HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.elsevier.com/locate/apjtb

Clinical research http://dx.doi.org/10.1016/j.apjtb.2015.09.014

Evaluation of febrile neutropenic patients hospitalized in a hematology clinic

Mücahit Görük[1], Mehmet Sinan Dal[1*], Tuba Dal[2], Abdullah Karakus[1], Recep Tekin[3], Nida Özcan[4], Orhan Ayyildiz[1]

[1]*Department of Internal Medicine, Dicle University School of Medicine, Diyarbakır, Turkey*

[2]*Department of Medical Microbiology, Yıldırım Beyazıt University School of Medicine, Ankara, Turkey*

[3]*Department of Clinical Microbiology and Infectious Diseases, Dicle University School of Medicine, Diyarbakır, Turkey*

[4]*Department of Medical Microbiology, Dicle University School of Medicine, Diyarbakır, Turkey*

ARTICLE INFO

Article history:
Received 25 May 2015
Received in revised form 4 Jul 2015
Accepted 4 Aug 2015
Available online 20 Oct 2015

Keywords:
Febrile neutropenia
Hematological malignancy
Leukemia
Multiple myeloma
Infections

ABSTRACT

Objective: To evaluate the febrile neutropenic patients with hematological malignancies hospitalized in hematology clinic with poor hygiene standards.

Methods: A total of 124 patients with hematological malignancies (69 male, 55 female) hospitalized in hematology clinic with poor hygiene conditions depending on hospital conditions, between January 2007 and December 2010, were evaluated, retrospectively.

Results: In this study, 250 febrile neutropenia episodes developing in 124 hospitalized patients were evaluated. Of the patients, 69 were men (56%) and 55 women (44%). A total of 40 patients (32%) had acute myeloid leukemia, 25 (20%) acute lymphoblastic leukemia, 19 (15%) non-Hodgkin's lymphoma, 10 (8%) multiple myeloma, and 8 (8%) chronic myeloid leukemia. In our study, 56 patients (22%) were diagnosed as pneumonia, 38 (15%) invasive aspergillosis, 38 (15%) sepsis, 16 (6%) typhlitis, 9 (4%) mucormycosis, and 4 (2%) urinary tract infection. Gram-positive cocci were isolated from 52% (n = 20), while Gram-negative bacilli 42% (n = 16) and yeasts from 6% (n = 2) of the sepsis patients, respectively. The most frequently isolated Gram-positive bacteria were methicillin-resistant coagulase-negative staphylococci (n = 18), while the most frequently isolated Gram-negative bacteria was *Escherichia coli* (n = 10).

Conclusions: Febrile neutropenia is still a problem in patients with hematological malignancies. The documentation of the flora and detection of causative agents of infections in each unit would help to decide appropriate empirical therapy. Infection control procedures should be applied for preventing infections and transmissions.

1. Introduction

Febrile neutropenia is the most important cause of morbidity and mortality in patients with malignancies [1]. Intensive chemotherapy programs, successful applications of stem cell transplantation, platelet transfusions, usage of colony-stimulating factors, developing diagnostic techniques and broad spectrum antimicrobials have led to prolonged survival. A large number of infectious complications can lead to mortality and morbidity in hematologic malignancy patients. Iatrogenic manipulations or damage of mucosal barriers due to chemotherapy or mucositis can cause opportunistic infections. In these patients, initiation of empirical antibiotic treatment within the first hour of the infection is life saving [1]. Other factors affecting mortality on febrile neutropenic patients are underlying hematologic malignancy type, stage of disease, and comorbid diseases. The medical hygiene practises including isolation or quarantine of infectious persons, private rooms for each patients or materials to prevent spread of infection, sterilization of instruments used in surgical procedures, the use of protective clothing and barriers, such as masks, gowns, caps, eyewear and gloves, proper bandaging and dressing of injuries, and hand-washing are very important for the prevention of infections developed in these patients [1–4]. Therefore in this study, we aimed to evaluate the febrile neutropenic patients

*Corresponding author: Mehmet Sinan Dal, Department of Internal medicine, Faculty of Medicine, Dicle University, Diyarbakir, Turkey.
Tel: +90 506 3572438
E-mail: dr.sinandal@hotmail.com
Peer review under responsibility of Hainan Medical University.

with hematological malignancies hospitalized in hematology clinic with poor hygiene conditions depending on hospital conditions.

2. Materials and methods

2.1. Sample collections

A total of 124 patients with hematological malignancies (69 male, 55 female) hospitalized in Department of Hematology, Faculty of Medicine, Dicle University, between January 2007 and December 2010, were evaluated, retrospectively. Hematology Clinic of Dicle University Hospital had poor hospital infection control practices depending on hospital conditions (the lack of a private room for each patient). Diagnosis of febrile neutropenia was based on axillary temperature measurement and peripheral blood neutrophil count. Measurement of oral or axillary temperature as $\geq$ 38.3 °C or of 38.0–38.2 °C for 1 h were defined as fever. If the neutrophil count was lower than 500/mm^3, or 500–1 000/mm^3 but expected to fall < 500/mm^3 in 48 h were defined as neutropenia. Profound neutropenia was defined as neutrophil count of < 100/mm^3 [1–4]. Patients included in the study were divided into three groups: diagnosed microbiologically, clinically, and radiologically. The age, sex, admission date, length of stay, clinical diagnosis, duration of neutropenia, count of neutropenia, duration of fever, hemoglobin, leukocytes, platelets, prothrombin time/international normalized ratio, alanine aminotransferase, aspartat aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, total bilirubin, albumin, globulin, lactate dehydrogenase, C-reactive protein, erythrocyte sedimentation rate, blood culture, urine culture, sputum culture, blood smear, posteroanterior chest X-ray, thorax, upper and lower abdominal computed tomography results were recorded. In the diagnosis of invasive aspergillosis, European Organization for Research and Treatment of Cancer criteria were used [4].

Outpatients with febrile neutropenia, patients with lung cancer, breast cancer, colorectal cancer and solid organ tumors, and febrile neutropenic patients hospitalized in hematology clinic but unclassified clinically, microbiologically and radiologically were excluded from the study.

2.2. Statistical analysis

SPSS program for Windows 7 was used in statistical evaluation of the data obtained in this study. Statistically, mean ± SD, SE, minimum and maximum values were calculated. Odds and percentages were determined. Frequency distributions were created. *Chi*-square test was applied. Student's *t*-test was used in comparisons of the binary. Pearson correlation analysis was performed. Significance level was considered as $P < 0.05$.

3. Results

A total of 250 febrile neutropenia episodes of 124 hospitalized patients were evaluated. Of the patients, 69 were men (56%) and 55 women (44%). The mean age of the patients was (45.0 ± 19.4) years. The average length of hospital stay was (22.7 ± 15.8) days, average duration of fever was (11.1 ± 6.8) days, while duration of neutropenia was (8.2 ± 5.9) days.

A total of 40 patients (32%) were diagnosed as acute myeloid leukemia (AML), 25 (20%) acute lymphoblastic leukemia (ALL), 19 (15%) non-Hodgkin's lymphoma (NHL), 10 (8%) multiple myeloma, and 8 patients (8%) chronic myeloid leukemia. Among the patients 7 patients were defined as unclassified leukemia, 6 patients were chronic lymphoblastic leukemia (Figure 1). Gender, age and the number of attacks in AML, ALL and NHL patients were shown in Table 1.

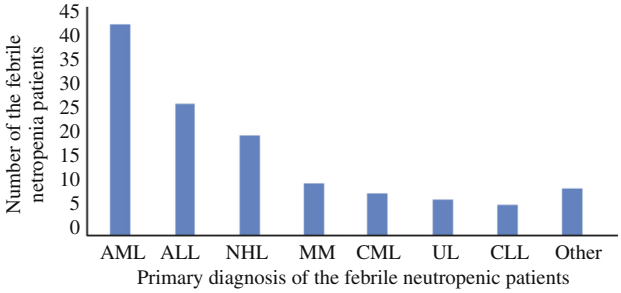

Figure 1. Distribution of primary diagnosis of the patients with febrile neutropenia.
MM: Multiple myeloma; CML: Chronic myeloid leukemia; UL: Unclassified leukemia; CLL: Chronic lymphoblastic leukemia.

Table 1
Gender, age and the number of attacks in AML, ALL and NHL patients.

Characteristics	AML	ALL	NHL
Sex (male/female)	18/22	13/12	10/9
Mean age of all patients	43.8 ± 16.9	34.3 ± 18.7	38.3 ± 13.4
Mean age of female	45.2 ± 19.1	36.7 ± 20.9	35.3 ± 13.1
Mean age of male	42.1 ± 14.2	29.3 ± 15.6	41.0 ± 13.8
Mean number of FN attacks	2.4 ± 1.9	2.4 ± 1.9	2.1 ± 1.8

FN: Febrile neutropenia.

In our study, 56 patients (22%) were diagnosed as pneumonia, 38 (15%) invasive aspergillosis, 38 (15%) sepsis, 16 (6%) typhlitis, 9 (4%) mucormycosis, and 4 (2%) urinary tract infection.

In 250 episodes of febrile neutropenia, 129 (51.6%) cases were diagnosed clinically, 104 (41.6%) radiologically and 71 (28.4%) microbiologically.

Of 56 cases with pneumonia, 42 cases had radiological diagnosis, 25 clinical diagnosis and 9 microbiological diagnosis. Two of them died. Mean hospitalization duration of patients with pneumonia was (20.1 ± 12.7) days, duration of fever was (9.9 ± 4.7) days and neutropenia duration was (6.9 ± 3.9) days.

Of 38 cases with invasive aspergillosis, 35 had radiological diagnosis, 10 clinical diagnosis and 5 microbiological diagnosis. The mortality was detected in 8 of 38 cases. Of cases with invasive aspergillosis, mean duration of hospitalization was (38.9 ± 20.6) days, while of fever and neutropenia were (20.1 ± 8.4) and (15.7 ± 8.7) days, respectively.

Of 38 cases with sepsis, mean duration of hospitalization, fever and neutropenia were (26.6 ± 17.6), (14.1 ± 8.3) and (9.4 ± 7.3) days, respectively.

Of 212 cases without sepsis, mean duration of hospitalization, fever and neutropenia were (22.0 ± 15.4), (10.6 ± 6.4) and (8.0 ± 5.6) days, respectively. The mean age of sepsis cases was (43.6 ± 16.6), while of cases without sepsis was (42.9 ± 19.8). No significant difference was found between the sepsis cases and non-sepsis cases in terms of the mean age (P = 0.869), duration of hospitalization (P = 0.098) and the duration of

neutropenia ($P = 0.191$). However, duration of fever ($P = 0.003$) was higher in patients with sepsis, significantly.

Gram-positive cocci, Gram-negative bacilli, and yeasts were isolated 52% ($n = 20$), 42% ($n = 16$), and 6% ($n = 2$) of blood cultures of the sepsis patients, respectively. The most frequent isolated Gram-positive bacteria were methicillin-resistant coagulase-negative staphylococci ($n = 18$), while the most frequently isolated Gram-negative bacteria was *Escherichia coli* ($n = 10$).

4. Discussion

Infections, type of underlying hematologic malignancy, stage of disease, and comorbid diseases are the significant factors affecting mortality in patients with febrile neutropenia. The most frequent underlying malignancies in patients with febrile neutropenia include AML, ALL, and lymphomas similar to our study [5].

Studies conducted in the patients with febrile neutropenia showed lung infections were important source of the fever with the rates ranging from 20% to 24% [6,7]. Alterations of oropharyngeal flora, damages of gastrointestinal and respiratory mucosa due to chemotherapy and aspiration have important roles in the development of pneumonia. In crowded hospital rooms, pneumoniae agents can spread between the patients. Pneumonia were associated with a greater risk of mortality, and most types of infection were associated with a longer hospital length of stay and higher cost or radiation therapy [8,9]. Pneumonia rate in our patients was 22%, which is not higher than the rates mentioned in literature. However our results showed that to take measures to reduce the incidence of pneumonia was necessary for our clinic.

Incidence of invasive aspergillosis is higher in patients with hematological malignancies having prolonged and severe neutropenia. Development of invasive aspergillosis is associated with duration of neutropenic phase. Especially, after bone marrow transplantation, this risk varies between 4% and 6% [10]. Despite antifungal therapies, the mortality rate ranges from 50% to 80% in invasive aspergillosis. Early diagnosis and treatment greatly affect the prognosis. The clinical diagnosis, radiological findings, histopathological examination, culture and serological methods (measurement of serum and bronchoalveolar lavage fluid galactomannan level), molecular methods are used for the diagnosis [4,11–16]. In our study, 15% of patients had invasive aspergillosis. We suggested that medical hygiene practises including isolation or quarantine of infectious persons, private rooms for each patients should be immediately implemented in our clinic or a new hematology unit should be built in our hospital.

The risk factors for the development of bacteremia are age, type of transplantation, and type of malignancy, duration of neutropenia, presence of an indwelling central venous catheter were associated with bloodstream infection by multidrug-resistant bacteria [17]. In a study that carried out to assess the isolation rate of bacterial and fungal causative agents in neutropenic adults with hematological neoplasia, 120 consecutive episodes of febrile neutropenia during one year was evaluated. These episodes were observed in 630 patients discharged with diagnoses of leukemia or lymphoma, or after bone marrow transplantation. At least one pathogen was isolated in 42 of 120 episodes (35%), and was presented in 39 patients with AML (43%), ALL (23%), and in patients who underwent bone marrow transplantation (20%). Primary bacteremia was the most frequent cause of fever (24 episodes, 57%), followed by intravascular device-related infections (5 episodes, 17%), and soft-tissue infections (5 episodes, 15%) [18]. In our study, sepsis was observed in 15% of cases. This result was in substantial value. We suggested that our sepsis rate can be reduced with the use of effective antibiotics in early period.

Mortality rate was found to be 24.5% in febrile neutropenic patients developing bacteremia in the study of Velasco *et al.* [19]. In a different study, 237 patients with febrile neutropenia were analyzed, and the mortality rate within 30 days was found to be 9% [20]. In our study, there was no difference in mortality between sepsis patients and non-sepsis patients. Differences between the distribution of patients' age groups, type of underlying disease, treatment regimens, isolated microorganism species may be responsible for the different results of the studies.

In the 1970s, the Gram-negative bacteria were the main microorganisms isolated from the infections. However, the incidence of Gram-positive microorganism infections have gradually increased since the mid-1980s due to permanent use of indwelling venous catheters, previous empirical antibiotic treatment regimens for Gram-positive microorganisms and increased use of chemotherapeutic agents [21–23]. In our study, Gram-positive cocci were isolated from 52% of the patients with sepsis, Gram-negative bacilli from 42%. Methicillin-resistant coagulase-negative staphylococci were the most frequently isolated Gram-positive bacteria while *Escherichia coli* was the most frequently isolated Gram-negative bacteria. In our study, we did not determine the pattern of antibiotic susceptibility of microorganisms. However, we suggested that bacteria are the important cause of infections in febrile neutropenic patients and in order to select the most effective empirical therapy, each hospital should evaluate developing infections, and detect distribution of causative agents with their antimicrobial susceptibility pattern. The data obtained from this study will guide to appropriate empirical treatment policies and treatment success in febrile neutropenic patients of our clinic. On the other hand in a total of 250 episodes of febrile neutropenia, only 28.5% of the cases were diagnosed microbiologically. We suggested that evidence-based therapy was significant for reducing mortality and morbidity in febrile neutropenic patients. Shortcomings related with microbiological sampling and specimen transport shortcomings should be corrected, the hematology staffs should be in cooperation with the microbiology laboratory.

In conclusion, febrile neutropenia is still an important cause of mortality and morbidity in patients with hematological malignancies. The documentation of the flora, determination of causative agents of infections, and detection of antibiotic and antifungal susceptibility profiles in each unit would help to decide appropriate empirical therapy. In addition to these it should be kept in mind that infection control procedures including hand hygiene, standard barrier precautions, private rooms, and don't allow plants and dried or fresh flowers into patient rooms may be effective means for preventing infections and transmissions.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Uys A, Rapoport BL, Anderson R. Febrile neutropenia: a prospective study to validate the Multinational Association of Supportive Care of Cancer (MASCC) risk-index score. *Support Care Cancer* 2004; **12**(8): 555-60.

[2] André S, Taboulet P, Elie C, Milpied N, Nahon M, Kierzek G, et al. Febrile neutropenia in French emergency departments: results of a prospective multicentre survey. *Crit Care* 2010; **14**(2): R68.

[3] Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Biol Blood Marrow Transplant* 2009; **15**(10): 1143-238.

[4] De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46**: 1813-21.

[5] Azap A, Bozkurt GY, Yüksel MK, Kutlu H, Topçuoğlu P, Aypak A, et al. Secondary infections in cancer patients with febrile neutropenia. *Turk J Hematol* 2012; **29**: 254-8.

[6] Velasco E, Thuler LCS, Martins CAS, Dias LMC, Gonçalves VMS. Risk factors for bloodstream infections at a cancer center. *Eur J Clin Microbiol Infect Dis* 1998; **17**: 587-90.

[7] Çelebi H, Akan H, Akçağlayan E, Ustün C, Arat M. Febrile neutropenia in allogeneic and autologous peripheral blood stem cell transplantation and conventional chemotherapy for malignancies. *Bone Marrow Transplant* 2000; **26**: 211-4.

[8] Yolin-Raley DS, Dagogo-Jack I, Niell HB, Soiffer RJ, Antin JH, Alyea EP 3rd, et al. The utility of routine chest radiography in the initial evaluation of adult patients with febrile neutropenia patients undergoing HSCT. *J Natl Compr Canc Netw* 2015; **13**(2): 184-9.

[9] Dulisse B, Li X, Gayle JA, Barron RL, Ernst FR, Rothman KJ, et al. A retrospective study of the clinical and economic burden during hospitalizations among cancer patients with febrile neutropenia. *J Med Econ* 2013; **16**(6): 720-35.

[10] Kolbe K, Domkin D, Derigs HG, Bhakdi S, Huber C, Aulitzky WE. Infectious complications during neutropenia subsequent to peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1997; **19**: 143-7.

[11] McWhinney PH, Kibbler CC, Hamon MD, Smith OP, Gandhi L, Berger LA, et al. Progress in the diagnosis and management of aspergillosis in bone marrow transplantation: 13 years' experience. *Clin Infect Dis* 1993; **17**: 397-404.

[12] Gheith S, Saghrouni F, Bannour W, Ben Youssef Y, Khelif A, Normand AC, et al. Characteristics of invasive aspergillosis in neutropenic haematology patients (Sousse, Tunisia). *Mycopathologia* 2014; **177**(5): 281-9.

[13] Cerikçioğlu N, Aksu B, Dal TD, Deniz U, Bilgen HS, Ozek E, et al. Seminested PCR for detection and identification of *Candida* species directly from blood culture bottles. *New Microbiol* 2010; **33**(1): 57-62.

[14] Demirkazık FB, Akın A, Uzun Ö, Akpınar MG, Arıyürek MO. CT findings in immunocompromised patients with pulmonary infections. *Diagn Interv Radiol* 2008; **14**(2): 75-82.

[15] Altınel E, Yaralı N, Işık P, Özakasap S, Bay A, Kara A, et al. [Evaluation of febrile neutropenia in children with acute leukemia]. *Turk J Pediatr Dis* 2012; **6**(2): 93-100. Turkish.

[16] Nicolle MC, Bénet T, Thiebaut A, Bienvenu AL, Voirin N, Duclos A, et al. Invasive aspergillosis in patients with hematologic malignancies: incidence and description of 127 cases enrolled in a single institution prospective survey from 2004 to 2009. *Haematologica* 2011; **96**(11): 1685-91.

[17] Gaytán-Martínez J, Mateos-García E, Sánchez-Cortés E, González-Llaven J, Casanova-Cardiel LJ, Fuentes-Allen JL. Microbiological findings in febrile neutropenia. *Arch Med Res* 2000; **31**(4): 388-92.

[18] Rosa RG, Goldani LZ, dos Santos RP. Risk factors for multidrug-resistant bacteremia in hospitalized cancer patients with febrile neutropenia: a cohort study. *Am J Infect Control* 2014; **42**(1): 74-6.

[19] Velasco E, Byington R, Martins CA, Schirmer M, Dias LM, Gonçalves VM. Prospective evaluation of the epidemiology, microbiology and outcome of bloodstream infections in hematologic patients in a single cancer center. *Eur J Clin Microbiol Infect Dis* 2003; **22**: 137-43.

[20] Combariza JF, Lombana M, Pino LE, Arango M. C-reactive protein and the MASCC risk index identify high-risk patients with febrile neutropenia and hematologic neoplasms. *Support Care Cancer* 2015; **23**(4): 1009-13.

[21] Butt T, Afzal RK, Ahmad RN, Salman M, Mahmood A, Anwar M. Bloodstream infections in febril neutropenic patients: bacterial spectrum and antimicrobial susceptibility pattern. *J Ayub Med Coll Abbottabad* 2004; **16**: 18-22.

[22] De Pauw BE, Meunier F. Infections in patients with acute leukemia and lymphoma. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's principles and practice of infectious disease*. Philadelphia: Churchill Livingstone; 2000, p. 3090.

[23] Cattaneo C, Quaresmini G, Casari S, Capucci MA, Micheletti M, Borlenghi E, et al. Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant *Escherichia coli* among patients with haematological malignancies: results of a prospective study on 823 patients at a single institution. *J Antimicrob Chemother* 2008; **61**: 721-8.