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Clinical and microbiological characteristics of bloodstream infections among patients with haematological malignancies with and without neutropenia at a medical centre in northern Taiwan, 2008–2013

Chien-Yuan Chen [a], Feng-Ming Tien [a], Wang-Huei Sheng [b], Shang-Yi Huang [a], Ming Yao [a], Jih-Luh Tang [a,c], Woei Tsay [a], Hwei-Fang Tien [a], Po-Ren Hsueh [b,d,*]

[a] Division of Haematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[b] Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[c] Tai-Cheng Stem Cell Centre, National Taiwan University Hospital, Taipei, Taiwan
[d] Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan

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ABSTRACT

This study aimed to investigate the epidemiology and microbiology of bloodstream infections (BSIs) in patients with haematological malignancies. Clinical characteristics and microbiology of 2083 patients with haematological malignancy who were treated for BSI from 2008 to 2013 at a medical centre in Taiwan were retrospectively reviewed. Lymphoma (38.1%) was the most common, followed by acute myeloid leukaemia (30.9%). Of the 2090 non-duplicate BSI isolates, 1310 (62.7%) were recovered from patients with neutropenia. Of the Gram-negatives (53.7%), *Escherichia coli* was predominant (13.8%), followed by *Klebsiella pneumoniae* (9.5%), *Acinetobacter calcoaceticus–baumannii* (ACB) complex (5.7%) and *Pseudomonas aeruginosa* (4.0%). Of the Gram-positives (40.2%), coagulase-negative staphylococci were the most common (20.5%), followed by *Enterococcus faecium* (5.6%). *Candida tropicalis* (2.0%) was the most commonly encountered yeast (5.0%). Multidrug resistance (MDR) was identified in 21.8% of ACB complex isolates. Among the 57 *Staphylococcus aureus* isolates, 24 (42.1%) were resistant to oxacillin (MRSA), and among the 118 *E. faecium* isolates, 55 (46.6%) were resistant to vancomycin (VRE). The overall 14-day mortality rate was 12.9% ($n = 269$). There was no significant difference in 14-day mortality among patients with (13.4%) and without (11.9%) neutropenia ($P = 0.315$). Multivariate analysis revealed that age ≥60 years, prior allogeneic transplantation, BSI due to VRE (*E. faecium*) and shock were independent predictors of 14-day mortality. Gram-negative organisms continued to be the most common cause of BSI in patients with haematological malignancies during the period 2008–2013. There was a significant increase in the prevalence of VRE (*E. faecium*) and MDR-ACB complex isolates.

1. Introduction

Infection is the most common complication of chemotherapy in patients with haematological malignancies [1–3]. Although a number of novel targeted cancer therapies have been shown to decrease the risk of neutropenia, the majority of patients with haematological malignancies are still treated with conventional cytotoxic chemotherapy [1–3]. Infection is not only associated with high rates of morbidity and mortality among patients with haematological malignancies but also results in prolonged length of hospitalisation and significant economic losses [4–7]. Studies on the epidemiology of bloodstream infections (BSIs) in cancer patients with neutropenia have shown a shift in prevalence over the past several decades from Gram-negative to Gram-positive pathogens, although some studies have found that the prevalence of Gram-negative pathogens is on the rise [8–10]. The microbiological spectrum and antimicrobial susceptibility of pathogens causing BSI in patients with neutropenia vary widely between geographic regions [8–10]. In the Asia-Pacific region, there are relatively limited epidemiological data on pathogens causing BSI in cancer patients with neutropenia.

At National Taiwan University Hospital (NTUH) (Taipei, Taiwan), the aetiology of BSIs in patients with haematological malignancies has been regularly monitored since 1996 [11,12]. During the period 1996–2006, the predominant pathogens causing BSI in patients with haematological malignancies were Gram-negative organisms [11,12]. The emergence of multidrug-resistant organisms (MDROs), an increasing threat to neutropenic cancer patients, was noted not only in our previous studies but also in studies from other countries in the past several decades [9–14]. Our previous

* Corresponding author. Department of Laboratory Medicine, National Taiwan University Hospital, 7 Chung Shan South Road, Taipei 100, Taiwan. Fax: +886 2 2395 5072.
E-mail address: hsporen@ntu.edu.tw (P.-R. Hsueh).

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studies conducted from 2002 to 2006 clearly demonstrated the emergence of extensively drug-resistant (XDR) *Acinetobacter calcoaceticus–baumannii* (ACB) complex and vancomycin-resistant enterococci (VRE) in patients with haematological malignancies [11,12]. Continuous surveillance of the aetiology of BSIs in patients with haematological malignancies (with or without neutropenia) is crucial because of the recent increase in infections caused by MDROs, which further limits the choice of suitable antimicrobial agents.

The Multinational Association for Supportive Care in Cancer (MASCC) risk index is a scoring system designed to identify cancer patients at low risk of developing neutropenia [15]. However, neutropenia is significantly more common in patients with haematological malignancy than in those with solid cancers. Infections in patients with haematological malignancies also differ from those in patients with solid cancer because of differences in many factors, including tumour biology, chemotherapy agents, adverse effects of chemotherapy, cell- or humoral-mediated immunity, severity and duration of neutropenia, and allogeneic transplantation. Risk factors for mortality in patients with haematological malignancy and neutropenia have not been well established. In this study, the medical records of patients with haematological malignancies during the period 2008–2013 were retrospectively reviewed and the epidemiology of BSIs in these patients was investigated.

The clinical characteristics and outcomes of the patients were also analysed.

2. Materials and methods

2.1. Setting and patients

NTUH is a 2600-bed teaching hospital in metropolitan Taipei that provides both primary and tertiary care. The medical records of patients admitted to the haematological ward at NTUH during the period 1 January 2008 to 31 December 2013 were retrospectively reviewed. Inclusion criteria included patients with acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), lymphoma, multiple myeloma (MM), chronic myeloid leukaemia (CML), myeloproliferative neoplasm (MPN), chronic lymphocytic leukaemia (CLL), myelodysplastic syndrome (MDS) and aplastic anaemia (AA). Patients who were admitted to the hospital for other haematological diseases such as haemolytic anaemia, idiopathic thrombocytopenia, haemophilia or coagulation disorders were excluded. A total of 2083 patients fulfilled the inclusion criteria and were included in the study. Most patients were admitted to receive induction chemotherapy, consolidation chemotherapy or salvage chemotherapy, or were undergoing haematopoietic stem cell transplantation (HSCT). Other patients were admitted for the treatment of complications of haematological malignancies such as infectious diseases or bleeding.

A complete physical examination was performed at baseline and at least once daily during therapy for malignancies. Imaging by computed tomography (CT), ultrasound and other examinations were performed if indicated according to clinical conditions. Laboratory data and radiographic images obtained before the start of antibiotic therapy included results from liver function tests, renal function tests, urinalysis, urine cultures and chest radiography. Two or three sets of blood cultures (aerobic and anaerobic bottles), with at least one set from peripheral veins and one set from intravascular catheters if present [16], were processed using a BD BACTEC™ 9240 Automated System (Becton Dickinson, Sparks, MD). Bacteria and fungi were identified by conventional biochemical methods and the Phoenix identification system (Becton Dickinson).

Febrile neutropenia was defined according to the criteria of the Infectious Disease Society of America (IDSA) [17,18]. Fever was defined as an axillary temperature of 38.3 °C on one occasion or a temperature of >38.0 °C on two or more occasions during a 12-h period. Neutropenia was defined as a neutrophil count of <500 cells/mm^3 or a count of <1000 cells/mm^3 with a predicted decrease to <500 cells/mm^3. Infections were classified as community-acquired if fever developed within 72 h of admission, whilst development of fever after this time indicated nosocomial infection. Catheter-related infection was defined as previously described [16].

2.2. Antimicrobial susceptibility testing

The antimicrobial susceptibilities of the isolates were determined using a Phoenix PMIC/ID-62 and PMIC/ID-72 system (Becton Dickinson). Non-duplicate isolates of the same species with identical susceptibility profiles recovered from an individual patient within 7 days were excluded from the calculation of susceptibility rates. Extended-spectrum β-lactamase (ESBL) phenotypes in *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Klebsiella oxytoca* isolates were detected using methods in accordance with the Clinical and Laboratory Standards Institute (CLSI) [19–21]. Isolates showing intermediate susceptibility to an antimicrobial agent were classified as resistant. MDROs included methicillin-resistant *Staphylococcus aureus* (MRSA), VRE, carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *Pseudomonas aeruginosa* and multidrug-resistant (MDR) ABC complex. Carbapenem-resistant isolates were defined as isolates resistant to imipenem, meropenem or ertapenem (Enterobacteriaceae only). MDR isolates were defined as isolates non-susceptible to at least one agent in three or more of the following antibiotic classes: extended-spectrum cephalosporins (cefotaxime, ceftazidime or cefepime); piperacillin/tazobactam (TZP); fluoroquinolones (ciprofloxacin or levofloxacin); carbapenems (imipenem or meropenem); and aminoglycosides (gentamicin or amikacin). XDR-ACB complex isolates were defined as ACB isolates showing non-susceptibility to at least one agent in all but two or fewer antimicrobial categories tested, including ampicillin/sulbactam, ceftazidime, cefepime, TZP, aztreonam, imipenem, meropenem, ciprofloxacin, levofloxacin, gentamicin and amikacin, with the exception of colistin and tigecycline. Pandrug-resistant (PDR) isolates were defined as isolates non-susceptible to all agents tested in all antimicrobial categories [22]. Isolates with colistin minimum inhibitory concentrations (MICs) of ≤2 mg/L were classified as susceptible and those with MICs of ≥4 mg/L were classified as resistant [20].

2.3. Antimicrobial prophylaxis, treatment and granulocyte-colony stimulating factor (G-CSF)

During the study period, prophylactic antibiotics such as oral levofloxacin or amoxicillin/clavulanic acid (AMC) were used in high-risk populations (e.g. acute leukaemia and HSCT) in whom chemotherapy-induced neutropenia (<500 neutrophils/mm^3) was expected to last >7 days. Antifungal prophylaxis was not routinely used after chemotherapy. Empirical antibiotic regimens for patients with neutropenia followed published guidelines [23,24]. G-CSF was administered to reduce the incidence of chemotherapy-induced neutropenia in adult patients with lymphoid malignancy or myeloid malignancy in remission status.

2.4. Statistical analysis

The χ^2 test was used for categorical comparisons of data. For the trend in resistance of MDROs, comparison of three ordinal time periods was analysed with Kruskal's gamma test. Significant predictors in the univariate analyses were included in a forward stepwise multiple logistic regression model to identify the most important risk factors for 14-day mortality. Cox proportional hazards analysis was used to determine the relative contribution of various factors to the risk of 14-day mortality. In the multivariate analysis, factors with a *P*-value of <0.1 in the univariate analysis were selected for