Case Report

Long-term effect of low-dose imatinib therapy for pulmonary hypertension due to chronic degenerative mitral valve disease in six dogs

Zi Ping Leong[1,2] Shinji Arita[3] Yoshiaki Hikasa[1,2*]

Abstract

Six dogs were diagnosed with pulmonary hypertension (PH) secondary to chronic degenerative mitral valve disease (CDMVD) on echocardiography. Imatinib (3 mg/kg, every 24 hours, PO) was initiated without any changes to the background therapy to treat the PH. Follow-up evaluations at 1, 3, 5 and 6 months revealed substantial clinical and hemodynamic improvements. One dog showed deterioration after the imatinib withdrawal to necessitate a restart therapy. No side effects were observed throughout the 6-month treatment course. Low-dose imatinib may provide a promising treatment alternative for CDMVD-associated PH in dogs.

Keywords: chronic degenerative mitral valve disease, low-dose imatinib, pulmonary hypertension

[1]*The United Graduate School of Veterinary Science Yamaguchi University, 1677-1 Yoshida, Yamaguchi 753-8515, Japan*
[2]*Laboratory of Veterinary Internal Medicine, Joint Department of Veterinary Medicine, Faculty of Agriculture, Tottori University, 4-101 Koyama Minami, Tottori 680-8553, Japan*
[3]*Arita Sougo Animal Hospital, 1-14-6 Nishi, Hachihonmatsu, Higashihiroshima-shi, Hiroshima 739-0147, Japan*
***Correspondence**: hikasa@muses.tottori-u.ac.jp*

Introduction

Chronic degenerative mitral valve disease (CDMVD) is the most common canine heart disease. It occurs in one-third of dog population aged more than 10 years old (Reynolds et al., 2012) and commonly results in post-capillary pulmonary hypertension (Kellihan and Stepien, 2010). The current therapy for canine PH depends mainly on vasodilating phosphodiesterase V inhibitors such as sildenafil (Kellihan and Stepien, 2010). Nevertheless, an effective treatment for PH is often hampered by the lack of a direct anti-remodeling property of the therapeutic agents.

In the past years, platelet-derived growth factor (PDGF) (Schermuly et al., 2005; Pankey et al., 2013) and c-KIT (Montani et al., 2011) receptors have been recognized to play a pathogenic role in the PH development. Imatinib, a tyrosine kinase inhibitor targeting PDGF and c-KIT receptors, reverses pulmonary and right ventricular (RV) remodeling (Schermuly et al., 2005; Pankey et al., 2013; Leong et al., 2018) and exhibits systemic and pulmonary vasodilatory effects (Pankey et al., 2013; Maihöfer et al., 2017) in rats. However, studies using a high imatinib dose (200 to 400 mg) in human PH patients have yielded controversial outcomes (Ghofrani, 2005; Ghofrani et al., 2010; Shah et al., 2015).

Recently, we have shown that imatinib at a dose of 15 mg/kg significantly reversed monocrotaline-induced RV hypertrophy and pulmonary arterial muscularization in rats (Leong et al., 2018). Consistently, Hatano et al. (2010) also reported significant improvement in diffusion capacity of the lung for carbon monoxide (DCLO) and varying hemodynamic responses in five PAH patients on low-dose imatinib (100 mg/day) for 24 weeks. Similar results were also demonstrated in our previous study in which the low-dose imatinib therapy (3 mg/kg) for 30 days improved clinical scores and echocardiographic outcomes in PH dogs (Arita et al., 2013). This case report represents the study continuation to investigate long-term effects and safety of the low-dose imatinib treatment for CDMVD-associated PH in six dogs.

Case description

Patient signalment, history and clinical findings of the dogs are summarized in Table 1. In general, the dogs were presented with cough, respiratory distress and exercise intolerance despite being treated for CDMVD (ISACHC Class II–IIIa) with polypharmacy approaches. A series of work-ups which included hematology and serum biochemistry, plasma atrial natriuretic peptide (ANP) and serum N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement, chest radiography, and echocardiography were carried out. The plasma ANP levels were measured by chemiluminescence enzyme immunoassay at Fukuyama Medical Laboratory, Hiroshima, whereas the serum NT-proBNP concentrations were measured by enzyme-linked immunosorbent assay (ELISA) at IDEXX Laboratories, Tokyo, Japan. The echocardiography was performed using methods as described in our previous study (Arita et al., 2013). For simplicity, all data are shown as mean ± standard deviation in the tables, and were analyzed for normality and statistical significance by one-way ANOVA and least significant difference post-hoc test for multiple comparisons.

The dogs had a VHS score of 11-11.5, indicating a cardiomegaly. On echocardiography, a mean maximal systolic tricuspid regurgitation velocity (TRmax) of greater than 2.8 m/s (3.34±0.58 m/s) was documented (Table 2). Using the modified Bernoulli's equation ($4\times TRmax^2$), a mean systolic pulmonary artery pressure (sPAP) of 45.68±16.19 mmHg was obtained, confirming a diagnosis of PH in the dogs. Besides, there were an enlarged right atrium (right atrium to aorta ratio [RA/Ao]; reference range [RR] 1.23±0.20) from the left parasternal apical 5-chamber view: 1.68±0.12, a decrease in the right myocardial performance (right Tei index: 0.31±0.09; RR: 0.17±0.10) (Teshima et al., 2006), and a reduced tricuspid annular plane systolic excursion (TAPSE) value (8.58±2.07 mm) (Pariaut et al., 2012) which collectively indicated compromised right heart functions. With owners' consent, imatinib (Glivec 100 mg, Novartis, United Kingdom), 3 mg/kg, every 24 hours, PO was initiated without changes to the current therapy for CDMVD.

The dogs were reevaluated at 1, 3, 5, and 6 months after the imatinib therapy. According to the owners, the dogs coughed less frequently. On follow-up echocardiography, significant and substantial decreases in TRmax, sPAP and RA/Ao were observed, implying reduced PH severity. Further, there were decreases in the right Tei index and increases in the TAPSE index, suggesting improved right heart functions.

In addition, the left heart echocardiography showed substantial decreases in the left ventricular internal diameter end systole (LVIDs), left ventricular internal diameter end diastole (LVIDd), and ratio of peak velocity of early diastolic transmitral flow to early mitral annulus motion velocity (E/Em), indicating reduced preload and left atrial pressure. There were no noticeable changes in cardiac output, fractional shortening and ejection fraction to indicate compromised systolic functions.

The levels of serum n-terminal pro-brain natriuretic peptide (NT-pro BNP) and plasma atrial natriuretic peptide (ANP) decreased remarkably after one month of the treatment (Table 3). Although we were not able to sample blood for cardiac biomarker analyses from all the dogs at every time point of revisits, the biomarker levels at 4 months post-treatment did not exceed the pre-treatment levels. Besides, hematology and serum biochemistry did not show remarkable abnormalities.

The imatinib therapy was discontinued in one dog (case 1) after it gained clinical stability. However, the owner claimed the dog became less active thereafter. Echocardiography on day 68 of the withdrawal showed increases in TRmax and sPAP, from 2.22 m/s to 2.76 m/s and from 19.71 mmHg to 30.36 mmHg, respectively, as well as worsened left heart functions. There were also drastic increases in the cardiac biomarkers levels (ANP: 106.2 ρg/mL, RR < 30 ρg/mL, NT-proBNP: 4419.0 ρmol/L, RR < 900 ρmol/L). Therefore, we decided to restart the dog on

Table 1 Summary of patient signalment, medication history, physical examination and thoracic radiographic findings

Case	1	2	3	4	5	6
Breed	Chihuahua	CKCS	Chihuahua	CKCS	Pomeranian	Shetland Sheepdog
Gender	Male castrated	Male castrated	Female intact	Male castrated	Male intact	Male castrated
Age	12	11	14	9	14	13
Clinical signs	Cough, exercise intolerance	Cough, exercise intolerance	Cough, lethargy, cyanosis when agitated	Cough, exercise intolerance	Syncope, frequent cough, cyanosis, tachypnea	Cough, exercise intolerance
Auscul-tation findings	Grade IV/VI LAM	Grade V/IV LAM	Grade IV/VI LAM, grade III/VI right apical murmur, harsh lung sounds	Grade IV/IV LAM	Grade IV/VI LAM, grade III/VI right apical murmur, harsh lung sounds	Grade IV/VI LAM, grade III/VI right apical murmur
Thoracic radio-graph findings	VHS: 11, vascular lung pattern, perihilar pulmonary edema	VHS: 11.5 bronchial compression, perihilar pulmonary edema	VHS: 11, moderate perihilar and caudodorsal pulmonary edema, tortuous pulmonary vessels	VHS: 11, left atrial enlargement	VHS: 11.5, perihilar pulmonary edema, engorged pulmonary vessels	VHS: 11.5 and moderate pulmonary edema
ISACHC	II	II	III a	II	III a	II
Treat-ment history prior to imatinib therapy	Alacepril (1.5 mg/kg, SID), pimobendan (0.15 mg/kg, BID)	Alacepril (1.5 mg/kg, SID), pimobendan (0.15 mg/kg, BID)	Enalapril (0.38 mg/kg, SID), isosorbide nitrate (2 mg/kg, SID)	Benazepril (0.5 mg/kg, SID)	Alacepril (1.5 mg/kg, BID), pimobendan (0.18 mg/kg, BID), furosemide (0.94 mg/kg, SID), vitamin B6 (10 mg/day), liver protectant Hepaact (1 tablet/day)	Benazepril (0.6 mg/kg, SID), pimobendan (0.15 mg/kg, BID), theophylline (6 mg/kg, BID), furosemide (1 mg/kg, BID)

CKCS, Cavalier King Charles Spaniel; LAM, left apical murmur; VHS, vertebral heart score; ISACHC, International Small Animal Cardiac Health Council; SID, every 12 hours; BID, every 24 hours

Table 2 Hemodynamic data (means ± standard deviation)

Time (Month)	0 (n=6)	1 (n=6)	3 (n=5)	5 (n=4)	6 (n=5)
Heart rate (bpm)	112.47±18.51	111.16±17.07	118.68±15.21	113.93±12.37	113.40±4.49
Right atrium/aorta ratio	1.68±0.12	1.45±0.09*	1.59±0.27	1.67±0.22	1.35±0.07*
Right Tei index	0.31±0.09	0.30±0.08	0.29±0.10	0.33±0.19	0.25±0.10
Maximal systolic tricuspid regurgitation velocity (m/s)	3.34±0.58	2.26±0.80*	2.16±0.52*	2.94±0.64	2.47±0.55*
Systolic pulmonary artery pressure (mmHg)	45.68±16.19	22.50±15.64*	19.54±10.38*	35.81±16.48	25.37±9.92*
Tricuspid annular plane systolic excursion (mm)	8.58±2.07	8.95±2.60	8.71±0.60	9.17±1.20	8.48±0.84
Left atrium/aorta ratio	2.22±0.12	1.92±0.33	2.10±0.18	2.38±0.47	1.95±0.28
Maximum systolic mitral regurgitation velocity (m/s)	7.70±4.02	6.47±1.34	6.22±1.19	6.04±0.38	4.99±2.06
Left ventricular internal diameter end systole (mm)	16.88±4.99	12.35±4.32	14.91±4.14	12.90±5.68	14.82±5.63
Left ventricular internal diameter end diastole (mm)	30.18±6.60	25.25±7.20	29.10±6.70	26.13±7.86	28.00±7.39
Fractioning shortening (%)	44.63±7.76	51.59±7.85	49.06±4.75	51.55±10.43	48.65±9.29
Ejection fraction (%)	76.68±8.33	83.67±6.84	81.65±4.76	83.21±8.07	81.93±7.05
E/A	1.22±0.34	1.13±0.33	1.28±0.32	1.18±0.35	1.14±0.39
Deceleration time of early diastolic transmitral wave (ms)	82.36±17.91	105.69±14.40	99.40±33.59	108.08±6.70	97.75±25.39
E/Em	9.11±1.02	6.12±0.59*	8.35±1.33	6.01±2.03*	6.83±1.38*
Left Tei index	0.31±0.09	0.22±0.11	0.37±0.12	0.28±0.10	0.38±0.16

E/A, ratio of peak velocity of early diastolic transmitral flow to peak velocity of late diastolic transmitral flow; E/Em, ratio of early mitral annulus motion velocity to atrial systolic mitral annulus motion velocity
*P<0.05 versus 0-month treatment by one-way ANOVA and post-hoc least significant difference (LSD) test for multiple comparisons

Table 3 Cardiac biomarker levels (means ± standard deviation)

Cardiac Biomarkers	Reference Range	Pre-Imatinib Therapy	1-Month Post Imatinib Therapy	4-Month Post Imatinib Therapy
Atrial natriuretic peptide (ANP) (ρg/mL)	< 30	74.64±6.40 (n=5)	52.64±30.86 (n=5)	58.1±28.57 (n=2)
N-terminal pro-brain natriuretic peptide (NT-proBNP) (ρmol/L)	< 900	2442.83±2221.62 (n=6)	1704.50±1412.54 (n=6)	2094.67±1384.52 (n=3)

the imatinib treatment after clinical improvement was observed.

Out of the six dogs which received the imatinib treatment, two dogs (cases 5 and 6) survived 13 and 48 months after the therapy, respectively, while the other dogs have continued to receive the therapy until present without obvious side effects observed.

Discussion

This case report describes six CDMVD dogs which developed PH and required a long-term, low-dose imatinib therapy despite polypharmacy approaches. A low-dose imatinib is defined as one-third of 10 mg/kg dosage indicated for treating canine neoplasms, and was given without any changes to the background therapy for CDMVD in the dogs to minimize influences from other drugs which might affect the study results. The imatinib therapy was chosen over the commonly used vasodilator, sildenafil, for treating PH according to its two properties: the direct, potent reversal effects on cardiopulmonary remodeling (Schermuly et al., 2005; Pankey et al., 2013; Leong et al., 2018) and the vasodilative properties in the lungs (Pankey et al., 2013; Maihöfer et al., 2017).

The advanced stage of CDMVD increased pulmonary capillary wedge pressure, leading to upregulation of PDGF (Schermuly et al., 2005; Pankey et al., 2013) and c-KIT (Montani et al., 2011) signaling pathways, which increased the downstream mitogen-activated protein kinase (MAPK) signalling pathway (Katz et al., 2007). This subsequently triggered angioproliferation of pulmonary arteries in a process known as remodeling, and resulted in PH in the dogs. Regardless of PH severity, the dogs showed improved PH and clinical signs after being treated with the low-dose imatinib. We believe that imatinib reversed pulmonary arterial muscularization via the PDGF inhibition (Schermuly et al., 2005), thus resulting in improved PH (decreased TRmax, sPAP, right atrial size) and RV functions (increased right Tei index, an increase in the TAPSE). Further, the LVIDd, left atrium/aorta ratio (LA/Ao), and ratio of peak velocity of early diastolic transmitral flow to peak velocity of late diastolic transmitral flow (E/A), as indicators of CDMVD poor prognosis (Hezzell et al., 2012), also improved. In addition, we also speculate that imatinib relaxed systemic and pulmonary venous relaxation which subsequently reduced preload and afterload (Pankey et al., 2013; Maihöfer et al., 2017).

In a study by Hatano et al. (2010), five human PAH patients who received a 100 mg/day imatinib dose (equivalent to canine dose of 3 mg/kg) for 12 weeks showed improved DLCO and hemodynamic parameters indicated by either decreased mean pulmonary arterial pressure, decreased pulmonary venous resistance, or an increased cardiac index. On an extension therapy to 24 weeks, only three patients with scleroderma-associated PAH showed sustained favorable results. However, the present study demonstrates sustained hemodynamic improvement in the dogs. Clinical and hemodynamic deterioration in the dog in case 1 after imatinib withdrawal also led us to believe that imatinib exhibits sustained, favorable effects on PH in dogs.

There were no remarkable changes in hematology and biochemistry profiles in the dogs to indicate an imatinib toxicity. In humans treated with a high-dose imatinib for PAH, adverse effects which included nausea, peripheral edema, thrombocytopenia, right ventricular failure, anemia, and subdural hematoma were reported (Hoeper et al., 2013; Frost et al., 2015). In the dogs which were treated with a neoplastic dose (10-12 mg/kg), neutropenia, vomiting or elevation of serum liver enzymes, blood urea nitrogen (BUN) and serum creatinine were documented (Bonkobara, 2015). However, these side effects were not observed in the present study, indicating that the 3 mg/kg imatinib dose was well tolerated by the dogs. Furthermore, the potent anti-remodeling activity of the low-dose imatinib (Leong et al., 2018) was reflected by substantial clinical and hemodynamic improvements in the dogs. Taken together, we believe that this therapy is effective yet safe for the long-term treatment of canine PH.

In conclusion, this case report highlights the encouraging, long-term clinical and hemodynamic outcomes of the low-dose imatinib treatment for CDMVD-associated PH in dogs, without noticeable side effects. Because there were no changes in the background therapy, the beneficial effects were solely due to the administration of the low-dose imatinib therapy, which is believed to have inhibited pulmonary vascular remodeling and dilated systemic and pulmonary vasculatures simultaneously in the dogs. This therapy can be conveniently administered once daily, and may provide a promising treatment alternative for the treatment of PH in dogs. However, a drug trial in a larger population of dogs may be deemed necessary.

Conflict of interest: The authors have no conflict of interest.

Acknowledgements

This study was supported in part by the Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (Grant No. 18K05993 to Y. Hikasa).

References

Arita S, Arita N and Hikasa Y 2013. Therapeutic effect of low-dose imatinib on pulmonary arterial hypertension in dogs. Can Vet J. 54(3)**:** 255-261.

Bonkobara M 2015. Dysregulation of tyrosine kinases and use of imatinib in small animal practice. Vet J. 205(2): 180-188.

Frost AE, Barst RJ, Hoeper MM, Chang HJ, Frantz RP, Fukumoto Y, et al. 2015. Long-term safety and efficacy of imatinib in pulmonary arterial hypertension. J Heart Lung Transplant. 34(11): 1366-1375.

Ghofrani HA 2005. Imatinib for the treatment of pulmonary arterial hypertension. N Engl J Med. 353: 1412-1413.

Ghofrani HA, Morrell NW, Hoeper MM, Olschewski H, Peacock AJ, Barst RJ, et al. 2010. Imatinib in pulmonary arterial hypertension patients with

inadequate response to established therapy. Am J Respir Crit Care Med. 182(9): 1171-1177.

Hatano M, Yao A, Shiga T, Kinugawa K, Hirata Y and Nagai R 2010. Imatinib mesylate has the potential to exert its efficacy by down-regulating the plasma concentration of platelet-derived growth factor in patients with pulmonary arterial hypertension. Int Heart J. 51(4): 272-276.

Hezzell MJ, Boswood A, Moonarmart W and Elliott J 2012. Selected echocardiographic variables change more rapidly in dogs that die from myxomatous mitral valve disease. J Vet Cardiol. 14(1): 269-279.

Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galié N, et al. 2013. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation. 127(10): 1128-1138.

Katz M, Amit I and Yarden Y 2007. Regulation of MAPKs by growth factors and receptor tyrosine kinases. Arch Biochem Biophys. 1773(8): 1161-1176.

Kellihan HB and Stepien RL 2010. Pulmonary hypertension in canine degenerative mitral valve disease. J Vet Cardiol. 14(1): 149-164.

Leong ZP, Okida A, Higuchi M, Yamano Y and Hikasa Y 2018. Reversal effects of low-dose imatinib compared with sunitinib on monocrotaline-induced pulmonary and right ventricular remodeling in rats. Vascul Pharmacol. 100: 41-50.

Maihöfer NA, Suleiman S, Dreymüller D, Manley PW, Rossaint R, Uhlig S, et al. 2017. Imatinib relaxes the pulmonary venous bed of guinea pigs. Respir Res. 18(1): 32.

Montani D, Perros F, Gambaryan N, Girerd B, Dorfmuller P, Price LC, et al. 2011. C-kit-positive cells accumulate in remodeled vessels of idiopathic pulmonary arterial hypertension. Am J Respir Crit Care Med. 184(1): 116-123.

Pankey EA, Thammasiboon S, Lasker GF, Baber S, Lasky JA and Kadowitz PJ 2013. Imatinib attenuates monocrotaline pulmonary hypertension and has potent vasodilator activity in pulmonary and systemic vascular beds in the rat. Am J Physiol Heart Circ Physiol. 305(9): H1288-H1296.

Reynolds CA, Brown DC, Rush JE, Fox PR, Nguyenba TP, Lehmkuhl LB, et al. 2012. Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve disease: the PREDICT cohort study. J Vet Cardiol. 14(1): 193-202.

Schermuly RT, Dony E, Ghofrani HA, Pullamsetti S, Savai R, Roth M, et al. 2005. Reversal of experimental pulmonary hypertension by PDGF inhibition. J Clin Invest. 115(10): 2811-2821.

Shah AM, Campbell P, Rocha GQ, Peacock A, Barst RJ, Quinn D, et al. 2015. Effect of imatinib as add-on therapy on echocardiographic measures of right ventricular function in patients with significant pulmonary arterial hypertension. Eur Heart J. 36(10): 623-632.

Teshima K, Asano K, Iwanaga K, Koie H, Uechi M, Kato Y, et al. 2006. Evaluation of right ventricular Tei index (index of myocardial performance) in healthy dogs and dogs with tricuspid regurgitation. J Vet Med Sci. 68(12): 1307-1313.

บทคัดย่อ

ผลระยะยาวของไอมาทินิบขนาดต่ำสำหรับรักษาภาวะความดันหลอดเลือดพัลโมนารีสูงเนื่องจากภาวะลิ้นหัวใจไมตรัลเสื่อมเรื้อรังในสุนัข 6 ตัว

ซี ปิง ลอง[1,2] ชินเจีย ริตะ[3] โยเชียกิ ฮิกาสะ[1,2*]

สุนัข 6 ตัว ถูกวินิจฉัยว่าป่วยเป็นภาวะความดันหลอดเลือดพัลโมนารีสูงเนื่องจากภาวะลิ้นหัวใจไมตรัลเสื่อมโดยใช้คลื่นเสียงสะท้อนความถี่สูง สุนัขได้รับยาไอมาทินิบขนาด 3 มิลลิกรัมต่อกิโลกรัมโดยการป้อนทุกๆ 24 ชั่วโมง เพิ่มจากการได้รับยาปกติที่ใช้รักษาภาวะความดันหลอดเลือดพัลโมนารีสูง สุนัขได้รับการตรวจติดตามภายหลังได้รับยาที่ 1 3 5 และ 6 เดือน พบว่าอาการทางคลินิกและการไหลเวียนโลหิตดีขึ้น สุนัข 1 ตัว แสดงอาการแย่ลงหลังจากหยุดยาไอมาทินิบ จึงจำเป็นต้องเริ่มให้ยาไอมาทินิบใหม่ ในการศึกษา 6 เดือน ไม่พบผลข้างเคียงใดๆ การทดลองนี้แสดงให้เห็นว่าการให้ยาไอมาทินิบขนาดต่ำๆ เป็นทางเลือกหนึ่งสำหรับการรักษาภาวะความดันหลอดเลือดพัลโมนารีสูงเนื่องจากภาวะลิ้นหัวใจไมตรัลเสื่อมเรื้อรังในสุนัข

คำสำคัญ: ภาวะลิ้นหัวใจไมตรัลเสื่อมเรื้อรัง ไอมาทินิบขนาดต่ำ ภาวะความดันหลอดเลือดพัลโมนารีสูง

[1]The United Graduate School of Veterinary Science Yamaguchi University, 1677-1 Yoshida, Yamaguchi 753-8515, Japan

[2]Laboratory of Veterinary Internal Medicine, Joint Department of Veterinary Medicine, Faculty of Agriculture, Tottori University, 4-101 Koyama Minami, Tottori 680-8553, Japan

[3]Arita Sougo Animal Hospital, 1-14-6 Nishi, Hachihonmatsu, Higashihiroshima-shi, Hiroshima 739-0147, Japan

****ผู้รับผิดชอบบทความ** E-mail: hikasa@muses.tottori-u.ac.jp*