Respiratory Medicine 131 (2017) 215–219

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Efficacy and safety of long-term imatinib therapy for patients with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis

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ARTICLE INFO

Article history:
Received 3 March 2017
Received in revised form
26 August 2017
Accepted 31 August 2017
Available online 12 September 2017

Keywords:
Epoprostenol
Hemodynamics
HRCT
Pulmonary arterial pressure
Survival
Treatment

ABSTRACT

Background: Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are categorized as Group 1′ in the clinical classification of pulmonary hypertension. No medical therapy has been proven to be effective in patients with PVOD/PCH. Imatinib is a molecular targeted drug and was expected to be effective in patients with pulmonary arterial hypertension. We evaluated its efficacy and safety in patients with PVOD/PCH.

Methods: In the present observational study, 9 patients with PVOD/PCH received imatinib. Clinical data including exercise capacity and hemodynamics at baseline and at follow-up were compared. Survival rate of patients treated with imatinib was compared to those of 7 patients who did not treated with imatinib.

Results: Imatinib was prescribed at doses of 100–400 mg/day and was well-tolerated. At follow-up, World Health Organization functional class and brain natriuretic peptide levels significantly improved. Mean pulmonary arterial pressure was significantly reduced (from 56.8 ± 8.3 to 43.7 ± 9.0 mmHg) with preserved cardiac index. Patients were treated with imatinib for 797.2 ± 487.0 days. Seven patients (77.8%) died and 2 patients (22.2%) underwent lung transplantation. Mean survival time in patients treated with imatinib therapy was 1493.7 ± 196.3 days (95% confidence interval, 1108.9–1878.5 days), significantly longer than those without imatinib treatment (713.0 ± 258.1 days, log-rank test, $P = 0.04$).

Conclusions: Imatinib improved exercise capacity, hemodynamics and survival in patients with PVOD/PCH. In patients with PVOD/PCH, who have no effective medical therapy available, imatinib might function as a bridge to lung transplantation, and may become a potential therapeutic option to improve their survival.

1. Background

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are rare causes of pulmonary hypertension, categorized as Group 1′ in the clinical classification of pulmonary hypertension [1]. The prevalence of PVOD/PCH is reported to be low, but histological examination revealed that 10% of patients clinically diagnosed with pulmonary arterial hypertension (PAH) had PVOD [2]. No medical therapy has been proven to be effective in patients with PVOD/PCH. PAH-targeted drugs may lead to pulmonary edema in patients with PVOD/PCH. Careful introduction of epoprostenol was reported to potentially improve patients' exercise capacity; however, the effect is limited and temporal [3,4]. Although lung transplantation is the only cure, many patients cannot survive until suitable organs become available because of the poor prognosis [5]. Disease progression is rapid and prognosis is reported to be worse than that of PAH. There is an urgent need for effective treatment of PVOD/PCH.

Imatinib is a tyrosine kinase inhibitor, which was expected to be effective in patients with PAH [6]. In a clinical trial in patients with advanced PAH treated with ≥2 PAH-targeted drugs, imatinib improved exercise capacity and hemodynamics [7]. Though, because of serious adverse effects including subdural hematoma,

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http://dx.doi.org/10.1016/j.rmed.2017.08.032
0954-6111/

Abbreviations

PVOD	pulmonary veno-occlusive disease
PCH	pulmonary capillary hemangiomatosis
PAH	pulmonary arterial hypertension
WHO	World Health Organization
6MWD	6-min walk distance
BNP	brain natriuretic peptide
HR	heart rate
SpO_2	oxygen saturation
mPAP	mean pulmonary arterial pressure
SvO_2	mixed venous oxygen saturation
PVR	pulmonary vascular resistance
CI	confidence interval

imatinib is not approved for PAH. Since patients with PVOD/PCH have no effective treatment available, we performed an observational study to evaluate the efficacy and safety of imatinib in patients with PVOD/PCH.

2. Methods

2.1. Patient selection

We prescribed imatinib to patients with PVOD/PCH beginning in March 2007. Imatinib was initiated at a dose of 100 mg/day. One month later, tolerability and adverse effects were evaluated and if the patients were considered to be tolerant, the dose could be increased by 50–100 mg/day. Maximum dose was 400 mg/day. The study protocol was approved by the Institutional Review Board of the National Hospital Organization Okayama Medical Center. Written informed consent was obtained from patients. Patients who were given imatinib under this protocol for more than 30 days were considered as patients in imatinib group.

2.2. Diagnosis of PVOD/PCH

First, diagnosis of pulmonary hypertension was made according to a standard diagnostic algorithm including physical examination and right heart catheterization [1,8,9]. And then, clinical diagnosis of PVOD/PCH was established by the clinical impression of treating physicians based on clinical characteristics known to suggest PVOD/PCH [2,10]. Presence of radiological abnormalities characteristic of PVOD/PCH on HRCT (centrilobular ground glass opacity, mosaic pattern, interlobular thickening), low diffusion capacity for carbon monoxide in pulmonary function tests, low oxygen saturation, severe desaturation during exercise, and mismatch of ventilation-perfusion scans suggests PVOD/PCH. Pulmonary edema after PAH-targeted therapy is specific to PVOD/PCH. Pathological diagnosis of PVOD/PCH was subsequently confirmed in 9 of 16 cases by autopsy or lung transplantation.

2.3. Data collection

We collected and compared patients' clinical and hemodynamic data before versus after application of imatinib in patients treated with imatinib. World Health Organization (WHO) functional class, 6-min walk distance (6MWD), plasma levels of brain natriuretic peptide (BNP), heart rate (HR), oxygen saturation (SpO_2), and hemodynamic parameters (right atrial pressure, pulmonary artery wedge pressure, mean pulmonary arterial pressure [mPAP], cardiac index, mixed venous oxygen saturation [SvO_2], and pulmonary vascular resistance [PVR]) were evaluated. Baseline characteristics were also compared between imatinib group and non-imatinib group. Three of the included patients (1 in the imatinib group and 2 in the non-imatinib group) were presented previously elsewhere [4,11].

2.4. Survival analysis

The follow-up period for analyses of survival data ended in July 2016. Patients who underwent lung transplantation were censored at the time of operation. Survival was compared between the imatinib and non-imatinib groups.

2.5. Statistical analyses

Results are expressed as the mean ± standard deviation, unless otherwise specified. Continuous parameters between groups were compared using Student's t-test or Mann-Whitney's *U* test. Categorical variables between groups were compared using chi-square test or Wilcoxon signed rank test.

Survival analyses were conducted using the Kaplan-Meier method. Survival time is expressed as mean ± standard error (95% confidence interval [CI]). Differences between survival curves were assessed using the log-rank test. All analyses were performed with IBM SPSS 20 (IBM, Armonk, NY, USA). Statistical significance was defined as $P < 0.05$.

3. Results

3.1. Patient characteristics at baseline

There were 9 patients with PVOD/PCH in imatinib group and 7 patients in non-imatinib group. Table 1 reports patients' characteristics. There were predominantly male patients included in the study, and the mean patient age was in the 40 s at the time of diagnosis. More than half of patients had a smoking history. Two patients had connective tissue disease: one with systemic sclerosis and one with Sjögren's syndrome. At baseline, all patients were diagnosed with WHO functional class III or IV. Hemodynamic parameters were severely impaired, with mPAP greater than 60 mm Hg and PVR >1000 dyn s/cm^5. In 7 patients in the non-imatinib group, baseline characteristics were not significantly different from those of the imatinib group.

3.2. Efficacy of imatinib

In imatinib group, follow-up data were obtained at 347.3 ± 183.0 days after initiation of imatinib treatment. Imatinib was prescribed at a mean dose of 216.7 ± 90.1 (100–400) mg/day, representing a relatively low dose. At follow-up, WHO functional class and BNP were significantly improved (Table 1 and Fig. 1). mPAP was significantly reduced with preserved cardiac index. Patients in non-imatinib group did not undergo scheduled evaluation and data could not be obtained at the same time period as imatinib group. Concomitant treatment regimens are shown in Table 2. For non-imatinib group, maximum treatment regimen of each patient was obtained. At baseline, all patients were on PAH-targeted drugs, indicating they were treatment resistant. At follow-up, more patients in both groups were on PAH-targeted drug combination therapy.

3.3. Safety and tolerability

All patients tolerated imatinib at follow-up. Patients were