RAPID COMMUNICATION

Thrombolysis treatment for submassive pulmonary thromboembolism in patients with cancer: a safe therapeutic tool

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INTRODUCTION

The number of cancer patients admitted to intensive care units (ICUs) around the world has increased with recent improvements in cancer therapies. Cancer is now recognized as a chronic disease that is associated with possible acute decompensation caused by cardiovascular, respiratory or infectious disorders, which makes treating these patients challenging.[1]

Pulmonary thromboembolism is a common cause of morbidity and mortality in cancer patients and is mainly caused by pulmonary hypertension and right ventricle dysfunction. A submassive embolism in a cancer patient may increase morbidity, delay anticancer therapy, and decrease the patient's quality of life.[2]

A submassive pulmonary embolism is diagnosed when the patient presents right ventricle failure and pulmonary hypertension without hemodynamic instability. Treatment with thrombolytic agents during routine medical practice has altered the natural treatment course for massive and submassive pulmonary embolism. Thrombolysis is currently the standard treatment for patients with a massive thromboembolism, and this treatment is associated with a significant reduction in mortality. However, thrombolytic treatment for submassive embolisms remains controversial.[2,3] Konstantinides et al[3] published a study reporting better outcomes in patients with submassive pulmonary embolism that were treated with thrombolysis, including a decreased need for mechanical ventilation and vasopressor use, as compared to anticoagulation alone.[3] However, in cancer patients, thrombolysis may be associated with an increased risk of bleeding.[4] The incidences of coagulopathy, thrombocytopenia, and hemorrhagic disorders in cancer patients are significantly higher compared to patients without cancer, what results in a higher risk of fatal bleeding.[5] For example, patients with brain metastasis of a solid tumor should never be treated with thrombolysis; thus, many cancer patients are ineligible for this treatment.[6,7]

Here, we describe four oncology patients with acute submassive pulmonary embolisms who were treated with alteplase and heparin. The aim of this study was to assess thrombolytic therapy in patients with a solid metastatic tumor, thereby assessing its potential therapeutic benefit in cancer patients with venous thromboembolism.

PATIENTS AND METHODS

The Local Ethics Committee of our hospital approved this study.

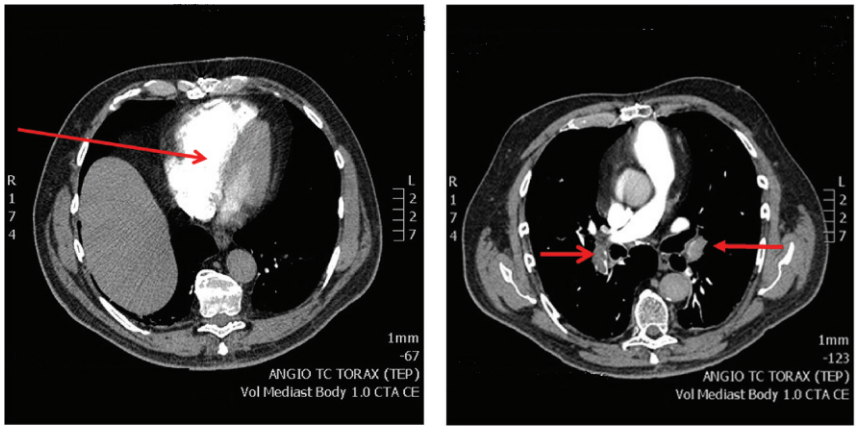
Four patients who developed or were admitted for a submassive pulmonary embolism to the Instituto do Cancer do Estado de Sao Paulo Intensive Care Unit (ICU) in Brazil between January 2009 and October 2010 were enrolled in this study. A submassive PE was defined as an acute thromboembolism with evidence of right ventricular dysfunction and no evidence of hemodynamic instability (no need for vasopressors).[7-9]

The patients' clinical parameters were prospectively collected and included each patient's demographic data, preexisting medical conditions, cancer status, previous cancer treatment, functional scores, risk scores, and organ dysfunction. At the time of admission, the patient's family members were questioned about the patient's status performance using the Karnofsky performance status scale.[10]

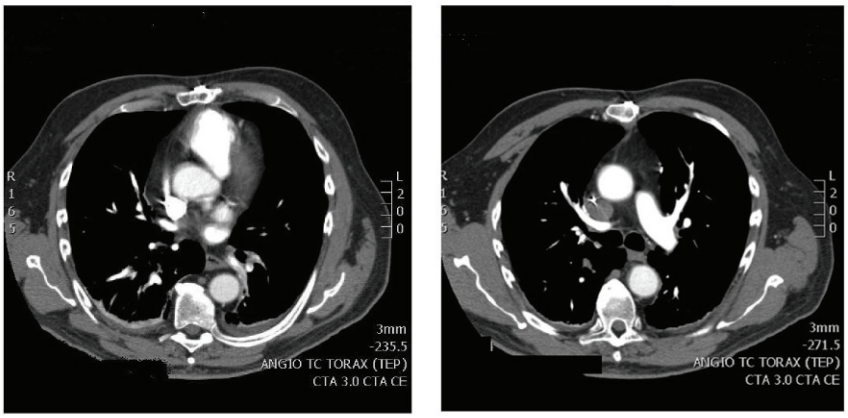
Echocardiography was used to evaluate right ventricular dysfunction. Moreover, cardiac biomarkers, including troponin, creatine-kinase MB (CKMB) and brain-type natriuretic peptide (BNP) were quantified. A pulmonary thromboembolism was confirmed by contrast-enhanced computed tomography (CT) of the chest (Figure 1).

A central venous catheter and an indwelling arterial catheter were placed in all of the patients. Either a pulmonary arterial catheter or a minimally invasive cardiac output measurement device (Vigileo-FloTrac) was used to monitor the cardiac output. Fluid management and the use of vasopressors or inotropic agents were applied according to the ICU's specific protocols.

Alteplase (Actilyse, Boehringer Ingelheim Pharma) was administered as deemed necessary by the ICU physician team. A 10 mg bolus followed by a 90 mg intravenous infusion over a period of two hours was administered, resulting in a total dose of 100 mg. Unfractionated heparin was continually administered at a rate of 12 U/kg/h, and the rate was subsequently adjusted to maintain an active partial thromboplastin time 2.0- to 2.5-fold above the normal upper limit.[6,7] After 24 hours, if there were no bleeding



a.b. contrast-enhanced computed tomography (CT) of the chest showing right ventricle dilation and thrombus in both segmentar arteries. (Patient 4)



c.d. contrast-enhanced computed tomography (CT) of the chest showing normalization of right ventricle dimension and reperfusion in both segmentar arteries. (Patient 4)

Figure 1 - Contrast-enhanced computed tomography of the chest (Patient 4).

complications or renal failure, heparin treatment was replaced by treatment with 1 mg/kg of enoxaparin twice a day subcutaneously. The patient's general clinical parameters and hemodynamic parameters were monitored for 24 hours after thrombolysis. The hemoglobin level, coagulogram and platelet count were analyzed every 4 hours. An echocardiogram and a CT were performed prior to thrombolysis and 24 hours after treatment.

Demographic and Clinical Data

Four patients were admitted to the ICU for a submassive pulmonary embolism (Table 1). The age of the patients

Table 1 - Patient characteristics.

Patient #	1	2	3	4
Age (years)	70	39	21	83
Gender	F	M	F	M
Neoplasm	Rectal cancer	Lung cancer	Osteosarcoma	Rectal cancer
Metastasis	Liver, retroperitoneum	Cervical and Thoracic Lymph nodes	Bone, Liver	Absent
Comorbidities	Hypertension, Diabetes	Absent	Absent	Chronic coronary disease
Karnofsky score (at least 30 days before ICU admission)	90	70	50	90
Chemotherapy (at least 4 weeks before hospitalization)	Yes	No	No	Yes
Active disease	Yes	Yes	Yes	Yes

F: female; M: male; ICU: intensive care unit.

ranged from 21 to 83 years, and two of the patients were male. All of the patients had an active solid tumor, and three of the patients had metastatic cancer. None of the patients had major comorbidities, and the patients' performance statuses, as evaluated by the Karnofsky scale, ranged from 50 to 90. Two patients received chemotherapy at least 30 days prior to ICU admission.

Chest pain and dyspnea were the most common symptoms reported for all of the patients (Table 2). At the time of presentation, two patients had a systolic blood pressure less than 90 mmHg, which normalized after fluid therapy. Echocardiography indicated right ventricular dysfunction and pulmonary hypertension in all of the patients. The systolic pulmonary arterial pressure, which was evaluated with echocardiography, ranged from 50 to 73 mmHg. No patient presented left ventricular dysfunction during the imaging studies, and two patients presented mildly elevated cardiac biomarker levels. The troponin level was measured immediately after ICU admission, and the values ranged between 0.01 and 0.09 ng/mL. The CKMB level ranged between 1.8 and 4.7 ng/mL. The brain natriuretic peptide level was analyzed at admission, and the data ranged between 62 and 187 pg/mL. Concomitant deep venous thrombosis was found in all of the patients, and one of the patients had a prior deep vein thrombosis. This patient also had a previous pulmonary thromboembolism and received vitamin K antagonists.

Table 2 - Patient clinical data and outcome.

Variable	Data
Symptom presentation (%)	
Chest pain	4 (100%)
Dyspnea	4 (100%)
Syncope	0
Cough	0
Hemoptysis	0
Time since symptoms to thrombolysis (median, hours)	40
Systolic pulmonary artery pressure (mmHg)	
Prior to thrombolysis	50 – 73
Post-thrombolysis	23 – 50
Right ventricular hypokinesis (%)	3 (75%)
Right heart thrombus (%)	1 (25%)
Left ventricular ejection fraction (range, %)	54 – 68
Concomitant deep vein thrombosis (%)	3 (75%)
Prior deep vein thrombosis (%)	1 (25%)
Prior pulmonary embolism (%)	1 (25%)
Chronic lung disease (%)	0
Heart failure (%)	0
Trauma within 2 mo.	0
Creatinine >2.0 mg/dL	0
Therapy (%)	
Thrombolysis	4 (100%)
Heparin	4 (100%)
Vitamin K antagonist	0
Inferior venous cave filter	1 (25%)
Catheter thrombectomy	0
Surgical embolectomy	0
No reperfusion therapy	0
Mechanical ventilation	0
Dialysis	0
Vasoactive agents (%)	2 (50%)
Dobutamine	2 (50%)
Norepinephrine	0
Vasopressin	0
Epinephrine	0
Hospital mortality	1 (25%)

All of the patients received systemic thrombolytic therapy with alteplase and anticoagulation with unfractionated heparin. An echocardiography that was performed 24 hours after thrombolysis indicated that all of the patients had visible recovery of right ventricular dysfunction and decreased pulmonary hypertension (range 23 to 50 mmHg). Three of the patients presented total vascular reperfusion, as was evident in the CT (Figure 1). One patient with a recurrent pulmonary thromboembolism received an inferior vena cava filter. None of the patients required thrombectomy, surgical embolectomy, mechanical ventilation or dialysis. There were no occurrences of intracranial bleeding, gastrointestinal or in-hospital bleeding. The hemoglobin level slightly decreased after thrombolytic therapy (mean hemoglobin decrease of 0.8 g/dL), although this decrease was not clinically significant. One patient (number 3 in Table 1) died 10 days after thrombolysis due to progressive cancer and multiple organ failure. This patient had liver and bone metastasis, and after 10 days, she developed multiple organ failure and died.

DISCUSSION

Although the data regarding thrombolysis treatment in patients with a submassive pulmonary thromboembolism are not definitive,[11,12] our data here illustrate the potential benefits of thrombolytic therapy in cancer patients. A large controlled clinical trial is needed to confirm the role of thrombolytic therapy in submassive pulmonary embolism. However, our data show that if a careful screen for potential bleeding is performed, this therapy may be safe and effective, even in critically ill cancer patients.[13-16]

Our patients presented significant clinical improvement after thrombolysis, which was confirmed by a rapid recovery of right ventricular function. Thrombolysis was relatively rapidly administered after the onset of the symptoms, which may explain the clinical success observed in these patients.

The use of submassive thromboembolism treatment has been controversial for decades.[11,12] In a controlled randomized trial with 256 patients, Konstantinides et al[3] compared heparin plus alteplase to heparin treatment alone in patients with a submassive pulmonary embolism using a composite primary end-point that included in-hospital death and clinical deterioration requiring escalation of care.[3] This study indicated that patients who received heparin and alteplase showed more improvement compared to patients who received heparin alone; however, there was no difference in the mortality rate for the two groups of patients. The number of patients with cancer in this study was not reported.

Patients with cancer must have a minimal performance status to receive chemotherapy and radiotherapy treatment. A delay in anticancer therapy may result in disease progression and worse outcomes in these patients. In a study with 200 patients with a submassive pulmonary embolism, Kline et al[17] compared heparin alone or alteplase plus heparin treatment; they observed a higher incidence of symptomatic persistent pulmonary hypertension in the heparin only group six months after treatment.[17] However, in this study, only two patients with cancer were treated with thrombolysis. Pulmonary hypertension due to a pulmonary embolism may negatively impact the prognosis of these patients, and in some patients, pulmonary embolism may be more common and serious due to the associated cardiotoxicity of chemotherapy.[18] Although the Konstantinides et al[3]

study did not show a decrease in mortality, the potential benefit of a lower morbidity in cancer patients treated with thrombolysis may improve the patient status performance and therefore allow for further treatment.[3]

Mikkola et al[13] compared 57 cancer patients to 254 patients without cancer who were treated in five clinical trials between 1985 and 1994 with alteplase or urokinase for pulmonary embolism. There was no difference in the hospital mortality, recurrent pulmonary embolism or major bleeding complications between the two groups. Nevertheless, thrombolytic therapy in cancer patients may be underused, even in patients with a massive pulmonary embolism. In an observational prospective study, Kucher et al[4] analyzed 2,392 patients with acute pulmonary embolism, including 108 patients with massive pulmonary embolism. Among the patients with massive PE, 23 patients also had cancer. However, thrombolysis was administered to only two of the cancer patients. The author did not report why a majority of the cancer patients did not receive thrombolytic treatment.

Although the thrombolytic therapy in cancer patients seems to be safe, many physicians still consider cancer a contraindication to thrombolysis. There is no evidence that thrombolysis reduces mortality in this group of patients. However, thrombolysis decreases pulmonary hypertension, improves the quality of life, and increases the probability of continuing anticancer therapy. Further data from controlled clinical trials are required to make a conclusive decision regarding the benefits of thrombolytic therapy in cancer patients.

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