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ORIGINAL ARTICLE

Survival of Idiopathic Pulmonary Arterial Hypertension Patients in the Modern Era in Australia and New Zealand

Geoff Strange [a,b,c,1], Edmund M. Lau [d,1*], Eleni Giannoulatou [e], Carolyn Corrigan [f], Eugene Kotlyar [f], Fiona Kermeen [g], Trevor Williams [h], David S. Celermajer [b,d], Nathan Dwyer [i], Helen Whitford [h], Jeremy P. Wrobel [a,j], John Feenstra [g], Melanie Lavender [j], Kenneth Whyte [k], Nicholas Collins [l], Peter Steele [m], Susanna Proudman [n], Vivek Thakkar [o], Dominic Keating [h], Anne Keogh [f], on behalf of PHSANZ Registry

[a]School of Medicine, University of Notre Dame, Perth, WA, Australia
[b]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia
[c]Pulmonary Hypertension Society of Australia and New Zealand, Sydney, NSW, Australia
[d]Sydney Medical School, University of Sydney and Royal Prince Alfred Hospital, Sydney, NSW, Australia
[e]Computational Genomics Laboratory, Victor Chang Cardiac Research Institute, Sydney, NSW, Australia
[f]Heart Transplant Unit, St Vincent's Hospital, Sydney, NSW, Australia
[g]Queensland Lung Transplant Service, Prince Charles Hospital, Brisbane, Qld, Australia
[h]Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, Melbourne, Vic, Australia
[i]Department of Cardiology, Royal Hobart Hospital, Hobart, Tas, Australia
[j]Advanced Lung Disease Unit, Fiona Stanley Hospital, Perth, WA, Australia
[k]Greenlane Clinical Centre, Auckland City Hospital, Auckland, New Zealand
[l]Department of Cardiology, John Hunter Hospital, Newcastle, NSW, Australia
[m]Department of Cardiology, Royal Adelaide Hospital, Adelaide, SA, Australia
[n]Rheumatology Unit, Royal Adelaide Hospital, Adelaide, SA, Australia
[o]Department of Rheumatology, Liverpool Hospital, Sydney, NSW, Australia

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Background Epidemiology and treatment strategies continue to evolve in pulmonary arterial hypertension (PAH). We sought to define the characteristics and survival of patients with idiopathic, heritable and drug-induced PAH in the current management era.

Methods Consecutive cases of idiopathic, heritable and drug-induced PAH were prospectively enrolled into an Australian and New Zealand Registry.

Results Between January 2012 and December 2016, a total of 220 incident cases were enrolled (mean age 57.2 ± 18.7 years, female 69.5%) and followed for a median duration of 26 months (IQR17–39). Co-morbidities were common such as obesity (34.1%), systemic hypertension (30.5%), coronary artery disease (16.4%) and diabetes mellitus (19.5%). Initial combination therapy was used in 54 patients (dual, n = 50; triple, n = 4). Estimated survival rates at 1-year, 2-years and 3-years were 95.6% (CI 92.8–98.5%), 87.3% (CI 82.5–92.4%) and 77.0% (CI 70.3–84.3%), respectively. Multivariate analysis showed that male sex and lower 6-minute distance at diagnosis independently predicted worse survival, whereas obesity was associated with improved survival. Co-morbidities other than obesity did not impact survival. Initial dual

*Corresponding author at: Department of Respiratory Medicine, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050, Australia., Email: edmund.lau@sydney.edu.au

[1]GS and EML contributed equally to the manuscript.

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oral combination therapy was associated with a trend towards better survival compared with initial oral monotherapy (adjusted HR = 0.27, CI 0.06-1.18, p = 0.082)

Conclusions The epidemiology and survival of patients with idiopathic PAH in Australia and New Zealand are similar to contemporary registries reported in Europe and North America. Male sex and poorer exercise capacity are predictive of mortality whereas obesity appears to exert a protective effect. Despite current therapies, PAH remains a life-threatening disease associated with significant early mortality.

Keywords Pulmonary arterial hypertension • Pulmonary hypertension • Survival

Introduction

Pulmonary arterial hypertension (PAH) is a rare cardiopulmonary disease with an estimated prevalence of 15 to 150 per million [1–4]. The importance of registry data to document outcomes in uncommon conditions such as PAH was already recognised in the 1980s when the first PAH registry (formerly termed primary pulmonary hypertension) was conducted by the National Institutes of Health (NIH) [5]. Since the NIH registry, multiple national and international registries have reported baseline characteristics and outcomes in the era of targeted PAH therapy [2,3,6–10]. These registries have been pivotal in providing important insights regarding the evolving epidemiology, treatment patterns, and survival of PAH [11].

In the past decade, pharmacotherapy has improved and efficacious agents targeting multiple disease pathways are now available. Combination therapy is now considered the standard of care for the majority of PAH patients [12]. Importantly, data from the recent Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) study [13], which compared first-line therapy with ambrisentan plus tadalafil versus either drug alone, demonstrated that initial combination therapy was associated with a reduction in clinical failure events. Similarly, sequential combination therapy has also been demonstrated to improve outcomes [14,15]. Since treatment approach in PAH continues to change as new evidence emerges from clinical trials, there is an ongoing need for registries to assess outcomes and survival based on current clinical practice strategies.

The Pulmonary Hypertension Society of Australian and New Zealand (PHSANZ) Registry was established in 2011 to delineate the clinical characteristics, management, and outcomes of pulmonary hypertension (PH) patients treated at specialist centres across Australia and New Zealand. In this report, we describe the characteristics and outcomes of a cohort of patients with newly diagnosed idiopathic, heritable and drug-induced PAH in the current treatment era.

Methods

The PHSANZ Registry collects data from patients with all subgroups of PH, although the primary target population is Group 1 PH. The PHSANZ registry commenced data collection in December 2011. Both prevalent and incident cases are included, and baseline data for patients diagnosed prior to December 2011 were collected retrospectively. A total of 16 Australian and two New Zealand centres contribute to the PHSANZ registry. All data are entered into the Registry database using a PH specific software platform. Ethical approval for the use of de-identified data was sought, and the protocol was reviewed and approved by the institutional review board of each participating centre.

For the present study, consecutive incident cases of idiopathic, heritable and drug-induced PAH (age ≥ 16 years) diagnosed between 1 January 2012 and 31 December 2016 were included for analysis. The designation of PAH subtype according to the current clinical classification [16] was based on the diagnosis provided by the treating physician. In addition, PAH was defined haemodynamically by a mean pulmonary artery pressure ≥25 mmHg and pulmonary artery wedge pressure or left ventricular end diastolic pressure ≤15 mmHg. As a requirement for government subsidised PAH therapy, patients were required to have a baseline right heart catheterisation (RHC), six-minute walk test (6MWT) and transthoracic echocardiography. Date of diagnosis corresponded to the date when the patient attended evaluation at the participating centre and was confirmed to have PAH with RHC. Pulmonary arterial hypertension therapy was given at the discretion of the treating physician. Since 2012, the majority of approved PAH agents were available in Australia and New Zealand including endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, and prostacyclin derivatives. In Australia, only PAH monotherapy is currently funded by the government, and access to combination therapy was via either compassionate access (industry or hospital support), and/or self-funding by patients.

Statistical Analysis

Continuous variables are expressed as mean ± SD unless otherwise stated. Survival analysis was performed using Kaplan-Meier analysis. Univariable Cox proportional hazard model was used to test baseline variables that were associated with survival, followed by multivariable Cox PH analysis to examine the independent effect of selected variables on survival, controlling for possible confounders. The interval from diagnosis to death was censored at the last date the subject was known to be alive. A p-value of <0.05 was

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