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Original Article

Analysis of pathogens and susceptibility in cancer patients with febrile neutropenia and bacteremia: Experience in a single institution in eastern Taiwan

Kuan-Po Huang [a,*], Tso-Fu Wang [b], Sung-Chao Chu [b], Yi-Feng Wu [b], Rou-Yun Wang [b], Ruey-Ho Kao [b,c]

[a] Department of Oncology and Hematology, Buddhist Tzu Chi General Hospital, Taichung Branch, Taiwan
[b] Department of Oncology and Hematology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
[c] Department of Oncology, Tzu Chi University, Hualien, Taiwan

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ABSTRACT

Objective: Febrile neutropenia is a major complication in patients with malignancies receiving chemotherapy. The pathogens vary in different geographic areas, however, and also may vary in different institutions. This retrospective study analyzed the profile of bacteria in cases of febrile neutropenia at a single medical center in eastern Taiwan.

Materials and Methods: From July 2006 to July 2007, we retrospectively evaluated 80 adult cancer patients who were admitted to the hematology and oncology ward in our hospital because of febrile neutropenia. The clinical characteristics of those who survived (survival group) and those who died (mortality group) were compared. The blood culture data and susceptibility to antibiotics during episodes of febrile neutropenia were obtained for interpretation.

Results: Among a total of 110 episodes of febrile neutropenia, 31% had documented bacteremia. The most common malignancy among these patients was acute leukemia (31%), followed by non-Hodgkin's lymphoma and breast cancer. The median time from the start of chemotherapy to febrile neutropenia was shorter in the mortality group than the survival group (8.5 days vs. 11 days; $p = 0.046$). The rate of positive blood cultures was much higher in those who died compared to those who survived (75% vs. 23%, $p = 0.0001$). Gram-negative bacilli were the predominant pathogens in these neutropenic patients, which is different from the trend in Western countries. Infection with *Escherichia coli* was more common in the survival group and *Pseudomonas* species were more common in the non-survival group. Gram-positive cocci occurred in similar proportions in both groups. *E coli* in patients with febrile neutropenia were still susceptible to all first-line antibiotics.

Conclusions: Adult cancer patients with febrile neutropenia are at a high risk of mortality, especially those with documented bacteremia and short times between chemotherapy and neutropenia. Gram-negative bacilli are still the predominant pathogens in patients with febrile neutropenia and most are still susceptible to all first-line antibiotics. Further investigation into the relationship between the patterns of different pathogens and mortality in this population is needed.

1. Introduction

Febrile neutropenia remains a common complication among patients with hematological diseases and solid cancers undergoing various cytotoxic therapies. Despite major improvements in antibiotics, febrile neutropenia is associated with substantial morbidity, mortality and costs. The principles that guide the management of these patients include identification of the source of infection and effective antibiotic treatment. Empirical antibiotic therapy is often given for broad-spectrum coverage of common pathogens in this situation [1,2]. Treatment often needs to be tailored to individual patients once the cause and antibiotic susceptibility pattern of the isolated organism are known. Over the past three decades, there has been a considerable change in the epidemiology of pathogens causing bacteremia in patients with febrile neutropenia. In the 1970s, Gram-negative bacilli caused 60–70% of bacteremia in neutropenic patients [3–5]; in the 1990s, the majority of cases of bacteremia were due to Gram-positive cocci. In several large studies

* Corresponding author. Department of Oncology and Hematology, Buddhist Tzu Chi General Hospital, Taichung Branch, 88, Section 1, Feng-Xing Road, Tanzi Dist, Taichung, Taiwan. Tel.: +886 4 36060666; fax: +886 4 36065928.
E-mail address: wheaty0948@yahoo.com.tw (K.-P. Huang).

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from Western countries, the rate of infection with Gram-negative bacteremia dropped approximately from 70% to 30% [3–7]. This trend may be attributed to many factors, such as the widespread use of prophylactic quinolones [8], the use of long-term indwelling intravascular catheters and an increased incidence of severe mucositis as a result of dose-intense chemotherapy.

The microbiological pattern in cancer patients with febrile neutropenia in Taiwan is different from that in Western countries. In medical centers in Taiwan, Gram-negative bacteria still account for most isolated pathogens, followed by Gram-positive bacteria, fungi and anaerobes [9–13]. Although bacteremia in cancer patients is not uncommonly reported in Taiwan, little is known about the differences in bacterial pathogens and antibiotic susceptibilities in cancer patients who survive or die during febrile neutropenia. The epidemiology of pathogens is dynamic, so it is important to have local data when making therapeutic decisions, especially in cancer patients. In this study, we investigated the pattern of bacteremic pathogens in adult cancer patients who survived or died with febrile neutropenia after chemotherapy in one hospital in eastern Taiwan.

2. Materials and methods

We retrospectively analyzed all adult cancer patients (>18 years) with febrile neutropenia who were admitted to the hematology and oncology wards in our hospital from July 1, 2006 to July 31, 2007. The inclusion criteria were as follows: (1) fever, defined as a single oral temperature of 38.3 °C or an oral temperature of 38 °C lasting 1 hour; and (2) neutropenia, defined as a neutrophil count of <500 cells/mm^3, or a count of <1000 cells/mm^3 with a predicted decrease to <500 cells/mm^3 within the next 48–72 hours. Each separate hospital admission for febrile neutropenia was defined as one episode. Patients who survived the episode of febrile neutropenia were referred as the "survival group". Patients who died in hospital with death being related to the episode of febrile neutropenia were referred as the "mortality group". The clinical characteristics and data of the survival and mortality groups were reviewed.

Bacteremia was defined as a blood culture yielding a pathogenic organism during febrile neutropenia. If the isolate was a potential skin contaminant (such as coagulase-negative *Staphylococcus* or *Corynebacterium* species), all of the following criteria had to be met when considering the pathogen: the presence of an intravascular catheter, initiation of antimicrobial therapy, and at least one episode of fever, temperature <36 °C, chills or hypotension [5].

Microbiological results were obtained from computerized laboratory reports, which were confirmed by standard culture protocols in our hospital. Antibiotic susceptibilities were assessed using the disk diffusion method. The empirical antibiotic regimen was determined by guidelines from the Infectious Disease Society of Taiwan and the Hematology Society of Taiwan [14]. Generally, a broad-spectrum penicillin (± an aminoglycoside), a third- or fourth-generation cephalosporin (± an aminoglycoside), or a carbapenem was given as empirical therapy after blood cultures were implemented. The antibiotics were modified according to the results of blood culture and sensitivity tests. A glycopeptide (vancomycin or teicoplanin) was added if Gram-positive bacteria or a skin infection was highly suspected. There was no routine antibacterial or antifungal prophylaxis in these patients before chemotherapy during the study period.

Continuous variables were compared by the Student *t* test, whereas categorical variables were compared by the Chi-square test. A *p* value of less than 0.05 was considered a significant difference. This study was approved by the Research Ethics Committee of our institution (IRB100-29).

3. Results

A total of 80 patients were included who had a total of 110 episodes of febrile neutropenia. The median age was 55 years (range from 19 to 89 years). Thirty-eight patients were men and 42 patients were women (the male to female ratio was 1:1.1). The episodes occurred mainly (93%) after chemotherapy for their underlying diseases. Thirty-three (30%) episodes occurred in patients diagnosed with solid cancers and 77 (70%) in patients with hematological diseases. The most common underlying solid cancer was breast cancer, followed by lung cancer. The most common underlying hematological disease was acute myeloid leukemia, followed by non-Hodgkin's lymphoma. The mean nadir of the absolute neutrophil count during febrile neutropenia was 150/μL, with counts of 152/μL in the non-survival group and 138/μL in the survival group (Table 1), which was not statistically significantly different ($p = 0.775$).

The chemotherapeutic agents used before the febrile neutropenic episodes are listed in Table 1, and the most common chemotherapy was an anthracycline-containing regimen (27%). The survival group contained more patients receiving anthracycline-based agents than the mortality group ($p = 0.041$).

Blood cultures were drawn in all 110 episodes. Bloodstream pathogens were recovered in 34 episodes (31%), in which 48 pathogens were isolated. Among these bloodstream isolates, 30 were Gram-negative bacilli (63%), 16 were Gram-positive cocci (33%) and 2 were fungi (4%); see Table 1. The most common Gram-negative bacillus was *E coli* ($n = 8$), followed by *Pseudomonas* species (with *Pseudomonas aeruginosa* being the most common) and *Klebsiella pneumoniae*. The most common Gram-positive cocci were *Staphylococcus* species, followed by *Streptococcus* species.

A total of 16 deaths (14%) occurred among the 110 episodes of febrile neutropenia (Table 1). The median time from the start of chemotherapy to febrile neutropenia was 8.5 days in the mortality group and 11 days in the survival group ($p = 0.046$). Central venous catheters (CVCs) were implanted during 86 episodes (78%) of febrile neutropenia. The percentage of patients with CVC implants in the morality group was 63% ($n = 10$) and the percentage in the survival group was 81% in ($n = 76$). Three-quarters of those who died had hematological diseases compared to 69% in the survival group ($p = 0.637$).

The positive blood culture rate was much higher in the mortality group than in the survival group (75% vs. 23%, $p = 0.0001$). The most common bacterial species isolated from patients who died were *P aeruginosa* and *K pneumoniae*. This was different from those who survived, in whom *E coli* and *Staphylococcus epidermidis* were dominant.

The antimicrobial susceptibilities of the major bacterial pathogens isolated in patients with febrile neutropenia are shown in Table 2. Most of the common Gram-negative bacteria were susceptible to common empirical antibiotics, such as piperacillin/tazobactam, ceftazidime and the carbapenems, with a response range of 67% to 100%. The most common Gram-negative bacillus, *E coli*, was 100% susceptible to all third-generation cephalosporins, carbapenems and fluoroquinolones. Most Gram-positive bacteria were resistant to either penicillin or oxacillin, but almost all were sensitive to vancomycin (88%) or teicoplanin (100%).

4. Discussion

Although bacteremia in cancer patients is not uncommonly reported in Taiwan, little is known about differences in bacterial pathogens between those who survive and those who die during an episode of febrile neutropenia. The mortality rate among our patients with febrile neutropenia was 14%.

Table 1
Clinical characteristics and bloodstream pathogens isolated in patients who died (mortality group) or survived (survival group) during febrile neutropenia (FN).

	Total number of episodes of FN ($n = 110$)	Mortality group ($n = 16$)	Survival group ($n = 94$)	p
Disease subtypes				
Hematological disease (%)	77	12 (75%)	65 (69%)	0.637
Acute leukemia	44	6	38	
Lymphoma	17	3	14	
Myeloma	9	2	7	
Myelodysplasia	1	1	—	
Others[a]	6	—	6	
Solid cancer (%)	33	4 (25%)	29 (31%)	
Colorectal cancer	2	2	—	
Breast cancer	12	—	12	
Lung cancer	9	—	9	
Head and neck cancer	4	—	4	
Esophageal cancer	1	1	—	
Others[a]	5	1	4	
Chemotherapy regimen				
Alkylator-containing	22	1	21	0.137
Platinum-containing	21	4	17	0.515
Anthracycline-containing	30	1	29	0.041
Taxane-containing	11	0	11	0.149
Other agents[b]	26	5	21	0.438
Number with bacteremia, (% of FN episodes)	34 (31%)	12 (75%)	22 (23%)	0.0001
Median time to FN after chemotherapy (d)	11	8.5	11	0.046
Central venous catheter	86 (78%)	10 (63%)	76 (81%)	0.10
Mean absolute neutrophil counts	150	138	152	0.775
Total number where pathogens were isolated	48	16	32	
Gram-positive cocci	16 (33%)	5 (31%)	11 (34%)	0.91
Staphylococcus	8	2	6	
Streptococcus	4	3	1	
Enterococcus	1	—	1	
Others[c]	3	—	3	
Gram-negative bacilli	30 (63%)	9 (56%)	21 (66%)	0.75
E coli	8	1	7	
Pseudomonas spp.	6	4	2	
K pneumonia	6	2	4	
A baumanii	3	1	2	
Others[d]	7	1	6	
Fungus	2 (4%)	2 (13%)	0	

[a] Other regimens include regimens without alkylator, anthracycline, platinum and taxane.
[b] Other hematological diseases include chronic leukemia ($n = 1$) and aplastic anemia ($n = 5$). Other solid cancers include primary peritoneal carcinoma, neuroendocrine carcinoma and metastatic carcinoma of unknown origin.
[c] Other Gram-positive cocci include *Enterococci cloacae* and *Corynebacterium*.
[d] Other Gram-negative bacilli include *Proteus mirabilis*, *Stenotrophomonas maltophilia*, *Vibrio parahaemolyticus*, *Aeromonas sobria*, *Alcaligenes faecalis* and *Chryseobacterium indologenes*.

Several factors are known to influence the survival of cancer patients with febrile neutropenia, such as uncontrolled infection, underlying malignant diseases, intensive cytotoxic agents and the functional reserve of the bone marrow [3].

In our study, the positive blood culture rate was much higher in the mortality group than the survival group (75% vs. 23%, $p = 0.0001$). Although bacteremia accounts for only about one-third of infections among cancer patients with febrile neutropenia, it is reasonable to assume that there is a higher risk of mortality in cancer patients with than those without bacteremia [15].

Our data also showed that the average time from chemotherapy to neutropenia was shorter in those who died compared to those who survived (8.5 days vs. 11 days, $p = 0.046$). This phenomenon may indicate the different susceptibilities of the patients in the former group to fatal infection. Different chemotherapy agents might influence the duration of neutropenia and time to neutropenia. More patients in the survival group received anthracycline-based agents compared with those who died, but there were no differences between other regimens, such as platinum- or taxane-based chemotherapy. Although limited by bias from the small sample size and the heterogeneity of the different regimens, there was a difference between patients receiving anthracycline-based regimens and those receiving other agents ($p = 0.041$). Confirmation of the different mechanisms by which cytotoxic drugs work and their impact on patients with febrile neutropenia requires further study.

The shift of balance of predominant pathogens in Western countries was not seen in our study. Gram-negative bacilli remained the dominant pathogens in our institution, comprising 63% of isolates from adults with febrile neutropenia. This percentage is similar to data from other medical centers in Taiwan [9–13]. In Kuderer's study [15], Gram-negative bacteremia was a risk factor for inpatient mortality in neutropenic patients. Although the culture rate of Gram-negative bacilli was similar in the groups in our study, the pathogens were somewhat different between groups. *P aeruginosa* and *K penumoniae* were the most common pathogens in the mortality group. In contrast, *E coli* was the most common pathogen in the patients who survived and occurred most frequently in patients with hematological malignancies, especially acute leukemia and lymphoma.

Different pathogens found between the groups might also have influenced the patients' survival. *P aeruginosa* and *K penumoniae* are less susceptible to common first-line antibiotics than *E coli* in our hospital. The strains of *E coli* were all susceptible to almost all first-line antibiotics used in febrile neutropenia. The antibiotic susceptibility of different pathogens may be an explanation for the differences in survival among cancer patients with febrile neutropenia, but clarification of the relationship between different bacterial virulence and survival in cancer patients requires further microbiological or molecular study.

The percentage of Gram-positive bacteremia in our cancer patients with febrile neutropenia was 33%. Most of the cancer patients needed CVC for the administration of intravenous chemotherapy. The percentage of CVC implants and Gram-positive bacteremia were similar in the two groups ($p = 0.10$). Although a CVC is known to be an important risk factor for infection with Gram-positive bacteremia, the exact relationship between CVC implants and the survival of febrile neutropenic patients is still unknown.

Table 2
In vitro antimicrobial susceptibility of bacteria isolated in patients with febrile neutropenia.

Bacteria	Percentage of total number of isolates from febrile neutropenia susceptible to						
	Piperacillin/Tazobactam	Ceftazidime	Levofloxacin	Imipenam	Meropenam	Amikacin	Vancomycin
Staphylococcus ($n = 8$)							88%
Streptococcus ($n = 4$)							100%
E coli ($n = 8$)	100%	100%	100%	100%	100%	100%	NA
Pseudomonas spp. ($n = 6$)	100%	83%	NA	83%	83%	100%	NA
Klebsiella pneumoniae ($n = 6$)	83%	83%	67%	83%	83%	83%	NA
Acinetobacter baumanii ($n = 3$)	67%	67%	33%	67%	67%	67%	NA

We found differences in the susceptibility of Gram-positive cocci and Gram-negative bacilli to available treatments. The Gram-positive cocci were all resistant to either penicillin or oxacillin, but were susceptible to vancomycin and teicoplanin. Although *E coli* resistance to fluoroquinolones is an emerging problem in Taiwan and Western countries [16–18], we did not find this phenomenon in our study population. The fact that the *E coli* isolates in our study were susceptible to almost all first-line antibiotics suggests that the application of antibiotics in this institution is still under reasonable control. Resistance to first-line antibiotics often emerges from extensive antibiotic treatment or prophylaxis. We did not routinely use prophylactic fluoroquinolone in these neutropenic patients, and this may explain the susceptibility of *E coli*. The number of cases for each species was small, however, and therefore the susceptibility rate might have been underestimated in this study. Further confirmation with a larger population is needed.

In addition to the intrinsic virulence of bacteria, the immunological competence of the host plays an important role in infection in cancer patients. Hematological malignancies, especially acute leukemia or lymphoma, often reflect the impaired marrow reserves and the need for more intensive chemotherapy than solid cancers. This accounts for the high mortality risk in febrile neutropenic patients. Infection in patients with various hematological malignancies were not statistically significantly different between the groups ($p = 0.637$), which is probably due to the small sample size. In the survival group, six episodes were categorized as "Others," which included chronic lymphocytic leukemia ($n = 1$) and aplastic anemia ($n = 5$). These two hematological diseases have more indolent clinical courses than acute leukemia and aggressive lymphoma. Patients with these indolent diseases did not appear in the non-survival group. The impact of different hematological malignancies and diseases on patients with febrile neutropenia is an interesting subject and further study is warranted.

5. Conclusions

Adult cancer patients with febrile neutropenia are at a high risk of mortality, especially those with documented bacteremia and a short time between chemotherapy and neutropenia. Gram-negative bacilli are still the predominant pathogens in patients with febrile neutropenia. The strains of *E coli* are still susceptible to all first-line antibiotics. Our study provides preliminary local data on cancer patients treated in eastern Taiwan. The relationships between different patterns of pathogens and mortality in patients with febrile neutropenia require further investigation in a larger cohort.

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