

Fondaparinux vs warfarin for the treatment of unsuspected pulmonary embolism in cancer patients

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Introduction: In cancer patients, the chest computer tomography (CT) can be used to identify asymptomatic pulmonary embolism (APE). In most cases, these patients are treated with anticoagulant drugs for at least 3 months. The American College of Physicians recommend treatment of these patients as patients with symptomatic pulmonary embolism. In this study, we evaluated and compared the efficacy and safety of fondaparinux vs warfarin in the prevention of unsuspected pulmonary embolism in patients with active cancer.

Materials and methods: A prospective and parallel group study was performed on 64 cancer patients (29 males and 35 females) with APE. A multidetector CT angiography with high spatial and temporal resolution and quality of arterial opacification was used to make the diagnosis. Lung scintigraphy was reserved to selected patients only. Patients were randomized to either the warfarin (Group A) or the fondaparinux (Group B) for 90 days. The first end point of efficacy was the persistence, reduction, or disappearance of thrombosis after 90 days. The second end point was the reappearance of thrombosis after 1 year. The first end point of safety was the development of major bleeding.

Results: We enrolled 32 patients into each treatment group. We reached the first end point of efficacy and safety in Group B which showed that fondaparinux was able to induce the disappearance of thrombotic pulmonary with a lower incidence of major bleeding events compared with warfarin. No difference in the secondary end point was recorded.

Conclusion: We suggest that the treatment of cancer patients with APE can be oriented with the administration of a standard dose of fondaparinux until the next CT lung control (3 months). However, the lack of a randomized clinical trial, including a larger patient cohort, does not allow formulation of final recommendations in these patients. A broader study would be desirable, involving a larger number of patients and a longer follow-up period.

Keywords: cancer patients, asymptomatic pulmonary embolism, fondaparinux, warfarin

Introduction

Cancer patients showed an increased risk of pulmonary embolism (PE) compared with the general population.^{1,2} These patients are subject, during the follow-ups, to imaging studies, including total body computer tomography (CT) with contrast and positron emission tomography–CT, to assess the extent of the malignancy and the response to the treatment. In these patients, the detection of unsuspected pulmonary embolism (UPE) related to asymptomatic pulmonary embolism (APE) has become increasingly common,^{3,4} with an increase in health cost.^{5,6}

In most cases, these patients are treated with anticoagulant drugs (eg, warfarin) for at least 3 months, since the American College of Chest Physicians recommends to consider these patients as patients with symptomatic PE.⁷

Warfarin is commonly used prophylactically in patients with a high risk of thromboembolic events. However, it has several potential adverse effects (eg, bleeding) and drug interactions;⁸ therefore, it requires frequent monitoring and dose adjustments with a negative impact on the quality of life.⁹

In contrast, low-molecular-weight heparins (LMWHs) have a predictable pharmacokinetic profile, few drug interactions, and good safety.¹⁰ Fondaparinux, a synthesized pentasaccharide with antifactor Xa activity, is the newest agent with venous thromboembolism (VTE) prophylaxis activity.¹¹

Here, we evaluated the efficacy and safety of fondaparinux vs warfarin in the prevention of UPE in patients with active cancer.

Materials and methods

Study design

A randomized, prospective, single-blind, and parallel group study was performed in the Department of Clinical Medicine and Surgery, “Federico II” University of Naples, between March 2013 and June 2015. The single-blind study was chosen in place of the double-blind due to the different methods of administration (eg, warfarin orally and fondaparinux subcutaneously). In order to exclude any risk for the patients, the physicians who evaluated the patients knew the protocol and the group that was being treated, whereas physicians who evaluated the data were not aware of the treatment.

The study was conducted according to the ethical principles of the Declaration of Helsinki, and the protocol was approved by the institutional review board – Independent Ethics Committee of Interuniversity Center of Phlebology (CIFL). International Research and Educational Program in Clinical and Experimental Biotechnology with the following approval number: ER.NA.2013.34. Before beginning the study, all participants signed the written informed consent.

Patients

We enrolled 64 patients (29 males and 35 females) of both sexes who were diagnosed with active primary cancer and were in anticancer treatment, with occasional finding of APE (Table 1).

Exclusion criteria consisted of the following: history of heart failure or stroke, drug allergies, psychiatric diseases, creatinine clearance <30 mL/min, or platelet count <100,000/mm³. Patients treated with dextran, thrombolytic agents, anticoagulants, or heparin or heparinoids for topical use were also excluded.

Table 1 Primary cancer site

Site	Number (64)	%
Gastrointestinal	29	45
Pancreas	13	20
Urogenital	11	17
Prostate	9	14
Hematologic	10	15
Lung	8	12
Breast	2	3.3
Renal	2	3.3
Others	2	3.3

APE characteristic

APE was documented most commonly using chest CT during the follow-up for restaging after therapy (34 patients, 53%) and during the baseline cancer staging (21 patients, 33%), whereas in nine patients (14%) it was documented for the assessment of extrathoracic diseases.

Moreover, the CT scan detected thrombi in all tracts of the pulmonary artery (Table 2).

Experimental protocol

Patients with primary active cancer regardless of age, sex, or medical history were randomized to receive either warfarin (Coumadin[®]; dose-adjusted to achieve an international normalized ratio of 2.0–3.0) or fondaparinux (Arixtra[®], 7.5 mg subcutaneously) once daily for 90 days (T1). The randomization was performed in agreement with our previous studies.^{12–16}

We used a computer program to generate a sequence of treatment allocations by block randomization using a random number generator. Investigators were not aware of the block size to avoid selection bias.

At the time of admission (T0) and during the follow-ups (90 days = T1, end of the treatment; 1 year = T2, end of the

Table 2 Thrombi localization in pulmonary artery as revealed by CT in enrolled patients with APE

Localization	Patients	
	n	%
Central nonocclusive position	6	9
Main lobar arteries (three in the right and five in the left)	8	13
Lobar arterial branches (eight in the right and five in the left)	13	20
Segmental branches of lobar arteries (16 in the right and ten in the left lung)	26	41
Subsegmental lobar pulmonary branches (seven in the right and four in the left)	11	17

Abbreviations: CT, computer tomography; APE, asymptomatic pulmonary embolism.

observation), the patients underwent clinical evaluation, chemical blood findings (complete blood count with platelet count, activated partial thromboplastin time, and erythrocyte sedimentation rate), urine analysis, and a chest X-ray. Moreover, at the same time (T0–T2) in agreement with 2014 ESC guidelines, we used the multidetector CT (MDCT) angiography to determine the presence of UPE.

All the MDCT angiography examinations were performed with a 64-slice scanner MDCT (Toshiba Aquilion, Tokyo, Japan) using 50–70 mL of 350 mg nonionic iso-osmolar contrast (fonexal and omnipaque). A hypodense intraluminal filling defect causing partial or total obliteration of vascular lumen in segmental and subsegmental arteries with or without corresponding increase in the diameter of the affected vessel was taken as a positive result for PE on MDCT. Considering the high diagnostic power of this scan, lung scintigraphy was performed only in patients with contraindications to CT scanning (eg, critically ill patients or patients with multiorgan dysfunction) or with diagnostic doubts.

Clinical and safety assessment

During the follow-ups (T1 and T2), the persistence, reduction, or disappearance of the thrombotic pulmonary findings was evaluated.

The safety of the study medications was assessed by monitoring for any adverse drug reactions for severity and causality. The relationship between adverse drug reactions and drug treatment was evaluated using the Naranjo adverse probability scale in agreement with our previous studies.^{17–19} The bleeding related to the treatments was evaluated as previously described.²⁰

Efficacy end points

The primary end point was defined as a statistically significant difference ($P<0.01$) in the thrombotic pulmonary CT findings between the two groups of treatment. The secondary end point was the recurrence/appearance of thrombotic events in other sites during the follow-ups (T1 and T2).

Safety end points

The primary end point was defined as a statistically significant difference ($P<0.01$) in the development of major bleeding between the two groups. Major bleeding was defined as hemorrhage occurring at a critical site (eg, intracranial hemorrhage), resulting in a major therapeutic intervention (eg, surgery), causing hemodynamic compromise, requiring at least one unit of red cell concentrates or resulting in death. Minor bleeding was defined as bleeding that did not fulfill the

criteria for major bleeding. The secondary safety end point was the difference in overall mortality.

Statistical analysis

All data are expressed as mean \pm standard deviation. The study analysis was based upon the intention to treat, therefore, all consented patients were included in the analysis. Data were checked for normality using the Kolmogorov–Smirnov test. The Student's *t*-test and the χ^2 test were used when appropriate to test the significance of the differences. The analysis of variance was used to evaluate the differences between multiple means. Once we determined that differences existed, a Bonferroni test was used to determine which means differed. The threshold of statistical significance was set at $P<0.05$. SPSS software Version 21 (IBM Corporation, Armonk, NY, USA) was used for statistical analyses.

Results

Patients

After a detailed clinical history and radiological examination, 64 patients (29 males and 35 females) were recruited and randomized into two groups:

Group A: 32 patients (13 males and 19 females) were treated with warfarin.

Group B: 32 patients (16 males and 16 females) were treated with fondaparinux.

All patients successfully completed the protocol, and all patients underwent follow-ups.

Efficacy outcomes

All the drugs were efficacious in the treatment of PE, even if the primary efficacy outcome was statistically significant ($P<0.01$) in Group B. In particular, persistence of thrombus occurred 14 times in Group A and four times in Group B; a reduction in thrombus was found in eight patients treated with warfarin (Group A) and in 12 treated with fondaparinux (Group B); and a complete disappearance of CT findings occurred in eleven Group A patients and in 16 Group B patients (Table 3).

We did not find statistically significant differences in recurrence (Group A: 7; Group B: 6; $P=0.32$), appearance of symptoms (Group A: 5; Group B: 4; $P=0.12$), and thrombotic events in other locations (Group A: 6; Group B: 6; $P=0.46$; Table 3).

Safety outcomes

Patients treated with fondaparinux experienced a lower incidence of major bleeding ($n=3$) compared with patients

Table 3 Efficacy outcome evaluation during the follow-ups (T0: 90 days and T1: 1 year) through computer tomography and documenting the persistence or recurrence of pulmonary thrombosis

	Group A, warfarin (n=32)	Group B, fondaparinux (n=32)	P-value
T0			
Persistence	14	4	<0.01
Reduction	8	12	<0.01
Disappearance	10	16	<0.01
T1			
Recurrence	7	6	0.32
Appearance of specific symptoms	5	4	0.12
Thrombotic events	6	6	0.46

treated with warfarin (n=6; $P<0.01$) and we did not find statistically significant differences in minor bleeding (Group A: 5; Group B: 4; $P=0.12$) and in overall mortality (Group A: 4; Group B: 3; $P=0.47$; Table 4).

Discussion

In this study, we evaluated the effects of fondaparinux and of warfarin in the treatment of APE in cancer patients. A previous study documented that LMWH reduce the recurrent VTE in patients with active cancer in a similar manner to warfarin, but with low bleeding.²¹ Moreover, the Comparison of Low Molecular Weight Heparin Versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer Patients With Venous Thromboembolism (CLOT) study showed that dalteparin is the most effective therapy vs vitamin K antagonists (VKAs), and the current guidelines recommend the treatment with dalteparin, enoxaparin, or tinzaparin in cancer patients with symptomatic VTE.²² Unfortunately, these recommendations are based on a single study, and the patients enrolled in the CLOT study came mostly from North America and do not represent the global population.

The lack of diversity and the other bias in the CLOT study partly explain why the VKAs are still widely used in several countries in patients with thrombosis associated with cancer. A multinational, Phase III, open-label, randomized, controlled trial documented the efficacy and safety of long-term tinzaparin vs warfarin for the treatment of acute VTE in cancer patients.²¹ However, more recently Lee et al,²³ in a randomized, open-label, multicenter study performed in

patients with active cancer and acute symptomatic VTE, documented that the use of a daily full-dose tinzaparin (175 IU/kg) compared with warfarin for 6 months did not significantly reduce the composite measure of recurrent VTE and was not associated with reductions in overall mortality or major bleeding.

In our study, we documented that fondaparinux induced a significant decrease in the development of thrombosis in cancer patients. In our study, the overall mortality in the two groups was comparable and in our opinion acceptable, considering the disease. There was no difference between the two groups in the long-term outcome (1-year follow-up), but a better response in the primary efficacy outcome was found in patients treated with fondaparinux. Baseline characteristics between either groups (fondaparinux and warfarin) were not statistically significant, therefore, we can conclude that these could play a role in the difference in response to the drugs.

Moreover, it is widely known that several factors (genetic, food, and drugs) are able to modify clinical efficacy of warfarin. However, to date the clinical efficacy is reported for value of international normalized ratio between 2.0 and 3.0. In our study, chemical blood evaluation documented that international normalized ratio was in a normal range in all patients throughout the study.

Cho et al²⁴ reported a patient with metastatic breast cancer, mobile right atrial thrombus, and PE who developed thrombocytopenia after heparin and warfarin treatment. Thrombocytopenia may represent a side effect during the treatment with heparin,^{25,26} and several authors have reported that fondaparinux can be used in patients who developed thrombocytopenia during heparin treatment.^{12,27,28}

Shetty et al,²⁹ in a single-arm observational cohort study of fondaparinux in 30 patients with intolerance to VKA therapy (16 had a history of recurrent VTE, eleven had idiopathic VTE, and three had cancer), did not record episodes of recurrent VTE or major bleeding.

Table 4 Safety outcome evaluation

	Group A, warfarin (n=32)	Group B, fondaparinux (n=32)	P-value
Major bleeding	6	3	<0.01
Minor bleeding	5	4	0.12
Overall mortality	4	3	0.47

Moreover, Pesavento et al,³⁰ reviewing the experience of the RIETE investigators with subacute fondaparinux therapy for VTE (47,378 patients enrolled in the RIETE study, 263 treated for at least 3 months with fondaparinux, and 78 of these patients had cancer), documented that there was no difference in recurrent PE in patients taking fondaparinux and VKA or LMWH. Moreover, they also documented that major bleeding was similar between cancer patients taking fondaparinux and LMWH.

In agreement with these authors, in our study we did not record the development of thrombocytopenia, whereas we recorded a lower incidence of major bleeding in patients treated with fondaparinux compared with those treated with warfarin, without significant difference in minor bleeding.

Conclusion

Our data suggest that a standard dose of fondaparinux may be used in cancer patients with APE until the next CT lung control (3 months). However, the lack of randomized clinical trials that include a larger patient cohort does not allow formulation of final recommendations in these patients, but it is desirable to carry out a broader study, with the involvement of a larger number of patients and a longer follow-up.

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BA and RC share the first authorship. LG, SdF, and RS share the senior authorship. The author Dr MA is the son of the author Prof BA. This work received no funding.

Disclosure

The authors report no conflicts of interest in this work.

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