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Regular Article

Long-term treatment with low-molecular-weight heparin prolonged the survival time for acute pulmonary embolism patients concurrent with malignancy: An observational analysis from a long-term follow-up study ☆

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ABSTRACT

Background: As a special group in pulmonary embolism (PE), the baseline characteristics, better therapeutic strategy and prognosis of patients with concurrent malignancy need to be investigated. Long-term low-molecular-weight heparin (LMWH) is recommended for these patients, however, whether therapeutic strategy affects long-term prognosis remains unclear.

Methods: In this prospective study, acute symptomatic PE patients confirmed by imaging examinations, with/without malignancy, were enrolled and followed. Qanadli score was used to assess the embolic burden. The clinical endpoints included symptomatic recurrent venous thromboembolism (VTE), all-cause death and clinic relevant bleeding.

Results: In the 627 patients enrolled, 92 patients had malignancy at baseline. The median follow-up period was 36 months. The Qanadli score at baseline was lower in malignancy group than non-malignancy group ($P = 0.003$). 48.9% of patients with malignancy died, while 11.4% of non-malignancy group died ($P < 0.001$). Malignancy was a risk factor of death (HR 5.659, 95%CI 3.090-10.366, $P < 0.001$). In malignancy group, 56 patients used long-term LMWH and 36 patients received oral vitamin K antagonist (VKA). The median survival time was 30 months in LMWH group, significantly longer than 12.5 months in VKA group ($P = 0.041$). The mortality in the first 6 months was lower in LMWH group than VKA group (19.6% vs. 41.7%, $P = 0.022$).

Conclusions: PE patients with malignancy had much higher incidence of all-cause death in spite of less embolic burden compared with patients without malignancy. Anticoagulation using long-term LMWH could prolong the survival time of PE patients with malignancy, and it was more effective than VKA.

Introduction

Venous thromboembolism (VTE) is a common complication of active cancer and antineoplastic treatment. Approximately 20% of new VTE events are associated with active malignancy [1]. It is notable that patients with cancer have a 4- to 6-fold higher risk for VTE compared with non-cancer patients [2].

VTE with concurrent malignancy is associated with considerable morbidity and mortality. Short-/medium-term observation studies show that pulmonary embolism (PE) patients with malignancy are at much higher risk for recurrent thrombosis and death in comparison to patients with PE who do not have malignancy [3–6]. Furthermore, patients with concurrent malignancy at the same time or within 1 year of VTE are associated more often with advanced stage and

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unfavorable prognosis compared with patients diagnosed with malignancy without a preceding VTE event [7].

Taken together, these data highlight the need for special attention and investigation for VTE in patients with tumors. As a large and special group in PE, the baseline characteristics, better therapeutic strategy and prognosis of patients with concurrent malignancy need to be investigated and emphasized. Among the baseline characteristics, the embolic burden is a predictor of short-term clinical outcomes [8–10]. Whether the embolic burden is different between PE patients with malignancy and those without malignancy remains unclear. Long-term low-molecular-weight heparin (LMWH) is recommended for VTE patients with malignancy rather than vitamin K antagonist (VKA) [11]. Although many studies have compared the effect of LMWH and VKA, the follow-up periods were not long enough to allow a meaningful assessment of therapeutic effect on survival time. Long-term benefit of LWMH therapy lacks valid evidence. Whether therapeutic strategy affects long-term prognosis in these patients needs to be identified.

In this prospective study, we enrolled and followed a large number of acute PE patients with or without malignant tumors. The embolic burden assessed by Qanadli score was compared between patients with malignant tumors and those without malignancy. The prognosis of patients with malignancy was compared between long-term LMWH group and VKA group.

Design and Methods

Study Population

We screened all the suspected acute PE patients in Beijing Chao-yang Hospital from Jan 2006 to Mar 2011. Consecutive patients with symptomatic acute PE, confirmed by at least one of the following objective imaging examinations: computed tomography pulmonary angiography (CTPA), pulmonary ventilation-perfusion scintigraphy (V/Q scan), pulmonary arteriography or magnetic resonance pulmonary angiography, were enrolled. The diagnosis of acute PE was based primarily on validated clinical criteria, including risk factors, acute onset, typical (chest pain, dyspnea, tachycardia, hemoptysis, syncope) and nontypical symptoms, combined with fresh thrombus in pulmonary arteries and branches shown in the imaging test mentioned above. Patients were excluded if they were younger than 14 years old, had previous episodes of PE or with a life-expectancy less than 3 months. A standardized questionnaire was used to record demographic and characteristics at baseline.

The study was approved by the Ethics Committee. Informed consent was obtained from all the patients.

Embolic Burden Assessment

The embolic burden was assessed by two independent investigators, using the Qanadli score [12]. The Qanadli score can be expressed as: $\Sigma(n \bullet d)/40 \times 100\%$, where n is the value of the proximal thrombus equal to the number of segmental branches arising distally (minimum, 1; maximum, 20), and d is the degree of obstruction (0 with no thrombus; 1 with partially occlusion; or 2, with total occlusion).

Treatment

The therapeutic strategy was determined based on the European Society of Cardiology guidelines [13]. High-risk and selected intermediate-risk PE patients received thrombolytic therapy if there weren't any absolute contraindications, while low-risk patients received anticoagulation therapy.

Patients received initial anticoagulation treatment with intravenous unfractionated heparin sodium, or a weight-adjusted, twice-daily dose of subcutaneous LMWH. The dose of LMWH remained the same during the period of anticoagulation therapy. Part of the patients received long-term (3 months at least) LMWH, while other patients received oral VKA for at least 3 months, with a target international normalized ratio of 2.0 to 3.0.

Follow-up and Endpoints

All the patients were followed in 3, 6, 12, 24, 36 and 60 months after the initial PE event. Patients with VTE symptoms or signs recurred or aggravated during the follow-up period received objective imaging examinations, including CTPA or V/Q scan, venous compression duplex ultrasound or computed tomographic venography. Recurrent PE was diagnosed with an acute onset, the presence of fresh thrombus in imaging

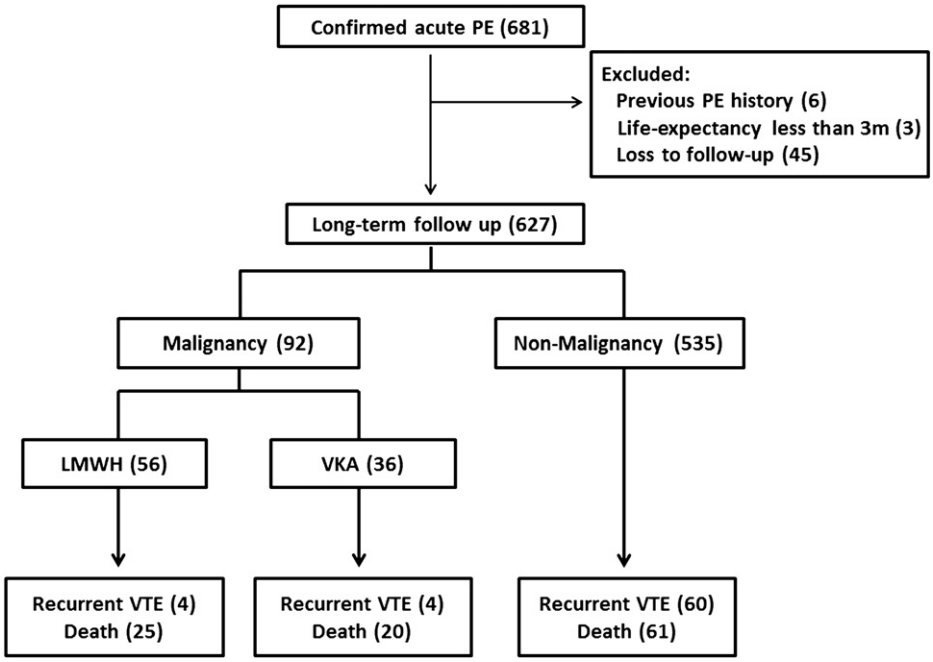

Fig. 1. The flow chart of the study. PE = pulmonary embolism, VKA = vitamin K antagonist, LMWH = low-molecular-weight heparin, VTE = venous thromboembolism.