PATTERN OF FEBRILE NEUTROPENIA IN SOLID TUMORS - A hospital based study

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ABSTRACT:
Objective: To review the pattern of febrile neutropenia (FN) presentations in patients with solid tumors at a university hospital in the western region of Saudi Arabia.
Design: Data of all patients with solid tumors (ST) admitted with FN between November 1998 and December 2003 were collected and analyzed.
Results: A total of 67 admissions of 56 patients admitted with FN. Almost two thirds (61.2%) were <50 years of age while 38.8% > 50 years. Males were 38.2% while females 67.2%. Saudis were 35.8% while non Saudis were 64.2%. Duration of neutropenia was <7days in 92.5%, 7-14 days in 7.5% and none more than 14 days. Only 16.4% presented with severe neutropenia (ANC < 100/ML). Positive cultures were found only in 11 patients (16.4%). Organisms isolated; 5 (7.5%) gram-positive bacteria, 5 (7.5%) gram-negative bacteria and fungal infection in 1 (1.5%). Medical co-morbidity was found in 25.4%. Patients were stratified in to; high (7.5%), intermediate (44.7%) and low risk (47.8%) according to the risk stratification criteria for morbidity and mortality. Treatment outcome revealed that 89.6% were alive and 10.4% were dead. Correlation of the outcome with all other variables in this study revealed that medical co-morbidity (p-value = 0.009) and risk group stratification (p-value = 0.034) were the only significant factors which have affected the outcome.
Conclusion: Pattern of febrile neutropenia presentations varies between institutions. Every hospital dealing with cancer should have their own assessment and guidelines in managing such patients.

KEY WORDS: *Febrile neutropenia, Solid tumors, Saudi Arabia.*

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INTRODUCTION

Febrile neutropenia is a serious complication to patients with solid tumors and hematological malignancies. Such complication can be severe and occasionally fatal. Although the mortality associated with febrile neutropenia has dramatically decreased over the past 3 decades, the overall death rate during or immediately after an episode of febrile neutropenia can be as high as 10% with half of the patients dying directly as a result of infection itself[1]. Much has changed in the patterns of microbial flora and the drugs used. Gram-positive organisms are becoming more common than gram-negative ones as causes of bacteremia[2,3]. This study was designed to review the pattern of febrile neutropenia presentations, pattern of microbial flora and other characteristic features in cancer patients with solid tumors. This will assess many factors in our institute which may lead to modifications in our practice and guideline recommendations for better outcome and improvement in morbidity and mortality.

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METHODS

Between November 1998 and December 2003, data of all patients admitted to King Abdul Aziz University Hospital (KAUH) with febrile neutropenia in ST were collected and

analyzed. All characteristic features were analyzed by using simple descriptive statistical analysis (frequency distribution, cross tabulation, chi- square and Fishers exact test) by SPSS statistical program and then correlated with treatment outcome.

Table-I: Patient characteristics with febrile neutropenia episodes in solid tumors

Character	*Solid Tumors*	
	No.	*(%)*
Age:		
< 50Y	41	61.2
= or > 50Y	26	38.8
Sex:-		
Males	22	32.8
Females	45	67.2
Race:		
Saudi	24	35.8
Non Saudi	43	64.2
Severity of Neutropenia (ANC):		
< 100	11	16.4
> 100	56	83.6
Duration of Neutropenia:		
< 7 days	62	92.5
7-14 days	5	7.5
> 14 days	0	0
Culture:-		
Positive	11	16.4
Negative	56	83.4
Culture site:-		
Blood	6	9
Other	5	7.5
Organisms isolated:		
Gram-positive	5	7.5
Gram negative	5	7.5
Fungal	1	1.5
Negative	56	83.6
Use of growth factors:		
Yes	45	67.2
No	22	32.8
Medical co-morbidity:		
Yes	17	25.4
No	50	74.6
Risk group stratification:		
High risk	5	7.5
Intermediate risk	30	44.7
Low risk	32	47.8
Treatment outcome:-		
Alive	60	89.6
Dead	7	10.4

RESULTS

Sixty seven febrile neutropenia episodes in 56 cancer patients with solid tumors were studied. All characteristic features were summarized in (Table-I). Almost two thirds (61.2%) were <50 years of age while 38.8% >50 years.

Table-II: Correlations between febrile neutropenia outcome and other variables & risk factors of all patients with solid tumors

Character	*Alive*	*Dead*	*P-Value*
	No.(%)	*No.(%)*	
Age:			
< 50Y	35 (52.2)	6 (9)	0.234
= or > 50Y	25 (37.3)	1 (1.5)	
Sex:			
Males	21 (31.3)	1 (1.5)	0.412
Females	39 (58.2)	6 (9)	
Race:			
Saudi	23 (34.3)	1 (1.5)	0.407
Non Saudi	37 (55.2)	6 (9)	
Duration of Neutropenia:			
< 7 days	57 (85.1)	5 (7.5)	0.081
7-14 days	3 (4.5)	2 (3)	
> 14 days	0 (0)	0 (0)	
Severity of Neutropenia (ANC):			
< 100	26 (38.8)	4 (6)	0.692
> 100	34 (50.7)	3 (4.5)	
Culture:			
Positive	8 (11.9)	3 (4.5)	0.081
Negative	52 (77.6)	4 (6)	
Organisms isolated:			
Gram-positive	4 (6)	1 (1.5)	0.115
Gram negative	3 (4.5)	2 (3)	
Fungal	1 (1.5)	0 (0)	
Negative	52 (77.6)	4 (6)	
Use of growth factors:			
Yes	41 (61.2)	4 (6)	0.675
No	19 (28.4)	3 (4.5)	
Medical Co-morbidity:			
Yes	12 (17.9)	5 (7.5)	0.009
No	48 (71.6)	2 (3)	
Risk group stratifications:			
High risk	3 (4.5)	2 (3)	0.034
Intermediate risk	26 (38.7)	4 (6)	
Low risk	31 (46.3)	1 (1.5)	

Males were 38.2% while females 67.2%. Saudis were 35.8% while non Saudis were 64.2%. Duration of neutropenia was <7days in 92.5%, 7-14 days in 7.5% and none more than 14 days. Only 16.4% presented with severe neutropenia (ANC < 100/ML). Positive cultures were found only in 11 patients (16.4%). Organisms isolated; 5 (7.5%) gram-positive bacteria, 5 (7.5%) gram-negative bacteria and fungal infection in 1 (1.5%). Medical co-morbidity was found in 25.4%. Patients were stratified in to; high (7.5%) when ANC <100M/L, prolonged neutropenia > 14 days, significant co-morbidity or poor performance status; intermediate (44.7%) when moderate duration of neutropenia (7-14 days), minimal medical co-morbidity and hemodynamic stability and low risk (47.8%) when short duration of neutropenia <7 days and hemodynamic stability according to the risk stratification criteria for morbidity and mortality[4]. Treatment outcome revealed that 89.6% were alive and 10.4% were dead. Correlation of treatment outcome with all other variables, are summarized in (Table-II). Medical co-morbidity (p-value = 0.009) and risk group stratification (p-value = 0.034) were the only significant factors which have affected the outcome.

DISCUSSION

Patients are diagnosed to have FN according to the Current National Comprehensive Cancer Network (NCCN) guidelines which is a temperature more than 38 degree Cent grey orally and Absolute Neutrophil Count (ANC) less than 500/ML with predicted decline to less than 500/ML over the following 48 hours[5]. There are many factors that may have an impact on morbidity and mortality. Known factors that may affect treatment outcome are; Diagnosis (ST vs HM), Severity of neutropenia (ANC < 100 vs > 100), Duration of neutropenia (< 7 days vs > 14 days), Type of chemotherapy (Intensive vs conventional), Medical co-morbidity (yes vs no) 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[6]. Characteristic features of all episodes of FN revealed that only 16.4% presents with severe neutropenia (ANC < 100) which reduces the risk of infection associated morbidity and mortality. Duration of neutropenia was < 7 days in 92.5% of patients which again reduces the risk of morbidity and mortality. Prolonged neutropenia is seen mainly in patients with hematological malignancies and intensive chemotherapy regimens[1]. Regarding the pattern of microbial flora; 5 out of 11 positive cultures were due to gram-positive organisms (Coagulase-negative Staphylococci and Staphylococcus aureus), 5 due to gram-negative organisms (E-Coli, Klebsiella and P. aeruginosa) and 1 due to fungal infection (Candida Albicans). Gram-negative bacilli were the predominant organisms causing infection between 1970,s – 1980,s in the neutropenic patients in approximately 60–80%, with P. aeruginosa being a leading isolate[7]. This confirms that gram positive organisms are increasing over gram-negative ones as a cause of infection in neutropenic patients[2]. Probable factors are; aggressive chemotherapeutic regimens that cause severe mucositis, longer duration of neutropenia, the use of long dwelling intravascular catheters, and the use of prophylactic antibacterial agents with relatively weak coverage of gram-positive organisms[8]. Regarding fungal infection, it is mainly encountered in hematological malignancies. Literature review revealed that up to 20% of patients with neutropenia may experience an invasive fungal infection[9]. Use of colony stimulating factors in FN patients like G-CSF or GM-CSF was to shorten the duration of neutropenia and not the duration of fever, use of antibiotics or cost[10]. No study has demonstrated a decrease in infection related mortality rates[11]. Routine use of hematopoietic growth factors in uncomplicated cases of fever and neutropenia is not recommended by the American Society of Clinical Oncology. Only under certain conditions, when there is an expected long-delay recovery of the bone marrow or worsening of the course is pre-

dicted. Use of hematopoietic growth factor in our study population did not change the outcome (p-value = 0.675). Medical Co-morbidity is a known risk factor for poor outcome. Co-morbidity was found in 25.4% of our patients. Correlations between FN outcome, either alive or dead and other variables in this study revealed significant impact of medical co-morbidity and the risk group stratifications (p-value, 0.009 and 0.034 respectively) (Table-II).

From this study, we conclude that gram-positive infections are increasing in patients with FN in relation to gram-negative ones. Optimal coverage of infections secondary to gram-positive bacteria should be considered in the initial empiric therapy of FN in our hospital, especially if infections are serious. Institutional variations are common and should be taken in to consideration.

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