A Retrospective Study of Patients with Chemotherapy-induced Febrile Neutropenia in Jeddah Cancer Center - King Abdullah Medical City, Kingdom of Saudi Arabia.

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ABSTRACT

Introduction: Febrile neutropenia is an oncologic emergency. Delayed antibiotic administration in patients with febrile neutropenia may result in adverse outcomes. Febrile neutropenia (FN) has high mortality and requires prompt antibiotic therapy. There is a high risk for morbidity and mortality in immunocompromised patients with fever if antibiotics are not received in a timely manner.

Aim Of Study: The aim of this study was to determine and analyze retrospectively the number of patients admitted with chemotherapy induced febrile neutropenia and to determine the time taken from triage to administration of first dose of antibiotic in Jeddah Cancer Center - King Abdullah Medical City over a period of one year.

Key words: Neutropenia, G-CSF, gender, age, febrile neutropenia.

Patients And Methods: This is a retrospective study of patients with solid tumor and hematological malignancy admitted to Jeddah Cancer Center - King Abdullah Medical City in the period between December 2013 to December 2014 who were treated with chemotherapy and as a result became neutropenic.

Ethical approval was obtained from the institutional review board prior to the initiation of data collection.

Results: A total of 459 patients starting chemotherapy were analyzed. 10 patients were admitted with postchemotherapy febrile neutropenia.

Discussion: Prompt administration of antibiotics within one hour of admission is imperative for patients with cancer who have febrile neutropenia, a potentially life threatening complication. Patients with neutropenic fever have an increased risk to develop the same problem during subsequent therapy, secondary prophylactic G-CSF should be strongly considered for the support of subsequent treatment cycle.

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INTRODUCTION

Fever in the neutropenic cancer patient is considered a medical emergency. Febrile neutropenia is defined as single oral temperature of 38.3°C (101.4°F) or 38.0°C (101°F) over 1 hour with less than 500 neutrophils/mm3 or less than 1,000 neutrophils/mm3 with a predicted decline to 500/mm3 over the next 48 hours. Patients with febrile neutropenia (FN) typically have a temperature 38°C and an absolute neutrophil count (ANC) <500 cells/mm3 and are known to be at elevated risk for serious bacterial infection. Chemotherapy is the primary treatment for many different types of cancer, including solid cancers and hematologic malignancies. Chemotherapeutic agents lead to potentially life-threatening adverse events, including neutropenia, which results in impairment of the body's ability to combat infectious pathogens. Neutropenia and its subsequent infectious complications represent the most common dose-limiting toxicity of cancer chemotherapy. Febrile neutropenia (FN) occurs with common chemotherapy regimens in treatment-naive patients, and its severity depends on the dose intensity of the chemotherapy regimen, the patient's prior history of either radiation therapy or the use of cytotoxic treatment, and comorbidities. The occurrence of FN often causes subsequent chemotherapy delays or dose reductions. It may also lengthen hospital stay, increase monitoring, diagnostic and treatment costs, and reduce patient quality of life. Despite efforts to risk-stratify oncology patients with neutropenic fever at select tertiary care medical centers,¹⁻³ the majority of cancer patients with FN who present to an emergency department (ED) receive inpatient care for close monitoring, evaluation for identification of a source of infection, and empiric antibiotics. These patients may appear relatively stable in the ED but subsequently experience clinical deterioration after several hours or days. In these patients with febrile neutropenia, fever is the first signal of opportunistic infection. Febrile neutropenia often leads to hospitalization, the need for intravenous antibiotics, additional interventional care and further treatment in the outpatient setting.^{4, 5} This may result in chemotherapy dose delays or dose reductions, and interferes with the delivery of optimal treatment, adversely affecting patient outcomes, including survival. Mortality associated with febrile neutropenia in cancer patients ranges from 5-11% of the adult population.⁶⁻⁸

Several studies have described wait times for adult oncology patients presenting to emergency department with episodes of febrile neutropenia. One study identified a 107 minute median wait time from triage to the

antibiotic administration for adult patients presenting to the ED with an episode of febrile neutropenia.⁹ The median time to antibiotic administration was 5 hours in a prospective study which examined the time from presentation in the ED to antibiotic administration in patients with a presumptive serious infection in need of immediate empiric antibiotic therapy.¹⁰ Another study identified a 210 minute median wait time from triage to the antibiotic administration for adult patients presenting to the ED with an episode of febrile neutropenia.¹¹ Another retrospective cohort study identified median time from triage to antibiotic administration just over 5 hours (range: 1.23–22.8 hours) and only 4 patients (6%) were administered antibiotics within 2 hours of triage.¹²

PATIENTS AND METHODS

We conducted a retrospective study at Jeddah Cancer Center - King Abdullah Medical City. This is a tertiary care hospital having both hematology and medical oncology departments. All the data collected retrospectively from the patient files. For the purpose of this analysis, we selected all patients who received chemotherapy in the period between December 2013 to December 2014 (Table 1) and documented patients who were admitted with febrile neutropenia (Table 2).

All patients who received chemotherapy was explained what to do in case they develop fever after receiving chemotherapy. They were advised to report to accident & emergency department immediately in case of fever. Patients who were from far areas were given febrile neutropenia form and were advised to report to the nearby hospital in case of fever.

Granulocyte CSF was used as primary prophylaxis in patients who were being treated for curative intent and received chemotherapy where the chances of neutropenic fever is approximately 20 percent or higher with a given regimen. GCSF was used as a secondary prophylaxis in patients who had one episode of febrile neutropenia to speed recovery due to a previous cycle of chemotherapy, thus preventing delays in the administration of a subsequent chemotherapy cycle.

RESULTS

Total of 10 patients were admitted to the oncology ward with febrile neutropenia (Table 2). In all, 6 patients (60%) were females and 4 (40%) were males. The median



age was 51 years (range: 19–77 years). 2 patients (20%) were admitted directly from OPD and 7 patients (70%) were seen in the accident and emergency department first. 1 patient (10%) developed febrile neutropenia after receiving inpatient chemotherapy as he was kept under observation post chemotherapy. The median time from arrival to administration of an antibiotic was 6:3 h (range: 1:41- 9:22 h). 4 out of 10 patients received antibiotics within 2 hours. Regarding clinical investigations: chest x-ray, blood culture, urine culture and stool culture were obtained in all 10 patients (100%).

All patients received empirical intravenous antibiotic pipracillin/tazobactem. In 2 patients (20%), blood cultures were positive. One patient required 'second-line' treatment, whereby antibiotics were changed as per culture result sensitivity after 48 h. In all, one patient received additional antifungal regimens. All patients received treatment with G-CSF. The median duration of hospital stay was 5 days (range: 4–10).

In all, 2 patients died during their admission to hospital for febrile neutropenia. A 55 year-old lady with advanced breast cancer with liver and lung metastasis died 5 days after admission. Her death was not attributed to febrile neutropenia but rather to co-morbidities, including respiratory failure due to lung metastasis and congestive cardiac failure. In other one case neutropenic sepsis was the main cause of death.

DISCUSSION

The administration of empirical antibiotic therapy is now standard practice in management of patients with febrile neutropania. There is still considerable controversy about the selection of an efficacious empirical antibiotic regimen. The American Society of Clinical Oncology and an international guideline panel of the Surviving Sepsis Campaign recommend administering the first dose as soon as possible after triage (within an hour) to the patients with febrile neutropenia.^{13, 14} Because there is very high risk of developing a life threatening infection, empirical antibiotic therapy should provide broad and adequate coverage of the most likely causative pathogens. In general, the regimen should include antibiotics which have antipseudomonal properties. There are many factors that may have an impact on morbidity and mortality.

Total number of	patients who	received	chemotherapy	(Table	1):
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Gender	Number Of Patinets	percentage
Male	104	22.6 %
Female	355	77.3 %
Total	459	

Number of patients admitted with febrile neutropenia (Table2):

Gender	Number Of Patinets	Percentage
Male	4	40%
Female	6	60%
Total	10	100%

Primary sites of malignancy of cancer patients presenting with febrile nutropenia. (Table3):

Underlying malignancy	Number of cases
Breast cancer	4
Lymphoma	3
Ca Ovary	1
Ewings sarcoma	1
CLL	1

Known factors that may affect treatment outcome are; diagnosis, Severity of neutropenia, duration of neutropenia, type of chemotherapy, medical co-morbidity and performance status. These factors were used to stratify patients for risk of infection-associated morbidity and mortality. This will facilitate treatment decision as; low, intermediate and high risk patients.¹⁵ Each patient can be assigned to a risk group after considering both treatmentand patient-related risk factors. High-risk patients have a > 20% chance of developing febrile neutropenia, while a 10%-20% chance indicates intermediate risk, and <10% indicates low risk.¹⁶ NCCN guidelines also help clinicians identify chemotherapy regimens that carry high or intermediate risk of febrile neutropenia (16). Effective methods for preventing neutropenic complications include the use of primary prophylaxis with growth factors during chemotherapy in high risk patients. Use of G-CSF in treatment of febrile neutropenia is controversial. All of our patients who were admitted with febrile neutropenia received G-CSF at the time of admission and as secondary prophylaxis in the subsequent chemotherapy cycles. A meta-analysis showed a significant reduction in the length of hospitalisation with the use of G-CSF, but only a marginally significant decrease in infectionrelated mortality and no significant reduction in overall mortality.¹⁷ ASCO guidelines recommend that secondary prophylaxis with colony stimulating factors be limited to patients who experience a neutropenic complication (i.e. fever) from a prior cycle of chemotherapy (for which primary prophylaxis was not received) if a reduced dose might compromise treatment outcome.

In our study secondary prophylaxis of GCSF was administrated to all the patients in the subsequent cycles of chemotherapy who already experienced an episode of febrile neutropenia during previous cycle of chemotherapy. These patients received GCSF during the subsequent course of same chemotherapy without any reduction of the chemotherapy dose intensity. With secondary prophylaxis the frequency of febrile neutropenia was 20% (two patients out of 10).

In our study delayed antibiotic administration was not associated with adverse effect in patients who had an episode of febrile neutropenia. However, patient care could be improved by implementing various strategies to shorten the time from triage to first dose of antibiotic administration. The delay in antibiotic administration noted in the present study is likely multifactorial; however, development of a standardized protocol to direct the flow of patients with an episode of FN through the ED would be of significant benefit.

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