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Autologous Stem Cell Infusion for Treatment of Pulmonary Disease

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1. Introduction

Over the past several decades stem cell therapy has been characterized as having the potential to dramatically change the treatment of human disease. Impact of such therapy on pulmonary disorders remains unknown. A lack of evidence for a function of exogenous cells in lung repair limits our ability to proceed into clinical trials. Therefore we must rely on personal experience and case series to better understand the clinical effects of stem cell therapy in pulmonary disease. In this report, we discuss four patients with common pulmonary diseases who were treated with the direct infusion of peripherally harvested autologous stem cells into the pulmonary arteries. Although these four patients were followed by Mayo Clinic, the procedure was performed by Regenocyte Therapeutic, a privately owned and operated Florida-based enterprise. The procedure is not approved by the United States Food and Drug Administration. In addition, it was not performed in the context of an approved clinical trial. Each of the patients in this series independently pursued and personally paid for this experimental and controversial treatment. Since the practice is not approved in the United States, the stem cell infusion was performed at the Centro Otorrino Laringologia Hospital in Santo Domingo, Dominican Republic. This report summarizes the clinical experience of these patients based on unrelated clinical assessments at the Mayo Clinic performed both before and after the procedure..

2. Case 1

2.1 Clinical history and course

A 44 year-old Caucasian man and former smoker (38 pack years, quit 2004) presented for evaluation in December 2006 for symptoms of progressive dyspnea (World Health Organization (WHO) functional class III), fatigue, and presyncopal spells. His past medical history was significant for mild chronic obstructive pulmonary disease (COPD) and pulmonary hypertension (PH) diagnosed in 2004, with right heart catheterization (RHC) revealing a mean pulmonary artery pressure (MPAP) of 37 mmHg. Additional PH risk factors included obesity (BMI 33.2), and mild obstructive sleep apnea. The patient had recently started sildenafil (25mg dose) on an as needed basis and reported some reduction in dyspnea after each use.

His laboratory evaluation at Mayo Clinic was normal except for an elevated hemoglobin (17.7 mg/dL). He was hypoxic on room air (pH 7.4, PaO₂ 49, PaCO₂ 33, SaO₂ 90%), and his

pulmonary function test (PFT) revealed mild obstruction with a reduction in diffusing capacity for carbon monoxide (DLCO) (Table 1). High-resolution computed tomography scan of the chest showed diffuse emphysema. The electrocardiogram was normal and the contrast echocardiogram (ECHO) demonstrated mild PH with a right ventricular systolic pressure (RVSP) of 49 mmHg and MPAP 31 mmHg. There was mild left-ventricular hypertrophy but right-ventricular (RV) size and function were normal with an estimated right atrial pressure (RAP) of 5 mmHg. There was no shunt identified (Table 2). A ventilation-perfusion (V/Q) lung scan excluded chronic thromboembolic disease (CTED). The patient achieved 519 meters in the six-minute walk test (6MWT) performed on 2 liters per minute (lpm) oxygen with a nadir saturation of 84%. Overnight oximetry on room air demonstrated a low baseline saturation (mean of 87%) and no significant sleep-disordered breathing.

The patient underwent a repeat RHC with cardiopulmonary exercise testing (CPX). The RHC revealed mild PH at rest that worsened significantly with exercise (MPAP increased from 30 to 58 mmHg) (Table 3). The maximal oxygen consumption was 15.7 mlO₂/kg/min with an inadequate increase in stroke volume with exercise. Pulmonary arterial vasodilator trial revealed no significant response to intravenous epoprostenol.

His PH was classified as WHO diagnostic group 3 (Simoneau 2009); therefore, regular use of adequate oxygen was recommended. He also started tiotropium inhaler. In addition he was instructed to take sildenafil regularly at 20mg three times daily (Alp 2006). Over the next 9 months the patient reported some improvement; however, he remained dyspneic with minimal exertion. Objective measures of his PH remained stable (Table 2). Sildenafil use had ceased and he remained non-compliant with oxygen, using it only at night or when significantly dyspneic. He was evaluated for possible lung transplantation but was not felt to be a good candidate due to noncompliance and his body mass index. The recommendations were for weight loss and improved compliance with his medical regimen.

In November 2007, he was seen in follow-up and was again counseled to be more compliant with oxygen and to restart sildenafil at 20mg three times daily. The patient had been seen by a cardiologist outside our institution for intermittent chest pain and palpitations and had been initiated on diltiazem 180mg daily.

After exploring alternative therapies at a private facility, the patient had blood collected for possible stem cell therapy. On March 4, 2008 he traveled to the Dominican Republic where he received multiple infusions, of what was reported to be the harvested stem cells, directly into the pulmonary arteries.

Shortly after the infusion, he reported feeling like "Superman," running 1 to 2 hours in the first few days. By his report, his room air saturations rose to 99% at 2 weeks, but deteriorated subsequently. Other perceived benefits included decreased fatigue, chest pain, palpitations, and leg pain and even improved vision and mental acuity. His symptomatic improvements persisted at subsequent visits despite becoming more sedentary and gaining 4.5 kg. Notably, he had become more compliant with the use of oxygen to about 3 lpm by nasal cannula at rest.

Objectively, there were also improvements noted in his 6MWT and in the echocardiographic estimates of his pulmonary pressures. (Table 2) These improvements were sustained at repeated follow-ups. However, the oxygen requirement remained 8 to 15 lpm with exertion.

During his evaluation in March 2010, the patient reported that many of the initial subjective improvements had waned. Overall his objective measures remained relatively stable. (Table 2) He had a repeat RHC demonstrating mild resting but severe exercise induced PH (Table 3).

3. Case 2

3.1 Clinical history and course

A 78 year-old Caucasian man presented with dyspnea on exertion (WHO functional class II). He had smoked cigars for 19 years and quit 20 years ago. He was diagnosed with moderate COPD and was treated with inhaled bronchodilators. A few months prior to his presentation at Mayo Clinic, an extensive evaluation including a RHC, a V/Q scan and a pulmonary arteriogram demonstrated PH due to CTED. Those studies were reviewed and felt to be conclusive. His medications included hydrochlorothiazide, furosemide, and warfarin. A PFT demonstrated moderate obstruction, air trapping, a reduced DLCO, and oxygen desaturation with exercise (Table 1). The 6MWT and ECHO results are reported in Table 2. Arterial blood gas on room air was: pH 7.47, PaO₂ 67, PaCO₂ 37; and the BNP was 178 pg/mL. Cardiac MRI revealed RV enlargement and hypertrophy with a reduced RV ejection fraction to 27%. A repeat RHC was performed, and it was felt the PH was multifactorial secondary to COPD, CTED, and mild pulmonary venous hypertension (Table 3). Given the patient's age, minimal symptoms, multiple mechanisms for his PH, and his comorbidities, he was considered a high risk for pulmonary endarterectomy, and the patient elected for conservative therapy. An inferior vena cava filter was placed and life-long anticoagulation was recommended. In addition, supplemental oxygen with exercise and sildenafil 20 mg three times daily (Reichenberger 2007) were initiated.

Six-months later, there was a slight improvement in the 6MWT (Table 2). He was now requiring increasing oxygen to maintain saturations at rest (1.5 lpm) and during exertion. Given persistently elevated right-heart pressures and RV enlargement and hypokinesia, bosentan was added to his regimen. Eight months after adding bosentan, he continued to show improvement in the 6MWT but the ECHO was unchanged. Oxygen needs continued to increase, now requiring 2 lpm at rest and 15 lpm for the 6MWT (Table 2).

Three months later, he underwent adult stem infusion. This date corresponded to 18 months on sildenafil 20 mg three times daily and 12 months on bosentan at full dose. One week after the harvest, he traveled to Santo Domingo for the infusion into his pulmonary arteries via a pulmonary artery catheter at Centro Otorrino Laringologia Hospital. Repeat ECHO one month later showed a RVSP of 55 mmHg which was exactly the same as his baseline value one month prior to the infusion. Another ECHO performed by Regenocyte Therapeutics three months after the stem cell infusion demonstrated a RVSP 41 mmHg. A PFT four months after stem cell infusion was essentially unchanged (Table 1).

The patient was seen in follow up at Mayo Clinic approximately 5 and 12 months after his stem cell infusion. He stated that he felt neither better nor worse after his stem cell treatment and was on 3 lpm oxygen to maintain an adequate resting saturation. His objective assessment showed some benefit at 5 months. That benefit had waned one year after stem cell infusion. His treatment regimen included diuretics, warfarin, sildenafil 20 mg three times daily, bosentan 125 mg twice daily (Jais 2008) and oxygen. He has also been regularly participating in a formal pulmonary rehabilitation program. No changes were made in his medical regimen.

Date	PFT Results				Pulse Oximetry				Six-Minute Walk
	FEV1	FEV1/FVC	TLC	RV	DLCO	Rest/Exercise	%	meters	
Case 1	L (%*)	%	L (%*)	L (%*)	ml/min/mmHg (%)				
Dec-06	3.31 (73)	73	6.68 (89)	2.06(119)	16.3 (49)		93/86	530	
Mar-08	STEM	CELL	INFUSION						
Sep-08	3.13 (71)	71	6.98 (95)	2.26(127)	16.3 (50)		94/87	536	
Case 2									
Oct-07	1.32 (54)	44	6.50 (111)	3.60 (138)	11.8 (64)		94/87	***	
Mar-09	STEM	CELL	INFUSION						
Jul-09	1.33 (55)	39	6.8 (115)	3.40 (132)	11.3 (62)		91**	***	
Case 3									
Jan-09	1.81 (49)	59	5.03 (71)	1.55 (70)	17.2 (62)		96/92	N/A	
Jun-09	1.84 (49)	58	5.29 (73)	1.98 (89)	17.2 (62)		95/92	N/A	
Jan-10	STEM	CELL	INFUSION						
Jun-10	1.74 (46)	57	5.39 (75)	2.19 (98)	17.7 (65)		97/94	N/A	
Case 4									
Jun-10	0.45 (12)	31	6.91 (116)	5.40 (369)	11.1 (33)		86	255**	
Jul-10	STEM	CELL	INFUSION						
Aug-10	0.45 (12)	33	6.72 (113)	5.06 (346)	10.7 (32)		92	341**	

Legend: Pulmonary function test results, oxygenation and modified Borg dyspnea score data on four patients who had pulmonary artery stem cell infusion. Key: FEV1 - Forced Expiratory Volume in One Second, FVC - Forced Vital Capacity, TLC - Total Lung Capacity, RV - Residual Volume, DLCO - Diffusing Capacity of Carbon Monoxide

* Percent Predicted. **Test performed on oxygen. ***See Table 2. N/A - Not Available

Table 1. Pulmonary Function and Six-Minute Walk Testing- Pre and Post Stem Cell Infusion

DATE	BNP pg/ml	WHO Function al Class	6 Minute Walk				Echo Data											
			Distance (meters)	SaO ₂ (%)/ FIO ₂ (L)	Borg Score	RAP	TR Jet Velocity	RVSP	MPAP	RV Size	RV Function							
CASE 1																		
Dec-06	20	3	530	84/8	1	5	3.3	49	31	Normal	Normal							
Apr-07	25	3	550	88/6	3	5	3.5	54	45	Mild	Normal							
Oct-07	17	3	470	91/10	3	10	3.5	59	43	Normal	Normal							
Nov-07	31	2	596	88/10	3	5	3.6	57		Mild	Normal							
Feb-08	54	3	512	91/10	2	5	3.6	57	41	Normal	Normal							
Mar-08	STEM	CELL																
May-08	26	2	556	91/8	1	5	3.1	43	28	Normal	Normal							
Nov-08	16	3	580	86/8	3	5	3.2	46	33	Normal	Normal							
Feb-09	39	3	600	93/15	4	5	3.3	49	29	Mild	Normal							
May-09	57	3	619	90/10	3	5	3.2	46	N/A*	Mild	Normal							
Mar-10	19	3	586	92/15	5	5	3.3	49	36	Normal	Normal							
CASE 2																		
Aug-07	178	2	291	91/4	5	5	4.3	79	47	Moderate	Moderate							
Apr-08	119	2	339	89/15	5	5	4.3	79	47	Moderate	Moderate							
Dec-08	38	2	384	90/15	4	15	4.0	79	58	Moderate	Moderate							
Mar-09	STEM	CELL																
Aug-09	40	2	401	94/15	3	N/A*	N/A*	N/A*	N/A*	Mild	Normal							
May-10	87	3	373	96/15	4	16	4.0	80	58	Moderate Severe	Moderate Severe							

Legend: Brain natriuretic peptide levels, WHO functional class (1 to 4 scale), six-minute walk distances with modified Borg dyspnea score and echocardiography results on Cases 1 and 2 who had pulmonary artery stem cell infusion. Key: BNP - Brain Natriuretic Peptide, WHO - World Health Organization, Borg Score - Modified Borg Dyspnea Score on a scale of 0 to 10, SaO₂ - Oxygen Saturation, FIO₂ - Fraction of Inspired Oxygen, RAP - Right Atrial Pressure, TR - Tricuspid Regurgitant (peak), RVSP - Right Ventricular Systolic Pressure, MPAP - Mean Pulmonary Artery Pressure, RV - Right Ventricle, Normal and Mild describe degree of enlargement and ventricular dysfunction

* Unable to estimate due to incomplete tricuspid regurgitant jet

Table 2. Cardiopulmonary Data for Cases 1 and 2

		RAP (mmHG)	PAP (mmHG)	MPAP (mmHg)	PAOP (mmHg)	CO/CI (L/min, L/min/m ²)	PVR (dyne sec cm ⁻⁵)	Vasodila- tor Response	MPAP During Exercise (mmHg)
Case 1	Baseline 1/2007	4	45/25	30	12	5.1/2.1	282	No	58
	Follow-up 3/2010	6	44/20	28	14	8.3/3.3	135	No	70
Case 2	Baseline 10/2007	11	85/34	51	16	5.8/3.2	478	No	N/A *
	Follow-up	NOT	DONE						

Legend: Hemodynamic data from right heart catheterization on Cases 1 and 2. Key: RAP - Right Atrial Pressure, PAP - Pulmonary Artery Pressure, MPAP - Mean Pulmonary Artery Pressure, PAOP - Pulmonary Artery Occlusion Pressure, CO - Cardiac Output, CI - Cardiac Index, PVR - Pulmonary Vascular Resistance

* Exercise study not performed

Table 3. Baseline and Post Stem Cell Transfusion Right Heart Catheter Data

4. Case 3

4.1 Clinical history and course

A 66-year-old Caucasian man presented in January of 2009 with symptoms of worsening dyspnea on exertion. Patient had a past medical history of hypertension and transient ischemic attacks. His pulmonary history dates back to 2002 at which time he was told to have scarring of his lungs. He had been followed by outside pulmonologist who had reported stable "scarring" of his lungs. The patient endorses a history of asbestos exposure, as well as a history of being in industrial chemical salesman. He had a less than 5 pack year history of smoking and denied any exposure to pets, birds, hot tubs, or other antigens suggestive for hypersensitivity pneumonitis.

Patient underwent extensive testing including high resolution CT scan, which revealed extensive upper and lower lobe fibrosis, focal atelectasis and pleural thickening at the left base, and extensive linear calcifications in both lungs associated with fibrosis. Comparing this study to a previous scan performed in 2002 the findings had progressed slightly. Pulmonary function testing was performed with spirometry showing a mixed pattern of obstruction and restriction, lung volumes consistent with mild restriction, and a mildly reduced DLCO (Table 1). Echocardiogram revealed normal left ventricular function, normal diastolic function, normal RV size and function, and indeterminate pulmonary pressures secondary to incomplete tricuspid regurgitant jet. Laboratory work was notable for negative hypersensitivity panel, fungal serologies, and normal blood counts. Patient underwent bronchoscopy for bronchoalveolar lavage and transbronchial biopsies. Cultures were negative and pathology of transbronchial biopsy revealed elastic fibrous tissue. Referral to cardiothoracic surgery was made for possible open lung biopsy however it was decided that the yield would be low given the extensive fibrotic changes and outweigh potential benefits. Patient was given a diagnosis of idiopathic pulmonary fibrosis and obstructive lung disease. Follow-up chest imaging and pulmonary function testing was planned. Bronchodilator therapy was offered, but refused by patient.

In June of 2009 patient returned with no significant change in his symptoms. A repeat CT scan showed stable diffuse fibrotic changes. Pulmonary function testing was

performed and found to be essentially unchanged (Table 1). Given the relative stability of patient's symptoms and pulmonary function testing further follow-up was recommended. At this time, the patient inquired about treatment of his pulmonary fibrosis with stem cell therapy. Given the lack of safety and efficacy data in the use of stem cell therapy for the patient's disease, treatment with this modality was discouraged.

In January 2010, under the oversight of Regenocyte Therapeutic, the patient underwent a bone marrow derived autologous stem cell infusion in the Dominican Republic. He reported that stem cells were infused into three different areas of each lung via a pulmonary artery catheter. Patient returned to Mayo Clinic in June 2010 for follow-up at which time he reported a significant subjective improvement in his symptoms of dyspnea on exertion. More specifically he states that immediately after the infusion he noted no change in. Approximately 3 months after stem cell infusion, he professed to less dyspnea with exercise. For example, in the past it would take him approximately one hour to walk 2 miles and several months following stem cell therapy he was able to do so in one half hour. The patient's subjective improvements were unfortunately not correlated with any improvement in his pulmonary function testing (Table 1). CT imaging also remained unchanged showing stable diffuse fibrotic lung disease.

5. Case 4

5.1 Clinical history and course

A 30-year-old man, originally from Albania who has lived in the United States for the past 25 years, presented in June 2010 with a primary complaint of recurrent pneumonias. Patient had a history of repeated pneumonias since the age of 2. He had been hospitalized numerous times throughout his life secondary to pneumonia. He described outside evaluation as including bronchoscopy and nasal endoscopy with biopsy. Suspected diagnosis at time of consultation was primary ciliary dyskinesia. Medications at time of evaluation included fluticasone/salmeterol 250/50, tiotropium, and oxygen use nightly. Past medical history was otherwise negative. The patient has been a lifelong nonsmoker and denied any pulmonary family history.

At Mayo Clinic, he underwent testing to further evaluate his history and suspected diagnosis of primary ciliary dyskinesia. CT Scan showed widespread hyperinflation with mosaic attenuation, bronchial wall thickening, and bronchiectasis. The distribution of this was diffuse and not lobar predominant. Pulmonary function testing revealed severe obstruction, hyperinflation, reduction in DLCO, and resting saturation of 86%. The patient was able to ambulate 255 meters on 6 minute walk with end-of-walk oxygen saturation 97% on 2 L nasal cannula (Table 1). Echocardiogram performed at time of evaluation revealed preserved left ventricular systolic and diastolic function, moderate to severe RV enlargement as well as decrease in RV systolic function. Right ventricular systolic pressure was estimated at 63 mmHg, with a Doppler derived MPAP of 45 mmHg. The patient was diagnosed with severe obstructive lung disease secondary to bronchiectasis, with secondary PH (WHO group 3). Primary ciliary dyskinesia was suspected to be the underlying cause. Given the severity of patient's disease he was referred to lung transplantation for evaluation. In August of 2010 the patient returned for follow-up evaluation. About one month prior to this visit he underwent harvesting of stem cells from bone marrow and subsequent infusion

into his pulmonary arteries for treatment of pulmonary hypertension under the direction of Regenocyte Therapeutic. Further details of the procedure were not available at the time of visit. He did report subjective improvements in cough, improved energy level, and decreased utilization of oxygen. He also denied any exacerbations of his bronchiectasis in the interim. Repeat pulmonary function testing showed unchanged lung volumes, persistent severe obstruction and reduction in DLCO. Interestingly the patient had an improvement in his resting oxygen saturation to 92% from previous measure of 86%. 6 minute walk also showed an improvement, with patient walking of 341 meters compared to 255 meters, with an end-of-walk oxygen saturation of 90% on 2 L nasal cannula (Table 1). Echocardiography continued to show preserved left ventricular function with slight improvement in patient's RV enlargement as well as right ventricular systolic function. Estimated RVSP was reduced to 49 mmHg with a Doppler derived MPAP of 35 mmHg.

The patient was evaluated by the lung transplantation service; however, he was not interested in proceeding given the subjective improvement he had experienced with his initial stem cell therapy.

6. Discussion

Use of stem cell therapy for the treatment of pulmonary diseases is gaining increasing attention. In the past decade, circulating bone marrow-derived cells similar to embryonal angioblasts have been identified (Asahara 1997) termed "endothelial progenitor cells (EPC)." These cells have the potential to proliferate and differentiate into mature endothelial cells. Two major types of these cells in human peripheral blood have been termed "early EPC's" and "late outgrowth EPC's," both of which appear to have potential in lung microvascular repair and restoring vascular structures of the lung. (Yoon 2005)

A number of trials are currently underway to evaluate the safety and effectiveness of the infusion of stem cells in pulmonary disease. A recently published report out of Brazil suggested both safety and improvement in quality of life in patients with severe COPD/emphysema (Ribeiro-Paes 2011). An ongoing multi-center trial is currently looking at the efficacy of PROCHYMAL™ (ex Vivo Cultured Adult Human Mesenchymal Stem Cells) intravenous infusion for treatment of moderate to severe COPD. A pilot trial of autologous EPC administration for idiopathic pulmonary arterial hypertension was conducted at Zhejiang University, Hangzhou, China. The trial was a 12 week follow-up of patients after systemic administration of autologous EPC's plus conventional therapy compared with patients receiving conventional therapy alone. (Wang 2007) The results included increased six-minute-walk capacity and improved hemodynamic variables, including MPAP, pulmonary vascular resistance, and cardiac output. No concerns with the safety of the administration of EPC's were encountered. The Pulmonary Hypertension and Cell Therapy (PHACeT) trial by the University of Toronto reported on the administration of autologous EPCs transduced to express exogenous nitric oxide synthase. Three patients in their initial panel showed a remarkable (nearly 50%) reduction in total pulmonary vascular resistance over the course of the 3-day delivery period. Subsequent study in additional patients is currently underway. (Weiss 2008)

In our report, we present four patients who had peripherally harvested autologous stem cells infused into the pulmonary arteries. The procedure was not endorsed by or performed by Mayo Clinic. In addition, it was not performed in the context of an approved clinical trial.

The procedures were performed by Regenocyte Therapeutic. The reported infusion occurred at the Centro Otorrino Laringologia Hospital in Santo Domingo, Dominican Republic, as the procedure is not approved by the United States Food and Drug Administration.

A variety of unusual challenges are illustrated by the care and interaction of these four patients at Mayo Clinic (Table 4). The inability to control for concomitant therapy complicates the interpretation of these patients' clinical course both pre and post stem cell infusion. The first patient (Case 1) reported significant subjective improvement. At the time of follow-up many of these improvements had waned; however, there may have been mild improvement in both his resting pulmonary pressures by ECHO and 6MWT. (Table 2) These reductions in MPAP appeared to be sustained up to 24 months post infusion. Unfortunately, these functional and hemodynamic improvements did not translate into any significant change in the severe hypoxemia. Case 2 did not have any change in his symptoms or WHO functional class. He continued to have increasing supplemental oxygen requirements. His six-minute walk distance had slightly improved, and his ECHO demonstrated improved RV function. Case 3 reported significant subjective improvement in exercise capacity. Objectively this did not translate into any improvement in PFT. Case 4 perhaps seemed to have the most significant improvement in objective measures including improvement in resting saturation, six minute walk distance and reduction in MPAP as estimated by ECHO.

Are any of the changes due to the stem cell infusion? It is impossible to determine in an uncontrolled setting. The role of multiple ongoing therapies and the limitations of the clinical assessments are particularly challenging to evaluate. Three of the four patients were on multiple therapies for treatment of PH and/or COPD at the time they received the stem cell infusion. Variations in oxygen requirements and supplementation may be particularly confounding since three of the four patients had obstructive lung disease with associated PH. Although validated surrogate endpoints in assessing response to therapy remain a source of ongoing discussion, measurements such as spirometry, ECHO, six minute walk distance, WHO functional class have been validated to monitor disease course, but remain imperfect. (Hoepfer 2005; Snow 2007; Aduen 2009)

If there were some benefit, it is unfortunate that it will remain inconclusive. Cases 1 and 3 had subjective improvement; however, their clinical scenario was complex as outlined above. Case 4's objective improvements are interesting but may represent concomitant therapies not disclosed in this uncontrolled setting. These cases present several challenging dilemmas for the clinician in this evolving area of science. Short of lung transplantation, there are generally no cures for the underlying pulmonary disease. In Cases 1, 3, and 4, we informed the patients that the only proven therapy for COPD/IPF in the setting of hypoxia was oxygen therapy. (Nocturnal Oxygen Therapy Trial Group 1980; Medical Research Council 1981) Nonetheless, these patients had a difficult time accepting more conventional treatment and instead sought experimental therapies.

The stem cell therapy raised the issue of unproven therapies to a new level as the patients personally paid approximately \$50,000 for the therapy that was administered outside the context of either a clinical or research setting. In addition, the therapy was pursued independently of our clinical recommendation or oversight. Also of interest in these particular cases, was the potential impact on the relationship between the physician and patient since the patients had pursued an unendorsed experimental therapy outside the

country. Although our stance on the experimental nature of stem cell therapy for pulmonary disease has always been clear, all of these patients researched, pursued and financed the therapy on their own accord. The clinician must be prepared for any potential conflict that may ensue if the patient seeks an experimental, unapproved therapy. In our practice, we maintain that such therapy should only be administered in the context of an approved research protocol. Nonetheless, we felt committed to the ongoing management of these patients regardless of their decision to seek unapproved stem cell infusion therapy.

Patient-Centered	Provider-Centered	Knowledge-Centered
End-stage disease generates desperate interest in unproven therapies	Limited time to discuss and counsel patients regarding unproven therapies	Conventional therapies are often of limited value in severe pulmonary disease
Patients may have strong desire to receive unproven therapies regardless of consequences	Brief, simplistic cautionary advice may be insufficient to dissuade the patient from seeking unproven therapy	Knowledge gap exists by definition with unproven therapies
Inability to distinguish between for-profit endeavors and academically-based clinical trials	Assessment of ethical, legal and professional nature of extra-mural practices often complex	Provision of unproven therapy in uncontrolled (non-research) manner precludes firm conclusions from results
Patient desires to maintain relationship with primary physician and to seek unconventional and/or unproven therapies	Physician must maintain objectivity as well as primary role as patient advocate and caregiver	Cooperative interaction and research between academic centers required to advance the science

Legend: Important challenges and limitations encountered in this series of 4 patients receiving stem cell infusion independent of your care.

Table 4. Illustrative Lessons

7. Conclusion

Stem cell therapy has emerged as an experimental therapy to potentially treat a number of diseases, including pulmonary disorders. Current ongoing safety and efficacy trials will likely add significantly to our current understanding of the field, with hopes of aiding in

future patient care. In a parallel fashion, patients are pursuing this form of therapy outside of controlled research trials. Such practices create significant challenges in evaluating efficacy and potentially stress the provider-patient relationship in unique ways (Table 4).

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New Advances in Stem Cell Transplantation

Edited by Prof. Taner Demirer

ISBN 978-953-51-0013-3

Hard cover, 582 pages

Publisher InTech

Published online 24, February, 2012

Published in print edition February, 2012

This book documents the increased number of stem cell-related research, clinical applications, and views for the future. The book covers a wide range of issues in cell-based therapy and regenerative medicine, and includes clinical and preclinical chapters from the respected authors involved with stem cell studies and research from around the world. It complements and extends the basics of stem cell physiology, hematopoietic stem cells, issues related to clinical problems, tissue typing, cryopreservation, dendritic cells, mesenchymal cells, neuroscience, endovascular cells and other tissues. In addition, tissue engineering that employs novel methods with stem cells is explored. Clearly, the continued use of biomedical engineering will depend heavily on stem cells, and this book is well positioned to provide comprehensive coverage of these developments.

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