Acta Cardiol Sin 2021;37:213–214
Letter to the Editor
doi: 10.6515/ACS.202103_37(2).20210118B

Correspondence to: Management of Venous Thromboembolisms: Part II. The Consensus for Pulmonary Embolism and Updates

Yu-Yun Shao[1,2] and Hung-Ju Lin[3]

Key Words: Anticoagulation • Cancer • Deep vein thrombosis • Pulmonary embolism

Dear Editors,

We read with great interests the article "Management of Venous Thromboembolisms: Part II. The Consensus for Pulmonary Embolism and Updates" in the journal.[1] We would like to point out that among patients with venous thromboembolism (VTE), those with cancers and without cancers differ from risk factors, treatment options, and treatment durations.

Several scoring systems can assist in predicting the risk of cancer-associated thrombosis (CAT), such as the Khorana score and the CATScore.[2,3] These scoring systems define gastric cancer and pancreatic cancer as cancers with very high risk of CAT. High-risk cancers include lung cancer, lymphoma, gynecological cancers, genitourinary cancers (except prostate cancer). The CATScore also considers esophageal cancer and lung cancer as high-risk cancers for CAT. Obesity, anemia, use of erythropoietin, leukocytosis, and thrombocytosis are also common risk factors of CAT. Central venous access device can increase the risk of CAT, as well as some anticancer treatments, such as thalidomide, lenalidomide, and tamoxifen.[4]

Before the availability of non-vitamin K antagonist oral anticoagulants (NOACs), the recommended treatment for CAT was low-molecular-weight heparins (LMWH). Thus, when testing the efficacy and safety of NOACs as treatment for CAT, the control arm was always LMWH. In the two phase 3 clinical trials, edoxaban and apixaban demonstrated noninferiority to LMWH.[5,6] In a pilot study, rivaroxaban treatment was associated with lower CAT recurrence compared to LWMH treatment.[7] However, in the studies with endoxaban and rivaroxaban, increased gastrointestinal bleeding was identified in patients with active upper gastrointestinal tract cancer lesions. Considering the convenience and compliance, NOACs become the recommended CAT treatment in patients without active gastroesophageal lesions. By contrast, in patients with active gastroesophageal lesions, the clinical benefit of NOACs should be balanced with the risk of major gastrointestinal bleeding.[4,8] Although dabigatran is approved as treatment for VTE, it has no clinical trial data on CAT treatment.

Because of the increased incidence of VTE among patients with cancer, the anticoagulation treatment needs to be prolonged. Several guidelines suggest continuous anticoagulation as long as the cancers remain active or the anticancer treatment is still ongoing.[4,8] If the CAT is catheter-related, anticoagulation should continue when the catheter is still in place.[4]

Pharmacologic prophylaxis of CAT might be considered in highly selected patients. Patients who receive lenalidomide or thalidomide for multiple myeloma have high risks of developing CAT, so many guidelines suggest using aspirin or anticoagulants in such patients. However, whether NOACs are suitable in such a scenario is unclear.[4,8] For patients with other solid cancers, how to select the high-risk patients who would benefit from pharmacologic prophylaxis is the key issue. The AVERT and CASSNI studies randomized patients with Khorana

Received: December 29, 2020 Accepted: January 18, 2021
[1]Graduate Institute of Oncology, National Taiwan University College of Medicine; [2]Department of Oncology; [3]Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.
Corresponding author: Dr. Yu-Yun Shao, Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 10002, Taiwan. Tel: 886-2-2312-3456 ext. 66008; Fax: 886-2-2371-1174; E-mail: yuyunshao@gmail.com

scores ≥ 2 to receive placebos or NOACs (apixaban and rivaroxaban, respectively).[9,10] Given the efficacy and safety of CAT prevention have been shown in above-mentioned trials, some concerns should be addressed before the results of the trials could be applied in clinical practice. First, although the studies yielded positive results, the reduction of CAT occurrences seemed too low to recommend such prophylaxis to all patients with Khorana scores ≥ 2. Second, both studies enrolled very few Asian patients, so their results may not be applicable to Taiwan patients. Third, net clinical benefit should be assessed to justify the anticoagulation treatment for CAT prevention, especially in patients with low-risk tumor sites, whose CAT risk might be subject to overestimation.[3]

Drug-drug interaction is a major issue for all oral anticoagulants, from warfarin to NOACs. Because many anticancer drugs are metabolized by p-glycoprotein and cytochrome P450, use of NOACs in patients with active anticancer therapy has to be more careful. Last but not least, the data regarding recurrent VTE in the SELECT-D study in the Figure 3 do not match the description on page 574. We found the description on page 574 (Hazard ratio, 0.43; 95% confidence interval, 0.19 to 0.99) to be the correct one.

Above all, CAT drastically differs from idiopathic VTE and requires extra consideration in management. CAT prophylaxis, especially in Asia, remains to be explored.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

1. Wang KL, Kao YT, Chang WT, et al. Management of venous thromboembolisms: part II. The consensus for pulmonary embolism and updates. *Acta Cardiol Sin* 2020;36:562-82.
2. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008;111:4902-7.
3. Pabinger I, van Es N, Heinze G, et al. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. *Lancet Haematol* 2018;5:e289-98.
4. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease, 2020. https://www.nccn.org/professionals/physician_gls/default.aspx#supportive. Accessed on Dec. 30, 2020.
5. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med* 2020;382:1599-607.
6. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2018;378:615-24.
7. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol* 2018;36:2017-23.
8. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol* 2020;38:496-520.
9. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med* 2019;380:711-9.
10. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med* 2019;380:720-8.