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RECOMMENDATIONS AND GUIDELINES

Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH

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Scope

Venous thromboembolism (VTE) is an unfortunately prevalent complication in patients with active cancer [1]. Direct oral anticoagulants (DOACs) have been approved for the treatment of VTE in general populations. However, for cancer patients, most guidelines continue to recommend low molecular weight heparin (LMWH) monotherapy for at least 3–6 months, owing to the lack of cancer-specific data regarding the use of these agents [2–4]. Both recent emerging data from clinical practice experience and new randomized clinical trials (RCTs) specifically for cancer patients may alter this approach. This statement incorporates these new data, and provides guidance on the current role of DOACs in the treatment of cancer-associated thrombosis.

The format of ISTH guidance statements has been described previously [5]. Briefly, this guidance outlines factors that may influence decision-making in individual patients (Data S1).

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Definitions

1 *Cancer patients*. Active cancer is defined as: cancer diagnosed within the previous 6 months; recurrent, regionally advanced or metastatic cancer; cancer for which treatment had been administered within 6 months; or hematological cancer that is not in complete remission.
2 *DOACs*. Four agents, i.e. the thrombin inhibitor dabigatran, and the activated factor X inhibitors apixaban, edoxaban, and rivaroxaban, are all currently approved in many countries for the treatment of VTE. A fifth agent, betrixaban, is currently only approved for prevention of VTE in hospitalized medically ill patients, and its use is not addressed by this guidance statement.

Background

Evidence from RCTs in cancer patients

Two randomized trials in cancer patients evaluating DOACs have been reported [6,7]. HOKUSAI Cancer was an open-label, non-inferiority trial that randomized 1050 patients with cancer and acute symptomatic or incidental VTE to LMWH for at least 5 days, followed by oral edoxaban 60 mg once daily or dalteparin 200 IU kg^{-1} daily in month 1, and 150 IU kg^{-1} in months 2–12 [6]. Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent VTE or major bleeding in the 12 months after randomization, and occurred in 12.8% of edoxaban arm patients and 13.5% of dalteparin arm patients (hazard ratio [HR] 0.97; 95% confidence interval [CI] 0.70–1.36; $P = 0.006$ for non-inferiority; $P = 0.87$ for superiority). Recurrent VTE occurred in 7.9% of edoxaban arm patients and in 11.3% of dalteparin arm patients (HR 0.71, 95% CI 0.48–1.06). Major

bleeding occurred in 6.9% of edoxaban arm patients and in 4.0% of dalteparin arm patients (HR 1.77, 95% CI 1.03–3.04), and clinically relevant non-major bleeding (CRNMB) occurred in 14.6% of edoxaban arm patients and in 11.1% of dalteparin arm patients (HR 1.38, 95% CI 0.98–1.94). The increase in the risk of major bleeding was especially high in patients with gastrointestinal cancers. Select-D was a prospective, randomized, open-label, multicenter pilot trial randomizing 406 cancer patients with acute VTE to dalteparin (200 IU kg^{-1} daily in month 1, and 150 IU kg^{-1} in months 2–6) and rivaroxaban (15 mg twice daily for 3 weeks, and then 20 mg once daily, for 6 months in total) [7]. The 6-month rates of recurrent VTE were 11% (95% CI 7–16%) and 4% (95% CI 2–9%) for patients receiving dalteparin and rivaroxaban, respectively. The 6-month cumulative major bleeding rates were 4% (95% CI 2–8%) for dalteparin and 6% (95% CI 3–11%) for rivaroxaban; CRNMB rates were 4% (95% CI 2–9%) and 13% (95% CI 9–19%), respectively. Gastric/esophageal cancer patients were especially at risk for major bleeding (four of 11 patients receiving rivaroxaban versus one of 19 receiving dalteparin), and these patients were excluded towards the end of the study. A meta-analysis of the two RCTs showed that patients receiving DOACs had a lower 6-month rate of recurrent VTE (42/725) than patients receiving LMWH (64/727) (risk ratio [RR] 0.65, 95% CI 0.42–1.01) [8]. However, patients receiving DOACs had a higher major bleeding rate (40/725) than patients receiving LMWH (23/727) (RR 1.74, 95% CI 1.05–2.88) and a higher CRNMB rate (RR 2.31, 95% CI 0.85–6.28). Mortality rates at 6 months in these studies were lower than in the trials comparing LMWH with vitamin K antagonists for the management of cancer-associated thrombosis (CLOT and CATCH) [9,10]. It is unclear whether these differences in mortality reflect the selection of higher-risk patients in the trials assessing LMWH (previously assumed to be more efficacious) or, partly, the known general decline in cancer mortality over time (the LMWH trials preceded the DOAC trials).

Evidence from clinical practice studies

Since the approval of DOACs for the treatment of acute VTE, the use of these agents in non-trial settings has been growing, and multiple observational cohort studies have been published describing initial experiences in the cancer population [11–15]. For instance, a single-institution cohort study limiting rivaroxaban use to patients without active gastrointestinal tract or urinary tract lesions and performing empirical dose reduction in elderly patients has reported rates of major bleeding and recurrent VTE of 2.2% (95% CI 0–4.2%) and 4.4% (95% CI 1.4–7.4%), respectively [15]. Similarly, in a large US claims dataset of 2428 patients, there were lower rates of recurrent VTE in rivaroxaban users than in LMWH users at 6 months (13.2% versus 17.1%; $P = 0.06$) and 12 months (16.5% versus 22.2%; $P = 0.03$) (HR 0.72, 95% CI, 0.52–0.95; $P = 0.02$), without any differences in major bleeding [11]. A recently published systematic review of the literature describing all observational studies on this topic reported that most studies used rivaroxaban and enoxaparin [8]. The on-treatment durations of DOAC were usually longer than that of LMWH, which may reflect unstated patient preferences for oral agents or cost barriers. Nearly all studies reported lower rates of recurrent VTE for patients receiving DOACs than for those receiving LMWHs [8]. These data are consistent with the RCTs discussed above. Major bleeding and CRNMB outcomes were heterogeneous across studies, and this may reflect patient selection bias by clinicians in practice [10]. Confounding by indication bias is also a limitation of these observational studies.

Patient preferences and values

The perceived benefits of DOACs (oral administration, lower recurrent VTE rate, and no monitoring) need to be considered against their perceived negative attributes (increased bleeding and drug–drug interactions) and the strength of value that an individual patient gives to each feature. In clinical decision-making, these competing factors need to be weighed within the context of individual patients' preferences and values. These are likely to be influenced by their previous experiences, understanding, and wishes for the future. There are limited data regarding cancer patients' anticoagulant preference within the context of VTE treatment. Qualitative data suggest that the experience of cancer-associated thrombosis is distressing, and that, within this context, LMWH is an acceptable intervention [16]. Furthermore, patients develop adaptive routines whereby a daily injection becomes normalized within their daily activities.

Data from a discrete choice experiment, in which cancer patients treated for VTE were asked to rate the importance they afforded to various attributes of their anticoagulants, provides important insights into their values [17]. Patients from Germany and the UK placed the greatest value on anticoagulants that did not interfere with their cancer treatments, highlighting the fact that they saw themselves as cancer patients first and foremost. They then ranked efficacy (i.e. recurrent VTE) followed by safety (i.e. major bleeding) as the next most important, followed by a preference for oral administration over injection. These findings highlight the complexity of discussing treatment options with patients, especially as their cancer and its treatments are prioritized over their VTE events. Also noteworthy is the considerable trust that patients have in the opinions of the advising clinicians, and it is important for clinicians to avoid imposing their own preferences and values without first exploring what matters most to the patients.

Limitations and precautions

There are several limitations to providing guidance for DOAC use in cancer patients. There does not appear to

be a concern regarding reduced efficacy (if anything, the data suggest improved efficacy), but there is concern regarding an increased risk of bleeding (major bleeding and CRNMB). Unfortunately, no formal bleeding assessment scores are currently available to predict the risk of bleeding in cancer patients receiving DOACs, so our cautionary statements regarding patients with gastrointestinal and genitourinary cancers are based on the available data from RCTs and observations from single-institution studies. As DOACs are administered orally, alternative approaches in cases of nausea and emesis need to be discussed with patients. Cancer medicine is rapidly evolving, and data on drug–drug interactions are difficult to obtain, although avoiding the concomitant use of drugs that are potent inhibitors or inducers of P-glycoprotein or cytochrome P450 3A4 is necessary [18]. Immunotherapy and its attendant toxicities, including autoimmune colitis, are becoming increasingly prevalent, but the risks of DOAC-associated bleeding in this specific setting have not been studied. Whether the relative efficacy and safety of a particular DOAC differ among different tumor types and anticancer regimens is unknown. There is a need to be cautious with both LMWHs and DOACs when they are used for patients with extremes of body weight and reduced renal clearance [19–22]. There are differences in the administration of DOACs: dabigatran and edoxaban have an LMWH lead-in period at the time of initiation of therapy, whereas apixaban and rivaroxaban do not. RCTs in cancer patients have been reported only for edoxaban and rivaroxaban, and not yet for apixaban or dabigatran. Furthermore, given the differences in anticoagulant mechanisms of action (dabigatran is a direct thrombin inhibitor, in contrast to other available DOACs) and metabolic clearance (P-glycoprotein alone or also cytochrome P450 3A4), a class effect of DOACs should not be readily assumed. It should also be noted that results from RCTs and observational studies do not inform us about *a priori* prestudy patient selection, which may have an impact on outcomes and the relative risks and benefits of various anticoagulants.

Guidance statement

1 We recommend individualized treatment regimens after shared decision-making with patients.
2 We suggest the use of specific DOACs for cancer patients with an acute diagnosis of VTE, a low risk of bleeding, and no drug–drug interactions with current systemic therapy. LMWHs constitute an acceptable alternative. Currently, edoxaban and rivaroxaban are the only DOACs that have been compared with LMWH in RCTs in cancer populations. A final treatment recommendation should be made after shared decision-making with patients regarding a potential reduction in recurrence but higher bleeding rates with specific DOACs, incorporating patient preferences and values.
3 We suggest 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, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis. Specific DOACs (edoxaban and rivaroxaban) are acceptable alternatives if there are no drug–drug interactions with current systemic therapy. A final treatment recommendation should be made after shared decision-making with patients regarding a potential reduction in recurrence but higher bleeding rates with specific DOACs, incorporating patient preferences and values.

Addendum

A. A. Khorana contributed to the concept, design, data interpretation, writing of the manuscript, and final approval of the submitted version. S. Noble contributed to the design, data interpretation, writing of the manuscript, and final approval of the submitted version. A. Y. Y. Lee contributed to the design, data interpretation, writing of the manuscript, and final approval of the submitted version. G. Soff contributed to the design, data interpretation, writing of the manuscript, and final approval of the submitted version. G. Meyer contributed to the design, data interpretation, writing of the manuscript, and final approval of the submitted version. C. O'Connell contributed to the design, data interpretation, writing of the manuscript, and final approval of the submitted version. M. Carrier contributed to the concept, design, data interpretation, writing of the manuscript, and final approval of the submitted version.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Data S1. Supplemental information.

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