



Original Article

Asymptomatic C-reactive protein elevation in neutropenic children

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Abstract *Background:* Febrile neutropenia (FN) can be a life-threatening complication in children with malignancies. There is no standardized preventive treatment for childhood FN, and information on C-reactive protein (CRP) elevation in afebrile patients with neutropenia (CEAN) is limited. The aim of this study was therefore to identify the association between CEAN and FN onset, and evaluate the efficacy of broad-spectrum antibiotics for FN prophylaxis.

Methods: We retrospectively reviewed the medical records of 22 consecutive pediatric patients with hematologic malignancies (acute myeloid leukemia, n = 2; acute lymphoid leukemia, n = 20) admitted to the present institution between 2006 and 2011. CEAN was defined as CRP elevation ≥ 0.05 mg/dL between the two most recent blood tests with no fever. We identified CEAN before FN onset, and assessed the efficacy of broad-spectrum antibiotics for FN prevention in CEAN. FN incidence within 48 h after CEAN detection was compared between prophylactic and non-prophylactic episodes.

Results: CEAN was observed before FN onset in 20 (55.6%), of 36 FN episodes. Among the 95 analyzed CEAN episodes, broad-spectrum antibiotics had been used for 30 episodes (prophylactic episodes), whereas these antibiotics had not been used in 60 episodes (non-prophylactic episodes). Prophylactic episodes had a significantly lower FN incidence than non-prophylactic episodes (6.7% and 31%, respectively, $P < 0.01$) within 48 h after CEAN detection. Bacteremia was observed in three non-prophylactic episodes.

Conclusion: Patients with CEAN are at higher risk of FN, and physicians may consider the use of broad-spectrum antibiotics to prevent FN development.

Key words broad-spectrum antibiotic, C-reactive protein, febrile neutropenia, prophylaxis.

Advancements in chemotherapy and supportive therapy have increased the survival rates for children with malignancy to 70–80%,¹ but infection remains a life-threatening complication in immunocompromised children, and frequently presents as febrile neutropenia (FN).² Moreover, patients who develop severe (common terminology criteria for adverse events grades 3 or 4) FN during chemotherapy frequently require dose reduction and/or delay to treatment, which can affect prognosis.³

Antibiotics and granulocyte colony-stimulating factor (G-CSF) are widely used for the prophylaxis of FN.^{4–8} A recent meta-analysis of randomized controlled trials reported that prophylaxis with antibiotics, particularly fluoroquinolones, reduces mortality in neutropenic patients.⁴ The overuse of these agents, however, may lead to the emergence of antibiotic-resistant pathogens. It is therefore important to limit the use of antibiotics to a reasonable minimum in the prophylaxis of FN.⁹

The most recent Japanese guidelines for pediatric leukemia and lymphoma recommend G-CSF when the speculative risk of FN exceeds 20%.¹⁰ When used in the context of intensive anti-leukemic therapy, however, the short-term use of G-CSF (particularly when combined with etoposide) may increase the risk of therapy-related myeloid leukemia or myelodysplasia.¹¹

C-reactive protein (CRP) is an acute-phase protein produced in the liver in response to inflammation. Highly sensitive quantification methods can detect serum CRP concentration < 0.3 mg/dL, the detection limit of conventional CRP assays; this enables the detection of minute levels of inflammation that conventional assays would overlook.¹² Even small elevations in serum CRP in atherosclerotic patients have been reported to be associated with increased risk of ischemic heart disease, suggesting that it may be clinically useful to monitor CRP concentration.¹³

The use of high-sensitivity CRP assays was introduced at Toyohashi Municipal Hospital, Japan, in August 2006. Following the availability of these assays, we gradually initiated a strategy of antibiotic prophylaxis to prevent FN in all patients with hematologic malignancy. This was because we had frequently observed minimal CRP elevation in afebrile patients with neutropenia (hereinafter referred to as CEAN) prior to FN onset. In general, we tend to administer antibiotics to patients with more severe neutropenia or relatively higher

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elevation in serum CRP concentration. Although narrow-spectrum antibiotics had been used initially in some patients, many of these patients developed FN. As a result, we eventually chose only broad-spectrum antibiotics for FN prophylaxis. The implementation of this new strategy was followed by a substantial reduction in the number of FN cases, but we have yet to quantitatively evaluate the efficacy of this strategy in the prevention of FN.

The aims of this study were therefore to identify an association between CEAN and FN onset, and to evaluate the efficacy of broad-spectrum antibiotics for the prophylaxis of FN in such patients.

Methods

We retrospectively analyzed the hospital records of consecutive patients with hematologic malignancy admitted to the Department of Pediatrics, Toyohashi Municipal Hospital (Aichi, Japan) between September 2006 and December 2011. Patients who received therapy in accordance with the Japanese Pediatric Leukemia/Lymphoma Study Group or the Japan Association of Childhood Leukemia Study standard protocols were included in analysis. All patients received chemotherapy during hospitalization for approximately 6 months, depending on stratified risk level. During hospitalization, serum CRP concentration was measured at least twice a week using latex immunoagglutination assay. The study was conducted after obtaining approval from the Ethics Committee, Kyoto University Graduate School and Faculty of Medicine (E1483).

We first investigated whether CRP concentration was elevated before FN onset, and then evaluated the efficacy of broad-spectrum antibiotics as prophylactic agents for the prevention of FN in patients with elevated CRP concentration.

CEAN

This study focused on CEAN, defined as elevation in CRP concentration ≥ 0.05 mg/dL in the most recent and second-most recent blood tests.

Febrile neutropenia

Febrile neutropenia was defined as at least one axillary temperature $\geq 38^\circ\text{C}$ in association with neutropenia (absolute neutrophil count [ANC] < 500 cells/ μL). After confirmation of FN, blood cultures were examined and broad-spectrum antibiotics initiated immediately.

Elevation of CRP concentration before FN onset

To determine the association between CEAN episodes and FN, we analyzed all FN episodes in subjects not already receiving antibiotics; these were designated “non-prophylactic FN episodes”. The proportion of CEAN episodes observed before onset of FN was evaluated in these episodes.

Prophylactic effect of broad-spectrum antibiotics

To evaluate the prophylactic effect of broad-spectrum antibiotics, we used “CEAN episode” as the unit of analysis, defined as the 48 h period after CEAN was observed. Patients would usually have one or more CEAN episodes (i.e. several units of analysis) over the 6 month hospitalization period.

We excluded CEAN episodes if they occurred in patients already been treated with antibiotics before the blood tests (e.g. for skin/soft tissue infection) and within 72 h after surgical intervention.

Broad-spectrum antibiotics had been used to prevent FN in some episodes in which the patients developed CEAN (designated “prophylactic episodes”), but these antibiotics had not been administered in other similar episodes (designated “non-prophylactic episodes”). The proportion of episodes in which the patients developed FN and bacteremia within 48 h of CEAN detection was compared between prophylactic and non-prophylactic episodes.

When a CEAN episode was identified, the patient was first observed without antibiotic treatment, and then re-examined after 24 h to determine if prophylactic antibiotics should be administered. For these episodes, a per-protocol set-like analysis was applied, in which only episodes that were in the same group (prophylactic or non-prophylactic) for 48 h after the first decision to administer broad-spectrum antibiotics (excluding episodes in which the first decision was to withhold antibiotic prophylaxis and the subsequent decision after 24 h was to administer antibiotic prophylaxis), were analyzed.

The decision to use antibiotic prophylaxis in patients with CEAN episodes was made by a pediatric hematology/oncology specialist throughout the study period.

Broad-spectrum antibiotics were defined as those that act against both Gram-positive and Gram-negative organisms (such as *Pseudomonas aeruginosa*); these included fourth-generation cephalosporins and carbapenems. These antibiotics were given i.v. every 6 h for both prophylaxis and therapy, and continued until the recovery of bone marrow function (ANC ≥ 500 cells/ μL).

Confounding factors associated with FN

Larger elevation of CRP concentration (exceeding the median of the dataset: 0.2 mg/dL), ANC, and the duration of neutropenia, and clinical mucositis occurrence were identified as possible confounding factors, and information collected on these variables. Clinical mucositis was defined as physician-documented oral aphthae and/or abdominal pain and/or diarrhea. Severe neutropenia was defined as white blood cell count < 100 cells/ μL or neutropenia duration > 7 days.

Adverse events of broad-spectrum antibiotic prophylaxis

To evaluate the adverse events associated with broad-spectrum antibiotic prophylaxis, we compared “prophylactic episodes” and “non-prophylactic FN episodes” (that eventually received

antibiotic treatment). The events for observation were duration of antibiotic treatment, changes in antibiotics (excluding de-escalation), bacteremia caused by antibiotic-resistant organisms, and incidence of infection by multidrug-resistant organisms. Decision to change antibiotics was based on the ineffectiveness of the initial antibiotic, which we considered a failure of the prophylactic or therapeutic strategy. The observation period for these events was from the start of antibiotic treatment to the recovery of bone marrow function.

Statistical analysis

All analysis was performed using STATA version 12.1 (Stata-Corp LP, College Station, TX, USA). Two-sided $P < 0.05$ was considered statistically significant.

Wilcoxon's test was used to evaluate change in CRP concentration before FN onset, defined as difference in CRP concentration between the most recent and second-most recent pre-FN blood tests. Chi-squared test was used to compare the prevalence of FN onset within 24 and 48 h of blood tests, between prophylactic episodes and non-prophylactic episodes.

Multivariate multilevel regression modeling was used to analyze the effects of antibiotic use while controlling for variation in health status, which may influence the occurrence of FN. For the evaluation of adverse events, chi-squared test was used to compare prophylactic episodes and non-prophylactic FN episodes.

Results

A total of 22 consecutive patients with hematologic malignancy (acute myeloid leukemia, $n = 2$; acute lymphoblastic leukemia, $n = 20$) admitted between September 2006 and December 2011 were included in the analysis (Table 1). Mean patient age was 6.7 years (at admission). Within a mean hospitalization period of 174.5 days, we observed 103 CEAN episodes (median, 4 episodes per patient) and 36 non-prophylactic FN episodes (mean, 1.6 episodes per patient).

Elevation of CRP concentration before FN onset

A total of 36 non-prophylactic FN episodes were analyzed (Table 2). CRP concentration was significantly higher in the

most recent pre-FN blood test compared with the second-most recent blood test ($P < 0.01$, Wilcoxon test). CEAN was observed before the development of FN in 20 (55.6%) of the 36 non-prophylactic FN episodes. Furthermore, CEAN was observed in 16 (69.6%) of the 23 non-prophylactic FN episodes for which the most recent blood test had been performed within 24 h before FN onset.

Prophylactic effect of broad-spectrum antibiotics

In total, 103 CEAN episodes were identified across 22 patients. Reassessment after 24 h of CEAN detection was performed in 11 episodes, and broad-spectrum antibiotic prophylaxis was initiated in eight episodes; consequently, 95 CEAN episodes were analyzed.

None of these patients received G-CSF for FN prophylaxis. All patients were prescribed polymyxin B sulfate daily and trimethoprim-sulfamethoxazole 2–3 days per week. Biweekly inhaled pentamidine isethionate was prescribed to patients who refused to take trimethoprim-sulfamethoxazole. Serum immunoglobulin G (IgG) was measured once a week, and i.v. immunoglobulin was used to maintain serum IgG >500 mg/dL.

Laboratory results for the prophylactic and non-prophylactic episodes are given in Table 3, Figure 1. When compared with non-prophylactic episodes, prophylactic episodes were associated with lower ANC and higher CRP elevation, which may have influenced decision to start broad-spectrum antibiotics for prophylaxis in these cases. The other laboratory parameters were similar between both groups.

In the prophylactic episodes, only two FN episodes occurred within 2–4 h after starting antibiotic prophylaxis; in contrast, 20 FN episodes were observed in the non-prophylactic episodes. The incidence of FN was significantly lower in the prophylactic episodes (6.7%) than in the non-prophylactic episodes (30.8%). Bacteremia was observed in a lower proportion of prophylactic episodes than non-prophylactic episodes, but the difference was not statistically significant (Table 4). On multivariate multilevel regression modeling, broad-spectrum antibiotic prophylaxis, higher ANC, and lower elevation

Table 1 Subject characteristics

Total patients (n)	22
Acute lymphoblastic leukemia (n)	20
Acute myeloid leukemia (n)	2
Male, n (%)	14 (64)
Age at admission (years), mean (range)	6.7 (0–14)
Days of hospitalization, mean (range)	174.5 (56–318)
CEAN episodes per patient, median (range)	4 (1–14)
Non-prophylactic FN episodes per patient, mean (range)	1.6 (0–4)

CEAN, C-reactive protein elevation in afebrile patients with neutropenia; FN, febrile neutropenia.

Table 2 FN without broad-spectrum antibiotic prophylaxis ($n = 22$ patients)

	Median (range) or n (%)
FN episodes (bacteremia episodes) (n)	36 (6)
CRP concentration (mg/dL)	
Second most recent pre-FN blood test	0.02 (0.01–0.42)**
Most recent pre-FN blood test	0.14 (0.01–1.65)**
CEAN	
n	20/36 (55.6)
Blood test within 24 h before FN onset	16/23 (69.6)

** $P < 0.01$ (Wilcoxon test). CEAN, CRP elevation in afebrile patients with neutropenia; CRP, C-reactive protein; FN, febrile neutropenia.

Table 3 Laboratory results on study entry (upon CEAN detection) (n = 22 patients)

	Total Median (range) or n (%)	Prophylactic episodes Median (range) or n (%)	Non-prophylactic episodes Median (range) or n (%)	P-value [†]
CEAN episodes	95	30	65	
CRP elevation (mg/dL)	0.21 (0.05–2.39)	0.59 (0.05–2.39)	0.12 (0.05–1.35)	<0.001
WBC (cells/ μ L)	260 (10–2520)	145 (10–550)	380 (10–2520)	<0.001
ANC (cells/ μ L)	10 (0–447)	1 (0–447)	25 (0–410)	0.007
Duration of neutropenia (days)	5 (1–36)	5 (1–11)	5 (1–36)	0.468
Clinical mucositis	23 (24.2)	6/30 (20)	17/65 (26.2)	0.515

[†]Mann–Whitney *U*-test (sequential variables) or chi-squared test (binary variables). ANC, absolute neutrophil count; CEAN, CRP elevation in afebrile patients with neutropenia; CRP, C-reactive protein; WBC, white blood cells.

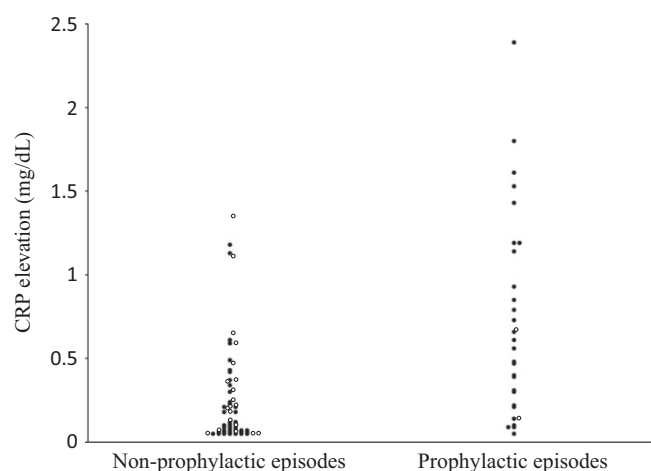


Fig. 1 C-reactive protein (CRP) elevation in analyzed prophylactic and non-prophylactic episodes (n = 95). (○) Febrile neutropenia (FN) and (●) no FN within 48 h after detecting CRP elevation in afebrile patients with neutropenia.

Table 4 FN and bacteremia occurring within 48 h after CEAN detection

	Prophylactic episodes n (%)	Non-prophylactic episodes n (%)
FN-positive cases in CAEN episodes**	2/30 (6.7)	20/65 (30.8)
Bacteremia-positive cases in CAEN episodes [†]	0/30 (0.0)	3/65 (4.6)

***P* = 0.01; [†]*P* = n.s. (chi-squared test). CEAN, C-reactive protein elevation in afebrile patients with neutropenia; FN, febrile neutropenia.

of CRP were independently associated with the lower occurrence of FN within 48 h after detection of CEAN (Table 5).

Adverse events of broad-spectrum antibiotic prophylaxis

Table 6 lists the characteristics of prophylactic episodes (prophylactic use of broad-spectrum antibiotics) and non-prophylactic FN episodes (therapeutic use of broad-spectrum

Table 5 Multivariate analysis of risk factors for FN onset within 48 h after CEAN detection

	OR (95%CI)	P-value
Broad-spectrum antibiotic prophylaxis	0.023 (0.0021–0.25)	0.002
CRP elevation >0.2 mg/dL	5.1 (1.03–24.9)	0.046
Absolute neutrophil count $\leq$ 100 cells/ μ L	39.6 (3.1–506)	0.005
Duration of neutropenia $\geq$ 7 days	0.17 (0.026–1.1)	0.47
Mucositis	0.54 (0.10–2.89)	0.47

CEAN, CRP elevation in afebrile patients with neutropenia; CRP, C-reactive protein; FN, febrile neutropenia. Variations in individual health status were adjusted using multivariate multilevel regression modeling.

Table 6 Adverse events associated with antibiotic use

	Prophylactic episodes [†] Median (range) or n (%)	Non-prophylactic FN episodes [‡] Median (range) or n (%)
No. episodes	30	36
Change in antibiotics	8 (26.7)	8 (22.2)
Bacteremia caused by antibiotic-resistant organisms	1 (3.3)	0 (0)
Total duration of antibiotics use (days)	12 (4–28)	11 (4–35)

[†]Broad-spectrum antibiotic use for prophylaxis of FN; [‡]without broad-spectrum antibiotic prophylaxis of FN. Observation was conducted from the start of antibiotics treatment to bone marrow function recovery (ANC >500 cell/ μ L). FN, febrile neutropenia.

antibiotics after FN onset). We observed one incidence of bacteremia caused by an antibiotic-resistant organism (methicillin-resistant coagulase-negative staphylococci) in a prophylactic episode 100 h after the start of antibiotic treatment.

In the observation periods, which were a median 12 days (range, 4–28 days) in prophylactic episodes and median 11 days (range, 4–35 days) in non-prophylactic FN episodes, there were no significant differences in the duration of antibiotic treatment or the number of antibiotic changes between episodes, indicating a relatively small risk of adverse events arising from broad-spectrum antibiotic prophylaxis.

Discussion

Febrile neutropenia remains an unavoidable life-threatening complication associated with intensive chemotherapy, and many studies have been done on prediction of risk of severe bacterial infection at the onset of FN.¹⁴ For this purpose, procalcitonin and interleukin-6 have been reported to be superior biomarkers compared with CRP.¹⁵ Studies to predict FN onset itself, however, are rare. Sato *et al.*¹⁶ examined the efficacy of high-sensitivity CRP measurement to predict the occurrence of an infectious event during neutropenia and shortly before the start of chemotherapy. In the present study, CRP concentration was elevated before FN onset. Next, we found that broad-spectrum antibiotics were efficacious in the prevention of FN. To the best of our knowledge, this is the first report to demonstrate the clinical importance of CEAN as a predictor of FN and to propose a strategy for preventing FN.

C-reactive protein is a systemic marker of inflammation and tissue damage as well as of infection.¹⁷ Elevation in CRP concentration may be indicative of some disease states that are risk factors for FN, such as subclinical infection, non-clinical mucositis, and other forms of tissue damage. Although the cause of CRP elevation could not be identified, CEAN was found to be a predictor of FN in the present study.

Prophylactic antibiotic regimens given during myelosuppressive chemotherapy have been shown to reduce mortality in adult cancer patients, including those with leukemia.⁴ The indications for antibiotic prophylaxis, however, remain controversial, primarily due to the risk of fostering antibiotic resistance.^{18,19} In order to minimize the use of prophylactic antibiotics in chemotherapy, it is essential to accurately identify patients at high risk of developing infection. We showed the usefulness of CEAN in identifying patients at high risk of FN, and the initiation of antibiotic prophylaxis in such patients presents a useful prophylactic strategy. Although antibiotic-resistant bacteremia occurred in one patient with prophylactic broad-spectrum antibiotics, duration of antibiotics use and proportion of strategic failures were similar between prophylactic and non-prophylactic FN episodes. Therefore, the prophylactic use of broad-spectrum antibiotics would be acceptable for patients at high risk of FN.

The optimal cut-off for CRP elevation remains controversial. As a sensitivity analysis, we investigated an alternate cut-off of CRP elevation using 0.1 mg/dL. If the cut-off was increased from 0.05 to 0.1 mg/dL, prophylactic antibiotics would be unnecessary in 29 patients; in addition, the new criterion would identify an additional four episodes of FN and one episode of bacteremia. In the clinical setting, the cut-off of CRP elevation should be determined for each individual patient based on clinical course and other risk factors of FN, such as lower ANC.

Among the prophylactic episodes, two patients had developed FN just after completing blood tests and starting broad-spectrum antibiotics (within 2–4 h after starting prophylaxis). The start of prophylaxis appeared to be too late to prevent the

development of FN in these patients, indicating that this strategy may not be effective for all patients.

Limitations

There were several limitations to the study. First, patient data were collected retrospectively, and there is therefore the risk of selection bias. This bias is likely to decrease the apparent efficacy of the strategy because antibiotic treatment tended to be given to patients with more pronounced CEAN episodes (lower ANC and higher CRP elevation), indicative of a higher risk of developing FN. Although prophylaxis with broad-spectrum antibiotics reduced the occurrence of FN by approximately 20%, the efficacy of broad-spectrum antibiotics may actually be higher if they had also been given to patients with relatively lower risk of developing FN.

Second, we did not examine chest radiography or urinalysis for every FN episode. Although chest radiography is not routinely recommended for this condition, it may be recommended for specific patients (such as after a short course of antibiotics) despite an absence of signs indicating lower respiratory tract infection.²⁰ Moreover, urinalysis has also been reported to be useful for identifying the cause of FN.²¹ Using these methods, the cause of FN may be identified in some of these episodes. Despite this, the proportion of FN occurrence in the prophylactic episodes (6.7%) was much lower than in non-prophylactic episodes (31%), suggesting that a large proportion of FN cases were caused by or associated with bacterial infection.

Third, although broad-spectrum antibiotics were associated with reduced FN incidence within 48 h of CEAN detection, eight patients with prophylactic episodes (26.7%) developed fever after the 48 h window, indicating a need to change antibiotics. The cause of these fevers could not be identified. Even if broad-spectrum antibiotics postpones FN onset, the patients would be at a lower risk of severe infection due to the additional time to allow for bone marrow function recovery.²²

Despite these limitations, this is the first report to describe the association between CEAN and FN onset, which has identified a new clinical role for high-sensitivity CRP measurement. Even though the present strategy may have external validity issues that could limit its use in other countries, the present findings may have applications for specific patients, such as those who have undergone bone marrow transplantation.

In conclusion, afebrile patients with neutropenia and elevated CRP are at higher risk of FN, and, depending on the case, physicians may consider the use of broad-spectrum antibiotics to prevent the development of FN.

Disclosure

The authors declare no conflict of interest.

Author contributions

S.S. and T.I. designed the study; S.S., T.I., and N.K. collected and analyzed data; S.S. wrote the manuscript; T.I., H.I., N.S., and Y.I. interpreted the data and critically reviewed the manuscript; Y.I. approved for the manuscript for publication. All authors read and approved the final manuscript.

References

- 1 Pritchard-Jones K, Kaatsch P, Steliarova-Foucher E *et al.* Cancer in children and adolescents in Europe: Developments over 20 years and future challenges. *Eur. J. Cancer* 2006; **42**: 2183–90.
- 2 Freycon F, Trombert-Paviot B, Casagrande L *et al.* Trends in treatment-related deaths (TRDs) in childhood cancer and leukemia over time: A follow-up of patients included in the childhood cancer registry of the Rhône-Alpes region in France (ARCERRA). *Pediatr. Blood Cancer* 2008; **50**: 1213–20.
- 3 Lyman GH. Impact of chemotherapy dose intensity on cancer patient outcomes. *J. Natl. Compr. Canc. Netw.* 2009; **7**: 99–108.
- 4 Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: Antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann. Intern. Med.* 2005; **142**: 979–95.
- 5 Barone A. Antibacterial prophylaxis in neutropenic children with cancer. *Pediatr. Rep.* 2011; **3** (1): e3.
- 6 Vogel CL, Wojtukiewicz MZ, Carroll RR *et al.* First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study. *J. Clin. Oncol.* 2005; **23**: 1178–84.
- 7 Pfreundschuh M, Truemper L, Kloess M *et al.* Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL. *Blood* 2004; **104**: 634–41.
- 8 Thatcher N, Girling DJ, Hopwood P *et al.* Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: Results of a British Medical Research Council Multicenter Randomized Trial. *J. Clin. Oncol.* 2000; **18**: 395–404.
- 9 Almyroudis NG, Segal BH. Antibacterial prophylaxis in patients with cancer and neutropenia. *N. Engl. J. Med.* 2006; **354**: 90–94.
- 10 The Japanese Society of Pediatric Hematology. [Clinical Guideline for Pediatric ALL and ML.] Kanehara, Tokyo, 2011 (in Japanese).
- 11 Relling MV, Boyett JM, Blanco JG *et al.* Granulocyte colony-stimulating factor and the risk of secondary myeloid malignancy after etoposide treatment. *Blood* 2003; **101**: 3862–7.
- 12 Pepys MB, Hirschfield GM. C-reactive protein: A critical update. *J. Clin. Invest.* 2003; **111**: 1805–12.
- 13 Ridker PM, Cushman M, Stampfer MJ *et al.* Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N. Engl. J. Med.* 1997; **336**: 973–9.
- 14 Phillips RS, Wade R, Lehrnbecher T *et al.* Systematic review and meta-analysis of the value of initial biomarkers in predicting adverse outcome in febrile neutropenic episodes in children and young people with cancer. *BMC Med.* 2012; **10**: 6.
- 15 Wu CW, Wu JY, Chen CK *et al.* Does procalcitonin, C-reactive protein, or interleukin-6 test have a role in the diagnosis of severe infection in patients with febrile neutropenia? A systematic review and meta-analysis. *Support. Care Cancer* 2015; **23**: 2863–72.
- 16 Sato M, Kako S, Oshima K *et al.* Prediction of infectious events by high-sensitivity C-reactive protein level before undergoing chemotherapy for acute myeloid leukaemia. *Scand. J. Infect. Dis.* 2010; **42**: 97–101.
- 17 Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. *Adv. Immunol.* 1983; **34**: 141–212.
- 18 Cometta A, Calandra T, Bille J, Glauser MP. *Escherichia coli* resistant to fluoroquinolones in patients with cancer and neutropenia. *N. Engl. J. Med.* 1994; **330**: 1240–41.
- 19 Carratalá J, Fernández-Sevilla A, Tubau F *et al.* Emergence of quinolone-resistant *Escherichia coli* bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. *Clin. Infect. Dis.* 1995; **20**: 557–60.
- 20 Phillips B, Wade R, Westwood M *et al.* Systematic review and meta-analysis of the value of clinical features to exclude radiographic pneumonia in febrile neutropenic episodes in children and young people. *J. Paediatr. Child Health* 2012; **48**: 641–8.
- 21 Sandoval C, Sinaki B, Weiss R *et al.* Urinary tract infections in pediatric oncology patients with fever and neutropenia. *Pediatr. Hematol. Oncol.* 2012; **29**: 68–72.
- 22 Klaassen RJ, Goodman TR, Pham B, Doyle JJ. “Low-risk” prediction rule for pediatric oncology patients presenting with fever and neutropenia. *J. Clin. Oncol.* 2000; **18**: 1012–19.