The Role of Prophylactic Antibiotics on ANC Value and Fever Duration in Cancer Patients with Post-Chemotherapy Neutropenia Fever

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Abstract. Chemotherapy has immunosuppressive side effects, one of which is neutropenia. In neutropenia, fever often occurs as a manifestation of infection. Antibiotics are given in neutropenia condition to prevent complication of infection. The aim of this study was to investigate the role of different prophylactic antibiotics on the increase of Absolute Neutrophil Count (ANC), duration of fever, and degree of improvement in ANC values in cancer patients with fever neutropenia. This study was an observational with quantitative descriptive analyses. Data were taken from medical records for the period January 2015 to December 2016. The sample size that met the inclusion criteria was 45 patients including 15 using ceftriaxone-gentamicin, 8 using ceftriaxone, 16 using ceftazidime-ciprofloxacin, and 6 using ceftazidime. The results showed a significant difference in the increase ANC values for different antibiotics (p = 0.001). However, the administration of different antibiotics did not provide a significant difference in the mean duration of fever (p = 0.341). Administration of different antibiotics was known to give a degree of improvement in the same ANC value (p = 0.711). The conclusion of this study was that the administration of different antibiotics in post-chemotherapy neutropenia fever patients has a significant influence on the ANC value where the type of antibiotic that has the highest influence is a combination of ceftazidime-ciprofloxacin. Keywords:ANC, Antibiotic, Cancer, Chemotherapy, Neutropenia Fever

1. Introduction
Neutropenia is one of the side effects of giving chemotherapy. After chemotherapy, hematology levels change every week, one of them is neutropenia. Neutropenia is a condition of the number of neutrophils in the blood less than 500/µL or less than 1000/µL with a tendency to decrease to 500/µL. Factors in the occurrence of neutropenia include disturbances in neutrophil formation, neutrophil distribution to tissues, increased consumption of neutrophils, and increased neutrophil damage to circulation.
Malignant cell infiltration and the myelosuppressive effects of chemotherapy are also one of the trigger factors for neutropenia. Through interference with Hexose Monophosphate Shunt activity, chemotherapy can reduce the ability of phagocytosis and bactericidal neutrophils [1].

Neutropenia fever is a fever that occurs in neutropenia with a body temperature of more than 38.3°C in one measurement or temperature increase > 38°C in two measurements in a 12 hour period or at least one hour of measurement on oral and axillary measurements [2]. Neutropenia fever is the most common complication in cancer patients who receive chemotherapy. This condition is a life-threatening condition with high mortality because it is susceptible to infection so that appropriate and efficient antibiotic therapy is needed to prevent the development of infection [3].

In Europe, with the right management guidelines for neutropenia fever produced a mortality rate due to neutropenia fever of 8.7% whereas in Indonesia, the reported mortality rate due to neutropenia fever is 12.5%-38.8%. This large difference in data is likely due to the fact that there are still no standard guidelines for diagnosis and management of neutropenia fever that are adapted to conditions and germ maps in Indonesia [1].

The management guidelines for neutropenia fever in Indonesia use the National Comprehensive Cancer Network (NCCN) guidelines, Clinical Practice Guideline for the Use of Antimicrobial Agent in Neutropenic Patients with Cancer, and Infectious Diseases Society of America (IDSA) guidelines. The guidelines recommend the use of ciprofloxacin and amoxicillin/clavulanic acid as empirical therapy in patients at low risk of infection. For second-line therapy, ciprofloxacin monotherapy or combination of ciprofloxacin and clindamycin can be chosen. Levofloxacin monotherapy can also be an alternative therapy of choice, but there is not enough data to support the efficacy of the use of levofloxacin. For patients with a high risk of infection, the recommended therapy is beta lactam (cefepime) or carbapenem (imipenem/cilastatin/tazobactam) [4].

The aim of this study was to determine the role of different antibiotics in increasing ANC values, duration of fever, and the degree of improvement in ANC values in cancer patients with neutropenia fever after chemotherapy.

2. Materials and Methods

This study was non-experimental with descriptive design. Retrieval of data was retrospective using secondary data in the form of medical records by purposive sampling. The number of samples that met the inclusion and exclusion criteria were 45 patients. Inclusion criteria included (a) male and female patients diagnosed with cancer with neutropenia fever; (b) cancer patients who have fever at the nadir of neutropenia which was 5-14 days after chemotherapy; (c) cancer patients with neutropenia fever who receive antibiotic therapy and Leukogen® as G-CSF; and (d) cancer patients with neutropenia fever who receive antipyretic therapy. The study was conducted in the Medical Record Room of Saiful Anwar General Hospital in Malang for the period of January 2015 to December 2016. This study has been stated as ethical conduct based on Ethical Clearance No. 400/05/K.3/302/2017 by the Saiful Anwar General Hospital Health Research Ethics Commission.

In this study we will observe the effect of antibiotic use on increasing ANC values, duration of fever, and degree of improvement in ANC values. ANC value data obtained from the calculation of the multiplication of leukocyte and neutrophil values. Then, the data were processed and analyzed by Kruskall Wallis to determine the difference in increasing ANC values. One Way ANOVA test to determine the difference in duration of fever. The Chi-Square combines cells test to determine differences in antibiotic use against the degree of improvement in ANC values. Data were statistically significant if the p value was < 0.05.

3. Results and Discussion

3.1. Sample Distribution

From this study, there were 45 samples that met the inclusion and exclusion criteria. A total of 22 female patients (48.89%) and 23 male patients (51.11%). The age of patients varied, consisting of 20 children (44.44%) with ages 1-11 years, 3 early adolescents (6.67%) with ages 12-16 years, 5 late adolescents
(11.11%) with ages 17-25 years, 11 adults (24.44%) with ages 26-45 years, and 6 early elderly (13.33%) with ages 46-55 years. The frequency of the most types of cancer experienced by patients was AML (Acute Myeloid Leukemia) in 16 patients (35.56%). Meanwhile, the frequency of the fewest types of cancer was CML (Chronic Myeloid Leukemia), skin cancer, and bone cancer, respectively in 1 patient (2.22%).

3.2. Pattern of Use of Antibiotics
There are four types of antibiotics given to study subjects as a therapy for neutropenia fever, namely single therapy ceftriaxone and ceftazidime as well as combination therapy of ceftazidime-ciprofloxacin and a combination of ceftriaxone-gentamicin. The number of patients receiving the ceftazidime-ciprofloxacin combination therapy regimen was 16 patients (35.56%), receiving a combination of ceftriaxone-gentamicin as many as 15 patient (33.33%), receiving single ceftriaxone therapy in 8 patients (17.78%), and received a single ceftazidime therapy in 6 patients (13.33%). The duration of antibiotic use ranges from 3-20 days.

### Table 1. Characteristics of Study Subjects.

| Patient Characteristics       | Number of Patients | Percentage (%) |
|-------------------------------|--------------------|----------------|
| **Gender**                    |                    |                |
| Male                          | 23                 | 51.11          |
| Female                        | 22                 | 48.89          |
| **Age**                       |                    |                |
| 1-11 years old (children)     | 20                 | 44.44          |
| 12-16 years (early adolescents)| 3                  | 6.67           |
| 17-25 years (late adolescents)| 5                  | 11.11          |
| 26-45 years (adults)          | 11                 | 24.44          |
| 46-55 years (early elderly)   | 6                  | 13.33          |
| **Duration of Neutropenia Fever** |                  |                |
| 1-2 days                      | 7                  | 15.56          |
| 3-4 days                      | 31                 | 68.88          |
| 5-6 days                      | 7                  | 15.56          |
| **Antibiotics Used**          |                    |                |
| ceftazidime-ciprofloxacin I.V | 16                 | 35.56          |
| ceftriaxone-gentamicin I.V    | 15                 | 33.33          |
| ceftriaxone I.V               | 8                  | 17.78          |
| ceftazidime I.V               | 6                  | 13.33          |

Notes:
I.V = intravenous

### 3.3. The Effect of Different Types of Antibiotics on Increasing ANC Value
The Kruskall-Wallis test was carried out between different antibiotics for increasing ANC values. From Table 2 it was known that the administration of different types of antibiotics gives a significant difference in the increase in ANC values (p = 0.001). Then, post hoc testing was performed using the Mann Whitney test (Table 3) and it was found that the group that experienced a significant difference was a combination of ceftriaxone-gentamicin with a combination of ceftazidime-ciprofloxacin; single ceftriaxone with a combination of ceftazidime-ciprofloxacin; single ceftriaxone with single ceftazidime; and a combination of ceftazidime-ciprofloxacin with a single ceftazidime.

Based on the results of the Kruskall Wallis test it was found that the average increase in the highest ANC value was indicated by a combination of ceftazidime-ciprofloxacin with a value of 34.00. This shows that the highest increase in ANC value occurs in a combination of ceftazidime-ciprofloxacin. Previous study has shown that 98% of patients showed improvement by ceftazidime-ciprofloxacin combination in patients with neutropenia fever, while the other 2% failed because of intolerant patients with a combination of these antibiotics. The combination of ceftazidime-ciprofloxacin shows good efficacy and tolerance as initiation therapy in patients with neutropenia and immunosuppressive. The
ceftazidime-ciprofloxacin combination regimen can replace the standard regimen namely a combination of antipseudomonal agents and aminoglycoside because the combination of ceftazidime-ciprofloxacin has no effect on nephrotoxicity and does not require monitoring of drug levels [6].

Table 2. Kruskall-Wallis Test Results for Increased ANC Value in Different Antibiotic Groups.

| Antibiotics                        | n  | Average ANC Value Increase | p   |
|------------------------------------|----|---------------------------|-----|
| ceftazidime-ciprofloxacin I.V      | 16 | 34.00                     | 0.001|
| ceftazidime I.V                    | 6  | 21.08                     |      |
| ceftriaxone-gentamicin I.V         | 15 | 18.37                     |      |
| ceftriaxone I.V                    | 8  | 11.13                     |      |
| **Total**                          | 45 |                           |      |

Table 3. Mann Whitney Test Results for ANC Value Increase.

| No. | Antibiotic Group             | n  | p   |
|-----|------------------------------|----|-----|
| 1.  | ceftriaxone-gentamicin       | 15 | 0.155|
|     | ceftriaxone                 | 8  |      |
| 2.  | ceftriaxone-gentamicin       | 15 | 0.001*|
|     | ceftazidime-ciprofloxacin   | 16 |      |
| 3.  | ceftriaxone-gentamicin       | 15 | 0.668|
|     | ceftazidime                 | 6  |      |
| 4.  | ceftriaxone                 | 8  | 0.001*|
|     | ceftazidime-ciprofloxacin   | 16 |      |
| 5.  | ceftriaxone                 | 8  | 0.039*|
|     | ceftazidime                 | 6  |      |
| 6.  | ceftazidime-ciprofloxacin   | 16 | 0.015*|
|     | ceftazidime                 | 6  |      |

Notes:
* Statistically significant because of p value < 0.05

3.4. The Effect of Different Types of Antibiotics on the Duration of Fever

One way ANOVA test was carried out to determine the difference in mean duration of fever in administration of different antibiotics. Table 4 shows that there was no significant difference in duration of fever in the administration of different antibiotic groups (p = 0.341). In addition, it was also known that the average duration of fever in each group was 3.9 days for the combination of ceftriaxone-gentamicin; 3.3 days for ceftazidime-ciprofloxacin combination; 3.2 days for single ceftriaxone; and 3 days for single ceftazidime. From the results of the study it was found that the highest average duration of fever was a combination of ceftriaxone-gentamicin which was equal to 3.9 days and the lowest average duration of fever was a single ceftazidime i.e. 3 days. This shows that giving different antibiotics does not provide a significant difference in the duration of fever experienced by patients. This condition was caused by all patients in this study getting antipyretic drugs during treatment with antibiotics. Therefore, giving different antibiotics does not have a significant effect on the duration of fever.

In this study the patients received antipyretics namely acetaminophen 3 x 500 mg if fever or metamizol 3 x 500 mg if fever. A study exhibits that acetamiophen and metamizol have similar efficacy as antipyretics and analgesics [8]. However, there are other studies which state that metamizol has a better effect as an antipyretic for children [9]. For this reason, antipyretic administration of neutropenia fever can be adjusted according to the age and condition of the patient to get better efficacy. However, statistically, the administration of different antibiotics does not have an effect on the difference in mean duration of fever.
Table 4. One Way ANOVA Test Results for Fever Duration in Different Antibiotic Groups.

| Antibiotics          | n  | Average ± s.d | p   |
|----------------------|----|---------------|-----|
| ceftriaxone-gentamicin| 15 | 3.9±1.33      | 0.341|
| ceftazidime-ciprofloxacin| 16 | 3.3±0.96      |     |
| ceftriaxone          | 8  | 3.2±1.58      |     |
| ceftazidime          | 6  | 3.0±0.89      |     |

3.5. The Effect of Different Types of Antibiotics on the Status of ANC Value Improvement

The data of this study did not meet the requirements for Chi-Square testing because there were more than 20% of cells that had an expected count below 5. Therefore, the alternative test was chosen, namely the Chi-Square test with cell merging. The cell-merging Chi-Square test was conducted to determine the association between administration of different types of antibiotics with the status of ANC value improvement. Improvement status of ANC values was divided into two categories, namely improvements with ANC values > 1000 U/µL and improvements with ANC values < 1000 U/µL. Table 5 showed that there was no difference between the administration of different types of antibiotics with improvement in ANC values. Thus, it can be seen that whatever type of antibiotic given was able to provide results of improvement in the value of ANC > 1000 U/µL.

Table 5. Chi-Square Cell Merging Test Results for Degree of Improvement of ANC Value at Different Antibiotic Groups.

| Degree of ANC Value Improvement* | > 1000 U/µL | < 1000 U/µL | P   |
|---------------------------------|------------|-------------|-----|
| n                               | %          | n           | %   |
| ceftriaxone-gentamicin + ceftriaxone | 19 | 42.22 | 4 | 8.89 | 0.722 |
| ceftazidime-ciprofloxacin + ceftazidime | 17 | 37.78 | 5 | 11.11 |     |
| **Total**                       | **36**     | **9**       | **20.00** |

Notes:
* Grouping based on the severity of neutropenia namely low-moderate neutropenia if ANC values > 1000 U/µL and severe neutropenia if the ANC value is < 1000 U/µL [5].

From the results of this study, the value of p = 0.711 means that there was no significant association between the administration of different types of antibiotics with the improvement in the ANC value. From these results it can be concluded that whatever type of antibiotic was given tends to give an improvement in the value of ANC > 1000 U/µL. These results indicate that any type of antibiotic given tends to give an improvement in the value of ANC > 1000 U/µL. From crosstable data before cell merging can be seen in column ANC value > 1000 U/µL, the biggest percentage within antibiotics was indicated by ceftazidime-ciprofloxacin combination that is equal to 93.8%. This means that 93.8% of 16 patients who received a combination of ceftazidime-ciprofloxacin experienced an improvement in the ANC value > 1000 U/µL. Therefore, from the four groups of antibiotics the highest percentage giving an improvement in the value of ANC > 1000 U/µL was a combination of ceftazidime-ciprofloxacin.

This was in line with the results of the analysis of the association of giving different types of antibiotics to increasing ANC values. The results of the analysis also showed that the highest increase in ANC values occurred in the ceftazidime-ciprofloxacin group. Although the use of prophylactic antibiotics in cancer patients with neutropenia fever was less in accordance with IDSA and NCCN guidelines, however, the antibiotics used in this study have a high effectiveness on increasing the ANC value of patients.

The combination of cephalosporin and quinolone group antibiotics has the ability to inhibit gram negative and gram positive bacterial activity. This is because third generation cephalosporins such as
Ceftazidime have effective antibacterial activity against gram negative bacteria. Meanwhile, quinolone group antibiotics such as ciprofloxacin besides being able to inhibit the growth of gram negative bacteria also have good activity in fighting gram-positive bacteria [10]. In a cost effective manner, the administration of antibiotics in combination with ceftazidime in the treatment of neutropenia fever requires a lower cost than the administration of ceftriaxone antibiotics [11].

From the three analyzes, it was known that administration of antibiotics in patients with neutropenia fever has an influence on increasing ANC values. Previous study has shown that antibiotics have a role in accelerating the maturation of neutrophils in the blood so that the expected ANC value increases and the body's immunity gets better. Moreover, antibiotics have a role in removing bacteria and reducing translocation and bacteremia so that the risk of infection also decreases [12]. Therefore, antibiotic therapy should be given to cancer patients with neutropenia fever to reduce mortality.

From the results of this study, researchers recommend the use of a ceftazidime-ciprofloxacin combination as prophylactic antibiotics in patients with neutropenia fever. This was because this combination of antibiotics showed the best increase in ANC value. Third-generation cephalosporin antibiotics such as ceftazidime active against Streptococci, Haemophilus influenza, Moraxella catarrhalis, and other gram-negative bacteria whereas quinolone group antibiotics such as ciprofloxacin also have activity against gram negative bacteria but also have activity against gram-positive bacteria. Ciprofloxacin is also known to be the most sensitive quinolone antibiotic against Pseudomonas aeruginosa [13].

The National Agency of Drug and Food Control explains that quinolone group antibiotics can cause arthropathy in the joints so that they should not be used in children and adolescents. The use of fluoroquinolones can also increase the risk of tendonitis and tendon rupture in all age ranges. This antibiotic also has side effects on the child's central nervous system, which can disrupt a child's psychology, memory loss, and concentration. Therefore, although a combination of ceftazidime-ciprofloxacin was known to have effectiveness in increasing high ANC values, but for children patients other antibiotics should be chosen. Based on the Kruskall-Wallis test, antibiotics that have the highest mean increase in ANC values sequentially after a combination of ceftazidime-ciprofloxacin were single ceftazidime, a combination of ceftriaxone-gentamicin, and single ceftriaxone. For this reason, a single ceftazidime therapy or a ceftriaxone-gentamicin combination can be selected in pediatric patients. However, gentamicin antibiotics are known to have a ototoxic and nephrotoxic effect. Nephrotoxic effects are reversible but the ototoxic effects are irreversible [14]. Therefore, in cancer patients who have previously experienced impaired kidney function and hearing loss it is better to choose antibiotics other than gentamicin.

4. Conclusion
The conclusion of this study was that the use of different types of antibiotics in neutropenia fever has a significant influence on the difference in increasing ANC values, where the type of antibiotic that produces the highest increase in ANC value was a combination of ceftazidime-ciprofloxacin. However, the use of different types of antibiotics did not have a significant effect on the duration of fever. All groups of antibiotics in this study provide similar effectiveness to the degree of improvement in ANC values, namely increasing the ANC value to > 1000 U/µL. Further study is needed regarding the molecular mechanism of the effect of antibiotic administration on increasing ANC values.

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