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Risk assessment and microbiological profile of infections in paediatric cancer patients with febrile neutropenia

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Abstract

Febrile neutropenia is a common and potentially fatal problem encountered in cancer patients undergoing chemotherapy. We carried out an observational study to evaluate the possible risk factors of developing fever amongst neutropenic children with an underlying malignancy. We also looked at the microbiological profile of causative pathogens in patients with febrile neutropenia. During a study period of 1 year, a total of 90 neutropenic episodes were recorded amongst 57 patients who were on treatment and follow–up during the study period. Multivariate analysis showed that factors such as chemotherapy status, underlying disease, existing central venous catheters, presenting white blood cell counts at chemotherapy, use of steroid therapy or hospitalisation at the onset of neutropenia, were not significant risk factors for developing fever during neutropenic episodes. Although the presence of a central venous catheter was associated with a higher risk of developing fever, it did not reach statistical significance (p=0.11). Of the 90 neutropenic episodes, 59 (65.6%) developed fever and 25 of these had positive blood cultures. The causative organisms include gram-negative bacteria (64%), gram positive bacteria (16%) and fungus (20%). Of the gram-negative organisms, *Klebsiella spp.* predominated (28%) with the extended spectrum beta-lactamase producing strain forming the majority (16%). Amongst those with fungaemia, *Candida spp.* and *Candida tropicalis* formed the majority (8% each) of the isolates.

Key words: microbiological profile, infections, febrile neutropenia, paediatric cancers

INTRODUCTION

There has been tremendous progress in the field of oncology with more intensive chemotherapeutic regimens being used over the past few decades. The overall survival of cancer patients has also improved. Unfortunately, the cytotoxic agents used affect not only the malignant cells but also normal proliferating cells in the haemopoeitic system. Neutropenia is therefore an inevitable consequence of chemotherapy in most cancer patients. Infection is the most frequent complication of neutropenia and if not detected and treated promptly could prove to be fatal. Cancer patients with febrile neutropenia are however a heterogeneous group hence it would therefore be ideal if these patients could be accurately stratified into high risk and low risk groups so that appropriate treatment strategies, either intensive or not, may be delivered accordingly. At present, there is no accurate method to identify patients at risk for developing febrile neutropenia.' Previous studies have identified several indices and factors that may help predict patients at higher risk of bacteraemia during hospitalisation. These include the degree of bone marrow recovery, the type of underlying disease and the disease status, whether in remission or relapse.[2,3] Blay *et al* suggested a risk assessment model, which identified risk factors in patients with fever and neutropenia using clinical information available from the first day of chemotherapy.' Two significant high risk factors were identified i.e. day 5 lymphopaenia of <700/μL and the administration of high dose chemotherapy. Of course, no model can absolutely predict or foresee all the possible circumstances and complications and because of this, the attending oncologist needs to be aware of the spectrum of infections that may occur in these febrile neutropenic patients. It is also especially important to know the local profile of causative pathogens within a particular institution to allow appropriate management strategies, such as the choice of first line empirical antibiotics and infection control programmes, to be effectively delivered.

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The aims of this study were to identify risk factors for febrile neutropenia induced by cytotoxic chemotherapy amongst children with an underlying cancer and to determine the microbiological profile of the causative pathogens involved.

MATERIALS AND METHODS

Patients

All patients on treatment and follow–up by the Paediatric Oncology and Haematology Unit, Hospital Universiti Kebangsaan Malaysia (HUKM) were eligible for inclusion into the study. The study was carried out within a study period of 12 months, from October 1998 to September 1999.

Data collection

The case notes of all oncology/haematology patients who were on treatment and follow – up during the aforementioned period of time were retrieved and subsequently reviewed. Patients with febrile neutropenia would have been investigated based on a standard ward protocol which included blood cultures, urine and stool cultures, swabs for cultures and a chest X-ray in addition to baseline complete blood count, renal profile and liver function test. Patients who had received intravenous antibiotic treatment during the same neutropenic episode or within the preceding 5 days were excluded. Oral anti-infective prophylaxis with trimethoprim/sulfomethoxazole or fluconazole was allowed. Those who developed febrile neutropenia as a consequence of cytotoxic chemotherapy were selected and reviewed in further detail. Certain parameters and indices were recorded accordingly into a datasheet. These were broadly categorised into 3 sections: (1) patients' characteristics which included demographic data (e.g. age, sex, race), underlying diagnosis, the presence of a central venous catheter and whether the patient was already an inpatient at the onset of neutropenia; (2) phase of chemotherapy (induction, reinduction or maintenance), onset of neutropenia in reference to the commencement of chemotherapy and the use of steroid therapy, and **(3)** the results of the investigations (according to the standard protocol) of patients who had developed neutropenia in relation to the commencement of chemotherapy. From this population base, the neutropenic episodes were then stratified into 2 large sub-groups, those with fever and those without fever. Those who developed febrile n'utropenic episodes were further analysed and classified into 3 categories i.e. microbiologically documented infection, clinically documented infection or fever of unknown origin. The causative pathogens, if isolated, were recorded in each episode.

Definitions

Fever was defined as two temperature readings, over a 4-hour period, either oral or rectal, $\geq$ 38°C during a 24-hour period or a single reading of $\geq$ 38.5°C. [4] Neutropenia was defined as an absolute neutrophil count (ANC) of <1000 polymorphonuclear leucocytes and band forms per microlitre. [5,6,7]

Microbiologically documented infection was defined as infection which is clinically evident and microbiologically proven whereas clinically documented infection were those with signs of localised infection in the absence of microbiological evidence.[8] Fever of unknown origin referred to presence of clinical evidence of infection in the absence of a focus of infection and microbiological proof. Bacteraemia was defined by the presence of pathogen isolated from blood, regardless of the existence of a site.[8]

Statistical methods

Statistical analyses were performed using the SSPS (7.5) software programmes. Potential predictors on the development of fever in the neutropenic population were analysed using the multivariate logistic regression models. A p value of < 0.05 was taken to be statistically significant.

RESULTS

Fifty-seven patients who developed neutropaenia were eligible to be included in the study and from these a total of 90 neutropenic episodes were recorded. The characteristics of these neutropenic episodes are shown in Table 1. The sex distribution (i.e. male versus female) was comparable but the Malays formed the majority (78.9%) of patients seen. The age of the patients ranged from 9 months to 204 months with a mean of 77 months. Haematological disorders formed the bulk of underlying diseases seen (78.8%) which included the leukaemias, both myelocytic (21.1%) and lymphocytic (53.3%), the lymphomas (2.2%) and aplastic anaemia (2.2%). A total of 50% of the neutropenic episodes were recorded in patients who were undergoing their first induction whereas only 4.4% were from the group of patients receiving only maintenance chemotherapy. A total of

TABLE 1: Characteristics of neutropenic events seen at the Paediatric Oncology/Haematology unit HUKM between October 1998 to September 1999

Characteristic	No. (SD)	%
Sex:		
Male	43	47.8
Female	47	52.2
Race:		
Malay	71	78.9
Chinese	8	8.9
Indian	8	8.9
Others	3	3.3
Age (months) :		
Mean	77.67 (± 47.41)	
Median	72	
Range	9 - 204	
Underlying disease:		
Haematological malignancy and marrow aplasia	67	78.8
Solid tumour	23	21.2
Treatment status:		
First induction chemotherapy	45	50.0
Reinduction chemotherapy	39	43.3
Maintenance chemotherapy	4	4.4
Immunosuppression for aplastic anemia	2	2.3
Steroid therapy:		
Yes	44	48.9
No	46	51.1
Indwelling CVC:		
Yes	22	24.4
No	68	75.6
In hospital before fever:		
Yes	64	71.1
No	26	28.9
Interval between chemotherapy and onset of neutropenia (days)		
Mean	8.6 (± 5.33)	
Median	9.0	

24.4% of the neutropenic episodes occurred in those who had an indwelling central venous catheter (CVC). Interestingly, a large proportion of the neutropenic episodes (71.1%) developed whilst the patients were in the ward whereas only 28.9% developed the neutropenia at home. The mean onset of development of neutropenia post–chemotherapy was 8.6 days.

TABLE 2: Categories of 59 febrile episodes amongst 90 neutropenic episodes seen at the Paediatric Oncology/Haematology unit HUKM between October 1998 to September 1999

Categories	No.	(%)
MDI with bacteraemia	19	32.2
MDI without bacteraemia	*3	5.0
MDI with fungaemia	6	10.1
MDI without fungaemia	**2	3.3
Clinically documented infection	6	10.1
Fever of unknown origin	23	39.3

MDI = Micobiologically documented infection

* There was 1 positive sputum culture for ESBL *Klebsiella,* 1 positive urine culture for Klebsiella (sensitive strain) and 1 positive urine culture for *Enterobacter*

** There was 1 positive sputum culture and 1 positive urine culture for *Candida spp.*

TABLE 3: Causes of bacteraemia/fungaemia amongst 25 febrile episodes with positive blood cultures

	No. of isolates	Percentage	Total(%)
Gram negative			16(64)
Single organism			
ESBL *Klebsiella*	3	12	
Multiresistant *Klebsiella*	2	8	
Klebsiella sensitive strain	1	4	
Acinetobacter	2	8	
Pseudomonas aeruginosa	1	4	
Pseudomonas spp	1	4	
Enterococci	1	4	
Enterobacter	1	4	
Aeromonas hydrophilia	1	*4*	
Bacillus spp	1	4	
E.coli	1	4	
Multiple organisms			
Multiresistant & ESBL *Klebsiella*	1	4	
Gram positive			4(16)
Single organism			
Staphylococcus aureus	1	4	
Streptococcus sanguis	1	4	
Streptococcus viridans	1	4	
Multiple organisms			
S. pneumoniae & S. aureus	1	4	
Fungal			5(20)
Candida spp.	2	8	
Candida tropicalis	2	8	
Candida parapsilosis	1	4	

TABLE 4: Results of multivariate analysis of predictive factors for developing fever amongst 90 neutropenic episodes seen at the Paediatric Oncology/Haematology unit HUKM between October 1998 to September 1999

Variables	SE	Odds ratio	CI 95%	P value
Chemotherapy status"):				
Induction	1.24	2.01	2.01 ± 6.82	0.57
Reinduction	1.37	2.62	2.62 ± 7.76	0.48
Underlying disease(2):				
Haematological disease	0.85	2.74	2.74 ± 4.58	0.23
Intravenous line (3):				
CVC	0.85	3.88	3.88 ± 4.62	0.11
Peripheral	0.80	1.20	1.20 ± 4.36	0.81
Steroid treatment(4):				
Use of steroid therapy	0.68	0.51	0.51 ± 3.86	0.32
In hospital before fever(5):				
Hospitalised before fever	0.75	0.36	0.36 ± 4.15	0.18
Day 1 anc [μl] (6):				
0 – 999	1.14	0.96	0.96 ± 6.12	0.97
1000 – 4999	0.89	0.31	0.31 ± 4.78	0.19
5000 – 9999	0.97	0.55	0.55 ± 5.20	0.54
Day 1 lymphocyte [μl] (7):				
0 – 699	1.19	2.43	2.43 ± 6.44	0.45
700 – 1499	0.93	0.57	0.57 ± 4.98	0.54
1500 – 4999	0.84	0.45	0.45 ± 4.55	0.34

SE: standard error; CI 95%: confidence interval at 95% for theoretical odds ratio.

(1) Reference category = maintenance chemotherapy.
(2) Reference category = solid tumours.
(3) Reference category = no intravenous line.
(4) Reference category = no steroid therapy.
(5) Reference category = not in hospital before fever.
(6) Reference category = Day 1 ANC ≥ 10000/mL.
(7) Reference category = Day 1 lymphocyte ≥ 5000/mL.

Of the 90 neutropenic episodes, 59 were associated with fever. A total of 50.6% of these febrile neutropenic episodes were microbiologically documented infection (MDI) and the majority (32.2%) had bacteraemia (Table 2). In comparison, a total of 13.4% were fungal MDI and 10.1% of the febrile episodes were clinically documented infection (CDI) which were mainly (83.3%) respiratory tract infections. Overall, the majority (39.3%) of the febrile neutropenic episodes was due to fever of unknown origin (FUO).

From the total of 59 febrile neutropenic episodes, 25 had positive blood cultures (bacteria and fungus included) [Table 3]. A notable finding was the predominance of gram-negative organisms (64%) over the gram-positive organisms (16%). Of the gram-negative pathogens, the *Klebsiella* group (28%) was predominantly isolated with 16% of it being the extended spectrum beta lactamase (ESBL) producing *Klebsiella* and 12% multi-resistant *Klebsiella*. Amongst the gram-positive pathogens, *Staphylococcus aureus* formed the majority (8%). The incidence of fungaemia

amongst the febrile neutropenic patients was 20%.

The results of a multivariate analysis performed to assess predictive risk factors for developing fever amongst neutropenic patients are shown in Table 4.

DISCUSSION

Febrile neutropenia is an important complication of cancer therapy with serious medical complications reported in as high as 21% of patients and death in 4–30%.[1] In view of this high morbidity and mortality rate, it would be ideal to be able to identify those at risk for developing febrile neutropenia. These patients may then be selected as potential candidates for the use of prophylactic treatments, for example haemopoietic growth factors. The administration of these growth factors has been reported to reduce the degree and duration of post-chemotherapy neutropenia, thereby reducing the overall incidence of febrile neutropenia.[9] Those at low risk for febrile neutropenia on the other hand, may also benefit from a risk stratification approach as they may then be safely discharged to receive either outpatient or home antibiotic therapy thereby decreasing costs of treatment.

In our study, none of the risk factors which we analysed using multivariate regression analysis, were found to be significant. These include the chemotherapy status, underlying disease, use of steroids in the chemotherapy regimes and inpatient status at the onset of fever. Although the presence of a central venous catheter conferred a higher risk for the development of fever in neutropenic patients, this was not statistically significant (p=0.11). The presence of an indwelling catheter has been shown in other studies to be an important prognostic factor in febrile neutropenic patients.[10] Both Day 1 ANC and Day 1 lymphocyte counts were not significant as predictive factors for the development of fever. Interestingly, those with ANC of 0–999/μL had a higher risk of developing fever compared to those with ANC of 1000–4999/μL (odds ratio 0.96 and 0.31 respectively) although this was not statistically significant. This was again shown in Day 1 lymphocyte count; those with a lymphocyte count of 0 – 699/μL had a higher risk of developing fever as opposed to those with a lymphocyte count of 700 – 1499/μL (odds ratio 2.43 and 0.57 respectively).

The trend of pathogens responsible for infection has been reported recently to be shifting from gram-negative organisms in the 1970s to gram-positive organisms especially in the western countries. Several factors have been incriminated for this changing pattern; amongst them the use of aggressive chemotherapy which injures the gastrointestinal tract mucosa and the increasing use of implantable devices such as intravenous catheters.[11] In our study however, gram-negative organisms continue to predominate whereas in another local study by Ariffin *et al*, both gram-negative and gram-positive organisms were isolated with similar frequency in a 5-year surveillance study conducted at the University Hospital Kuala Lumpur.[12] The fact that a smaller proportion of patients in our set-up use CVC is a probable explanation for this persistent pattern of gram-negative predominance.

Amongst the gram-negative pathogens, ESBL *Klebsiella* was predominantly isolated. Ariffin *et al* reported that ESBL production amongst *Klehsiella spp* was 50%.[12] A notable but rather alarming finding in our study was the relatively higher incidence of fungaemia amongst the febrile neutropenic patients (20%). Most other centres reported an incidence of 1-13.6%.[7,13] As a large proportion of our patients were already hospitalised at the onset of fever, it was likely that these episodes were actually acquired from within the ward itself. What is certain is that infection control must be continually improved and that strict isolation protocols be observed. However, with limited isolation rooms available in our setting, some of the neutropenic cases had to be nursed in the open ward hence this would have increased the risk of fungal infection.

In conclusion, firstly, there were no statistically significant factors derived from this study that predicted for the development of fever amongst the neutropenic patients. The major limitation was the relatively small sample size. Secondly, in view of the relatively high incidence of fungal infection in this study population, a more vigilant approach with regard to infection control is warranted in addition to having a higher index of suspicion for the occurrence of fungaemia in neutropenic patients with unresolving fever. It has been proposed that prompt administration of anti-fungal should be instituted to patients with febrile neutropenia if there is no response to antibiotic therapy after 96 hours of commencement of first-line antibiotics therapy.[11] A larger and multicentre study involving all 3 tertiary paediatric oncology units in the Klang Valley should also be proposed to provide adequate number of cases for a higher

level of 'study power'. Only then can important issues such as predictive risk factors be assessed with more confidence and conclusions made with more certainty.

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