Editorial

Current therapy of Eisenmenger syndrome

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Eisenmenger syndrome (ES) is a complex and disastrous medical problem with profound cyanosis and clinical deterioration by significant right to left shunting. This syndrome is the most advanced form of pulmonary arterial hypertension (PAH) associated with congenital heart disease (PAH-CHD). Inverted shunt changes structures of pulmonary vasculature like all forms of PAH in ES (1). In the past, the management of patients with ES was limited to conventional therapy with an emphasis on regular informed cardiovascular follow-up. Subsequent clinical studies have made it possible to improve to patient survival and functional capacity. There are major therapeutic targets in PAH treatment using endothelin-receptor antagonists, phosphodiesterase type-5 inhibitors, and prostacyclin derivatives.

In the REVEAL registry, patient's survival of advanced PAH remains poor despite advanced targeted therapy. Survival rates in newly diagnosed PAH patients after the development of PAH-specific therapies were 86.3% and 61.2% at 1 and 5 years, respectively (2). This result is still disappointing although PAH-CHD shows better outcomes compare to other etiologies of PAH. Nevertheless, many studies suggest advanced PAH therapies should be needed to improve the survival of PAH patients. The BREATHE-5 trial, first placebo-controlled trial in patients with ES, demonstrated a significant improvement of hemodynamics and exercise capacity without adversely affecting systemic arterial oxygen saturation on bosentan-treated patients (3). Other recent randomized controlled trials in ES with phosphodiesterase type-5 inhibitors have shown improvements in exercise capacity and hemodynamics (4,5). In common with other world registries, our group also reports the importance of specialized therapies to improve the survival of PAH patients in Korean Registry of pulmonary arterial hypertension (KORPAH) (*Table 1*) (6). The demographics of the KORPAH registry participants were similar to those of western registry including 159 patients of PAH-CHD (26.9%) of all patients (n=625) (*Figure 1*) (6).

The World Health Organization (WHO) functional classification at the time of diagnosis has major implications as a clinical predictor of mortality and survival for patients with PAH (7). We reported the same results already in the retrospective cohort (*Figure 2*) (8). The EARLY study, randomized controlled trial of a PAH-targeted therapy in WHO functional class (FC) II patients, suggested that patients with WHO FC II PAH have a severe and often fatally progressive disease (9). These findings demonstrated the importance of the advanced targeted therapy in a timely manner.

Several studies have reported beneficial effects of inhaled iloprost, resulting in improved WHO functional class, hemodynamics, an increased 6-minute walking distance, and quality of life (10,11). A retrospective study of adult patients with PAH to CHD in Korea also suggested that inhaled iloprost as a perioperative medical intervention for patients with PAH-CHD is safe and effective in improving the systemic oxygen saturation and for early recovery in the postoperative course (*Table 2*) (12). Also, a prospective single-arm study which 18 patients with ES and exertional dyspnea according to WHO functional class III or IV were prospectively recruited had showed that 24 weeks of inhaled iloprost therapy in patients with ES led to significant improvements in exercise capacity, quality of life, and right ventricular function. These results likely explain the symptomatic relief reported by patients with ES receiving iloprost therapy (13).

The recent study of the German National Resister for congenital heart defects (GNR-CHD) contains a nation-

Table 1 PAH-specific medications of KORPAH in all patients and incident patients

Medications	Treatments in all patients (n=625) (%)	Treatments in incidence cases (n=297) (%)
No. of patients receiving PAH-specific medications in all treatments	380 (60.8)	182 (61.3)
No. of medications in all PAH-specific treatments	155 (40.9)	93 (51.1)
Single sildenafil	45 (11.8)	21 (11.6)
Single inhaled iloprost	22 (5.8)	17 (9.3)
Single beraprost	86 (22.6)	23 (12.6)
Combinations of above single medications	72 (18.9)	28 (15.4)

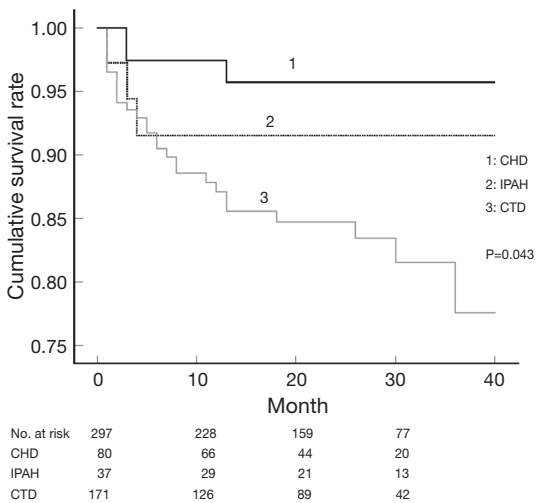

Figure 1 Comparison of survival according to the etiologies of PAH of the incident cases in the KORPAH (n=297). This figure presents a comparison of prognoses according to the etiologies of PAH. PAH with CTD corresponded to the highest mortality (18.8%), followed by idiopathic PAH (IPAH) (8.1%) and PAH with congenital heart disease CHD (3.9%) (P=0.043). CHD, congenital heart disease; CTD, connective tissue disease. [Reproduced by permission of the Korean Academy of Medical Sciences (6)].

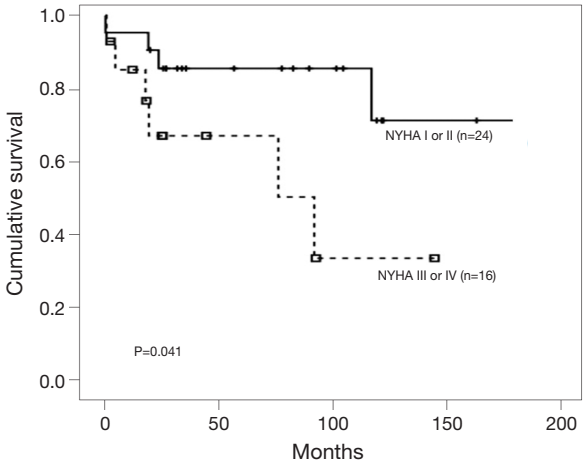

Figure 2 Median overall survival time of patients by NYHA functional classification. Patients with NYHA class I or II at the time of diagnosis showed significantly better survival than those with more severe functional class. [Reprinted with permission (8)].

Table 2 Clinical course of the iloprost group *vs.* the control group

Medications	Iloprost group (n=28)	Control group (n=17)	P value
Mortality			
Use of iNO[a] (%)	4 (17.9)	8 (52.9)	0.021
Use of iNO[a] (ppm)	24 *vs.* 8	31 *vs.* 7	0.064
Use of iNO[a] (h)	11.2 *vs.* 4.5	25 *vs.* 6.8	0.031
Plasma BNP[b] (pg/mL)	98 *vs.* 46	265 *vs.* 92	0.008
Mechanical ventilation time (h)	10.1 *vs.* 12.5	41.1 *vs.* 46.1	0.018
ICU stay (h)	39.4 *vs.* 26.4	90.3 *vs.* 60.8	0.005
Chest tube use (h)	63.9 *vs.* 22.7	89.3 *vs.* 42.8	0.039
Inotropic support (h)	103.8 *vs.* 88.2	74.5 *vs.* 56.0	0.246
Drug used (μg/kg/h)			
Milrinone	0.375–0.5	0.375–0.5	
Dopamine	5–10	5–10	

[a], administered via an endotracheal tube before weaning when clinically necessary for the immediate postoperative period; [b], Checked on the 7th postoperative day.

wide data with a large population of ES patients in the community (14). Among 153 patients with ES, 57.5% of patients were treated with PAH-specific medical therapies. Of those, 17.6% of patients received combination therapy; 76.1% of patients on monotherapy were on bosentan and 44.4% of patients treated primarily with Sildenafil were also on this drug as a second line. The GNR-CHD is a well-designed study and recruited a large number of patients representing the community-based population. The result of this study may be valuable data on advanced targeted therapy. However, as the intrinsic drawback of registry, the lack of uniform treatment strategy couldn't explain effective

and timely treatments in PAH-targeted therapy. This limitation was shown as no outcome difference between monotherapy and dual targeted therapy because of the long escalation time. Nevertheless, the strongest message from GNR-CHD is the better clinical outcome in the large volume centers than remaining centers that means the need of expert care from centers of excellence.

In summary, the GNR-CHD demonstrated better survival of advanced targeted therapy based on the real world as well as tertiary referrals in the Germany. This modern real world registry data reinforce the reason why specialized medical therapies in PAH expert center should be considered in ES patients.

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Footnote

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