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Platelet-Derived Growth Factor Receptor-Tyrosine Kinase Inhibitor, Imatinib, Is Effective for Treating Pulmonary Hypertension Induced by Pulmonary Tumor Thrombotic Microangiopathy

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SUMMARY

Pulmonary hypertension (PH) induced by pulmonary tumor thrombotic microangiopathy (PTTM) can be fatal because its rapid progression confounds diagnosis, and it is difficult to control with therapy. Here we describe a woman with symptomatic PTTM-PH accompanying gastric cancer that was suspected from perfusion scintigraphy. PTTM-PH was diagnosed by gastroesophageal endoscopy and lung biopsy after partial control of PH using the platelet-derived growth factor (PDGF) receptor (PDGFR) tyrosine kinase inhibitor, imatinib. Treatment with sildenafil and ambrisentan further decreased PH, and she underwent total gastrectomy followed by adjuvant TS-1 chemotherapy. PH did not recur before her death from metastasis. Postmortem histopathology showed recanalized pulmonary arteries where the embolized cancer masses disappeared. PDGF-A, -B, and PDGFR-α, β expression was detected in cancer cells and proliferating pulmonary vascular endothelial cells. Thus, PTTM-PH was successfully controlled using a combination of imatinib, drugs to treat pulmonary arterial hypertension, and cancer management. (Int Heart J 2015; 56: 245-248)

Key words : Circulatory disturbance, Cancer, Treatment

Pulmonary tumor thrombotic microangiopathy (PTTM) is an uncommon disease and sometimes accompanies pulmonary hypertension (PTTM-PH). PTTM-PH is directly caused by multiple microthrombi of cancer cells surrounded by fibrotic intimal cell proliferation [1] and/or indirectly due to vascular remodeling mediated by growth factors such as platelet-derived growth factor (PDGF),[2-4] vascular endothelial growth factor,[5,6] and osteopontin [7] that are released by cancer cells. Because PTTM-PH progresses rapidly, it is rarely diagnosed before autopsy. Therefore, PTTM-PH is not managed, and patients survive 1–3 months after symptoms appear.[8]

CASE REPORT

In September 2011, a 64-year-old woman was admitted to our hospital with the main complaints of persistent cough, progressing dyspnea, and a 10-kg weight loss during the previous 3 months. Because the electrocardiogram showed right axis deviation and right ventricle hypertrophy (Figure 1A) and echocardiography revealed a markedly elevated right ventricular systolic pressure (85 mmHg) and a significantly dilated right ventricle with a counter-compressed left ventricle (Figure 1C), she was diagnosed with pulmonary hypertension (PH) and immediately admitted. A pulmonary perfusion scintigram showed diffuse and peripheral perfusion defects (Figure 2A) indicating diffuse micro-occlusions of pulmonary arteries (PA). Neither contrast-computed tomography nor pulmonary arteriogram detected a thrombus. Right heart catheterization confirmed severe PH (Figure 3), suggesting PTTM-PH.

Gastroesophageal endoscopy detected early gastric cancer that was characterized as a poorly differentiated adenocarcinoma involving signet-ring cells. After PH was controlled using imatinib (Figure 3), video-assisted thoracic surgery was performed to acquire a lung biopsy. Histopathology revealed that a considerable number of the small PA were occluded by gastric cancer cells (GCC) and organized tissue that included proliferating vascular intimal cells (Figure 4A). While PH was further controlled with sildenafil and ambrisentan combined with imatinib, she underwent total gastrectomy followed by adjuvant chemotherapy with TS-1 (Figure 3). In January 2012, her hemodynamic parameters were normal, including arterial oxygen-saturation (Figure 3) and the diffuse pulmonary perfusion defects (Figure 2B). The abnormal electrocardiogram

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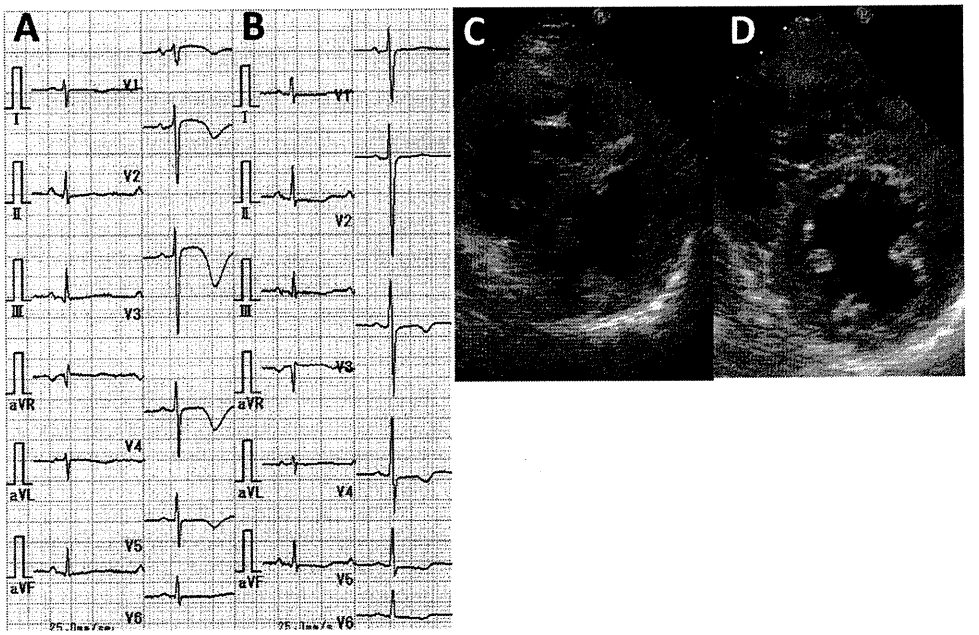

Figure 1. Electrocardiogram and Echocardiogram. **A, B:** The electrocardiogram at admission (**A**) shows right axis deviation and right ventricle hypertrophy. At discharge, these findings were normalized (**B**). **C, D:** The short-axis view of the echocardiogram at admission (**C**) demonstrates dilatation of a right ventricle with a counter-compressed left ventricle. These findings were not seen at discharge (**D**).

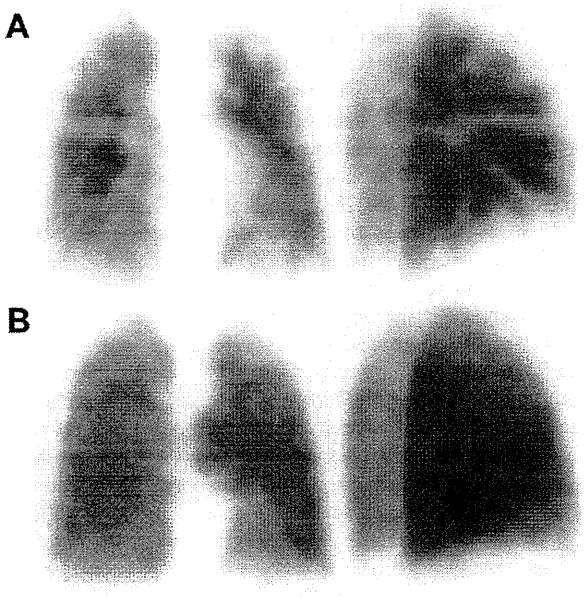

Figure 2. Pulmonary Perfusion Scintigraphy. **A:** Pulmonary perfusion scintigram shows diffuse peripheral perfusion defects, suggesting diffuse and peripheral occlusions at the level of the small PA. **B:** Pulmonary perfusion defects are undetectable in the scintigram performed after hemodynamic normalization, suggesting reperfusion of the occluded PA.

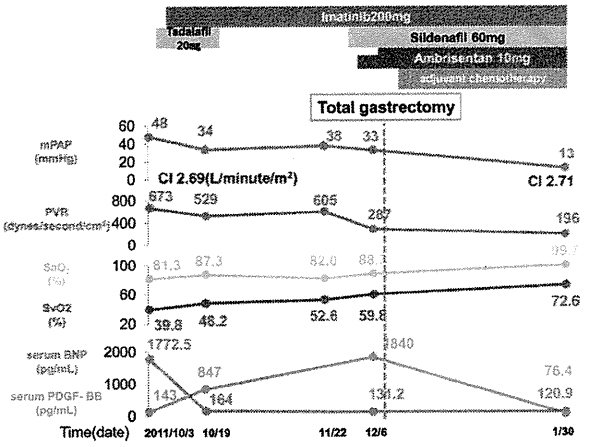

Figure 3. Clinical course during hospitalization. The initial and sequential administration of tadalafil and imatinib decreased mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR). Although administration of tadalafil was discontinued due to congestion suspected from the results of X-ray, mPAP was maintained below 40 mmHg in the presence of imatinib. The sequential addition of sildenafil and ambrisentan further decreased mPAP and PVR with improved arterial oxygen saturation (SaO_2). This allowed us to perform total gastrectomy followed by the adjuvant chemotherapy with TS-1. The serum level of PDGF-BB increased until total gastrectomy and administration of adjuvant chemotherapy, suggesting that proliferating cancer cells were the primary source of PDGF-BB. On January 30, 2012, the serum levels of brain natriuretic peptide and PDGF-BB were rather high, but the hemodynamic parameters and SaO_2 level were normalized. SvO_2: mixed venous oxygen saturation.

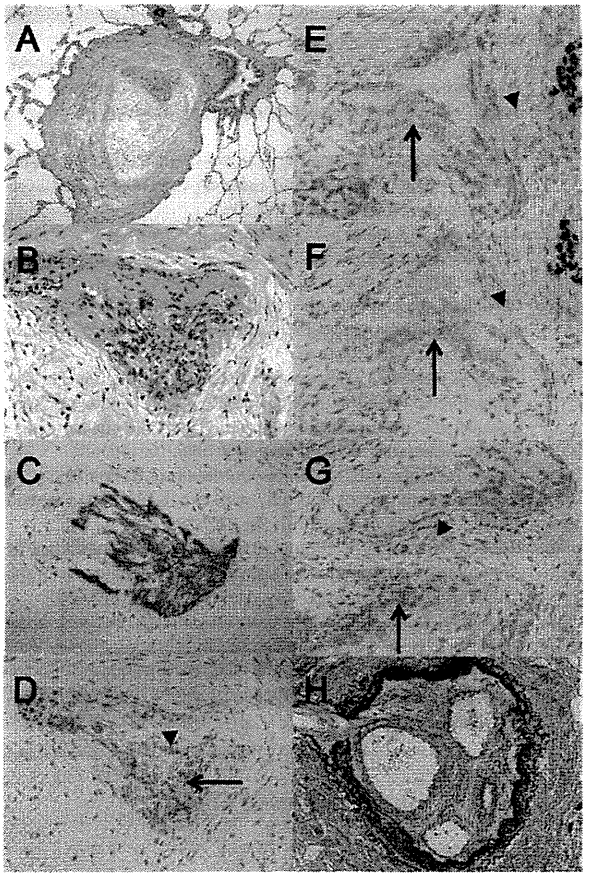

Figure 4. Histopathological findings. **A:** Representative histology of occluded PA. The lumen was occluded by the embolized tumor cells and the fibrocellular intimal proliferation within the myxoid matrix (H&E, 4×). **B:** Magnified image of embolized tumor cells shown in **A**. The mass of cancer cells showing atypical nuclei and vascular endothelial cells was surrounded by proliferating fibrous and fibroblastic cells within the myxoid matrix (H&E, 40×). **C:** Immunohistochemical staining for keratin (clone: CAM5.2) that was strongly positive was indicative of embolized gastric cancer cells (magnification 40×). **D:** Immunohistochemical analysis using an anti-PDGF-A antibody (N-30, rabbit polyclonal: sc-128) revealed that PDGF-A was expressed in the embolized cancer cells (arrow) and vascular endothelial cells (arrowhead). **E:** In another embolized vessel, immunohistochemical analysis using an anti-PDGF-B antibody (N-30 rabbit polyclonal: sc-127) showed the expression of PDGF-B in the embolized cancer (arrow) and vascular endothelial cells (arrowhead). **F:** In similar specimens sectioned subsequently to E, probing with the anti-phospho-PDGFR-α (Tyr754: sc-12911) generated positive signals in the embolized cancer (arrow) and vascular endothelial cells (arrowhead). **G:** The anti-PDGFR-β antibody (P-20 rabbit polyclonal: sc-339) generated a signal in the embolized cancer cells (arrow) and vascular endothelial cells (arrowhead). **H:** Recanalization of the pulmonary arteries in the autopsy specimen was suggested by their characteristic shape and cylindrical removal of the tissue (EVG stain: 10×). The volume of the cancer cells in the PA was quite low in the autopsy specimens compared with the biopsy specimens.

and echocardiogram findings were also normalized (Figure 1B and D). She was discharged and periodically visited our hospital as an outpatient. However, she died of systemic metastasis on September 18, 2012.

Discussion

In cardiovascular disease, common causes of rapid progressing dyspnea are heart failure due to acute coronary syndrome, pulmonary embolism and worsening of chronic heart failure. Amniotic fluid embolism[9] and eosinophilic myocarditis[10] were previously reported as rare but important causes.

PTTM can also induce rapid progressive dyspnea. Furthermore, not all patients with PTTM are proven to have a malignant tumor at admission like this case. It is quite rare, however, and an early diagnosis is very important for rescue.

PTTM is detected in 3.3% of autopsies of patients with carcinoma.[2] The key to our diagnosis was a perfusion scintigram showing diffuse and peripheral perfusion defects (Figure 2A). Because Von Herbay, *et al* reported that PTTM-PH is most frequently caused by gastric cancer,[2] we decided to perform gastroesophageal endoscopy. PTTM-PH is typically uncontrollable.[8] The authors of several pathological studies suggest that PDGF secreted from tumor cells is associated with vascular remodeling in PTTM-PH,[2-4,11,12] and that PDGF is secreted because of the endothelial damage induced by attachment of tumor thrombi.[2] Moreover, PDGF-regulated expression of osteopontin is associated with fibrosis, neointima formation, and PA occlusion.[13] Taken together, these findings suggested to us that inhibition of PDGF or PDGFR improves PTTM-PH. Moreover, Ogawa, *et al*[14] reported that imatinib treatment stabilized PTTM-PH. On the other hand, imatinib has been reported to be effective in patients with pulmonary arterial hypertension,[15] and our own studies showed that imatinib treatment reduced serum levels of PDGF-BB in patients with pulmonary arterial hypertension,[16] as reported in the patient with PTTM-PH by Ogawa, *et al*[14] However, our patient's serum level of PDGF-BB increased until she underwent total gastrectomy and received adjuvant chemotherapy (Figure 3). From the immunohistochemistry results, we conclude that PDGF-A and -B may primarily originate from the GCC in PA (Figure 4D and E) and the stomach (Supplemental Figure 1B and C). Positive staining using the anti-phospho-PDGFR-α of the vascular endothelial cells and the GCC in the PA and the stomach indicates that PDGF signaling was likely activated through autocrine and paracrine mechanisms, which were unlikely to have been inhibited by circulating imatinib (Figure 4F, Supplemental Figure 1D). Administration of imatinib and other PH drugs and suppression of GCC-proliferation by TS-1 resulted in normalization of hemodynamics, the lung perfusion scintigram, and arterial oxygen saturation. Histological analysis and comparison of the biopsy with the autopsy revealed recanalization of the previously occluded small PA (Figure 4A and 4H), which most likely occurred during the clinical course. We attribute this to the elimination of embolized cancer cells. In addition, the rate of normal vasculature was increased in the autopsy samples, which was most likely attributable to reverse remodeling of the intimal cell proliferation (Supplemental Figure 2). Both phenomena mainly contribute to a decrease in the mean value of the luminal stenotic rate of the PA. Because PH did not recur, the present case suggests the first strategy effective for treating PTTM-PH.

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DISCLOSURE

Conflict of interest: No conflict of interest exists for the specified authors.

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SUPPLEMENTAL FILES

Supplemental Table I, II
Please find supplemental files;
http://www.jstage.jst.go.jp/article/ihj/56/2/56_14-220/_article/supplement

Imatinib Alleviated Pulmonary Hypertension Caused by Pulmonary Tumor Thrombotic Microangiopathy in a Patient With Metastatic Breast Cancer

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Clinical Practice Points

- Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare cancer-related complication leading to hypoxia, pulmonary hypertension, and heart failure.
- The standard treatment for PTTM is not established. However, imatinib, a tyrosine kinase inhibitor of platelet-derived growth factor receptor (PDGFR), may cause regression of pulmonary hypertension and pulmonary artery remodeling in PTTM.
- We report a case of a 61-year-old woman in whom PTTM developed during chemotherapy for metastatic breast cancer. Although imatinib alleviated pulmonary hypertension, she died because of progression of metastatic breast cancer 54 days after her initial admission to our hospital.
- It would be advisable to conduct a well-designed clinical trial using chemotherapy regimens combined with imatinib for PTTM.

Clinical Breast Cancer, Vol. 15, No. 2, e167-70
Keywords: Imatinib, Metastatic breast cancer, PDGFR, Pulmonary hypertension, Pulmonary tumor thrombotic microangiopathy (PTTM)

Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare cancer-related complication that causes hypoxia, pulmonary hypertension, and heart failure. We report a case of PTTM that occurred during chemotherapy for metastatic breast cancer.

Case Report

The patient was a 61-year-old woman who had undergone resection of the left breast and axillary lymph node dissection. Subsequently, she received adjuvant chemotherapy: CAF (cyclophosphamide 500 mg/m^2, doxorubicin [Adriamycin] 50 mg/m^2, and 5-fluorouracil 500 mg/m^2) followed by docetaxel and then tamoxifen followed by anastrozole for a total of 5 years. Twelve years after surgery, she experienced multiple bone and mediastinal lymph node metastases. She was treated with eribulin for 1 year. She came in with a 2-day history of progressing dyspnea and was admitted to our hospital for further medical care. On admission, her body temperature was 36.9°C, blood pressure was 117/72 mm Hg, heart rate was 74 bpm, respiratory rate was 20 breaths per minute, and oxygen saturation was 94% (room air). A chest radiograph showed normal lung fields. Results of arterial blood gas analysis in room air revealed hypoxemia: pH, 7.497; P_{CO_2}, 27.6 mm Hg; P_{O_2}, 59.7 mm Hg; and HCO^3, 20.9 mmol/L. Base excess was −0.9 (room air). Further laboratory examination showed the following: white blood cell count, 3300/mm^3 with normal differential counts; hemoglobin value,12.0 g/dL; platelet count, 75,000/mm^3; total bilirubin, 1.2 mg/dL (normal, 0.2-0.9 mg/dL); aspartate aminotransferase level, 69 IU/L (normal, 10-30 IU/L); alanine aminotransferase level, 50 IU/L (normal, 5-35 IU/L); and C-reactive protein level, 0.03 mg/dL (normal, 0-0.50 mg/dL). A blood coagulation test showed that the D-dimer was elevated to 10.67μg/mL

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(normal, < 0.49 μg/mL), and fibrin degradation products were also elevated to 44.57 μg/mL (normal, < 10 μg/mL), suggesting microthromboembolic disease.

On radiographic evaluation, enhanced computed tomography detected no pulmonary embolism (Figure 1A). However, ventilation-perfusion scintigraphy demonstrated multiple small peripheral perfusion defects in both lungs on the second day after admission (Figure 1B). A transthoracic echocardiogram showed normal left ventricular systolic function (left ventricular ejection fraction, 75%) with paradoxical movement of the interventricular septum. In addition to right ventricular and atrial enlargement, severe pulmonary hypertension was seen, with estimated right ventricular systolic pressure of 76 mm Hg.

On the fifth day after admission, she was transferred to the Department of Cardiovascular Medicine for a more precise diagnosis and intensive treatment. Subsequently, wedged pulmonary artery blood cell sampling showed histologically malignant cells, which highly suggested the diagnosis of pulmonary tumor thrombotic microangiopathy (PTTM). There were 3-dimensional clusters of atypical epithelial cells, focal glandular structures were present, and the nuclear-cytoplasm ratio was high. The cells had hyperchromatic nuclei and prominent nucleoli (Figure 2). Pulmonary artery pressure (PAP) was measured at 93/39 (60) mm Hg, and the cardiac index (CI) was 1.63 L/min/m^2. Imatinib (200 mg/d) was administered as part of a clinical trial, which was approved by the Institutional Review Board of the University of Tokyo Hospital. Nine days after administering the anti–platelet-derived growth factor (PDGF) agent imatinib, the PAP was reduced to 87/30 (50) mm Hg, and the CI was improved to 2.83 L/min/m^2. Because this suggested that imatinib might be effective for this patient, we increased the dose to 400 mg, adding tadalafil (40 mg/d). Afterward the patient was able to discontinue the use of the inotropic agent. Although the PAP was slightly elevated to 95/44 (56) mm Hg, the CI was 2.97 L/min/m^2, and it was possible to maintain hemodynamic stability. There was no worsening of the respiratory condition or right heart failure. However, the patient died of progression of breast cancer 54 days after her initial admission to our hospital.

During autopsy, an embolus of tumor cells was noted in the pulmonary artery, accompanied by intimal hyperplasia. The lumen of the pulmonary artery was severely narrowed. Tumor cells were immunohistochemically positive for PDGF-B (Figure 3).

Discussion

PTTM is a rare cancer-related pulmonary complications, leading to hypoxia, pulmonary hypertension, and heart failure. von Herbay et al reported that the incidence of PTTM was 3.3% (21 cases in 630 carcinoma autopsies).[1] They showed that all 21 cases had carcinoma with distant metastases and that 19 cases had adenocarcinomas in various organs. Among these were 2 cases of breast cancer, whereas stomach cancer was the most common. Okubo et al also reported 6 cases of PTTM in 37 gastric carcinoma autopsies, the incidence being 16.2%.[2]

No diagnostic methods for PTTM have yet been established. Generally, enhanced computed tomography shows no evidence of pulmonary embolism, but ventilation- perfusion scanning tends to be useful. Scintigraphy characteristically reveals multiple subsegmental mismatched defects. Pulmonary angiography might be expected to be the gold standard method for PTTM. However, it has been reported that its sensitivity and specificity for detecting tumor emboli were both poor.[3] For our patient, right-heart catheterization and wedged pulmonary artery blood cell sampling did confirm the clinical diagnosis of PTTM.

Figure 1 (A) Enhanced Computed Tomography Revealed No Evidence of Pulmonary Embolism. (B) Ventilation-Perfusion Scanning Scintigraphy Demonstrated Multiple Small Wedged-Shaped Perfusion Defects in Bilateral Lungs

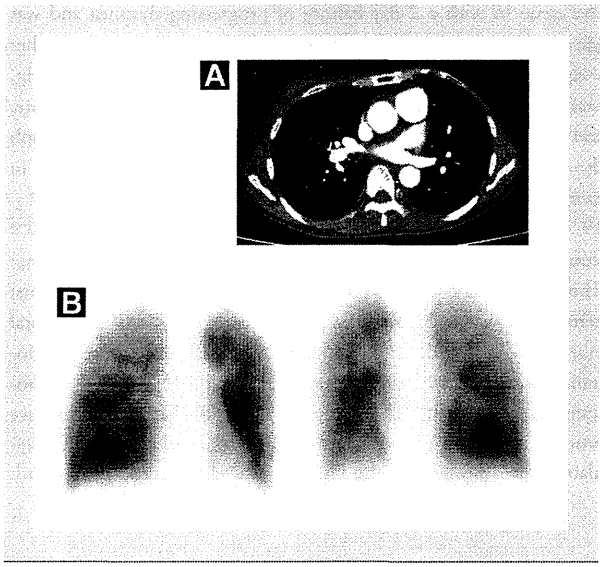


Figure 2 Cytologic Findings From Pulmonary Artery Adenocarcinoma Cells Identified by Cytologic Examination of the Blood in the Pulmonary Artery (Papanicolaou Stain). There Were 3-Dimensional Clusters of Atypical Epithelial Cells. Focal Glandular Structures Were Present, and the Nuclear-Cytoplasm Ratio Was High. The Cells Had Hyperchromatic Nuclei and Prominent Nucleoli

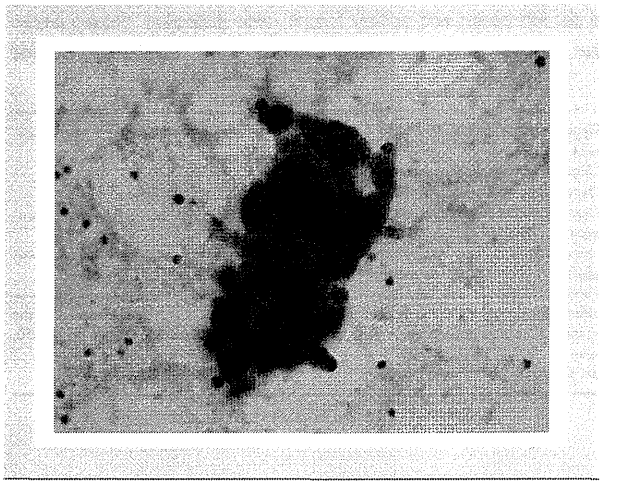
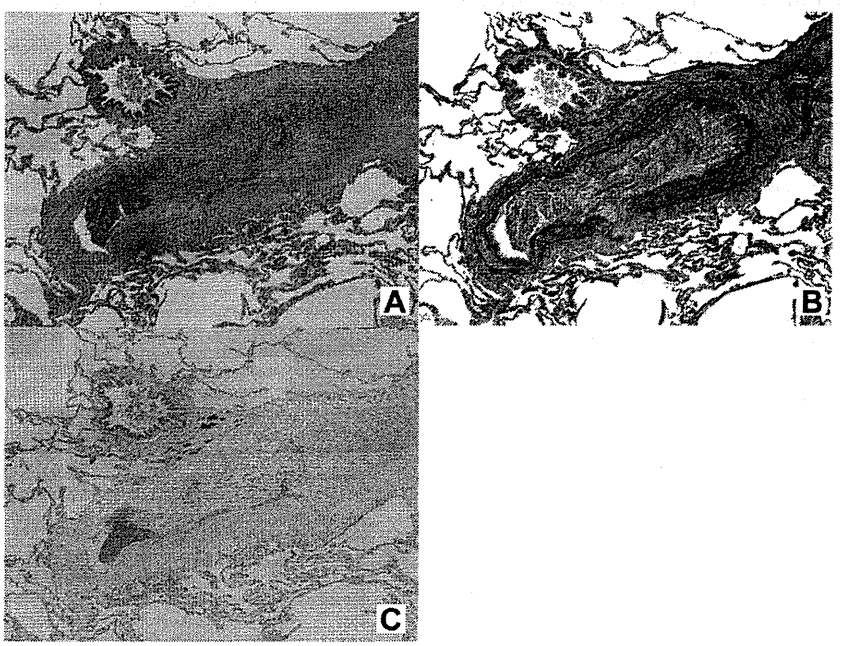


Figure 3 (A-C) Autopsy Findings. Lesion of Pulmonary Tumor Thrombotic Microangiopathy (PTTM) in the Autopsied Specimen. Embolus of Tumor Cells Was Noted in the Pulmonary Artery accompanied by Intimal Hyperplasia. The Lumen of the Pulmonary Artery Was Severely Narrowed. Tumor Cells Were Immunohistochemically Positive for PDGF-B. (A) Hematoxylin and Eosin. (B) Elastica van Gieson. (C) Immunohistochemical Findings of PDGF-B



Despite the recent development of morphometric and immunohistochemical analyses, the mechanism of PTTM is still unclear. Roberts et al presented 2 hypotheses for the development of pulmonary hypertension and right-heart failure in pulmonary tumor embolism.[4] The first is that the dysregulation of signaling pathways, which respond to the presence of an embolic cell or other intravascular insult, cause vascular remodeling.

The second hypothesis proposes that tumor emboli occlude the pulmonary artery bed and increase pulmonary vascular resistance.

von Herbay et al described the morphologic findings of PTTM in a previous report.[1] They revealed that PTTM induced both local activation of coagulation and fibrocellular intimal proliferation. This study reported that tumor cells invaded the pulmonary vascular system and occluded the small arteries and arterioles that activate coagulation systems, releasing inflammatory mediators and growth factors. This process induced fibrocellular proliferation and luminal stenosis.[5] Okubo et al also reported the morphometric analysis of pulmonary arteries and suggested that pulmonary artery remodeling induced by carcinomatous cell adhesion to the endothelium affected the status of pulmonary hypertension.[2]

Several studies revealed that cancer cells produced the molecules that cause PTTM. Okubo et al revealed that all 6 of their PTTM cases showed positive reactivity for tissue factor (TF), 5 showed positive reactivity for vascular endothelial growth factor (VEGF), and 3 showed positive reactivity for osteopontin (OPN). There were some reports suggesting that VEGF and TF might play important roles in the pathogenesis of PTTM. VEGF and TF expression by carcinoma cells has been confirmed in many cases.[5-10] VEGF has been known to be an endothelial cell–specific angiogenetic mitogen.[6] VEGF is associated with the proliferation of endothelial cells and includes angiogenesis involved in embryonic development, tumor angiogenesis, and wound healing.[11] Recently, VEGF has been reported to be involved in pulmonary hypertension.[12,13] In addition to VEGF, TF also is an important factor involved in intracellular signaling, cellular proliferation, and the development of blood vessels. TF contributes to factor VIIa–catalyzed activation of factors IX and X.[8] It has been reported that TF produced by tumor cells might play an important role in the pathogenesis of PTTM[14] and that expression of TF upregulated the *VEGF* gene and enhanced tumor angiogenesis.[15,16]

Takahashi et al reported a case of PTTM with OPN expression.[10] OPN is an arginine-glycine-aspartic acid–containing protein secreted by a variety of cells, including osteoclasts, activated T cells, activated macrophages, and various cancer cells.[17] In Takahashi et al's autopsied case of gastric adenocarcinoma, the tumor cells (both in PTTM lesions and primary gastric carcinoma) and proliferating fibromuscular intimal cells also showed positive immunoreactivity for OPN, PDGF, and VEGF. They suggested that OPN promoted fibrocellular intimal proliferation as well as thrombus formation and pulmonary hypertension in the pathogenesis of PTTM.[10]

It is also important to consider PDGF and PDGF receptor (PDGFR).[18] von Herbay et al speculated that attachment of tumor cell emboli might damage endothelial cells and release PDGF in

PTTM.[1] Yokomine et al reported an autopsied case of PTTM caused by a gastric carcinoma that expressed PDGF and PDGFR in tumor cells.[11] They also revealed that the overexpression of PDGF was detected in alveolar macrophages and PDGFR in intimal mesenchymal cells in the pulmonary artery wall, which suggested the contribution of the activated alveolar macrophages to the onset of PTTM.

The standard treatment for PTTM is not established, but it is possible that imatinib, which is a tyrosine kinase inhibitor of the PDGFR, led to regression of pulmonary hypertension and pulmonary artery remodeling in PTTM in a Japanese case report.[19]

In our patient, imatinib was administered as part of a clinical trial approved by the Institutional Review Board of the University of Tokyo Hospital. Although both PAP and the CI temporarily improved after administration of imatinib, the single-agent administration of imatinib did not suppress the disease progression of breast cancer itself. However, imatinib was efficacious in preventing the deterioration of hemodynamics and the progression of respiratory failure. The fact that tumor cells were immunohistochemically positive for PDGF-B suggested that PDGF played a role in causing PTTM and seemed to support, in this case, the efficacy of imatinib. The patient had not been able to tolerate chemotherapy at symptom onset because of her poor physical condition. It would be valuable to conduct a well-designed clinical trial to evaluate the use of chemotherapy combined with imatinib for PTTM.

Conclusion

PTTM is a cancer-related pulmonary complication that is fatal because of its extremely rapid progression. Therefore, it is important to be aware of PTTM as a differential diagnosis for patients with progressing hypoxia without pulmonary embolism. Imatinib might prove to be an effective therapy for PTTM, but further investigation will be necessary to confirm whether this is the case.

Disclosure

The authors have stated that they have no conflicts of interest.

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肺高血圧治療の新展開

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Point

- 肺高血圧治療薬は次々と新薬が登場しているが、最近においても昨年トレプロスチニルおよびリオシグアト(CTEPHに対する適応。本年PAHに対しても適応拡大)が、本年マシテンタンが承認された。
- かつてPAHの治療目標は短期間の自覚症状や運動耐容能の改善などであったが、近年ではより長期に渡る予後の改善にシフトしてきている。臨床試験も死亡や肺高血圧による入院、肺移植といった臨床的悪化までの期間を主要評価項目としたものに変化してきている。
- PAHにおける初期併用療法の現在のガイドラインにおける推奨度は低いが、近年アンブリセンタンとタダラフィルの初期併用療法の有効性を示した臨床試験の結果が発表された。これに伴い、今後初期併用療法の推奨度は高まるものと予想される。
- CTEPHの分野でもBPAやリオシグアトなど、新たな治療オプションが次々と登場している。NOACの静脈血栓症に対する有効性の報告も相次いでおり、CTEPHへの臨床応用も進みつつある。

近年の治療薬の進歩に伴って肺動脈性高血圧症(pulmonary arterial hypertension；PAH)の治療成績は飛躍的に進歩している。これに伴い、PAHの治療目標も以前は短期間の自覚症状や運動耐容能の改善などであったものが、近年ではより長期に渡る予後の改善にシフトしてきており、臨床試験も死亡や肺高血圧による入院、肺移植といった臨床的悪化までの期間を主要評価項目としたものに変化してきている。本項では近年承認された、あるいは承認される見込みの薬剤を紹介するとともに、このような新たなエビデンスに基づいた治療戦略の変化について解説する。

一方、慢性血栓塞栓性肺高血圧症(chronic thromboembolic pulmonary hypertension；CTEPH)においては、わが国では世界に先駆けて肺動脈バルーン形成術(balloon pulmonary angioplasty；BPA)が普及しているが、近年肺血管拡張薬としてリオシグアトが世界で初めてCTEPH治療薬として承認された。また、CTEPHの支持療法として抗凝固薬は必須であるが、新規凝固薬[非ビタミンK拮抗抗凝固薬(non-vitamin K antagonist oral anticoagulant；NOAC)]の静脈血栓症に対する有効性の報告も相次いでいる。国内で静脈血栓症に対して適応を取得しているNOACは現時点ではエドキサバンのみであるが、今後CTEPHに対するNOACの使用も広まってくることが予想される。このような現状を踏まえたCTEPHに対する最新の治療方針についても解説する。

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近年承認された/承認が期待される治療薬

リオシグアト(アデムパス®)

sGC刺激薬であるリオシグアトはsGC活性を刺激して細胞内のcGMPの濃度を上昇させ、血管平滑筋を弛緩させる。これはNO経路に含まれるものではあるが、リオシグアトにはsGCの内因性NOに対する反応性を増強する作用のみならず、NOによる刺激がない状況、すなわちNO非依存性にもsGCを直接刺激するという2つの作用があるという点が大きな特徴であり、この点においてより強力な血管拡張作用を発揮することが期待される。

リオシグアトはPAHおよびCTEPHに対して開発が進められ[1,2]、わが国では2014年にCTEPH治療薬として承認され、2015年2月にPAHに対する適応拡大が承認された。特にCTEPHに対しては、現時点では運動耐容能及び血行動態を改善することが示された世界で唯一の肺血管拡張薬である。

リオシグアトは最高1回2.5mgまでで1日3回内服するが、効果および副作用には個人差があるため、1回1.0mgから開始し、2週間ごとに0.5mgずつ量を増減する。原則として収縮期血圧が95mmHg以上あれば増量可能であり、95mmHg未満で低血圧症状を伴う場合には減量を考慮する。副作用としては頭痛、めまい、末梢性浮腫、低血圧、失神、胸焼けなどがある。

なお、リオシグアトと同じNO経路の薬剤であるホスホジエステラーゼ5阻害薬(phosphodiesterase 5 inhibitor；PDE5)阻害薬との併用の効果を検討する試験が行われたが、この試験ではリオシグアトは肺血行動態、6分間歩行距離などにおいて併用の有効性を示すことができなかった[3]。さらに、併用群、PDE5阻害薬単剤群の両群において同様に体血圧が低下し、12週間の試験期間中には両群間で投与中止イベントの差はなかったものの、全例に対して実薬投与を行った長期継続試験に移行後、投与中止に至る有害事象が多発したため、安全性の面でPDE5阻害薬とリオシグアトの併用は原則禁忌である。

トレプロスチニル(トレプロスト®)

トレプロスチニルは持続静注もしくは皮下注により投与するプロスタサイクリン製剤であり、わが国では2014年9月に薬価収載となった。力価はエポプロステノールの2/3～1/2程度と考えられており、エポプロステノールと同等の治療効果を得るためには1.5～2倍程度の投与量が必要である。インスリンポンプを用いた持続皮下注が可能であるが、穿刺部痛が必発なので疼痛対策が必要である。通常は薬液の交換の度に針も刺し変えるが、同一の穿刺部位を長期(1週間以上)継続すると疼痛が軽減するとの報告もあり、疼痛の強い患者に対しては試みる価値があると思われる[4]。常温で安定であるため、薬液の交換は2～3日に1回でよい(ただし、高用量となり薬液が不足してしまう場合にはこの限りではない)。持続静注で投与する場合の投与法はエポプロステノールに準じる。溶解液として蒸留水、生理食塩水も使用可能であるが、中性の溶解液はカテーテル感染のリスクを高めるため、アルカリ性のフローラン®の溶解液を用いるのがよい[5]。

マシテンタン(オプスミット®)

マシテンタンはET_AとET_Bの両者を阻害するエンドセリン受容体拮抗薬(endothelin receptor antagonist；ERA)であり、既存のERAと比べ肝機能障害、浮腫いずれの発現頻度も低い。海外でPAH患者742人が参加して行われた第Ⅲ相試験(SERAPHIN試験)では、複合エンドポイント(死亡、心房中隔裂開術、肺移植、静注または皮下注プロスタノイドの開始、PAH増悪)発生のプラセボ群に対するハザード比がマシテンタン10mg投与群で0.55(97.5％CI 0.39-0.76；$p<0.001$)と、マシテンタンは臨床的悪化イベントを有意に抑制することが示された(図1)[6]。この結果をもとに欧米ではすでに保険適用となっており、国内でも2015年3月に承認を得て現在発売準備中である。

Selexipag

経口のプロスタサイクリン製剤であり、海外で

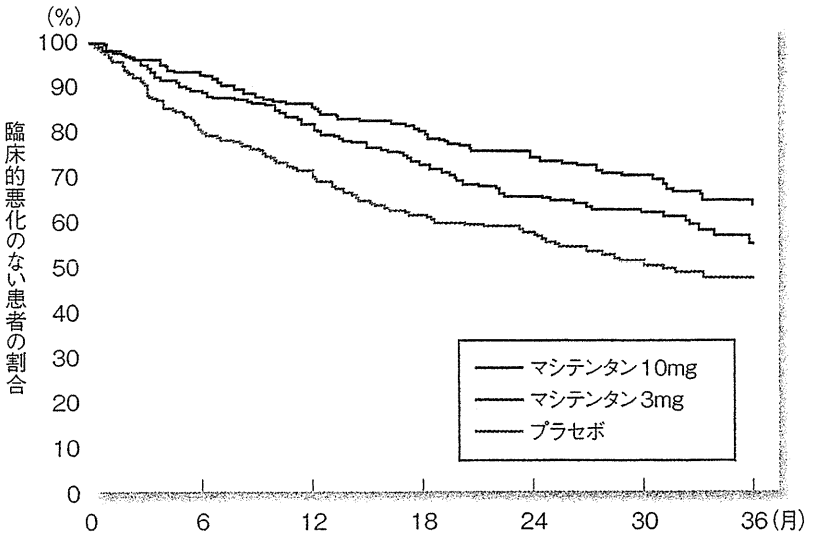

図1　マシテンタンの臨床的悪化に対する効果
(文献6より引用)

臨床的悪化：死亡、心房中隔裂開術、肺移植、静注または皮下注プロスタノイドの開始、PAH増悪

PAH患者1,156人が参加して行われた第Ⅲ相試験(GRIPHON試験)では、病態悪化/死亡イベントの発生リスクをプラセボ群に比較して39%抑制した($p < 0.0001$)。本薬剤は非経口のプロスタサイクリン製剤であるエポプロステノールやトレプロスチニル同様に、幅広い投与量選択ができるよう臨床試験がデザインされたことが特徴であり、高用量の本剤投与に認容性のある患者においては、既存の経口プロスタサイクリン製剤よりも高い有用性が得られる可能性がある。欧州ではGRIPHON試験の結果を得て現在販売承認申請中であり、国内でも近い将来の承認申請が期待される。

Iloprost

吸入のプロスタサイクリン製剤。I-neb AAD systemという専用の吸入器を用いて1回2.5～5.0 μgを1日6～9回吸入する。欧米ではすでに60カ国以上で使用されており、国内でも現在第Ⅲ相試験中である。

新たな臨床試験のデザインと初期併用療法のエビデンス

古くからPAH治療薬の効果を見る指標として6分間歩行が使用され、多くの臨床試験の主要評価項目とされてきた。しかしながら、ベースラインの6分間歩行距離は予後予測に有用であるものの、22の臨床試験のメタ解析では6分間歩行距離の改善度と予後は相関しないことが示され、試験デザインの見直しが求められるようになってきている(図2)[7]。このため、近年の臨床試験は死亡や肺高血圧による入院、肺移植といった臨床的悪化までの期間を主要評価項目としたものに変化してきており、前項で取り上げたマシテンタンおよびselexipagの臨床試験はこのような新しい試験デザインを取り入れて行われた(図3)[8]。

近年、始めから2剤ないし3剤の併用を行う方法(初期併用療法)の有効性も報告されてきているが、論文化されているものはパイロットスタディにとどまり、エビデンスが不足しているとの理由で現在のガイドラインにおける推奨度は低いものにとどまっている(図4)[9]。しかし、初期併用療法においても臨床的悪化までの期間を主要評価項目とした大規模臨床試験(AMBITION試験)が初めて行われ、2014年の欧州呼吸器学会においてその結果が発表された。これはアンブリセンタンとタダラフィルの初期併用療法の有効性を検討したもので、初期併用療法群(253人)はいずれか一方の単剤治療群(アンブリセンタン単剤群126人、タダラフィル単剤群121人)に比べ、イベント(死亡、PAH増悪による入院、疾患進行あるいは十分な治

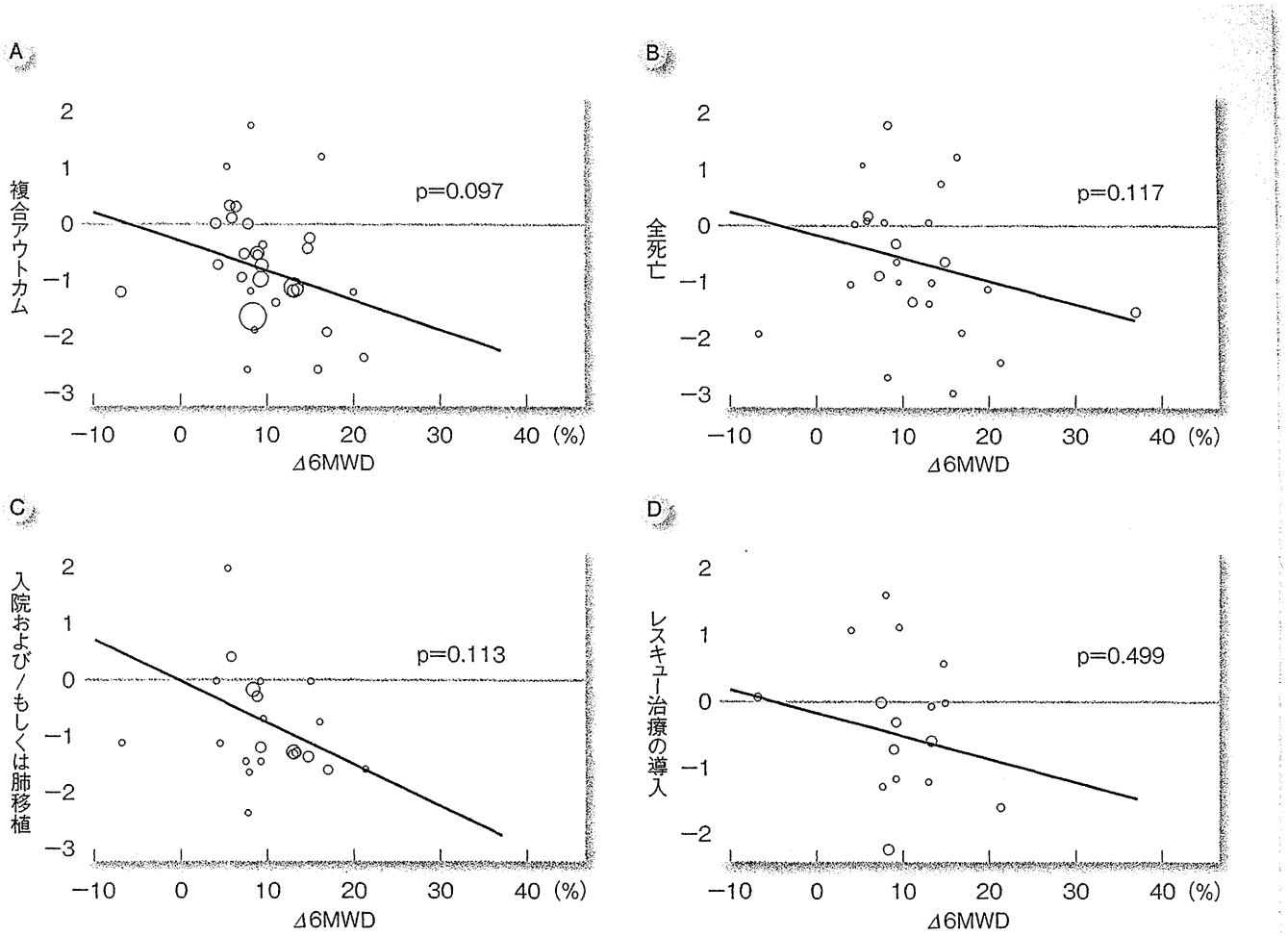

図2　6分間歩行距離の変化(Δ6MWD)と予後および臨床的悪化との相関(文献7より引用)

Δ6MWDは全死亡(B)、入院および/もしくは肺移植(C)、レスキュー治療の導入(D)、およびこれらを複合したもの(A)のいずれとも相関を認めなかった。

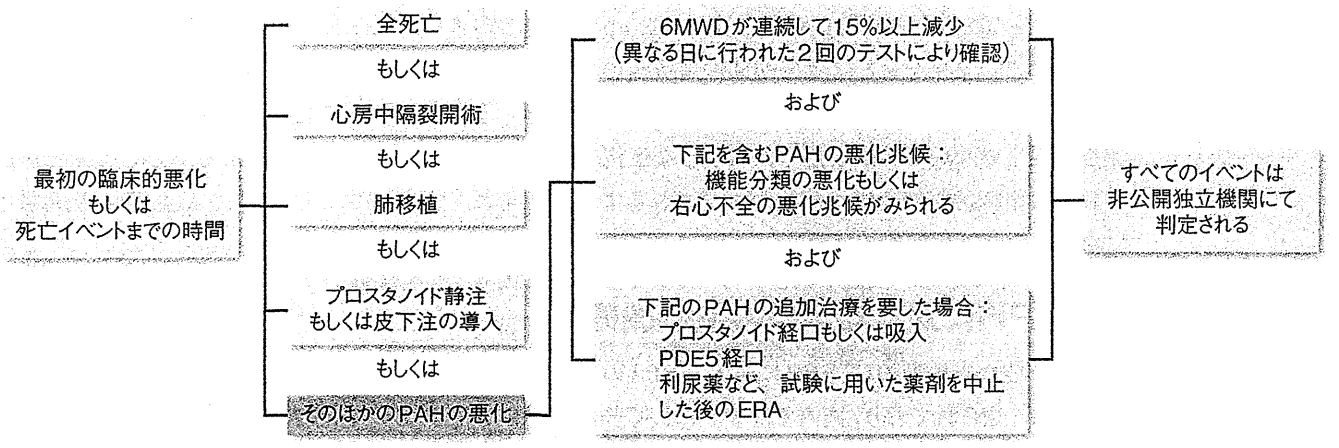

図3　SERAPHIN試験における主要評価項目(文献8より引用)

PAH：肺動脈性高血圧症、6MWD：6分間歩行距離、PDE5：ホスホジエステラーゼ5阻害薬、ERA：エンドセリン受容体拮抗薬

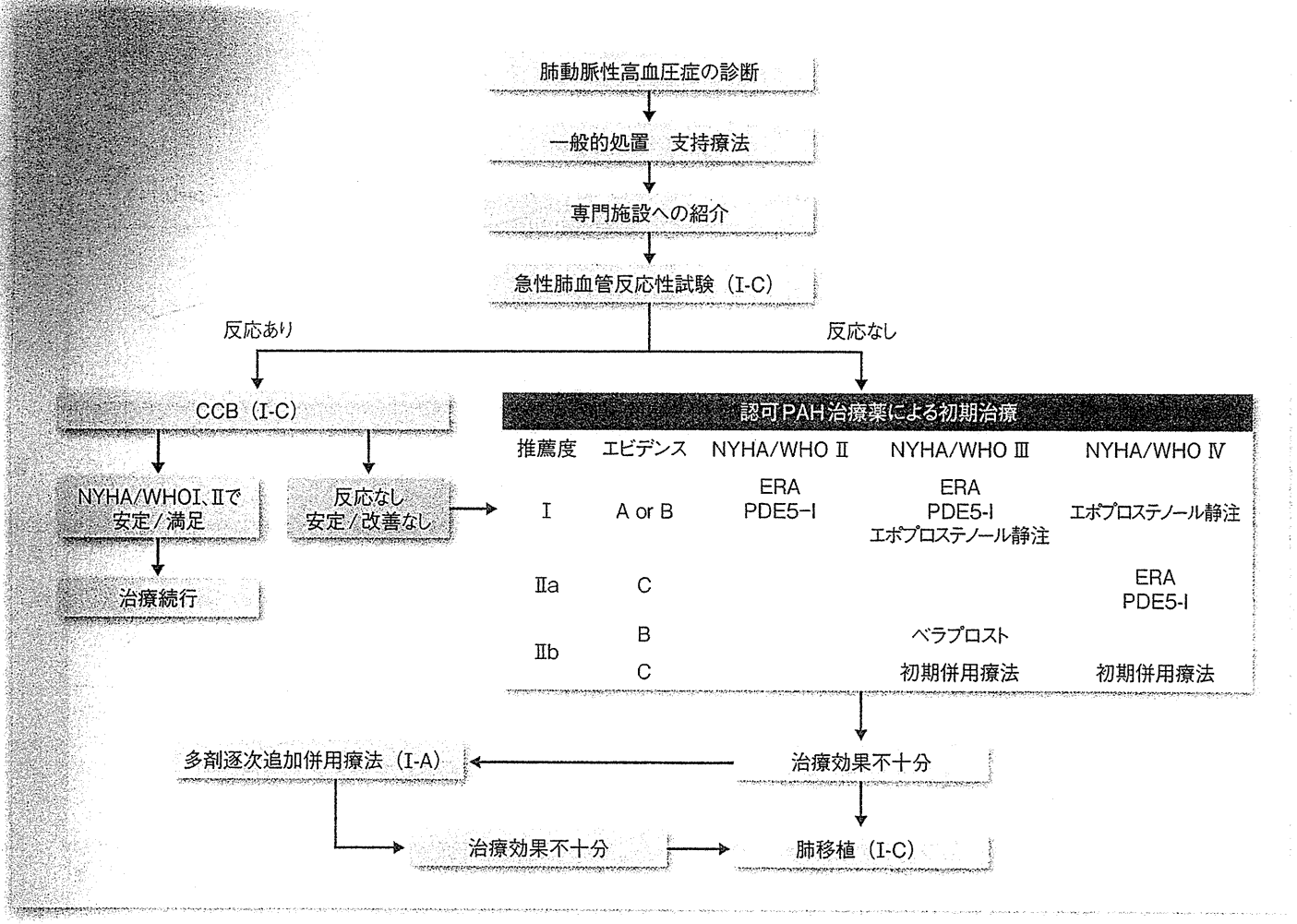

図4　肺動脈性肺高血圧症に対する治療手順(文献9より引用)

現在のガイドライン上は、初期併用療法は推奨度IIb、エビデンスレベルCと低いものにとどまっている。
ERA：エンドセリン受容体拮抗薬(アンブリセンタン、ボセンタン)
PDE5-I：ホスホジエステラーゼ5阻害薬(シルデナフィル、タダラフィル)

療効果が認められない状態の長期継続で定義)発生リスクを50%低下させた(ハザード比0.502；p＝0.0002)。この結果をもとに今後初期併用療法のエビデンスレベルが上がり、初めから1剤では治療目標を達成できないことが予想されるような症例に対しては積極的な初期併用療法が推奨されるようになるものと思われる。

CTEPHに対する最新の治療戦略

手術不能な末梢型のCTEPHに対するBPAの有用性はよく知られており、国内ではすでに広く普及している。一方で、近年肺血管拡張薬としてリオシグアトが世界で初めてCTEPH治療薬として承認された。このように新しい治療法が出現して治療が進歩していく一方で、今後は内服薬とBPAをどのように組み合わせて治療していくべきか、新たなガイドラインの作成が求められる(図5)[9]。

また、CTEPHにおいて抗凝固療法は必須であるが、近年静脈血栓症に対するNOACの開発が進められており、すでに海外の大規模臨床試験においてダビガトラン、リバーロキサバン、アピキサバン、エドキサバンのいずれも静脈血栓塞栓症に対してワーファリンと有効性においては非劣勢であり、安全性においては大出血の頻度は低いことが示されている(表1)[10]。実際、エドキサバン(リクシアナ®)は国内ですでに静脈血栓塞栓症に対する適応を取得済みであり、リバーロキサバン(イグザレルト®)も国内臨床試験の結果が発表さ

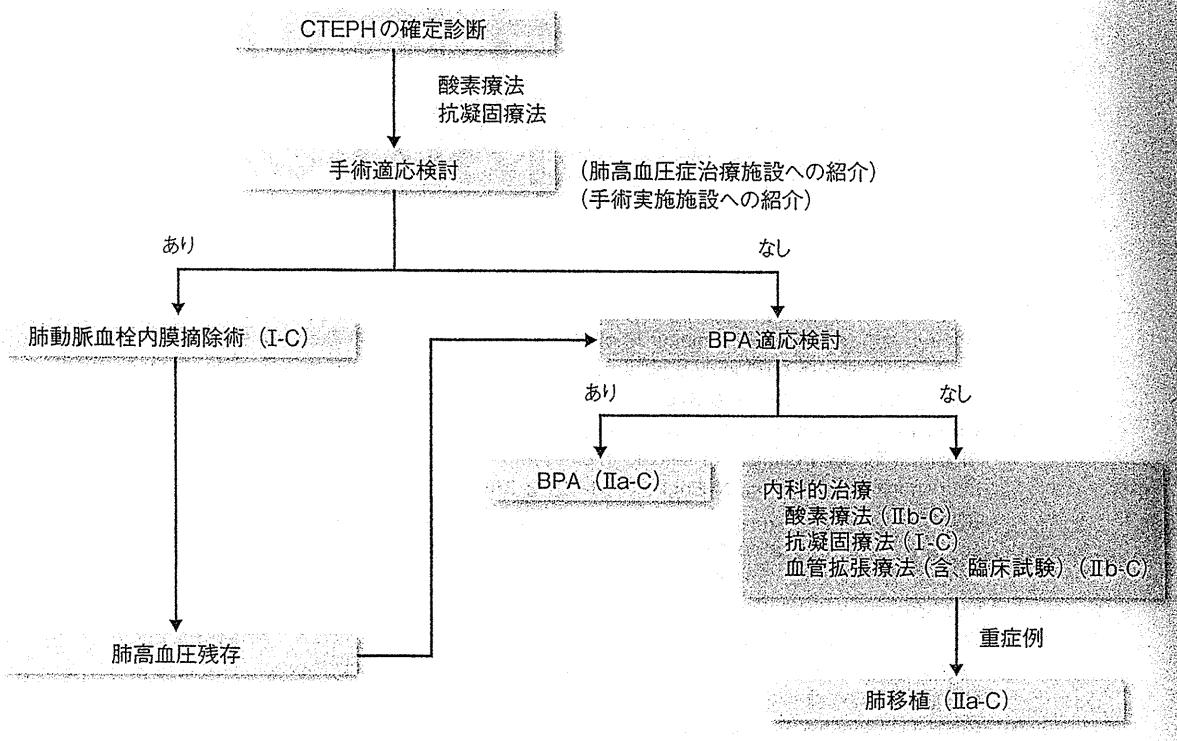

図5　CTEPHの治療手順(文献9より引用)

現在のガイドラインはリオシグアトが承認になる前に作成されたものであることに注意が必要である。
BPA：肺動脈バルーン形成術

薬剤	試験	期間	有効性			安全性		
			VTE再発 NOAC	VTE再発 VKA	HR (95%CI)	NOACによる大出血	VKAによる大出血	HR (95%CI)
ダビガトラン	RE-COVER	6カ月	2.4%	2.1%	1.10 (0.65-1.84)	1.6%	1.9%	0.82 (0.45-1.48)
	RE-COVER II		2.3%	2.2%	1.08 (0.64-1.80)	1.2%	1.7%	0.69 (0.36-1.32)
リバーロキサバン	EINSTEIN-DVT	3〜12カ月	2.1%	3.0%	0.68 (0.44-1.04)	0.8%	1.2%	0.65 (0.33-1.30)
	EINSTEIN-PE	3〜12カ月	2.1%	1.8%	1.12 (0.75-1.68)	1.1%	2.2%	0.49 (0.31-0.79)
アピキサバン	AMPLIFY	6カ月	2.3%	2.7%	0.84 (0.60-1.18)	0.6%	1.8%	0.31 (0.17-0.55)
エドキサバン	HOKUSAI-VTE	3〜12カ月	3.2%	3.5%	0.89 (0.70-1.13)	1.4%	1.6%	0.84 (0.59-1.21)

表1　静脈血栓塞栓症に対するNOACの有効性・安全性を検討した第Ⅲ相試験の結果一覧
(文献10より引用)

NOACはワルファリンと比し、有効性の面では非劣勢であり、安全性の面では大出血の頻度は低い。
注：2015年3月末時点でエドキサバン以外は静脈塞栓症に関して国内未承認。
NOAC：非ビタミンK拮抗抗凝固薬、VKA：ビタミンK拮抗薬、VTE：静脈血栓塞栓症

れ[11]、現在静脈血栓塞栓症への適応拡大の承認申請中である。今後NOACはCTEPHにおける抗凝固療法としても使用が拡大していくものと思われる。

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臨　床

右心機能に着目した肺高血圧症の治療戦略

Treatment strategy for pulmonary hypertension focused on right ventricular function

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KEY WORD
右心不全，TAPSE，三次元心エコー，Upfront combination therapy

はじめに

肺高血圧症(pulmonary hypertension：PH)はかつて予後不良の疾患であり，その死因の多くは右心不全であった。このため，PH治療の目指すべきところは右心機能の保持，改善にあることは言うまでもない。PHにおいてスクリーニングや早期診断の重要性が広く認識されるようになった現代では，右心不全が顕在化する前に治療が開始されるケースが多くなってきていると思われるが，実際に右心不全に陥ってしまった場合の管理上重要なポイント，さらには慢性期に右心機能を保持して長期予後を改善するための治療戦略について解説する。なお，本項におけるPHとは主として肺動脈性肺高血圧症(pulmonary arterial hypertension：PAH)を念頭においていることに注意されたいが，慢性血栓塞栓性肺高血圧症(chronic thromboembolic pulmonary hypertension：CTEPH)における右心不全の管理は概ねPAHと同様であると考えてよい。

PH患者における右心不全の定義

PH患者における右心不全とは，右室の後負荷増大に引き続き循環不全と静脈圧上昇が生じた状態と定義される。臨床的には運動耐容能低下と体液貯留の兆候を示す。心拍出量が高度に低下した場合には失神を認めることもある。日本循環器学会の肺高血圧症治療ガイドラインでは，PAHの重症度/予後評価の決定因子を表1のように定めており，心拍出量や運動耐容能低下を表す因子としてWHO機能分類Ⅲ，Ⅳ度，6分間歩行距離300m以下，最大酸素摂取量12mL/min/kg以下，心係数(cardiac index：CI)2.0L/min/m^2以下を，体液貯留を表す因子として心嚢液貯留および右房圧(right atrium pressure：RAP)8mmHg以上を予後不良の因子としている。

右心不全合併PH患者の管理

初診時に重症の右心不全を呈しているPH患者，あるいは治療の過程で右心不全に陥ってしまったPH患者を管理する際に重要な点として，Vonk-Noordegraafらは以下の3つを挙げている[2]。

1．体液貯留のある(RAP＞10～15mmHg)患者に対しては容量負荷を避ける

容量負荷はさらなる右室拡大や心室中隔の左室側へのシフトを招き，右心機能を一層低下させてしまう。

■体液貯留のある(RAP>10～15mmHg)患者に対しては容量負荷を避ける。
■右心不全を呈している患者に対しては，血圧低下やさらなる血行動態の悪化を防ぐためのあらゆる処置を行う。

表1．肺動脈性肺高血圧症の重症度/予後評価

予後良好	予後決定因子	予後不良
無	右心不全の既往	有
遅	症状の進行度	速
無	失神	有
Ⅰ，Ⅱ	WHO-機能分類	Ⅲ，Ⅳ
500m以上	6 MWT	300m以下
15mL/min/kg以上	CPX(最大酸素摂取量)	12mL/min/kg以下
正常，ほぼ正常	BNP	非常に高値，上昇傾向
心嚢液(－)，TAPSE>2.0cm	心エコー所見	心嚢液(＋)，TAPSE<1.5cm
RA圧＜8 mmHg CI>2.5L/min/m^2	肺血行動態	RA圧≧8 mmHg CI<2.0L/min/m^2

CPX：心肺運動負荷試験

(文献1より引用)

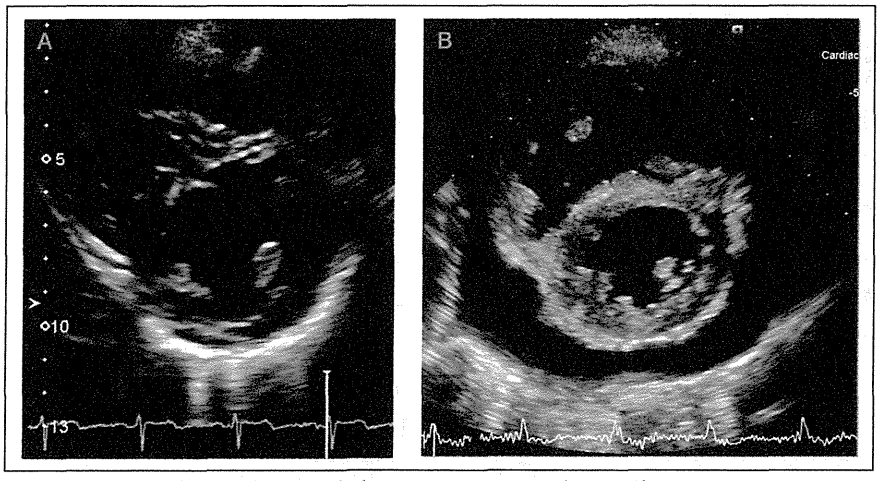

図1 症例1(A)および症例2(B)の心エコー短軸像(自験例)

症例1では心嚢液の貯留なく右心系の拡大も軽度なのに対し，症例2では右心系が著明に拡大し，大量の心嚢液貯留を認める。

2．血圧低下，心筋虚血ならびにさらなる血行動態の悪化を防ぐためのあらゆる処置を行う

不整脈に対する早急な電気的除細動，早期の強心剤・昇圧剤サポート，高炭酸ガス血症や胸腔内圧上昇を避けるなど。必要に応じて膜型人工肺(extracorporeal membrane oxygenation：ECMO)の使用も考慮する。

3．どの強心剤・昇圧剤を選択するべきかについてはいまだに結論は出ていない

ドブタミン，ドパミン，ノルアドレナリンが実際の日常臨床において使用頻度が高い。

PHの治療目標

PHの究極的な治療目標は血行動態の正常化であり，わが国では肺動脈圧の低下を目指した治療が広く行われているものと思われる。Ogawaらは，特発性/遺伝性PAH(I/HPAH)であれば平均肺動脈圧(mPAP)を42.5mmHg未満に低下させれば15年生存率が100%であることを報告しており[3]，1つの治療目標として重要な数字と考えられる。一方で，右心不全がPHの予後を規定することを考えると，肺動脈圧だけを治療目標とするのは不十分である。以下にその一例を示す。

症例1：経過9年のIPAHの27歳女性。エポプロステノール 51ng/kg/min，ボセンタン 250mg，タダラフィル 40mg，ジルチアゼム 200mg投与によりWHO機能分類Ⅱ度，BNP 20.2pg/mL，RAP 6 mmHg，mPAP 38mmHg，CI 4.26L/min/m^2，PVR 4.3WU。

症例2：経過20年のHPAHの70歳女性。エポプロステノール 28ng/kg/

■PHの予後を改善するには右心機能を保持／改善することが重要である。
■右心機能の評価には心エコーおよびMRIが優れている。

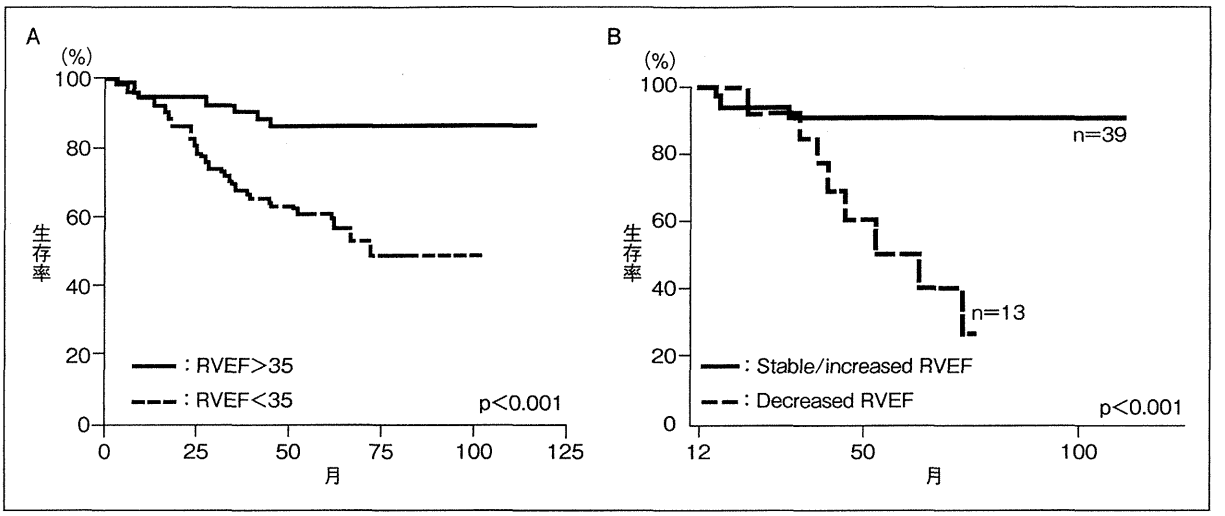

図2　右心機能と予後

A：治療開始時にRVEF＞35%であった群はRVEF＜35%の群に比べて有意に予後良好であった。
B：治療開始12ヵ月後にRVEFが改善ないし維持されていた群では，低下した群より有意に予後良好であった。

（文献4より改変引用）

min，アンブリセンタン 10mg，シルデナフィル 60mg，タダラフィル 40mg，ジルチアゼム 100mg投与によりWHO機能分類Ⅲ度，BNP 27.3pg/mL，RAP 8mmHg，mPAP 36mmHg，CI 3.61L/min/m^2，PVR 6.0WU。
PVR：肺血管抵抗，WU：wood単位

両者のmPAPはいずれも40mmHgを下回っており，肺動脈圧の面からは先に述べた治療目標を達成しているし，症例2については実際すでに発症から15年以上生存している。しかしながら，この時点から先の予後を推測するにはこれだけのデータでは不十分である。両者の心エコーの短軸像を図1に示す。右心系拡大の程度や心嚢液貯留の有無などから症例2の方が明らかに右心不全としては重症であることがわかる。このように同様の血行動態であっても年齢や病歴，基礎疾患などによって右心不全の程度は異なるため，PHの予後予測や治療目標を立てるにあたっては，右心機能の評価がきわめて重要となる。ガイドライン上の予後評価因子も右心機能・右心不全に重点を置いたものであるということができ，表1では予後良好，すなわち右心不全がないかもしくはコントロール良好な指標として，WHO機能分類Ⅰ，Ⅱ度，6分間歩行距離500m以上，最大酸素摂取量15mL/min/kg以下，心嚢液なし，RAP 8mmHg未満，CI 2.5L/min/m^2以上を挙げている。

右心機能の評価にあたって最も優れた検査は心エコーおよびMRIである。これらによる評価法の詳細は次項および次々項を参照されたい。ガイドライン上は心エコーによるTAPSEが予後予測因子として取り上げられており，1.5cm未満で予後不良，2.0cm以上で予後良好とされる。これは簡便で再現性に優れていることから，日常臨床における右心機能評価には非常に優れているといえる。一方，MRIはエポプロステノール持続静注療法施行中の患者には施行できないなどの問題点はあるものの，容量の評価には最も優れている。Vonk-NoordegraafらはPAH患者110名のMRI画像を解析し，治療開始時のRVEFが35%未満であると予後不良であり，また，12ヵ月後のRVEFが

■三次元心エコーはMRIと同等の容量評価が可能であり，エポプロステノール持続療法施行中の患者の評価に有効である。

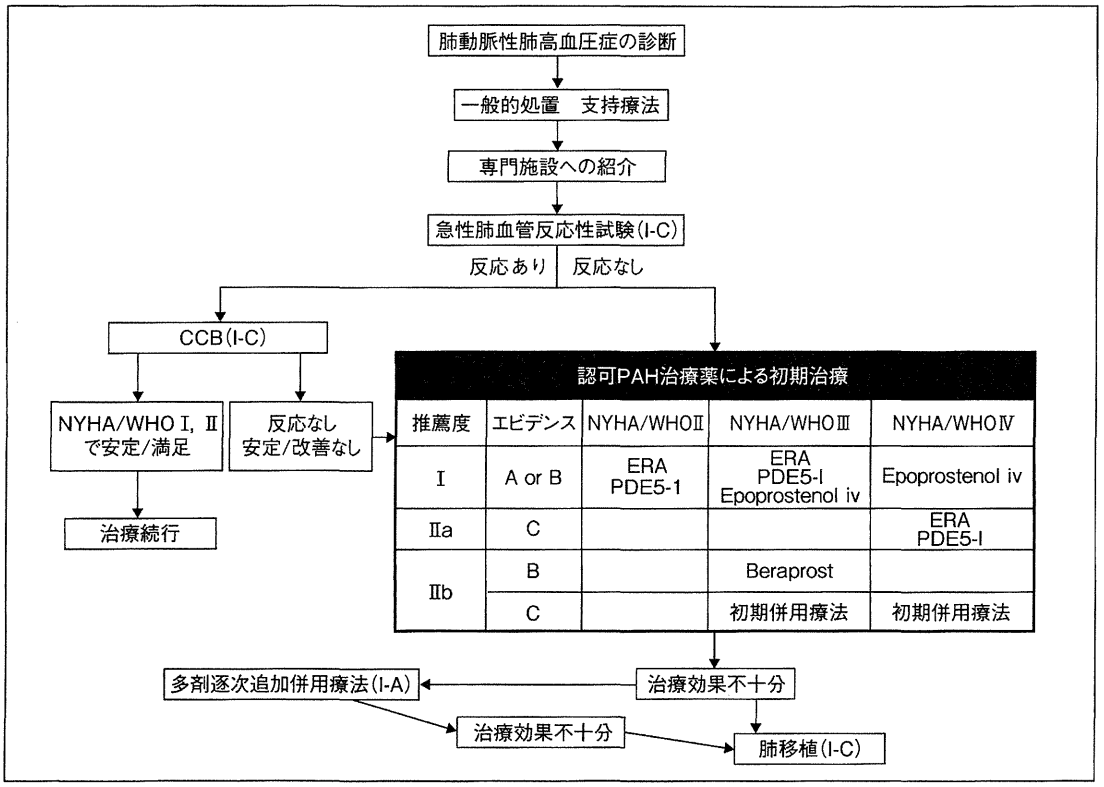

図3　肺動脈性肺高血圧症に対する治療手順

ERA：エンドセリン受容体拮抗薬（アンブリセンタン，ボセンタン）
PDE5Ⅰ：ホスホジエステラーゼ5阻害薬（シルデナフィル，タダラフィル）

（文献1より引用）

保持もしくは改善していた群では低下していた群よりも有意に予後が良好であることを報告している（図2）[4]。このように右心機能の保持/改善が予後改善のために重要であり，治療効果判定の際には右心カテーテルのみならず，必ず心エコーもしくはMRIによる評価も行うべきである。近年開発された三次元心エコーならばMRIと同等の容量評価が可能であることが報告されており[5][6]，エポプロステノール持続静注療法施行中の患者を評価する際などには有効であろう。

右心機能に着目したPHの治療戦略

さて，それでは右心機能を保持/改善することを目指したPHの治療戦略とはどのようなものであろうか。Bergotらは，エポプロステノール持続静注療法を施行されたI/HPAH患者の予後を解析したところ，内服薬による治療を一定期間（平均7ヵ月）行った後にエポプロステノールを導入された群の方が，最初からエポプロステノールを導入された群よりも予後が不良であったことを報告している[7]。さらに，最初からエポプロステノールを導入された群の中でも，初めから内服薬も併用する，いわゆるUpfront combination therapyを行われた群が1年生存率92%，3年生存率88%と最も予後がよかった。治療開始平均4ヵ