ORIGINAL ARTICLE

Epidemiology of Culture-positive Infection in Adult Patients with Haematological Malignancies in Sarawak

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INTRODUCTION

Haematology malignancy patients undergoing chemotherapy are at a high risk of developing infectious complications and the risk of infection varies considerably across different patient populations and treatment regimens used[1]. Advances in the treatment of malignant diseases have improved prognosis but have also resulted in increased susceptibility to opportunistic infections. Although empirical usage of antibiotics and prophylaxis have improved the outcome of these infections, the emergence of multidrug resistant organisms is an emerging concern for physician [2,3] and it varies among different institution, considering the amount of antibiotics received for each episode of neutropenic fever.

We conducted this retrospective study on microbiologically documented infections (MDI) in adult haematological malignancy patients with the aim to identify the risk factors, to assess the clinical outcome of such infection, and determine the commonest microorganism.

MATERIALS AND METHODS

A retrospective analysis was conducted to look at all MDI in post chemotherapy adult haematological malignancy patients admitted between 1st March 2009 and 31st December 2010 to an adult haematology unit at a public funded, tertiary referral community hospital on the Borneo Island in Malaysia, the Sarawak General Hospital. The unit has two 4 bedded cubicles with naturally-ventilated room and 2 single bedded rooms with centralized air condition. The unit follows the standard recommendation of strict infection control measures.

During the study period, all post chemotherapy haematological malignancy patients presenting with fever and symptoms suspicious of an infection were admitted to the same unit and exposed to the same environmental risks. Full septic workup was performed consisting of blood culture and if chest symptoms existed, sputum culture were taken.

Demographic and clinical data of patients including malignancy type; state of disease (induction/relapse/refractory); source of infection; type and intensity of chemotherapy; presence of co-morbids; central line or mucositis; if prophylaxis antibiotic were given; degree of absolute neutrophil count (ANC) at the onset of positive culture, organism isolated and outcome were recorded. Each MDI was treated as separate episodes as host factors change with each hospital admission for suspected infection. Microbiologically documented infection (MDI) must meet the following criteria:

1. Patient has a recognized pathogen cultured from one or more blood, cerebrospinal fluid (CSF) or sputum. (In positive sputum samples , a positive culture is regarded as positive only if patient presents with suspicion of pneumonia with pus cell >25/hpf)
2. Patient has at least one symptom of infection such as fever (>38°C), chills, cough with sputum or hypotension.

Blood cultures were performed in aerobic and anaerobic bottles and incubated in an automated system. Bacteria was identified using standard microbiological methods. Oral amoxicillin/clavulanate with or without ciprofloxacin were prescribed as antibiotic prophylaxis based on physician discretion. Antifungals with oral fluconazole were prescribed to patients predicted with prolonged neutropenia (>one week) or very ill patients with oral thrush.

Once infection was established, intravenous piperacillin/tazobactum were initiated until a culture and sensitivity result is available and antibiotic will be adjusted accordingly. Antibiotic will be escalated in the event of no clinical responds at day 3 of infection. If fungal infection was highly suspected, intravenous amphotericin B deoxycholate was started. Granulocyte colony stimulating factor (G-CSF) was only given when ANC < 1.0 x 109/L due to limited resources and witheld with recovery of ANC.

Septic death was death directly related to or contributed by an infectious episode (death within 28 days of documented infection). Death due to disease progression was not designated as a septic death.

Descriptive statistics were presented in frequency with percentage for categorical variables and median (IQR) for numerical variables since normality assumption was not assumed. Pearson Chi square test was used to determine the association between all the predictors towards the outcome. All the significant predictors were then analyzed again using multivariate logistics regression using enter method procedure. All analyses were carried out using SPSS version 20.0 (Chicago,IL).

RESULTS

During the 21 months period, a total of 316 episodes in post chemotherapy patients with fever and suspected infection

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were investigated. A positive culture were reported in 61 (19.3%) of which 80.7% were from blood, 17.5% sputum and 1.8% from CSF. However, only fifty seven of these positive culture cases in 43 patients were analyzed due to missing data.

The demographic pattern and clinical characteristics of the cases are shown in Table I. Acute leukaemia accounted for almost two third (60%) of all cases with positive cultures. Intensive chemotherapy (Flag-Ida, HyperCVAD, Midac/Hidac) was given to 42% of these culture positive patients.

Gram negative organism were isolated in 77.2% of those with positive culture (see Table II). The extended-spectrum ß-lactamases (ESBLs) rate was 15% among *Klebsiella pneumoniae (K. pneumoniae)* and *Escherichia coli (E. coli)*. Resistance to ciprofloxacin was mainly seen in *K. pneumoniae, E. coli* and *Acinetobacter baumanii (A. baumanii)*; with resistance rates of more than 60%. The resistance rate for amoxicillin/clavulanate in *K. pneumoniae* and *E. coli* was at least 63% and 55% respectively. There was no incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in our population of patient.

Outcome of these infection are shown in Table III. Almost half of our patient with positive culture died; in which 16% succumbed to pneumonia. 32% of gram negative infections' and 10% of gram positive infections' patients died. From our study (Table IV), we found that patients above 40 years old (P = 0.013) and with ANC of < 0.5x109/L (P = 0.022) were associated with increased mortality risk. Sex, introduction of GCSF and antibiotic prophylaxis were not significantly associated with increased mortality, respectively.

DISCUSSION

This is the first retrospective study done in a public hospital in Malaysia which looked at MDI in adult haematological malignancy patients undergoing chemotherapy. The positive culture rate in our study was 19.3%, similar to that reported

Table I: Demographic Characteristics of Microbiologically Documented Infection Cases

Characteristics	No. of Cases (%)
Sex :	
M	35 (61.4)
F	22 (38.6)
Age (years): Median (IQR)	49.0 (27.0)
Age group (years) :	
0-20	6 (10.5)
21-40	16 (28.1)
41-60	27 (47.4)
>60	8 (14.0)
Haematological disease :	
Acute Leukaemia	34 (59.6)
Lymphoproliferative disease	20 (35.1)
Multiple Myeloma	3 (5.3)
State of disease :	
Induction	32 (56.1)
Relapse	13 (22.8)
Refractory	12 (21.1)
Intensity of chemotherapy :	
Intensive (Flag-Ida, HyperCVAD, MIDAC/HIDAC)	24 (42.1)
Non intensive (All others)	33 (57.9)
Central catheter	19 (33.3)
Mucositis (>Gd 2)	17 (29.8)
GCSF given	42 (73.7)
Prophylactic antibiotic	47 (82.5)
Comorbids :	
None	48 (84.2)
Hepatitis B carrier	4 (7.0)
Renal failure	5 (8.8)
Absolute neutrophil counts	
Median (IQR)	0.3 (0.8)
Category:	
≥1 x10^9 /L	13 (22.8)
≥0.5 to <1x10^9 /L	7 (12.3)
≥0.1 to <0.5 x10^9/L	22 (38.6)
<0.1 x10^9 /L	15 (26.3)
Death (total) :	29 (50.9)
Due to sepsis	15 (51.7)
Related to progressive disease	14 (48.3)

Table II: Aetiological agents of microbiological documented infections

Organism	Total no. of organisms n (%)	Total no. of organism causing death n(%)
Gram Negative (n= 44)		
Klebsiella pneumoniae	11 (25.0)	4 (36.0)
Pseudomonas aeruginosa	8 (18.2)	2 (25.0)
Escherichia coli	11 (25.0)	1 (9.1)
Acinetobacter baumanii	4 (9.1)	3 (75.0)
Salmonella enteriditis	6 (13.6)	2 (33.3)
Sphingomonas paucimobilis	1 (2.3)	0 (0.0)
Enterobacter cloacae	1 (2.3)	1 (100.0)
Stenotrophomonas maltophilia	2 (4.5)	1 (50.0)
Gram positive (n=10)		
Staphylococcus aureus	2 (20.0)	1 (50.0)
coagulase- negative Staphylococcus	4 (40.0)	0 (0.0)
Corynebacterium bovis	1 (10.0)	0 (0.0)
Streptococci Group D	1 (10.0)	0 (0.0)
viridans group Streptococci	2 (20.0)	0 (0.0)
Fungus (n=3)		
Aspergillus penicillioides	1 (33.3)	0 (0.0)
Candida albicans	1 (33.3)	0 (0.0)
Candida glabrata	1 (33.3)	0 (0.0)

Table III: Analysis of Infection Related Mortality Risk Factors

	Variable	n Freq (%)	Septic Death Freq (%)	Not septic death (df)	χ^2 statistic Value	P
Sex	Male	35	11 (73.3)	24 (57.1)	1.22 (1)	0.269
	Female	22	4 (26.7)	18 (42.9)		
Age (years old)	< 40	22	2 (13.3)	20 (47.6)	5.48 (1)	0.019
	> 40	35	13 (86.7)	22 (52.4)		
Intensity of chemotherapy	Intensive	24	4 (26.7)	20 (47.6)	1.99 (1)	0.158
	Non intensive	33	11 (73.3)	22 (52.4)		
Neutrophils ($x10^9$/L)	≥0.5	20	2 (13.3)	18 (42.9)	4.23 (1)	0.040
	<0.5	37	13 (86.7)	24 (57.1)		
GCSF	Yes	40	9 (60.0)	31 (73.8)	1.00 (1)	0.185
	No	17	6 (40.0)	11 (26.2)		
Prophylactic antibiotic	Yes	47	12 (80.0)	35 (85.4)	0.23 (1)	0.713
	No	10	3 (20.0)	7 (14.6)		

Table IV: Determine the association between age group and neutrophil count towards outcome using multivariate logistic regression

Predictors	Coefficient	OR	95%CI	P value
Constant	-3.984			
Age group	2.126			
< 40	ref			
>40		8.384	1.567, 44.871	0.013
Neutrophils category	1.974			
>0.5	ref			
< 0.5		7.196	1.329, 38.951	0.022

in earlier trials[4,5]. The low positivity rate could be due to routine use of antibiotic prophylaxis[6] and use of culture based method, which is still the gold standard for detection of bacterial pathogens which has its limitation in terms of rapidity and low sensitivity[7]. Therefore, empirical treatment based on patient clinical findings and history of presenting complain remains the cornerstone of the overall strategy employed for our patient population.

Our study showed that more than 60% of patient above 40 years old were more likely to develop infection despite the fact that majority of them were given significantly less intense chemotherapy (P = 0.000) , had almost equal incidence of mucositis (P= 0.353) and had higher ANC (P= 0.327). We believe that with more profound neutropenia[11], infection increases and we showed that MDI rates were high in patient with ANC less than $0.5x10^9$/L (64.9%). More importantly, death due to sepsis was also statistically significant in this group of patients, which is consistent with a study which stated that age was an independent risk factor for neutropenic complications[8,9]. In our study, we found that patients above 40 years old and those with severe neutropenia (ANC less than $0.5x10^9$/L) were 8.4 times (p=0.013) and 7.2 times (p=0.022) more likely to succumb to sepsis respectively. In contrast to an earlier study[10] which demonstrated that elderly patients had similar outcomes as their younger counterparts, we strongly believe that older patients need more aggressive management as well as appropriate empirical antibiotic therapy.

It is interesting to note that highly intense chemotherapy, which is known to produce more profound neutropenia[12] (p=0.03) did not increase mortality (p= 0.158) in our study. Intensive chemotherapy that were used by our patient were Flag-Ida, HyperCVAD, Midac/Hidac consisting of high dose methrotrexate and cytosine arabinoside.

Identification of the possible causative infectious agent is important in the management of infection in haematological malignancy patients. Despite a worldwide shift of gram negative to gram positive infections [13-15], gram negative infection remained our main pathogen of infection at our centre (77.2%). The reason could be due to less usage of indwelling catheters, as only 33% of patients had central catheters, and antacid was not commonly prescribed in our population compared to developed countries [16,17]. There were few studies, mainly from Asia that also reported predominant gram negative pathogens causing infection[18-20].

The common organisms cultured were *K pneumoniae* and *E. coli* (25%) followed by *P aeruginosa* (20%). Although there was no MRSA isolated in our study population, we noticed a resistance rate of more than sixty percent among *K pneumoniae* and *E. coli*. The ESBL rate among *K pneumoniae* and *E. coli* were 15%, quite similar to a study done in a teaching hospital in Malaysia[18]. This could likely due to high usage of amoxicillin/clavulanate and/or ciprofloxacin as prophylactic antibiotic in eighty two percent of our study population. Perhaps, antibiotic prophylaxis should be used judiciously in a more selective group of patient. There were contradicting views as to the routine use of fluoroquinolones

as prophylactic antibiotics in neutropenic patients with haematological malignancies in terms of reducing mortality and selection of resistant bacteria pathogens[19,21-24].

Our overall mortality rate was 27% which was higher than reported mortality rate of 7% and 14% in Singapore[19] and Thailand[25] respectively. Mortality was higher in gram negative infection group (31%). When we looked at mortality among specific organism group, *Enterobacter cloacae* has the highest mortality (100%), followed by *A. baumanii* (75%) and *Stenotrophomonas maltophilia* as well as *S.aureus* (50% each).

In this study, our patients population is small and there was no availability of a control group which are matched for age, disease and other risk factors, this being our biggest limitation. We initiated this study to look at our centre's adult haematological malignancy patients' risk factors profile and causative microorganism as our local data is limited. Therefore, we hope by performing this study we will have a platform to initiate a prospective study with matched controlled groups in the future.

CONCLUSION

Infection with gram negative organisms remained the major problem and main cause of mortality in management of haematological malignancy patients on chemotherapy in our centre. Our study showed that patient age more than 40 years old and ANC < $0.5x10^9$/L being two statistically significant risk factors associated with infection and mortality. There is strong need to relook into usage of antibiotic prophylaxis and perform continuous surveillance of resistant organisms in view of high rate of antibiotic resistance documented in this study.

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