October 2017

Outcomes of high risk Patients with febrile neutropenia at a tertiary care center

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RESEARCH ARTICLE

Outcomes of High Risk Patients with Febrile Neutropenia at a Tertiary Care Center

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Abstract

Fever during chemotherapy-induced neutropenia continues to be a major cause of morbidity and mortality in cancer patients. Mortality depends on the duration and degree of neutropenia, bacteremia, sepsis, performance status, comorbidities and other parameters. The highest mortality rates in cancer patients hospitalized with febrile neutropenia (FN) are observed in those with documented infection. The objectives of the study were to present available tools for risk assessment, to review pathogens causing infections in adult FN patients and to assess outcomes. **Methods:** This cross sectional study was conducted on adult culture positive FN patients admitted to the Hematology/Oncology service at the Aga Khan University Hospital, Karachi, Pakistan from 1st January 2009 to 31st December 2012. High-risk criteria were defined as profound neutropenia, short latency from a previous chemotherapy cycle, sepsis or clinically documented infection at presentation, severe co-morbidity and a performance status greater than or equal to 3. All types of organisms in blood culture and the outcomes of the patients were recorded on Proforma. **Results:** A total of 156 patients with culture-positive febrile neutropenia were identified during the study period. The mean age was 47 years with a slight male predominance of 54%. One hundred and sixteen patients fulfilled the criteria for the high risk group. Fifty two percent had a single high risk factor and 40 % had two. All patients harbored either single or multiple bacterial organisms including gram positive, gram negative or both types. Some 34% of patients had gram positive bacteremia, 57 % had gram negative and 9 % were infected with both. Among 73 gram positive cultures 44 % were Staphylococcus species and among 123 gram negative cultures 43 % were E. coli. One hundred and fifteen patients recovered uneventfully and could be discharged. Thirty two patients in the high risk and 9 in the low risk groups deceased with an overall mortality of 26 %. The mean hospital stays of patients with solid tumors and hematological malignancies were 7.58 and 15.0 days, respectively. Mortality was higher in the latter group, and also in high risk patients with both gram positive and negative bacteremia. **Conclusion:** We emphasize the importance of risk stratification and continuous surveillance of the spectrum of locally prevalent pathogens and their susceptibility patterns for formulation of therapeutic regimens for febrile neutropenic patients.

Keywords: Febrile neutropenia (FN)- high risk (HR)- outcomes

Asian Pac J Cancer Prev, **18 (10)**, 2741-2745

Introduction

Fever during chemotherapy-induced neutropenia continues to be a major cause of morbidity and mortality in cancer patients (Meunier et al.,1990). Although it is Potentially serious and may lead to a lethal outcome, yet many patients respond quickly to broad empiric spectrum antibiotic treatment and exibit an indolent course. However, 2 to 10% of patients develop severe complications and eventually die before resolution of the episode. Even for those patients who recover,it is also associated with increase in costs of anticancer treatments and may adversely affect patients quality of life. (Paesmans et al., 2007). Over the past few decades there has been considerable change in the pattern of pathogens causing infections in FN. Staphylococcus aureus was the most frequent bacterial isolate from these patients in 1950s and early 1960s but was later replaced by Gram- negative bacilli organisms including Escherichia coli, Klebsiella species and Pseudomonas aeruginosa (Jones et al., 1999). However, since 1980s, resurgence of Gram-positive organisms is evident in these patient population (Sharma et al., 2005). Recently reports from developing countries have shown continued predominance of Gram negative bacilli in FN (Kanafani et al., 2007; Baskaran et al., 2007).

Mortality in FN has been shown to be associated with several factors like duration and degree of neutropenia, bacteremia, isolation of resistant organisms, identifiable focus (e.g., pneumonia, soft tissue infections, or catheter related infections), performance status, comorbidities, type and advance stage of underlying malignancy, etc. Though, these criteria are mostly used to stratify FN

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episodes into low risk or high risk with implications for its management as inpatient or as outpatient , respectively (Klastersky et al., 2000) ; still, these are rather less well defined for those who are high-risk patient being treated as inpatient (Kuderer et al., 2006).

The mortality rate for cancer patients with FN averaged 9.3% per hospital database (range, 0% to 50%), with as much as 35.5% of institutions reporting mortality rates of 10% or greater.8 The overall mortality in our previous study was 13.7% (Osmani et al., 2012) . The highest mortality rates in cancer patients hospitalized with FN were observed with infections such as invasive fungal infections like, aspergillosis (39.2%) and invasive candidiasis (36.7%) followed by Gram-negative sepsis (33.9%), pneumonia (26.5%) or Gram-positive sepsis (21.2%), and those patients with major co-morbid conditions (Kuderer et al., 2006).

The objective of the study is to present the available tools for risk assessment, and to review the patterns of pathogens in adult febrile neutropenic patients and to see their outcomes based on mortality.

Materials and Methods

This cross sectional study was conducted on adult patients with culture positive FN admitted under Hematology/Oncology service at Aga Khan University Hospital, Karachi, Pakistan from 1st January 2009 to 31st December 2012. The data set included patients demographics; age, sex and types of cancers; ANC at presentation; High-risk or low risk. High risk criteria were defined as: profound neutropenia (ANC <100/mm3), short latency from previous chemotherapy cycle (<10days), sepsis or clinically documented infection at presentation, severe co morbidity, performance status greater than or equal to 3 [Eastern Cooperative Oncology Group -ECOG-scale. An ERC (Ethics Review Committee) approval was taken and later all the information was recorded on pretested Performa. All febrile neutropenic patients were treated initially empirically with broad spectrum intravenous antibiotics which were modified later based on culture results. However, decision of vancomycin and amphotericin B was according to established guidelines for the management of febrile neutropenia. All patients were managed in the oncology unit while neutropenic septic shock patients were managed in intensive care unit.

The data was retrieved through the data was retrieved through hospital's registration system and was analyzed by using Statistical Package for Social Sciences (SPSS) Version 19. Frequencies and percentages were computed for baseline characteristics, risk factors, bacterial isolates and outcome.

Results

Total of 156 patients with culture positive febrile neutropenia were identified during the study period. The mean age was 47 (SD±11) years and there was a slight male predominance 54 % and females 46 % respectively. The proportion of distribution of patients was equal between solid and hematological malignancies. However, among

Table 1. Baseline Demographic and Clinical Characteristics of Febrile Neutropenic Patients

Characteristics	No. of Patients, n=156
Age in years	47 years (SD ±16)
Number of hospital stay in days	11 (SD ± 11)
Solid tumor	7.58 (SD±6.22)
Hematological Malignancy	14.95(SD±11.76)
Gender, Male/Female	84/72
Outcome (Percentage)	
Alive	115 (74 %)
Dead	41 (26%)
Cancer type:	
Solid n=78 (50%)	
Head & Neck	08 (10%)
Breast	14 (18%)
Lung	07 (09%)
Gastrointestinal malignancy	19 (24%)
Genitourinary	16 (21%)
Germ cell tumor	02 (03%)
Sarcoma	09 (11%)
Others	03 (04%)
Hematological malignancies n=78 (50%)	
Acute Myeloid leukemia	25 (32%)
Acute lymphocytic leukemia	13 (17%)
Lymphoma	36 (46%)
Myeloma	01 (01%)
Others	03 (04%)
Prophylactic antibiotic	80 (51%)
GCSF	36 (23%)
Risk factor	
High	116 (74)
Low	40 (26)
Profound neutropenia	65
Short latency period	74
Sepsis	30
Performance status (PS 3-4)	8
Comorbidity	3
No of high risk	
1	60 (52%)
2	46 (40%)
3	9 (8%)
4	1 (0.8%)
Lines and catheters	
PICC	64 (41%)
Porta Cath	19 (12%)
Indwelling catheter	1 (0.6)
PEG	2 (1%)
Culture	
Gram positive	53 (34%)
Gram negative	89 (57%)
Gram positive and negative	14 (9%)

Incidence of death, 41/ 156*100 = 26.2 per 100 patients

Table 2. Outcomes of Febrile Neutropenic Patients with Bacteremia

Variable	Alive	Deceased
Gender		
Male	66 (79%)	18 (21%)
Female	49 (68%)	23 (32%)
Malignancy		
Solid	62 (79%)	16 (21%)
Hematological	53 (68%)	25 (32%)
Prophylactic antibiotics	57(71%)	23 (29%)
Risk criteria		
High	84 (72%)	32 (29%)
Low	31(78%)	09(22%)
Profound neutropenia	47	18
Short latency period	51	23
Sepsis	17	13
Performance status	6	2
Comorbidity	2	1
No of high risk		
1	47 (78%)	13 (22%)
2	30 (65%)	16 (35%)
3	05 (56%)	04 (44%)
4	1	0

Table 3. Bacterial Cultures

Cultures		
Gram positive	41 (77%)	12 (23%)
Gram negative	64 (72%)	25 (28%)
Gram positive and negative	10 (71%)	04 (29%)

hematological malignancies 49 percent patients had acute leukemias and 46 percent had lymphomas. Eighty patients were already on prophylactic antibiotics while 36 patients received prophylactic granulocyte colony stimulating factors. Overall, 116 patients fulfilled the criteria for high risk group; 65 presenting with profound neutropenia, 74 with short latency period, 30 with sepsis, 8 with poor performance status and 3 with co-morbid conditions. Fifty two percent had 1 high risk factor, 40 % had 2 high risk factors, 9% had 3 high risks factors while 1 patient had all high-risk factors. All patients harbored either single or multiple bacterial organisms including gram positive, gram negative or both. 34% patients had gram positive bacteremia, 57 % with gram negative and 9 % were infected with both gram positive and negative organisms (Table 1).

Among 73 gram positive cultures 44 % were staphylococcus species 16 % were enterococcus and 15 % were staphylococcus aureus, whereas among 123 gram negative cultures 43 % were E. coli followed by Aeruginosa and klebsiella 18 and 17 % respectively (Table 4).

Outcomes

One hundred and fifteen patients recovered uneventfully and discharged home. Overall mortality was 26 percent : 32 in hematological and 21 percent in solid tumors respectively. The mean hospital stay of patients with solid tumor and hematological Malignancies were 7.58 (SD±6.22) and 14.95(SD±11.776) days respectively. Mortality was higher in females and in patients with hematological malignancies i.e. 32 % (Table 2).

Table 4. Spectrum of Bacterial Isolates

Gram positive organism	N=73	Gram negative organism	N=123
Staphylococcus aureus	11(15%)	E. coli	53 (43%)
staphylococcus spp	32(44%)	P. Aureginosa	22(18%)
streptococcus spp	04(05%)	Enterobacter	02(02%)
enterococcus spp.	12(16%)	Klebsiella	18(17%)
bacillus spp.	07(10%)	Acinetobacter	10(08%)
Nocardia	03(04%)	Proteus	01(01%)
Corynebacterium	01(01%)	Salmonella	03(02%)
Other gram+ve organism	03(04%)	Aeromonas	04(03%)
		Stenotrophomonas	05(04%)
		Others	05(04%)

23 deceased patients were already on prophylactic antibiotics at the time of presentation with febrile neutropenia. Mortality was higher in high risk group and in patients with both gram positive and negative bacteremia (Table 2 and 3).

Discussion

While evaluating 156 patients with FN with bacteremia we found 74% were high risk and mortality was slightly higher in this category. This was similar to the result of Carbonero et al study; patients with high risk had a higher incidence of prolonged neutropenia and serious medical complications and death than patients with no such risks (Carbonero et al., 2001). This study concurred with the previous study that the percentage of mortality gets higher with increase in number of risk factors. However, Carbonero's study didn't demonstrate whether patients were bacteremic or not. In another study, 26% of high risk patients were bacteremic with higher incidence of mortality when compared with non bacteremic group (Paesmans et al., 2007).

Majority of our bacteremic patients had acute leukemias which followed in frequency by lymphoma and other solid tumors. This was likely due to myelosuppressive chemotherapy which resulted in longer duration of neutropenia: a known risk of developing infections (Bodey et al., 1966). The mean hospital stay in FN was longer when compared with our contemporary study and reported literature this could probably be due to harboring of documented bacterial infection or high risk group or intrinsic low immunity of patients (Osmani et al., 2012; Berghmans et al., 2002). However, this cannot be ascertained due to retrospective nature of study; thus, a limitation of our study. Similarly mortality in FN with bacteremia was 26 % with slightly higher than seen in hematological malignancies due to prolonged neutropenia.

Lal's study, also showed that bacteremia was significantly associated with increase length of hospital stay and mortality (Lal et al., 2008).

The spectrum of bacterial isolates was similar to what has been reported in both national and International literature i.e., Coagulase negative staphylococci were the most commonly isolated gram positive organisms (Butt et al., 2004; Blahova et al., 2004) and Escherichia coli was the most frequently isolated gram negative pathogen (Butt et al ., 2004; Sigurdardottir et al., 2005; Kirby et al., 2006).

Mortality was higher in patients with both gram positive and gram negative culture positive bacteremic patients followed by gram negative and lastly gram positive patients. Mortalities cannot be attributed to single organism as few patients had polymicrobial infection.

The main concern regarding the use of prophylactic antibiotics remains the emergence of antibiotic resistance. There is no doubt that routine prophylactic use of antibiotics can cause colonization of individual patients with resistant organisms, but its clinical relevance unclear (M Cullen et al., 2009). We observed that half of our bacteremic patients were already on prophylactic antibiotics (Fluoroquinolones with or without Amoxicillin with clavulanic acid) which included all patients with acute leukemia receiving myeloablative treatment protocols. Despite that the mortality in this group was 29%. As death from FN is relatively rare, meta-analyses are necessary to examine the effects of interventions on mortality. Gafter-Gvili et al, undertook a meta- analysis of trials comparing prophylactic antibiotic therapy (fluoroquinolone-based and other regimens) with placebo or no intervention in patients receiving chemotherapy. They analysed 95 randomized controlled trials conducted between 1973 and 2004 involving 9283 patients. The primary outcome was all-cause mortality, and secondary outcomes included infection-related death, febrile episodes, bacteremia, adverse events and emergence of bacterial resistance. This meta analysis showed a statistically significant reduction in all causes mortality of 34% in patients receiving prophylaxis compared with placebo or no intervention, and a 45% reduction in mortality in those receiving fluoroquinolones (Gafter-Gvili et al., 2005).

In another meta-analysis included data from GIMEMA (Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto) and the Significant Trial, Among patients with acute leukemia, one-third reduction as compared with the control group, who did not receive prophylaxis. Among patients with solid tumors and lymphomas, fluoroquinolone prophylaxis had a significant impact on all-cause mortality during initial cycle of chemotherapy, with a relative risk of 0.48 (0.26–0.88), compared with controls (Leibovici et al., 2006).

In our study, since all acute leukemia patients were receiving prophylactic antibiotics, we did not have a control arm to show its benefits. In a recent study patients with low risk have shown benefits of using single agent moxifloxacin as prophylaxis when compared with either ciprofloxacin and Amoxicillin with clavulanic acid. Moxifloxacin is an extended-spectrum fluoroquinolone with a half life allowing convenient once-daily dosing. The drug is approved for pulmonary, skin/soft tissue, and intra-abdominal infections in many countries. When compared with ciprofloxacin, its antimicrobial activity against most Gram-positive bacteria is enhanced, whereas it has more limited activity against Pseudomonas aeruginosa (Kern et al., 2013) .

In conclusion, we emphasize the importance of risk stratification and continuous surveillance of the spectrum of locally prevalent pathogens and their susceptibility patterns which is essential for formulation of therapeutic regimens for chemotherapy induced febrile neutropenic patients.

Competing interests

The authors declare that they have no competing interests.

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