Febrile **Neutropenia** Comparison **Between** **Solid** Tumours **and** Hematological **Malignancies**

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Our aim was to study all patients with febrile neutropenia (FN) admitted between April 2000 and December 2003 at King Abdul Aziz University Hospital (KAUH). Data of all patients with FN in solid tumours (ST) and hematological malignancies (HM) were collected and analyzed. A total of 73 admissions of 51 patients admitted with FN (46 admissions with ST and 27 with HM). Seventy four percent were < 50 years of age and 26% > 50 years. Males were 46.6% while females 53.4%. Saudis were 19.2% while non Saudis were 80.8%. Duration of neutropenia was <7days in 43 (58.9%) admissions with ST, 3 (4.1%) admissions with HM while >7days, 3 (4.1%) admissions with ST and 24 (32.9%) with HM (p-value <0.001). Positive cultures were found only in 7 (9.6%) patients with ST vs 18 (24.7%) in HM (p-value <0.001). Positive blood cultures were higher in HM compared to ST (68% vs 16%; p-value 0.053). There was no difference between ST and HM in use of growth factors (p-value 0.606), presence of medical co-morbidity (p-value 0.348) or treatment outcome (p-value 0.137). Twenty one out of 25 positive cultures were found in the blood; 14 with gram-positive bacteria, 5 with gram-negative bacteria, fungal infection in 4 and mixed organisms in 2 cultures. Duration of neutropenia and co-morbidity were the only factors which have leaded to poor outcome. Conclusion: Febrile neutropenia is more common and serious in HM than ST. Culture with gram-positive organisms are higher than gram-negative ones. Pattern of infection varies between hospitals for which each institute should have their own guidelines to manage such cases.

Introduction

Hematological toxicity from chemotherapy is the most frequent serious side effect encountered in clinical practice. Reduction in white blood cell lineage can lead to complications such as febrile neutropenia. Febrile neutropenia is a serious complication to patients with ST or HM. 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

Character	Solid Tumours	Hematological Malignancies	Total		P-Value
	No.(%)	No.(%)	No.	(%)	
Age:					
- < 50Y	28 (38.4)	26 (35.6)	54	(74)	0,001
- = or > 50Y	18 (24.7)	1 (1.3)	19	(26)	
Sex:					
- Males	14 (19.2)	20 (27.4)	34	(46.6)	0,001
- Females	32 (43.8)	7 (9.6)	39	(53.4)	
Race:					
- Saudi	14 (19.2)	0 (0)	14	(19.2)	0.001
- Non Saudi	32 (43.8)	27 (37)	59	(80.8)	
Severity of Neutropenia (ANC):					
- < 100	19 (26)	8 (11)	27	(37)	0.452
- > 100	27 (37)	19 (26)	46	(63)	
Duration of Neutropenia:					
- < 7 days	43 (58.9)	3 (4.1)	46	(63)	<0.001
- > 7 days	3 (4.1)	24 (32.9)	27	(37)	
Culture:					
- Positive	7 (9.6)	18 (24.7)	25	(34.2)	<0.001
- Negative	39 (53.4)	9 (12.3)	48	(65.8)	
Culture site:					
- Blood	4 (16)	17 (68)	21	(84)	0.053
- Other	3 (12)	1 (4)	4	(16)	
Growth factors:					
- Yes	31 (42.5)	20 (27.4)	51	(69.9)	0.606
- No	15 (20.5)	7 (9.6)	22	(30.1)	
Co-morbidity:					
- Yes	10 (13.7)	3 (4.1)	13	(17.8)	0.348
- No	36 (49.3)	24 (32.9)	60	(82.2)	
Outcome:					
- Alive	43 (58.9)	22 (30.1)	65	(89)	0.137
- Dead	3 (4.1)	5 (6.8)	8	(11)	

Table 1 *- Patient characteristics with febrile neutropenia in solid tumours and hematological malignancies.*

itself (1). Much has changed in the patterns of microbial flora and the drugs used. Gram-positive organisms have overshadowed the gram-negative ones as causes of bacteremia (2, 3). For these reasons, this study was designed to review the pattern of febrile neutropenia presentations, pattern of microbial flora and other important variables among patients with ST and HM. This will give us an idea about febrile neutropenia in our hospital which may lead to change in our practice and guideline modifications in managing such patients for better outcome and improvement in morbidity and mortality.

Methods

Between April 2000 and December 2003, data of all patients admitted to KAUH with febrile neutropenia either with ST or HM, were collected and analyzed. Comparisons between ST and HM were made using simple descriptive statistical analysis (frequency distribution, chi- square, cross tabulation) by SPSS statistical program.

Discussion

Patients are diagnosed to have febrile neutropenia according to the Current National Comprehensive Cancer Network (NCCN) guidelines which is 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 (4). Pattern of febrile neutropenia presentations varies not only between hospitals but also between patients due to many factors. These factors may have an impact on morbidity and mortality. Known factors that may affect the outcome of such patients 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 (5, 6). In our study, we have reviewed seventy three admissions with febrile neutropenia of 51 patients (46 admissions of 38 patients with ST and 27 admissions of 13 patients with HM). Characteristic features of all these admissions with febrile neutropenia as well as comparisons between ST and HM are summarized in (Table.1). All positive cultures for these patients were analyzed looking in to the causative organism, culture site and comparison between ST and HM are summarized in (Table.2). Correlations between febrile neutropenia outcome and other variables like; age, sex, race, diagnosis, duration and severity of neutropenia and finally use of growth factors are all summarized in (Table.3).

Comparisons of all characteristic features and risk factors for morbidity and mortality between patients with ST and HM revealed that almost all patients with HM are < 50 years of age compared to ST (96.3% vs 60.9%, p-value 0.001). Regarding sex, males were higher in HM while females were higher in ST (74.1% vs 30.4%, p-value 0.001). The majority of our patients were non Saudis, (100% with HM vs 69.6% with ST,

p-value=0.001). The reason of having only non Saudi patients in HM in our hospital because all Saudis were referred to centers having the facility of bone marrow transplantation which is lacking in our hospital as well as the poor acceptance of other governmental hospitals to these patients. Severity of neutropenia of either (ANC < 100 or > 100) is one of the important risk stratifying factor for risk of infection associated morbidity and mortality. There was no difference between ST and HM in this issue with a p-value of 0.452 (Table.1). Duration of neutropenia was < 7 days in the majority of patients with ST compared to HM (58.9% vs 4.1%) while > 7 days was mainly in HM (32.9% for HM vs 4.1% for ST, p-value <0.001) which makes patients with HM at higher risk of infection associated morbidity and mortality (1). Regarding cultures to assess the pattern of microbial flora, positive cultures were significantly higher in HM compared to ST (24.7% vs 9.6%, p-value <0.001). This can be explained by the higher risk of infection associated morbidity and the frequent use of central lines in HM and the prolonged neutropenia. Positive blood cultures were higher in HM than ST (68% vs 16%, p-value= 0.053). Comparison of the pattern of microbial organisms in positive cultures between patients with ST and HM are summarized in (Table.2). Fourteen out of 25 positive cultures (56%) were due to gram-positive organisms while only 5 positive cultures (20%) were due to gram-negative organisms. Coagulase-negative Staphylococci and Staphylococcus aureus were the predominant organisms. 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 the gram positive organisms overshadowed the gram–negative ones as the bacteria causing infection in the neutropenic patients (2). Probable factors of why gram-positive organisms are increasing as follows; 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, 4 out of 25 (16%) positive cultures, were due to fungal infection in our study population which is mainly encountered in HM. The fungi isolated were; Candida Tropicalis, Candida Krusei, Aspergillous Flavis and Aspergillous

Organisms in positive cultures	Solid Tumours (Total No. of Febrile Neutropenia 46)			Hematological Malignancies (Total No. of Febrile Neutropenia 27)		
	No.	Site		No.	Site	
		Blood	Other		Blood	Other
G +ve bacteria	4	3	1	10	10	0
G –ve bacteria	2	1	1	3	2	1
Fungal	1	0	1	3	3	0
Viral	0	0	0	0	0	0
Mixed organisms	0	0	0	2	2	0
Total	7	4	3	18	17	1

Table 2 *- Comparison of positive cultures during febrile neutropenia between patients with solid tumours versus hematological malignancies.*

Character	Alive No. (%)	Dead No. (%)	P-Value
Age:			
- < 50Y	46 (63)	8 (11)	0.102
- = or > 50Y	19 (26)	0 (0)	
Sex:			
- Males	31 (42.5)	3 (4.1)	0.716
- Females	34 (46.6)	5 (6.8)	
Race:			
- Saudi	13 (17.8)	1 (1.4)	1.000
- Non Saudi	52 (71.2)	7 (9.6)	
Diagnosis:			
- Solid tumours	43 (58.9)	3 (4.1)	0.137
- Hematologic malignancies	22 (30.1)	5 (6.8)	
Severity of Neutropenia (ANC):			
- < 100	23 (31.5)	4 (5.5)	0.457
- > 100	42 (57.5)	4 (5.5)	
Duration of Neutropenia:			
- < 7 days	44 (60.3)	2 (2.7)	0.045
- > 7 days	21 (28.8)	6 (8.2)	
Co-morbidity:			
- Yes	8 (11)	5 (6.8)	0.004
- No	57 (78.1)	3 (4.1)	
Culture:			
- Positive	22 (30.1)	3 (4.1)	1.000
- Negative	43 (58.9)	5 (6.8)	
Growth factors:			
- Yes	46 (63)	5 (6.8)	0.691
- No	19 (26)	3 (4.1)	

Table 3 *- Correlations between febrile neutropenia outcome and other variables.*

Parapsilosis. Literature review revealed that up to 20% of patients with neutropenia may experience an invasive fungal infection (9).

Use of colony stimulating factors in febrile neutropenic 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, 11).

From this study, we conclude that febrile neutropenia is more common and serious in HM than ST

No study has demonstrated a decrease in infection related mortality rates. 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 predicted. Use of hematopoietic growth factor in our study population showed no difference between ST and HM (42.5% vs 27.4%, p-value= 0.606) and no significant impact in the outcome (Table.3, p-value 0.691). Medical Co-morbidity is a known risk factor for poor outcome in patients with febrile neutropenia. Co-morbidity was found in 13.7% in patients with ST and 4.1% in patients with HM with a p-value of 0.348. Regarding treatment outcome, there was no difference between ST and HM (58.9% alive in ST vs 30.1% alive in HM, p-value= 0.137). The trend of mortality was higher in patients with HM than ST but it did not reach statistical significance probably because of small number of patients. Correlations between febrile neutropenia outcome, either alive or dead and other variables in this study revealed significant impact of the duration of neutropenia and the presence of medical co-morbidity (Table.3). Duration of neutropenia revealed (< 7 days 60.3%, > 7 days in 28.8% for alive patients and < 7 days of 2.7%, > 7 days 8.2% for dead patients with a p-value of 0.045). Regarding patients with medical co-morbidity (11% were alive while 6.8% were dead with a p-value of 0.004).

From this study, we conclude that febrile neutropenia is more common and serious in HM than ST. Gram-positive infections are increasing which is more common than gram-negative ones. Optimal coverage of infections secondary to gram-positive bacteria should be considered in the initial empiric therapy of febrile neutropenia in our hospital, especially if infections are serious. General guidelines should be followed in the management of patients with febrile neutropenia. Institutional variations should be considered especially for the pattern of causative organisms.

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