Incidence and Outcomes of Febrile Neutropenia in Pediatric Cancer Patients: A Retrospective Descriptive Study

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Abstract

Background: Febrile neutropenia is the most common life-threatening complication of pediatric cancer patients. Early diagnosis and empirical antibiotic administration especially within 60 minutes improve outcomes and reduce mortality from febrile neutropenia.

Objective: To investigate on the incidence rate of febrile neutropenia, time to antibiotic, and outcomes of patients.

Study design: A retrospective descriptive study

Material and methods: Pediatric cancer patients less than 15 years of age who were diagnosed with febrile neutropenia in Pediatric Department, Bhumibol Adulyadej Hospital between 1st January 2012 and 31st December 2018 were reviewed and analyzed. The protocol was approved by the ethic review committee.

Results: There were fifty-four patients with 170 episodes of febrile neutropenia in this study. The incidence of febrile neutropenia was 5.58 per 1,000 days of chemotherapy. The most common underlying disease was acute lymphoblastic leukemia (68.2%). Time to antibiotic within 60 minutes was reported in 39 episodes (22.9%). The mortality rate was 24%. The length of hospital stays and mortality rate of patients who had time to antibiotic less than 60 minutes was not statistically different than those who had time to antibiotic more than 60 minutes (p-value = 0.33).

Conclusions: The incidence of febrile neutropenia was 5.58 per 1,000 days of chemotherapy. Knowledge of the local distribution of pathogens and their susceptibility patterns and prompt initiation of effective antimicrobial treatment are essential in febrile neutropenia patients.

Keyword: Incidence, Febrile neutropenia, Pediatric cancer, Antibiotic, Outcome

Introduction

Despite being an uncommon disease in pediatric, an estimated of over 360,000 total childhood cancers occurring worldwide; 54% in Asia and 28% in Africa[1]. The incidence was around 187 per 1 million in children age below 19 year-old[2]. In Thailand, the incidence of cancer was around 75 per 1 million[3]. The majority of pediatric malignancies were hematologic malignancies including acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), lymphoma and non-hematologic malignancies such as neoplasm of the central nervous system. The treatment of malignancies varied from medical to surgical management depending on the site of neoplasm. Child patients suffered from hematologic malignancy. The adjuvant treatment was mainly focused on chemotherapy. Though

yielding a good prognosis of treatment, the chemotherapy has main side effects of suppressing blood components mainly anemia, leukopenia, and thrombocytopenia that leading to infection and other complications in patients[4].

Febrile neutropenia (FN) is the most common complication of patients with chemotherapy. FN is defined as a single oral temperature measurement of higher than 38.3 °C or more than 38 °C for two consecutive times in 1-hour interval, with absolute neutrophil count (ANC) less than 500 cells/mm^3 or less than 1,000 cells/mm^3 with the tendency of decreasing in the future[5]. Anusha et.al. reported incidence of pediatric FN was 12.9 to 18.1 per 100,000 population in United States[6]. Wasithep et. al. reported incidence of FN in adult patients was 24.8 per 1,000 days of chemotherapy per year in Thailand[7]. There were few studies on incidence of pediatric FN in Thailand. Empirical antibiotic therapy had been shown to be beneficial and decrease mortality rate[8]. The American Society of Clinical Oncology (ASCO) recommended antipseudomonal β-lactam antimicrobial agents as empiric therapy in FN patients[9]. Time to antibiotic more than 60 minutes was associated with complications and decrease survival[10]. Previous study reported mortality rate of pediatric FN was 1.0 to 18.2% in Thailand[3,11-12].

Therefore, we conducted this study to determine the incidence rate of FN, time to antibiotic, and outcomes of cancer patients.

Material and method

Pediatric cancer patients less than 15 years of age who were diagnosed with FN in Pediatric Department, Bhumibol Adulyadej Hospital (BAH) between 1st January 2012 and 31st December 2018 were reviewed and analyzed. The retrospective study was approved by the ethic committee (IRB no. 51/62).

All pediatric cancer patients less than 15 years of age who were diagnosed with FN by a pediatrician, and admitted at the inpatient ward BAH between 1st January 2012 and 31st December 2018 were enrolled. Exclusion criteria any cases with incomplete data.

The international statistical classification of diseases and related health problems (ICD-10) and hematologic chart were reviewed. Positive diagnosis in ICD-10 chosen included agranulocytosis, ALL, AML, and chemotherapy. Patient's record forms were used to record demographic data of all patients, including gender, age, underlying diseases, type of chemotherapy, type and duration of antibiotic, time to antibiotic, laboratory included complete blood count (CBC) and urinary analysis (UA), pathogens and source of infection, length of hospital stay, and outcomes of the patients[11].

Definition of time to antibiotic was duration between time of diagnosis FN and time of patients receiving antimicrobial agents. High-risk patients were patients who had absolute neutrophil count (ANC) less than 100 cells/mm^3 or had signs and symptoms of septic shock, including agitation, confusion, poor tissue perfusion, hypotension, and acute respiratory distress syndrome (ARDS)[13]. Low-risk patients were patients who had AND more than 100 cells/mm^3 and no complications.

The number of cases was 195 with is based on a similar study in Thailand[3]. Sample size calculation was chosen according to Noordzij's work[14].

Data were analyzed by statistical package for the social sciences (SPSS) version 27. Descriptive statistics was used for the general characteristic of sample groups, namely frequency, percentage, mean, and standard deviation. Chi-square test was applied to analyze the association of time to antibiotic with length of hospital stay and mortality rate. The significantly statistical analysis was set at *p*-value less than 0.05.

Results

Fifty-four patients experienced 170 episodes of FN in 30, 451 days of chemotherapy. The incidence of FN was 5.58 per 1,000 days of chemotherapy. Male was 61.1%. Mean age was 7.1 ± 4.5 year-old. Median age was 1.8 to 10.8-year-old. One hundred forty-eight episodes (87%) occurred in patients with hematologic malignancies. The most common type of pediatric

malignancy in the present study was ALL (68.2%). Mean of initial ANC was 142 ± 175.5 cells/mm^3. Mean of duration after chemotherapy was 8.8 ± 6.1 days. Demographic data and clinical characteristics of FN patients were shown in Table 1.

Table1: Demographic data and clinical characteristics of patients with febrile neutropenia.

Characteristics and parameters	n (%)
Gender	
Male	33(61.1)
Female	21(38.9)
Age(years)*	7.1±4.5
Type of cancer*	
ALL	116(68.2)
AML	24(14.1)
Rhabdomyosarcoma	6(3.5)
Ewing sarcoma	6(3.5)
JMMoL	5(2.9)
Neuroblastoma	4(2.4)
Osteosarcoma	3(1.8)
HLH	2(1.2)
Brain tumor	2(1.2)
Others[a]	2(1.2)
Complete blood count*	
Hematocrit(%)	24.5±5.2
WBC(cells/mm3)	987.5±1,422.2
ANC (cells/mm3)	142.0±175.5
Platelets(cells/mm3)	80,020.6±87,883.9
Duration after last chemotherapy(days)	8.8±6.1

*mean±standard deviation, [a] Synovial sarcoma and Burkitt's lymphoma, ALL: Acute lymphoblastic leukemia, AML: Acute myeloblastic leukemia, JMMoL: Juvenile myelomonocytic leukemia, HLH: Hemophagocytic lymphohistiocytosis, WBC: White blood cell, ANC: Absolute neutrophil count

The most common cause of fever was unknown (45.3%). Clinically documented infection was found in 54.7% including septicemia (29.1%), respiratory tract infection (25.6%), urinary tract infection (23.9%), and gastrointestinal infection (15.4%). Microbiologically documented infection was diagnosed in gram-negative bacteria (69.0%), gram-positive bacteria (28.6%), and fungus (2.4%). Three of the most common causative pathogens of septicemia were *Escherichia coli* (24.4%), *Klebsiella pneumoniae* (19.5%), and *Acinetobacter baumanii* (14.6%). The most common regimen of initial antibiotics was combination of ceftazidime plus amikacin. This regimen was the first choice of antibiotic prescription in low-risk patients. Time to antibiotic within 60 minutes was reported in 39 episodes (22.9%). More than half of the patients (53.5%) received empirical antibiotics within 120 minutes. (shown in Table 2 and Figure 1)

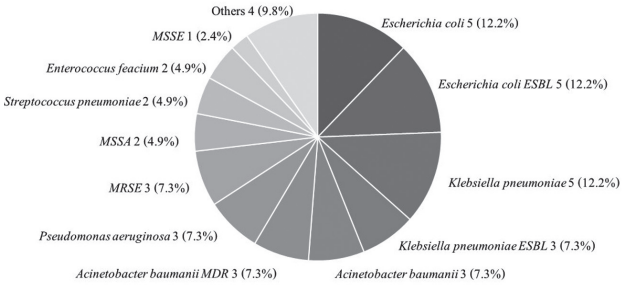

Figure 1 Type of bacterial infection in febrile neutropenia patients

ESBL: Extended spectrum beta-lactamase, MDR: Multidrug-resistant, MRSE: Methicillin-resistant Staphylococcus epidermidis, MSSA: Methicillin-sensitive Staphylococcus aureus, MSSE: Methicillin-sensitive Staphylococcis epidermidis

Table2: Sources of infection, causative agents and initial antibiotic used in febrile neutropenia patients (n=170)

Characteristics of infection	Frequency (%)
Sources of infection [a]	
Unidentified	77(45.3)
Septicemia	34(29.1)
Respiratory tract infection	30(25.6)
Urinary tract infection	28(23.9)
Gastrointestinal infection	18(15.4)
Others	7(6.0)
No growth hemoculture	136(80.0)
Organism of hemoculture [b]	34(20.0)
Gram positive	12(28.6)
Gram negative	29(69.0)
Fungus	1(2.4)
Initial antibiotics	
Ceftazidime + Amikacin	152(87.8)
Piperacillin/Tazobactam	9(5.2)
Meropenem	6(3.5)
Others	6(3.5)
Time to antibiotic (min)	
≤60	39(22.9)
61-120	52(30.6)
>120	79(46.5)
Duration of antibiotic (days)*	10.5±6.6

*mean± standard deviation, [a] some patients have ≥ 1 source of infection, [b] some patients have ≥ 1 organisms

Antibiotic susceptibility of gram-negative pathogens was shown in Table 3. Five episodes of *Extended spectrum beta-lactamase (ESBL)-producing Escherichia coli* (50% of *Escherichia spp.)* and 3 episodes of *ESBL-producing Klebsiella pneumoniae* (37.5% of *Klebsiella spp.)* were found. Three episodes of *Acinetobacter baumanii* resisted to Ceftazidime, Amikacin, Piperacillin/Tazobactam, and Meropenem. All patients who infected with *MDR-Acinetobacter baumanii* died.

The length of hospital stay and mortality rate of FN patients for different time to antibiotics were shown in Table 4. Mean of length of hospital stay of patients who had time to antibiotic less than 60 minutes was 21.5 ± 16.8 days and those who had time to antibiotic more than 60 minutes was 18.5 ± 16.7 days. There was no statistically significant different (p-value = 0.33). The mortality rate in the present study was 24% (13 patients). Mortality rate of patients who had time to antibiotic less than 60 minutes and those who had time to antibiotic more than 60 minutes were 12.8% (5 patients) and 6.5% (8 patients), respectively. There was not statistically significant different between two groups (p-value = 0.16).

Table 3: Antibiotic susceptibility of gram-negative pathogens

Pathogens	Drug sensitivity			
	Ceftazidime	Amikacin	Piperacillin/ Tazobactam	Meropenem
E. coli (n=10)	5	10	9	10
K. pneumoniae (n=8)	5	7	6	8
A. baumanii (n=6)	3	3	3	3
P. aeruginosa (n=3)	3	3	3	3

*E. coli: Escherichia coli, K. pneumoniae: Klebsiella pneumoniae, A. baumanii: Acinetobacter baumanii, P. aeruginosa: Pseudomonas aeruginos*a

Table 4: The outcomes of febrile neutropenia patients for different time to antibiotics (n=170)

	Time to antibiotic (min)		*p*-value
	≤60	>60	
Length of stay (days)**	21.5±16.8	18.5±16.7	0.33
Death*	5(12.8)	8(6.5)	0.16

*n(%),**mean±standard deviation

Discussion

FN is a medical emergency, and patients suspected to have an FN should be treated with empiric, broad-spectrum antibiotics immediately after collecting a culture sample.

The incidence rate of FN in this study was 5.58 per 1,000 days of chemotherapy in comparison with Wasithep's study which reported an incidence rate of 24.8 per 1,000 days of chemotherapy[3]. As adults may have other medical conditions, such as diabetes, chronic kidney disease, they were a higher risk of infection more than children. We had a limitation on studies in Thailand were small and few researches were released to determine incidence of pediatric FN.

Hematologic malignancy was found to be the most common type of cancer (87%), consisting of ALL (68.2%), AML (14.1%), juvenile myelomonocytic leukemia (JMMoL) (2.9%), hemophagocytic lymphohistiocytosis (HLH) (1.2%), and burkitt's lymphoma (0.6%). These results were similar to those reported by Chanchai et.al., in which the most frequent type of cancer was also hematologic malignancy (91.7%), consisting of ALL (66.7%), AML (21.7%), and lymphoma (3.3%)[11]. Therefore, hematologic malignancy had a higher risk factor of FN than non-hematologic malignancy.

Infection was the most common complication, that cause of increase mortality in pediatric cancer patients with FN. Gram-negative bacteria was the most common pathogen in this study (69%). *Escherichia coli* represented the most common species (mean frequency of isolation 24.4%), followed by *Klebsiella pneumoniae* (19.5%), and *Acinetobacter baumanii* (14.6%). An increasing of multidrug-resistant *A. baumanii* was also reported. These results were similar to those reported by Chanchai et.al. that gram-negative bacteria was the most common pathogen (42.2%), consisting of *Pseudomonas aeruginosa* and *Escherichia col*[12].

American Society of Clinical Oncology (ASCO) guideline recommended anti-pseudomonal antimicrobial agents for initial treatment in FN patients[15]. According to hospital protocol of FN for low-risk patients includes combination therapy with ceftazidime and amikacin was the first line treatment. For FN cases who were in septic shock status, meropenem was an initial treatment. The decision to add vancomycin should be discussed with the Infectious Disease specialist. Sanpakit and colleagues reported meropenem plus aminoglycoside used in a high-risk group remarked in shock, hypotension, poor tissue perfusion, ARDS, and sepsis. In the low-risk group, Piperacillin/Tazobactam or 4th generation cephalosporin were prescribed[13].

Matthew et.al. reported 20% of FN patients received antibiotics after diagnosis within 60 minutes[16]. The finding from the present study supported Matthew's work. Some patients experienced prolonged time to start antibiotics after diagnosis due to a long period of transfer from the out-patient department to the in-patient department. Therefore, our setting should revise protocols for shortening time to antibiotic and transfer period.

Chanchai et.al. reported a mortality rate of 18.8%[12]. In this study, the mortality rate of patients with FN was 24% (13 patients). Five dead cases from 13 cases were classified in FN patients who received antibiotics administration within 60 minutes. One patient died from *MDR-Acinetobacter baumanii* septicemia. Two patients died from *ESBL-producing* gram-negative septicemia, that delayed carbapenem administration. One patient died from invasive fungal infection. And the last one died from intracerebral hemorrhage as a result of complication of underlying disease.

In this study, length of hospital stay and mortality rate were not statistically significant different between patients who had time to antibiotic less than 60 minutes and more than 60 minutes because limitation of small size of population.

The mortality of FN patients can be impacted by several factors, including severity of underlying disease, host factor, virulent of pathogens and treatment failure[3]. In the recent years, multidrug resistant gram-negative bacteria have emerged as important pathogens and a serious challenge in the treatment of neutropenic patients. In addition, antimicrobial resistance and inappropriate empirical antibiotic treatment have been linked to a worse outcome in cancer

patients. The identification of a specific gap between the institutional guidelines for FN management and current practice will facilitate updating currently available hospital guidelines. According to our study, we need to adjust the FN clinical practice guideline depending on recent hospital antibiograms and microbial sensitivity to guide empiric antibiotic treatment. Increased rates of multidrug-resistance gram-negative strains have been highlighted among Enterobacteriaceae and nonfermenting gram-negative rods, discontinuation of ceftazidime for empiric therapy FN patients should be reviewed. The limitation of our study are small size of population and conducted in single cancer center.

Conclusion

In conclusion, this retrospective study demonstrated the incidence of FN in pediatric patients with cancer. The incidence of FN was 5.58 per 1,000 days of chemotherapy. Twenty-three percent of patients received antibiotics within 60 minutes. The mortality rate was 24%, with gram negative septicemia being the most common cause of death. Multidrug resistant gram-negative rods have emerged as important pathogens and demonstrate a worse outcome. Knowledge of the local distribution of pathogens and their susceptibility patterns and prompt initiation of effective antimicrobial treatment are essential in FN patients.

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Conflict of interest

The authors declare no conflict of interest

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อุบัติการณ์และผลการรักษาภาวะไข้ในผู้ป่วยเด็กโรคมะเร็งที่มีระดับเม็ดเลือดขาวนิวโทรฟิลต่ำ

วันทิพย์ แสงธรรมวรคุณ, สุรกานต์ เจนสัจวรรณ์, ศิริพร ผ่องจิตสิริ, ณัฐพรทิรา ผลากรกุล

ความเป็นมา: ภาวะไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำเป็นภาวะแทรกซ้อนที่รุนแรงในผู้ป่วยเด็กโรคมะเร็งที่ได้รับการรักษาด้วยยาเคมีบำบัด การวินิจฉัยและให้ยาปฏิชีวนะที่รวดเร็วภายใน 60 นาที สามารถทำให้ผลการรักษาดีขึ้นและลดอัตราตายได้

วัตถุประสงค์: เพื่อศึกษาอุบัติการณ์, ระยะเวลาที่ได้รับยาปฏิชีวนะและผลการรักษาของภาวะไข้ในผู้ป่วยเด็กโรคมะเร็งที่มีระดับเม็ดเลือดขาวนิวโทรฟิลต่ำ

วิธีการศึกษา: ทำการศึกษาย้อนหลังเชิงพรรณนา ในผู้ป่วยเด็กโรคมะเร็งที่มีอายุต่ำกว่า 15 ปี ซึ่งได้รับการวินิจฉัยภาวะไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำ และรับการรักษาที่โรงพยาบาลภูมิพลอดุลยเดช กรมแพทย์ทหารอากาศ ตั้งแต่ 1 มกราคม 2555 ถึง 31 ธันวาคม 2561

ผลการศึกษา: พบผู้ป่วยเด็กโรคมะเร็งที่ได้รับการวินิจฉัยภาวะไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำ 170 ครั้ง จากผู้ป่วยจำนวน 54 คน อุบัติการณ์ของภาวะไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำเท่ากับ 5.58 ครั้งต่อ 1,000 วันที่ได้รับยาเคมีบำบัด โดยส่วนใหญ่พบผู้ป่วยโรคมะเร็งเม็ดเลือดขาวชนิด Acute lymphoblastic leukemia (ALL) มากที่สุด (68.2%) มีผู้ป่วยได้รับยาปฏิชีวนะภายใน 60 นาที 39 ครั้ง (22.9%) พบอัตราตาย 24% เมื่อเปรียบเทียบระหว่างระยะเวลาการนอนโรงพยาบาลและอัตราตายของผู้ป่วย กับการได้รับยาปฏิชีวนะภายใน 60 นาที และมากกว่า 60 นาที พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p-value = 0.33)

สรุป: พบอุบัติการณ์ของภาวะไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำเท่ากับ 5.58 ครั้งต่อ 1,000 วันที่ได้รับยาเคมีบำบัด การรู้จักเชื้อก่อโรคประจำถิ่นและการรักษาด้วยยาปฏิชีวนะที่รวดเร็วเป็นสิ่งสำคัญในผู้ป่วยที่มีภาวะไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำ[1]

คำสำคัญ: อุบัติการณ์, ภาวะไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำ, โรคมะเร็งในเด็ก, ยาปฏิชีวนะ, ผลการรักษา

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