Review article

Pulmonary hypertension—“state of the art” management in 2012

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KEYWORDS

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ABSTRACT

Pulmonary artery hypertension (PAH) is a pathological condition of small pulmonary arteries, characterised by vascular proliferation and remodelling. The pulmonary artery pressure and pulmonary vascular resistance progressively rise, leading to right heart failure and death. Pulmonary artery hypertension may be secondary to various conditions, or it may be idiopathic where no underlying cause is identifiable. Earlier, only symptomatic treatment was available for such patients which did not change the natural history of the disease. However, over the years, improvement in understanding the pathogenesis has resulted in the development of targeted approaches to the treatment of PAH. Survival advantage has also been shown with some of the pharmacologic agents. This review article discusses the current management strategy for PAH with special emphasis on an idiopathic variety, in an Indian context.

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Introduction

Pulmonary artery hypertension (PAH) is defined as the sustained increase in mean pulmonary arterial pressure to a level ≥ 25 mmHg at rest, as assessed by right heart catheterisation.¹ It is a progressive disease involving small pulmonary arteries and is characterised by vascular proliferation and remodelling. The pulmonary vascular resistance (PVR) gradually rises, often leading to right heart failure and death. Pulmonary artery hypertension is classified based on the underlying diagnosis. If no known risk factors are identified, it is called primary PAH or more recently, idiopathic PAH (iPAH). The diagnostic classification of PAH is given in Table 1, as updated in 2008 by an expert working group (Dana Point, 2008).² Although there are various conditions producing PAH, the histopathological features and response to various drugs tend to be similar for most. Treatment of the underlying condition like left heart disease or pulmonary parenchymal disease is most rewarding if PAH is secondary to one of these causes. Over the last 10 years, rapid advancements in understanding

the pathogenesis and therefore treatment options have taken place, most of these being for group 1. This article will focus primarily on the management of iPAH.

Epidemiology

The reported prevalence of PAH is 15 per million, females constitute 50–75% of those affected.^{3,4} Primary or iPAH is a rare disorder, the frequency is estimated at 1–2 cases/million people.⁵ A study from Scotland, however, cited the incidence as 2.5 cases/million/yr in men and 4.0 cases/million/yr in women.⁶ Any age group can be affected, but most often iPAH occurs in the third decade of life in women and fourth decade of life in men. No ethnic predisposition has been reported. The average duration between symptom and diagnosis of PAH is >2 years.³ It was further confirmed by the National Institute of Health Registry, where the mean interval from symptoms onset to diagnosis was 2 years, it was shorter in cases with family history of pulmonary artery hypertension (PAH).⁷ The familial PAH shows an autosomal inheritance with 10–20% penetrance. There is genetic anticipation in familial PAH, i.e. the onset of disease occurs at an

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Table 1

Updated clinical classification of pulmonary hypertension (Dana Point, 2008).

1. Pulmonary arterial hypertension (PAH)
 - 1.1 Idiopathic PAH
 - 1.2 Heritable
 - 1.2.1 BMPR2
 - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
 - 1.2.3 Unknown
 - 1.3 Drug- and toxin-induced
 - 1.4 Associated with
 - 1.4.1 Connective tissue diseases
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart diseases
 - 1.4.5 Schistosomiasis
 - 1.4.6 Chronic haemolytic anaemia
 - 1.5 Persistent pulmonary hypertension of the newborn
- 1* Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary haemangiomatosis (PCH)
2. Pulmonary hypertension owing to left heart disease
 - 2.1 Systolic dysfunction
 - 2.2 Diastolic dysfunction
 - 2.3 Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
 - 3.1 Chronic obstructive pulmonary disease
 - 3.2 Interstitial lung disease
 - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
 - 3.4 Sleep-disordered breathing
 - 3.5 Alveolar hypoventilation disorders
 - 3.6 Chronic exposure to high altitude
 - 3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
 - 5.1 Haematologic disorders: myeloproliferative disorders, splenectomy
 - 5.2 Systemic disorders: sarcoidosis, pulmonary langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
 - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
 - 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

earlier age in successive generations.^{8,9} Group 1 of Dana Point classification also includes drugs and toxins associated with development of PAH; the most notorious of these include the appetite suppressants fenfluramine and dexfenfluramine. More recently, methamphetamine is being indicated as the cause of drug-related PAH.^{10,11}

Pathogenesis

The detailed pathophysiology of PAH is beyond the scope of this article. Suffice it to say that the pathogenesis of PAH is multifactorial (Table 2) and is not completely understood. The normal pulmonary circulation is very compliant and can accommodate the entire cardiac output at one fifth perfusion

Table 2

Pathophysiological mechanisms for pulmonary artery hypertension.

Site	Abnormality	Effects
Endothelial	Decrease NO, PGI ₂ Increase Endothelin-1 Increase thromboxane A2	Thrombosis Platelet aggregation Smooth muscle proliferation
	Increase VEGF	
Platelets	Increase serotonin Increase PDGF and VEGF	Platelet aggregation Smooth muscle proliferation Vasoconstriction
Smooth muscle cells	Dysfunctional K ⁺ channels	Vasoconstriction
	Increase angiotensin II	Smooth muscle proliferation

NO: nitric oxide, PDGF: platelet derived growth factor, PGI₂: prostaglandin I₂, VEGF: vascular endothelial growth factor.

pressures when compared with systemic circulation. This is accomplished by dilation of the existing vasculature and recruitment of unused vasculature. These changes maximise gas exchange surface area with no or little increase in perfusion pressure. Several humoral mediators, such as nitric oxide (NO) and prostacyclin, which are produced locally, contribute to the maintenance of a compliant vasculature.

Pulmonary artery hypertension is caused by disturbance of one or more of these protective mechanisms. Three factors are considered important in raising PVR. These are vasoconstriction, remodelling of the pulmonary vessel wall and thrombosis in situ.¹² Vasoconstriction may not be very important as only a small fraction of iPAH cases respond favourably to vasodilator therapy. High PVR causes hypertrophy of the right ventricle and in late stages the cardiac output falls. Hypoxaemia may occur secondary to ventilation perfusion mismatch and/or right to left shunting through a patent foramen ovale.

Endothelial dysfunction seems to play a key role in the pathogenesis of PAH. An imbalance between the 'bad' vasoconstrictive/proliferative endothelin system and the 'good' vasodilatory/anti-proliferative NO and prostacyclin system is a key contributor to the initiation and progression of disease.¹² Platelets also play an important role as procoagulant and by releasing serotonin (vasoconstrictor), platelet derived growth factor (PDGF), and vascular endothelial growth factor (VEGF).¹³

Recent data suggests a primary defect in certain potassium channels in some patients with PAH.¹⁴ Dysfunctional voltage-gated potassium channels may explain the vasoconstriction and smooth muscle cell proliferation accompanying PAH. In PAH, the classic histological finding is the plexiform lesion. Activation and expression of adhesion molecules by endothelial cells results in a procoagulant state, resulting in thrombin deposition and platelet adhesion. All these abnormalities in the pulmonary vasculature of patients with PAH result in unregulated vasoconstriction, smooth muscle cell proliferation out of proportion to apoptosis, and microvascular thrombosis.¹⁵

Natural history

Idiopathic PAH is a progressive disease and before the introduction of various therapeutic drugs, the survival was dismal. The median survival in 1980s was reported as 2.8 years in 194 patients with iPAH after the diagnosis was made.¹⁶ The actuarial survival rates were 68–77% at 1 year, 40–56% at 3 years and 22–38% at 5 years in two different studies.^{16,17} At that time most patient received conventional therapy including oral anticoagulants, diuretics, oxygen, cardiac glycosides, and calcium channel blockers. Poor prognosis was associated with New York Heart Association (NYHA) functional class III or IV, right heart failure, elevated right atrial pressure, decreased cardiac output or low mixed venous saturation.

Functional class III and IV continue to have extremely poor survival even in the current era as shown in data from registries.¹⁸

Over the years, however, improvement in understanding of the disease process has resulted in development of targeted approaches to treatment of PAH. Survival advantage has also been reported with various pharmacologic agents as will be described later.

Assessment of therapeutic strategies

Once the patient has been diagnosed with PAH and initiated on specific therapy, he or she should be assessed to monitor response to therapy at 3–6 months intervals depending on the severity of disease. Although a general assessment of the patient will provide important information whether the patient has improved symptomatically or in activities of daily living, objective evaluation is very important. As PAH is a rapidly progressive disease, long-term survival cannot be used for assessing the efficacy of a new treatment. Therefore, the commonly used end points are 6 minutes' walk test (6MWT, the distance walked over a 6-minute period) and NYHA/WHO (World Health Organization) functional class.¹⁹ WHO functional class is described in detail in Table 3. Pulmonary artery pressure (PAP) (derived by echo-Doppler and/or by right heart catheterisation) and cardiac output are also used for assessment of efficacy of the treatment. Assessment by serum biomarkers and right heart function may also be helpful.²⁰

Treatment of pulmonary artery hypertension

Regardless of the aetiology of PAH, general supportive care is similar for all patients. The supportive care aims at improving symptoms and quality of life, preventing progression of the disease, and improving mortality. Unfortunately very few large randomised controlled trials (RCT) have been conducted for determining the best treatment options for patients with PAH, most of these have been restricted to those with iPAH. Extrapolation to other populations with PAH is based mainly on expert recommendation rather than sound evidence-based medicine.^{21–23}

Table 3

World Health Organization functional classification.

WHO functional class	Clinical description
I	Patients with PH with no limitation of usual physical activity; ordinary physical activity does not cause dyspnoea, chest pain or pre-syncope
II	Patients with PH with mild limitation of physical activity; no discomfort at rest but normal physical activity causes dyspnoea, fatigue, chest pain or pre-syncope
III	Patients with PH with marked limitation of physical activity; no discomfort at rest but < ordinary activity causes dyspnoea, fatigue, chest pain or pre-syncope
IV	Patients with PH who are unable to perform any physical activity; dyspnoea and/or fatigue are present at rest and symptoms are worsened with any physical activity. Syncope may occur with exertion

WHO: World Health Organization.

General measures

General measures include strategies to avoid circumstances that may aggravate the disease. Any external stimulus that increases oxygen demand may worsen PAH and result in right heart failure. Non-steroidal anti-inflammatory drugs (NSAIDs) are best avoided due to their effect on fluid balance and renal function.

Physical activity

Heavy physical activity can be potentially dangerous in patients with PAH and may trigger dyspnoea, chest pain or syncope. Therefore physical activity limited to a symptom free level is advised. This prevents deconditioning and muscular involution. Patients in functional class III or IV need to be more careful as life-threatening syncope may be induced on exercise.²⁴ Bathing in hot water should be avoided as it can precipitate cutaneous vasodilatation thereby reducing cardiac output.

Pregnancy and contraception

Pregnancy results in increase cardiac output and blood volume by as much as 40%. In PAH patients, the ability of right heart to compensate for the increased cardiovascular demand is limited. Hence, pregnancy poses an extreme risk to the health of women with PAH and is contraindicated. Maternal mortality can be as high as 30–50% according to some reports, with most deaths occurring in the immediate post-partum period due to refractory right heart failure, sudden cardiac death, or thromboembolism.^{25–27}

A safe and effective method of contraception must be recommended in women of child bearing age. Since, safety of hormonal contraception is questionable due to its prothrombotic potential, mechanical contraception (intrauterine device) or surgical sterilisation is generally recommended. In some

centres, oral contraception with progesterone derivatives or low dose oestrogen has been given to women with PAH who are on oral anticoagulants with no history of thromboembolism.²⁸ Similarly, post-menopausal women with intolerable menopausal symptoms can also receive hormone therapy in conjunction with anticoagulation.

High altitude

Hypoxia aggravates vasoconstriction in PAH patients. Therefore such patients must avoid living at high altitudes (>1500–2000 m). Commercial airplanes are generally pressurised to an altitude between 1600 m and 2500 m. Some of these patients may need supplemental oxygen when travelling by airplanes.

Prevention of infections

Respiratory infections can be fatal in patients with PAH. Pneumonia is the cause of death in 7% of cases.²³ Pulmonary infections must be promptly recognised and treated with antibiotics. Regular vaccination against influenza and pneumococcal pneumonia is recommended. Persistent fever can also occur in patients on continuous intravenous epoprostenol infusion due to catheter related infection and sepsis.

Haemoglobin/haematocrit

Anaemia is not uncommon in patients with PAH and if detected, should be promptly treated. Conversely, some of the patients with long-standing hypoxia secondary to right to left shunt may develop polycythaemia. Phlebotomy is indicated only in symptomatic cases that have a high haematocrit (>65%) and volume replacement with saline or dextrose is recommended during phlebotomy.²⁹

Anaesthesia and surgery

Patients with PAH are at a high-risk during anaesthesia and surgery. The risk is higher in those who are in functional class III or IV. Epidural anaesthesia may be better than general anaesthesia. Anticoagulant treatment should be stopped for the shortest possible time.

Pharmacologic treatment anticoagulants

The rationale for anticoagulant therapy is based on the presence of traditional risk factors for venous thromboembolism, like heart failure, sedentary lifestyle and a thrombophilic predisposition. Anticoagulant therapy has been widely used for PAH, although the evidence supporting this approach has not come from well-designed trials. In a retrospective study by Fuster and colleagues, 7 patients who were given coumadin had better survival than 37 patients who were not given

oral anticoagulant.³⁰ In another small prospective study, Rich et al. showed that patients who did not respond to calcium channel blockers and who were treated with anticoagulants had improved survival as compared with those who were not anticoagulated.³¹ Three year survival improved from 21% to 49% in the series by Fuster et al. and from 31% to 47% in the series from Rich et al. Warfarin is the most widely used drug and the target international normalised ratio (INR) is generally kept around 2.0. Some authors from European centres prefer to have INR between 2.0 and 3.0. The usage of anticoagulants in some of the recent trials for newer drugs has been in 51–86% of patients. Highest prevalence of anticoagulants use was in trials involving iPAH patients in NYHA/WHO functional class III and IV. Thus, while there is consistent evidence that anticoagulation improves outcomes in those with PAH, there is as of yet no RCT showing a benefit.

Diuretics

Diuretics improve symptoms and signs of right heart failure in decompensated patients of PAH. On the other hand, too much diuresis can cause hypovolaemia and further reduce cardiac output by decreasing right ventricular preload.³² No trials have been performed for diuretics, but clear symptomatic benefit has been shown in patients of PAH who were decompensated and have fluid retention. Some form of diuretic therapy is prescribed to 49–70% of patients in well-studied trials.²³ Furosemide or spironolactone is generally used. The dosages are modified according to the individual case. Serum electrolytes and renal functions should be carefully monitored in patients receiving diuretic therapy.

Oxygen therapy

Mild degree of hypoxaemia at rest is a common finding in PAH. This occurs as a consequence of low mixed venous oxygen saturation caused by low cardiac output. The ventilation perfusion matching is minimally altered and therefore does not contribute significantly to hypoxaemia. A small number of cases have severe hypoxaemia caused by a right to left shunt through a patent foramen ovale. No consistent data are available on the effect of long-term oxygen therapy in PAH. However, since hypoxaemia may aggravate PAH by increasing pulmonary vasoconstriction, supplemental oxygen therapy should be considered in patients with severe hypoxaemia at rest ($\text{PaO}_2 < 55 \text{ mmHg}$). Improvement in PAH with low flow supplemental oxygen has been reported in some cases. The goal of oxygen therapy is to maintain arterial saturation at >90%. Oxygen therapy can also improve quality of life by reducing dyspnoea and by increasing exercise capacity.

Cardiac glycosides

In cases with right heart failure secondary to PAH, myocardial contractility is likely to be impaired and inotropic agents

may help. Short-term intravenous digoxin has been reported to increase cardiac output by a modest degree.³³ Long-term data on effect of digoxin in PAH is not available. In the rare patient of PAH with supraventricular tachyarrhythmia (like atrial flutter or fibrillation), digoxin should be used to slow the ventricular rate. It must be noted that digoxin toxicity is more likely in PAH patients especially if hypoxaemia and/or hypokalaemia are also present. Patients with end stage PAH have been treated with intravenous dobutamine in most expert centres.³²

Specific therapies

Based on pathogenesis of PAH, there are three major classes of specific therapies. These include prostanoids, endothelial receptor antagonists (ETRA) and phosphodiesterase-5 (PDE5) inhibitors. However, calcium channel blockers have been used to treat PAH patients for a long time before specific drugs became available. Prior to initiating any of these drugs, all efforts must be made to look for any underlying cause as the cause of PAH. If discovered it should be treated promptly.

Several articles have published expert opinions regarding treatment, which is based on WHO functional class and risk assessment.³⁴

Calcium channel blockers

Since, vasoconstriction of pulmonary arterioles is often one of the several abnormalities responsible for PAH, vasodilator therapy has long been used in the treatment of PAH. Calcium channel blockers like nifedipine and diltiazem are widely used oral vasodilators, but only a small percentage of patients actually respond to these drugs. Calcium channel blockers do not have the selectivity for the pulmonary vascular bed and may cause systemic hypotension in some cases.

Vasodilator challenge

Calcium channel blockers should be used only in cases where a clear acute vasodilator response is demonstrated haemodynamically. Acute vasodilator testing is performed using short acting agents like intravenous epoprostenol, adenosine or inhaled NO. A decrease of at least 20% in PAP from the baseline value and a decrease of >30% in PVR with an increased or unchanged cardiac output is usually predictive of a favourable response.^{31–35} Some workers accept a decrease in mean PAP by >10 mmHg, to a value <40 mmHg with no reduction in cardiac output.³⁶ Generally only 10–15% of iPAH patients show a positive acute vasoreactive response and about half of them will continue to respond to calcium channel blockers over a long period of time.¹ In a recent study, Sitbon and colleagues showed that of 12.6% patients with iPAH who displayed acute pulmonary vasoreactivity, only 54% had a sustained, long-term benefit with oral calcium channel

blockers as monotherapy.³⁷ Hence overall <7% of 557 patients with iPAH were long-term responders. Long-term therapy with a calcium channel blocker is not recommended in those not showing acute response to vasodilator testing in the catheterisation lab. Further, these drugs should not be used as a screening agent for pulmonary vascular responsiveness in patients with PAH because severe adverse reactions can occur.

Calcium channel blockers are indicated in class II and III patients who show response on acute vasodilator testing. These drugs are much cheaper compared to some of the newer drugs. The choice of agent depends on the underlying heart rate. Those with heart rate of >80 beats/min are better given diltiazem and those with slower heart rates are given nifedipine. Verapamil is not used due to its negative inotropic effect. Amlodipine has been used, but its long-term efficacy is not known. The dosages used are quite high; 90–180 mg/day for nifedipine (up to 240 mg/day) and 240–720 mg/day for diltiazem (up to 900 mg/day). Systemic hypotension and limb oedema can occur; concomitant diuretics can alleviate lower limb oedema.

Prostanoid therapy

Prostacyclin, a prostanoid, is released from the endothelial cell membranes of the vascular intima and its levels are decreased in iPAH. Based on this rationale, prostacyclin is being used in patients with PAH. The precise mechanism of action of prostacyclin in PAH is likely to be multifactorial. It may include relaxation of vascular smooth muscle cell, inhibition of platelet aggregation, healing of endothelial injury, inhibition of smooth cell proliferation, facilitating reverse remodelling of pulmonary vascular changes and so on. Stable analogues of prostacyclin have been synthesised and are in use for patients with PAH over the last several years.

Epoprostenol

Intravenous epoprostenol was first used to treat iPAH in early 1980s.³⁸ Since then, it has proved to be lifesaving in a large number of patients with PAH of varied aetiology. In 1990, Rubin et al. reported the first randomised unblinded trial with intravenous epoprostenol in 25 patients with iPAH.³⁹ An improvement in exercise capacity as well as haemodynamics was shown after 2 months in those treated with intravenous epoprostenol. Second prospective randomised open trial reported improvement in 6MWT by 32 m, in the epoprostenol group after 12 weeks of therapy.⁴⁰ Survival advantage was also demonstrated in this trial in the group of patients on epoprostenol. Following these studies, intravenous epoprostenol was approved in USA and France for treatment of iPAH for those in functional class III or IV. In another study by Barst et al., the survival with epoprostenol was 87% at 1 year, 63% at 3 years and 54% at 5 years compared to 77%, 41%, and 27%, respectively in historic controls.⁴¹ There are other reports of improved survival with intravenous epoprostenol.^{42–44}

Intravenous epoprostenol is typically reserved for individuals with severe PAH. To date it is the only medication that has a mortality benefit.⁴⁰

Intravenous epoprostenol is now considered as a first line therapy in the western world. In a survey collected from 19 centres in the US, it was shown that more than two-thirds of patients with iPAH who were treated with intravenous epoprostenol could be taken off the list for lung transplantation.⁴⁵ This drug may be useful even in patients who do not show an acute haemodynamic response to it in the catheterisation lab.

Epoprostenol is dispensed as freeze-dried preparation that needs to be dissolved together with an alkaline buffer (glycine) and is given intravenously. Since, it has a very short half-life (3–5 minutes), it has to be given as a continuous infusion. Fresh solution has to be prepared every 24 hours due to the unstable nature of the drug. Epoprostenol is delivered by infusion pumps through long-indwelling venous catheters. The initial dose is 2–4 ng/kg/min and increased gradually. The target dose is 10–15 ng/kg/min for the first 2–4 weeks and then periodic dose increases are done to maximise efficacy. The optimal dose usually varies from 20–40 ng/kg/min in majority of patients. Dose adjustments are made based on clinical symptoms, distance walked during 6MWT and occurrence of side effects.

Common side effects include headache, flushing, jaw pain, diarrhoea, nausea, vomiting, and rarely ascites. Most of these side effects are generally mild and dose related. More serious complications are related to the delivery system and include exit site infections, bleeding, bacteraemia and sepsis. The incidence of catheter related sepsis has been reported to be 0.1–0.4 per patient-year.⁴⁰ Severe catheter related sepsis has resulted in death in some cases. Delivery system malfunction can be the other serious complication resulting in sudden, sometimes fatal decompensation due to interruption of drug supply. Patients suspected of veno-occlusive disease or pulmonary capillary haemangiomatosis which may masquerade as iPAH can develop fatal pulmonary oedema if given epoprostenol.

Despite favourable results from intravenous epoprostenol for cases with PAH, it is far from ideal treatment, primarily because of its route of delivery. It is very expensive over long-term use and is not curative. Currently this drug is not available in India for general use.

Treprostinil

The difficulties in delivering intravenous epoprostenol have stimulated interest in developing stable analogues of this compound which can be administered using less complex delivery systems. Treprostinil is one such analogue which has chemical stability at room temperature and can be given both intravenously and subcutaneously. It also has a longer half-life and needs to be prepared once in 48 hours.

The largest multicentre RCT was reported by Simonneau et al. involving 470 patients with PAH.⁴⁶ There was statistically significant improvement in median exercise capacity,

haemodynamics and clinical events compared to placebo group after 12 weeks of treatment with subcutaneous treprostinil. The effect was dose related.

The drug can be given through small subcutaneous catheters similar to those utilised for insulin administration in diabetics. The management of this system is much simpler compared to epoprostenol infusion system. Common side effects include headache, jaw pain, diarrhoea, nausea, and rash. Infusion site pain is seen in 85% of cases. Food and Drug Administration (FDA) has approved this drug in 2002 for class II, III and IV patients with PAH. It is not available in India.

Sodium beraprost

Beraprost sodium is the first biologically stable and orally active prostacyclin analogue. It is absorbed rapidly, peak concentration is reached after 30 minutes and the elimination half-life is 35–40 minutes after a single oral dose. Initial trials have shown an improvement in 6MWT, functional class and survival.^{47,48} In the RCT reported by Galie et al, there was significant improvement in exercise capacity at 12 weeks.⁴⁹ However, the data from Barst et al showed no difference in 6MWT distance with oral beraprost compared to placebo at 12 months follow-up, although improvement was observed at 3 and 6 months.⁵⁰ Beraprost sodium is approved in Japan and South Korea but not in USA and Europe. This drug is also not available in India.

Iloprost

Iloprost is a chemically stable prostacyclin analogue available for intravenous, oral, and aerosol usage. Inhaled therapy may provide selectivity of the haemodynamic effects to the lung vasculature, avoiding systemic side effects. Iloprost has a half-life of 20–25 minutes and can be delivered by inhaler, the aerosolised particles should be small enough (diameter 0.5–3 µm) to ensure alveolar deposition. Since, it has a short duration of action, it must be inhaled 6–12 times a day.⁵¹ With jet inhalers, the duration of each inhalation takes about 15 minutes.

In a randomised, multicentre, placebo-controlled study of 207 patients (all in functional class III or IV) with PAH, the 6MWT improved by 36 m at 12 weeks in those on iloprost.⁵² In the subgroup with iPAH, the improvement in 6MWT was even greater (59 m). The haemodynamic values were also much improved. In another study of 76 patients with inhaled iloprost as monotherapy, the 1 year, 3 years, and 5 years survival free of lung transplantation and addition or switch to other drugs were 53%, 20%, and 13%, respectively.⁵³ Thus, the role of iloprost as monotherapy is limited.

Side effects include cough, flushing, and headache. The short-term results are encouraging; however, long-term efficacy needs to be established. Inhaled iloprost is approved in Europe, Australia and New Zealand. It is not available in India.

Endothelin receptor antagonists

Increased levels of endothelin-1 have been found in the pulmonary arteries of PAH patients. Endothelin-1 is a potent vasoconstrictor and mitogen for smooth muscle cells. Levels of endothelin-1 have been related to disease severity and survival.^{54,55} The effects of endothelin-1 are mediated through two types of receptors ET_A and ET_B. ET_A receptors cause sustained vasoconstriction and proliferation of vascular smooth muscles and ET_B receptors induce production of NO and prostacyclin by the endothelial cells, thereby producing vasodilatation.⁵⁶ Therefore use of endothelin-1 receptor antagonists that can block either ET_A or both ET_A and ET_B receptors will help patients with PAH.

Bosentan

Bosentan is an orally active dual (ET_A and ET_B) endothelin receptor antagonist. It is the first molecule of this class of drugs to be synthesised. Bosentan has been evaluated in two RCT. In the larger BREATHE-1 study, 213 patients with PAH who were in functional class III or IV were randomised to receive placebo or bosentan.⁵⁷ The initial dose used was 62.5 mg twice daily for 4 weeks; thereafter either 125 mg or 250 mg twice daily dose was given for at least another 12 weeks. The mean effect of treatment on the 6MWT was a gain of 44 m in the overall study population and 52 m among patients with iPAH. Improvement was also seen in the time to clinical worsening. No dose-response effect on the efficacy could be ascertained. Similar response was seen in another RCT.⁵⁸ Sustained improvement at 6 months and 1 year in NYHA functional class and haemodynamic parameters was reported by Sitbon et al. in an open label extension study with bosentan.⁵⁹

Survival analysis of iPAH patients treated with oral bosentan as first line therapy in 177 patients has been published in 2005.⁶⁰ The dose used was 125 mg twice daily in majority and the mean follow-up period was 2.1 ± 0.5 years. Kaplan-Meier survival estimates were 96% at 1 year, 89% at 2 years as compared to the predicted survival of 69% at 1 year and 57% at 2 years with no specific treatment. According to the analysis by McLaughlin, treatment with bosentan was considered superior to epoprostenol in 139 iPAH patients in WHO functional class III.⁶¹ Oral bosentan has been proposed as a transition therapy in patients having severe side effects due to epoprostenol therapy. An uncontrolled study in children between 4 and 17 years of age with PAH (BREATHE-3) has confirmed the beneficial effects of bosentan as seen in adults. There was significant improvement in haemodynamics at 12 weeks in the 18 children given either bosentan alone or with epoprostenol.⁶²

Bosentan has also been used in mildly symptomatic adult patients with PAH in the EARLY trial.⁶³ Although a significant fall was seen in PVR, there was no significant change in 6MWT distance. Currently, this drug is perhaps best reserved for patients with WHO or NYHA functional class III or more.

Bosentan is metabolised in the liver and may increase hepatic aminotransferase levels. In the BREATHE-1 study, increases in hepatic aminotransferases were seen in 10% of the subjects, and were found to be dose dependent and reversible after dose reduction or discontinuation.⁵⁷ Elevation in liver enzymes to >8 times the upper limit of normal range occurred in 3% in those receiving 125 mg twice a day dose. Liver function tests must be performed at least once a month in those receiving bosentan. This drug is contraindicated in pregnancy due to its potential teratogenic effect. It is approved for use in NYHA/WHO functional class III and IV PAH patients in USA, Canada and Europe. The drug has become available in India but is quite expensive for long-term use for most Indian patients.

Sitaxsentan and ambrisentan

These drugs are specific ET_A receptor blockers and can be given orally once daily. Sitaxsentan was used in one RCT on 178 patients with PAH in NYHA class II, III or IV.⁶⁴ The drug was given over a period of 12 weeks. Improvement in exercise capacity, haemodynamics and clinical events was seen. The incidence of abnormal liver function test was 0% for 100 mg once daily and 9.5% for 300 mg once daily dose. Ambrisentan is currently being tested. It was shown to improve exercise capacity in ARIES I and ARIES II study.⁶⁵

Although hepatotoxicity seems to be less common in patients taking selective ET_A receptors antagonists, cases of acute hepatitis have been described. Hence liver functions should be constantly monitored.

There is currently no data to establish the benefit of one ETRA over the other. Patients may prefer Ambrisentan due to its daily dosing and lower incidence of hepatotoxicity.

Type 5 phosphodiesterase inhibitors

Sildenafil

Inhibition of type 5 phosphodiesterase leads to increased concentration of cyclic guanosine monophosphate (cGMP) in the smooth muscles of the vessels leading to vasodilatation. Sildenafil is an orally active, potent selective inhibitor of cGMP-phosphodiesterase type 5, increasing the intracellular concentration of cGMP. Since, this enzyme is present in high concentration in pulmonary vasculature, sildenafil can reduce PAP in patients with PAH.⁶⁶ Sildenafil proved to be a potent pulmonary selective vasodilator when used for treating PAH in animal experiments with very little fall in systemic pressure.⁶⁷ An acute vasodilatory effect on the pulmonary circulation was seen in patients with iPAH when combined with inhaled iloprost in the study by Wilkens and colleagues.⁶⁸ The fall in PVR was dose dependent in this study using intravenous sildenafil during right heart catheterisation. In another study, addition of sildenafil improved exercise capacity and pulmonary haemodynamics in patients who were deteriorating in spite of on-going inhaled iloprost therapy.⁶⁹ These encouraging findings led to several RCT. Some of the trials

Table 4

Studies on use of sildenafil in pulmonary artery hypertension.

Author/yr	Type of trial	No.	Duration	Improvement in		
				6MWT/Ex time	Func Cl	PAP
Kothari, 2002 ⁷⁰	Observational	14	7.3±2.4 mo	Y	Y	Y
Sastry, 2004 ⁷¹	RCT	22	6 wk	Y	Y	N
Bharani, 2003 ⁷²	RCT	9	2 wk	Y	N	Y
Singh, 2006 ⁷³	RCT	2	6 wk	Y	Y	Y
Galie, 2005 ⁷⁴ (SUPER)	RCT	278	12 wk	Y	Y	Y

Func Cl: Functional class (NYHA/WHO/others), N: No, PAP: pulmonary artery pressure, RCT: randomised controlled trial, Y: Yes.

with sildenafil are summarised in Table 4. An observational study from India showed improvement in 6MWT distance and fall in right ventricular systolic pressure in 14 cases with severe PAH treated with sildenafil.⁷⁰ The initial randomised controlled cross over trial carried out in 22 patients showed improvement in treadmill time, quality of life and cardiac output.⁷¹ Similar study by Bharani and colleagues also reported significant improvement in exercise capacity, but no significant improvement was found in the NYHA functional class.⁷² Similar results are reported in 20 patients in another study, also from India.⁷³ A much larger, double-blind, placebo-controlled randomised trial is reported in the New England Journal of Medicine in 2005.⁷⁴ In this multicentre Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study, 278 symptomatic patients with PAH (idiopathic associated with connective tissue disease or with operated left-to-right shunts) were enrolled. These were randomised to placebo or sildenafil (20 mg, 40 mg, or 80 mg) orally 3 times a day for 12 weeks. At the end of 12 weeks, 6MWT distance improved in all sildenafil groups. The mean placebo corrected treatment effects were 45 m (99% CI 21–70), 46 m (99% CI 20–72) and 50 m (99% CI 23–77) for 20 mg, 40 mg and 80 mg of sildenafil, respectively ($P < 0.001$ for all comparisons). The WHO functional class also improved in more patients on sildenafil than on placebo. Two hundred and twenty patients completed 1 year of treatment with sildenafil monotherapy and the improvement in 6MWT distance from baseline at 1 year was reported as 51 m. The PAP reduced and cardiac index improved with sildenafil. The drug was well tolerated with minor side effects. This study was not powered to assess mortality and there was no evidence of a dose-response relationship associated with the primary end points in the 12 weeks study. It is possible that the lower dose of 20 mg 3 times a day is good enough for complete inhibition of phosphodiesterase type 5. In the long-term, a smaller dose may not be desirable when using in combination with bosentan as bosentan decreases the plasma level of sildenafil.⁷⁵ SUPER-1 study was later extended as SUPER-2 study in which SUPER-1 subjects taking 80 mg sildenafil 3 times a day for at least 3 years were followed; the majority of these cases were in WHO functional class II–III.⁷⁶ One hundred and seventy patients completed both studies and were followed for a median of 1242 days. Sixty percent of these patients either improved or maintained

their functional class. Additional specific therapies were required in 3%, 10%, and 18%, at 1 year, 2 years, and 3 years, respectively. Those with a baseline 6MWT distance of < 325 m and did not improve in SUPER-1 during the first 12 weeks fared worse in terms of survival.

One study has compared bosentan with sildenafil.⁷⁷ Both drugs seem to be equally effective with a trend towards better improvement with sildenafil when 6MWT distance was compared.

Food and drug administration approved sildenafil for patients with PAH in any functional class only at a dose of 20 mg 3 times a day. Sildenafil can be recommended as first line drug in patients with PAH in India, where other modes of treatment like prostenoid therapy, endothelin antagonists and lung transplantation are either not available or are prohibitively expensive.

Recently intravenous preparation of sildenafil has become available and can be used for hospitalised patients who were on chronic oral sildenafil but are unable to take it orally.

In a recent open label study, the pharmacokinetic and pharmacodynamic effects of 10 mg of IV sildenafil were compared to 20 mg of oral sildenafil and were found to be similar.⁷⁸ tadalafil is another phosphodiesterase inhibitor which can be used once daily, data is emerging on the use of this drug.⁷⁹ It has recently been used in Public Health Institutional Review, Submission Tracking (PHIRST) trial (PAH and response to tadalafil). This trial was a 16-week, randomised, double-blind, placebo-controlled multicentre trial which studied the efficacy and tolerability of 4 doses of tadalafil on 405 PAH subjects with and without background bosentan therapy.⁸⁰ 40 mg of tadalafil had significantly reduced the incidence of clinical worsening and improved time to clinical worsening when compared to placebo. This drug improved exercise capacity in a dose dependent manner, but only the 40 mg dose met the pre-specified value for statistical significance of < 0.01 . Haemodynamics also improved with 40 mg of tadalafil, although this data was available for 93 patients only. Better results were noticeable in tadalafil naive patients.

Presently there is little to choose between tadalafil and sildenafil. Although once daily dosing with tadalafil is more appealing, most of clinical experience is with sildenafil.

Nitrates are contraindicated in patients treated with phosphodiesterase inhibitors.

The side effect profile for phosphodiesterase inhibitors includes headache, flushing, nasal congestion, dyspepsia, and myalgias, these effects are primarily due to the drug's vasodilatory effects.

Investigational therapies

Nitric oxide

Inhaled NO is a potent selective pulmonary vasodilator that directly relaxes vascular smooth muscle through stimulation of soluble guanylate cyclase and increased production of cGMP. Nitric oxide lowers pulmonary pressures, improves haemodynamics and has been used in critical care setting.⁸¹ However, its use has been limited by concerns regarding the toxicity of the gas and by the lack of a practical delivery system for long-term use.

L-arginine

L-arginine is essential in the production of NO and has been used for reducing PAP in some studies. Mehta et al. have reported a reduction in PAP and PVR with L-arginine.⁸² These beneficial results have not been seen in other studies.

Vasoactive intestinal peptide

Vasoactive intestinal peptide inhibits platelet activation and proliferation of smooth muscle cells acting as potent pulmonary vasodilator. In a small study, inhalation of this agent led to significant fall in PAP with functional improvement in 8 patients with iPAH.⁸³

Imatinib mesylate

Imatinib is a tyrosine kinase receptor blocker which prevents phosphorylation of PDGF and inhibits smooth cell proliferation. An animal study has reported its beneficial effect in reducing PAP in rat models with PAH.⁸⁴ Clinical improvement with increase in 6MWT distance was seen in one case which did not respond to iloprost, bosentan, and sildenafil.⁸⁵ Experience with this drug is limited to a few cases only in other reports also. An additional study evaluating the long-term safety and efficacy of imatinib in PAH is on-going

Riociguat

Since, the beneficial effects of phosphodiesterase inhibitors are mediated through soluble guanylate cyclase (sGC) and the second messenger cGMP, augmenting the NO pathway by direct stimulation of sGC can be another approach. Riociguat is such a drug that activates sGC independently of NO.⁸⁶ This drug has been used in a phase II study in PAH patients. The

drug appears promising as it improved 6MWT distance and haemodynamics. It was well tolerated.⁸⁷ Phase III trials are currently on-going.

Dichloroacetate

Dichloroacetate is another drug which has been used in experimental animals. It prevents and reverses monocrotaline-induced PAH in rats. It has been shown to partially regress established PAH in mice. A phase I trial of this drug is currently underway in patients with PAH who are in functional class III–IV and are stable on other specific drugs.⁸⁸

Other drugs

Statins may be useful by repressing vascular smooth muscle cell proliferation secondary to PDGF, as seen in rats with hypoxic PAH.⁸⁹ However, this drug has not been used in human beings. **Nikorandil** has been used as potassium channel abnormalities are known in patients with PAH.⁹⁰

Meta-analyses of drug therapy

Meta-analyses for drug treatment in PAH have been published. One was reported in 2007 which included 16 RCT and 1962 patients.⁹¹ According to their results, limited benefits were achieved for clinical end points, but no significant survival advantage could be demonstrated. A more recent meta-analysis addressed the all-cause mortality and survival.⁹² Twenty-three RCT were included, majority of patients were in WHO class III. A reduction of 43% in overall mortality was demonstrable in patients randomised to active drug treatment as compared to those randomised to the placebo arm (data from 21 trials). The benefit was seen with prostanoids, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors. Besides reduction in all-cause mortality, the functional class and haemodynamic parameters also improved in those on drugs.

Combination therapy

Current therapies for PAH target the three known intracellular pathways; NO, prostacyclin and endothelin, which are known to be abnormal in patients with PAH. Therefore, it appears logical to use a combination of two or more drugs which act on different pathways especially in cases with incomplete response to a single agent. This is similar to the situation in systemic hypertension where a combination of drugs acting on different pathophysiological mechanisms results in better control of blood pressure than monotherapy. It is also possible that one pathway may play a more dominant role than others in pathogenesis of PAH and one drug may be more effective than the others. One can start with one drug and add the second in those with incomplete response. Alternatively two drugs

combination may be used to begin with and a third drug added later in those with insufficient clinical and haemodynamic response. At present, the choice of the drug or the order in which drugs should be used is not clear due to lack of large trials addressing this issue. Combination therapy is also recommended by “Consensus statement on the management of pulmonary hypertension in clinical practice in UK and Ireland”.⁹³

The use of initial or “upfront” combination therapy has been suggested for WHO class IV PAH patients in recent guidelines.⁹⁴ However, there is limited data on the comparative efficacy of this strategy. The combination of sildenafil and inhaled iloprost was seen to cause more potent pulmonary vasodilation than either agent alone.⁶⁸ Similarly, patients who were deteriorating on iloprost therapy improved with addition of sildenafil.⁹⁵ Similarly adjunctive therapy with bosentan and intravenous prostacyclin produced favourable, though statistically non-significant, outcomes in a small study of 33 patients.⁹⁶ On the other hand, another report indicated that addition of long-term treatment with sildenafil had minimal effects on functional class and right heart failure in 13 patients already receiving vasodilators for PAH (calcium channel blockers, epoprostenol or bosentan).⁹⁷ There is no randomised trial addressing the issue of combination therapy in PAH. Non-randomised data from Hoeper et al. suggests that an approach using bosentan, sildenafil and iloprost in combination yields acceptable long-term results.⁹⁸ These authors called it a goal-oriented therapeutic strategy. The study included 123 patients with PAH. All of these were started on bosentan up to a maximum dose of 125 mg twice a day to achieve the therapeutic goals of: (a) a 6MWT distance >380 m; (b) a peak oxygen uptake >10.4 mL/min/kg; and (c) a peak systolic blood pressure during exercise of >120 mmHg. In those, not able to achieve these goals, sildenafil was added in a maximum dose of 50 mg 3 times a day. Similarly inhaled iloprost was given to the group which still did not achieve the therapeutic goals on combination of bosentan and sildenafil. Survival with this goal-oriented combination therapy was much better as compared to historic controls. A two drug combination was required in 43% and a three drug combination, in 16% of patients. Six patients did not achieve the desired goals even with triple drug regimen and were switched over to intravenous iloprost (5) or underwent lung transplantation (1). The combinations were well tolerated.

The strategy of sequential addition of drugs appears to be promising, although additional studies, preferably RCTs are needed to confirm these results. In countries like India, one needs to explore the benefits of combining calcium channel blockers with sildenafil, since bosentan and prostacyclines are either not available or are too expensive.

Interventional procedures

Balloon atrial septostomy

Observational and epidemiologic studies have shown that Eisenmenger's syndrome patients and patients with iPAH who have a patent foramen ovale had a better prognosis than

those without intracardiac shunting.^{99,100} Because of these observations atrial septostomy has been used for patients with disabling right heart failure. Blade balloon atrial septostomy was first reported by Rich in 1983 in patients with refractory PAH.¹⁰¹ The presence of an atrial septal defect allows right to left shunting which increases systemic output resulting in an increased systemic oxygen transport despite a fall in systemic arterial oxygen saturation. The shunt at atrial level also allows for the decompression of the right atrium and right ventricle with improvement in signs and symptoms of right heart failure. A study in children with iPAH has demonstrated a significant long-lasting benefit with clinical, haemodynamic and survival advantage following blade-balloon atrial septostomy.¹⁰² In adults, a large series is reported by Sandoval and colleagues from Mexico.¹⁰³ The atrial septum is first punctured percutaneously. The septal defect is then gradually dilated using balloon catheters with incremental diameter of 8–14 mm. Unfortunately, the procedure related mortality is high, varying from 5% to 15%. This high mortality may be due to the patient profile as this procedure is often done in severely ill cases as a palliative bridge to lung transplantation. According to Sitbon et al., a mean right atrial pressure >20 mmHg, PVR >55 units/m², and a predicted 1 year survival <40% are significant predictors of procedure related deaths.²⁸ Currently the indications for atrial septostomy may be recurrent syncope or right heart failure despite maximal medical therapy including intravenous prostacyclin's. This procedure may have more relevance in India since treatment with other modes of therapy, i.e. drugs and lung transplantation has limited scope. The data from the All India Institute of Medical Sciences by Kothari et al. reports improvement in clinical status and haemodynamic variables in 11 patients with severe PAH.¹⁰⁴ However, the procedure related mortality was high at 18.2%. Authors suggested that the procedure was high-risk in very sick patients and hence balloon atrial septostomy may be advocated early in the course of the disease. Atrial septostomy should be performed only in specialised centres to reduce procedure related risks.

Lung transplantation

For patients with PAH who cannot be managed medically, lung transplantation remains the ultimate alternative. Heart-lung, single lung and double lung transplantations have been performed successfully in patients with iPAH.^{105,106} These modes of treatment have been assessed in uncontrolled series since RCTs are unethical. Survival is reported to be 65%, 55%, and 44% at 1 year, 3 years, and 5 years, respectively.^{107,108} Lung transplantation is indicated in PAH patients with advanced functional class III and IV. The problem of donor shortage makes this mode of therapy relatively difficult even in western countries. Bilateral lung transplantation is generally preferred due to less postoperative complications. Functional recovery is generally good after lung transplantation, but long-term survival has been limited by the high prevalence of chronic allograft rejection.¹⁰³ No relapse of PAH has been reported.

The choice of whether to perform heart-lung or bilateral lung transplantation is largely dependent on centre policy and donor availability. Both techniques have a range of advantages and disadvantages, but overall survival rates have been reported to be similar. It is claimed that heart-lung transplantation is less likely to result in death from obliterative bronchiolitis.¹⁰⁹ Generally, heart-lung transplantation is performed when there is either significant impairment of cardiac function (inotrope dependence) or PAH is secondary to a complex congenital heart disease.¹¹⁰

Treatment algorithm

Treatment algorithm have been published for WHO functional class III and IV patients based on the grade of recommendation and the level of evidence as derived by the clinical trials. However, very little data is available for class I and II patients on the most appropriate treatment strategy. Perhaps calcium channel blockers should be used in those who show vasoreactivity in the cardiac catheterisation lab, as these drugs are relatively safer.

Before initiating treatment, all efforts should be made to diagnose the underlying condition which may be responsible for PAH in a given case.

The suggested approach includes the adoption of general measures as described earlier and initiation of therapy with oral anticoagulants (if no contraindication), diuretics (if fluid retention), supplemental oxygen (if hypoxaemia) and digoxin (in those with refractory right heart failure and/or supraventricular arrhythmias). All such patients should be referred to a specialised centre for treatment. Acute vasoreactivity testing should be undertaken and the patients with positive response should be treated with maximal tolerated dose of calcium channel blockers. The dose should be increased in a stepwise fashion.

Non-responders who remain in functional class III or IV should be considered for treatment with bosentan or prostanoïd. In India, perhaps sildenafil should be the first drug to be used in non-responders. For class IV patients, intravenous epoprostenol is recommended as survival benefit has been demonstrated with this drug. Combination therapy is recommended for those who fail to improve on monotherapy. In children who respond to a specific treatment, the survival is usually better than in adults. On the other hand, if they fail to respond to the available drugs, their survival is often shorter than that of adults.

In an earlier issue of the European Respiratory Review, a strategy of goal-oriented therapy has been recommended.¹¹¹ In this review, prognostic indicators of survival are used as treatment targets. Setting of WHO functional class II rather than class III as a treatment goal is likely to improve survival. Hence, it is important to escalate therapy even if a given case has improved from class IV to III. A future treatment trend may be to start therapy upfront with double or triple combination therapy, more so for patients in the advanced stage of the disease who represent a particularly challenging population.

Balloon atrial septostomy and/or lung transplantation are indicated for refractory PAH cases or where medical treatments are unavailable. These procedures should be done in centres with expertise available. Again, balloon atrial septostomy may have a more important role in our setup, especially for cases with recurrent syncope, if their oxygen saturation is good. The suggested treatment algorithm for Indian patients is shown in the Figure 1.

Prognosis

The natural history has been significantly modified by available therapies. In a recent study of American and French cohorts,

Figure 1 Treatment algorithm.

3-years survival rates have increased to 58–72%.^{112,113} In general, PAH secondary to connective tissue diseases, particularly systemic sclerosis, have a worse prognosis than those with idiopathic PAH. Those with PAH due to congenital heart disease have a better prognosis.

Conclusion

Presently PAH is an incurable condition and is generally diagnosed late in the course of the disease. Pulmonary artery hypertension is not a diagnosis per se and it is necessary to fully evaluate all such patients to rule out an underlying cause which may be amenable to successful treatment. Several effective treatments are available, but a step wise treatment strategy must be applied. All patients require a careful on-going clinical assessment to determine if the drug dosage needs to be increased or use of additional modality of treatment is required. Over the past several decades, our understanding of pathophysiology has improved. This has led to introduction of new drugs and regimens, which have been tested in RCTs. Increasing data is emerging for use of upfront combination therapy using a drug from each class of drug rather than sequential therapy, especially for those in WHO functional class III or IV.

The on-going research in multiple directions is likely to result in emergence of advances in the diagnosis, treatment and prognosis for this devastating disease in the next decade. However, much more research is required to assess the impact of drug therapy over long-term follow-up.

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