Chula Med J Vol. 47 No. 3 March 2003

Febrile neutropenia after chemotherapy in patients with non-hematologic malignancies

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Voravud N, Sriuranpong V. Febrile neutropenia after chemotherapy in patients with non-hematologic malignancies. Chula Med J 2003 Mar; 47(3): 151 - 61

Objectives : *To determine clinical course and prognosis of febrile neutropenia in patients with non-hematologic malignancies.*

Patients and methods : *Retrospective study of 100 patients with non-hematologic malignancies who developed 123 episodes of febrile neutropenia after receiving chemotherapy at King Chulalongkorn Memorial Hospital. Prognostic variables were analyzed by logistic regression analysis.*

Results : *Among 123 episodes of neutropenic fever, median absolute nadir granulocyte (ANC) count was 130/mm^3 (ranged 10-940/mm^3) and 44.7 % of the patients had ANC nadir less than 100/mm^3. Documented infection rate was 39.8% and hemoculture was positive in 26 % of the patients. The most common infection was pneumonia 12.2 %; and Klebsiella was the most common causative pathogen (28.1 %). Mortality rate was 17 % and significant mortality risk factors were hypotension at presentation, poor performance status (p = 0.008) and steroid treatment (p = 0.0429)*

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Conclusions : *The prevalence of infection was 39.8 %. Pneumonitis and Klebsiella infection were the most common etiology of febrile neutropenia. Prognostic factors were significantly associated with hypotension, poor performance status and steroid treatment.*

Keywords : *Febrile neutropenia, Chemotherapy, Non-hematologic, Malignancies, Prognostic factor.*

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Received for publication. December 15, 2002.

นรินทร์ วรวุฒิ, วิโรจน์ ศรีอุฬารพงศ์. ภาวะไข้ร่วมกับเม็ดเลือดขาวต่ำจากยาเคมีบำบัดในผู้ป่วยมะเร็งที่ไม่ใช่มะเร็งเม็ดเลือด. จุฬาลงกรณ์เวชสาร 2546 มี.ค; 47(3): 151 - 61

จุดประสงค์ : *ศึกษาลักษณะทางคลินิกและปัจจัยการพยากรณ์โรคของผู้ป่วยมะเร็งที่ไม่ใช่เม็ดเลือดที่เกิดภาวะไข้ร่วมกับเม็ดเลือดขาวต่ำจากยาเคมีบำบัด*

วิธีการและผู้ป่วย : *ศึกษาแบบย้อนหลังในผู้ป่วยมะเร็งที่ไม่ใช่มะเร็งเม็ดเลือดขาวจำนวน 100 ราย ที่เกิดภาวะไข้ร่วมกับเม็ดเลือดขาวต่ำจากยาเคมีบำบัด 123 ครั้ง ที่รักษาในโรงพยาบาลจุฬาลงกรณ์ วิเคราะห์ปัจจัยการพยากรณ์โรคด้วยการวิเคราะห์แบบ logistic regression*

ผลการศึกษา : *ผู้ป่วยมีค่ามัธยฐานของระดับเม็ดเลือดขาว นิวโทรฟิลต่ำสุด 130 เซลล์ต่อลูกบาศก์มิลลิเมตร (10-940 เซลล์ต่อลูกบาศก์มิลลิเมตร) และผู้ป่วยร้อยละ 44.7 มีระดับเม็ดเลือดขาว นิวโทรฟิลต่ำสุด น้อยกว่า 100 เซลล์ต่อลูกบาศก์มิลลิเมตร สาเหตุของไข้จากการติดเชื้อพบร้อยละ 39.8 ของผู้ป่วย และผลเพาะเชื้อขึ้นเชื้อโรคร้อยละ 26 โรคติดเชื้อที่พบบ่อยที่สุด คือ ปอดบวม พบร้อยละ 12.2 และเชื้อโรคสาเหตุที่พบมากที่สุดคือ Klebsiella พบร้อยละ 28.1 อัตราตายของผู้ป่วยคิดเป็นร้อยละ 17 และปัจจัยการพยากรณ์โรคที่ไม่ดี คือ ความดันโลหิตต่ำ ($p=0.0001$) สมรรถภาพของร่างกายไม่ดี ($p<0.008$) และการใช้ยาสเตียรอยด์ ($p=0.0429$)*

บทสรุป : *อุบัติการณ์ของการติดเชื้อในภาวะไข้ร่วมกับเม็ดเลือดขาวต่ำ พบร้อยละ 39.8 ปอดบวมและการติดเชื้อ Klebsiella เป็นสาเหตุที่พบบ่อยที่สุด ปัจจัยการพยากรณ์ที่ไม่ดี คือ ความดันโลหิตต่ำ สมรรถภาพไม่ดี และการใช้ยาสเตียรอยด์*

Fever and granulocytopenia is a common complication of cytotoxic chemotherapy. Although many factors including the underlying malignancy can cause fever, the majority of fevers that occur in granulocytopenic cancer patients are caused by infection. With the increased use of myelosuppressive agents in the treatment of neoplastic diseases, infection in granulocytopenia has become more common. Granulocytopenia markedly alters host's inflammatory response. Therefore, typical symptoms and signs of infection are often missing in granulocytopenic cancer patients. The failure to diagnose accurately and to treat promptly the infection in granulocytopenic patients can be a major cause of morbidity and mortality. Moreover, the identification of the site of infection and diagnosis of responsible organisms is usually incomplete. The difficulty in obtaining the diagnosis of infection associated with this condition may be attributed to the scarcity and subtlety of presenting signs and symptoms of the infection encountered in the absence of sufficiency granulocyte response. Therefore, clinical features and prognostic factors should be identified as prerequisites to better management of fever in patients with cancer and chemotherapy-induced neutropenia. The present study examines clinical spectrums including prognostic factors and etiologies in patients with non-hematologic malignancies who developed chemotherapy-associated febrile neutropenia.

Patients and method

To determine clinical course and prognosis of febrile neutropenia, we retrospectively reviewed records of non-hematologic cancer patients who developed fever with neutropenia after receiving cytotoxic chemotherapy at King Chulalongkorn Memorial Hospital. Febrile neutropenia was defined when the body temperature reached 38.5 ^{0}C or higher, presumed or proved to have infection with an absolute neutrophil count (ANC) of less than 500/mm^3 following myelosuppression chemotherapy. Patients who were eligible for analysis should have histological or cytological proven non-hematologic malignancies.

A total number of 123 episodes of febrile neutropenia that occurred in 100 patients were identified. Their clinical history and laboratory data were carefully examined to determine the clinical manifestations, course of the disease, interventions, sequeles and prognostic factors of the patients.

Criteria for the diagnosis of pneumonitis were, namely: 1) documented infection-definite signs and symptoms of pneumonia plus culture proof from blood, sputum or lung tissue; 2) probable infection-definite clinical evidence of pneumonia but negative blood cultures and sputum or lung tissue either unobtainable or without a predominating organisms. Diagnosis of cellulitis depend on fulfillment of at least one of three conditions: 1) typical clinical findings, or 2) histological evidence of tissue invasion by microorganisms similar in morphology to those cultured, or 3) improvement in equivocal clinical findings temporally related to an appropriate (cultured-based) prescribed antibiotic regimen. No cases with equivocal clinical findings were included for analysis unless positive cultures were obtained directly from infected tissues. Urinary tract infection was defined by clean-catch urine culture with growth higher than 100,000 colonies /mm^3 of a potentially pathogenic organisms.

Statistical analysis of prognosis factors was performed by logistic regression analysis using SPSS

for window (Version 6.0) statistical program.

Result

During the study period of 3 years, 123 episodes (in 100 patients) fulfilled the eligibility criteria for febrile neutropenia were evaluated. As shown in Table 1, 46 patients were male, and 54 were female. The median age of the patients was 52 years (ranged 19 -77 years). The median baseline absolute granulocyte count at the onset of fever was 300/mm^3 and the median absolute neutrophil count nadir was 130/mm^3 (Table 2). Overall incidence of fever from documented infection was 53 episodes (39.8 %). Pneumonia was the most common infection seen in 15 of 123 episodes (12.2 %). Presumably, the gastrointestinal tract served as a portal of entry for many of septic episodes; however, primary gastrointestinal infection was uncommon (8.1 %). Similarly, genitourinary tract infections were uncommon (8.9 %). Cellulitis developed in 13 episodes (10.5 %). Although catheter-related sepsis was commonly reported elsewhere as a common source of infection, only 4.9% of the source was identified because an access device to the central vascular system is not yet a common practice in the administration of chemotherapy in our institution. The types of infections that occurred during granulocytopenia were comparable for patients with different histological

Table 1. Patient characteristics.

Patients with febrile neutropenia	Number (%)
No. of patients	100
Male : female	46.54
No. of episodes	123
Median age	52
Range	19 - 77
Performance status	
1	16 (13.0)
2	53 (43.1)
3	32 (26.0)
4	22 (17.9)

Table 2. Complete blood count of patients with febrile neutropenia.

Patients with febrile neutropenia	Number (%)
Baseline hematologic data/mm^3	
ANC	300 (20 -980)
Platelet ($x10^3$)	100 (3 - 495)
Hb (gm%)	9.7 (5.916.8)
ANC nadir	
<100	55 (44.7)
101-500	58 (47.2)
>500	10 (8.1)
Median ANC nadir	130
Range	10 - 940

ANC = absolute neutrophil count

Table 3. Etiology of Septicemia.

Etiology	Number (n = 32)
Klebsieillar spp.	9 (28.1)
E.coli	7 (21.9)
Enterobactor spp.	3 (9.4)
Psudomonas	3 (9.4)
Aeruginosa	1 (3.1)
Psudomonas capasia	6 (18.8)
Stap auereaus	1 (3.1)
Stap epidermidis	1 (3.1)
Aeromonas hydrophillia	1 (3.1)
Salmonellar gr.D	-

types of solid tumors. Once rendered granulocytopenic by chemotherapy, they shared a comparable risk of serious infection that was irrespective of their underlying malignancies. In a similar fashion, the microbial isolates obtained in the documented infectious episodes were also similar regardless of their underlying disease. As seen in Table 3, hemocultures were positive in 30 of the 123 episodes (24.4 %); they were gram-positive (21.9 %), and gram-negative bacteria (78.1%). *Klebsiella* was the most common bacteria in 28 % of the cases, followed by *Escherichia coli* 21.9 %; *Enterobacter* (9.4 %) and *Pseudomonas aeruginosa* (9.4 %); *Staphylococcus aereaus* was seen in 6 episodes (18.8 %). Although fungal organisms may occur in patients with protracted granulocytopenia and prolonged antibiotics exposure, only one fungal colony was found in our study.

Attempts were made to identify clinical presentations of patients with febrile neutropenia. As seen in Table 4, the most common presentation was fever (100 %). The second most common presentation was gastrointestinal disturbance that consisted of diarrhea of 40 episodes (26 %), sore mouth 16 (13 %), sore throat and dysphagia 11 (8.9 %), abdominal pain 12 (9.7 %) at the initial presentation; and it occurred mainly in patients with gastrointestinal infection 3 in 10 episodes (30 %).

Pneumonitis was the most common documented source of infection (Table 5) in 15 of 123 episodes (12.2 %). Fever and cough, leading presentations of pneumonitis, was seen in 14 episodes (93.3 %). Fever without respiratory symptoms was detected in 1 episode (6.7 %), Table 6. Gram negative bacterial infection was more common than gram positive in pneumonitis. Microbiologic documented pneumonia was staphylococcus aereaus 4 episodes, Klebsiella 5, Pseudomonas aerugenosa 2, and Acinetobactor 1. Hemoculture was positive in 5 of 15 episodes (33.3 %).

Common clinical presentations of gastro-intestinal tract infection in patients with neutropenic

Table 4. Clinical presentations of patients with febrile neutropenia.

Clinical presentation	Number (n=123)
Fever	123 (100 %)
Shock	9 (7.3)
Drowsiness	21 (17.1)
Alteration of concious	8 (6.5)
Dyspnea	21 (17.1)
Tachypnea	40 (32.5)
Diarrhea	32 (26.0)
Sore mouth	16 (13.0)
Malaise	41 (33.3)
Severe nausea and vomiting	10 (8.1)
Sore throat and dysphagia	11 (8.9)
Cough	19 (15.4)
Abdominal pain	12 (9.7)
Urinary symptoms	10 (8.1)
Bleeding disorder	8 (6.5)
Skin lesion, ulceration and	15 (12.2)
Discharge	22 (17.9)

Table 5. Source of infection in febrile neutropenia.

Source of infection	Number (n=123) (%)
GI infection	10 (8.1)
Pneumonia	15 (12.2)
Local cellulitis	13 (10.6)
Catheter induced Infection	6 (4.9)
UTI	11 (8.9)
Unidentified	70 (56.9)

Table 6. Clinical presentations of pneumonia in neutropenic patients.

Clinical presentation of pneumonia	n = 15
Cough	14 (93.%)
Dyspnea	8 (78.6 %)
Fever	15 (100 %)
Malaise	8 (53.3 %)
Drowsiness	6 (40 %)
Shock or hypotension	1 (7.1 %)
Mucositis	3 (21.4 %)
Fever only	1 (6.7 %)
Fever with cough	8 (53.3 %)
Fever with cough and dyspnea	6 (40 %)

fever were fever with diarrhea (Table 7). Abdominal pain and nausea/vomiting were seen in 30 % of the patients. Thirty percent of the patients presented with hypotension and alteration of consciousness was seen in 10 % of the patients. The causative pathogens were *Eschericia coli* (60 %), *Klebsiella* (30 %), *Salmonellar group D* (40 %), *Proteus* (10 %), *Pseudomonas capasia* (10 %), and *Enterobacter* (10%)

Patients with cellulitis (Table 8) presented with fever (100 %), discharge (61.5 %), erythema (53.8 %), and ulceration (38.4 %). The etiologies of cellulitis were, namely: *Klebsiella*, *Staphylococcus aereus, Eschericia coli, Enterobacter, Acinetobacter Staphylococcus epidermidis, Streptococcus group D* and *Proteus*. Multiple organisms were isolated consisting of *Eschericia coli* and *Enterobacter* in 1 patient, *Klebsiella* and *Acinetobacter* in another patient. In three patients the causative organisms could not be identified.

Table 7. Clinical presentations of gastrointestinal infection in neutropenic patients.

Clinical presentation of GI infection	n = 10
Diarrhea	10 (100 %)
Fever	10 (100 %)
Abdominal pain	3 (30 %)
Dyspnea and tachypnea	1 (10 %)
Nausea and vomiting	3 (30 %)
Hypotension or shock	3 (30 %)
Alteration of conciousness	1 (10 %)

Table 8. Clinical presentations of cellulitis in neutropenic patients.

Clinical presentation of cellulitis	n = 13 (%)
Fever	13 (100)
Discharge	8 (61.5)
Erythema	7 (53.8)
Ulceration	5 (38.4)
Ichthing	5 (38.4)
Swelling	4 (30.7)
Drowsiness	2 (15.4)

Table 9. Clinical presentations of urinary tract Infection in neutropenic patients.

Clinical presentation of UTI	n = 11 (%)
Fever	11 (100)
Dysuria	6 (54.5)
Frequent urination	2 (18.2)
Flank pain	1 (9.1)
Diarrhea	
Fever with chill only	4 (36.4)
Fever with dysuria	6 (54.5)
Fever with flank pain	1 (9.1)
Fever with dysuria and pain	2 (18.1)

The most common clinical presentation (Table 9) of urinary tract infection in patients with neutropenic fever were fever (100 %), dysuria (54.5 %), and chill (36.4 %). Flank pain was uncommon presentations and was seen in only 1 patient. Hemoculture was positive in 18.2 % of the patients. Causative organisms were *Eschericia coli* (36.4 %), *Streptococcus* (18.2 %), *Klebsiella* (9.1 %), *Citrobactor* (9.1 %), *Proteus* (9.1 %), *Staphyloccus* (9.1 %), and *Enterobactor* (9.1 %).

Overall survival rate of the patients with febrile neutropenia was 82.93 %. Prognostic variables employed in mortality analysis consisted of age, nadir absolute granulocyte count, delayed antibiotic treatment (>24 hours), multiple chemotherapy cycles (>6 cycles), positive hemocultures, hypotension at presentation, multiple sites of infection (> 2 sites), major organ failure (CNS, CVS, renal and hepatic), poor performance status (Zubrod's scale > 3), granulocyte colony-stimulating factor treatment, steroid treatment, and concomitant chemoradiation. (Table 10). Significant prognostic factors in Logistic Regression Analysis were, namely: hypotension at presentation ($p < 0.0001$; $R=0.0376$), poor performance status ($p = 0.008$; $R = 0.210$), and steroid treatment ($p = 0.0429$; $R = 0.137$).

Table 10. Prognostic variables of mortality risk factors in patients with febrile neutropenia after chemotherapy (logistic regression analysis)

Prognostic variables	P value
Age	0.5914
Nadir absolute granulocyte count	0.0511
Delayed Antibiotic Treatment (> 24 hours)	0.6007
Multiple chemotherapy (> 6 cycles)	0.2994
Positive hemoculture	0.1568
Hypotension at presentation	0.0001
Multiple site of infection (> 2 sites)	0.6675
Multiple organ failure	0.3568
Poor performance status (Zubrod's scale > 23)	0.0080*
Granulocyte colony-stimulating factor treatment	0.1077
Steroid treatment	0.0429*
Concomittant chemoradiation	0.4981

*statistical significance

Discussion

Cancer patients with febrile neutropenic often have established or occult infection. In our series fever from documented infection was 39.8 %, and bacteremia was documented in 26 % of the cases. Four European Organizations for Research and Treatment of Cancer (EORTC) reported incidence of bacteremia in neutropenic fever was approximately 20 %[1] The risk of infection in patients receiving cancer chemotherapy is dependent upon the duration and severity of neutropenia. The likelihood of infection is related to the intensity and the duration of neutropenia; the greatest risk arose when absolute neutrophil count was less than 100/mm^3.[2] In our study, the median absolute granulocyte count was 300 / mm^3 and the median absolute a nadir granulocyte count was 130 / mm^3.

The common sites of infection in neutropenic patients were namely: lungs, skin and soft tissues, urinary tract, gastrointestinal tract and catheter-related infections. Infection was generally caused by microorganisms already colonized in the patient, although some are hospital acquired pathogens.

The hospital acquired infections are more likely to be resistant to the commonly used antimicrobial agents. Common etiologies of bacteremia in this study were namely: *Klebsiella, Escherichia coli, Enterobacter*, and *Pseudomonas species*. The major pathogens in other two studies conducted in Thailand were also gram negative bacteria (71.8 %). The most common agent of infection was *Escherichia coli*,[3] and *Enterobactericeae*,[4] respectively. However, some studies reported higher incidence of gram-positive bacteria and decreased incidence of gram-negative bacteria as a causative pathogen in febrile neutropenia.[5-8] The predominant gram-negative bacteremia as causative pathogens of febrile neutropenia in our series, might be attributed to lesser use of central line and prophylactic antibiotics. In addition, the patients in our study were not hematologic malignancy patients.

Neutropenic patients often fail to develop characteristic signs and symptoms of infection, since they are unable to mount an adequate inflammatory response.[9] In patients with neutropenic fever, inflammatory exudates such as sputum or urine may be devoid of neutrophils and they may contain only few lymphocytes and monocytes. Moreover, neutropenic patients who develop pneumonia may not have pulmonary infiltrates on routine chest roentgenograms. However, fever, dyspnea, and cough were still common presentations in neutroponic patients with pneumonia in our study; and this may be used as diagnostic clues for pneumonia in neutropenic patients. Interestingly, fever with chill was detected in only one-third of the neutropenic patients with urinary tract infection whereas fever and dysuria was more common presentation than half of the patients.

Usually, neutropenic patients do not form abscesses at the site of skin infection; rather they develop spreading cellulitis which is often associated with septicemia. Discharge was a common presentation (61.5 %) in our study where an erythema was seen; only 53.8 % of the neutropenic patients developed cellulitis. Gastrointestinal infection was not common in patients with febrile neutropenia (8.1 %). Often, neutropenic patients cannot mount on adequate inflammatory response, and therefore may have serious gastrointestinal complications such as peritonitis without significant symptom. In our series, most common presentations of gastrointestinal infection in febrile neutropenia were fever and acute diarrhea. Typhlitis or agranulocytic colitis is a disease that occurs in patients with neutropenia also presents with fever, abdominal pain and watery diarrhea as well as paralytic ileus.[10] However, none of our neutropenic patients developed necrotizing colitis.

Patients with neutropenic fever are associated with significant morbidity and mortality. Mortality rates ranged from 4-30 % in different studies.[11-13] Mortality rate of neutropenic fever in patients with non-hematogic malignancy in our study was 17 %, whereas other studies in Thailand reported mortality rates of 20 %.[3,14] Mortality risk analysis revealed three important prognostic factors: hypotension at presentation, poor performance status, and steroid treatment. Prompt intensive therapy and close monitoring are recommended for these patients.

The need for prompt institution of therapy is due to serious complications from febrile neutropenia especially those with the afore-mentioned prognostic factors. Empirical therapy for febrile neutropenic patients should be prompt. Empirical broad spectrum

bactericidal antimicrobial therapy should be given in full dosage to achieve maximal efficacy.[15] Primary prophylaxis of chemotherapy-associated febrile neutropenia with granulocyte colony-stimulating factor G-CSF has previously been reported to effectively abolish granulocytopenia in cancer patients receiving systemic chemotherapy.[16,17] G-CSF has been recommended for primary prophylaxis for myelosuppressive chemotherapy regimen with more than 40 % incidence of severe granulocytopenia.[18] However, G-CSF should not be used routinely in patients with febrile neutropenia or uncomplicated neutropenic fever.[19] The use of G-CSF in our study did not improve the outcome of the treatment in patients with neutropenic fever when analyzed as a prognostic variable.

In conclusion, one hundred patients with non-hematologic malignancy who developed 123 episodes of febrile neutropenia treated at King Chulalongkorn Memorial Hospital. Fever from documented infection was 39.8 % and pneumonitis was the most common cause of infection in 12.2 %. Hemoculture was positive in 26 % and the most common causative pathogen was Klebsiella. Mortality rate was 17 % and mortality risk factors were hypotension at presentation, poor performance status, and steroid treatment.

Achnowledgement

We would like to thank our former research nurse, Miss Nuchara Nithipaijit, for her assistance in data collection in this study, and Miss Tawita Thetiworapong for preparation of the manuscript.

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