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Infectious complications in patients with hematological malignancies consulted by the Infectious Diseases team: a retrospective cohort study (1997–2001)

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Abstract In order to identify the characteristics of patients with hematological malignancies (HM) in the presence/suspicion of any accompanying infectious disease, and to find the predictors of mortality in this group, hospital charts of patients with HM consulted by the Infectious Diseases (ID) team for signs/symptoms of any infection between January 1, 1997 and December 31, 2001 were retrospectively reviewed. A total of 1,132 consultations were done for 641 patients: 59.4% of the patients were male and the mean (±standard deviation) age of the study participants was 47.9±1.4 years. The most common underlying diseases were non-Hodgkin's lymphoma (30.9%), acute myelogenous leukemia (26.2%), and multiple myeloma (10.9%). Clinically and microbiologically documented infections and fever of unknown origin were observed in 43.3%, 38.1%, and 18.5% of the participants, respectively. Bloodstream infections were detected in 134 episodes (20.9%): 56.5% were caused by gram-negative microorganisms. In logistic regression analysis, the presence of pneumonia (OR 7.56, 95% CI 4.84–12.486), invasive fungal infection (OR 4.12, 95% CI 1.78–9.55), relapse or recent diagnosis of the underlying disease (OR 2.82, 95% CI 1.53–5.21) and neutropenia (OR 2.70, 95% CI 1.70–4.31) were identified as statistically significant predictors of mortality.

Keywords Hematological malignancy · Infection · Cancer

Introduction

Infectious complications in patients with hematological malignancies are still a major cause of morbidity and mortality despite significant advances in diagnostic techniques and antimicrobial therapy [1]. Infections may go undetected in cancer patients due to the absence of any obvious signs and symptoms, except for fever [2]. A comprehensive understanding of the characteristics of hematological cancer patients with infection, and identification of predictors of mortality in this group will help clinicians to undertake timely preventive measures in high-risk patients.

In this study, we describe the characteristics of patients with hematological malignancies who were referred to the Infectious Diseases (ID) team for suspected infection, and the predictors of mortality in these patients.

Materials and methods

The study was conducted at Hacettepe University Hospital, a 900-bed tertiary care university hospital in Ankara, Turkey. Hacettepe University hospital has an active hematology–oncology unit and approximately half of the inpatients have underlying malignancy. A strong collaboration exists among the ID, Hematology, and Oncology Units. All cancer patients suspected of an infection were routinely examined by the ID team.

A retrospective chart review was conducted for all episodes of adult patients (17 years or older) with hematologic malignancies who consecutively consulted with the ID Team for fever or any other signs or symptoms of infection between January 1, 1997–December 31, 2001. Data were collected on some demographic and disease char-

acteristics, and hospital outcome of the study participants, using a standardized data collection form. Infectious complications identified by the ID team were categorized into three groups: "clinically documented infections," "microbiologically documented infections," and "fever of unknown origin" (FUO). In the group, in 59.2% (N=675) of the episodes, patients were neutropenic. Of the 239 FUO episodes, 209 (87.4%) were neutropenic.

Statistical analysis included frequency and percent distributions, and logistic regression modeling. Statistical significance of differences between groups was tested using chi-square test, and Student's t test when appropriate. Odds ratios and 95% confidence intervals were calculated to evaluate the size of effect and its significance. Univariate and bivariate analyses were conducted for a total of 1,132 episodes, but multivariate analysis of predictors of mortality was limited only to the first episode of each participant (n=641). All statistical analyses were conducted using SPSS version 10.0 statistical software package.

Results

A total of 1,132 consultations were done over a period of 5 years for 641 patients. Of the patients, 59.4% were male and the mean (±standard deviation) age of the study participants was 47.9±1.4 years.

The most common underlying disease was non-Hodgkin's lymphoma (30.9%), followed by acute myelogenous leukemia (26.2%), multiple myeloma (10.9%), and Hodgkin's disease (8.1%) (Table 1).

In 30.7% of the episodes the underlying disease was in remission at the time of infection diagnosis, in 31.2% it was newly diagnosed, and in 35.6% it was either refractory to treatment or had relapse. The patient was neutropenic in 60% of the episodes.

Table 1 Baseline characteristics of study participants (N=641)

	Number	Percent
Gender		
Male	381	59.4
Female	260	31.6
Age (mean±SD) [years]=	47.9±1.4	
Underlying disease		
Non-Hodgkin's lymphoma	198	30.9
Acute myelogenous leukemia	168	26.2
Multiple myeloma	70	10.9
Hodgkin's disease	52	8.1
Acute lymphocytic leukemia	45	7.0
Chronic lymphocytic leukemia	43	6.7
Chronic myelocytic leukemia	40	6.3
Myelodysplastic syndrome	16	2.5
Other	9	1.4
Total	641	100.0

In 116 (10.2%) consultations, no infection was detected, and in an additional 241 episodes (18.5%) the patients were febrile, although no cause was identified, and were considered as FUO. More than one (maximum 3) infection was detected in 278 (24.6%) episodes (Table 2).

Of 1,306 infections detected, 567 (43.4%) were documented clinically, and 498 (38.1%) microbiologically. Pneumonia was the most common clinically documented infection and was detected in 173 episodes.

Bloodstream infections were present in 134 episodes, 122 were bacteremias and 12 fungemias; 56.5% of bacteremias were caused by gram-negative microorganisms (Table 3).

In 22 of the episodes, we clinically detected herpes labialis, although no other viral infections were reported, possibly due to our inability to microbiologically detect viral infections.

Invasive mould infections were diagnosed in 51 episodes, including 20 pulmonary involvement.

A total of 163 patients (25.4%) died during the infectious episode. The fatality rate was even higher in the presence of invasive aspergillosis, and 13 of the 29 patients with invasive aspergillosis died, corresponding to a fatality rate of

Table 2 Infectious complications identified during the study period*

Type of infections	Number	Percent
Clinically documented infections	567	43.4
Pneumonia	173	30.5
Skin, soft tissue, infections	119	20.9
Catheter-related	40	7.1
Head, neck, and upper respiratory tract infections	119	21.0
Perianal infections	77	13.6
Gastrointestinal tract infections	17	3.0
Tuberculosis	13	2.3
Bone and joint infections	8	1.4
Pericarditis	1	0.2
Microbiologic infections	498	38.1
Oral/eosophageal candidiasis	142	28.5
Gastrointestinal tract infections	124	24.9
Bacteremia	122	24.5
Fungemia	12	16.1
Genitourinary infections	80	2.4
Respiratory tract infections	11	2.2
Central nervous system infections	5	1.0
Other	2	0.4
Fever of unknown origin (FUO)	241	18.5
Neutropenic	209	86.7
Nosocomial	32	13.3
Total	1,306	100.0

*In 1,132 consultations, a total of 1,306 infections were detected. Percentage values were calculated either out of 1,306 or out of the total number of infections in a particular group

Table 3 Pathogens isolated in 134 episodes of bloodstream infections

Microorganism	Number	Percent
Gram-negative bacilli	69	
Escherichia coli	21	30.4
Klebsiella spp.	15	21.7
Pseudomonas aeruginosa	12	17.4
Enterobacter spp.	10	14.5
Stenotrophomonas maltophilia	4	5.8
Other*	7	10.2
Gram-positive bacteria	53	
MSSA	17	32.1
MRSE	10	18.9
MSSE	8	15.1
MRSA	8	15.1
Enterococcus faecalis	6	11.3
Streptococcus viridans	4	7.5
Fungi	12	
Candida albicans	3	25.0
Candida tropicalis	3	25.0
Candida parapsilosis	3	25.0
Candida lusitaniae	1	8.3
Unspecified *Candida* spp.	1	8.3
Fusarium spp.	1	8.3

**Serratia marcescens* 1; *Acinetobacter lwoffi* 1; *Aeromonas hydrophila* 1; *Citrobacter freundii* 1; and Polymicrobial 3
MRSA Methicillin Resistant Staphylococcus Aureus; *MSSA* Methicillin Sensitive Staphylococcus Aureus; *MRSE* Methicillin Resistant Staphylococcus Epidermidis; *MSSE* Methicillin Sensitive Staphylococcus Epidermidis

44.8%. In logistic regression analysis, the presence of pneumonia (OR 7.56, 95% CI 4.84–12.49), invasive fungal infection (OR 4.12, 95% CI 1.78–9.55), relapse or recent diagnosis of underlying disease (OR 2.82, 95% CI 1.53–5.21), and neutropenia (OR 2.70, 95% CI 1.70–4.31) were identified as statistically significant predictors of mortality, controlling for age and gender (Table 4).

Discussion

Major advances in medicine over the recent decades have prolonged the survival of cancer patients, although they can not always be provided with a disease-free life. The price paid for "death" of cancer cells is the major risk of compromised host defense mechanisms, leading to a patient population prone to infectious complications with high morbidity and mortality. Numerous studies have reported on infectious complications in these patients; these studies were based either on a certain type of infection (i.e., bacteremia, fungemia) [3, 4] or the efficacy of a certain antimicrobial regimen [5, 6]. There are a few reports on the overall distribution of infectious episodes in patients with hematological malignancies, the outcome and the impact of several factors on the outcome [7, 8]. In this study, we summarize the experience of an ID team in more than 1,000 consultations involving patients with hematological malignancies in an attempt to increase the awareness of infectious disease specialists and oncologists regarding potential infections and related risk factors they might face in the management of such patients.

There are several aspects of our findings that merit attention. First, pneumonia is a major infectious complication in this patient population. One third of our patients with a clinical documentation of infection had pneumonia. The lung appears to be highly vulnerable to damage by chemotherapy and is extensively susceptible to infection. In addition, the presence of pneumonia was an ominous sign of poor prognosis. Second, bloodstream infections occur in a substantial proportion of episodes (11.8%). Gram-negative bacilli were identified as pathogens in 52.5% of episodes with bloodstream infection. This finding parallels with the results obtained by Homsi et al. [7] in a population of nonneutropenic patients with solid tumors (48.0%) and by Feliu et al. [9], in a similar study that focused on febrile neutropenic patients with cancer. In contrast, Marie et al. [10] found in their population of severely neutropenic patients that 63 out of 105 isolated organisms were gram-positive in type. They linked the predominance of gram-

Table 4 Logistic regression model for predictors of mortality in patients with hematological malignancies and infectious complications

Variable name*	Beta	Standard error	Wald	Degrees of freedom (d.f.)	*P* value	Odds ratio (OR)	95% confidence interval (CI) for OR
Constant	−3.372	0.506	44.378	1	0.000	0.03	
Age	0.001	0.006	0.042	1	0.838	1.00	0.99–1.01
Sex	0.123	0.218	0.319	1	0.572	1.13	0.74–1.73
Neutropenia	0.997	0.237	17.746	1	0.000	2.71	1.70–4.31
Relapse/recent diagnosis	1.039	0.312	11.088	1	0.001	2.83	1.53–5.21
Pneumonia	2.047	0.244	70.575	1	0.000	7.75	4.80–12.49
Fungal infection	1.417	0.429	10.930	1	0.001	4.13	1.78–9.56

*Age was treated as a continuous variable, whereas other variables were grouped as sex (male vs female), neutropenia (present vs absent), remission (absent vs present), pneumonia (present vs absent), and fungal infection (present vs absent)

positive infections in these patients to repeated courses of chemotherapy, extensive use of indwelling catheters, and long duration of neutropenia. In the mid-1980s, there was a steady increase in gram-positive infections. Although several factors—including widespread use of catheters, longer duration of neutropenia, mucositis caused by more aggressive chemotherapeutic agents and prophylaxis targeted against gram-negative organisms with the use of fluoroquinolones—have been proposed as contributors to this change in the pattern of causative agents, the underlying reasons are not absolutely clear [11]. However, in recent years the number of cases of gram-negative bacteremia has risen again [12].

In our study population, the observation that gram-negative bacilli is an important cause of bacteremia could at least be partially explained by our hospital's ID policy of not using fluoroquinolones prophylactically.

Incomplete chart information limited our ability to detect frequency of central venous catheterization (CVC) use in the study population; thus, the potential role of CVC use on bloodstream infection could not be investigated.

The incidence of invasive fungal infections has increased substantially during the past 30 years [13]. Prolonged neutropenia is a major, well-known risk factor for fungal infection [14]. Other host-related factors include broad-spectrum antibiotic use, corticosteroid therapy, indwelling venous catheters, mucositis. Environmental exposure is also important in the case of invasive aspergillosis [15]. Several of such risk factors might have played a role in the occurrence of invasive fungal infections in 51 episodes in our study population. We believe that the ongoing renovation activities in our hospital might be a major contributor to the predominance of invasive mould infections compared to candidemia in our patient population, despite the fact that we do not use routine antifungal prophylaxis except for the allogeneic hematopoietic stem-cell transplantation setting.

Our findings on the prognostic factors of the presence of neutropenia, pneumonia and fungal infections and the absence of remission appeared as poor prognostic indicators in patients with hematalogical malignancies confirm the findings of previous research in this field. The mortality due to infection in our study is 25.4%, which is higher than the rate reported usually. The high fatality rate (44.8%) of invasive aspergillosis and high rate of pneumonia, which was detected in one third of the episodes, could at least partially explain the high mortality rate in our study population.

In conclusion, infection has a major impact in the management of patients with hematalogical malignancies. The presence of neutropenia, pneumonia and fungal infections and absence of remission should alert the physician to take a more meticulous approach in the treatment of these patients.

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