

Pulmonary complications within the first year after bone marrow transplantation

Amal Abd El-Azem Sadon^a, Rehab S. El-Hagrasy^c, Mohamed A. Saraya^b

Background Pulmonary complications (PCs) are a significant cause of morbidity and mortality in hematopoietic stem cell transplant (HSCT) recipients. Pulmonary infiltrates in such patients pose a major challenge for clinicians because of the wide differential diagnosis of infectious and noninfectious conditions. It is rare for the diagnosis to be made by chest radiograph, and commonly these patients will need further invasive and noninvasive studies to confirm the etiology of the pulmonary infiltrates.

Aim The aim of this research was to study the pattern of lower respiratory tract infection within the first year after HSCT.

Patients and methods This is a prospective study of 60 patients receiving HSCT (because of hematological and nonhematological malignancy) at Kuwait Cancer Center within the first year after transplantation for any suspicious respiratory tract infection. Patients were subjected to sputum and blood examination along with bronchoscopic examination and bronchoalveolar lavage if indicated, and all samples were subjected to microbiological examination for diagnosis of the causative organism.

Results Sixty patients were studied for PCs either infectious or noninfectious within the first year after HSCT. The most common complications were infectious complications (70%). Severe PCs were the main causes of death in 13 (21.6%) cases. The PCs were more common and recurrent in allogeneic bone marrow transplantation (BMT) recipients, in

whom PCs contributed to death in 12 cases. Bacterial infection, pulmonary edema, and diffuse alveolar hemorrhage were seen more in the early post-BMT period (<100 days), whereas viral, fungal infection, graft-versus-host disease, and bronchiolitis obliterans were seen more in the late post-BMT period (>100 days).

Conclusion Lower respiratory tract infection is a serious complication after BMT transplantation. Mixed bacterial and opportunistic infections are the most common etiologies.

Pulmonary infiltrates in such patients pose a wide differential diagnosis of infectious and noninfectious conditions. PCs are a significant causes of death in BMT recipients.

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Departments of, ^aChest Diseases and Tuberculosis, ^bTropical, Faculty of Medicine, Zagazig University, Zagazig, ^cInternal Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Correspondence to Amal Abd El-Azem Sadon, MD, Chest Diseases and Tuberculosis Department, Faculty of Medicine, Zagazig University, Zagazig, 44511, Egypt. Tel: 00201118686807; e-mail: amalsadon@yahoo.com

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Introduction

Hematopoietic stem cell transplantation (HSCT) refers to the intravenous infusion of hematopoietic progenitor cells to re-establish marrow function in a patient after a course of chemoradiotherapy [1]. HSCT is used in malignant diseases such as acute and chronic leukemia, Hodgkin and non-Hodgkin lymphoma, and multiple myeloma, as well as in nonmalignant disorders such as aplastic anemia and congenital immunodeficiency syndromes [2]. The donor source may be the patient (autologous), a sibling or unrelated person (allogeneic), or an identical twin (syngeneic). The process of HSCT involves three stages:

- (1) Conditioning of the recipient.
- (2) Infusion of hematopoietic stem cells.
- (3) Engraftment.

Conditioning may involve treatment with high-dose chemotherapy, usually combined with total body irradiation (TBI), to ablate the bone marrow, destroy the malignant cells, and to induce immunosuppression to prevent rejection of the donor stem cells in case of

allogeneic HSCT [3]. Some chemotherapeutic agents (e.g. cyclophosphamide and busulfan) are direct pulmonary toxins that can lead to the development of drug-induced lung injury and interstitial pneumonitis. TBI also may cause radiation-induced lung injury; the combination of high-dose chemotherapy and TBI synergistically increases the incidence and severity of pulmonary complications (PCs) [4].

The engraftment involves the recovery of the neutrophil count and platelet count, which typically occurs 3 weeks after HSCT [5].

However, it takes up to 1 year before the patient's immune system is totally recovered [6]. Patients who underwent bone marrow transplantation (BMT) are at risk for granulocytopenia, impairment of barrier

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defenses, and impairment of cell-mediated immunity and humoral immunity. This impairment leads to an immunocompromised state, allowing microorganisms to cause infection [7]. PCs, which occur in 40–60% of HSCT patients, cause significant morbidity and mortality [8]. Multiple factors lead to PCs, including immunological defects secondary to the underlying disease and its treatment, conditioning regimen, and development of graft-versus-host disease (GVHD) [9].

It is useful to divide the post-transplant period into three phases: phase 1 (the first 30 days); phase 2 (days 31–100); and phase 3 (>100 days after the transplant) [10,11].

Post-transplant phase 1 (days 1–30)

Phase 1 precedes engraftment and is characterized by prolonged neutropenia with disruption of mucosal barriers as a direct result of the conditioning regimen [12].

Post-transplant phase 2 (days 31–100)

Neutropenia usually resolves by the second month after BMT, but humoral and cell-mediated immunity are still impaired during phase 2. Pulmonary infection in this phase is caused by viral infections, such as cytomegalovirus (CMV), respiratory syncytial virus, influenza, and parainfluenza. Pneumocystis jirovecii pneumonia (PJP) also may occur during this phase [13].

Post-transplant phase 3 (day 100+)

The third post-transplant phase is marked by the appearance of chronic GVHD and CMV, and fungal infections also may occur. Noninfectious PCs during this phase consist of restrictive and obstructive airway diseases such as bronchiolitis obliterans (BO) and cryptogenic organizing pneumonia [14].

As a standard method (unless contraindicated), all HSCT patients received antimicrobial prophylaxis with trimethoprim/sulfamethoxazole, voriconazole, and acyclovir for 6 months after transplantation; the prophylactic medication regimen was followed up by the outpatient hematologist.

Aim

The aim of this review is to study the patterns of the PCs within the first year after BMT.

Patients and methods

In this retrospective review, 60 patients with HSCT [either admitted to the bone marrow transplant unit (BMTU) or followed up in the Outpatient Department

in Kuwait Cancer Center] were included in the study during the period between November 2012 and December 2016. They presented with respiratory symptoms suggestive of PCs within the first year after BMT.

All the admitted patients in the BMTU were under care of a hematologist in association with follow-up by the respiratory unit.

Written consent was taken from all patients before starting the study and also before bronchoscopy. All patients were subjected to the following:

- (1) History taking and clinical examination.
- (2) Sputum study by:
 - (a) Direct microscopic examination.
 - (b) Gram's stain and Ziehl–Neelsen stain (3 successive days).
 - (c) Culture and sensitivity.
 - (d) Special test for viral and fungal elements, and for PJP.
Sputum induction was performed for all cases not producing sputum.
- (3) Blood tests such as:
 - (a) Culture and sensitivity.
 - (b) Fungal culture.
 - (c) Galactomanan antigen for fungal infection.
 - (d) PCR for CMV, herpes simplex virus (HSV), Epstein–Barr virus (EBV).
 - (e) Serology for CMV, HSV, and EBV.
 - (f) Serology for atypical organisms (mycoplasma, legionella, and chlamydia)
- (4) Urine legionella antigen.
- (5) Complete blood count.
- (6) Liver and kidney functions.
- (7) Urine analysis and culture.
- (8) Chest radiography.
- (9) CT chest with or without contrast.
- (10) Full pulmonary function test.
- (11) Bronchoscopy and bronchoalveolar lavage (BAL).
Bronchoscopy was performed according to a standardized protocol within 24 h of admission.

An Olympus BF260 videobronchoscope (Olympus Medical Systems Corporation, Tokyo, Japan) was used to perform airway evaluation and BAL was done for all cases, according to radiologic assessment: if the disease is localized BAL was done from the affected segment, and if the infiltrate is generalized in the whole lung field BAL was done from the middle lobe or lingual. BAL was performed using 120 ml of sterile saline in six equal aliquots, and samples were sent for

cytological and microbiological examination including PCR for tuberculosis and common viruses as CMV, HSV, and EBV.

- (12) The infectious PCs are diagnosed according to the following criteria [15]:
- (a) Respiratory symptoms such as cough, sputum production, or chest pain with or without fever not explained by other causes including lung congestion or upper respiratory tract infection or esophageal reflux.
 - (b) Newly developed infiltrates in the CXR with exclusion of cases of pulmonary edema.
 - (c) Positive culture with more than 10^3 colony forming unit/ml from sputum or BAL sample in case of bacterial pneumonia.
 - (d) Positive special stains in sputum or BAL in case of PJP (Gomori methenamine silver stain) or mycobacteria (Ziehl–Neelsen).
 - (e) Elevated IgM titer in case of atypical pneumonia (mycoplasma, chlamydia, or legionella).
 - (f) Presence of hyphae and positive fungal culture from sputum or BAL in case of fungal pneumonia.
 - (g) Elevated IgM titer of specific virus or positive PCR of virus in sputum or BAL.
- (13) The noninfectious PCs are diagnosed according to the following criteria:
- (a) Pulmonary edema typically occurs in the second or third week after the transplant. Patients usually complain of dyspnea and have typical clinical findings that include weight gain, bilateral pulmonary rales, and hypoxemia. Chest radiographic abnormalities include bilateral interstitial infiltrates mostly perihilar, with or without pleural effusions [3].
 - (b) Diffuse alveolar hemorrhage (DAH) is characterized by the sudden onset of dyspnea, nonproductive cough, fever, and hypoxemia; hemoptysis is rare. Most episodes of DAH occur around day 12 after BMT. The infiltrates are usually bilateral, interstitial, and centrally predominant. DAH is typically diagnosed with BAL, when successive aliquots of BAL fluid become increasingly hemorrhagic; the diagnosis is established if all cytologic, pathologic, and microbiologic studies exclude the presence of pulmonary infection [16].
 - (c) GVHD – The incidence of GVHD is higher in allogeneic BMT than in autologous (nearly not found in autologous transplantation). It is an attack of the ‘new’ bone marrow’s immune cells against the recipient’s tissues. This can

occur even if the donor and recipient are HLA-identical because the immune system can still recognize other differences between their tissues. Respiratory symptoms and signs include dyspnea, nonproductive cough, crackles, and chest wheezes. Chest radiography and HRCT showed focal or diffuse infiltrates. Obstructive ventilatory dysfunction in PFT [11].

- (d) BO affecting the small airways. The clinical presentations are progressive dyspnea accompanied by dry cough and expiratory wheeze. The chest radiography shows hyperinflation. Computed tomography can show a mosaic pattern, and air trapping on an expiratory scan. PFT showed air flow limitation. Diffusing capacity is usually reduced, and occasionally there is a restrictive ventilatory component combined with reduction in exercise capacity. The diagnosis of BO is based on the clinical manifestations, HRCT, and PFT abnormalities. The gold standard for the diagnosis is done by histopathology that requires lung biopsy or bronchoscopic biopsy [17].

Statistical analysis

Descriptive statistics were used for presentation of the results in our population. Mean, median, and SD were calculated using Microsoft Excel (Sharkia, Zagazig, Egypt). Analysis was used to compare the groups with respect to the discrete variables. Qualitative data were described using numbers and percentages.

Results

Table 1 shows 60 patients who were treated with HSCT in Kuwait Cancer Center in the BMTU (27 female and 33 male). Sixty-eight percent were ex-smokers. Forty-two percent were transplanted to treat leukemia, 33% for lymphoma, 12% for multiple myeloma, and 13% for aplastic anemia. Of these 60 patients, 49 patients received allogeneic HSCT and 11 received autologous HSCT. Eleven (18.3%) patients received from the bone marrow as a source of HSCT and 49 (81.7%) patients received from peripheral blood. Thirteen (22%) patients died, whereas 78% survived.

Table 2 shows the infectious and noninfectious PCs among the studied patients. Forty-two (70%) patients developed infectious PCs: 33 were allogeneic and nine were autologous with positive microbiological results

that revealed some pathogens in sputum or BAL culture.

Many patients showed mixed infection of bacterial, viral, and fungal pathogens. *Staphylococcus* spp. was the most common among bacterial infections (19%), *Candida* spp. was the most common among fungal infections (40%), and CMV was the most common among viral infections (12%). Only 18 (30%) patients developed noninfectious PCs: 16 were allogeneic and two were autologous, in whom the most frequent was pulmonary edema (55%).

Table 3 shows early versus late PCs after HSCT. For example, bacterial infection, pulmonary edema, and DAH were most commonly found during the first 100 days after HSCT, whereas fungal and viral infections, GVHD, and BO were found in a higher percentage after the first 100 days of HSCT. Patients with bacterial and fungal infection were the most critically ill, which necessitates mechanical ventilation. The radiological findings varied according to the cause. The cause of death was respiratory failure, sepsis, and gastrointestinal tract bleeding. The mortality rate was higher among bacterial and fungal infections.

Autologous HSCTs caused less immunosuppression and cellular activation than allogeneic HSCTs and fewer immunosuppression-associated pulmonary

infections. The incidence of rejection or host defense was nil. Even the noninfectious complications were less, as shown in Table 4. The incidence of recurrent infection was more in allogeneic HSCT. Also the severity and mortality rates were higher among allogeneic HSCT than autologous HBCT.

Discussion

PCs were the most common causes of mortality in BMT recipients. The recipients had significant immunosuppression owing to the underlying disorder and the conditioning therapy (chemotherapy and TBI) that was given before transplantation, leading to impaired cell-mediated and humoral immunity for up to 6 months, and may extend to 12 months. The immune system was impaired during the first 5 months after BMT, with leukocytes recovering in 2–4 weeks and the lymphocytic count taking months to return to normal values, leading to serious life-threatening infections in the lungs and other organ systems [18]. The aim of the present study was to study the pattern of lower respiratory tract infection within the first year after HSCT transplantation. The results of our study revealed that the most common PCs were infectious (70%), in which the most common etiology was *Staphylococcus* spp. (19%) among bacterial causes and opportunistic *Candida* spp. (40%) among fungal infections, and CMV viral infection was the most prevalent (12%) among viral infections.

Table 1 Characteristics of the recipients in the study (N=60)

	n (%)
Sex	
Female	27 (45)
Male	33 (55)
Age at transplant (mean±SD)	47±10
Smoking status	
Ex-smoker	41 (68)
Current smoker	9 (15)
Nonsmoker	10 (17)
Indications for transplantation	
Leukemia	25 (42)
Lymphoma	20 (33)
Multiple myeloma	7 (12)
Aplastic anemia	8 (13)
Type of transplant	
Allogeneic	49 (81.7)
Autologous	11 (18.3)
Stem cell source	
Bone marrow	11 (18.3)
Peripheral blood	49 (81.7)
Mortality	
Died	13 (22)
Survived	47 (78)

Table 2 Pulmonary complications within the first year after (hematopoietic stem cell transplantation) transplantation

	n/N (%)
Infectious complications [n (%)]	42 (70)
Bacteria	
<i>Staphylococcus</i> spp.	8/42 (19)
<i>Streptococcus</i> spp.	4/42 (10)
<i>Acinetobacter</i>	3/42 (7)
<i>Pseudomonas</i>	6/42 (14)
<i>Escherichia coli</i>	1/42 (2)
<i>Klebsiella</i>	3/42 (7)
<i>Legionella</i>	1/42 (2)
Fungi	
<i>Candida</i> spp.	17/42 (40)
<i>Aspergillus</i>	3/42 (7)
Yeast (pneumocystis jiroveci pneumonia)	4/42 (10)
Virus	
CMV	5/42 (12)
Epstein–Barr virus	2/42 (5)
Herpes simplex virus	1/42 (2)
Noninfectious complications [n (%)]	18 (30)
Pulmonary edema	10/18 (55)
Graft-versus-host disease	5/18 (28)
Bronchiolitis obliterans	2/18 (11)
Diffuse alveolar hemorrhage	1/18 (6)

Table 3 Early versus late pulmonary complications, mechanical ventilation, radiographic infiltrate, cause of death, and mortality rate among the studied patients within the first year after hematopoietic stem cell transplantation

Complications	Early (<100 days) [n/N (%)]	Late (>100 days) [n/N (%)]	Mechanical ventilation [n (%)]	Radiographic infiltrate	Cause of death	Mortality rate [n (%)]
Bacterial infection (n=26)	19/26 (73)	7/26 (27)	9 (34.6)	Lobar and patchy	Respiratory failure and sepsis	6 (23)
Fungal infection (n=24)	6/24 (25)	18/24 (75)	8 (33)	Multifocal and nodular	Respiratory failure and sepsis	4 (17)
Viral infection (n=8)	2/8 (25)	6/8 (75)	4 (50)	Widespread interstitial	Respiratory failure and sepsis	2 (25)
Pulmonary edema (n=10)	10/10 (100)	0/10 (0)	0 (0)	Diffuse alveolar	No death	0 (0)
Graft-versus-host disease (n=5)	2 (40)	3 (60)	1 (20)	Patchy ground glass	Respiratory failure and gastrointestinal tract bleeding	1 (20)
Bronchiolitis obliterans (n=2)	0 (0)	2 (100)	0 (0)	Diffuse ground glass	No death	0 (0)
Diffuse alveolar hemorrhage (n=1)	1 (100)	0 (0)	0 (0)	Diffuse ground glass	No death	0 (0)

Table 4 Comparison between autologous versus allogeneic hematopoietic stem cell transplantation regarding the recurrence of infection and mortality rate

	Autologous [n/N (%)]	Allogeneic [n/N (%)]
Infectious		
Bacterial infection (n=26)	7/26 (27)	19/26 (73)
Fungal infection (n=24)	5/24 (21)	19/24 (79)
Viral infection (n=8)	3/8 (38)	5/8 (62)
Noninfectious		
Pulmonary edema (n=10)	2/10 (20)	8/10 (80)
Graft-versus-host disease (n=5)	0/5 (0)	5/5 (100)
Bronchiolitis obliterans (n=2)	0/2 (0)	2/2 (100)
Diffuse alveolar hemorrhage (n=1)	0/1 (0)	1/1 (100)
Mortality rate (n=13)	1/13 (8)	12/13 (92)

It was found that bacterial infection was frequent and recurrent. In some patients there was mixed fungal, bacterial, and viral infection. The present study results were consistent with those found by Lucena *et al.* [19], who documented that PCs were common after HSCT, involving almost 30% of the recipients, and were particularly prevalent over the first 6 months after transplantation. These PCs are mostly infectious (68%) with an associated mortality of 18%. The present study showed that there was a high incidence of recurrent and mixed infections among the studied patients, especially allogeneic recipients. This was consistent with that found by Lucena *et al.* [19], as they confirmed that coinfection (bacterial with viral or fungal infection) was a common occurrence in these patients, but against the present study results they found that viruses were the most common causes of pulmonary infections, representing 47% of pneumonias; this can be explained by early administration of valgancyclovir to our patients as prophylaxis after transplantation. The noninfectious PCs were documented in only 30% of the present

study cases; these results were consistent with those found by Sirithanakul *et al.* [1], who mentioned that the infectious PCs were higher than the noninfectious complications and are the main contributing causes for pulmonary infiltrates seen in CXR. Similar results were also found by Lucena *et al.* [19], who documented that the noninfectious PCs were identified in only 29% among all PCs. Similar results also were documented by Afessa *et al.* [20]. Autologous HSCT involves reinfusion of the patient's own stem cells following chemotherapy or radiation therapy to eradicate the malignant cells. This type of transplantation has the advantages of no risk of rejection (no GVHD) because the patient is being transfused with his or her own blood. Additionally, there is no need for immunosuppression; therefore, they have a lower morbidity and mortality in comparison with patients after allogeneic transplantation (however, there's a higher relapse rate after autologous transplantation), so there is low risk of infections [21]. In the present study, severe PCs occurred among bacterial, fungal, and viral infections, which

showed higher morbidity indicating the need for mechanical ventilation and higher mortality rate. In the present study, mechanical ventilation was considered as a predictor of poor outcome and higher morbidity and mortality. These results were consistent with those found by Lim *et al.* [22], as they concluded that viral and fungal infections were associated with high morbidity and mortality. On the other hand, in allogeneic HSCT, the cells were taken from another individual (donor) either related or unrelated. In this type of transplantation, the patient must undergo pretransplant immunosuppression to prevent rejection of the donor's stem cells, so there is high risk of infection and GVHD [2]. The present study results were in agreement with these data and also consistent with those found by Roychowdhury and Pambuccian [18], as they found a higher incidence of PCs either infectious or noninfectious complications among allogeneic BMT patients. The findings of the present study were also consistent with those found by Sahin *et al.* [23]. They found that PCs remain the leading cause of mortality in allogeneic BMT recipients and are a major cause of morbidity among recipients of autologous transplants. Furthermore, PCs and respiratory failure occur more often with allogeneic than with autologous bone marrow. This may be because of the effects of GVHD, which occurred in allogeneic transplantation only, as well as the intense immunosuppressive therapy that was used to prevent it. These results were consistent with those found by Zaza Dit Yafawi *et al.* [24], as they concluded that more than 25% of autologous HSCT recipients developed PCs within 1 year of transplantation.

Conclusion

HSCT is considered now the best therapeutic option for many hematological and nonhematological malignancies. However, PCs, either infectious or noninfectious, remain a major problem after HSCT. These complications were classified into early (within 100 days after transplantation) and late (after 100 days from transplantation).

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Conflicts of interest

There are no conflicts of interest.

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