Clinical research
Congenital heart disease

Advanced therapy may delay the need for transplantation in patients with the Eisenmenger syndrome

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Aims Advanced therapies (prostacyclin analogues, endothelin receptor antagonists) are successfully used in the treatment of idiopathic pulmonary arterial hypertension. In addition, patients with the Eisenmenger syndrome (ES) seem to benefit from these new drugs regarding symptoms, but there is still no evidence for changes in outcome.

Methods and results The clinical course of 43 patients (M/F 13/30, age 34.0 ± 12.7 years), registered with unstable ES in our database, was retrospectively analysed. These patients were divided into two groups: those treated with and those treated without advanced therapy. The primary endpoint was defined as death from any cause. Death or inscription on the active waiting list of heart–lung transplantation was considered as secondary endpoint. Kaplan–Meier survival and log rank testing were performed to determine differences in outcome between the two groups. The total cohort was followed for a median period of 4.9 (range 0.2–14.9) years. Mean survival time for patients treated with (n = 26) and without (n = 17) advanced therapy therapies were 8.5 ± 1.5 and 8.5 ± 0.9 years, respectively (log rank testing, P = 0.31). However, the mean time to death or inscription on the active waiting list was significantly longer for patients treated with advanced therapy when compared with those without (7.8 ± 1.0 vs. 3.4 ± 0.9 years, P = 0.006).

Conclusion For the given follow-up period, no improvement in survival time could be documented in adult patients with unstable ES treated with advanced therapy. However, we might suggest with these data that the need for heart–lung transplantation can be substantially delayed with new drugs.

Introduction

In patients with a large systemic-to-pulmonary connection, blood initially shunts from the systemic to the pulmonary circulation. When pulmonary vascular resistance and pulmonary arterial pressure approach systemic vascular resistance and systemic arterial pressure, respectively, the shunt reverses.¹⁻³ The resultant right-to-left or bidirectional shunt leads to clinical cyanosis and the secondary manifestations of chronic hypoxaemia. This pathophysiological concept is referred to the Eisenmenger syndrome (ES).²

Classical therapy of the ES remains directed towards avoiding complications from all factors, such as erythrocytosis, treatment of congestive heart failure, prevention of infection, and secondary haematological abnormalities such as iron deficiency and coagulation disorders.⁴ However, the only definite treatment is heart–lung transplantation, but morbidity and mortality after transplantation remain substantially high.⁵ Furthermore, waiting lists for heart–lung transplantation are long,⁴ so some patients will not survive while waiting on the transplant list even if survival on the waiting list is much better for ES than for idiopathic pulmonary arterial hypertension (IPAH).⁶ In the last decade, new therapies designed to impair smooth muscle cell proliferation, thereby inducing reverse remodelling of the pulmonary vessels, have been shown to improve exercise capacity⁷⁻¹¹ and long-term survival¹²⁻¹⁴ in patients with IPAH. In addition, patients with the ES seem to benefit from these advanced therapies regarding symptoms,¹⁵,¹⁶ but there is still no evidence for changes in outcome. Therefore, we wanted to examine whether the use of these new drugs would provide any benefit as to survival or need for heart–lung transplantation in adult patients with unstable ES.

Methods

Patients' selection

All patients with unstable ES registered in the database of adult congenital heart disease of the University Hospitals of Leuven since 1990 until February 2005 were included in the study. ES was considered to be unstable when conservative treatment was failing. Criteria of
instability were progressive systemic desaturation over a short-time period, occurrence of right heart failure, fast increasing number of phlebotomies, documentation of malignant arrhythmias, syncope, fast increasing New York Heart Association (NYHA) functional class, and fast decreasing 6-min walking distance. The Ethics Committee of our institution agreed with the analysis of the registered data.

Demographic data and follow-up parameters
Demographic data and follow-up parameters referring to outcome were obtained by reviewing the database data and medical files. Follow-up time was defined as the time period between instability of ES (=inclusion in the study) and the last follow-up date. The following parameters were noted: NYHA class, mean pulmonary artery pressure (PAP) obtained by right heart catheterization, 6-min walking distance, transthoracic systemic oxygen saturation at rest, haematocrit, and serum uric acid. All these parameters were scored at inclusion and, thereafter, at intervals of 6 months, until death or end of follow-up.

Treatment regimen
The entire cohort was made of two groups. In one group, patients did not receive any specific treatment (=‘standard care’). The other group was treated with ‘advanced therapy’, starting in 1996. For the latter, changes in the type of advanced therapy and combination therapies were allowed during the registered follow-up period. The aim of dividing the cohort into two groups was mainly to compare standard care with advanced therapy.

Statistical analysis
Data were tested on normality. When normality was found to be present, the results were reported as means ± standard deviation. When normality was found to be absent, data were reported as median and range (minimum and maximum). Proportions were reported in percentages. Continuous variables were compared by the unpaired t-test. Nominal variables were analysed by the Mann–Whitney and Kruskal–Wallis test, and proportions by the χ² test.

Kaplan–Meier event-free survival curves were plotted for the primary and secondary endpoints. Survival times were compared by log ranking. Statistical significance level was set at P < 0.05. All tests were two-sided. Software used for statistical analysis was SPSS 11.5 for Windows.

Results
Patients’ characteristics
At inclusion, the mean age of the 43 selected patients was 34.0 ± 12.7 years. The entire group consisted of 13 male and 30 female patients. Seventeen patients (4 male and 13 female patients) and 26 patients (9 males and 17 females) were treated without and with new drugs, respectively. Nine patients were characterized by an atrial septal defect (ASD), 12 patients by a ventricular septal defect (VSD), and 22 patients suffered from a more complex congenital heart defect as cause of the development of the ES. Table 1 summarizes the distribution of the number of patients with ASD, VSD, or more complex congenital heart defects between the two treatment groups. Details are given about which new drug was given. The patients with more than one advanced therapy were treated subsequently with these drugs. Most of the patients, who received more than one drug (subsequently), were, at the end of our study, treated with an endothelin receptor antagonist. Advanced therapy with beraprost was, in a few patients, discontinued because of side effects, and at the end of the study, almost all of them were converted to an endothelin receptor antagonist because of the commercial unavailability of beraprost. None of these advanced drugs was given simultaneously during the study, although we currently started to combine advanced therapy in a more recent cohort. In general, the patients’ characteristics between the two treatment groups were highly comparable. Also, the distribution of complex congenital cardiac pathologies between standard and advanced therapy was similar. In Table 2, the clinical and haemodynamic characteristics of both treatment groups at inclusion are summarized.

Clinical parameters at inclusion
The total cohort was followed for a median period of 4.9 (range 0.2–14.9) years. For those patients who underwent heart-lung transplantation, the measurements just before transplantation were used for analysis. For patients who died and had not been transplanted, the measurements just before death were used. For patients who were not transplanted and survived, follow-up was conducted until 1 April 2005.

Outcomes
Kaplan–Meier curves for the primary endpoint (death from any cause) are illustrated by Figure 1. For both groups, mean survival time was 8.5 ± 1.5 and 8.5 ± 0.9 years, respectively (log rank testing, P = 0.31). If patients with a follow-up time of more than 9 years were censored (n = 10 patients excluded), mean survival time for patients with advanced therapy was significantly longer than for patients with standard care (6.7 ± 0.7 vs. 2.7 ± 0.5 years, respectively, log rank testing, P = 0.004). As to the major and minor secondary endpoints, highly significant differences in event-free survival times were found. Kaplan–Meier curves are plotted in Figures 2 and 3, respectively. For the standard care group, mean time until death or inscription on the waiting list for heart-lung transplantation of 4.0 ± 1.2 years was significantly lower when compared with 7.4 ± 1.0 years for the advanced therapy group (log rank testing, P = 0.0062). The same was found for the minor secondary endpoint. For standard care, mean time until death or effective heart-lung transplantation was 3.5 ± 0.9 years when compared with 7.8 ± 1.0 years for the advanced therapy group (log rank testing, P = 0.0011). The median time between inscription on the transplantation list and effective transplantation was 11.6 months (range 0.8–23.5 months) for the entire group. The median time
between inscription on the transplantation list and effective transplantation did not differ significantly between the group with advanced therapy and the patients with standard care [4.1 months (range 1.0–23.5 months) vs. 12.3 months (range 0.8–20.4 months), \( P = 0.28 \)]. Two patients (one on standard care and the other on advanced therapy) were on the active waiting list and still not transplanted at the time of the data analysis.

### Table 1

<table>
<thead>
<tr>
<th>Underlying CHD</th>
<th>Standard care (n)</th>
<th>Advanced therapy (n)</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>3</td>
<td>6</td>
<td>Sitaxsentan, Beraprost, treprostinil, bosentan</td>
</tr>
<tr>
<td>VSD</td>
<td>4</td>
<td>8</td>
<td>Treprostinil, Beraprost</td>
</tr>
<tr>
<td>Complex lesions</td>
<td>10</td>
<td>12</td>
<td>Beraprost, bosentan, sitaxsentan</td>
</tr>
<tr>
<td>ASD + PAPVC</td>
<td>1</td>
<td>1</td>
<td>Beraprost, bosentan</td>
</tr>
<tr>
<td>DD + ASD</td>
<td>1</td>
<td>1</td>
<td>Beraprost, treprostinil</td>
</tr>
<tr>
<td>DD + VSD</td>
<td>2</td>
<td>1</td>
<td>Beraprost, treprostinil</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>1</td>
<td>3</td>
<td>Bosentan, Beraprost, treprostinil</td>
</tr>
<tr>
<td>UVH + DILV + DD</td>
<td>2</td>
<td>2</td>
<td>Beraprost, bosentan</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>1</td>
<td>1</td>
<td>Beraprost, treprostinil</td>
</tr>
<tr>
<td>DORV + VSD + PAD</td>
<td>1</td>
<td>1</td>
<td>Beraprost, treprostinil</td>
</tr>
<tr>
<td>ASD + SVC in LA</td>
<td>1</td>
<td>1</td>
<td>Beraprost, treprostinil, bosentan</td>
</tr>
<tr>
<td>DILV</td>
<td>1</td>
<td>1</td>
<td>Beraprost, treprostinil, bosentan</td>
</tr>
<tr>
<td>VSD + PAD</td>
<td>2</td>
<td>2</td>
<td>Sildenafil, Sitaxsentan</td>
</tr>
</tbody>
</table>

CHD, congenital heart defect; PAPVC, partial abnormal pulmonary vein connection; DD, double discordance; UVH, univentricular heart; DILV, double inlet left ventricle; DORV, double outlet right ventricle; PDA, persistent arterial duct; SVC, superior vena cava; LA, left atrium.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Standard care</th>
<th>Advanced therapy</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>17</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>33.1 ± 13.1</td>
<td>34.1 ± 12.7</td>
<td>0.72</td>
</tr>
<tr>
<td>Length of follow-up period (years) median (range)</td>
<td>3.9 (0.2–14.9)</td>
<td>4.9 (0.7–11.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>At inclusion (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAP systol (mmHg)</td>
<td>111 ± 24</td>
<td>99 ± 27</td>
<td>0.3</td>
</tr>
<tr>
<td>PAP diastol (mmHg)</td>
<td>55 ± 17</td>
<td>47 ± 20</td>
<td>0.32</td>
</tr>
<tr>
<td>PAP mean (mmHg)</td>
<td>76.6 ± 19.9</td>
<td>67.7 ± 22.1</td>
<td>0.37</td>
</tr>
<tr>
<td>6-min WT (m)</td>
<td>372 ± 118</td>
<td>376 ± 120</td>
<td>0.94</td>
</tr>
<tr>
<td>O2 sat (%)</td>
<td>84 ± 7</td>
<td>85 ± 9</td>
<td>0.6</td>
</tr>
<tr>
<td>Uric acid (mg%)</td>
<td>6.8 ± 2.3</td>
<td>7.0 ± 2.0</td>
<td>0.85</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>52.8 ± 7.0</td>
<td>57.4 ± 10.2</td>
<td>0.21</td>
</tr>
</tbody>
</table>
| NYHA classification, median (range) | 2 (1–4) | 2 (1–4) | 0.29 

WT, walk test; sat, saturation.

### Discussion

The main finding in our study suggests that advanced therapy could significantly delay the need for heart–lung transplantation in patients with unstable ES, but without improving outcome.

Most patients with ES survive into adulthood with a reported 77 and 42% survival rate at the age of 15 and
25 years, respectively. However, others, like Daliento et al., found a better outcome and could clearly demonstrate differences in survival in simple vs. complex congenital heart defects. Median survival time was between 30 and 35 years for patients with a complex underlying congenital heart defect vs. 55 and 60 years for patients with a simple defect. In addition, recent advances in understanding the molecular mechanisms suggest that endothelial dysfunction plays a key role in disease progression and subsequently in prognosis of patients with pulmonary arterial hypertension. Chronically impaired production of vasoactive mediators, such as nitric oxide and prostacyclin, along with prolonged overexpression of vasoconstrictors, such as endothelin-1, not only affects vascular tone, but also promotes vascular remodelling. These insights have led to the development of new therapeutic drugs not only with more selective pulmonary vasodilating effects, but also with antiproliferative properties (prostacyclin analogues as intravenous epoprostenol, subcutaneous treprostinil, and oral beraprost and endothelin receptor antagonists as oral bosentan and sitaxsentan). The use of these new drugs has shown to be beneficial in patients with IPAH, but there are only limited data about their effect in the treatment of patients with ES. Uncontrolled data suggest that these medications lead to functional and haemodynamic improvement in some treated ES patients, but no changes in outcome could be determined. Indeed, continuous intravenous infusion of epoprostenol improved significantly functional capacity, oxygen saturation, and cardiopulmonary haemodynamics, and moreover, the clinical benefit in patients with ES from the endothelin receptor antagonists starts to become more clear. Although only small series of patients showed improved oxygenation and functional status after oral administration of bosentan in patients with the ES, Schulze-Neick et al. could demonstrate that mid-term (mean follow-up time of 2.1 years) bosentan treatment in adult congenital heart disease patients with pulmonary arterial hypertension was well tolerated and could improve functional status as well as exercise capacity. These data were recently enforced by the data of the BREATHE-5 trial, the first randomized placebo-controlled trial in Eisenmenger physiology. However, taken together, none of these studies demonstrated any influence on patients’ survival.

The ultimate treatment of patients with ES is heart–lung transplantation or lung transplantation (single or bilateral) with intracardiac repair. Most centres, including ours, prefer heart–lung transplantation. This policy is consistent with the findings of the United Network for Organ Sharing/International Society for Heart and Lung Transplantation joint thoracic registry. Although considered as the only ‘curative’ treatment for patients with ES, transplantation is reserved for severely symptomatic patients because, for stable patients, overall survival with medical management is usually quite good. Indeed, the natural survival of patients with the ES may exceed survival after heart–lung transplantation in many patients. In addition, the increasingly limited supply of transplant organs and longer waiting lists might complicate the decision taking for transplantation. Finally, a number of patients with ES are simply not suitable for transplantation because of technical reasons or altered mental status. Therefore, any measures that could delay the need for transplantation without affecting
survival in a negative way should be considered of great benefit.

We showed that the use of new drugs did not influence mortality, but suggested a delay in the need for transplantation. However, we want to indicate that only 'unstable' patients were selected for our study. The steep decline in the overall survival curves of both patients’ groups could serve as an indirect indicator of the general unstable status of our study population. Moreover, in the group treated with advanced therapy, the decline in the survival curve is less steeper than in patients who were not treated with advanced therapy. We hypothesize that non-responders to these drugs are responsible for the initial steep decline in survival curve.

However, this study has limitations. First, the only strong and most objective endpoint in our study is the primary endpoint, defined as dead. We could not document a survival benefit of patients receiving advanced therapy. However, despite the fact that no survival benefit could be documented in the current study, the possibility cannot be excluded that this may be related to insufficient power. Indeed, there appeared to be trend towards improved survival with advanced therapies. Concerning the secondary endpoints, inscription on the transplantation list may contain a rather subjective component. The date of transplantation can be influenced by the availability of the suitable organs; however, the latter is an uncontrollable variable in this study. Nevertheless, we found that time between inscription on the transplantation list and effective transplantation was similar in both groups. Moreover, the tendency for a shorter waiting time for patients who received advanced therapy might suggest the validity of the minor secondary endpoint. Secondly, the patients without advanced therapies were recruited predominantly at the beginning of the inclusion period, whereas those patients on advanced therapy are the most recent ones included. However, the standard care group could be considered as a ‘historical control’. Standard care for the ES has not evolved the last 15 years. Therefore, in our opinion, the fact that, under standard care, patients need to be inscribed earlier on the transplantation list let us suggest a benefit of advanced therapy.

Furthermore, a selection bias was inevitable. The rather small number of patients were selected from one single database/centre, the analysis was retrospective, and no randomization could be done; therefore, extrapolation of these results needs careful interpretation. Finally, because in several patients different types of new drugs were used, the beneficial effect is not related to one limited drug.

In summary, we may conclude that advanced therapy in patients with ES might be a valuable tool in stabilizing patients as a bridge to transplantation. Longer follow-up times and more powered trials will be needed to define whether it is possible to stabilize patients with ES for many years with these new drugs and finally influence survival.

Supplementary material

Supplementary material is available at European Heart Journal online.

Conflict of interest: M.D. received a research grant from Actelion and GSK and payments for speaker’s bureau appointments from Actelion. She was also a member of an advisory board of Pfizer, Leo Pharma, and Actelion when conducting trials with antiproliferative therapies.

References