The Outcome of Fungal Pneumonia with Hematological Cancer

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ABSTRACT

Background: Fungal pneumonia is a common infectious complication of hematological cancer (HC) patients. In this retrospective study, the objective was set to identify the risk factors and outcome of fungal pneumonia in adult HC patients.

Materials and Methods: This retrospective study was conducted with adult (>16 years) HC patients from January 2017 and December 2018.

Results: During the study period, of 181 patients included 76 were diagnosed with fungal pneumonia. The most common HC was identified as acute myeloid leukaemia (40%). Of the participating patients, 52 (29%) were hematopoietic stem cell transplant (HSCT) recipients. The median age of patients with fungal pneumonia was significantly greater: 57 vs. 48 (odds ratio [OR]: 1.08) and they had longer hospitalization durations (OR: 1.14). Overall, 37 patients (20%) died, and 28-day mortality was significantly greater among patients with fungal pneumonia than without fungal pneumonia (33% vs. 11%). The most significant risk factors for mortality in fungal pneumonia were identified as need of intensive care unit (ICU) (OR: 191.2, P <0.001) and the need of vasopressor support (OR:81.6, P <0.012). ICU-mortality was (88%).

Conclusion: Fungal pneumonia is a lethal complication in HC patients. Intensive care need is the most important predictive factor for mortality.

Keywords: Hematological cancer; Intensive care; Fungal pneumonia

INTRODUCTION

Hematological cancer (HC) incidences are increasing worldwide, and cancer patients receive intensive chemotherapy that may cause undesirable complications [1]. Infectious complications, especially fungal pneumonia, are the most important and frequent cause of death in patients with HC [2, 3]. About one-third of leukemia patients receiving chemotherapy and 80% of hematopoietic stem cell transplant recipients have at least one episode of pneumonia, and mortality may be as high as 80% in some cases [4]. Both innate and adaptive immune functions are suppressed by the cancer itself and chemotherapeutic
agents. Fungal pneumonia is common in patients with hematological cancer due to mucosal damage caused by cytotoxic chemotherapies and steroids, neutropenia and leukocyte defects, hematopoietic stem cell transplantation (HSCT) and subsequent immunosuppressive agents used for the treatment of graft versus host disease (GVHD) [5].

The diagnosis of pneumonia in HC patients may be difficult due to fuzzy clinical and radiological signs. In HC patients, early administration of antimicrobials is critical for survival [6, 7]. This study aimed to evaluate of the risk factors and prognosis of fungal pneumonia in HC patients.

**MATERIALS AND METHODS**

This retrospective study was performed in a tertiary referral hospital in 1,300-bed capacity. The hematology department has a 38-bed capacity, and HSCT unit has a 37-bed capacity. All types of adult hematological cancer patients are treated at the hematology unit, and autologous and allogeneic HSCT is performed in HSCT center.

**1. Patients**

All HC patients consecutively hospitalized into the hematology unit and HSCT hospital between January 2017 and December 2018 were screened. Patients with fungal pneumonia were included in the study. Patients who had no infection were included as the control group.

Patients’ data on infection were recorded from the infection control committee data and hospital data processing system. The demographic and clinical condition of patients; comorbidities, type of HC, the status of HC (new diagnosis, refractory, recurrence, remission), neutropenia and duration, infection episodes and antibiotics used in the last three months, prophylactic agents, were recorded from hospital electronic patient registration system.

During the study period, the patients were evaluated in two groups as fungal pneumonia and non-pneumonia group. The patients who developed fungal pneumonia were also grouped as survivors and non-survivors. The factors affecting 28-day mortality were also evaluated in this study. The patients are grouped according to their need of mechanically ventilator and vasopressor agent. The mortality is calculated for each group.

**2. Definitions**

In the present study, Invasive Pulmonary Aspergillosis (IPA) was defined according to The European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) criteria [8]. IPA was categorized as proven, probable or possible IPA. In our center, galactomannan is tested weekly.

An multi drug resistant (MDR) characteristic was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [9]. In the present hematology center, patients are screened weekly for rectal bacterial colonization with a rectal swab sample.

The Sequential Organ Failure Assessment (SOFA) score is the organ failure score consisted of organ system function variables. The higher score indicates the higher severity of organ system failure [10].
Definitions of sepsis, septic shock and organ dysfunctions were used from The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [10, 11].

The Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system is the severity of disease classification system. It uses 12 different physiological factors to evaluate critically ill patients within their first 24 hours of admission to the intensive care unit (ICU) [12].

3. Ethics
This research was approved by the Non-invasive Clinical Research Ethics Committee of Erciyes University (Date: 07.07.2017 No: 2017/358). The need for patient consent was waived due to the retrospective nature of the study.

4. Statistical analysis
The collected information was processed using version by 22.0 of the Statistical Package for Social. The Shapiro-Wilk test was performed to check the normality assumption of the data. The Mann-Whitney U-test was used for the comparison of continuous variables. Variables that $P$-value ≤0.05 were included in the multivariate logistic regression analysis. A second analysis was also conducted to determine risk factors for mortality in patients with fungal pneumonia. Similarly, values with $P ≤0.05$ were taken in multivariate analysis. A power analysis program was used to calculate the post hoc power analysis. It was done considering fungal pneumonia as a primary outcome measure. It was determined that the study was designed to have 81% power to detect in pneumonia scoring between both groups.

RESULTS
A total of 181 adult patients with HC were included in the study, 76 (42%) of them were diagnosed with fungal pneumonia.

Clinical characteristics of the patients are provided in Table 1. The median age (min-max) was 53 (18-87) years and 60% of participant patients were male. The most frequent comorbidity was diabetes mellitus (20%). The most common HCs were acute myeloid leukemia (AML) (40%), acute lymphoblastic leukemia (ALL) (11%) and multiple myeloma (MM) (11%). Of the participating patients, 70 (41%) were in remission, and 19 (25%) were in relapse. Again, of the participating patients, 53 (29%) were HSCT recipients, and 29 of the recipients had allogeneic HSCT.

28-day mortality rate was 20% in all patients, 33% in the fungal pneumonia group and 11% in the non-pneumonia group.

1. Risk for fungal pneumonia
The groups with/without fungal pneumonia were compared, the risk factors for the fungal pneumonia are provided in Table 1.

In the patients with fungal pneumonia, the median age (range) was 57 (18-84) years and 60% of participant patients were male. In univariate analysis; the median age of patients with fungal pneumonia was higher than the non-pneumonia group (odds ratio [OR]: 1.08, $P = 0.02$). The duration of neutropenia and hospital stay were longer in the pneumonia group. Neutropenia was present in 80% of those with fungal pneumonia and 53% of those
without pneumonia \((P = 0.001)\). Chronic obstructive pulmonary disease (COPD) (12\% vs. 4\%), previous using prophylactic posaconazole (38\% vs. 13\%) and acyclovir (10\% vs. 4\%), febrile neutropenia episode in the past three months (39\% vs. 11\%), prior use of piperacillin/tazobactam (79\% vs. 15\%) or amikacin (41\% vs. 4\%) were also higher in the group with fungal

Table 1. Risk factors of pneumonia in hematological cancer patients

| Pneumonia (n = 76), n (%) | No Pneumonia (n = 105), n (%) | \(p\) value | Multivariate Analysis | \(OR\) (95\% CI) | \(p\) value |
|--------------------------|-------------------------------|-------------|-----------------------|------------------|------------|
| Age median (min-max)     | 57 (18 - 84)                  | 48 (18 - 87) | 0.020                 | 1.08 (1.04 - 1.13) | 0.001      |
| Male gender              | 46 (60)                       | 62 (59)     | 0.482                 |                  |            |
| Neutropenia              | 61 (80)                       | 56 (53)     | 0.001                 |                  |            |
| Neutropenia duration     | 11 (4 - 40)                   | 10 (3 - 21)  | 0.048                 |                  |            |
| Duration of hospitalization | 35 (15 - 120)               | 16 (5 - 76)  | 0.001                 | 1.14 (1.09 - 1.20) | 0.001      |
| Comorbidities            |                               |             |                       |                  |            |
| Diabetes Mellitus        | 20 (26)                       | 17 (16)     | 0.133                 |                  |            |
| Chronic Obstructive Pulmonary Disease | 9 (12) | 4 (4) | 0.046 | 28.17 (3.11 - 255.21) | 0.003 |
| Congestive Heart Failure | 7 (9)                         | 6 (6)       | 0.369                 |                  |            |
| Chronic Renal Disease    | 7 (9)                         | 6 (6)       | 0.395                 |                  |            |
| Hematological Cancer diagnosis |        |             |                       |                  |            |
| Acute Myeloid Leukemia   | 35 (46)                       | 37 (35)     | 0.167                 |                  |            |
| Multiple Myeloma         | 7 (9)                         | 13 (12)     | 0.633                 |                  |            |
| Acute Lymphoblastic Leukemia | 9 (12) | 11 (10)   | 0.716                 |                  |            |
| Myelodysplastic Syndrome | 6 (8)                         | 4 (4)       | 0.235                 |                  |            |
| Hodgkin Lymphoma         | 3 (4)                         | 6 (6)       | 0.736                 |                  |            |
| Non-Hodgkin Lymphoma     |                               |             |                       |                  |            |
| Diffuse Large Cell       | 3 (4)                         | 13 (12)     | 0.088                 |                  |            |
| Mantle Cell Lymphoma     | 3 (4)                         | 3 (3)       | 0.382                 |                  |            |
| Low-Grade Lymphoma       | 2 (2)                         | 1 (1)       | 0.573                 |                  |            |
| Follicular Lymphoma      | 2 (3)                         | 1 (1)       | 0.394                 |                  |            |
| Marginal Zone Lymphoma   | -                             | 2 (2)       | 0.955                 |                  |            |
| Other                    | 6 (8)                         | 14 (12)     | 0.140                 |                  |            |
| Disease status           |                               |             |                       |                  |            |
| New diagnosis            | 17 (22)                       | 19 (18)     | 0.572                 |                  |            |
| Relapse                  | 19 (25)                       | 24 (23)     | 0.252                 |                  |            |
| Refractory disease       | 9 (12)                        | 21 (20)     | 0.162                 |                  |            |
| Remission                | 31 (41)                       | 39 (37)     | 0.645                 |                  |            |
| Hematopoietic Stem Cell Transplantation (HSCT) | 22 (29) | 30 (29) | 0.956 |                  |            |
| Allogeneic HSCT          | 14 (18)                       | 15 (14)     | 0.465                 |                  |            |
| Autologous HSCT          | 8 (10)                        | 16 (15)     | 0.385                 |                  |            |
| Graft Versus Host Disease | 6 (8)                        | 12 (11.4)   | 0.433                 |                  |            |
| Hematological Cancer Treatment |        |             |                       |                  |            |
| Steroid                  | 22 (29)                       | 25 (24)     | 0.493                 |                  |            |
| Monoclonal antibody      | 11 (14)                       | 14 (13)     | 0.826                 |                  |            |
| Chemotherapy in the past 3 months | 46 (60.5) | 76 (72.4) | 0.109 |                  |            |
| Remission induction treatment |        |             |                       |                  |            |
| 7/3 Chemotherapy protocols | 14 (18) | 11 (10) | 0.134 |                  |            |
| FLAG                     | 14 (18)                       | 13 (12)     | 0.260                 |                  |            |
| GMALL induction          | 1 (1)                         | 6 (6)       | 0.130                 |                  |            |
| HOLZER                   | 1 (1)                         | 3 (3)       | 0.213                 |                  |            |
| Hyper CVAD               | 4 (5)                         | 2 (2)       | 0.403                 |                  |            |
| Toronto                  | 2 (2.6)                       | 6 (5.7)     | 0.471                 |                  |            |
| Consolidation            | 7 (9)                         | 8 (8)       | 0.701                 |                  |            |
| Previous use of antimicrobials for prophylaxis |        |             |                       |                  |            |
| Fluoroquinolones         | 29 (38)                       | 24 (23)     | 0.552                 |                  |            |
| Trimethoprim-sulfamethoxazole | 17 (22) | 12 (11) | 0.064 |                  |            |
| Fluconazole              | 19 (25)                       | 15 (14)     | 0.083                 |                  |            |
| Posaconazole             | 29 (38)                       | 14 (13)     | 0.001                 |                  |            |
| Voriconazole             | 1 (1)                         | 3 (2)       | 0.486                 |                  |            |
| Acyclovir                | 7 (10)                        | 5 (4)       | 0.001                 |                  |            |

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pneumonia. Numeric data and table number were added. Rectal colonization with MDR bacteria was more common in the fungal pneumonia group (Table 1).

However, in multivariate analysis; the significant risk factors for fungal pneumonia were identified as; age (57 vs. 48) (OR: 1.08), median duration of hospitalization (35 days vs. 16 days (OR:1.14, P < 0.001), Chronic obstructive pulmonary disease (COPD) (OR: 28.17 , P = 0.003), previous use of antibiotics (OR: 9.76, P <0.001) and previous episode in past three months (OR: 8.33) and previous use of piperacillin/tazobactam (OR: 6.48, P = 0.012).

2. Outcome of Fungal pneumonia
The Incidence of death was observed in 25 (33%) patients with fungal pneumonia. The risk factors of mortality in HC patients with fungal pneumonia are provided in Table 2. Twenty-three patients were transferred to ICU, 16 patients were mechanically ventilated, four patients received high flow oxygen therapy, and three patients received nasal oxygen therapy. ICU-mortality was observed in 86% of the patients. Mortality risk was higher in patients who needed for respiratory care (mechanical or non-invasive ventilation) or oxygen supplementation. Lactate levels >2 mmol/L, APACHE II (26 vs. 14) score and SOFA of >6 on infection day and complications of fungal pneumonia; acute respiratory distress syndrome (ARDS), septic shock and MODS were associated with high mortality (P <0.05). Patients in need of intensive care due to sepsis, septic shock or multi organ dysfunction syndrome (MODS) were evaluated according to prognosis provided in Table 3. Accordingly, 15 patients supported by both vasopressor and mechanical ventilator died. The mortality rate was 57% in patients receiving only vasopressor support, 33% in patients receiving only mechanical ventilation (Table 3).

In multivariate analysis; the necessity of mechanically ventilation (OR: 191.22) and vasopressor support (OR: 2.07 - 79.6, P <0.001) were considered as a risk factor for mortality remission of the hematological cancer was seen as a mortality reducing factor (P = 0.01).

### Table 1. (Continued) Risk factors of pneumonia in hematological cancer patients

| Risk Factor | Pneumonia (n = 76), n (%) | No Pneumonia (n = 105), n (%) | p value | Multivariate Analysis OR (95% CI) | p value |
|-------------|--------------------------|------------------------------|---------|-----------------------------------|---------|
| Previous use of antimicrobials for treatment | | | | | |
| Piperacillin-tazobactam | 60 (79) | 16 (15) | 0.001 | 6.48 (1.51 - 27.87) | 0.012 |
| Meropenem | 14 (18) | 15 (14) | 0.281 | | |
| Amikacin | 31 (41) | 4 (4) | 0.001 | | |
| Tigecycline | 4 (5) | 8 (8) | 0.566 | | |
| Colistin | 3 (4) | 5 (5) | 0.792 | | |
| Moxifloxacin | 12 (16) | 8 (8) | 0.096 | | |
| Voriconazole | 8 (10) | 4 (4) | 0.127 | | |
| Other therapies | | | | | |
| Granulocyte | 21 (28) | 13 (12) | 0.012 | | |
| GM-CSF | 60 (79) | 56 (53) | 0.001 | | |
| A previous infectious episode in 3 months | | | | | |
| Febrile Neutropenia | 39 (51) | 11 (10) | 0.001 | 8.33 (1.44 - 48.24) | 0.018 |
| Urinary Tract Infection | 2 (2.6) | 2 (1.9) | 0.560 | | |
| Pneumonia | 14 (18) | 13 (12) | 0.180 | | |
| Soft Tissue Infection | 1 (2) | 1 (1) | 0.665 | | |
| Other | 4 (5) | 5 (5) | - | | |
| Rectal colonization | | | | | |
| Vancomycin-resistant enterococcus | 17 (22) | 10 (9) | 0.020 | | |
| Carbapenem-resistant Enterobacteriacea | 15 (19) | 7 (7) | 0.011 | | |

OR, odds ratio; CI, confidence interval; 7/3 Chemotherapy, 7 days of standard-dose cytarabine/3 days of an anthracycline; FLAG, fludarabine/high-dose cytarabine/granulocyte colony-stimulating factor; GMALL, German multicenter study group for adult ALL protocol; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone = Methotrexate/Cytarabine; ARA-C, Cytarabine; GM-CSF, granulocyte-macrophage colony-stimulating factor.
DISCUSSION

In this retrospective study, we found that; older age, longer length of stay COPD, previous infection episode and using antibiotics for infection treatment recently increase the risk of fungal pneumonia in patients with HC. In patients with fungal pneumonia, need for intensive care and vasopressor support were the most important prognostic factors.
Previous studies reported that higher SOFA and APACHE II score on the day of infection have a poor prognosis in hematological cancer patients [13]. In a previous study, it was shown that APACHE II score of ≥25 was of poor prognosis when hematologic cancer patients needed intensive care [14]. In our results, ICU need and vasopressor support were the most important prognostic factors for mortality in HC patients with fungal pneumonia (Table 3). Similarly, the APACHE II score was 26 in non-surviving and 14 in surviving patients. The differences in APACHE II scores were found to be significant. Also, SOFA of >6 increases the mortality rate about 2.5 times. Based on the results of the available data, ICU and in hospital mortality rates remain high in this patient population. Reported hospital mortality is 50% and ICU mortality has ranged from 33% to 84% for patients with HM [15-19]. Present hospital mortality and ICU mortality were identified as 32% and 85%, respectively. It was concluded based on the present findings that HC patients in the intensive care unit should be supported within the framework of ethical rules.

In recent years, the treatment of hematologic malignancies has advanced considerably. The treatment also leads to a longer risk of neutropenia and a higher risk of fungal pneumonia. Neutropenia, which is usually caused by chemotherapy or radiotherapy, is a major risk factor for bacterial and fungal lung infections [5]. Similarly, in this study, the Incidence of neutropenia was found to be higher in patients with fungal pneumonia than in non-fungal pneumonia patients (80% vs. 53%).

In our results, longer length of stay period had a greater risk of fungal pneumonia as compared to patients with shorter hospitalization periods (35 days vs. 16 days).

Besides, our patients with febrile neutropenia episodes within three months were at higher risk of fungal pneumonia. Besides, the risk of fungal pneumonia was found to be increased in patients using piperacillin/tazobactam and amikacin therapy within three months. In the present center, these two agents are used in the empirical treatment of febrile neutropenia.

Based on our data, we found that patients using posaconazole prophylaxis had a higher risk of fungal pneumonia. In line with the guidelines, posaconazole is used prophylactically for patients receiving high-risk chemotherapy regimens [20]. Also, these patients were at high risk for bacterial or fungal infection. Besides, there may be reasons that prevent absorption such as mucositis. High fungal pneumonia rate was attributed to this group.

Older age is a risk factor for fungal pneumonia in HC patients. In previous studies, at an age more aged than 60 years has been found as a risk factor for fungal pneumonia and fungal pneumonia-related deaths [21, 22]. It was found in this study that older age increased the risk of fungal pneumonia by about 1.08 times in HC patients.

Although there are some limitations such as retrospective or single center in our study, it may provide valuable information because there are few reports on the Incidence, risk factors and outcomes in patients with fungal pneumonia and HC patients.

**ACKNOWLEDGEMENTS**

This study was presented as an oral presentation in 7-Turkey EKMUD (Infectious Diseases and Clinical Microbiology Specialty Society of Turkey) International Congress 8-13 May 2018.
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