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

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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.

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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.