International Journal of Infectious Diseases 44 (2016) 4–7

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Differences in characteristics between first and breakthrough neutropenic fever after chemotherapy in patients with hematologic disease

Eun Young Nam [a], Kyoung-Ho Song [a,b,*], Nak-Hyun Kim [a], Moonsuk Kim [a], Chung-Jong Kim [a,1], Jeong-Ok Lee [a,b], Pyoeng Gyun Choe [b], Wan Beom Park [b], Ji-Hwan Bang [b], Eu Suk Kim [a,b], Sang-Won Park [b], Hong Bin Kim [a,b], Soo-Mee Bang [a,b], Nam Joong Kim [b], Myoung-don Oh [b]

[a] Department of Internal Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173 beon-gil, Bundang-gu, Seongnam 463-707, Korea
[b] Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

ARTICLE INFO

Article history:
Received 25 November 2015
Received in revised form 10 January 2016
Accepted 11 January 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Breakthrough infections
Febrile neutropenia
Hematologic malignancy

SUMMARY

Objective: This study was conducted to compare the clinical and microbiological characteristics of first and breakthrough neutropenic fever in hematologic malignancy patients after chemotherapy.
Methods: Breakthrough neutropenic fever was any episode of fever, not present initially, that developed either during antibiotic therapy or within 1 week of discontinuation of therapy. A total of 687 neutropenic fever episodes in 241 patients were observed from April 2003 to March 2014.
Results: Blood cultures revealed 210 causative microorganisms: 199 (94.8%) were bacteria and 11 (5.2%) were fungi. Gram-negative bacteria predominated in both types of neutropenic episode (first 75% (120/160) vs. breakthrough 56% (18/32)) and the most common pathogen was *Escherichia coli*. Antibiotic resistance rates were higher in breakthrough episodes than first episodes (piperacillin/tazobactam 6% vs. 31%, $p = 0.006$; ceftazidime 9% vs. 31%, $p = 0.025$). Inappropriate empirical antibiotic treatment was also more frequent (0% vs. 19%, $p = 0.001$), as was the 30-day mortality rate (4.3% (19/442) vs. 7.9% (19/245), $p = 0.058$), although the latter effect was not statistically significant.
Conclusion: It is concluded that the epidemiological profile of breakthrough neutropenic fever is different from that of first episode fever. These data reinforce the view that pooled reporting of neutropenic fever may be misleading, and that clinicians should approach breakthrough fever as a distinct entity.

1. Introduction

Patients with hematologic disease may develop several episodes of fever and infection during the period of chemotherapy-induced neutropenia.[1,2] Published guidelines for the management of febrile neutropenia specify risk stratification, investigation, selection, modification, and cessation of initial empirical antibiotic therapy.[3–6] They also address breakthrough fever during broad-spectrum antibiotic therapy and prolonged neutropenia. However, the basic epidemiological data on which most guidelines are based do not distinguish between first fever and breakthrough fever.[3–6] Only a few surveys have focused on differences in epidemiological profiles between first and breakthrough neutropenic fever episodes.[1,2,7,8]

This study was conducted to identify differences in the clinical and microbiological characteristics of first and breakthrough neutropenic fever episodes after chemotherapy in patients with hematologic diseases.

* Corresponding author. Tel.: +82 31 787 7021; fax: +82 31 787 4052.
E-mail address: khsongmd@gmail.com (K.-H. Song).
[1] Current affiliation: Department of Internal Medicine, Ewha Womans University Mokdong Hospital, Seoul, Korea.

http://dx.doi.org/10.1016/j.ijid.2016.01.006

2. Methods

2.1. Patients and definitions

The cases of all patients who underwent chemotherapy for acute leukemia or hematopoietic stem cell transplantation between April 2003 and March 2014, at a single tertiary hospital (Seoul National University Bundang Hospital, Seongnam, Republic of Korea), were reviewed retrospectively. Patients aged ≥15 years with neutropenia after chemotherapy (absolute neutrophil count $<0.5 \times 10^9$ cells/l, or $<1.0 \times 10^9$ cells/l with an expectation of a decrease to $<0.5 \times 10^9$ cells/l during the ensuing 48 h)[3] and fever (a single tympanic temperature measurement ≥38.0 °C)[9] were enrolled.

Breakthrough fever was any instance of fever not present at the initial episode and that developed either during antibiotic therapy or within 1 week after discontinuation of therapy.[2] Febrile episodes were categorized as microbiologically documented infection (MDI), clinically documented infection (CDI), or unexplained fever (UF), according to the Immunocompromised Host Society consensus definition.[10] Febrile episodes related to blood transfusion, chemotherapy, or the underlying disease itself were excluded.

The revised definition of invasive fungal infections proposed by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG),[11] and the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) surveillance definition of health care-associated infection for infection sites were used.[12] Primary bacteremia was defined as an unknown source of bacteremia in a neutropenic patient who showed no other symptoms or signs besides fever.

Empirical antibiotic therapy was defined as initial antibiotics started within 24 h of fever without identification of the causative microorganism.[3] Appropriate antibiotic treatment was defined as treatment matching the in vitro susceptibility of subsequently isolated bacteria.[8] The following Gram-negative bacteria were considered to be multidrug-resistant (MDR): (1) MDR strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* resistant to at least three classes of antibiotics: carbapenems, ureidopenicillins, cephalosporins, monobactams, aminoglycosides, and fluoroquinolones; (2) extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*.[13]

2.2. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the baseline characteristics of patients. Categorical variables were compared by Chi-square tests or two-tailed Fisher's exact tests. Two-sided *p*-values less than 0.05 were considered statistically significant.

3. Results

A total of 687 febrile episodes among 241 patients were identified. Underlying hematologic diseases were acute myeloid leukemia (AML) ($n = 570$ episodes), acute lymphoid leukemia ($n = 86$), acute biphenotypic leukemia ($n = 4$), and other hematologic diseases ($n = 27$) including multiple myeloma, lymphoma, aplastic anemia, etc. (Table 1). AML was more common as the

Table 1
Clinical characteristics of febrile neutropenic episodes in patients with fever after chemotherapy

Febrile episode	Total ($N = 687$)	First ($n = 442$)	Breakthrough ($n = 245$)	*p*-Value
Disease				
AML	570 (83.0)	355 (80.3)	215 (87.8)	0.015
ALL	86 (12.5)	64 (14.4)	22 (9.0)	0.041
Biphenotypic	4 (0.6)	1 (0.2)	3 (1.2)	0.132
Other	27 (3.9)	22 (5.0)	5 (2.0)	0.066
Chemotherapy				
Induction	285 (41.5)	125 (28.3)	160 (65.3)	<0.001
Consolidation	299 (43.5)	246 (55.7)	53 (21.6)	<0.001
Reinduction	64 (9.3)	41 (9.3)	23 (9.4)	1.000
BMT conditioning	39 (5.7)	30 (6.8)	9 (3.7)	0.120
Classification of infection				
MDI	195 (28.4)	155 (35.1)	40 (16.3)	<0.001
CDI	273 (39.7)	142 (32.1)	131 (53.5)	<0.001
UF	219 (31.9)	145 (32.8)	74 (30.2)	0.495
Primary sites of infection[a]	468 (100)[a]	297 (100)[a]	171 (100)[a]	
Abdomen	161 (34.4)	105 (35.4)	56 (32.7)	0.614
Primary bacteremia	69 (14.7)	58 (19.5)	11 (6.4)	<0.001
Lung	62 (13.2)	22 (7.4)	40 (23.4)	<0.001
Catheter	51 (10.9)	28 (9.4)	23 (13.5)	0.217
Perianal site	50 (10.7)	35 (11.8)	15 (8.8)	0.353
Skin and soft tissue	36 (7.7)	24 (8.1)	12 (7.0)	0.723
Pharyngo-tonsil	16 (3.5)	11 (3.7)	5 (2.9)	0.795
Paranasal sinus or ear	10 (2.1)	6 (2.0)	4 (2.3)	1.000
Urinary tract	7 (1.5)	6 (2.0)	1 (0.6)	0.431
Other (CNS, joint)	6 (1.3)	2 (0.7)	4 (2.3)	0.197
Invasive fungal infections	34 (7.3)[b]	6 (2.0)[b]	28 (16.4)[b]	<0.001
30-day mortality rate	38 (5.5)	19 (4.3)	19 (7.8)	0.058
Microorganism isolated	210	168	42	<0.001
Inappropriate empirical antibiotic treatment	30 (14.3)[c]	19 (11.3)[c]	11 (26.0)[c]	0.049

AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; BMT, bone marrow transplantation; MDI, microbiologically documented infection; CDI, clinically documented infection; UF, unexplained fever; CNS, central nervous system.

[a] Number of primary infection sites: MDI and/or CDI.

[b] Of MDI and/or CDI, proportion of invasive fungal infections.

[c] The frequency of inappropriate empirical antibiotic administration in cases where the microorganism was isolated.

underlying disease in breakthrough episodes than in first episodes, and induction chemotherapy was also more common in breakthrough episodes.

There were 442 febrile episodes classified as first episodes and 245 classified as breakthrough episodes. Of the 687 episodes, 195 (28.4%) were classified as MDIs, 273 (39.7%) as CDIs, and 219 (31.9%) as UF. In the 468 episodes of CDI or MDI, intra-abdominal infection (161, 34.4%) was the most frequent primary site of infection, followed by primary bacteremia and the lung. Pneumonia and catheter-related infections were more common in breakthrough episodes than in first episodes, whereas primary bacteremia was more common in first episodes. Invasive fungal infections (IFIs) (proven or probable) developed more frequently in breakthrough episodes (16.4% (28/171) vs. 2.0% (6/297), $p < 0.001$).

Blood cultures revealed 210 causative microorganisms: 199 (94.8%) were bacteria and 11 (5.2%) were fungi (Table 2). In both groups, Gram-negative bacteria predominated among the bacterial infections (75% (126/168) of first and 45.2% (19/42) of breakthrough episodes) and *Escherichia coli* was the most common Gram-negative species (29.1% of first and 16.7% of breakthrough episodes). *Streptococcus* species were the most common Gram-positive bacteria in patients with first MDIs, while coagulase-negative staphylococci were most common in breakthrough MDIs. Fungemia were present as 0.5% (2/442) of first MDIs and 3.7% (9/245) of breakthrough MDIs.

Among Gram-negative MDIs, antibiotic resistance rates were higher in breakthrough episodes than first ones: for piperacillin/tazobactam, 6% of the causative microorganisms of first MDIs were non-susceptible to piperacillin/tazobactam vs. 31% of breakthrough MDIs ($p = 0.006$); for ceftazidime this was 9% vs. 31% ($p = 0.025$) and for gentamicin this was 6% vs. 53% ($p < 0.001$). Notably, carbapenem resistance was only encountered in breakthrough episodes (0% vs. 19%; $p = 0.001$). Moreover a similar trend was observed among the Gram-positive bacteria: oxacillin 45% vs. 71% ($p = 0.385$), piperacillin 7% vs. 100% ($p = 0.012$), and vancomycin 0% vs. 7% ($p = 0.264$). The frequency of MDR Gram-negative bacteria was higher in breakthrough episodes (11/120, 9% vs. 5/19, 28%, $p = 0.037$). However, methicillin resistance rates of *Staphylococcus aureus* and coagulase-negative staphylococci did not differ between the two groups (45% (9/20) vs. 63% (5/8), $p = 0.403$).

Inappropriate use of empirical antibiotic treatment was more frequent in breakthrough episodes than first episodes ($p = 0.049$), and 30-day mortality also showed a tendency to be higher ($p = 0.058$).

Table 2
Microorganisms isolated from blood cultures in neutropenic patients after chemotherapy

Number of isolated microorganisms (%)	First ($n = 168$)	Breakthrough ($n = 42$)	p-Value
Gram-positive	40 (23.8)	14 (33.3)	0.237
Coagulase-negative staphylococci	9	7	0.022
Methicillin-resistant	6	5	0.046
Staphylococcus aureus	11	1	0.467
Methicillin-resistant	3	0	1.000
Streptococcus species	14	1	0.313
Enterococcus species	2	5	0.004
Ampicillin-resistant	2	3	0.560
Vancomycin-resistant	0	1	0.200
Bacillus species	4	0	0.586
Gram-negative	126 (75.0)	19 (45.2)	<0.001
Escherichia coli	49	7	0.120
ESBL-producing	4	1	1.000
Ciprofloxacin-resistant	11	3	1.000
Klebsiella species	37	5	0.195
ESBL-producing	4	1	1.000
Ciprofloxacin-resistant	5	1	1.000
Pseudomonas aeruginosa	15	3	1.000
Ciprofloxacin-resistant	2	2	0.173
Carbapenem-resistant	0	2	0.038
Enterobacter species	14	2	0.744
Other[a]	11	2	1.000
Fungus	2 (1.2)	9 (21.5)	<0.001
Candida species	2	7	<0.001
Trichosporon asahii	0	2	0.039

ESBL; extended-spectrum beta-lactamase.
[a] Infections with the following: *Fusobacterium spp*, *Aeromonas spp*, *Bacteroides spp*, *Achromobacter spp*, *Citrobacter spp*, *Moraxella spp*, *Serratia spp*, *Stenotrophomonas spp*.

4. Discussion

The clinical and microbiological characteristics of first and breakthrough neutropenic fever episodes are described. There were similarities and differences between them. The abdomen was the most common primary site of infection in both groups. It is well known that damage to the mucosal barrier due to chemotherapy can cause bloodstream infections leading to bacterial translocation.[3] However, primary bacteremia was more common in first episodes, whereas pneumonia and catheter-related infections were more common in breakthrough episodes. These findings are consistent with a previous study by Aslıhan Demirel et al., in which the respiratory system was found to be the most common primary site of infection in secondary breakthrough infections.[14]

In both groups, Gram-negative bacteria were the predominant cause of bacteremia. However, among the Gram-positive bacterial and fungal episodes there were higher frequencies of bacteremia in breakthrough fever than in first episodes. Moreover, among the breakthrough episodes, a higher proportion of the Gram-negative bacteria were resistant to broad-spectrum antibiotics. As a result, the proportion of patients receiving inappropriate empirical antibiotics was higher in breakthrough MDIs than in first MDIs. Overall mortality rates at 30 days after bloodstream infection also tended to be higher in breakthrough MDIs, and the proportion of patients receiving induction chemotherapy for underlying hematologic diseases was higher in breakthrough fever episodes than first episodes. As is widely known, induction chemotherapy is usually more intensive than chemotherapy at other times and this exposes the patient to a higher risk of infectious complications. Thus a higher proportion of induction chemotherapy could itself lead to higher mortality. However, the higher mortality in secondary breakthrough fever is consistent with previous studies,[7,14] and it is considered that it is probably a characteristic of breakthrough episodes.

Proven or probable invasive fungal infections were more frequent among breakthrough episodes, and a similar observation has been reported by several researchers. Fungi accounted for 48% of the secondary infections in the study of Akova et al., 24.7% in the study of Serra et al., and 11% in the study of Aslıhan et al.[2,14,15] This may be explained by the fact that prolonged neutropenia and the long-term use of broad-spectrum antibiotics are risk factors for fungal infection. Interestingly, the proportion of Gram-positive bacteria was higher in breakthrough fever, but the rates of methicillin resistance were similar in the two groups. This is in contrast with the situation for MDR Gram-negative bacteria. Although the reason for the difference was not explained by the present findings, awareness of the difference could be helpful when clinicians select empirical antibiotics.

This study was conducted retrospectively in a single tertiary hospital in Korea. As a result, the data represent the local epidemiological properties and clinical characteristics of neutropenic fevers. However, the concept of first and breakthrough fever are applicable to other institutions and the data suggest a general need to characterize the subpopulations of neutropenic fever. In this study, several factors that could have influenced outcomes

among the neutropenic patients with MDIs (such as severity of underlying disease, and severity and duration of mucositis) were not assessed. Thus, the risk factors for mortality due to neutropenic fever and the corresponding differences between the two groups could not be identified.

In conclusion, the epidemiological profile of breakthrough neutropenic fever is different from that of first episode fever. These data reinforce the view that pooled reporting of neutropenic fever could be misleading and that clinicians should approach breakthrough fever as distinct from first episode fever.

Acknowledgements

We express our gratitude to Professor Julian D. Gross, University of Oxford, for English editing.

Funding: No funding source.

Ethical approval: The study was approved by the institutional review boards of Seoul National University Bundang Hospital (Seongnam, South Korea) (B-1509-314-101, September 2015).

Conflict of interest: None declared.

References

1. Nucci M, Spector N, Bueno AP, Solza C, Perecmanis T, Bacha PC, et al. Risk factors and attributable mortality associated with superinfections in neutropenic patients with cancer. *Clin Infect Dis* 1997;**24**:575–9.
2. Akova M, Paesmans M, Calandra T, Viscoli C. A European Organization for Research and Treatment of Cancer–International Antimicrobial Therapy Group study of secondary infections in febrile, neutropenic patients with cancer. *Clin Infect Dis* 2005;**40**:239–45.
3. 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.
4. Baden LR, Bensinger W, Angarone M, Casper C, Dubberke ER, Freifeld AG, et al. Prevention and treatment of cancer-related infections. *J Natl Compr Canc Netw* 2012;**10**:1412–45.
5. Lee DG, Kim SH, Kim SY, Kim CJ, Park WB, Song YG, et al. Evidence-based guidelines for empirical therapy of neutropenic fever in Korea. *Korean J Intern Med* 2011;**26**:220–52.
6. Meunier F, Lukan C. The first European Conference on Infections in Leukaemia–ECIL1: a current perspective. *Eur J Cancer* 2008;**44**:2112–7.
7. Ram R, Farbman L, Leibovici L, Raanani P, Yeshurun M, Vidal L, et al. Characteristics of initial compared with subsequent bacterial infections among hospitalised haemato-oncological patients. *Int J Antimicrob Agents* 2012;**40**:123–6.
8. Azap A, Bozkurt GY, Yüksel MK, Kutlu H, Topçuoğlu P, Aypak A, et al. Secondary infections in cancer patients with febrile neutropenia. *Turk J Haematol* 2012;**29**:254.
9. Jun HX, Zhixiang S, Chun W, Reksodiputro AH, Ranuhardy D, Tamura K, et al. Clinical guidelines for the management of cancer patients with neutropenia and unexplained fever. *Int J Antimicrob Agents* 2005;**26**:128–32.
10. Pizzo PA, Armstrong D, Bodey G, Pauw B, Feld R, Glauser M, et al. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. *J Infect Dis* 1990;**161**:397–401.
11. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008;**46**:1813–21.
12. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;**36**:309–32.
13. Falagas ME, Koletsi PK, Bliziotis IA. The diversity of definitions of multidrug-resistant (MDR) and pandrug-resistant (PDR) *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *J Med Microbiol* 2006;**55**:1619–29.
14. Demirel A, Tabak F, Ar MC, Mete B, Öngören S, Yemişen M, et al. Secondary infections in febrile neutropenia in hematological malignancies: more than another febrile neutropenic episode. *Turk J Haematol* 2015;**32**:243–50.
15. Serra P, Santini C, Venditti M, Mandelli F, Martino P. Superinfections during antimicrobial treatment with betalactam–aminoglycoside combinations in neutropenic patients with hematologic malignancies. *Infection* 1985;**13**(Suppl 1):115–22.