

Lung India. 2015 Sep-Oct; 32(5): 486–488.
doi: [10.4103/0970-2113.164156](https://doi.org/10.4103/0970-2113.164156)

PMCID: PMC4587005

Mesenchymal stromal stem cell therapy in advanced interstitial lung disease - Anaphylaxis and short-term follow-up

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Abstract

There are limited treatment options for advanced interstitial lung disease (ILD). We describe a patient of ILD treated with mesenchymal stromal stem cell infusion. The index patient had end-stage ILD due to a combination of insults including treatment with radiotherapy and a tyrosine kinase inhibitor Erlotinib. He was oxygen-dependent and this was hampering his quality of life. He tolerated the first infusion stem cells without any problem. During the second infusion he developed anaphylactic shock, which was appropriately managed. At 6-months follow-up he had no improvement in oxygenation, pulmonary function or CT scan parameters. In view of anaphylaxis, further infusions of MSC were withheld. A longer follow-up may reveal long-term benefits or side effects, if any. However the occurrence of anaphylaxis is of concern suggesting that further trials should be conducted with intensive monitoring.

KEY WORDS: Anaphylaxis, interstitial lung disease, stem cell therapy

INTRODUCTION

Mr. A is 73-year-old gentleman who had left upper lobectomy for adenocarcinoma of left lung 4 years back. The pathological stage was pT2N2M0. He received adjuvant conformal radiation therapy. Few weeks after radiation he developed increasing cough and dyspnea. The imaging findings were in favor of radiation pneumonitis. He was treated with systemic steroids. Subsequently he was treated with tyrosine kinase inhibitor Erlotinib; in view of positive EGFR mutation status. He developed worsening of respiratory symptoms and imaging showed further progress of the interstitial shadows. He developed pneumonia, which required prolonged mechanical ventilation. He subsequently recovered. On account of poor lung function and low PaO₂, he required long-term oxygen therapy. Sequentially a trial of treatment with steroids and pirfenidone did not help the lung function or the oxygenation status. However, there was no recurrence of malignancy for a 4-year period after the surgery. He had other co-morbidities including atrial fibrillation and subclavian vein thrombosis which were treated medically. In view of his poor quality of life, the patient wished to undergo stem cell therapy. Written informed consent was obtained after extensive repeated discussion with the patient and his family. The case was discussed in the institutional clinical ethics committee and approval was obtained for this experimental therapy.

The patient was shifted to intensive care unit for the procedure. Mesenchymal stromal cells (MSC) were prepared in-house from a cohort of voluntary donors who are not HLA matched [[Figure 1](#)]. The cells are cryopreserved using a chemical di-methyl sulfoxide (DMSO). We planned to give four; monthly intravenous infusions each containing 100×10^6 cells of MSCs. This dose was decided based on the previous study by Weiss *et al.* [[1](#)] Patient was premedicated with injection hydrocortisone 100 mg and

pheniramine 25 mg. The patient tolerated the first infusion of MSC, which was given in the intensive care unit with continuous hemodynamic and respiratory monitoring, without any problem. After 1 month, the second infusion was given the same way. Immediately after the infusion, the patient developed hypotension with systolic blood pressure falling to 70 mmHg and he developed a skin rash. He was resuscitated with intravenous fluids and further doses of hydrocortisone, following which he quickly recovered. The serial serum tryptase levels were 48.5 and 83.7 ug/L (normal <11.4 ug/L); which confirmed anaphylaxis. The patient was discharged in a stable condition after a couple of days. He was reviewed after 1, 3 and 6 months and there were no changes in arterial blood gas parameters, pulmonary function parameters or 6-minute walk distance.

DISCUSSION

Interstitial fibrosis is a devastating disease with no effective treatment. The treatment options varied from removal of offending agents, steroids and immunosuppressive agents. More recently pirfenidone treatment has shown some promise. But none of the agents have been proven to be effective in majority of patients with advanced interstitial fibrosis. In relatively young patients with limited comorbidities, lung transplantation is an option. In the majority of patients, supportive measures, oxygen therapy and pulmonary rehabilitation are the only modalities that could be offered.

Mesenchymal stromal stem cells are pluri-potent cells; which can differentiate in various cell lines and have anti-proliferative and local immune-modulatory properties. Mesenchymal stem cells are known to home to site of cell injury, inhibit inflammation and hasten cell repair.[2] Hence MSC are being considered for treatment of advanced lung diseases like COPD and ILD. Another advantage is that MSC lack HLA expression and hence HLA matching is not required.

There are human trials using MSC in conditions like myocardial infarction, graft-vs-host disease and refractory lupus erythematosus.[3,4,5] No significant adverse effects were noted in these trials. Weiss *et al.* did a randomized control trial with MSC in 62 patients with advanced COPD.[1] There were no immediate serious adverse events attributable to MSC administration. In the 2-year follow-up period, there were no significant differences in the adverse events, frequency of COPD exacerbations, pulmonary function parameters or quality of life indicators. Our patient needs a longer follow-up to see whether there are any long-term benefits. Tzouvelekis *et al.*, studied three endobronchial infusions of autologous adipose derived stromal cells in 14 patients with ILD.[6] No clinically significant adverse effects were noted and functional parameters were stable for 12 months.

Although our patient tolerated the first infusion well, the second infusion was complicated by anaphylaxis. This could be due to foreign proteins/peptides in the infusate or the DMSO; which was used as a preservative. He may have developed sensitization to the reagent during the first infusion and subsequently reacted to the second infusion. DMSO is the most favorable cryoprotectant; however, it is associated with significant side effects.[7] Nausea, vomiting, and abdominal cramps occur in about half of all the cases. Cardiovascular side effects occur in around 27% of patients.[8] Fatal cardiac arrhythmias have been reported.[9] Anaphylaxis is rare. From FDA and social media reports, it appears that 3 patients have developed anaphylaxis.[10] All the three patients were males aged more than 60 years. Various methods including dose reduction of DMSO are being tried to reduce its toxicity.[8]

Many trials are currently underway on the role of MSC therapy in pulmonary fibrosis.[11] Once the results are available we will have more definite information regarding the hope of successful treatment of this debilitating and fatal disease. In conclusion, our attempt to use MSC treatment for extensive lung fibrosis has so far not produced positive results, but has resulted in serious side effects. Therefore, any human trial should be offered with knowledge of this and only done in an intensive care unit set up.

ACKNOWLEDGMENT

Augustine Thambiah. P, Technical officer, Centre for Stem Cell Research, Christian Medical Collge, Bagayam, Vellore, for providing the photograph.

Footnotes

Source of Support: Nil

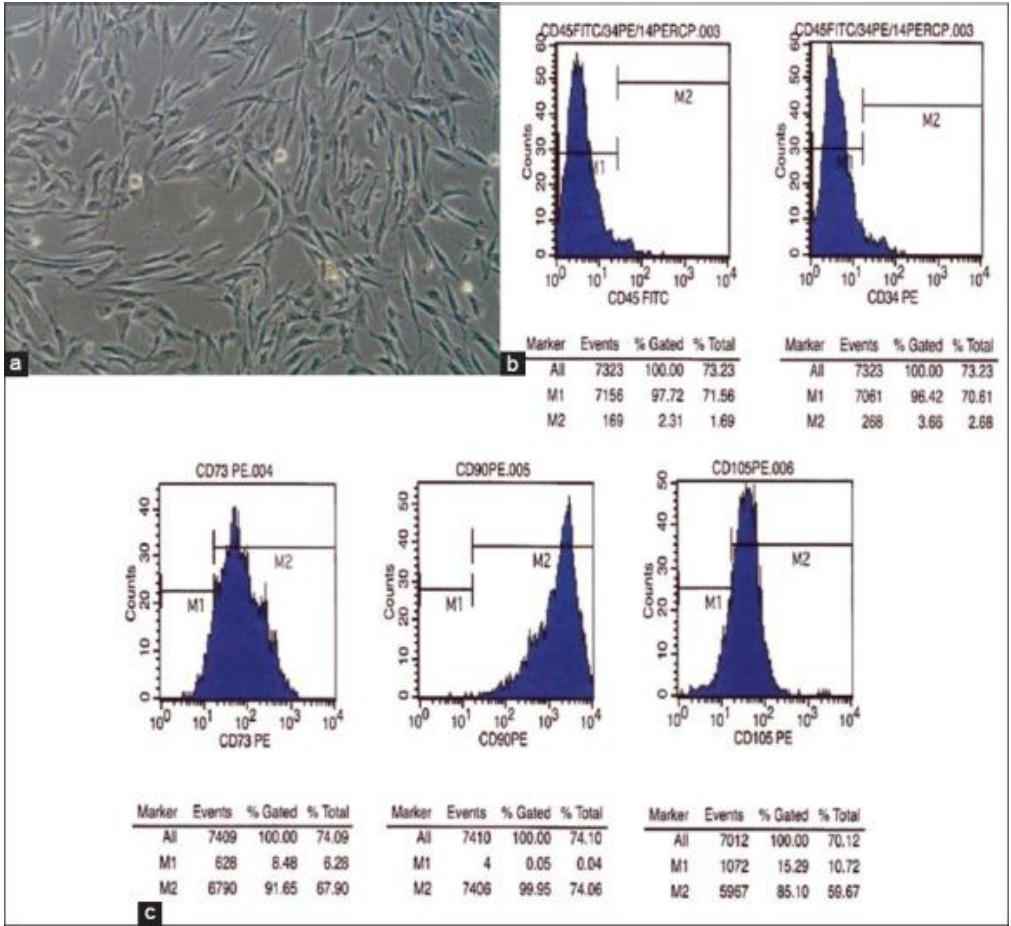
Conflict of Interest: None declared.

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Figures and Tables

Figure 1



Mesenchymal stromal cells (MSC) are characterized post *ex-vivo* expansion by the characteristic (a) Morphology (spindle shaped) and flowcytometry pattern of the expanded cells which are (b) Negative for CD45 and CD34 (excludes hematopoietic elements) and (c) Positive for CD73, CD90 and CD103 (classical positive in MSC)