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ORIGINAL PAPER

Standard PAH therapy improves long term survival in CTEPH patients

Hans-Juergen Seyfarth · Michael Halank · Heinrike Wilkens · Hans-Joachim Schäfers · Ralf Ewert · Martin Riedel · Ernst Schuster · Hans Pankau · Stefan Hammerschmidt · Hubert Wirtz

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Abstract
Background Chronic thromboembolic pulmonary hypertension (CTEPH), subsequent to pulmonary embolism is a relatively frequent cause of pulmonary hypertension. Similar to patients with pulmonary arterial hypertension (PAH), CTEPH carries a poor prognosis. There is no hard evidence for any other therapy except pulmonary endarterectomy and none for those patients that are not eligible for this procedure.
Patients and methods Fifty patients with confirmed, inoperable CTEPH receiving specific vasodilative therapy (prostanoids, endothelin receptor antagonists, PDE 5-inhibitors or combination) were included in this retrospective study (mean age 55 years, range 16–76 years; 36 female, 14 male). Kaplan–Meier plots of these patients were compared with Kaplan–Meier plots of two historical CTEPH patient groups without any specific vasodilative treatment by log rank tests.
Results CTEPH patients treated with specific vasodilative compounds as used for therapy of PAH were followed up for 52 ± 30 months and had a significantly improved survival compared with patients treated without PAH type vasodilators ($p \leq 0.0002$).
Conclusion Our data may generate the hypothesis that specific vasodilative treatment improves outcome in patients with inoperable CTEPH.

Keywords Pulmonary hypertension · Pulmonary embolism · Survival · Vasodilator agents

Abbreviations

CI	Cardiac index
CTEPH	Chronic thromboembolic pulmonary hypertension
IPAH	Idiopathic pulmonary arterial hypertension
mPAP	Mean pulmonary arterial pressure
PAH	Pulmonary arterial hypertension
PEA	Pulmonary endarterectomy
PVR	Pulmonary vascular resistance

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) has been estimated to occur in up to 3.8% 2 years following an episode of confirmed pulmonary embolism [20]. The incidence of CTEPH may even be higher because pulmonary embolism occurs without apparent symptoms in many patients [9]. The mechanisms leading to persistence

H.-J. Seyfarth (✉) · H. Pankau · S. Hammerschmidt · H. Wirtz
Department of Respiratory Medicine, University of Leipzig, Liebigstrasse 20, 04103 Leipzig, Germany
e-mail: hans-juergen.seyfarth@uniklinik-leipzig.de

M. Halank
Internal Medicine I, University of Dresden, Dresden, Germany

H. Wilkens · H.-J. Schäfers
Universitätsklinikum Homburg/Saar, Homburg, Germany

R. Ewert
University of Greifswald, Greifswald, Germany

M. Riedel
Deutsches Herzzentrum, Klinikum Der TU München, Munich, Germany

E. Schuster
Institut for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany

of an increased pulmonary artery pressure have not yet been identified in detail [1, 5, 7].

Similar to pulmonary arterial hypertension (PAH), CTEPH has been recognized to carry a poor prognosis [21]. Survival is markedly reduced when mean pulmonary arterial pressure (mPAP) exceeds 30 mmHg or when a decreased partial oxygen pressure and severe exercise intolerance are present [21]. In particular, when right heart failure is apparent survival is comparable to survival in patients with idiopathic pulmonary arterial hypertension (IPAH) not receiving vasodilator therapy [21]. The most effective treatment for CTEPH is surgical desobliteration of the pulmonary arteries (pulmonary endarterectomy, PEA). PEA has been established as the first line treatment in CTEPH [22]. However, PEA is a treatment with considerable operative risk, and it is restricted to cases, in which obstruction begins in more proximally located pulmonary vessels which are large enough for the desobliteration to be carried out [6]. In our experience the number of patients not suitable for PEA for various reasons is relevant. CTEPH patients that are not eligible for PEA receive medical treatment options including anticoagulants, diuretics and supplemental oxygen [17].

Histology of pulmonary arteries in CTEPH reveals changes similar to those in IPAH, including plexogenic lesions and an increase in the vascular smooth muscle mass [15]. Because recently developed vasodilators have been of great use in PAH several authors have suggested to use the same vasodilator therapy in CTEPH [8, 14, 16–18, 26].

Recently, the first randomized, placebo controlled trial, including only patients suffering from CTEPH, was finished. In this trial CTEPH patients treated with bosentan over a period of 16 weeks showed a significant decrease of the pulmonary vascular resistance (PVR) in comparison with placebo group. However, the study failed his second coprimary end point—the significant increase of 6 min walking distance (6MWD) in patients receiving the vasodilating agent bosentan [13].

Moreover, few retrospective studies exist examining prostanoids, endothelin receptor antagonists or phosphodiesterase 5-inhibitors in patients with CTEPH not eligible for PEA [23]. These investigations suggest that pulmonary vasodilators improve hemodynamics and exercise tolerance in these patients [2–4, 10–12, 16, 18, 19, 24, 25]. The effects of therapy with bosentan or prostanoids in patients with CTEPH during a longer period were studied in two trials [12, 19]. However, the influence of pulmonary vasodilators on long-term survival in CTEPH patients has not yet been addressed.

The aim of our investigation was to test whether pulmonary vasodilator therapy improves long term survival in patients with inoperable CTEPH. For that purpose we compared survival of our treated patient group with data from two groups of patients without pulmonary vasodilator therapy published in the past.

Patients and methods

Patients

Fifty patients with confirmed CTEPH not eligible for pulmonary PEA from four German pulmonary centers with special experience in pulmonary hypertension were included in this retrospective study (mean age: 55 years (±16); 36 female, 14 male). Initial hemodynamic measurements demonstrated severe pulmonary hypertension: mean pulmonary arterial pressure (mPAP): 52.52 ± 10.13 mmHg; cardiac index (CI) 2.11 ± 0.48 L/min m^{-2}; PVR: 1057.50 ± 424.61 dyne s cm^{-5}. The distribution of WHO functional classes was as follows: II/III/IV: $n = 4/37/9$. All patients were evaluated with computed tomography and a lung ventilation perfusion scan. Pulmonary angiography was performed to confirm the distribution and location of obstruction and to rule out the possibility of PEA. All patients were discussed by the same experienced interdisciplinary board including an experienced cardiovascular surgeon, who confirmed the diagnosis and agreed to the decision not to perform PEA. The decision pro or against PEA was based on the ACCP evidence-based clinical practice guidelines for surgical treatments and interventions. These guidelines postulate selection criteria for CTEPH patients considered to be suitable for PTE: WHO functional class III or IV; PVR > 300 dyne s cm^{-5}; surgically accessible thrombus (in segmental pulmonary arteries or proximal); no severe comorbidities [6]. Because there was no other specific treatment, and because of the bad prognostic perspective for these CTEPH patients, they were treated according to PAH treatment standards (at the times of treatment). Pulmonary vasodilator treatment consisted of inhaled iloprost ($n = 4$), oral beraprost sodium ($n = 3$), intravenous iloprost ($n = 5$), bosentan ($n = 24$), sildenafil ($n = 4$), and a combination of bosentan/inhaled iloprost ($n = 1$), bosentan/sildenafil ($n = 6$), bosentan/beraprost ($n = 1$); bosentan/sildenafil/prostanoids ($n = 2$) (therapy at the latest follow up).

The mean time from the establishment of diagnosis CTEPH to the start of specific treatment was 13.6 months (range 3–58 months). The mean duration of vasodilator therapy was 36 ± 22.4 months (range 1–124 months). Patients received pulmonary vasodilator treatment for at least 6 months or died within 6 months while on vasodilator therapy. CTEPH patients receiving standard therapy (anticoagulants, diuretics and supplemental oxygen) reported by Ono et al. ($n = 23$; mean age 52 ± 14 years; mPAP 46 ± 12 mmHg; WHO functional class II/III/IV

5/14/4) and by Riedel et al. ($n = 20$; mean age 46 ± 12; mPAP 55 ± 16) were compared with patients treated with vasodilators [19, 21].

Methods of data analysis/statistics

Survival data of CTEPH patients was analyzed by the Kaplan–Meier method. Log rank test was applied for comparison of survival data used for the Kaplan–Meier plot. Statistical significance was accepted at the 0.01 level (SPSS12.0, SSPS Incorporation).

Results

CTEPH patients treated with specific vasodilative compounds in our study were followed up for 52 ± 30 months. Seven individuals died from right heart failure. The follow up period of the two historical groups was 58 ± 45 [19] and 24 ± 23 [21] months respectively. Patients receiving specific vasodilator therapy showed a significantly improved survival compared with both historical groups without specific vasodilator therapy using log rank test ($p = 0.0001$ and $p = 0.0002$ respectively, Fig. 1). Survival was not much different in the two historical patient groups ($p = 0.172$).

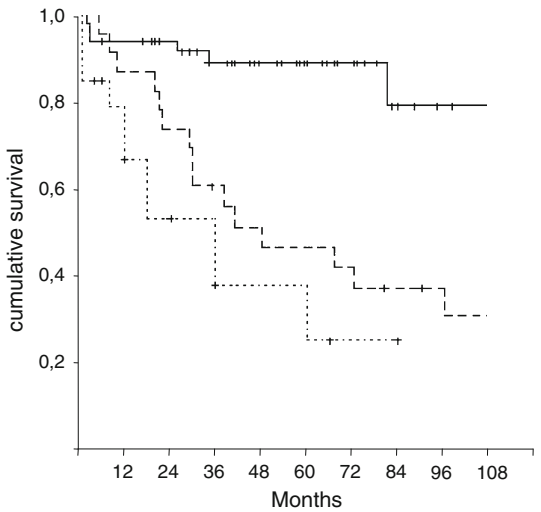

Fig. 1 Kaplan–Meier plots of CTEPH patients treated with specific vasodilative compounds ($n = 50$, *continuous line*) and of two historical CTEPH patient collectives receiving conservative treatment ($n = 20$, *dashed line* [21]; $n = 23$, *dotted line* [19]) are depicted. Kaplan–Meier plots of specifically treated CTEPH patients and of the historical collectives are significant different by log rank analysis ($p < 0.001$)

Discussion

This study compares survival data from 50 CTEPH patients treated with specific vasodilator therapy with two previously reported patients groups without specific vasodilator treatment [19, 21]. The Kaplan–Meier analysis demonstrates a significantly improved survival for patients treated with vasodilators typically used in the therapy of PAH.

Survival of patients with CTEPH depends among other things on disease severity. The mPAP of our patients was similar to the mPAP of the CTEPH patients in the two groups used for comparison. Although mPAP is not an excellent parameter for comparison of the extent of pulmonary hypertension, it will still indicate acceptable comparability of the patient groups. Cardiac index of the historical controls was not available which adds to the limitations of this comparison.

A further limitation is the historical control group in our study. Although the use of historical controls is used by others in the field of pulmonary hypertension as well, it causes several disadvantages, e.g. the change in conventional treatment [14, 26]. For this reason our results can be considered only as a hypothesis generating observation.

Recently, the first randomized, controlled, double blind trial investigating the effect of the dual endothelin receptor antagonist bosentan in patients CTEPH was finished. Data of this study suggest an improvement of PVR in the bosentan group over a period of 16 weeks [13]. However, these studies, in contrast to our, will provide data on the short term effect of the compound studied. Our survival data of 50 CTEPH patients treated with several vasodilators for 52 ± 30 months is also within the range of survival observed in a 1-year follow up of 47 CTEPH patients treated with bosentan [12].

In conclusion, we interpret our observation as a hypothesis-generating study, which suggests a beneficial effect of a specific vasodilative treatment on overall survival in inoperable CTEPH patients. This hypothesis that a specific vasodilative therapy improves survival in CTEPH patients not eligible for PEA has to be investigated in a large confirmatory trial.

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References

1. Bonderman D, Jakowitsch J, Adlbrecht C, Schemper M, Kyrle PA, Schonauer V, Exner M, Klepetko W, Kneussl MP, Maurer G, Lang I (2005) Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. Thromb Haemost 93:512–516

2. Bonderman D, Nowotny R, Skoro-Sajer N, Jakowitsch J, Adlbrecht C, Klepetko W, Lang IM (2005) Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. Chest 128:2599–2603
3. Bresser P, Fedullo PF, Auger WR, Channick RN, Robbins IM, Kerr KM, Jamieson SW, Rubin LJ (2004) Continuous intravenous epoprostenol for chronic thromboembolic pulmonary hypertension. Eur Respir J 23:595–600
4. Bresser P, Pepke-Zaba J, Jais X, Humbert M, Hoeper MM (2006) Medical therapies for chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc 3:594–600
5. Dartevelle P, Fadel E, Mussot S, Chapelier A, Hervé P, de Perrot M, Cerrina J, Ladurie FL, Lehouerou D, Humbert M, Sitbon O, Simonneau G (2004) Chronic thromboembolic pulmonary hypertension. Eur Respir J 23:637–648
6. Doyle RL, McC Douglas, Channick RN, Simmonneau G, Conte J (2004) Surgical treatments/interventions for pulmonary arterial hypertension. ACCP evidence-based clinical practice guidelines. Chest 126:63S–71S
7. Egermayer P, Peacock AJ (2000) Is pulmonary embolism a common cause of chronic pulmonary hypertension? Limitations of the embolic hypothesis. Eur Respir J 15:440–448
8. Ewert R, Opitz CF, Wensel R, Winkler J, Halank M, Felix SB (2007) Continous intravenous iloprost to revert treatment failure of first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. Clin Res Cardiol 96:207–211
9. Fedullo PF, Auger WR, Kerr KM, Rubin LJ (2001) Chronic thromboembolic pulmonary hypertension. N Engl J Med 345:1465–1472
10. Ghofrani HA, Schermuly RT, Rose F, Wiedemann R, Kohstall MG, Kreckel A, Olschewski H, Weissmann N, Enke B, Ghofrani S, Seeger W, Grimminger F (2003) Sildenafil for long-term treatment of nonoperable chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 167:1139–1141
11. Hoeper MM, Kramm T, Wilkens H, Schulze C, Schaefers HJ, Welte T, Mayer E (2005) Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. Chest 128:2363–2367
12. Hughes RJ, Jais X, Bonderman D, Suntharalingam J, Humbert M, Lang I, Simonneau G, Pepke-Zaba J (2006) The efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension: a 1-year follow-up study. Eur Respir J 28:138–143
13. Jaïs X, D'Armini AM, Jansa P, Torbicki A, Delcroix M, Ghofrani HA, Hoeper MM, Lang IM, Mayer E, Pepke-Zaba J, Perchenet L, Morganti A, Simonneau G, Rubin LJ, for the BENEFiT Study Group (2008) Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension. JACC 52:2127–2134
14. Mc Laughlin VV, Sitbon O, Badesch DB, Barst RJ, Black C, Galie N, Rainisio M, Simonneau G, Rubin LJ (2005) Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 25:244–249
15. Moser KM, Bloor CM (1993) Pulmonary vascular lesions occuring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 103:685–692
16. Nagaya N, Shimizu Y, Satoh T, Oya H, Uematsu M, Kyotani S, Sakamaki F, Sato N, Nakanishi N, Miyatake K (2002) Oral beraprost sodium improves exercise capacity and ventilatory efficiency in patients with primary or thromboembolic pulmonary hypertension. Heart 87:340–345
17. Olschewski H, Hoeper MM, Borst MM, Ewert R, Grünig E, Kleber FX, Kopp B, Opitz C, Reichenberger F, Schmeisser A, Schranz D, Schulze-Neick I, Wilkens H, Winkler J, Worth H (2007) Diagnosis and therapy of chronic pulmonary hypertension. Clin Res Cardiol 96:301–330
18. Olschewski H, Simonneau G, Galie N, Higgenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hoeper MM, Behr J, Winkler J, Sitbon O, Popov W, Ghofrani HA, Manes A, Kiely DG, Ewert R, Meyer A, Corris PA, Delcroix M, Gomez-Sanchez M, Siedentop H, Seeger W (2002) Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 347:322–329
19. Ono F, Nagaya N, Okumura H, Shimizu Y, Kyotani S, Nakanishi N, Miyatake K (2003) Effect of orally active prostacyclin analogue on survival in patients with chronic thromboembolic pulmonary hypertension without major vessel obstruction. Chest 123:1583–1588
20. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, Albanese P, Biasiolo A, Pegoraro C, Iliceto S, Prandoni P (2004) Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 350:2257–2264
21. Riedel M, Stanek V, Widimsky J, Prerovsky I (1982) Longterm follow-up of patients with pulmonary thromboembolism. Chest 81:151–158
22. Rosenkranz S (2007) Pulmonary hypertension: current diagnosis and treatment. Clin Res Cardiol 96:527–541
23. Seyfarth HJ, Hammerschmidt S, Gessner C, Halank M, Wirtz H (2006) Chronic thromboembolic pulmonary hypertension—therapeutic options. Curr Respir Med Rev 2:431–438
24. Seyfarth HJ, Hammerschmidt S, Pankau H, Winkler J, Wirtz H (2006) Long-term bosentan in chronic thromboembolic pulmonary hypertension. Respiration 569:1–6
25. Seyfarth HJ, Pankau H, Hammerschmidt S, Schauer J, Wirtz H, Winkler J (2005) Bosentan improves exercise tolerance and Tei index in pulmonary hypertension patients with prostanoid therapy. Chest 128:709–713
26. Sitbon O, McLaughlin VV, Badesch DB, Barst RJ, Black C, Galie N, Humbert M, Rainisio M, Rubin LJ, Simonneau G (2005) Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. Thorax 60:1025–1030