Two years of multidisciplinary diagnostic and therapeutic experience in patients with pulmonary arterial hypertension

Pulmoner arter hipertansiyonunda multidisipliner yaklaşımla iki yıllık tanı ve tedavi deneyimimiz

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Objectives: Information is limited on the prognosis of patients with pulmonary arterial hypertension (PAH) in Turkey. We evaluated our multidisciplinary diagnostic and therapeutic experience in PAH patients.

Study design: The study included 51 patients (32 women, 19 men; mean age 45.4±9.7 years) who were prospectively monitored during a two-year period by the PAH Working Group in our hospital. The diagnoses were as follows: idiopathic/familial PAH (n=9); PAH associated with connective tissue disease (n=16), and with congenital heart disease (n=11); pulmonary veno-occlusive disease (n=1); chronic thromboembolic pulmonary hypertension (n=10), and other causes (n=4). The patients were assessed every three months by clinical examination, six-minute walk test, transthoracic echocardiography, and BNP levels.

Results: The mean pulmonary artery pressure was 54.7±18.8 mmHg. Functional capacity was NYHA class II in nine patients (17.7%), class III in 28 patients (54.9%), and class IV in 14 patients (27.5%). Thirty-seven patients (72.6%) received treatment with specific pharmacologic agents, in whom 19 patients (51.4%) required modifications during treatment. Nine patients (17.7%) benefited from treatment with decreases of at least one NYHA class, whereas NYHA class remained unchanged in 25 patients (49%). Seventeen patients (33.3%) exhibited clinical deterioration, of whom 11 died with an overall mortality of 21.6%. Patients who died were all in NYHA class III or IV and significantly differed from those who survived with respect to mean pulmonary artery pressure (72.5±18.7 mmHg vs. 49.8±21.2 mmHg), BNP level at the time of diagnosis (293.8±88.3 pg/ml vs. 141.6±62.1 pg/ml), and six-minute walk distance (123.8±41.3 m vs. 200.7±52.1 m) ($p<0.05$).

Conclusion: Despite relative improvements in the end points over the last two decades, PAH is detected late in the course of the disease, resulting in severe functional and hemodynamic problems in the majority of patients.

Key words: Hypertension, pulmonary/etiology/therapy; Turkey/epidemiology; treatment outcome.

Amaç: Ülkemizde pulmoner arter hipertansiyonlu (PAH) hastaların prognozuna ait veriler sınırlıdır. Bu çalışmada, multidisipliner yaklaşımla ileriye dönük olarak takip edilen PAH'li hastalarda tanı ve tedavi deneyimimiz değerlendirildi.

Çalışma planı: Hastanemizin Pulmoner Hipertansiyon Çalışma Grubu tarafından iki yıl boyunca ileriye dönük olarak izlenen 51 hasta (32 kadın, 19 erkek; ort. yaş 45.4±9.7) çalışmaya alındı. Hastaların tanı dağılımı şu şekildeydi: İdiyopatik/ailesel PAH (n=9), bağ doku hastalıkları ile ilişkili PAH (n=16), doğuştan kalp hastalıkları ile ilişkili PAH (n=11), pulmoner venookluziv hastalık (n=1), kronik tromboembolik pulmoner hipertansiyon (n=10) ve diğer nedenler (n=4). Hastalar üç ayda bir klinik olarak ve altı dakika yürüme testi, transtorasik ekokardiyografi ve BNP düzeyleriyle değerlendirildi.

Bulgular: Ortalama pulmoner arter basıncı 54.7±18.8 mmHg bulundu. Tanı anında fonksiyonel kapasite dokuz hastada (%17.7) NYHA sınıf II, 28 hastada (%54.9) sınıf III, 14 hastada (%27.5) sınıf IV idi. Otuz yedi hastaya (%72.6) spesifik farmakolojik ajanlar ile tedavi uygulandı. On dokuz hastanın (%51.4) tedavisinde değişiklik yapıldı. Dokuz hastada (%17.7) tedaviyle NYHA sınıfında en az bir basamak azalma görülürken, 25 hastanın (%49) fonksiyonel kapasitesinde değişiklik olmadı. On yedi hastada (%33.3) klinik kötüleşme izlendi ve bu hastaların 11'i (toplam grubun %21.6'sı) kaybedildi. Ölen tüm hastaların NYHA fonksiyonel kapasitesi sınıf III-IV idi. Ölen ve yaşayan hastalar arasında ortalama pulmoner arter basıncı (72.5±18.7 mmHg ve 49.8±21.2 mmHg), tanı anındaki BNP düzeyi (293.8±88.3 pg/ml ve 141.6±62.1 pg/ml) ve altı dakika yürüme mesafesi (123.8±41.3 m ve 200.7±52.1 m) anlamlı derecede farklılık gösterdi ($p<0.05$).

Sonuç: Son 20 yılda sonlanım noktalarında iyileşmelere rağmen PAH tanısı hastalığın ancak geç döneminde konmakta ve hastaların çoğunluğunda şiddetli işlevsel ve hemodinamik sorunlar yaratmaktadır.

Anahtar sözcükler: Hipertansiyon, pulmoner/etyoloji/tedavi; Türkiye/epidemiyoloji; tedavi sonucu.

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Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterized by a progressive increase in pulmonary artery pressure (PAP) and pulmonary vascular resistance.[1,2] In the last decade, improvements in pathogenesis and treatment of PAH which is associated with a poor prognosis have aroused great interest and new expectations.[1] Pulmonary hypertension (PH) is defined as a mean PAP of >25 mmHg at rest, or of >30 mmHg during exercise.[1,3] It most frequently develops in association with cardiac or pulmonary diseases. Other reasons include chronic thromboembolic pulmonary hypertension and connective tissue diseases. Despite limited epidemiological data regarding the incidence of pulmonary hypertension, idiopathic pulmonary arterial hypertension has been reported to be the main cause of PAH in France and Switzerland, while connective tissue diseases have been reported to be the most common cause of PAH in Scotland.[4,5]

Cardiac diseases lead to PH by increasing pulmonary blood flow or venous pressure, while pulmonary diseases result in PH through compression and distortion of the arterioles, hypoxic vasoconstriction and intravascular obstruction.[1,3,6] Idiopathic PAH is more common in middle-aged women, whereas the incidence of chronic thromboembolic PH is higher in men. Small muscular pulmonary artery and arteriolar damage, which leads to intimal proliferation, are among the causes of idiopathic PAH. Endothelial dysfunction, functions of ion channels, calcium homeostasis, changes in the platelet-endothelial interaction, intravascular thrombosis, increased vascular reactivity, proliferation, remodeling, progressive obliterative vasculopathy are the other factors which play a role in the pathogenesis of idiopathic PAH.[1,3,6] Fatigue and dyspnea may be initial complaints, however, they may be overlooked in the absence of high level of clinical suspicion. Angina-like pain may also present with dyspnea in some cases.[1] Diagnosis is very difficult at the early stages of the disease.

As pulmonary arterial hypertension is a multifactorial clinical condition, a multidisciplinary approach is required for diagnosis and treatment of the disease. There is limited information about the treatment and prognosis of the patients with PAH in Turkey; however, an archiving system for PAH is currently being developed. In this study, the two-year multidisciplinary follow-up, mortality and morbidity rates of patients were evaluated by the Pulmonary Hypertension Working Group of our hospital.

PATIENTS AND METHODS

The Pulmonary Hypertension Working Group, which initiated its work in March, 2007, was formed by members of the departments of adult cardiology, pulmonary medicine and cardiovascular surgery, divisions of rheumatology and intensive care unit of the department of internal medicine, division of cardiology of the department of pediatrics, and the department of physical therapy and rehabilitation.

The study included 51 patients (32 women, 19 men; mean age 45.4±9.7 years) who were prospectively monitored during a two-year period (March 2007-March 2009). Diagnosis which was not found to be adequate by echocardiography was confirmed by right cardiac catheterization in all patients. Heart rate, respiratory rate, body temperature, blood pressure, arterial oxygen saturation by pulse oximetry and ECG monitoring were performed before and after the procedure. Right cardiac catheterization was performed using the Swan-Ganz catheter. The mean right atrial pressure, right ventricular end-systolic and end-diastolic pressures, pulmonary arterial end-systolic and diastolic pressures, and central venous oxygen saturation were recorded. Pulmonary vascular resistance was calculated using these data. Cardiac output was measured by the thermodilution technique. Vasoreactivity testing with adenosine was performed on all patients. Complete blood count, liver function tests, thyroid function tests, hematological and serological assays (anti-HIV antibodies, anti-phospholipid antibodies, anti-nuclear antibodies, anti-centromere antibodies, anti-SCL 70 and ribonucleoproteins), pulmonary function tests, arterial blood gas analysis, nocturnal pulse oximetry, chest CT scan, ventilation/perfusion scintigraphy, and abdominal ultrasonography were used in the differential diagnosis.

Patients were classified based on the Venice Classification were as follows: idiopathic/familial PAH (n=9); PAH associated with connective tissue disease (n=16), and with congenital heart disease (n=11); pulmonary veno-occlusive disease (n=1); chronic thromboembolic pulmonary hypertension (n=10), and other causes (n=4). The patients were assessed every three months for a period of two years with evaluation of symptoms, six-minute walk test, transthoracic echocardiography, and BNP levels. Information about the cause of deaths occurring out of our hospital was obtained from the relatives.

Statistical analysis. Statistical analysis was performed using the SPSS program (version 15.0 for Windows). Data were expressed in mean±standard deviation (SD), establishing the smallest and largest values. The Kruskal-Wallis test was performed to compare PAH groups with different etiologies due to non-parametric properties of data. The Mann-Whitney U test was used for the comparison of continuous variables of

Table 1. Clinical characteristics of the patients

	Causes of Pulmonary arterial hypertension				Total
	Idiopathic (n=9)	Chronic thromboembolic (n=10)	Congestive heart disease (n=11)	Connective tissue diseases (n=16)	
Age	47.0±8.3	55.0±4.0	32.6±7.3	47.1±6.1	45.4±9.7
Pulmonary artery pressure					
Systolic (mmHg)	75.7±25.4	97.2±27.8	87.0±23.6	61.8±16.2	81.5±27.8
Mean (mmHg)	53.8±21.1	65.4±21.8	58.4±14.5	44.7±10.2	54.7±18.8
Diastolic (mmHg)	38.5±16.9	43.4±16.5	40.6±14.4	30.9±10.7	38.9±14.9
Six-minute walk test (m)	161.4±42.1	193.8±51.3	201.4±51.9	159.1±39.0	184.3±46.7
BNP level (pg/mL)*	140.4±72.1	203.8±58.1	129.1±39.0	191.4±51.9	174.3±66.7
Percent and number of patients died	1 (11.1%)	5 (50%)	-	4 (25%)	11 (21.6%)**

*BNP levels at the time of diagnosis; **One patient died due to other causes-related PAH.

patients who died or survived. P <0.05 was considered as statistical significant.

RESULTS

Clinical characteristics of the patients are shown in Table 1. In terms of mean age, the patient group with PAH associated with congestive heart disease was the youngest patient population (32.6±7.3), while the oldest group included patients with chronic thromboembolic PH (55±4). Connective tissue diseases were the most common cause of PAH (16 patients, 31.4%). Of these, 12 patients with systemic sclerosis, two patients with rheumatoid arthritis, one patient with rheumatoid arthritis and Sjogren's syndrome, and one patient with scleromyxedema were being followed-up. Only one patient had familial PAH in the idiopathic/familial PAH group. Also, 10 patients had ventricular septal defect, while one had atrial septal defect in the PAH associated with congestive heart failure group. Three of the patients with ventricular septal defect had previously undergone corrective surgery. Two of the four patients with PAH due to other causes had high PAP which was inconsistent with parenchymal lung disease. One of the patients was being followed-up for the preliminary diagnosis of sarcoidosis, while one patient had chronic liver disease and portal hypertension. In the chronic thromboembolic PH group, one patient was diagnosed with antiphospholipid syndrome, while one was diagnosed with systemic lupus erythematosus and antiphospholipid syndrome. One patient was also being follow-up for systemic sclerosis.

The mean PAP was found to be 54.7±18.8 mmHg in all patients. Patients with thromboembolic PH had the highest level of PAP (65.4±21.8 mmHg), while patients with PAH associated with connective tissue diseases had the lowest level (44.7±10.2 mmHg).

The functional capacity at diagnosis was NYHA class III in most of the patients (n=28, 54.9%), class II in nine patients (17.7%), and class IV in 14 patients (27.5%).

The mean six-minute walk test distance was found to be 184.3±46.7 m. Patients with PAH associated with congestive heart disease had the highest value of the test (201.4±51.9 m), while patients with PAH associated with connective tissue diseases had the lowest value (159.1±39.0 m). At the time of diagnosis, patients with chronic thromboembolic PH (203.8±58.1 pg/mL) had the highest BNP levels (203.8±58.1 pg/mL), while patients with PAH associated with congestive heart failure were found to have the lowest BNP levels (129.1±39.0 pg/mL).

The vasoreactivity test result was positive in four patients (7.8%) including one with rheumatoid arthritis and three with idiopathic PAH. A total of 37 patients (72.6%) were given treatment with specific pharmacologic agents (bosentan, sildenafil, iloprost, or epoprostenol). Six of them (16.2%) were in the idiopathic/familial PAH group, 14 (37.8%) in the PAH associated with connective tissue diseases group, six (16.2%) in the PAH associated with congestive heart disease group, one (2.7%) in pulmonary veno-occlusive disease, three (8.1%) in the other causes of PAH group, and seven (18.9%) were in the chronic thromboembolic PH group. Treatment modification was permitted for 19 patients (51.4%) through out the follow-up period. A total of 28 patients (75.7%) received one drug, while nine of the patients (24.3%) were given multi-drug treatment (sildenafil and iloprost for two patients; bosentan and sildenafil for two patients; bosentan and iloprost for two patients, bosentan, iloprost and sildenafil for three patients). Patients who were given multi-drug treatment had previously received monotherapy (bosentan for four patients; iloprost for three patients; sil-

denafil for two patients). Sildenafil was initiated for one of the patients with the diagnosis of pulmonary veno-occlusive disease. Due to the absence of any clinical improvement, the patient was given imatinib which was reported in only one case report in the literature.[7] However, no significant clinical benefit was obtained.

One of the patients with familial PAH was scheduled for transplantation abroad. Three of the 10 patients with thromboembolic PH were eligible for endarterectomy. One of the patients died before the surgery; the functional capacity of NYHA class IV regressed to NYHA class II in one of the remaining two patients, while the patient in NYHA class IV was reported dead in early stages after surgery.

Functional capacity improved with treatment (at least one class regression) in nine of the patients (17.7%), whereas no significant difference was observed in the functional capacity of 25 patients (49%). The clinical condition worsened in 17 patients (33.3%), 11 of whom (21.6% of the whole group) died. All death events were due to causes associated with PAH/chronic thromboembolic PH. In addition, one of the patients died after surgery, while two were reported to die by sudden death. Exacerbation of symptoms of right heart failure also accounted for death events in eight of the patients (72.7%). One of the patients was receiving treatment for urinary tract infection, while one of them was receiving treatment for pneumonia. Distribution of patients who died according to the disease groups is given in Table 1. On the other hand, no death event was reported in patients with PAH associated with congestive heart disease.

The functional capacity was NYHA class III or IV in all patients who died, with a mortality rate of 26.2%. Comparison of patients who died and those survived demonstrated that there was no difference between the groups in terms of mean age (45.7±8.0 and 45.3±8.9) and sex (7 females-4 males and 25 females-15 males); however mean PAP (72.5±18.7 mmHg and 49.8±21.2 mmHg; $p<0.05$) and BNP levels at the time of diagnosis (293.8±88.3 pg/mL and 141.6±62.1 pg/mL; $p<0.05$) were significantly higher, while the six-minute walk distance (123.8±41.3 m and 200.7±52.1 m; $p<0.05$) was shorter in the patients who died.

DISCUSSION

Despite great advances of treatment of PAH in the past 10 years, the prognosis of the disease is still poor. All studies which have been conducted so far have reported a poor prognosis and the need for additional treatment modalities.[8,9] Similarly, approximately one fifth of the patients died during the follow-up period, while treatment modification was required in half of the patients in our study. These data confirmed the poor prognosis and progressive course of PAH.

Starting treatment at and early stage or concomitant use of new pharmacological agents are the treatment strategies which are still a matter of debate in the clinical prognosis of PAH. Multi-drug treatment regarding the dynamic follow-up of the patients as well as clinical and hemodynamic targets is suggested to increase the success rate of treatment.[9] However, there is limited data on multi-drug treatment in PAH. Although concomitant use of phosphodiesterase inhibitors, endothelin-1 receptor antagonists and prostaglandin analogues produced positive results, these treatments were administered in only a small group of patients and the results were not significant.[1,6]

A randomized controlled trial with bosentan, the endothelin-1 receptor antagonist, demonstrated that early treatment might prevent exacerbation of the disease in patients with functional capacity in NYHA class II.[10] Recently published treatment guidelines recommend using sildenafil both in patients with functional capacity of NYHA class II and III.[2,6] However, there are still questions to be answered. Similar to our study, majority of the patients were diagnosed in the late stage of the disease in a multicenter study conducted in 17 centers in France and including 674 patients. The results showed that the functional capacities of NYHA class remained unchanged in patients who were diagnosed 20 years later.[11] In addition, 68% of patients with PH were reported to have functional capacities of NYHA class III-IV at the time of diagnosis in a study conducted by Kayikcioglu and Kultursay.[12] It seems almost impossible to diagnose PAH at the early stage due to the indistinctive nature and late-onset of symptoms. Echocardiography is considered to be a reasonable diagnosis technique in the risk group of patients, and an annual echocardiography is currently recommended only in patients with systemic sclerosis for PAH screening. Genetic counseling should also be considered for relatives of the patients with idiopathic and familial PAH. [1,6]

Pulmonary arterial hypertension is a clinical presentation associated with a heterogeneous group of diseases. The current data about the efficacy of existing pharmacologic agents are mostly obtained from the patients with idiopathic PAH. The majority of our patients have PAH associated with connective tissue diseases. This difference in distribution of the patients may be explained by the tertiary nature of our center. In our study, the majority of death events were observed in patients with PAH associated with connective tissue di-

sease and in those with chronic thromboembolic PH. This data is consistent with the literature.[13,14] Higher levels of BNP at the time of diagnosis in patients of these two groups compared to others support the finding suggesting that right heart failure is in the advanced stages of the diseases. In addition, the six-minute walk test distance was shorter in patients with PAH associated with connective tissue diseases, compared to others. The significant difference between patients who died and those who survived in terms of mean PAP, BNP levels at the time of diagnosis and six-minute walk test distance may be explained by the advanced stage of right heart failure and late diagnosis of the disease in patients who died.

The success rate of treatment is known to be higher in patients with idiopathic PAH.[1,6] Heterogeneity of the diseases should be considered in respect of initiating treatment at an early stage. Right ventricular functions are preserved longer and disease progression is slower in patients with PAH associated with congenital heart disease compared to others.[15] This finding may suggest that treatment initiation may vary in the various patient groups. The lowest level of BNP and highest level of six-minute walk test distance in patients with PAH associated with congestive heart diseases support the finding that the prognosis is better in these patients compared to others. In addition, no death event was observed in this patient group during the follow-up period.

Pulmonary thromboembolism and deep vein thrombosis are common clinical presentations. Only 0.1%-0.5% of the patients with pulmonary thromboembolism are considered to experience chronic thromboembolic PH.[16] Other risk factors for the development of chronic thromboembolic PH include ventriculoatrial shunt, infected pacemakers, splenectomy, positive anti-phospholipid antibodies, and high level of factor VIII.[17] Pulmonary arterial hypertension and chronic thromboembolic PH are considered to have common pathogeneses,, and it is suggested that patients may benefit from similar treatments.[13] Although endarterectomy remains the most effective approach in the treatment of chronic thromboembolic PH, patients should be assessed cautiously with regards to surgery.[17] In our study only three patients were eligible for surgery, and one of the two patients who underwent surgery was reported to have clinical improvement. The effects of the new pharmacologic agents before and after surgery are being investigated. Transplantation is also an important option in patients with PAH or chronic thromboembolic PH refractory to treatment. However, there is currently a limited number of centers which perform the intervention and on a limited number of patients.[1,6]

In conclusion, many issues are still to be clarified concerning the diagnosis and treatment of rare and high mortality PAH. Studies which have so far been conducted show a significantly poor clinical prognosis in the majority of the patients and there is a need for additional treatment. Although diagnosis in the early stages of the disease is critical in the treatment of pulmonary hypertension, most of the patients are only able to be diagnosed in the late stages of the disease. Although effective treatments are available, it is obvious that long-term placebo controlled studies cannot be conducted in this patient population with a high mortality rate. Highly prognostic parameters and methods are required to better assess the response to treatment in further studies. It is important to collect highly reliable data at this stage of the disease to overcome challenges which are encountered during treatment. A multidisciplinary approach in the diagnosis, treatment, and follow-up will increase the success rate of PAH treatment in experienced centers.

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