there was a significant difference in body temperature at the onset

Table 2 Clinical responses at commence of antibiotic treatment

	[( ): number of cases]
Clinical response	Markedly effective (14)
	Effective (4)
	Moderately effective (4)
	Ineffective (23)
Period until alleviation of fever	7 (range 1–28) days
Medicine change or addition	20 cases
Antifungal agents	ITCZ-OS (37)
	VRCZ (5)
	FLCZ (3)
Additional treatment with G-CSF	2 cases
Additional glycopeptides	VCM (12), TEIC (2)
Blood culture positive	Methicillin-Resistant *Staphylococcus epidermidis* (2)
	Streptococcus mitis (8)
	Methicillin-Resistant *Staphylococcus haemolyticus* (1)
	Stenotrophomonas maltophilia (1)
	Enterococcus faecium (2)

The results were obtained from 45 cases in 30 patients. ITCZ-OS: itraconazole oral solution, VRCZ: voriconazole, FLCS: fluconazole, G-CSF: granulocyte colony-stimulating factor

of FN between the successfully and unsuccessfully treated cases ($P < 0.01$; odds ratio, 0.22 confidence interval, 0.05 to 0.63) (Table 3).

DISCUSSION

Refractory and rapidly progressing FN is often present in patients who are treated for hematological malignancies. Prompt and appropriate treatment of FN is critical for a favorable prognosis. Patients with infections in whom causal microorganisms are not identified typically undergo empirical antibiotic therapy. In patients with AML, myelosuppression is frequently exacerbated by intense chemotherapy, and therefore such patients are at risk for serious or even fatal infections. This risk is further exacerbated by persistent neutropenia. Chemotherapy-induced damage to the oral and gastrointestinal mucosae may provide entry routes for infectious agents. In our hospital, the therapeutic administration of G-CSF is applied in accordance with the FN guideline that recommend in cases of sever neutropenia. Some studies have noted that the administration of G-CSF induces adverse effects in patients with AML.[8,9] In the present survey, 2 cases were treated with G-CSF, and all cases were promptly treated with antibiotic agents immediately after the onset of FN. Most cases (84.4%) were treated with a combination of CZOP and AMK. CFPM is widely used to treat FN in Japan; however, the susceptibility of *P. aeruginosa* to CFPM has decreased progressively.[10] The findings of this report were consistent with the finding of our survey that the susceptibility of *P. aeruginosa* to CFPM in patients who were treated at our Hematology Department had decreased to 66.7% in the fiscal year 2008 (100% in the fiscal year 2015). We found

Table 3 Comparison of characteristics of patients

	Successful (N=18)	Unsuccessful (N=27)	P	Logistic regression analysis		
				OR	95%CI	P
Age (years old)	51.7 ± 18.7	49.4 ± 16.7	0.67[a)]	1.01	0.97–1.05	0.67
Gender	M13, F5	M20, F7	1.00[b)]	0.91	–0.65–0.72	0.89
Body weight (kg)	56.8 ± 10.5	53.2 ± 11.9	0.30[a)]	1.03	0.98–1.09	0.29
Albumin levels (g/dL)	3.68 ± 0.42	3.71 ± 0.40	0.82[a)]	0.84	0.18–3.80	0.82
Creatinine levels (mg/dL)	0.61 ± 0.18	0.67 ± 0.24	0.38[a)]	0.27	0.01–4.44	0.38
CRP levels (mg/dL)	2.38 ± 2.22	3.53 ± 4.32	0.31[a)]	0.90	0.72–1.08	0.28
Neutrophilic count (/μL)	34.6 ± 56.9	36.9 ± 81.8	0.92[a)]	1.00	0.99–1.01	0.92
Period less than neutrophils 500/μL (days)	21.7 ± 14.2	20.0 ± 7.5	0.59[a)]	1.02	0.96–1.08	0.58
Period less than neutrophils 100/μL (days)	10.3 ± 4.2	11.6 ± 5.0	0.35[a)]	0.93	0.80–1.07	0.33
Body temperature at commence of Antibiotic treatment (°C)	38.2 ± 0.5	38.9 ± 0.9	0.0053[a)]	0.22	0.05–0.63	0.02
Therapeutic regimen (HDAra-C/others)	HD1, other17	HD6, other21	0.22[a)]	0.21	0.01–1.37	0.16
Treatment phase	Induction (6) Re-induction (1) Consolidation (11)	Induction (6) Re-induction (7) Consolidation (14)	0.24[b]	–	–	–
First-line antibiotic treatment regimen	CZOP+AMK (14) CZOP (1) CFPM+AMK (1) CFPM (2) PIPC+AMK (0)	CZOP+AMK (24) CZOP (0) CFPM+AMK (1) CFPM (0) PIPC+AMK (2)	0.152[b)]	–	–	–
Therapeutic regimen	High dose Ara-C (1) HAM (0) IDR+Ara-C100 (3) DNR+Ara-C100 (3) MIT+Ara-C200 (7) DNR+Ara-C202 (2) ACR+Ara-C200 (1) A tripleV (0) MEC (0) CAG (1)	High dose Ara-C (5) HAM (1) IDR+Ara-C100 (1) DNR+Ara-C100 (5) MIT+Ara-C200 (3) DNR+Ara-C200 (4) ACR+Ara-C200 (0) A tripleV (2) MEC (4) CAG (2)	0.14[b)]	–	–	–

The results were obtained from 45 cases in 30 patients. M: male, F: female, P: probability value, N: number, HD: high dose cytarabine, CRP: C-reactive protein, CZOP: cefozopran, AMK: amikacin, CFPM: cefepime, PIPC: piperacillin, IDR: idarubicin, HDAra-C: high dose cytarabine, Ara-C100: cytarabine 100 mg/m^2, Ara-C200: cytarabine 200 mg/m^2, DNR: daunorubicin, MIT: mitoxantrone, ACR: aclarbicin, A tripleV: cytarabine + etoposide + vincristine + vindesine, MEC: mitoxantrone + cytarabine + etoposide, CAG: cytarabine + aclarbicin + granulocyte colony-stimulating factor (G-CSF), HAM: mitoxantrone + High dose Ara-C, CRP: C-reactive protein, VCM: vancomycin ,TEIC: teicoplanin. OR: odds ratio, 95%CI: 95% confidence interval. [a)] Student's t-test, [b)] Fisher's exact test.

that CZOP was used more often than CFPM for treatment, and this finding suggested that physicians may be concerned about the decrease in susceptibility of *P. aeruginosa* to CFPM. As CZOP is currently being used for most patients, we need to monitor the susceptibility of infectious agents to CZOP. Hashino *et al*.[11] reported that cycling therapy is associated with a larger decrease in the incidence of infections caused by multidrug-resistant bacteria. Taken together with our results, these data suggested that treatments incorporating fourth-generation cephalosporins, carbapenems, and tazobactam (TAZ)/PIPC may help in combating the multidrug-resistant bacterial infections.

In the present survey, we found that 40.0% of FN cases were successfully treated by first-line antibiotic agents. In addition, 36.8% of FN cases were successfully treated with CZOP+AMK as first-line treatment. Previous studies have investigated the effectiveness of fourth-generation cephalosporins as first-line treatments for FN in patients with hematopoietic cancers. In patients with neutrophil counts of ≤500/μL, treatments with CFPM and CFPM + AMK regimens resulted in success rates of 27.6% and 45.0%, respectively, 72 hours after administration.[12] In patients with neutrophil counts of ≤100/μL, treatment with CZOP resulted in a success rate of 61.8%, after 7 days;[13] the success rate with TAZ/PIPC treatment in such patients was reported to be 57.7%, after 72 hours.[14] Tamura *et al*.[12] also reported that the success rate with CFPM treatment in hematopoietic cancers without leukemia was higher (74.0%) than that with leukemia (53.3%). Taken together with the results of our survey, fourth-generation cephalosporins (CFPM and CZOP) shows clinically equivalent effectiveness as to FN, whereas the success rate in leukemia including AML is likely to be lower than other hematopoietic cancers. It is not possible to directly compare these results with those of studies evaluating patients with other hematological malignancies, because the present survey was limited to AML patients. AML is a cancer of immune cells in which neutropenia is a notable feature, and FN occurs at a higher frequency in patients with AML than in those with other hematopoietic malignancies.[15] Therefore, it is necessary to determine whether responses to first-line treatments for FN are dependent on the type of cancers or on other background factors. In this survey, there was a significant difference in body temperature at the onset of FN between the successfully and unsuccessfully treated cases, suggesting that the monitoring of body temperature is necessary to assess the efficacy of first-line antibiotic agents, as well to predict the risk of unsuccessful outcomes.

Combination treatments with aminoglycoside antimicrobial agents have been widely used as standard therapy for FN because of their high success rates of treatment.[12] Compared to treatments with single agents, combination treatments induce many side effects, particularly higher incidences of renal toxicity. The failure rate of such treatments is high; they do not significantly improve survival in patients.[16-18] Therefore, combination therapy as first-line treatment for FN is presently not recommended in principle. In patients with acute leukemia or with hematopoietic stem cell transplantations who exhibited severe neutropenia persistently over long periods, combination treatments showed rapid antipyretic effects. IDSA guideline and a report recommend that combination treatments should be used to treat FN in patients at early stages when changes in vital signs, such as decreases in blood pressure, are observed, when infection with drug-resistant bacteria is suspected or verified, or if the general health of the patient is unstable.[19] In fact, combination treatments including AMK have often been used to treat patients with AML in our Hematology Department.

In the IDSA and NCCN guidelines, combination treatments with anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drugs are recommended as first-line treatments for FN in the following cases: (1) in patients who are MRSA carriers, (2) in patients who have severe mucositis, (3) in cases of severe sepsis, or (4) in patients prior to the confirmation of gram-

positive bacteria in blood cultures.[4,20] In the present survey, patients either had gram-positive cocci in blood cultures or had severe mucositis, suggesting that our use of combination treatments in such cases was appropriate.

We found impairment of renal functions in 11 cases (24.4%), all of whom had undergone combination treatments with AMK. In 9 of these cases, the patients had been treated with combinations that included vancomycin (VCM) or teicoplanin. It is known that these drugs induce impairment of renal functions, and combining them together further enhances this property. Nevertheless, dose reduction or drug discontinuation can help to recover renal functions. For FN, an initial treatment incorporating AMK is not recommended because this increases the risk of kidney damage.[18] Combination treatments are recommended as first-line therapy for patients with AML because they are extremely susceptible to infections, especially due to the prevalence of neutropenia.[4] Thus, as combination treatment with AMK and VCM is known to significantly increase the incidence of kidney damage,[21] this treatment should be administered with extreme caution.

In the present survey, there were no significant differences between the therapeutic responses of patients who were treated with a regimen that included a high dose of cytarabine (2 g/m^2) and those treated by no high dose cytarabine regimen or regimen included cytarabine (100–200 mg/m^2). A report published by the Japan Adult Leukemia Study Group suggested that treatment regimens including a high dose of cytarabine (2 g/m^2) indicated significantly higher rates of infections than those that included cytarabine (200 mg/m^2); however, there was no significant difference in the incidence of FN, between both the groups.[22] In the present survey, we evaluated a relatively smaller number of cases. Thus, we need to conduct a similar study on a larger scale to confirm whether the success of first-line treatments for FN is affected by differences in treatment regimens for AML.

FN is a serious disease. Thus, insufficient first-line treatments for FN induce infections with drug-resistant bacteria, and strongly influence prognoses in patients. Although the initial treatments with fourth-generation cephalosporins are expected to provide some benefits, the well-balanced use of antimicrobial agents may prevent infections with less-sensitive bacteria, such as multidrug-resistant *P. aeruginosa* and extended spectrum beta lactamase. In our facility, we continue to further evaluate the differential effects of antimicrobial agents, or the susceptibility of bacteria to them, and to treat to patients with AML.

There are some limitations to conclude our findings. First, since the present survey was performed to evaluate multiple episodes from the same patients in one facility, we should consider about sampling biases. Second, we excluded APL because of the difference in the standard treatment regimens between APL and other types of AML. Third, since the majority of FN cases were treated with CZOP+AMK as first-line treatment, we could not compare to other first-line antibiotic regimens. Further study is needed to analyse the independent patients in multiple facilities, and to conduct comparative analyses including other hematopoietic cancers and various regimens of first-line antibiotic agents.

ACKNOWLEDGEMENTS

This study was supported in part by Meijo University Research Institute Grant, and by Grants-in-Aid for Scientific Research C (24590219, 16K08421) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan. We would like to thank Ms. Aya Goto of and all staff members Faculty of Pharmacy, Meijo University and Department of Pharmacy Japanese Red Cross Nagoya Daiichi Hospital that were involved in this study.

CONFLICT OF INTEREST

The authors report no declarations of interest.

REFERENCES

1) Yoshida M. Infections in patients with hematological diseases: recent advances in serological diagnosis and empiric therapy. *Int J Hematol,* 1997; 66: 279–289.
2) Tamura K. Clinical guidelines for the management of neutropenic patients with unexplained fever in Japan: validation by the Japan Febrile Neutropenia Study Group. *Int J Antimicrob Agents,* 2005; 26 Suppl 2: S123–127; discussion S133–140.
3) Japanese Society of Medical Oncology. Practical Guideline of Febrile Neutropenia (FN) 2012, 2012, Nankodo Co., Ltd., Tokyo.
4) Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, *et al*. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis,* 2011; 52: e56–93.
5) Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. *Antimicrob Agents Chemother,* 2008; 52: 1330–1336.
6) Rybak M, Lomaestro B, Rotschafer JC, Moellering R, Jr., Craig W, Billeter M, *et al*. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm,* 2009; 66: 82–98.
7) Takaku F, Nagai K, Maekawa T, Masaoka T. Criteria for the estimation of the clinical effect of antimicrobial drugs in treatment of infections associated with granulocytopenia. *Jpn J Clin Hematol,* 1984; 25: 588–592.
8) Fujita H, Yoshida M, Miura K, Sano T, Kito K, Takahashi M, *et al*. Management of infection in patients with acute leukemia during chemotherapy in Japan: questionnaire analysis by the Japan Adult Leukemia Study Group. *Int J Hematol,* 2009; 90: 191–198.
9) Hershman D, Neugut AI, Jacobson JS, Wang J, Tsai WY, McBride R, *et al*. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. *J Natl Cancer Inst,* 2007; 99: 196–205.
10) Kanayama A, Kida M, Iyoda T, Matsuzaki K, Shibuya S, Hasegawa M, *et al*. Annual changes in drug susceptibility of Pseudomonas aeruginosa isolated from blood and other clinical specimens. *Jpn J Chemother,* 2010; 58: 7–13.
11) Hashino S, Morita L, Kanamori H, Takahata M, Onozawa M, Nakagawa M, *et al*. Clinical impact of cycling the administration of antibiotics for febrile neutropenia in Japanese patients with hematological malignancy. *Eur J Clin Microbiol Infect Dis,* 2012; 31: 173–178.
12) Tamura K, Imajo K, Akiyama N, Suzuki K, Urabe A, Ohyashiki K, *et al*. Randomized trial of cefepime monotherapy or cefepime in combination with amikacin as empirical therapy for febrile neutropenia. *Clin Infect Dis,* 2004; 39 Suppl 1: S15–24.
13) Masaoka T, Hayashi K, Hasegawa M, Kageyama T, Tsubakio T, Tominaga N, *et al*. Pilot study of CZOP for febrile neutropenia. *Jpn J Chemother,* 2004; 52: 219–222.
14) Bow EJ, Rotstein C, Noskin GA, Laverdiere M, Schwarer AP, Segal BH, *et al*. A randomized, open-label, multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. *Clin Infect Dis,* 2006; 43: 447–459.
15) Lakshmaiah KC, Malabagi AS, Govindbabu, Shetty R, Sinha M, Jayashree RS. Febrile neutropenia in hematological malignancies: clinical and microbiological profile and outcome in high risk patients. *J Lab Physicians,* 2015; 7: 116–120.
16) Marcus R, Paul M, Elphick H, Leibovici L. Clinical implications of beta-lactam-aminoglycoside synergism: systematic review of randomised trials. *Int J Antimicrob Agents,* 2011; 37: 491–503.
17) Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. *BMJ,* 2004; 328: 668.
18) Paul M, Soares-Weiser K, Grozinsky S, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropaenia. *Cochrane Database Syst Rev,* 2003: CD003038.

19) Kumar A, Zarychanski R, Light B, Parrillo J, Maki D, Simon D, *et al*. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. *Crit Care Med,* 2010; 38: 1773–1785.
20) Baden LR, Swaminathan S, Angarone M, Blouin G, Camins BC, Casper C, *et al*. Prevention and treatment of cancer-related infections, version 2.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw,* 2016; 14: 882–913.
21) European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group and the National Cancer Institute of Canada-Clinical Trials Group. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. *J Infect Dis,* 1991; 163: 951–958.
22) Miyawaki S, Ohtake S, Fujisawa S, Kiyoi H, Shinagawa K, Usui N, *et al*. A randomized comparison of 4 courses of standard-dose multiagent chemotherapy versus 3 courses of high-dose cytarabine alone in postremission therapy for acute myeloid leukemia in adults: the JALSG AML201 Study. *Blood,* 2011; 117: 2366–2372.