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Upfront triple combination therapy in severe paediatric pulmonary arterial hypertension

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Upfront triple combination therapy in severe paediatric PAH resulted in significant clinical, haemodynamic and echocardiographic improvement and favourable 1-, 2- and 3-year survival rates, albeit with 47% receiving a Potts shunt during follow-up https://bit.ly/3iG92PA

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ABSTRACT Treatment strategies in paediatric pulmonary arterial hypertension (PAH) have evolved over the last years, but survival is still poor. Recently, in adults with severe PAH, upfront triple combination therapy (uTCT) from diagnosis has been reported to show significant clinical improvement and excellent long-term outcome. This retrospective, observational study aimed to assess the efficacy of uTCT in paediatric PAH.

Children diagnosed with PAH between 2010 and 2019 and started with uTCT were included. World Health Organization Functional Class (WHO-FC), haemodynamics, echocardiography, 6-min walking distance and serum level of *N*-terminal pro-brain-natriuretic-peptide were assessed at baseline, after 3 and 6 months and at last available follow-up. Events were defined as death, lung transplantation or Potts shunt.

21 children (median age 4.8 years (2.5–12.8), 57% females) were included. All children except one were in WHO-FC III or IV (28% and 67%, respectively). After 3 months, one child had died and one child had received a Potts shunt. The remaining 19 children showed clinical and echocardiographic improvement, which persisted at 6 months. Children with idiopathic and heritable PAH showed one-, two- and three-year transplant-free survival estimates of 100%, 94% and 87%, albeit 47% of them receiving a Potts shunt during follow-up.

Children with severe PAH, but not pulmonary veno-occlusive disease, improved significantly with uTCT and showed beneficial up to 3-year survival rates, albeit 47% of them receiving a Potts shunt during follow-up. The role of a Potts shunt in conjunction to uTCT in paediatric PAH needs to be further established.

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Introduction

Pulmonary arterial hypertension (PAH) is a rare and life-threatening disease with an untreated median survival below 3 years in adult patients and even less in children [1–3].

Treatment strategies have evolved over the last years and have been associated with improved outcomes. Currently, available drugs intervene in three different pathways: the endothelin, nitric oxide (NO) and prostacyclin pathway. Phosphodiesterase 5-inhibitors (PDE5i) inhibit the breakdown of cyclic guanosine monophosphate, which is part of the NO pathway, endothelin receptor antagonists (ERA) inhibit the effects of endothelin-1 and hereby antagonise vasoconstriction, inflammation and proliferation, while prostacyclin-analogues induce vasodilation, antiproliferation and inhibit platelet aggregation [4].

Initially, patients were started on monotherapies using these drugs, but nowadays guidelines recommend initiation of combination therapies [5–7]. Various studies showed improvement of clinical symptoms and a reduced risk of clinical worsening in adult PAH-patients treated with various combinations of ERAs, PDE5is and prostanoids [8–10]. Children on ERA therapy receiving subsequent add-on sildenafil therapy showed improvement of World Health Organization Functional Class (WHO-FC) and 6-min walking distance (6MWD) [11]. Also, observational data suggest that survival is better in children receiving combination therapy compared with those receiving monotherapy [12].

Recently, two studies reported on upfront triple combination therapy (uTCT), meaning targeting the three pathways simultaneously directly from time of diagnosis, including parenteral prostanoid therapy, in selected adult patients with severe PAH. These studies showed that uTCT was associated with significant clinical and echocardiographic improvement and an excellent long-term outcome after a mean follow-up of 41 and 24 months reported by Sitbon *et al.* [13] and D'Alto *et al.* [14], respectively. Also, uTCT induced reversed remodelling of the right ventricle [14].

This study aimed to assess the efficacy of uTCT in children with severe PAH.

Methods

This retrospective observational study reports the experience from two expert centres for children with PAH in two different countries. In France, the Hôpital Necker Enfants malades serves as a French referral centre for Paediatric Pulmonary Hypertension. In the Netherlands, the University Medical Center Groningen (UMCG) serves as the National Referral Center for Pulmonary Hypertension in Childhood, where all Dutch paediatric patients suspected for PAH are referred. Patients in both centres are diagnosed and prospectively followed according to a standardised protocol and enrolled in respective registries. Ethical approval for the ongoing registries was obtained from the Medical Ethics Review Board from respectively the Hôpital Necker Enfants malades (NCK-2020-R-062 TCT HTAP) and the UMCG (METc 2008.009). Written informed consent from the patients (and/or their guardians) is given at enrolment in the registry.

Patients

Children (⩽18 years of age) with idiopathic (IPAH) or heritable PAH (HPAH), PAH associated with congenital heart disease (PAH-CHD), or PAH associated with other conditions, referred between June 2010 and February 2019 to the French or Dutch Referral Center and started with uTCT were included. In all children PAH diagnosis was confirmed by right heart catheterisation (RHC) (mean pulmonary arterial pressure (mPAP) ⩾25 mmHg, pulmonary vascular resistance index (PVRi) ⩾3 Wood units·m^2, and mean pulmonary capillary wedge pressure ⩽15 mmHg) [15]. The current study cohort consists of those children, who were considered at highest risk according to the paediatric risk stratification tool, including WHO-FC III or IV, a reduced right ventricle function, significantly elevated *N*-terminal pro-brain-natriuretic-peptide (NT-proBNP) level, and a PVRi >20 Wood units·m^2 [5, 15].

Therapy

For this study, uTCT was defined as the initiation of a PDE5i, an ERA, and prostanoids (subcutaneousor intravenous) within 6 weeks after diagnosis.

Clinical assessment

Clinical assessment took place at diagnosis/start of therapy (baseline), after 3 and 6 months, and at the last available follow-up. Clinical signs of right ventricle failure (including hepatomegaly, peripheral oedema, anorexia, nausea, fatigue and dyspnoea), WHO-FC, echocardiography, 6MWD and NT-proBNP level were assessed. Systolic right ventricle function was assessed by echocardiography and included qualitative assessment by eyeballing (good/moderate/poor), and quantitative assessment using tricuspid annular plane systolic excursion (TAPSE). Invasive haemodynamics were assessed at baseline. Follow-up catheterisations were done at discretion of the treating physician.

Statistics

Data are presented as median (interquartile range) or frequencies (%). Differences in clinical parameters at baseline and follow-up were analysed using Wilcoxon signed rank test or McNemar test.

Survival was defined as no death (lung transplantation (LTx) as censored event), transplant-free survival as no death or LTx and event-free survival as no death, LTx or Potts shunt. Differences in characteristics between patients with and without an event were compared using Mann-Whitney U-test, Chi-squared test or Fisher's exact test.

Cox proportional hazard analysis and time-dependent Cox regression analysis were used to test the predictive value for (transplant-free/event-free) survival of the parameters assessed at baseline, at 3 months and the change between baseline and 3 months. Kaplan–Meier method was used to estimate (transplant-free/event-free) survival with the date of diagnostic RHC as the start point with truncating at 36 months because of low number of patients thereafter and for comparing with adult studies [13, 14]. A p-value <0.05 was considered statistically significant.

Results

Between June 2010 and February 2019 in the two participating centres, 21 children were initiated with uTCT. 19 children were diagnosed either IPAH or HPAH, whereas two children had PAH-CHD (one child with PAH-CHD and coincidental shunt (atrial septal defect) with a *SOX17* mutation and one child with PAH-CHD after neonatal arterial switch operation for simple transposition of the great arteries (respectively PAH-CHD group 3 and 4 according to the most recent clinical classification of pulmonary hypertension (PH))) [5, 16, 17].

In two children, initially diagnosed as IPAH, the diagnosis was eventually changed into pulmonary veno-occlusive disease (PVOD) by histopathological examination of lung tissue collected either post-mortem or at LTx (respectively 0.7 months and 10.6 months after start of uTCT).

Seven children were diagnosed HPAH (*BMPR2* mutation n=5 and *TBX4* variant n=2), and one child had PAH associated with a Von Hippel-Lindau gene mutation (included in the IPAH/HPAH-population) [18]. Median age at time of diagnosis was 4.8 years (2.5–12.8) with a slight dominance of females (57%). All children except one were in WHO-FC III or IV (28% and 67% respectively). Baseline clinical, echocardiographic and haemodynamic characteristics are shown in tables 1 and 2, respectively. Poor systolic right ventricle function was present in 86% of the children and TAPSE was clearly decreased. Pericardial effusion (PE) was present in 33%. Haemodynamic evaluation at baseline was performed between 15 days before and 19 days after baseline.

TABLE 1 Baseline clinical characteristics

Age at diagnosis years	4.8 (2.5–12.8)
Sex female	12 (57)
Type of PAH	
IPAH/HPAH[#]	19 (90)
PAH-CHD	2 (10)
WHO-FC	
I	0 (0)
II	1 (5)
III	6 (28)
IV	14 (67)
Clinical symptoms of right heart failure yes	6 (30)
Systolic blood pressure mmHg	91 (88–104)
Diastolic blood pressure mmHg	56 (46–65)
6MWD	
m	286 (155–337)
z-score[¶]	−5.5 (−7.7 to −3.9)
NT-proBNP ng·L^{-1}	1530 (277–3354)
NT-proBNP <300 ng·L^{-1}	5 (24)

Data are presented as median (interquartile range) or n (%). PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; CHD: congenital heart disease; WHO-FC: World Health Organization Functional Class; *BMPR2*: bone morphogenetic protein receptor type II; *TBX4*: T-Box factor 4; 6MWD: 6-min walking distance; NT-proBNP: *N*-terminal pro-brain-natriuretic-peptide. [#]: *BMPR2* mutation, n=5; *TBX4* variant, n=2. [¶]: 6MWD was not performed in 11 (52%) children because of too young an age.

TABLE 2 Baseline echocardiographic and haemodynamic characteristics

	n	
Echocardiographic characteristics		
TAPSE	21	
mm		15.0 (13.1–17.7)
z-score		−2.1 (−4.5–0.9)
Poor systolic RV function	21	18 (86)
TI V_{max} m·s^{-1}	20	4.6 (4.5–5.0)
Pericardial effusion yes	21	7 (33)
Haemodynamic characteristics		
mPAP mmHg	21	70 (62–86)
mPCWP mmHg	21	10 (6–11)
mSAP mmHg	21	62 (56–74)
mRAP mmHg	21	8 (5–9)
PVRi WU.m^2	20	17.3 (13.1–25.3)
SVRi WU.m^2	8	19.1 (13.9–25.3)
Cardiac index L·min^{-1}·m^{-2}	20	3.8 (2.7–4.3)
S_{vo_2} %	21	65 (52–72)

Data are presented as median (interquartiel range) or n (%), unless otherwise stated. TAPSE: tricuspid annular plane systolic excursion; RV: right ventricle; TI: tricuspid insufficiency; V_{max}: maximum velocity; mPAP: mean pulmonary arterial pressure; mPCWP: mean pulmonary capillary wedge pressure; mSAP: mean systemic arterial pressure; mRAP: mean right atrial pressure; PVRi: pulmonary vascular resistance index; SVRi: systemic vascular resistance index; S_{vo_2}: systemic venous oxygen saturation.

Treatment

The median time between initiation of the first and third PAH-targeted therapy was 0.2 months (0.0–0.4). All children received sildenafil (10 mg and 20 mg three times per day for children with a body weight below and above 20 kg, respectively) and bosentan (2 mg·kg^{-1} twice per day) [19, 20]. Ten children received *i.v.* epoprostenol (maximum dose 20–33 ng·kg^{-1}·min^{-1}) and 11 children *s.c.* treprostinil (maximum dose 22–50 ng·kg^{-1}·min^{-1}).

In nine children uTCT was initiated at the paediatric intensive care unit (PICU) either because of clinical condition at presentation or because of institutional policy to initiate parenteral vasoactive agents in a PICU setting. Supportive therapy at time of initiation of uTCT included: inotropic support (10%), diuretics (29%), anticoagulation (19%), or oxygen suppletion (33%). None of the children received ventilatory support.

Assessments of treatment effect

Between the start of uTCT and 3 months follow-up assessment one patient died 0.7 months after start of uTCT, with a revised *post mortem* diagnosis of PVOD. One IPAH-patient received a Potts shunt after 0.8 months since start of uTCT.

At 3 months follow-up (interquartile range: 2.8–3.6), 17 out of the remaining 19 children had improved to WHO-FC I or II, whereas two IPAH/HPAH-patients improved to WHO-FC III. Clinical right ventricle failure, present in nearly 30% of the children before the start of uTCT, had recovered in all. Echocardiographic evaluation of right ventricle function, judged poor at baseline in 16 out of 19 children, had recovered in all but one, also reflected by significant improvement of TAPSE. The one child in whom right ventricle function did not improve was diagnosed with PVOD 10.6 months after start of uTCT. NT-proBNP had decreased in 15 out of 19 children and 6MWD, available in ten children, improved significantly (table 3). Between 3 and 6 months follow-up no further patients died. The improvements observed at 3 months follow-up persisted at 6 months follow-up.

In ten patients, a follow-up RHC was performed at discretion of the treating physician after a median (interquartile range) follow-up of 6.8 (5.5–7.2) months. Median mPAP had decreased from 72 (62–99) mmHg to 48 (40–70) mmHg, median PVRi from 18.6 (13.8–22.5) Wood units·m^2 to 9.2 (5.8–14.5) Wood units·m^2, whereas median cardiac index had increased from 4.3 (3.2–4.4) L·min^{-1}·m^{-2} to 5.1 (3.9–5.5) L·min^{-1}·m^{-2} and median systemic venous oxygen saturation (S_{vo2}) from 63 (57–70) % to 71 (69–75)% (all comparisons $p<0.05$).

Outcome

Median follow-up of the total study cohort of 21 children was 2.5 (1.1–6.3) years.

TABLE 3 Comparison of clinical and echocardiographic characteristics between baseline and 3 months follow-up in 19 surviving patients

	At baseline n=19	At 3 months n=19	p-value
WHO-FC			**<0.001**
I	0 (0)	4 (21)	
II	1 (5)	13 (68)	
III	5 (26)	2 (11)	
IV	13 (68)	0 (0)	
Clinical symptoms of right heart failure, yes	5 (26)	0 (0)	0.063
Systolic blood pressure mmHg	94 (88–105)	98 (94–108)	**0.037**
6MWD			
m	262 (143–342)	413 (372–488)	**0.008**
z-score	−5.6 (−7.9 to −4.5)	−2.9 (−3.8 to −2.2)	**0.008**
NT-proBNP ng·L^{-1}	1530 (254–3580)	197 (66–433)	**0.001**
NT-proBNP <300 ng·L^{-1}	5 (26)	13 (68)	**0.008**
TAPSE			
mm	14.0 (13.0–17.3)	19.2 (16.0–21.4)	**0.002**
z-score	−2.1 (−4.5–0.7)	−0.2 (−1.7–1.4)	**0.004**
Poor systolic RV function	16 (84)	1 (5)	**<0.001**
TI V_{max} m·s^{-1}	4.5 (4.5–5.0)	4.2 (3.3–4.5)	**0.004**
Pericardial effusion, yes	5 (26)	1 (5)	0.219

Data are presented as median (interquartile range) or n (%). WHO-FC: World Health Organization Functional Class; 6MWD: 6-min walking distance; NT-proBNP: N-terminal pro-brain-natriuretic peptide; TAPSE: tricuspid annular plane systolic excursion; RV: right ventricle; TI: tricuspid insufficiency; V_{max}: maximum velocity.

Two children (eventually diagnosed PVOD) reached an endpoint within 1 year after initiation of uTCT (one death, one LTx). Two children with PAH-CHD survived without events with a follow-up of 0.3 and 1.1 years, respectively.

Of the 17 children with IPAH/HPAH, two children underwent LTx 2.4 and 4.1 years after start of uTCT (one *BMPR2* mutation carrier and one IPAH-patient, respectively). Two children with IPAH/HPAH died: one *BMPR2* mutation carrier died 1 day after undergoing percutaneous Potts procedure (13.1 months after start of uTCT); the other child (IPAH) died 4.4 years after a Potts procedure (6.3 years after start of uTCT), not PAH-associated but due to cachexia associated with anorexia nervosa. In total, eight children with IPAH/HPAH underwent a Potts shunt during follow-up. The timeline of events is shown in figure 1.

Indications for Potts shunt consisted of clinical worsening (n=5), lack of improvement (n=2), or recurrent line infections under *i.v.* epoprostenol therapy (n=1). Clinical worsening was defined as recurrent syncope, worsening of WHO-FC, function deterioration, and/or increasing NT-proBNP level during follow-up. Lack of improvement was defined as sustained high WHO-FC (III or IV), sustained poor right ventricle function and/or sustained high NT-proBNP level.

1-,2- and 3-year survival rates and transplant-free survival rates in all patients were 95%, 90% and 90%, and 90%, 85%, and 78%, respectively (figure 2a). Figure 2b displays the Kaplan–Meier curves of the transplant-free survival stratified for type of PAH.

Children with IPAH/HPAH on uTCT had 1-, 2- and 3-year survival rates of 100%, 94% and 94%, respectively. 1-, 2- and 3-year transplant-free survival rates were 100%, 94%, and 87%, respectively (figure 3).

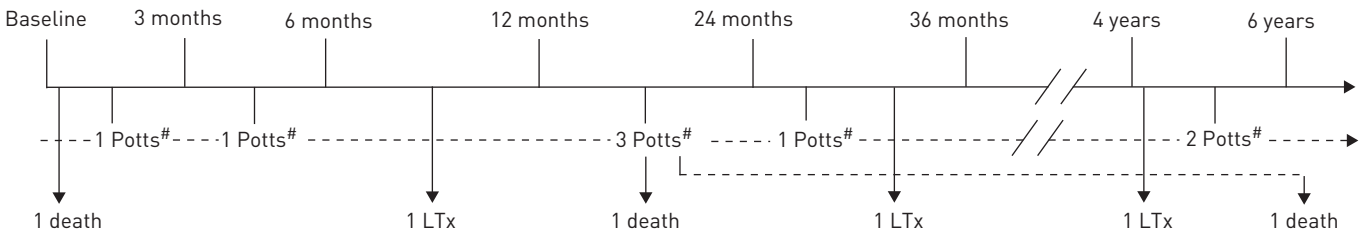

FIGURE 1 Timeline of all patients included in the study and the number of deaths, lung transplantation and Potts shunt. #: Patients undergoing a Potts shunt continued in follow-up. A Potts shunt is defined as an event in all event-free analyses. LTx: lung transplantation.

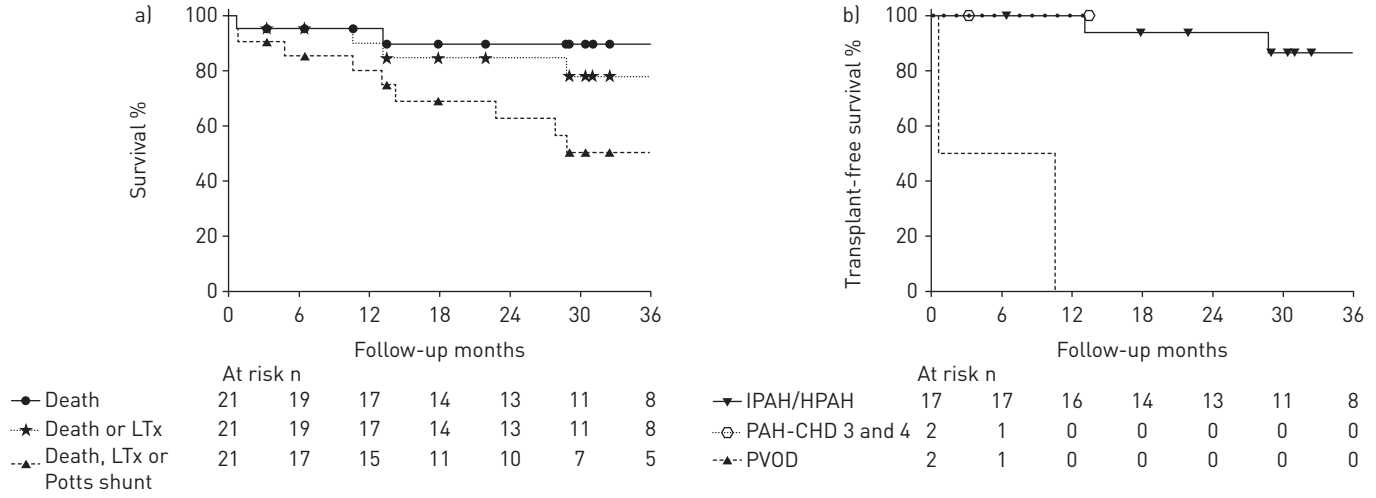

FIGURE 2 a) Survival, transplant-free and event-free survival (no death, lung transplantation and Potts shunt) in all patients and b) Transplant-free survival stratified for diagnosis. Follow-up was truncated at 36 months. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; CHD: congenital heart disease; PVOD: pulmonary veno-occlusive disease; LTx: lung transplantation.

These compare more favourable to transplant-free survival predicted by the paediatric risk stratification tool proposed at the World Symposium on Pulmonary Hypertension (WSPH) (67% and 42% for 1- and 3-year transplant-free survival rates, respectively) [15, 21]. Observed 1-, 2- and 3-year event-free survival rates were 88%, 69% and 55%, respectively (figure 3).

Children with an event more often carried a *BMPR2* mutation (p=0.045) and had lower S_vO2 at baseline RHC (p=0.025). Time-dependent Cox regression analysis did not identify any of the collected variables as predictor for survival, not at baseline nor after 3 months uTCT.

Clinical condition of survivors at last follow-up

13 of 17 children with IPAH/HPAH survived without LTx during the study period. Six of these had received a Potts shunt during follow-up. Of the seven surviving children without a Potts shunt, five were still on uTCT a median (interquartile range) of 2.5 (2.0–3.3) years after the start of uTCT. In two children, *s.c.* treprostinil was stopped, either because of clinical and echocardiographic improvement (infantile *TBX4* mutation carrier) or because of parental will (IPAH). Both children continued on oral dual combination therapy and were in a good clinical condition at last available follow-up 1 month and 5.4 years after termination of prostanoids, respectively. All children except one were in WHO-FC I or II, and median NT-proBNP level was 66 (46–236) ng·L^{-1}. None of the children had clinical signs of right ventricle failure, and echocardiographic evaluation revealed a good systolic right ventricle function with no pericardial effusion in all seven children (table 4).

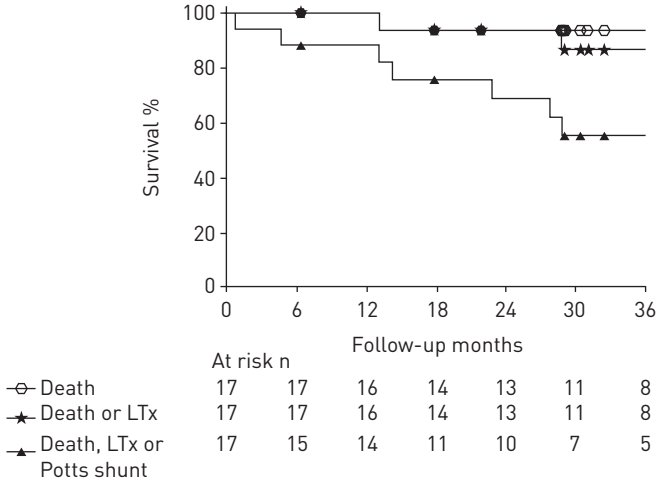

FIGURE 3 Survival, transplant-free and event-free survival (no death, lung transplantation and Potts shunt) in children with IPAH/HPAH started on upfront triple combination therapy. Follow-up was truncated at 36 months. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; LTx: lung transplantation.

TABLE 4 Outcome in children with IPAH/HPAH

	Potts shunt n=8		No Potts shunt n=9
Death (all cause)/LTx n	2/0		0/2
		Survivors	
	n=6		**n=7**
Median follow-up years			
Since initiation of upfront triple combination therapy	7.3 (2.4–8.3)		2.5 (1.5–4.0)
Since Potts procedure	2.6 (0.5–7.0)		NA
Prostanoids stopped n	5 (83)		2 (29)
WHO-FC I/II	6 (100)		6 (86)
Clinical symptoms of right heart failure yes	0		0
NT-proBNP ng·L^{-1}	70 (61–179)		66 (46–236)
NT-proBNP <300 ng·L^{-1}	5 (83)		6 (86)
Poor systolic RV function	0		0
Pericardial effusion yes	0		0

Data are presented as median (interquartile range) or n (%). PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; LTx: lung transplantation; WHO-FC: World Health Organization Functional Class; NT-proBNP: *N*-terminal pro-brain-natriuretic peptide; RV: right ventricle; NA: not applicable.

Of the six surviving children with a Potts shunt, parenteral prostanoid therapy was stopped in five, while oral dual combination therapy was continued. In one child, uTCT with *i.v.* epoprostenol was weaned after the Potts shunt but then restarted within 14 months because of clinical worsening. All "Potts children" were in WHO-FC I or II, had no clinical signs of right ventricle failure, had a median NT-proBNP level of 70 (61–179) ng·L^{-1}, and echocardiography showed a good systolic right ventricle function with no pericardial effusion in all six children (table 4).

Discussion

This study shows that children with severe PAH, but not PVOD, improved significantly with uTCT. This improvement sustained up to 1 year in the majority of children. Transplant-free survival rates at 1-, 2- and 3-years showed superior to predicted transplant-free survival estimates calculated using the WSPH paediatric risk stratification tool. However, almost half of the children received a Potts shunt during follow-up. The role of a Potts shunt in conjunction to uTCT in paediatric PAH needs to be further established.

Current guidelines for the treatment of IPAH/HPAH recommend start of combination therapy instead of monotherapy in patients at high risk. Recently a more aggressive, alternative treatment strategy for these patients has been proposed. In two separate studies, Sitbon *et al.* [13] and D'Alto *et al.* [14] reported the use of uTCT in high-risk adult PAH-patients and showed dramatic improvements in clinical condition, haemodynamics and reversed remodelling of the right ventricle [12, 14]. After median follow-up periods of two and over 3 years respectively, uTCT, including either *i.v.* epoprostenol or *s.c.* treprostinil, resulted in an impressive 70% reduction in PVR, 30% reduction in mPAP and over 100% increase in cardiac index. Sitbon *et al.* [13] reported 1-, 2- and 3-year survival of 94%, 94% and 94%, respectively and D'Alto *et al.* [14] a 2-year survival of 100%, both comparing substantially more favourable to predicted survival in these high-risk patients based on current era risk scores. Survival in paediatric PAH is reported to be worse than in adults, with young age as independent risk factor. Nevertheless, the current pilot study shows that uTCT also in children with PAH at high risk resulted in significant clinical and echocardiographic improvement after 3 and 6 months. Clinical risk factors in these children, such as WHO-FC III/IV and PVRi >20 Wood units·m^2, were comparable to the adult population of Sitbon *et al.* [13] and D'Alto *et al.* [14]. Both recruiting centres follow the most current algorithms for treatment of children with PAH, recommending the initiation of intravenous prostanoid therapy, either or not in combination with other PAH-targeted therapy, in high-risk children [5, 15]. Although in this retrospective study no predefined criteria were used for initiating uTCT, all children (except one) were in WHO-FC III or IV with either RV dysfunction and/or seriously increased NT-proBNP values and/or PVRi >20 WU·m^2 (as shown in tables 1 and 2).

Invasive haemodynamics, assessed in half of the children, showed a 50% reduction in PVRi, 30% reduction of mPAP and 20% increase in cardiac index. Since in contrast to adults, cardiac index is generally longtime preserved in children with severe PAH, the proportional smaller increase in cardiac index in children compared to adults, may be explained by the rather preserved cardiac index in children with severe PAH [22, 23]. With a median follow-up time of more than 2.5 years, observed 1-, 2- and 3-year transplant-free survival rates in children with IPAH/HPAH were 100%, 94% and 87%, respectively,

more favourable than 1- and 3-year transplant-free survival estimates of 67% and 42% predicted by the WSPH paediatric risk stratification tool [15, 21].

However, in the current cohort, eight out of 17 children with IPAH/HPAH underwent a Potts shunt during follow-up, resulting in 1-, 2- and 3-year event-free survival rates of 88%, 69% and 55%, respectively. This observation suggests that from 1 year after start of uTCT a substantial number of the children with IPAH/HPAH were considered to need additional intervention, mainly due to clinical worsening or lack of improvement. The Potts shunt is a procedure that is performed selectively in children with IPAH/HPAH and the availability and access to the Potts shunt in the study centres may have biased this number of events. The exact role of the Potts shunt in conjunction to uTCT in this group of children with severe IPAH/HPAH needs to be further established. One patient died perioperatively after undergoing a Potts procedure, illustrating associated risks with this procedure and the need for proper patient selection. Follow-up of surviving children with and without a Potts shunt, revealed that patients in both groups were in good clinical condition at last follow-up, although follow-up time since diagnosis was substantial longer in those who underwent a Potts procedure, making direct comparisons hazardous. Parenteral prostanoid therapy was stopped in five out of six children with a Potts shunt *versus* two out of seven children without Potts shunt. Whether the good clinical condition of the patients without a Potts shunt will last until similar follow-up time of the Potts patients, or whether the Potts patients have persisted in good clinical condition due to or despite the Potts shunt, cannot be answered by the current study [24–26].

None of the collected variables were identified as predictor for survival, not at baseline nor after 3 months uTCT. The selected high-risk status of the children in this cohort, with high WHO-FC, high PVRi, poor systolic right ventricle function and high NT-pro-BNP, may explain why the established prognostic value of these factors in paediatric PAH, were not predictive for outcome within this high-risk cohort. The current study clearly illustrates that uTCT including parenteral prostanoids, is not an appropriate therapy in children with POVD, with both children with PVOD having an event (death or LTx) within the first year after diagnosis. It does also underscore that the differentiation between IPAH and PVOD at diagnosis may be difficult. The collection of lung tissue at time of diagnosis for confirmation of the diagnosis PVOD is not advised due to the high risks of lung biopsy in these patients, while CT-diagnosis may be ambiguous. Adverse response to vasodilating therapy is one of the diagnostic features of PVOD [27]; however, one of the PVOD-patients in the current study showed both clinical and echocardiographic (TAPSE) improvement with uTCT at three and 6 months. The rapid clinical deterioration of the children with PVOD underscores the need for early, proper diagnosis and every means should be used to accelerate this, including genetic testing to help refine treatment [28].

Limitations

The current study is a retrospective observational study in a small number of selected patients accompanied by associated limitations. To demonstrate superiority of uTCT above other treatment strategies, for instance upfront double combination therapy, direct comparisons in a randomised controlled trial (RCT) would be required. However, conventional drug RCTs in paediatric PAH have been proven extremely challenging and therefore it is highly unlikely that such a trial will be performed any time soon. In the absence of RCTs, therefore the current observational data are instrumental in designing optimal treatment strategies for children with PAH. These current findings suggest excellent long-term effects of uTCT in children with severe PAH, with sustained effect in a substantial proportion of children.

Conclusion

This study provides preliminary evidence that in children with severe PAH uTCT is associated with substantial improvement in clinical condition, haemodynamics and right ventricle function, and with favourable transplant-free survival during 3 years follow-up. Nevertheless, during follow-up almost half of the children with IPAH/HPAH underwent a Potts procedure. The role of the Potts shunt in conjunction to uTCT in paediatric PAH needs to be further established.

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