Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH

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Scope and methodology

Modern computed tomography (CT), with its high sensitivity and resolution, has increased the detection of incidental venous thromboembolism (VTE) in the venous and pulmonary vasculature during routine imaging for cancer staging and response assessment [1]. As a result, up to half of all VTEs diagnosed in oncology centers are incidental [1–5]. Although widely accepted, the diagnosis of incidental VTE is made without using the standard imaging studies required for confirming the presence of symptomatic VTE (i.e. compression ultrasonography for deep vein thrombosis [DVT], and CT pulmonary angiography [CTPA] or ventilation/perfusion lung scan for pulmonary embolism [PE]). The accuracy and reliability of staging imaging in making a diagnosis of DVT or PE have not been established.

In addition, the appropriate treatment of incidental VTE has been poorly studied. International clinical practice guidelines suggest or recommend standard anticoagulation as for symptomatic VTE [6–8]. However, these recommendations are extrapolated from studies in symptomatic VTE, and may not apply to all cases of incidental VTE, because of the uncertainty regarding the age of the clots (which may vary from days to months), the clinical significance of isolated peripheral clots, such as isolated subsegmental PE (SSPE), and the fact that the risk/benefit ratio for anticoagulation may differ from that for incidental vs. symptomatic VTE.

This guidance statement will provide clinicians with practical advice on the diagnosis and management of incidental VTE in cancer patients. As previously defined, ‘recommend’ indicates a strong guidance statement with good consensus among the panelists, whereby the clinician should consider adopting the practice in most cases, whereas ‘suggest’ reflects a weak guidance statement with moderate consensus among the panel members, whereby the clinician may adopt the guidance statement or use an alternative approach to manage patients [9].

Diagnosing incidental VTE

Incidental vs. symptomatic VTE

Incidental VTE refers to DVT or PE that is clinically unsuspected at the time of the diagnosis [10]. Although incidental PE may be asymptomatic, as many as two-thirds of affected patients report having symptoms consistent with PE, such as fatigue or shortness of breath [11]. However, these non-specific symptoms are often attributed to the cancer or side effects of treatment. Consequently, clinicians should carefully review the clinical presentation to determine whether a patient with an incidental VTE has had symptoms consistent with DVT or PE.

Accuracy of staging imaging for diagnosis of VTE

The accuracy of contrast studies used for cancer staging in diagnosing PE or DVT has not been formally evaluated. Although CT of the chest has a high sensitivity for
proximal PE that may approach that of CTPA [12], the main concern is the false-positive rate when peripheral PE or SSPE is incidentally detected. Performing confirmatory testing such as CTPA is often not practical or feasible, because it exposes the patient to additional radiation and contrast, and increases healthcare costs.

More recently, the interobserver agreement for isolated SSPE in CTPA has been questioned. In a retrospective single-center study, CTPA images of 70 cases (45% with cancer) diagnosed with symptomatic SSPE underwent a second review by an experienced chest radiologist [13]. In only 51% of cases did the reviewing radiologist agree with the initial diagnosis; 11% were judged to be false positives. Performing lower limb ultrasonography has been suggested in patients with incidental isolated SSPE, as the presence of concomitant DVT would provide support for the incidental SSPE being probably clinically relevant [14,15].

Similarly, compression ultrasonography is advocated for confirming the presence of incidental ileofemoral DVT, because filling defect artefacts may be caused by the low flow state of contrast in the pelvic region. Imaging the lower limbs may also detect silent DVT involving the femoral and popliteal veins. CT and magnetic resonance have better accuracy than ultrasonography, and are the imaging methods of choice for the diagnosis of splanchnic DVT [16,17].

Guidance statement

1. In cancer patients with a diagnosis of incidental VTE, we recommend a careful review of the history to exclude symptomatic VTE.
2. In patients with incidental PE involving the main, lobar, segmental or multiple subsegmental pulmonary arteries, we suggest that no further testing is required to confirm the diagnosis.
3. In patients with isolated SSPE, we recommend careful review of the images by radiologists, and suggest that compression ultrasonography of the lower limbs be performed to detect concomitant incidental DVT.
4. In patients with incidental ileofemoral DVT on CT of the abdomen and pelvis, we suggest confirming the diagnosis with Doppler ultrasonography of the pelvis and compression ultrasonography of the lower limbs.

Treatment of incidental VTE

Although the evidence is largely based on observational and retrospective data, incidental VTE seems to carry a similarly poor prognosis in terms of recurrent VTE, bleeding and mortality as symptomatic VTE [3,4,18–22]. Furthermore, autopsy studies have suggested that incidental PE represents a frequently unrecognized cause of death in cancer patients [23]. Consequently, anticoagulant therapy is recommended for incidental VTE by major clinical practice guidelines [7]. However, given the associated increased risk of bleeding, potential interference with anti-neoplastic treatments, impact on patient quality of life, and added cost, the decision to initiate anticoagulant therapy should be made with due consideration of these consequences and with the informed consent of the patient.

Anticoagulation for incidental distal thrombi or emboli such as isolated SSPE, although they represent a small minority of incidental VTEs, is particularly controversial [13–15]. Case-control and observational studies in patients with incidental isolated SSPE have reported uneventful follow-up and similar survival as in patients without PE among those who were not treated with anticoagulation, whereas major bleeding occurred in as many as 5% of those treated [19,24]. These findings suggest that routine anticoagulation may unnecessarily expose some patients to the risk of anticoagulant-related bleeding without meaningful benefit. However, a recent meta-analysis demonstrated that the risk of recurrent symptomatic VTE in patients with SSPE is comparable to that in those with more proximal PE, and suggested that untreated SSPE has a high risk of recurrence [22].

There are no studies that have specifically evaluated the management of incidental distal DVT. As for symptomatic cases, the approach could range from anticoagulation in all patients to serial ultrasonography to detect and treat those extending to the proximal veins [25].

Splanchnic DVT constitutes a significant proportion of incidental VTE [16,17]. However, very little is known about the natural history or need for anticoagulation of such thrombi. In cohort studies, approximately one-half are untreated by physicians [17]. Some clinicians favor a prompt start of anticoagulation in all of these patients [7,16,26], whereas others consider treatment on a case-by-case basis, targeting only those with acute symptoms or additional high-risk features [6].

A suggested approach to managing cancer patients with incidental VTE, based on currently available evidence, is outlined in Fig. 1.

Anticoagulant options

Extrapolating from symptomatic cancer-associated VTE, low molecular weight heparin (LMWH) is preferred, and can be given at full therapeutic doses for the first month, with tapering to 75% of the full dose thereafter [27]. Warfarin is an option if LMWH is not available or acceptable to patients, or in patients without active cancer. In the absence of cancer-specific studies, newer oral anticoagulants cannot be currently recommended [28]. Filter insertion should be avoided, especially in patients who are asymptomatic and do not have any contraindications for anticoagulation.

Duration of anticoagulation

The optimal duration of therapy has not been studied in cancer patients with thrombosis. The published literature
Guidance statement

1 In cancer patients with incidental VTE, we recommend standard anticoagulation with LMWH in those with symptoms compatible with VTE.

2 In patients with incidental proximal DVT, or PE of the main, lobar, segmental or multiple subsegmental pulmonary arteries, we recommend therapeutic anticoagulation for at least 6 months.

3 In patients with isolated SSPE with proximal DVT, we recommend therapeutic anticoagulation for at least 6 months.

4 In patients with isolated SSPE with distal DVT or without DVT, we suggest that the decision to provide anticoagulation be made on a case-by-case basis, considering the risk of bleeding, the presence of risk factors for recurrent thrombosis, the performance status of the patient, and patient preference. If the decision is not to anticoagulate, we suggest clinical monitoring and serial bilateral compression ultrasonography after 1 week in those with distal DVT, to detect thrombus extension.

5 In patients with incidental splanchic vein thrombosis, we suggest anticoagulant therapy in patients with thrombosis that appears to be acute, or that shows progression or extension over time, and in those who are neither actively bleeding nor have a very high risk of bleeding.

6 In cancer patients with evidence of disease or ongoing systemic or locoregional therapy, we suggest periodic re-evaluation of the risks of bleeding and VTE recurrence, as well as patient preferences, to guide the decision of whether to extend LMWH beyond 6 months.

Addendum

M. Di Nisio, A. Y. Y. Lee, and A. A. Khorana were responsible for concept and design. M. Di Nisio, A. Y. Y. Lee, M. Carrier, H. A. Liebman, and A. A. Khorana were responsible for interpretation of data, critical writing or revision of the intellectual content, and final approval of the version to be published.

Disclosure of Conflict of Interests

M. Di Nisio reports providing consultation to Bayer Health Care. A. Y. Y. Lee reports providing consultation to or receiving honoraria from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, LEO Pharma, Pfizer, and Sanofi Aventis. M. Carrier reports receiving grants from Bristol-Myers Squibb and LEO Pharma, and personal fees from Pfizer, Bayer, and LEO Pharma. H. A. Liebman reports receiving personal fees from Janssen and Portola. A. A. Khorana reports receiving personal fees from Boehringer Ingelheim, Pfizer, Leo Pharma, Roche, Janssen, and Daiichi Sankyo.

References


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