Effect of Febrile Neutropenia Guideline's Implementation on Death Rate in Dharmais Cancer Center Hospital

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ABSTRACT

Febrile neutropenia may have a high morbidity and mortality impact for the patient. The death rate of febrile neutropenia in 2002 was 38.8%, while in 2009 was 27.3%. The difference in mortality rates could caused by several factors such as availability of the Neutropenic Fever Management Guidelines in 2006, in addition to infrastructure, human resources and equipment. This study aims to determine the effect of the availability of the guideline and other factors to cancer mortality rate in the compromised immune isolation room of Dharmais Hospital. This study is a cross-sectional retrospective study which investigate mortality rates and compare with adherence to febrile neutropenia guidelines for the period 2008-2012. Data were taken from the patient's medical record file, then analyzed using univariate and bivariate analysis. The mortality rate in the period 2008-2012 was 20,7%. The effect of age, sex, and degree of risk factor on mortality was not significantly different (p=0,409, p=0,404, and p=0,324). The proportion of deaths was higher in patients borne by third parties (26.8%) than in the case of personal (10%) although not statistically significant (p=0,065). Of the three types of adherence, only one had a significant effect of adherence to treatment flow (p=0,033).

Keywords*: guidelines of febrile neutropenia; compromised immune isolation room; mortality rate.*

INTRODUCTION

Febrile neutropenia (FN) is defined as an oral temperature >38.5ºC or two consecutive readings of >38.0ºC for 2 hours and an absolute neutrophil count <0.5x10^9/l, or expected to fall below 0.5x10^9/l).[1] Febrile neutropenia is a common complication in cancer patients who are undergoing treatment and may have impacts on morbidity and mortality.[1-3] Rates of neutropenia who receive chemotherapy for solid tumors was 5-10%, whereas patients with hematological malignancy have rates more than 20%, and incidence in patients who have bone marrow transplant was 70-100%.[4] Dharmais Hospital National Cancer Center, Jakarta recorded febrile neutropenia death rate in 1999, 2000, and 2002 in a row was 12,5%, 22,5%, and 38,8%. While in Indonesia, there is no national data about the magnitude of neutropenic febrile death rate.

Mortality rate due to neutropenic fever is increasing, except in 2009, there was a considerable decrease in mortality rate. From 38,8% in 2002 became 27,3% in 2009. The difference in mortality rate may be due to several factors, including the availability of guideline on neutropenic fever in 2006, in addition to infrastructure, human resources, equipment, and systems.

The current management of neutropenia includes modification of chemotherapy doses, prolonged dose interval, and primary prophylaxis with recombinant G-CFS.[7] Guidelines of FN in cancer patients itself aims to achieve the same perception and understanding of neutropenic fever management in Indonesia; more effective, safe, efficient and rational use of antibiotics; avoid accelerated antibiotic resistance; and obtain empirical data that can be continuously updated.[6]

The more detail clarification and evaluation about guidelines of febrile neutropenia management in isolation room, Dharmais Hospital National Cancer Center which was enforced since 2006 is required. This evaluation should have an outcome in mortality rate and factors that influence. A clinical audit of this management guidelines has not been done. The aim of this study is to obtain the effects availability of guideline management and other factors in mortality rate of on neutropenic fever patients in Dharmais Hospital National Cancer Center in the year 2008-2012.

RESEARCH METHODOLOGY

This is a retrospective, *cross-sectional* study using secondary data from Dharmais Hospital National Cancer Center in the period between 2008-2012. The data were obtained from the medical records. Subjects are all of patients who were diagnosed febrile neutropenia in Dharmais Hospital National Cancer Center.

Inclusion criteria for subjects are treated in isolation room, fever (axillary temperature $\geq 38^0$C at two measurements within an hour or more for solid tumor, $\geq 37,5^0$C for hematologic cancer, or $\geq 38,3^0$C at first measurement and no signs of non-infection), neutropenia (neutrophils <500 cells/mm^3 or <1000 cells/mm^3 with downward trend towards 500 cells/mm^3 in next two days). While exclusion criteria of this study are incomplete data, both related to recording in medical record or loss of data in the medical record. Data of patients who met inclusion and exclusion criteria were collected and then tabulated. While the data of patients' compliance was done scoring to perform statistical analysis.

The variables seen in this study were medication flow adherence, medication principal adherence, initiation or termination of medication, age, gender, degree of neutropenic fever, and cost capability. All of these factors were associated with mortality rate.

Ethical Approval

This study used patients' medical record data retrospectively and did not intervene the patient. This study was unrelated to patient safety and did not require informed consent. Ethics in this study includes respecting subject's privacy by not displaying identity, either name or origin address of subjects and using initials as substitution of identity.

RESULTS AND DISCUSSION

Data which obtained through patient registration in isolation room of immunity decreased throughout 2008-2012 were 212. Data which did not meet fever criteria was 43 cases, neutropenia criteria were 2 cases, and incomplete data were 56 cases. So total data that could be processed was 111 cases.

Characteristics of Subject's Demography

The mean of age was 37,8 years old with deviation standard 13,8. The youngest was 13 and the oldest was 70. Then subjects were divided into two groups. Younger patients (13-38) was 58 patients (52,3%) and the rest (47,7%) were over 38 years old. In this study, men (57,7%) are more likely to have neutropenic fever than women (42,3%). Neutropenic fever patients which have the third party as person in charge were 64%. The guarantors as the third party include Jaminan Perusahaan, Asuransi, Askes, Jamkesda, and Jamkesmas. Based on the degree of risk factor, high risk became the most commonly obtained. The degree of risk factor was based on Guideline of FN Management (show in table 1).

Characteristics of Physician Compliance on Guideline of Neutropenic Fever Management

Physician compliance of management algorithm was based on Guideline of FN Management that includes 5 parameters: (1) empirical antibiotics utilization at the start of treatment according to degree of risk, (2) replace the type of antibiotic in case of worsening after 72 hours, (3) Did examination for reevaluation after 72 hours, (4) provide anti-fungal drugs according to degree of risk, (5) discontinue antibiotic/anti-fungal treatment according to degree of risk.

While parameter of physician compliance on treatment principal, there are (1) start antibiotic as soon as possible, (2) empirical according to guideline, (3) utilization of

bactericidal antibiotic, not bacteriostatic, and (4) utilization of broad-spectrum antibiotic. Both groups of parameter were scored, 0 (zero) is not appropriate and 5 (five) if appropriate. Categorized obedient if the total score is ≥15.

Doctors who adhere to the management algorithm (67,6%) are more than those who do not (32,4%). As well as management algorithm, doctors who adhere to treatment principal (81,1%) were are more than those who do not (18,9%) (Table 2).
For the starting treatment criteria, the parameter used started at <24 hours are obedient and started at >24 hours are disobedient. Doctors who adhere to starting treatment (81,1%) were are more than those who do not (18,9%) (show in table 2).

Number of Cases

Life cases (79,3%) were more than death cases (20,7%). This data showed that the number of death cases in Dharmais Cancer Hospital at the period 2008-2012 was 20,7%.

Data Analysis

This study found that adherence to management algorithm had a significant effect on death rate compared with disobedient. Death rate in obedient was 15,5% and disobedient was 37% (p=0,033). While the adherence to treatment principle and starting treatment had no significant effect on death rate of neutropenic fever (respectively, p=0,556 and p=0,556) (show in table 3).

Other factors that were seen in this study were age, gender, a person in charge, and degree of risk. All of this factors had no significant effect in neutropenic fever death rate (p>0,05) (show in table 4).

Data that could be processed from isolation room during the period 2008-2012 was 111 data (52,35%). Data that could not be processed was caused by did not meet the criteria for neutropenic fever (21,2%) and data was incomplete (26,45%). This problem occurred due to medical record document that in the 10 years period is not used anymore, considered to be inactive and will be transferred to the warehouse. In addition, a neutropenic fever diagnosis was rarely written as a diagnosis, both primary or secondary diagnose in the medical record.
Clinical guidelines are essential if problems are frequent or costly, there is wide variation in management practices and there is sufficient scientific evidence for optimal implementation. Guideline of neutropenic fever management qualified as a good clinical guide and can be implemented because it meets most of prescribed requirements, ie certified areas which clinically important, based on *Randomized Controlled Trials*, the intended target is very clear, easy to understand, supported by resources and as a tool for clinical staff to provide the best service to the patient. The three unfulfilled items of this guideline have measured the improvements, keeping updated, and rewarding.

The Death rate in isolation room at the period after the availability of neutropenic fever guideline is better (20,7%) than previous, ie in 2000 (22,5%) and 2002 (38,8%). Although this number is still higher compared with Europe and America. The mortality rate becomes very important related to service quality. Based on Health Department of Indonesia, one of the indicators in hospital service quality assessment is Gross Death Rate (GDR). GDR is whole of mortality rate that occurred both before and after 48 hours compared to 1000 outpatients.

Although the death rate was higher in older age and women, statistically age and gender differences did not significantly affect neutropenic fever death rate (p=0,409 and p=0,404). Whether it is related to physical and emotional condition still needs to be proven.[9] Age, gender, and type of chemotherapy actually are marginally significant's factors.

The proportion of death cases was higher in patients who bear a third party (26,8%) than personal (10%), although not statistically significant (p=0,065). This is caused by a third party did not fully warrant the cost. They used cost-sharing system, so patients with financial constraints would face treatment problems, such as the selection of antibiotics and other unaccounted examinations.

In terms of degree of risk factors, the mortality rate was higher in high-risk (22,3%) than moderate (0%) or low (0%), although not statistically significant. It could be

understood because most cases which treated in isolation room was acute leukemia (90%). High frequency of mortality rate in high-risk may be due to the availability of some equipment, such as sterile rooms, human resources, and better service system including the availability of neutropenic fever guideline.

This study obtain adherence to management algorithm (33,3%) had a very significant effect on death rate compared to disobedient (p=14,7%) (p=0,043). The disobedient of doctors to the principle of treatment that caused mortality rate by 14,3% was due to delays in empiric antibiotics, non-bactericidal empirical, or narrow-spectrum antibiotics, and consent from the third party. Other possibilities were patients came on holiday so that constrained the problem of a person in charge agreement and the availability of antibiotic in pharmaceutical installation.

Although patients should receive their initial treatment within an hour of presentation to an emergency department, this goal is problematic for many reasons, such as clinical and administration. For example, patients must be properly evaluated with laboratory tests and radiographs to determine neutropenia and identify a possible source of infection.[10] Meisenberg B, et al showed the longest delayed treatment were a consequence of the conscious or functional decision to pause the delivery of antibiotics while awaiting transfer to an inpatient unit. This delayed treatment is a result of lack of appreciation for the pathophysiology of infection and potential sepsis.

To answer the objectives of this study, a multivariate analysis should be established. Because there was only one variable (adherence to management algorithm) that was significant, multivariate analysis was not done.

CONCLUSIONS AND RECOMMENDATIONS

The mortality rate of febrile neutropenia fever during 2008-2012 (20,7%) in isolation room, Dharmais Hospital was better than 2000 (22,5%) and 2002 (38,8%). The effect of age, sex, and degree of risk factors did not differ significantly to mortality (p=0,477, 0,404, 0,324). The proportion of mortality rates was higher in case with the third person in charge (26,8%) than private (10%) although statistically was not significant (p=0,065). From the three types of adherence, only adherence to the flow of treatment that had a significant effect on mortality rate (p=0,033). A significant in this case to stop antibiotic or antifungal treatment according to the degree of risk. This was caused by the doctors in charge in isolation room are consultant of hematology and medical oncology who had the competence, awareness, and understanding of the guideline.

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Table 1. Variable Characteristic Based on Age, Gender, A Person In Charge

Variable	Frequency	Percentage
Group of age:		
13-38 years old	58	52,3
>38 years old	53	47,7
Gender:		
Men	47	42,3
Women	64	57,7
Person in charge		
Personal	40	36
Third party	71	64
The degree of risk factor		
Low	5	4,5
Moderate	3	2,7
High	103	92,8

Table 2. Variable of Physician Compliance to Guideline of Neutropenic Fever Management

Variable of compliance	Frequency (n)	Percentage (%)
Management algorithm		
Obedient	75	67,6
Disobedient	36	32,4
Treatment principal		
Obedient	90	81,1
Disobedient	21	18,9
Starting treatment		
Obedient	90	81,1
Disobedient	21	18,9

Table 3. Relationship between Adherence to Guideline of Neutropenic Fever Management and Death Rate

Variable of compliance	Number of life N (%)	Number of death N (%)	P value
Management algorithm			
Obedient	71 (84,5)	13 (15,5)	0,033*
Disobedient	17 (63,0)	10 (37,0)	
Treatment principal			
Obedient	70 (77,8)	20 (22,2)	0,556**
Disobedient	18 (85,7)	3 (14,3)	
Starting treatment			
Obedient	70 (77,8)	20 (22,2)	0,556*
Disobedient	18 (85,7)	3 (14,3)	

*Chi-Square Test
**Fisher's Exact Test

Table 4. Relationship between Other Factors and Death Rate

Variable	Number of life N (%)	Number of death N (%)	P value
Group of age:			
13-38 years old	48 (82,8)	10 (17,2)	0,477*
>38 years old	40 (75,5)	13 (24,5)	
Gender:			
Men	35 (74,5)	12 (25,5)	0,404*
Women	53 (82,8)	11 (17,2)	
Person in charge			
Personal	36 (90,0)	4 (10,0)	0,065*
Third party	52 (73,2)	19 (26,8)	
The degree of risk factor			
Low	5 (100)	0 (0)	0,324**
Moderate	3 (100)	0 (0)	
High	80 (77,7)	23 (22,3)	

*Chi Square Test
**Fisher's Exact Test