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Mini Review

Treatment of Asian Patients with Cancer-Associated Venous Thromboembolism in Direct Oral Anticoagulants Era – a Mini review of the Literature

Yoshinori Imamura, M.D., Ph.D*

Department of Medical Oncology/Hematology, Kobe University Hospital

*Corresponding author: Yoshinori Imamura, M.D., Ph.D, Department of Medical Oncology and Hematology and Cancer Center, Kobe University Hospital, 7-5- 1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.

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Abstract

Cancer-associated venous thromboembolism is a serious and potentially life-threating event. In the last few years, results of several randomized control trials were published, and direct oral anticoagulants are recommended as new standard care for this disease, however, Asian patients were rarely included in these trials. This article will highlight the limited evidence for Asian patients with cancer-associated venous thromboembolism.

Keywords: cancer-associated venous thromboembolism; Asian patients; direct oral anticoagulant; randomized controlled trial

Introduction

Venous thromboembolism (VTE) is the most common type of thromboembolism occurring in cancer patients and is an important cause of morbidity and mortality among patients with cancer [1,2]. Although the major inherited risk factors for thrombophilia (e.g. factor V Leiden, prothrombin G20210A, and protein S K196E) are different between Asians and Caucasians [3,4], the main acquired risk factors are shared. Around 16-40% of VTE cases are cancer-associated among Asian patients [5]. A recent Japanese nationwide prospective cohort study revealed that the prevalence of VTE among treatment naïve Japanese cancer patients was 5.9% (571/9735) overall, and that VTE prevalence appeared to increase as the cancer stage increased, reaching a level of 11.2% at stage IV [6]. It implies that protective effect of Asian ethnicity on VTE development disappears as tumor stage increases similar to a previous Korean study [7].

Although anticoagulant treatment is the recommended standard of care for acute cancer-associated VTE, this treatment is complicated by both a high risk of recurrent VTE and bleeding events [8]. Until recently, based on the results of randomized controlled trials (RCTs) comparing low molecular weight heparin (LMWH) with vitamin K antagonists (VKAs) [9-12], LMWH was the recommended standard of care for the treatment of cancer-associated VTE in numerous guidelines [13-16] and a review from the 9th congress of the Asian-Pacific Society on Thrombosis and Hemostasis [17]. In the last few years, the results of four published RCTs comparing direct oral anticoagulants (DOACs) with the LWMH dalteparin, Hokusai-VTE cancer, SELECT-D, ADAM VTE, CARAVAGGIO provide novel evidence for the use of DOACs as an alternative to LMWH [18-21]. These four trials will contribute to the development of new guidelines; however, Asian patients were rarely included in the trials. Thus, clinicians should pay attention to apply the latest evidence to Asian patients. This article will highlight the limited evidence for Asian patients with cancer-associated VTE.

Methods

A review of the existing literature on the cancer-associated VTE treatment was carried out using with the term "venous thromboembolism", "pulmonary embolism", "venous thrombosis", "vein thrombosis", "warfarin", "vitamin K antagonist", "dalteparin", "low molecular weight heparin", "dabigatran", "edoxaban", "rivaroxaban", "apixaban", "direct oral anticoagulant", and "randomized trial". MEDLINE searches were performed via PubMed through Nov 1, 2020. Studies were considered potentially eligible for the current minireview if they met the following criteria: (1) they were RCTs enrolling >100 patients over 18 years of age; (2) fixed dose of DOACs were compared with therapeutic doses of VKA or LMWH for the treatment of acute VTE and the secondary prevention of VTE. Then, the most important and informative articles were selected, with special attention to Asian patients.

The Mantel-Haenszel method for a random effects model was used for calculations of pooled risk ratio (RR) associated 95% confidence interval (CI) for each outcome. Statistical analyses were performed using SPSS for Windows, version 23.0 (IBM, Armonk, NY).

Discussion

The most updated meta-analysis demonstrated that the incidence of recurrent VTE was significantly lower with DOACs compared with LMWH (RR, 0.62; 95% CI, 0.43- 0.91), and that the risk of major bleeding was non-significantly higher with DOACs compared with LMWH (RR, 1.31; 95% CI, 0.83-2.08) [22]. Unfortunately, no formal

bleeding assessment scores are currently available to predict the risk of bleeding in cancer patients receiving DOACs for VTE. The latest guidance from international society on thrombosis and haemostasis suggested the use of LMWHs for cancer patients with an acute diagnosis of VTE and a high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary [23]. Of note, gastric cancer is the one of the most common cancer types in Asian countries [24] and among Asian Americans [25]. Asian patients were rarely included in the four pivotal trials comparing DOACs with the LWMH dalteparin [18-21], and no Asian specific data is available (Table 1).

A generation ago, Asian patients with VTE were included in six RCTs comparing DOACs with VKAs, and several subgroup analyses were performed [26-35] (Table 1). A pooled analysis revealed that RRs of DOACs were less recurrent VTE (0.79 vs 0.97) and bleeding events (0.75 vs 0.89) (Table 2,3). In addition, another pooled analysis demonstrated that RRs of DOACs were less among Asian patients than non-Asian patients in bleeding events at least (0.67 vs 0.77) (Table 3). No Asian cancer patients' specific data is evaluable, neither. Nevertheless, the best available clinical evidence as mentioned above suggests that treatment with DOACs is a reasonable option for Asian patients with cancer associated VTE, especially without a high risk of bleeding, such as intact gastrointestinal diseases.

	Dabigatran	**Edoxaban**	**Rivaroxaban**	**Apixaban**	
Cancer patients' specific trial		HOKUSAI-VTE cancer [18] (n = 522)	SELECT-D [19] (n = 203)	ADAM VTE [20] (n = 145)	CARAVVAGIO [21] (n=579)
Major bleeding (%)	(NA)	6.9	5.4	0	3.8
Major/CRNM bleeding (%)	(NA)	18.6	17.7	6.2	12.2
Recurrent VTE/VTE-related death (%)	(NA)	7.9	3.9	0.7	5.6
Cancer patients (subgroup analysis)	RE-COVER I+II [26] (n = 159)	HOKUSAI-VTE [27] (n = 378)	EINSTEIN DVT+PE [28] (n = 353)	AMPLIFY [29] (n = 87)	
Major bleeding (%)	3.8	2.6	2.3	2.3	
Major/CRNM bleeding (%)	14.5	15.1	15.9	12.6	
Recurrent VTE/VTE-related death (%)	5.8	3.7	4.5	1.1	
Asian patients (subgroup analysis)	RE-COVER I+II [30,31] (n = 292)	HOKUSAI-VTE [32] (n = 866)	EINSTEIN DVT+PE [33,34] (n = 388)	AMPLIFY [35] (n = 223)	
Major bleeding (%)	(NA)	(NA)	(NA)	(NA)	
Major/CRNM bleeding (%)	6.8	8.7	9.0	3.1	
Recurrent VTE/VTE-related death (%)	2.4	3.1	2.4	3.1	

Table 1. Comparison of VTE and bleeding events among cancer patients prescribed direct oral anticoagulant in pivotal trials.

	Direct oral anticoagulant (%)	Warfarin (%)	Relative risk (95% confidential interval)
Cancer patients [26-29]	55/543 (10.1)	61/475 (12.8)	0.79 (0.56-1.11)
Non-cancer patients [26-29]	282/10776 (2.6)	291/10807 (2.7)	0.97 (0.83-1.14)
Asian patients [30-35]	52/1773 (2.9)	59/1769 (3.3)	0.88 (0.61-1.27)
Non-Asian patients [30-35]	283/11657 (2.4)	308/11701 (2.6)	0.92 (0.78-1.08)

Table 2. A pooled analysis of recurrent venous thromboembolism among phase III trials comparing direct oral anticoagulant with warfarin

	Direct oral anticoagulant (%)	Warfarin (%)	Relative risk (95% confidential interval)
Cancer patients [26-29]	79/549 (14.4)	92/477 (19.3)	0.75 (0.57-0.98)
Non-cancer patients [26-29]	888/10759 (8.3)	1001/10795 (9.3)	0.89 (0.82-0.97)
Asian patients [30-35]	139/1769 (7.9)	208/1765 (11.8)	0.67 (0.54-0.82)
Non-Asian patients [30-35]	849/11708 (7.3)	1105/11716 (9.4)	0.77 (0.71-0.84)

Table 3. A pooled analysis of Major and clinically relevant non-major bleeding events among phase III trials comparing direct oral anticoagulant with warfarin.

Conclusions

According to the latest evidence of DOACs for cancer associated VTE, DOACs will be more common all over the world. It should be noted that Asian cancer patients were rarely included in the pivotal RCTs using DOACs. Further complementary Asian studies are warranted in order to optimize patients care and outcomes.

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Conflicts of interest

The author declares no conflict of interest.

Abbreviations

CI:confidential interval; DOAC: direct oral anticoagulant; LMWH: low molecular weight heparin; RCT: randomized controlled trial; RR: relative risk; VKA vitamin K agonist;VTE: venous thromboembolism

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