Bronchiolitis Obliterans Following Hematopoietic Stem Cell Transplantation: Risk Factors and Diagnostic Methods

Keyvan Gohari Moghadam,[1] Bahareh Marghoob,[2] Kamran Alimoghaddam,[2] Shapour Shirani,[3] Ardeshir Ghavamzadeh [2]

[1]Pulmonoary Medicine Department, Shariati Hospital, Tehran University of Medical Sciences, Teran, Iran
[2]Hematology-Oncology Department, Shariati Hospital, Tehran University of Medical Sciences, Teran, Iran
[3]Radiology Department, Shariati Hospital, Tehran University of Medical Sciences, Teran, Iran

Corresponding Author: Dr Bahareh Mafghoob, MD, Board Degree of Internal Medicine
Hematology-Oncology Department
Shariati Hospital, Tehran University of Medical Sciences
Teran, Iran
Tel.: 09113936375
E-mail: bahareh_marghoob@yahoo.com

Abstract

Introduction: Bronchiolitis Obliterans (BO) is one of the most important pulmonary complications of Hematopoietic Stem Cell Transplantation (HSCT). We decided to evaluate the prevalence and risk factors of BO in HSCT patients in the Shariati Hospital Oncology Research Center.

Materials and Methods: Forty two patients, who had had HSCT for at least 6 months ago, completed the study. The diagnosis of BO was confirmed either by spirometry or inspiratory and expiratory views of HRCT with a FEV_1/FVC lower than 75% or more than a 10% drop of FEV_1/FVC from a baseline value and mosaic or air trapping on HRCT, respectively.

Results: Nineteen out of forty two patients were BO, with a prevalence of 45.2%; seventeen cases by HRCT and eleven by spirometry criteria. Identified risk factors for BO were acute and chronic GVHD, age 21-40 yrs. Female donor to male recipient and unmatched genders. There was a strong negative predictve value of symptoms under age 20.

Conclusion: Young patients under 20, without respiratory symptoms, need no further evaluation. Acute and chronic GVHD are again the main risk factors regarding female donors to male recipients within the age group of 21-40.

Key words: Hematopoetic Stem Cell Transplantation, Bronchiolitis Oblitetrans, Pulmonary Complications

Received: 10, June, 2010
Accepted: 26, Sep., 2010

Introduction

About fifty percent of Hematopoietic Stem Cell Transplant (HSCT) patients suffer from non infectious pulmonary complications.(1,2) One of the most important causes of morbidity and mortality after HSCT is bronchiolitis obliterans, which sometimes leads to irreversible, sometimes progressive air flow obstruction (AFO), which was first discussed about explained in the early 1980s.(3-4) This complication can be seen after allogeneic transplantation in up to 26% of the cases(5), but rare cases are reported following autologus transplantation.

Radiographically, bronchiolitis obliterans can display diffuse miliary, nodular or reticulonodular patterns and even normal patterns. High Resolution Computed Tomography (HRCT) is a sensitive and specific method. Mosaic patterns and air trapping which may be exaggerated on expiration along with peribronchial thickening and bronchial dilatation, are useful signs on HRCT.(6)

Another diagnostic method is spirometry. It is not unusual to observe some degree of AFO in the first months after BMT,(7) which is attributable to increased airway hyperresponsiveness, but a lack of response to bronchodilators and irreversibility are the main features of BO, which discriminate it from airway hyperresponsiveness(6,7,8)

Due to the invasive nature of the procedures, patchy involvement and often poor condition of the patient,

histopathology is usually not applied to make a diagnosis.(6) Bronchoalveolar lavage is taken to rule out infections.

The most recognized and consistent risk factor of BO is Chronic Graft Versus Host disease (CGVHD).(5-8)

This cross sectional study was done in one of the largest centers in Asia for HSCT in Iran to compare diagnostic methods and to reveal some or additional risk factors using two diagnostic factors.

Materials and methods

Allogeneic HSCT patients, who were transplanted in the Hematology-Oncology Research center of Shariati Hospital in Tehran, were followed up from January to June, 2009.

The patients who had been allogeneic HSCT at least six months ago, were included in the study. Criteria for exclusion were smokers, history of asthma, COPD and bronchiectasis, more than one HSCT and those patients with abnormal spirometry with FEV1/FVC less than 70%.

Sixty one patients were selected and questionnaires were completed and physical examinations were carried out by an internist. All of the patients underwent spirometry (VIASYS) and HRCT (Siemens Spiral Plus 4) in inspiratory and expiratory phases. All of the spirometric results were reported by a pulmonologist (KGM) and HRCT by a radiologist (SS) who did not access to clinical, radiologic and PFT data respectively.

The spirometric criteria for a diagnosis of bronchiolitis obliterans without taking into consideration the age of patient was defined as FEV_1/FVC less than 75% or more than 10% decrement of FEV_1/FVC from the baseline value. HRCT criteria were air trapping, or a mosaic pattern or air trapping, which exaggerated on expiratory views.

Statistical methods used in analysis were the chi square, T-test, Fisher's exact test, Kappa statistics and Mann-whitnney test. Values less than 0.05 considered statistically meaningful.

Results

Nineteen patients were excluded from the study. Of these, four patients had no baseline spirometry, one was a smoker and one patient had a history of asthma. Thirteen patients were excluded due to noncompliance of the ordered HRCT or spirometry.

Forty two patients completed the study. The age range was 17-50 yrs with a mean value of 29.8± 10.7 yrs. There were 10 in the under twenty (23.8%), 22 in the age group of 21-40 yrs (52.4%) and in the age group of 41-60 yrs of age, there were 10 (23.8%) patients. There were 33 (78.6%) male and 9 (21.4%) females.

There was a range of 2 to 220 months with a median age of 8 months. Fifty percent had received HSCT about 8 months after the diagnosis of the primary disease. Seventeen were (40.5%) AML, nine were (21.4%) CML, eight (19%) were ALL, three were (7.1%) thalassemia, one was (2.4%) Hodgkin's disease and one had (2.4 %) were myelofibrosis.

25 (59.5%) patients were gender matched and 17 (40.5 %) were not. These individuals include:

Female to male, 15 (35.7%), female to female, 7 (16.7%), male to female, 2 (4.8%) and male to male, 18 (42.9%).

The stem cell source was from sibling HLA matched donor bone marrow in 5 (11.9%) and peripheral blood in 37 (88.1%) of donors. All of the donors and recipients were CMV IgG positive. There was no CMV antigenemia after BMT. All of the patients receive cyclosporine and methotrexate as Graft Versus Host Disease (GVHD) prophylaxis. Only one patient received Anti Thymocyte Globulin in addition to these drugs. Only 10 (23.8%) had no history of acute or chronic GVHD, 11 (26.2%) had history of acute GVHD and 21 (50%) had history of chronic GVHD.

Table- 1. Demographic and spirometric findings

Age range	29.8+/_ 10.7
<20	10(23.8)
21-40	22(52.4)
41-60	10(23.8)
Recipient Sex M/F	3.6/1
Sex match : Recipient –Donor	
Female –Female	7 (16.7)
Female-Male	15(35.7)
Male-Male	18(42.9)
Male-Female	2(4.80)
Donor Match	
Related Match	25(59.5)
Stem cell source	
Bone marrow	5(11.9)
Related mismatch	37(88.1)
Pretransplant FEV_1	
90%	31(73.8)
81-90	7(16.7)
66-79	3(7.1)
51-65	1(2.4)
GVHD category	
No	10(23.8%)
Acute GVHD	11(26.2)
Chronic GVHD	21(50%)
Symptom	
With	29(69)
Without	13(31)

M: Male, F: Female

Only 29 (69%) had respiratory symptoms and 13 (31%) had no symptoms at all. The demographic data are shown in Table- 1.

HRCT was normal in 25(59.5%) 13 (31%) had air trapping 4 (9.5%) mosaic pattern. Other HRCT findings were tubular bronchiectasis in 7, bronchial wall thickening in 5 and peripheral bronchial attenuation in 2 patients.

Only 11 (26.2%) had an abnormal spirometry and 31 (73.8%) had normal spirometry. So, based on the HRCT criteria of 17 (40%) and those with a spirometry criteria a 11 (26.2%) patients were considered to be cases of BO.

The mean age of BO group was 31.8± 9.9 yrs and the normal group was 28.2± 11.3 (p- value= 0.275) which was not meaningful.

Based on age groups, BO prevalence was 10% in those patients less than 20 yrs of age, 59% in the 21-40 yrs age group and 50% in the 41-60 yrs age group which with a p- value of 0.03 in the 21-40 yrs age group, was more prevalent.

Age was considered an independent risk factor for BO; the age range of 21-40 yrs had a greater chance of developing BO compared to those under age 20 yrs. This risk factor was as high as 22.6 times greater (OR= 22.6, CI95%: 1.8-277.9, p-value= 0.015). The age range of 41-60 yrs had a risk factor of 16.6 times of developing BO as compared with those patients under 20 yrs (OR= 16.6, CI95%: 1.1-246.8, p-value= 0.041).

The median time of diagnosis of the primary disease to transplantation in the normal group was 12 months (2- 204) and in the BO group, it was 8 months (2- 220). Those was no statistically significant difference (p-value= 0.713, Mann-whitney test).

There was no difference between the gender matching of the donors and receipients. The greatest number of BO belonged to the group of female to male (66.7%) donors and recipients and the smallest number of BO was in the group of male to male (27.8%), (p-value= 0.12, Fisher's exact test). Donor related mismatch with a p- value of 0.037 differed from related matchs in the number of BO cases.

If the other groups (male to male, male to female and female to female) were considered as a group and compared with female to male group, there was a significant difference (p-value= 0.38) and the gender mismatching of female to male was considered a risk factor .When compared the other three groups, the female to male group had a seven times greater chance of developing BO (0R= 7.1, CI 95%: 1.3-39, p-value= 0.26).

There was a correlation between BO and GVHD (p-value= 0.037). Only one case was in the non GVHD group (10%), six cases were in the acute GVHD group (54.5%) and twelve cases were in the chronic GVHD group (57.1%).

There was no significant difference between the stem cell or peripheral blood source of donors and possibility of BO (p-value= 1) as was the gender of the patient and BO (p-value= 1).

Although BO was detected in 66.7% of the CML patients, which constituted 31.6% of all of the BO patients, there was no statistically significant correlation (p-value= 0.24).

The CT and spirometry findings had a correlation with the symptoms. The sensitivity of the symptoms was 90% and specificity of 48%. The positive Predictive Value (PPV) of patient symptoms was 59% and the Negative Predictive Value (NPV) of patient symptoms was 85%.

Patient symptoms in the youngest group were 100% NPV and 17% PPV. In the group 21-40 yrs of age NPV was 80% and for the oldest group, NPV was 75%.

Only 57% of BO patients had a FEV_1 less than 80% and 68% had $FEF_{25\%-75\%}$ less than 75%.

The severity of the dyspnea based on the NYHA classification, had a correlation with BO (p-value= 0.001). All of the patients with class 2 or more had a BO diagnosis. On the other hand, 13.6% of the patients, who were asymptomatic, had a diagnosis of BO.

The correlation of the two diagnostic tests was 0.48. In the other words, in 48% of the cases, they correlated with each other and were statistically significant (p-value= 0.01, kappa statistic).

If spirometry was regarded as the only diagnostic tool, eight (26%) patients had undergone this procedure. If HRCT was regarded as the only diagnostic method, two (8%) patients had not undergone this procedure. Table- 2 shows some specific risk factors.

Discussion

Although spirometric abnormalities are common after HSCT in the first 100 days,(7) abnormal spirometric values beyond this period,(5,6,8) upper respiratory symptoms, which may be misdiagnosed as upper respiratory tract infections,(9) should alert the physician for the presence of BO. Unfortunately, up to 20% of patients may be asymptomatic.(6) So making a decision in up or down grading immunosuppressive therapy not only dependends on the general status of the recipient but also on the presence or absence of the one of the

most devasting complications of HSCT: BO. Unfortunately, there are different spirometric criteria criteria for definition of this complication and there is no consensus. The incidence is 8%-27%, depending on spirometric and other diagnostic criteria. An annual decline of 5% FEV_1 and FEV_1/FVC<80%,(5) $FEF_{25\%-75\%}$< 60%,(6) a 10% fractional drop in the FEV_1/FVC ratio from a previous best spirometry(10) are used in studies. On the other hand, in many studies, TBLB and OLB, due to their invasive nature and patchy involvement of lung, are avoided.(6)

HRCT has a sensitivity and specificity of 74% and 91%, respectively, in making a diagnosis of BO.(6)

In our study, we used spirometry criteria of FEV_1/FVC< 75% or a 10% fractional drop in FEV_1/FVC from a previous best spirometry, or HRCT criteria of exaggerated air trapping in the expiratory phase or mosaic pattern.

Our study included a wide age range and HSCT from either bone marrow or from peripheral blood. Only ten (23.8%) patients had no history of acute or chronic GVHD and only 13 (31%) patients had no respiratory symptoms at all.

There was an increased risk of BO in the age range of 41-60 yrs (p-value= 0.03) and in the age range of 21-40 yrs with OR= 22.6, CI 95%: 1.8-277.9, p-value= 0.015) when compared to the age range of <20 yrs. This finding is compatible with some studies,(5) which showed age >20 yrs as a risk factor for BO. In our study, the age range 21-40 had the greatest chance of BO. Chien, et al, in a large study, showed an increased chance of BO with the increasing age of their patients.(5)

Gender was not a risk factor in our study, although some studies found being male was a risk factor (p-value= 0.02),(11) but gender matching in the form of female to male (donor-recipient) with a p- value of 0.038 was considered a risk factor for BO when compared with the other three groups as a whole, as some studies showed a relationship between BO and female to male gender.(14,15)

To some extent, male-male gender matches may play a protective role. Although it was not statistically significant (p- value= 0.078), to some extent male-male gender matches may play a protective role.

Since chronic GVHD is considered an immune disease, alloreactivity to Y chromosome and some minor gender related antigens may be implicated.(12) The fact that autoimmune diseases are more common in females, the increased risk of BO in male recipients from female donors may be explained.

Table- 2. Risk Factors for development of HSCT related air flow obstruction

Risk factors	Prevalence	p- value
Age median	BO: 31.8+/_9.9	0.275
<20	1 (10)	
21-40	13 (59)	**0.03**
41-60	5 (50)	
Recipient sex		
Male	15 (45.5%)	
Female	4 (44.4)	1
Sex match recipient – donor		
Female-Female	3 (42.9)	0.12
Female-Male	10 (66.7)	
Male-Male	5 (27.8)	
Male-Female	1 (50)	
Donor match		
Related match	8 (32)	**0.037**
Related mismatch	11 (64.7)	
Stem cell source		
Bone Marrow	2 (40)	1
Peripheral Blood	11 (64.7)	
GVHD category		
W/O	1 (10)	
Acute	6 (54.5)	**0.037**
Chronic	12 (57.1)	
Time between diagnosis to treatment		
<14 mo.	13 (44.8)	0.936
>14 mo.	6 (46.2)	
Back ground disease	0.244	

There was no significant difference among the source of stem cells. This may be due to the low number of patients, who had received BM as a source of stem cells, although some showed a correlation between peripheral blood stem cells and BO.(11)

The primary diagnosis of disease is considered a risk factor in some studies. CML is also considered a risk factor.(6, 12) Some studies have proposed that an increase in the incidence of BO in patients with the primary disease of CML is due to Busulfan based regimens, which is considered a risk factor for BO, per se.(13) In our study, 66.7% of CML patients constituted 31.6% of all BO patients and were regarded as a large group, but we did not find a statistically significant correlation (p- value= 0.244). This may be due to the low number of patients in the group of those with primary disease.

Only one case of BO (5%) was in the group without GVHD. This finding was close to 7% in one study.(12) Only one case of BO was in the non-GVHD group and twelve cases were in the CGVHD group which makes a statistical difference (p-value= 0.037). Although CGVHD carries about a 44% mortality rate which when complicated by air flow obstruction, this figure rises to about 65% over a period of 3 years. Again, this study showed

GVHD, either acute or chronic, as the main risk factor for BO. Although some consider BO a pulmonary manifestation of CGVHD, the presence of some patients with CGVHD without BO, and probably the different mechanism of acute GVHD without the autoimmune features of CGVHD, the possible relationship of BO with interstitial pneumonitis and eventually, BO patients with no history of GVHD, suggests that BO should be considered a multifactorial disease, which includes pretransplant conditioning and post transplant events such as respiratory viral infections and GVHD prophylaxis regimens.(12,8) In one study, the presence of the sicca syndrome was significantly associated with the development of BO ($p< 0.0001$), whereas the liver and skin involvement of CGVHD was not associated.(14) In some reports, the histologic characteristics of bronchial glands of late onset noninfectious pulmonary complications of transplanted patients were similar to those seen in the salivary glands of CGVHD. It can be supposed that alloreactive lymphocytes attack the bronchial glands and make the respiratory tract dry, decreasing Igs.(14) In addition, the reported stabilization of BO in some HSCT recipients by systemic corticosteroids and immunosuppressives which support the immune basis, viral infections and recurrent aspiration,(15) and decreased Ig are other possible mechanisms.(6) Often, when the diagnosis of CGVHD has been made, immunosuppressive therapy is accentuated, but the role of this upgrading of immunosuppressive therapy for BO patients in the context of CGVHD is much less clear. Again, it may be multifactorial nature.(8) This may be, to some extent, due to delayed diagnosis of BO and a cicatricial change of the bronchioles, which make an irreversible air flow obstruction. The most severe decline in the first year (from day 100 to the end of the first year) had the worst prognosis and the greatest mortality rate.(8)

We used two diagnostic methods together for a more accurate diagnosis and to rule out infectious, BOOP and interstitial pneumonitis in our patients and the possibility that some patients by spirometric methods especially in the GVHD group, may be underdiagnosed. On the other hand, since there is no defined gold standard for the diagnosis of BO, we compared the results of spirometry and HRCT alone with combinations of HRCT and spirometry. HRCT shows air trapping in an expiratory view. In one study, the diagnosis of 76 cases of BO were made by PFT alone (21%), PFT and CT scanning (7%) and CT alone in (11%) of the cases.(12) Another study showed both a composite CT, BO score and the CT AT score could potentially identify BO earlier than FEV_1.(16) They have been suggested that, due to variances in CT scans, the composite score may be more sensitive and specific than the airtrapping score.(16) The composite score included six variables: bronchiectasis, mucus plugging, airway wall thickening, consolidation, mosaic pattern in inspiratory view and airtrapping in expiratory view with scoring from 0-3 for each.(16) This study suggested that use of composite and air trapping scores should replace subjective interpretation of HRCT which has a tendency of interobserver variability. For these reasons, the study suggested that CT scanning could identify BO earlier than FEV_1, at a time when changes in immunosuppression therapy may result in improved clinical outcomes.(16) Although this study was carried out on lung transplant patients, it may be extended to HSCT patients.

Nineteen patients out of forty two patients were considered to have BO by using two diagnostic methods. In other words, 45% of our patients were diagnosed as having BO, which is a greater percentage than previous studies. It may be due to a low number of study cases or a selection bias, since the more symptomatic patients were referred to pulmonologists. The groups of older patients which were considered as a risk factor had the presence of CGVHD in 50% of our patients. Another reason is the use of methotrexate use as a GVHD prophylaxis, which is considered by some a risk factor,(11) although not with the use of cyclosporine, the conventional regimen which was used with all of our patients. Finally, large percentages (21.4%) of our patients were CML, which is considered a risk factor for BO by some.

Another explanation is use of two instead of one diagnostic method. Seventeen (40.5%) patients who had been diagnosed on the basis of HRCT findings and eleven (26.2%) had abnormal spirometry. Spirometry per se is not a suitable method to be used, especially with symptomatic patients. The findings of HRCT and spirometry as diagnostic methods were compatible with the symptoms. The sensitivity of symptoms was 90%. The Negative Predictive Value (NPV) of the symptoms were 85%; in other words, if all of the asymptomatic patients had not been referred for diagnostic testing, 15% would not have been counted.

One of the interesting findings in our study was that 100% NPV for symptoms in the group of <20 yrs, ie; was that if patients <20 yrs are asymptomatic; they probably need no further work up. The severity

of the dyspnea grading, according to NYHA classification, had a significant correlation with BO, In other words, the more sensation and degree of dyspnea, the more greater the chance of having BO (p- value= 0.001).

The degree of correlation of the two diagnostic tests was 0.48, ie; in 48% of the cases, they had a correlation and were statistically significant (p-value= 0.01). If we had considered spirometry a sole diagnostic method, we would not have included 8 (26%) patients, and, if we had considered HRCT a sole diagnostic method, we would have not included 2 (8%) patients.

Since early diagnosis is important in making treatment decisions, it may be necessary to add HRCT to PFT, even in asymptomatic cases over 20 yrs of age.

Our study had some limitations and shortcomings: first, the low number of patients, second, had a prospective study been done with a follow up, the patients will be certainly superior. Third, the possible presence of air trapping in normal populations makes some cases false positive. On the other hand, we did not have a baseline HRCT and scoring system for HRCT grading.

In conclusion, we found that the greater the degree of dyspnea, the more chance of BO. There is a strong NPV of symptoms in patients <20 yrs, which makes no further work up in this asymptomatic group necessary. Acute and chronic GVHD, female donor to male recipient, being age 21-40, were identified as risk factors.

References

1. Soubani AO, Miller KB, Hassoun PM. Pulmonary Complications of Bone Marrow Transplantation. Chest, 1996; 109: 1066-1070.
2. Quabeck K. The Lung as a Critical Organ in Marrow Transplant. Bone Marrow Transplantation, 1994; 14 Suppl 4: S19- 28.
3. Ostrow D, Buskard N, Hill Rs, et al. Bronchiolitis Complicating Bone Marrow Transplantation. Chest, 1985; 87: 828-830.
4. Epler GR, Colby TV. The Spectrum of Bronchiolitis Oblitertans. Chest, 1983; 83: 161- 162.
5. Chien JW, Martin PJ, Gooley TA, et al. Airflow Obstruction after Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation. Am J Resp Critic Care; Med 2003, 168; 208- 214.
6. Soubani AO, Uberti JP. Bronchiolitis Obliterans Following Hematopoietic Stem Cell Transplantation. ERJ 2007; 29: 1007- 1019.
7. Marras TK, Szalai JP, Chan CK, et al. Pulmonary Function Abnormalities after Allogeneic Marrow Transplantation: A Systematic Review and Assessment of an Existing Predictive Instrument. Bone Marrow Transplantation, 2002; 30, 599-607.
8. Chien JW, Martin PJ, Flowers ME, et al. Implications of Early Airflow Decline after Myeloablative Allogeneic Stem Cell Transplantation. Bone Marrow Transplantation, 2004; 33, 759- 764.
9. Estenna M, Maurer J, Boehler A. Bronchiolitis Obliterans Syndrome 2001: An Updates of the Diagnostic Criteria. J Heart Lung Transplant. 2002; 21(3): 297-310.
10. Clark JG, Scwartz DA. Risk Factors for Airflow Obstruction in Recipients of Bone Marrow Transplantation. Ann Int Med, 1987; 107: 648- 656.
11. Santo Tomas LH, Loberzia F R, Klein JP, et al. Risk Factors for Bronchiolitis Obliterans in Allogeneic Hematopoietic Stem Cell Transplantation for Leukemia. Chest, 2005; 128 (1): 153- 161.
12. Beinert T, Dull T, Wolfket M. Late Pulmonary Impairment Following Allogeneic Bone Marrow Transplantation. ERJ, 1996; 343- 348.
13. Chan CK, Hyland RH, hutcheon MA. Risk Factors for Obstructive Airway Disease after Allogeneic Bone Marrow Transplantation. Am Rev Resp, 1988; 137: 111- 118.
14. Sakaido E, Nanseko C, Harima A. Late Onset non-Infectious Pulmonary Complications after Allogeneic Stem Cell Transplantation. Blood, 2003; 102(12): 4236- 42.
15. Hadjiliadis D, Duanne D, Steele MP, et al. Gastroesophaeal Refux Disease in" Clinical Transplant 2003; 17: 363- 368.
16. de Jong PA, Dodd JD, Coxson HO, et al. Bronchiolitis Obliterans Following Lung Transplantation: Early Detection Using Computed Tomographic Scanning. Thorax, 2006; 61: 799- 804.