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LETTER

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

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Dear editor

We read with great interest the study published on June 23, 2016 by Amato et al entitled "Fondaparinux vs warfarin for the treatment of unsuspected pulmonary embolism in cancer patients."[1] While we value the importance of this study in highlighting this important topic, we have several issues to be addressed.

Venous thromboembolisms (VTEs), especially pulmonary embolism (PE), in asymptomatic patients are well-described clinical entities that are usually underrecognized. It is believed that most fatal PEs are not suspected clinically and are not treated.[2,3] This issue is even more important in cancer patients where respiratory symptoms can often be attributed to the cancer itself or its treatment.

We fully agree with the authors that incidental, or unsuspected PE, is not a benign diagnosis especially in cancer patients. We previously reported our experience in 34 incidental PEs in such patients.[4] Except for five (15%), all other patients were anticoagulated; all with low-molecular-weight heparin (LMWH). With follow-up, two patients developed recurrent PE, two others had clinical and echocardiographic evidence of pulmonary hypertension, and nine (26%) died suddenly within 30 days of the diagnosis of PE; two of these were among the five patients who were not anticoagulated.

In their introduction, the authors stated that "Warfarin is commonly used prophylactically in patients with a high risk of thromboembolic events." This statement is not accurate as warfarin is not used for VTE prophylaxis. We assume that the authors meant active treatment (not prophylaxis) of VTE.

Also, the authors stated that "Fondaparinux, is the newest agent with venous thromboembolism (VTE) prophylaxis activity" and this statement is not accurate, either. Fondaparinux, which was introduced and approved initially for VTE prophylaxis then for active treatment of both deep vein thrombosis and PE for over 15 years now, is not new anymore.[5,6] The "relatively new" oral anticoagulants, the direct thrombin inhibitors (dabigatran) and the direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), are the most recently introduced anticoagulants in clinical practice.[7,8]

The authors clearly stated that asymptomatic PE should be treated the same way symptomatic PE is treated; a statement that is fully supported by many published guidelines, including the American College of Chest Physicians.[9] The authors also stated, based at least on the CLOT trial,[10] that LMWH (dalteparin) is superior to warfarin. Yet, the authors used warfarin, not LMWH, to compare fondaparinux with.

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Though we agree with the authors that the recently published CATCH trial failed to show superiority of LMWH (tinzaparin) over warfarin in this setting,[11] however, due to many factors addressed by the authors in their paper, LMWHs are still the preferred agents for active VTE treatment in cancer patients.

Additionally, the CATCH study showed that tinzaparin significantly reduced the risk of clinically relevant nonmajor bleeding compared with warfarin. Together with the adverse events data, CATCH demonstrated that tinzaparin, even when given at a full therapeutic dose for up to 6 months, is a safe and convenient drug in cancer patients. It should also be noted that the CATCH study results were published after enrolling all patients in the current study under discussion.

More recently, our group participated in a pooled analysis of 926 cancer patients from eleven cohorts, all with incidental PE. While VTE recurrence risk was comparable under LMWH and warfarin (6.2% vs 6.4%; hazard ratio 0.9; 95% confidence interval 0.3–3.1), the risk of major hemorrhage was higher under warfarin than under LMWH (13% vs 3.9%; hazard ratio 3.9; 95% confidence interval 1.6–10).[12]

We believe that the era of having warfarin as a drug to compare new anticoagulants within clinical trials, in cancer patients, is not attractive anymore. Researchers are moving forward, comparing the new oral anticoagulants, such as rivaroxaban versus LMWH, in a huge research program called the "CALLISTO". This program is evaluating cancer patient populations being treated for VTEs or at high risk for developing them. Such a program will encompass the field of cancer-associated thrombosis through nine studies, including seven clinical trials and two registries across various cancer types, in >4,000 patients globally.[13]

Fondaparinux, on the other hand, has a major advantage over all other heparins, including LMWH. Being a small molecule with just five sugars (pentasaccharide), it is rarely associated with thrombocytopenia, thus allowing its clinical use in the treatment of heparin-induced thrombocytopenia.[14]

In conclusion, we want to congratulate the authors for addressing such an important topic, but we believe that such a study would have a better impact if the authors chose one of the LMWHs to compare fondaparinux with. The real excitement in antithrombotic therapy in cancer patients will be the introduction of oral direct thrombin and anti-Xa inhibitors.

Disclosure

The authors report no conflicts of interest in this communication.

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Authors' reply

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Dear editor

We appreciate the interest and the well-advised comments on our paper[1] and we thank the authors of the letter to the editor for the opportunity to clarify briefly some aspects of our paper.

First of all, we used the term "prophylaxis" meaning "secondary prevention", and therefore as a synonym of "treatment", but we agree that the word "treatment" would be more appropriate.

We agree with the authors of the letter – fondaparinux is an old agent approved by European Medicines Agency in 2002 and marketed in Italy from 2003. However, it has been the last one after LMWH was approved, and therefore we used the term "newest agent".

Finally, we fully agree with the authors' statement: "The real excitement in antithrombotic therapy in cancer patients will be the introduction of oral direct thrombin and anti-Xa inhibitors". In fact, we think that these "relatively new" oral anticoagulants may represent a clinical benefit in these patients.

However, to date, no clinical trials in cancer patients have been performed, even if recently Schulman et al,[2] reviewing the literature data in six clinical trials, suggest that direct-acting oral anticoagulants have a good safety profile with respect to warfarin in cancer patients.

Disclosure

The authors report no conflicts of interest in this work.

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