

Original Research Article

A STUDY ON EVALUATION OF PULMONARY FUNCTION IN PRE AND POST AUTOLOGOUS STEM CELL TRANSPLANT AND ITS EFFECT IN NEWLY DIAGNOSED CASE OF MULTIPLE MYELOMA

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ABSTRACT

Background: Pulmonary complications constitute a major cause of post hematopoietic stem cell transfusion (HSCT) morbidity and mortality. The pulmonary function test (PFT) is now a days an important tool for the assessment and follow up of patients submitted to HSCT. It includes measurement of Lung volume, Spirometry and diffusion capacity of lung for carbon monoxide (DLCO). Performing PFT after HSCT makes early identification of Noninfectious pulmonary complications (NIPCS) which enables early preventive and therapeutic interventions in at-risk patients.

Materials and Methods: An institution based longitudinal study.

Results: In this study total 32 cases were taken amongst whom 50-59 years age group was most common (68.75%) and male to female ratio was 1.66:1. In pre-transplant check-up 37.5% were having normal DLCO and 62.5% had below normal DLCO values. It was also observed that 25% patients had normal total lung capacity and 75% had total lung capacity below normal range. 3 parameters (FEV1, FVC and DLCO) decreased consistently during 1st, 2nd and 3rd follow up and restoring to pre transplant value after 12 months i.e. at 4th follow up. Out of 12 patients having pre transplant restrictive spirometry change, 8 cases (66.6%) develop noninfectious pulmonary complication during the course after BMT and 6 cases (50%) among them died.

Conclusion: Bone marrow transplantation was associated with decline in lung function during the course after transplantation and with subsequent recovery within one year. The abnormal lung function before bone marrow transplantation found to be positively associated with both development of non-infectious pulmonary complication after bone marrow transplantation and post-transplant mortality.

Keywords: Hematopoietic stem cell transfusion, pulmonary function test, diffusion capacity of lung for carbon monoxide, non-infectious pulmonary complications.

INTRODUCTION

Bone marrow transplantation (BMT) is a medical procedure which involves replacement of damaged bone marrow tissue by healthy blood stem cells, resulting in new blood cells formation and promote growth of new bone marrow. Hematopoietic stem cell transplant (HSCT) now has become the standard technique of BMT and is being used to treat malignant and non-malignant hematological

disorders, solid tumor, metabolic and genetic disorder.^[1]

Once diagnosis of multiple myeloma is made, the patient undergone staging evaluation in order to start an appropriate line of therapy. The international staging system (ISS) divides multiple myeloma patients into three categories according to serum albumin and Beta2 microglobulin level in blood. Pulmonary complications which occurs in 30% to 60% of HSCT recipients constitute a major cause of

post HSCT morbidity and mortality.^[2] Pulmonary complication includes infectious and non-infectious complication. As the incidence of infectious pulmonary complication has been diminished as a result of effective prophylactic therapy, Noninfectious pulmonary complications have emerged as a major cause of post HSCT morbidity and mortality. Early diagnosis and treatment of such complications can change the prognosis of HSCT recipients.^[2] The pulmonary function test (PFT) is now a days an important tool for the assessment and follow up of patients submitted to HSCT. It includes measurement of Lung volume, Spirometry and diffusion capacity of lung for carbon monoxide (DLCO).

Performing PFT more frequently after HSCT not only allow the early identification of Noninfectious pulmonary complications (NIPCS) but also enable early preventive and therapeutic interventions in at-risk patients. Interestingly very minimal data is available regarding the relation of PFT with post HSCT development of NIPCS and mortality, so this study was chosen to find out the association of abnormal PFT towards the development of post HSCT NIPCS. So that early preventive and therapeutic measures can be taken to reduce its incidence and to provide a better success rate to bone marrow transplantation cases.

Aims & objectives:

Primary objective: To study the risk of development of non-infectious pulmonary complications in newly diagnosed cases of multiple myeloma after haematopoietic stem cell transplantation

Secondary Objective: To find out whether abnormal pre transplantation pulmonary function test is associated with development of non-infectious pulmonary complications after transplantation and post-transplant mortality.

MATERIALS AND METHODS

This study is a longitudinal study where multiple myeloma patients who were planned for autologous stem cell transplantation, evaluated prior to transplantation and followed up at 1month, 3 months, 6months and 12 months after transplantation.

Inclusion Criteria

Newly diagnosed multiple myeloma patients who were planned for autologous bone marrow transplantation have been included in this study.

Exclusion Criteria: Not specific.

Methodology: According to institutional protocol, any newly diagnosed cases of multiple myeloma before submitting to HSCT, are treated by 4-6 cycles of chemotherapy regimen in order to reduce the load of tumor cells or get rid of tumor cells. Once the patient is considered for stem cell transplantation detailed blood investigation and imaging tests along with PFT were done before transplantation.

To start with patient was given Filgrastim injection (1 vial each 300µg subcutaneously for 4 days to facilitate mobilization of stem cells to peripheral blood). Adequacy of stem cells was considered by measuring CD34+ cell count. A level of CD34+ cell count > 3x10⁶ per µl of blood was taken as standard. Apheresis was done to collect the stem cells and then it is cryopreserved at a temperature of -180-c. After one day of apheresis patient was administered conditioning regimen. The conditioning regimen was injection Melphalan at a dose of 200 mg/m² over 2 hours and in case of chronic kidney disease the dose reduced to 140 mg/m². Patient was administered with growth factor Filgrastim at a dose of 1 vial (300µg) subcutaneous daily for consecutive 7 days following 24-48 hr of infusion of cryopreserved stem cells. Prophylactic regimen used to avoid infection were antibacterial prophylaxis (injection Levofloxacin 750mg), antifungal (inj. Fluconazole 200mg) and antiviral (inj.acyclovir 600mg) atleast for 10 days. Engraftment is ensured when the absolute neutrophil count reaches 0.5x10⁹/lit and that of platelet count to 20x10⁹/lit.

All transplanted patients were being followed up weekly for the first month and then monthly up to 1 yr with all routine blood investigation after discharge from the hospital. Follow up of patients by PFT at 1month,3months,6months and 12 months after BMT with HRCT thorax when needed.

RESULTS

Total 32 cases were studied. Among them 20(62.5%) cases were male and 12(37.5%) cases were female. Most common age group over all was 50- 59 years (68.75%). Male to female ratio was 1.66:1.

Table 1: stage of multiple myeloma

Stage	Number	Percentage (%)	Total(n=32)	%
I	A	2	2	6.25
	B	0		
II	A	6	8	25
	B	2		
III	A	18	22	68.75
	B	4		
Total	32	100	32	100

In this study multiple myeloma cases belong to all 3 stages. Most common among them were stage-3(A),

18 cases (56.25%) out of total 32 cases. 2nd most common stage was stage 2(A).

Table 2: pre transplant spirometry

Parameters (n = 32)	Post Bronchodilator Percentage Value (Mean± SD)
FEV 1	94.5±14.99
FVC	81.5±12.27
FEV 1 / FVC	92±6.78

In this study all patients had FEV1/FVC ratio >70% of predicted value suggesting either normal or restrictive pattern.

Table 3: pre transplant DLCO values

Parameters	Mean ±SD(n=32)
TLC	4.29±1.14
RV	1.37±0.31
DLCO	81±11.9

Here the DLCO values in pre transplant check up giving the results that 12 patients (37.5%) were having normal DLCO values and 20 patients (62.5%) having diminished DLCO indicating restriction. From the above findings it is found that, 8 patients (25%) had normal total lung capacity and 24 patients (75%) had total lung capacity below the normal range.

On analysis of pre transplant spirometry in our study, 12 patients (37.5%) had restrictive changes and 20 patients (62.5%) were having normal spirometry pattern.

Out of 32 patients who were undergone hematopoietic stem cell transplantation, 10 cases died

within 30 days after transplantation, so only 22 cases remained who were followed up. During first follow up, 8 patients complained of cough with or without expectoration and 2 cases having breathlessness. During 2nd follow up, 8 cases were having cough and 14 cases had complained of breathlessness. During 3rd follow up 6 cases were lost to follow up, out of remaining 16 cases 12 patients had cough and 12 cases were having breathlessness. 12 patients were followed up till the end of 1 year i.e 4th follow up, among them 6 cases were having complain of cough and 8 patients having breathlessness.

Table 4: post transplant pulmonary function changes (Mean±SD)

Parameters	Pre-Transplant Evaluation	First Follow- Up (At 1 Month)	P- Value	2 nd Follow- Up (At 3 Months)	P Value	3 rd Follow- Up (At 6 Months)	P Value	4 th Follow- Up (At 12 Months)	P Value
FEV 1	94.5±14.99	90.09±18	0.017	81.64±12.47	<0.001	76.88±18.47	<0.001	94.33±25.17	0.073
FVC	81.5±12.27	76.36±13.23	0.007	71.8±8.78	<0.001	65.88±14.02	<0.001	81.5±18.07	0.104
FEV 1/ FVC	92±6.78	93.3±8.06	0.137	93.73±8.54	0.068	87.1±10.4	0.05	89.4±11.12	0.137
TLC	4.29±1.14	4.31±1.01	0.423	3.56±0.48	0.0008	3.74±1.47	0.245	4.27±1.07	0.559
RV	1.37±0.31	1.45 ±0.41	0.825	1.34±0.41	0.494	1.39±0.502	0.62	1.505±0.525	0.118
Dlco	81±11.88	76.3±9.06	0.03	70±8.97	0.0004	67.5±9.46	0.013	72±11.8	0.199

3 parameters (FEV1, FVC and DLCO) decreased consistently during 1st, 2nd and 3rd follow up and restoring to pre transplant value after 12 months i.e. at 4th follow up. Other 3 parameters (FEV1/FVC, TLC and RV) had no relationship between pre transplant value with 1st and 2nd follow up values.

In this study pulmonary complications developed in 14 cases(43.75%) out of total 32 cases and remaining

18 cases (56.25%) were not having any pulmonary complications.

Out of 12 patients having pre transplant restrictive spirometry change, 8 cases (66.6%) develop noninfectious pulmonary complication during the course after BMT and 6 cases (50%) among them died.

Table 5: duration of appearance of pulmonary complications

Time duration	Non-infectious Complication		Infectious Complications		Total	
	No	%	NO	%	NO	%
Phase – I (0-30 days)	6	18.75	4	12.5	10	31.25
Phase – II (31-100 days)	0	0	0	0	0	0
Phase – III (>100 days)	4	12.5	0	0	4	12.5
Total	10	31.25	4	12.5	14	43.75

All 4 infectious complications arised during phase-1. Among the 10 cases having non-infectious pulmonary complications, 6 cases had happened in phase-1 and rest 4 cases in phase-3 post

transplantation period. There were no complications detected during phase-2 of post transplantation period.

Table 6: Duration of appearance of non- infectious pulmonary complications

Non-Infectious Pulmonary Complications	PHASE- I (0-30 days)		PHASE – II (31-100 days)		PHASE- III (> 100 days)		Total	
	No	%	No	%	No	%	No	%
BOS	0	0	0	0	2	6.25	2	6.25
DAH	0	0	0	0	0	0	0	0
IPS	4	12.5	0	0	0	0	4	12.5
AIP	0	0	0	0	2	6.25	2	6.25
PULMONARY EDEMA	2	6.25	0	0	0	0	2	6.25
Total	6	18.75	0	0	4	12.5	10	31.25

Most common time period for occurrence of Bronchiolitis obliterans (BOS) and acute interstitial pneumonitis (AIP) were in phase-3. Time frame for development of idiopathic pneumonia syndrome and pulmonary oedema was phase-1 post transplantation period.

DISCUSSION

In this study pretransplant spirometry mean values (%) of FEV1, FVC and FEV1/FVC were (94.5±14.99) %, (81.5±12.27) % and (92±6.78) % respectively. M. B Lund et al,^[3] had pre transplant FEV1, FVC and FEV1/FVC in percentage were 103±12, 108±15 and 80±7 respectively. K Matsumoto et al,^[4] had pre transplant FEV1% and FVC% as (90±17) % and (101±15) % respectively. Zuhre Kaya et al,^[5] in his study found the pre BMT FEV1 and FVC to be (97±20)% and (99±17)% respectively. Our study matches with above studies as mean spirometry values >80%.

Pre transplant diffusion test values(mean)of TLC and DLCO in our study were (4.29±1.14)liter and (81±11.9)% respectively. Our study matches with more or less with all above studies.

Elizabeth M Gore et al,^[6] in his study found that FEV1, FVC and DLCO were decreased at 6 month and 1 yr after transplantation and subsequent recovery occurred 2 years after transplantation. M. B Lund et al,^[3] observed in his study that all parameters (FEV1, FVC, FEV1/FVC, TLC and DLCO) declined through out the first year after BMT and recovered to base line 5 years after transplantation. Zuhre Kaya et al,^[7] observed a statistically significant reduction in FEV1, FVC, TLC and DLCO at 3 months post BMT and similar reduction at 6 months post BMT except DLCO (not significant). Between 12 and 24 months all improved significantly from earlier declined post BMT value. The findings of above studies are matching with our study but the delayed recovery of spirometry and gas transfer value in other studies may be explained by more cases of chronic graft versus host disease due to allogenic bone marrow transplantation.

According to this study the incidence of pulmonary oedema is 6.25%. The incidence of AIP in our study was 6.25%.

In our study among 12 patients who found to be having abnormal spirometry change before transplantation, 8 cases (66.6%) developed noninfectious pulmonary complications. Out of 10 death, 6 cases had abnormal pre transplant spirometry. So this analytical data suggests a positive

association between abnormal PFT changes before transplantation with development of NIPCS and mortality after transplantation.

In our study all cases of BOS developed in phase-3, which is matching with the finding of all other studies.

In this study incidence of all cases of IPS had occurred during phase-1 post transplantation period which is similar to Kasem Sirithanakul et al,^[8] and Ayman O. Soubani et al.^[9]

In our study all cases of pulmonary oedema developed in phase-1 post transplantation period. I Khurshid et al,^[1] described its occurrence seen in 2nd or 3rd week, which matches with our study.

In our study maximum incidence of NIPCS had been associated with Stage-3 multiple myeloma staging (12.5%).

CONCLUSION

This study demonstrate that bone marrow transplantation was associated with decline in lung function during the course after transplantation and with subsequent recovery within one year after transplantation. The abnormal lung function before bone marrow transplantation found to be positively associated with both development of non-infectious pulmonary complication after bone marrow transplantation and post-transplant mortality. So pre HSCT pulmonary function test is important because it not only provides base line values for future comparisons but also in addition, abnormal PFT values before BMT found to be having a higher risk of post HSCT mortality.

So better selection of patient, least toxic conditioning regimen, early recognition and treatment of non-infectious pulmonary complications may be able to prevent severe form of pulmonary complications, death and will provide a better outcome to the success rate of bone marrow transplantation.

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