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Original Article

Secondary infections after cytotoxic chemotherapy in patient with hematological malignancies

Seyit Ali Büyüktuna[1], Rabin Saba[2], Mustafa Gökhan Gözel[1], Özge Turhan[3], Dilara İnan[3], Zahide Asık[4], Adem Köse[5]

[1] Department of Infectious Diseases and Clinical Microbiology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey
[2] Department of Infectious Diseases and Clinical Microbiology, Medstar Antalya Hospital Center, Antalya, Turkey
[3] Department of Infectious Diseases and Clinical Microbiology, Akdeniz University Faculty of Medicine, Antalya, Turkey
[4] Department of Infectious Diseases and Clinical Microbiology, Tokat State Hospital, Tokat, Turkey
[5] Department of Infectious Diseases and Clinical Microbiology, Inonu University Faculty of Medicine, Malatya, Turkey

Abstract

Introduction: This study was initiated to investigate the risk factors of secondary infections in febrile neutropenic patients following chemotherapy, and to evaluate the clinical, microbiological, and mortality outcomes of these infections.

Methodology: An evaluation was done on all patients with hematological malignancy who developed a febrile neutropenic episode (FNE) after cytotoxic chemotherapy in the Department of Hematology, Akdeniz University Faculty of Medicine, between January 2007 and December 2008.

Results: A total of 294 primary FNEs that responded to the initial empirical or targeted treatment were included in the study, and secondary infections developed after 72 (24.5%) of 294 primary FNEs. Risk factors for secondary infections were determined as acute leukemia as the underlying disease, salvage chemotherapy for refractory/relapse diseases, prolonged neutropenia (10 days and over), Multinational Association of Supportive Care in Cancer (MASSC) score < 21, and fungal infection during the primary episode. The mortality rate of patients who developed secondary infections was significantly higher compared to patients without secondary infections (27.8% and 5.4%, respectively; p = 0.001).

Conclusions: The development of secondary infections in patients with hematological malignancy was not very rare. Greater concern should be shown for these infections to increase patient survival rates.

Key words: hematological malignancy; cytotoxic chemotherapy; febrile neutropenia; secondary infection.

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Introduction

Chemotherapy is one of the major approaches in cancer treatment, involving the delivery of a cytotoxic agent to the cancer cells [1]. However, all these drugs are associated with suppression of bone marrow and severe neutropenia, which causes the patients to become vulnerable to life-threatening infections [2-4]. The resulting neutropenia is a major cause of morbidity and mortality in these patients [5]. Nevertheless, more than 80% of patients treated with cytotoxic drugs experience at least one febrile neutropenic episode (FNE), which leads to excessive broad-spectrum antibiotic use and the selection of resistant microorganisms [6]. A successfully controlled initial febrile neutropenic episode (FNE) may be followed by a new febrile episode known as a secondary infection [7]. There have been a few studies in the literature investigating the frequency and risk factors of secondary infections [8-11]. These secondary infections delay the next round of chemotherapy, and cause prolonged hospitalization and increased mortality [8,12]. The aim of this study was to investigate the risk factors and outcomes of secondary infections developing after primary FNEs in patients with hematological malignancies.

Methodology

This retrospective study included all patients with hematological malignancies who were hospitalized in the Department of Hematology, Akdeniz University

Faculty of Medicine, between January 2007 and December 2008. Patients who developed FNEs following chemotherapy were included in the study, and patients who had fever and neutropenia as a result of their underlying diseases, without having received chemotherapy, were excluded. Each separate hospital admission for FNE was defined as one episode. Subsequent hospital admissions for FNE in the same patient were included as separate FNEs. This study was approved by the local ethics committee.

Fever was defined as a single temperature measurement of ≥ 38.5°C or ≥ 2 measurements of 38.0°C within a 12-hour period. Neutropenia was defined as an absolute neutrophil count < 500 cells/mm^3 or absolute neutrophil count expected to decrease to < 500 cells/mm^3 over the next 48 hours. Primary FNEs were classified as clinically documented infections (CDI; FNE with objective and detectable sign of infection, but undetectable microbiological evidence), microbiologically documented infections (MDI; FNE with bacteria or fungi isolated from samples of infected origins), and fever of undetermined origin (FUO; FNE with no objective and detectable sign of infection to suggest any origins and no growth in the cultures). Secondary infection was defined as any episode that met the following criteria: fever and/or infection not present at the initial evaluation occurring either during empirical/targeted therapy (fever responded to empirical/targeted therapy, but recurred after an afebrile period of 48 hours) or within 1 week after discontinuation of therapy [8]. Secondary infections

Table 1. The baseline characteristics of primary febrile neutropenic episodes (FNEs) and risk factors associated with secondary infections.

Characteristics	Total FNEs n = 294	Group 1[1] n = 222	Group 2[2] n = 72	P
Age, mean ± SD	49.96 ± 17.29	50.57 ± 18.03	46.2 ± 16.5	0.118
Age				
< 60 years	220 (74.8)	162 (73)	58 (80.6)	0.198
≥ 60 years	74 (25.2)	60 (27)	14 (19.4)	
Sex				
Female	177 (60.2)	139 (62.6)	38 (52.8)	0.138
Male	117 (39.8)	83 (37.4)	34 (47.2)	
Underlying diseases				
Acute leukemia	180 (61.2)	121 (54.5)	59 (81.9)	0.001
Other[3]	114 (38.8)	101 (45.5)	13 (18.1)	
State of diseases				
Induction or remission chemotherapy	155 (52.7)	125 (56.3)	30 (41.7)	0.031
Salvage chemotherapy for refractory/relapses	139 (47.3)	97 (43.7)	42 (58.3)	
Neutrophil count (/mm^3)				
≥ 100	186 (63.3)	138 (62.2)	48 (66.7)	0.491
< 100	108 (36.7)	84 (37.8)	24 (33.3)	
Duration of neutropenia				
1-10 day	146 (49.7)	130 (58.6)	16 (22.2)	0.001
>10 day	148 (50.3)	92 (41.4)	56 (77.8)	
MASCC score				
< 21	102 (34.7)	69 (31.1)	33 (45.8)	0.022
≥ 21	192 (65.3)	153 (68.9)	39 (54.2)	
Prophylaxis[4]				
No	178 (60.5)	135 (60.8)	43 (59.7)	0.870
Yes	116 (39.5)	87 (39.2)	29 (40.3)	
Classification of infection				
FUO	114 (38.8)	86 (38.7)	28 (38.9)	0.164
CDI	76 (25.8)	52 (23.4)	24 (33.3)	
MDI	104 (35.4)	84 (37.9)	20 (27.8)	
Fungal infection				
Yes[5]	66 (22.4)	32 (14.4)	34 (47.2)	0.001
No	228 (77.6)	190 (85.6)	38 (52.8)	

MASCC: Multinational Association of Supportive Care in Cancer; FUO: fever of undetermined origin; CDI: clinically documented infection; MDI: microbiologically documented infection; [1] Primary FNEs that did not develop secondary infections; [2] Primary FNEs that developed secondary infections; [3] Lymphoma, multiple myeloma, myelodysplasia syndrome, chronic myeloid leukemia, chronic lymphoblastic leukemia; [4] Antibacterial, antifungal and antiviral prophylaxis; [5] Total of 66 fungal infections: 3 of them MDI (3 *C. albicans* isolated from specimens) and 63 of them CDI (probable and possible invasive aspergillozis according to serology and pulmonary tomography).

Table 2. Comparison of clinically documented infection, microbiologically documented infection, and fever of undetermined origin in the primary febrile neutropenic episodes and secondary infections.

Classification	Primary FNEs n = 294	Secondary infections n = 72
CDI	76 (25.8)	28 (38.9)
MDI	104 (35.4)	40 (55.6)
FUO	114 (38.8)	4 (5.5)

FNEs: febrile neutropenic episodes; FUO: fever of undetermined origin; CDI: clinically documented infection; MDI: microbiologically documented infection.

were classified as CDI, MDI, and FUO similar to primary FNE.

The age, gender, underlying diseases (acute leukemia, lymphoma, and others), state of disease and response assessment (first induction chemotherapy, remission/stable disease ongoing chemotherapy, and salvage chemotherapy for refractory/relapse disease), severity of neutropenia, MASCC score, administration of antibacterial and antifungal prophylaxis, classification of infection (CDI, MDI, or FUO), and detected fungal infection during primary FNE were recorded for every patient. The risk factors of secondary infection were investigated by comparing the two groups of primary FNEs: those which were followed by secondary infection and those not followed by secondary infection (Table 1).

The Chi-squared test was used to compare statistically categorical variables, and the Mann-Whitney U test or the t test was used to compare continuous variables. Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 14 for Windows (IBM, Armonk, USA), and a p value < 0.05 was considered statistically significant.

Results

The study included a total of 294 cases of primary FNEs that responded to the initial empirical treatment and targeted treatment (goal-oriented treatment was initiated according to microbiological, radiological, and clinical signs within the first three days of the episode, even if empirical therapy was not appropriate). The mean age of the patients was 51.08 years (SD 17.4 years), and there were 114 male (60.6%) and 74 female (39.4%) patients. Acute myeloid leukemia (AML) (38.4%) was the most common underlying disease of 294 primary FNEs, followed by lymphoma (24.5%), acute lymphoblastic leukemia (22.8%), and others (chronic myeloid leukemia, chronic lymphoblastic leukemia, multiple myeloma, and myelodysplastic syndrome) (14.3%).

Secondary infections occurred after 72 (24.5%) of 294 primary FNEs, and 222 (75.5%) of 294 primary FNEs did not develop secondary infections. The baseline characteristics of FNEs and risk factors associated with secondary infections are shown in Table 1. There were no statistically significant differences between the groups with respect to gender and age ($p > 0.05$). Higher rates of secondary infection in patients with acute leukemia were detected ($p = 0.001$). Significant differences were determined between first induction/remission induction chemotherapy and salvage chemotherapy for refractory/relapse diseases in terms of secondary infection ($p = 0.031$). While there were no differences in the severity of neutropenia ($p = 0.491$), prolonged neutropenia (≥10 days) was associated with an increased risk of secondary infection ($p = 0.001$) (Table 1).

Antibacterial and antifungal prophylaxis was given to 116 (39.5%) FNEs, and no significant difference was determined between the two groups with respect to developing secondary infections ($p > 0.05$) (Table 1).

Classification of primary FNEs (CDI, MDI, and FUO) were examined between the two groups and there were no significant differences ($p > 0.05$), although fungal infection during the primary episode was found to be a risk factor for secondary infection ($p = 0.001$) (Table 1).

Table 3. Types of infections determined in clinically documented infection and microbiologically documented infection in primary febrile neutropenic episodes (FNEs) and secondary infections.

Types of infection	Primary FNEs n = 180	Secondary infections n = 68
Pulmonary infection	47 (26.1)	25 (36.8)
Primary blood stream infection	34 (18.9)	20 (29.4)
Urinary tract infection	39 (21.7)	4 (5.9)
Skin/soft tissue infection	16 (8.9)	2 (2.9)
Intra-abdominal infection	11 (6.1)	7 (10.3)
Other*	33 (18.3)	10 (14.7)

* Venous catheter related infection (no bacteremia), upper respiratory tract infection, central nervous system infection.

The classifications of infection (CDI, MDI, and FUO) in 294 primary FNEs and 72 secondary infections are shown in Table 2. While FUO (38.8%) was the most frequently detected type of infection in all primary FNEs, more than half of the secondary infections were MDI (55.6%). The types of infection in the CDI and MDI are shown in Table 3. Pulmonary infection was determined as the most frequent origin of infection in both groups (26.1% and 36.8%, respectively). Urinary tract infection was the second most common origin of infection in the primary episode, whereas bloodstream infection was the second most common in the secondary infection.

A total of 104 and 40 bacterial or fungal microorganisms were isolated in primary FNEs and secondary infections, respectively (Table 4). Of these, 69 (67.7%) and 13 (32.5%) were Gram-negative bacteria, 32 (31.4%) and 24 (60%) were Gram-positive bacteria, and 3 (2.9%) and 3 (7.5%) were fungi, respectively.

The mortality rate of patients who developed secondary infections was significantly higher compared to patients without secondary infections (27.8% and 5.4%, respectively; p = 0.001).

Discussion

The frequency of secondary infection in neutropenic patients with hematological malignancy and associated risk factors has been investigated in a few studies in the medical literature [7-11]. The rate of secondary infection has been reported to vary between 12% and 24% [7,8,13,14]. In the current study, a slightly elevated rate (24.5%) of secondary infection was determined; this study, however, differs from previous studies. In previous studies, only when a new febrile episode responded to initial empirical therapy was it evaluated as secondary infection. In the present study, emerging febrile episodes in both groups of patients which responded to the initial empirical therapy and modified targeted therapy were evaluated for the development of secondary infections and were included in the study. In this way, an attempt was made to include all febrile and neutropenic patients to provide a general perspective of cancer patients.

Contrary to general literature data, Azap *et al.* reported a very high secondary infection rate (138/259 [53%] FNEs) [15]. They emphasized that this high rate could be associated with the underlying disease of patients and the chemotherapeutic regimen. In 64.5% of patients, the underlying disease was reported to be acute myeloid leukemia. In addition, prophylactic use of antibiotics such as quinolones was not practiced at the time of that study, which could be another reason. The ratio of patients with acute myeloid leukemia was lower in studies reported by Demirel *et al.* and Nucci *et al.* (acute myeloid leukemia comprised 32.3% and 48.9% of patients, respectively) [7,9]. Other studies have demonstrated that acute leukemia was the major underlying disease, constituting more than half of the cases in febrile neutropenic patients [16-18]. In the current study, 38.4% of FNEs were AML and 61.2% of FNEs were acute leukemia. Prophylactic antibiotics were given to 39.2% of FNEs.

Akova *et al*. reported that age (≥ 16 years), acute leukemia as the underlying disease, use of intravenous line, use of oral antibacterial or antifungal therapy

Table 4. Etiology of microbiologically documented infection in 104 primary febrile neutropenic episodes (FNEs) and 40 secondary infections.

Microorganism	Primary FNEs n = 104	Secondary infections n = 40
Gram-negative bacteria	69 (67.7)	13 (32.5)
Escherichia coli	34 (33.3)	6 (15)
Klebsiella pneumonia	19 (18.7)	2 (5)
Pseudomonas aeruginosa	11 (10.8)	1 (2.5)
Enterobacter spp.	4 (4)	-
Aeromonas spp.	1 (0.9)	-
Stenotrophomonas maltophilia	-	3 (7.5)
Acinetobacter baumannii	-	1 (2.5)
Gram-positive bacteria	32 (31.4)	24 (60)
Staphylococcus aureus	4 (4)	1 (2.5)
Coagulase-negative *Staphylococcus*	13 (12.7)	6 (15)
Enterococcus faecalis	9 (8.8)	2 (2.5)
Enterococcus faecium	1 (0.9)	15 (37.5)
Corynebacterium jeikeium	1 (0.9)	-
Streptococcus spp.	4 (4)	-
Fungus	3 (2.9)	3 (7.5)
Candida albicans	3 (2.9)	3 (7.5)

before trial and oral antifungal therapy during trial were risk factors associated with secondary infections [8]. In another study, the presence of central venous catheter (CVC), acute myelogenous leukemia (AML) as the underlying disease, diarrhea, and invasive aspergillosis during primary infections were reported to be risk factors for secondary infections [15]. Using multivariate analysis, Nucci *et al.* showed four independent risk factors for secondary infection, which included a longer duration of severe neutropenia, lack of use of prophylactic quinolones, persistence of fever on day 4 of the initial regimen, and use of CVC [9]. The duration of neutropenia was also reported by Demirel *et al.* as a risk factor for secondary infections [7]. In the current study, there was no relationship between the development of secondary infection and age, underlying diseases, or usage of antibacterial/antifungal prophylaxis. However, acute leukemia as the underlying disease, salvage chemotherapy for refractory/relapse diseases, low MASCC score, duration of neutropenia (≥ 10 days), and fungal infection during the primary episode were found to be risk factors associated with secondary infections. These findings support our current information that acute leukemia, refractory/relapse diseases, and low MASCC score are risk factors for primary or secondary infection [7,8,15]. It is also not surprising that prolonged neutropenia and fungal infection during primary episodes increase the risk of secondary infection [8,19], because the prolonged duration of neutropenia is one of the most important risk factors for fungal infections [7,20]. However, patients with fungal infection are also frequently prolonged neutropenic patients. As in the current study, invasive aspergillosis during primary episodes was found to be a risk factor for secondary infection in a study published by Azap *et al.* [15]. Common use of antibiotics before a febrile episode, use of broad-spectrum antibiotics during febrile episodes, and relatively lower prophylactic antifungal usage greatly increase the risk of fungal infection in these patients.

Serra *et al.* found that the rate of MDI was higher in secondary infections than in primary infections (90.1% and 39.8%, respectively) [13]. Contrary to that study, Demirel *et al.* reported that MDI was higher in primary episodes than in secondary infections (26% and 19%, respectively) and found CDI to be significantly higher in secondary infections. That was explained by the inability to perform interventions for microbiological diagnosis due to severe thrombocytopenia in most patients and the higher rate of fungal infections [7]. In the current study, both were higher in secondary infections (Table 2). More than half of secondary infections are fungal infections, diagnosed clinically or microbiologically, and that may be explained by an increase in serological diagnosis of fungal infections and the development of radiological examinations and microbiological diagnosis.

Prognostic factors affecting mortality in patients with hematological malignancy have been investigated in several studies [21-24]. It has been demonstrated in the literature that fungal infections and development of secondary infections are major risk factors for increased mortality [7-9]. Consistent with literature, the current study demonstrated that development of secondary infections increases mortality in these patients (27.8% in patients with developed secondary infections and 5.4% in patients who did not develop secondary infections). This may be explained by the fact that half of secondary infections are fungal infections, which may be the most important risk factor increasing mortality. In addition, two-thirds of pulmonary infections and bloodstream infections are composed of secondary infections, and the mortality rate of these infections is higher than that of urinary tract or skin/soft tissue infections (Table 3). Urinary tract and skin/soft tissue infections comprise one-third of primary episodes, and less than half of primary episodes have infections with higher mortality. Therefore, the distribution of types of infections may be another reason for the increased mortality in secondary infections.

Conclusions

The development of secondary infections in patients with hematological malignancy was not very rare. Major risk factors for secondary infections were determined to be disease severity, such as patients with acute leukemia and more intensive chemotherapy (salvage chemotherapy for relapse/refractory state), and prolonged neutropenia (≥ 10 days). Although fungal infection was found to be a risk factor, it was not appropriate to evaluate it as an individual risk factor because prolonged neutropenia was also the most important risk factor for fungal infection. Mortality was also significantly increased in patients with secondary infections due to higher fungal infection and higher rates of severe infection such as pneumonia and bloodstream infection. Therefore, greater concern should be shown for these infections in order to to improve patient survival.

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Corresponding author

Seyit Ali Büyüktuna, Assistant Professor
Department of Infectious Diseases and Clinical Microbiology
Cumhuriyet University Faculty of Medicine
Kayseri Caddesi. No: 69
58140 İmaret/Sivas, Turkey
Phone: +90 505 386 98 82
Fax: +90 346 258 00 24
Email: alibuyuktuna@gmail.com

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