Curr Oncol, Vol. 22, pp. 49-59; doi: http://dx.doi.org/10.3747/co.22.2392

PRACTICE GUIDELINE

Clinical challenges in patients with cancer-associated thrombosis: Canadian expert consensus recommendations

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ABSTRACT

Venous thromboembolism is a common complication in cancer patients, and thromboembolism is the second most common cause of death after cancer progression. A number of clinical practice guidelines provide recommendations for the management of cancer-associated thrombosis. However, the guidelines lack recommendations covering commonly encountered clinical challenges (for example, thrombocytopenia, recurrent venous thromboembolism, etc.) for which little or no evidence exists. Accordingly, recommendations were developed to provide expert guidance to medical oncologists and other health care professionals caring for patients with cancer-associated thrombosis. The current expert consensus was developed by a team of 21 clinical experts. For each identified clinical challenge, the literature in MEDLINE, EMBASE, and Evidence Based Medicine Reviews was systematically reviewed. The quality of the evidence was assessed, summarized, and graded. Consensus statements were generated, and the experts voted anonymously using a modified Delphi process on their level of agreement with the various statements. Statements were progressively revised through separate voting iterations and were then finalized. Clinicians using these recommendations and suggestions should tailor patient management according to the risks and benefits of the treatment options, patient values and preferences, and local cost and resource allocations.

KEY WORDS

Venous thromboembolism, deep-vein thrombosis, pulmonary embolism, recommendations

1. INTRODUCTION

Venous thromboembolism (VTE)—which includes both pulmonary embolism (PE) and deep vein thrombosis (DVT)—is a common complication in cancer patients, whose risk compared with the risk in the general population is increased by a factor of 4[1]. In the cancer patient population, thromboembolism is associated with significant morbidity and mortality, and it is the second most common cause of death after cancer progression[2]. A number of published clinical practice guidelines have provided recommendations to medical oncologists for the management of cancer-associated thrombosis[3–5]; however, currently available guidelines do not provide recommendations for challenging clinical situations (for example, thrombocytopenia, recurrent VTE, catheter-related upper extremity DVT, etc.) encountered by health care practitioners caring for this patient population.

2. METHODS

The purpose of the consensus process was to develop specific recommendations and to provide expert guidance for challenging cases that are not currently addressed in clinical practice guidelines on the treatment and prevention of VTE in patients with cancer. The specific questions to be addressed were identified by the participants and supplemented by a systematic review of the available literature.

2.1 Sources and Searches

For each of the identified challenges, the literature in MEDLINE (1946 to March 2014), EMBASE (1947 to March 2014), the Cochrane Central Register of Controlled Trials, and all Evidence Based Medicine Reviews (using the OVID interface) was systematically reviewed. References in included studies and previous systematic reviews were also reviewed for additional potential studies. The search was limited to human studies reported in the English language. One of the MEDLINE search strategies is depicted in Table I.

2.2 Grading of the Evidence and Consensus Process

The multidisciplinary expert consensus group, which included 21 voting participants with expertise

TABLE I MEDLINE searches for clinical challenges

1.	Role of direct oral anticoagulants: ("Neoplasms"[MeSH] OR "Carcinoma"[MeSH]) AND ("Venous Thromboembolism"[MeSH] OR "Venous thrombosis"[MeSH] OR "Pulmonary Embolism"[MeSH]) AND ("Warfarin"[MeSH]) AND ("Apixaban"[MeSH]);OR ("Dabigatran"[MeSH]) OR ("Rivaroxaban"[MeSH]) OR ("Edoxaban"[MeSH])
2.	Treatment beyond 6 months: ("Neoplasms"[MeSH] OR "Carcinoma"[MeSH]) AND ("Anticoagulants"[MeSH] OR "Heparin, Low-Molecular-Weight"[MeSH] OR "Warfarin"[MeSH]) AND ("secondary prevention")
3.	Incidental venous thromboembolism (VTE): ("Neoplasms"[MeSH] OR "Carcinoma"[MeSH]) AND (("Venous Thromboembolism"[MeSH]) AND ("Pulmonary Embolism"[MeSH]) OR ("Venous Thrombosis"[MeSH])) AND ("Tomography, X-Ray Computed"[MeSH]) AND ("incidental" OR "asymptomatic" OR "unexpected" OR "unsuspected")
4.	Catheter-related VTE: ("Neoplasms"[MeSH] OR "Carcinoma"[MeSH]) AND ("Venous Thromboembolism"[MeSH] OR "Venous thrombosis"[MeSH] OR "Pulmonary Embolism"[MeSH]) AND ("Warfarin"[MeSH]) AND ("Central Venous Catheters"[MeSH])
5.	Recurrent VTE despite anticoagulation: ("Neoplasms"[MeSH] OR "Carcinoma"[MeSH]) AND ("Anticoagulants"[MeSH] OR "Heparin, Low-Molecular-Weight"[MeSH] OR "Warfarin"[MeSH]) AND ("recurrent venous" OR "recurrent pulmonary embolism")
6.	Thrombocytopenia due to chemotherapy or marrow infiltration by cancer: ("Neoplasms"[MeSH] OR "Carcinoma"[MeSH]) AND ("Anticoagulants"[MeSH] OR "Heparin, Low-Molecular-Weight"[MeSH] OR "Warfarin"[MeSH]) AND (("Venous Thromboembolism"[MeSH]) AND ("Pulmonary Embolism"[MeSH]) OR ("Venous Thrombosis"[MeSH])) AND ("Thrombocytopenia"[MeSH])
7.	Moderate-to-severe renal impairment: ("Neoplasms"[MeSH] OR "Carcinoma"[MeSH]) AND ("Venous Thromboembolism"[MeSH] OR "Venous Thrombosis"[MeSH] OR "Pulmonary Embolism"[MeSH]) AND ("Renal Insufficiency"[MeSH])

in the areas of hematology, medical oncology, and internal medicine, identified important clinical challenges in the management of cancer-associated thrombosis. A steering committee of 8 voting participants developed the initial statements. A Web-based consensus platform (supplier: MedPlan Communications, Montreal, QC) was used to facilitate most aspects of the consensus process. The consensus statements, associated summaries of the evidence graded according to level of evidence, and clinical rationales were uploaded to the Web-based platform. The quality of the evidence for each statement was assessed and reported as depicted in Table II. The assessment was performed by the authors, and disagreement was resolved by consensus. A validation committee that included 13 additional expert members reviewed each consensus statement. Both expert groups (the steering and validation committees) used a modified Delphi process to vote anonymously on their level of agreement with the various statements, and they suggested revisions to statements and provided comments on specific references.

Statements were progressively revised through separate voting and commenting iterations and were finalized at a face-to-face steering committee meeting. Expert members were asked to vote on their level of agreement with each statement on a scale of 1 to 5 (1, strongly agree; 2, somewhat agree; 3, neutral; 4, somewhat disagree; 5, strongly disagree). The recommendations were adapted to indicate the overall strength of agreement, with the terms "strongly recommend" being used for statements with which

TABLE II Suggested levels of evidence

Level of evidence	*Evidence type*
IA	Systematic review of randomized controlled trials
IB	Individual randomized controlled trials with narrow confidence intervals
IIA	Systematic reviews of cohort studies
IIB	Individual cohort studies or low-quality randomized controlled trials
IIIA	Systematic reviews of case–control studies
IIIB	Individual case–control studies
IV	Case series
V	Expert opinion or formal consensus

all members were strongly in agreement, "recommend" being used for statements with which there was no strong disagreement, and "suggest" being used for statements with which there was some strong disagreement. For clinicians, a strong recommendation means that they should follow this course of action in treating most patients. A recommendation or suggestion implies that clinicians should provide patient-specific management based on the risks and benefits of the various options, with consideration for patient values and preferences and for cost and resource allocations[6].

The expert consensus statements were formulated under the observation of Thrombosis Canada. To ensure transparency, minutes of the various meetings were sent to executive members of Thrombosis Canada.

2.3 Role of the Funding Sources

The conferences and Web platform were funded by an unrestricted grant from Pfizer Canada. The authors administered all aspects of the meeting, and the funding source had no role in drafting or approving the guideline statements.

3. RECOMMENDATION STATEMENTS

3.1 Role of Direct Oral Anticoagulants for the Acute Treatment of Cancer-Associated VTE

Statement 1: We do not recommend the use of the direct oral anticoagulants [DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban)] for acute treatment of cancer-associated thrombosis. [Level of evidence: V; Level of agreement: 86% (n = 18) strongly agreed, 14% (n = 3) somewhat agreed]

The American Society of Clinical Oncology, the U.S. National Comprehensive Cancer Network, the American College of Chest Physicians, and the European Society for Medical Oncology all recommend monotherapy with low molecular weight heparin (LMWH) for up to 6 months in acute cancer-related thrombosis[3–5]. The use of warfarin for the long-term management of cancer patients with VTE is suggested as an acceptable option if LMWH is not available. The DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) can offer an attractive alternative for management of acute cancer-related thrombosis. Although recent studies showed that DOACs are comparable to conventional therapy for the acute treatment of VTE, their efficacy and safety in cancer patients is uncertain. A number of recently published systematic reviews and meta-analyses assessed the efficacy and safety of the DOACs for the treatment of cancer-associated thrombosis[7–9]. The reviews identified five randomized controlled trials (RCTs) involving 1132 patients with cancer-associated thrombosis that compared various DOACs with warfarin. Overall, the use of DOACs rather than warfarin to treat acute cancer-related thrombosis was associated with a nonsignificant lower risk of recurrent VTE (risk ratio: 0.66; 95% confidence interval: 0.39 to 1.11) and major bleeding episodes (risk ratio: 0.78; 95% confidence interval: 0.42 to 1.44). Those results indicate that the efficacy and safety of DOACs in cancer patients are at least comparable to those of warfarin. However, the quality of the evidence is low considering that the studies were underpowered to show noninferiority or superiority of DOACs with respect to warfarin in cancer patients. Furthermore, the cancer patient populations in the trials were substantially different from those in trials comparing LMWH with warfarin monotherapy. Patients in the LMWH trials had a higher annualized risk of recurrent VTE and major bleeding, suggesting that the LMWH trials included a higher-risk cancer population[9]. Therefore, until large RCTs comparing DOACs with LMWH in cancer patients with VTE are performed to properly discern the safety and efficacy of the new agents, the use of DOACs in patients with cancer is discouraged.

3.2 Management of Anticoagulation for Cancer-Associated Thrombosis Beyond the Initial 6 Months of Therapy

Statement 2: We recommend that continuation of anticoagulation with the most appropriate agent is required in most circumstances if an indication for anticoagulation was present before the incident cancer (for example, in cases of atrial fibrillation or previous VTE not felt to be related to malignancy). Reasonable options for therapy include well-controlled warfarin, LMWH, and DOACs. The chosen therapy has to be adapted to the indication, clinical setting, and cancer treatment. [Level of evidence: V; Level of agreement: 76% (n = 16) strongly agreed, 24% (n = 5) somewhat agreed]

Statement 3: We recommend that anticoagulation can be terminated after a minimum of 6 months of anticoagulant therapy if the underlying cancer has been treated with curative intent and any ongoing therapy is associated with a low risk of thrombosis. [Level of evidence: V; Level of agreement: 86% (n = 18) strongly agreed, 14% (n = 3) somewhat agreed]

Statement 4: In patients with advanced cancer in complete remission for whom the short-term risk of cancer recurrence is high, or in the presence of other ongoing major risk factors for thrombosis, we recommend continuation of anticoagulant therapy as a reasonable option. In such situations, the continuation of LMWH could be preferable to other alternatives. [Level of evidence: V; Level of agreement: 62% (n = 13) strongly agreed, 24% (n = 5) somewhat agreed, 14% (n = 3) somewhat disagreed]

Statement 5: In patients with advanced cancer in complete remission with a low or moderate risk of cancer recurrence, we suggest these options:

- Treatment discontinuation
- Therapy with a LMWH until the risk of cancer or VTE recurrence is felt to be low
- Substitution therapy with warfarin
- Therapy with a DOAC

[Level of evidence: V; Level of agreement: 62% (*n* = 13) strongly agreed, 19% (*n* = 4) somewhat agreed, 14% (*n* = 3) somewhat disagreed, 5% (*n* = 1) strongly disagreed]

Statement 6: In the absence of a contraindication to anticoagulation, we suggest continuation of anticoagulant therapy beyond 6 months as the preferred option in patients with active advanced cancer. Although no data are available to guide selection of therapy, continuation of LMWH at the established dose is the preferred option for most situations. Individualization of therapy (including warfarin and DOACS) could be reasonable in certain settings after consideration of patient preference and other clinical factors. [Level of evidence: V; Level of agreement: 76% (*n* = 16) strongly agreed, 10% (*n* = 2) somewhat agreed, 10% (*n* = 2) somewhat disagreed, 5% (*n* = 1) strongly disagreed]

Data guiding clinicians on the length of anticoagulation beyond the initial 6 months of therapy for cancer-associated thrombosis are scarce. Based on expert discussions and widespread clinical practice, anticoagulation treatment after a 6-month treatment period is usually guided by a thorough assessment of the factors contributing directly to the risk of recurrent cancer-associated thrombosis (including the risk of cancer recurrence). Risk stratification based on the tumour type or biology; stage of disease; and patient comorbidities (hospitalization or immobilization, surgery, chemotherapy or radiation therapy, central venous catheter insertion, or localized tumour compression) is important[10].

Optimal therapy after 6 months of anticoagulation is still debated, and clinical studies are ongoing (search for NCT01817257 at http://ClinicalTrials.gov/). Only one prospective cohort study evaluated the safety of extending anticoagulation with LMWH beyond the initial 6 months (up to 12 months) in patients with cancer-associated thrombosis[11]. Of 334 patients with VTE and active cancer who were treated with dalteparin, 185 (55.4%) completed 6 months of therapy, and 109 (32.6%) completed 12 months. Therapy with LMWH in patients with cancer-associated thrombosis beyond 6 months (compared with the initial period of therapy) did not seem to be associated with an increased risk of major bleeding episodes or recurrent VTE. No available data support the use of warfarin or DOACS beyond the initial 6 months of anticoagulation therapy. As reviewed in Statement 1, DOACS seem to be comparable to warfarin for the acute treatment of cancer-associated thrombosis and might be a reasonable alternative to warfarin in patients at low risk of recurrence and for whom warfarin is being considered instead of LMWH. Although LMWH is realistically superior to cessation of therapy, data to support its substitution for warfarin or DOACS in this setting is poor.

3.3 Incidental Cancer-Associated Thrombosis

Statement 7: In cancer patients with objectively confirmed incidental (asymptomatic) PE detected on computed tomography (CT) or magnetic resonance imaging performed for other reasons, we suggest management with anticoagulation therapy as for symptomatic PE for most patients. [Level of evidence: IIB; Level of agreement: 86% (*n* = 18) strongly agreed, 10% (*n* = 2) somewhat agreed, 5% (*n* = 1) strongly disagreed]

Statement 8: In cancer patients with incidental (asymptomatic) proximal limb DVT detected on CT or magnetic resonance imaging for other reasons, we suggest confirmatory imaging and treatment as for symptomatic DVT. [Level of evidence: IIB; Level of agreement: 86% (*n* = 18) strongly agreed, 10% (*n* = 2) somewhat agreed, 5% (*n* = 1) strongly disagreed]

Statement 9: If considering no anticoagulation therapy in cancer patients with incidental (asymptomatic) PE in an isolated single subsegmental pulmonary artery, we recommend imaging (which could include CT pulmonary angiography, or ultrasonography of pelvis and serial bilateral proximal lower limb deep veins, or both). [Level of evidence: IIB; Level of agreement: 38% (*n* = 8) strongly agreed, 52% (*n* = 11) somewhat agreed, 5% (*n* = 1) neutral, 5% (*n* = 1) somewhat disagreed]

Statement 10: Expert consensus strongly recommends that an individualized approach is appropriate for patients with incidental (asymptomatic) abdominal vein or splanchnic vein VTE. The decision to initiate anticoagulation therapy should consider

- risk of bleeding;
- chronicity of thrombus (nonocclusive thrombus, cavernous transformation, presence of collaterals, etc.);
- risk of thrombosis-related complications (for example, bowel ischemia, Budd–Chiari syndrome);
- primary tumour site (for example, pancreatic versus renal cell carcinoma);
- comparisons to previous and serial diagnostic imaging; and
- patient preference.

Anticoagulation should be considered in patients at low risk of bleeding and with a thrombus that appears acute. [Level of evidence: V; Level of agreement: 100% ($n = 21$) strongly agreed]

The use of high-resolution, multi-detector CT images in the staging, response assessment, and follow-up of cancer patients has led to an increase in the incidental reports of cancer-associated thrombosis. The literature on the management of incidental cancer-associated thrombosis is scarce. Only a small number of observational studies have been published to date[12–17]. Outcomes (recurrent VTE, major bleeding, and overall mortality) in anticoagulated patients with symptomatic proximal cancer-associated PE are similar to those in patients with incidental findings, suggesting a potential benefit of therapy[12–14]. Patients with incidental isolated subsegmental PE might have a prognosis similar to that in cancer patients without PE[15], and therefore, more conservative management (for example, serial ultrasonography of pelvis and bilateral proximal lower limb deep veins) without the use of anticoagulation therapy might be reasonable.

Some observational studies reported a low risk of recurrence for cancer patients with incidental abdominal or splanchnic vein thrombosis when left untreated[18,19], but others have not [Ramasamy SM, Bozas G, Avery G, Maraveyas A. Incidental splanchnic thrombosis in cancer patients. Poster (PP-WE-503) presented at the XXII Congress of the International Society on Thrombosis and Haemostasis; Boston, MA, U.S.A.; July 11–16, 2009]. The final decision to treat or not to treat should therefore take into consideration individual patient features such as thrombosis burden, cancer status (active or remission), treatment options, prognosis, and risk of major bleeding episodes. In making a decision on duration of anticoagulation therapy, practitioners should frequently re-evaluate the cancer status, cancer treatment, prognosis, quality of life, and risk of bleeding in their patients receiving anticoagulant treatment for incidental VTE.

3.4 Catheter-Related Cancer-Associated Thrombosis

Statement 11: We strongly recommend that a suspected symptomatic catheter-related upper-extremity DVT be investigated initially with ultrasonography. [Level of evidence: IIA; Level of agreement: 100% ($n = 21$) strongly agreed]

Statement 12: In the presence of a high index of suspicion for catheter-related upper extremity DVT, but of negative ultrasonography findings, we suggest further diagnostic testing, which can include contrast venography and CT venography. We recommend against serial ultrasonography in this setting. [Level of evidence: V; Level of agreement: 33% ($n = 7$) strongly agreed, 57% ($n = 12$) somewhat agreed, 10% ($n = 2$) strongly disagreed]

Statement 13: Catheter-related cancer-associated DVT requires treatment if the thrombus involves the deep veins, such as the axillary and subclavian, or more proximal veins. We recommend that close clinical surveillance (for example, symptom resolution, serial ultrasonography, etc.) is a reasonable alternative to treatment for thrombosis involving the brachial deep vein or the basilic and cephalic superficial veins. [Level of evidence: V; Level of agreement: 62% ($n = 13$) strongly agreed, 29% ($n = 6$) somewhat agreed, 10% ($n = 2$) somewhat disagreed]

Statement 14: Thrombolysis for treatment of symptomatic catheter-associated DVT in patients with cancer is not routinely recommended, but can be considered in refractory or extensive cases if catheter removal does not result in symptomatic improvement. [Level of evidence: IIB; Level of agreement: 67% ($n = 14$) strongly agreed, 14% ($n = 3$) somewhat agreed, 10% ($n = 2$) neutral, 10% ($n = 2$) somewhat disagreed]

Statement 15: Appropriate anticoagulation therapy options for catheter-related cancer-associated thrombosis include LMWH monotherapy and LMWH overlapped with warfarin. Most experts favour the use of LMWH monotherapy. There is currently no evidence for the use of DOACs in the treatment of catheter-related thrombosis in patients with cancer. We recommend against the use of those agents outside of clinical trials. [Level of evidence: IIB–V; Level of agreement: 81% ($n = 17$) strongly agreed, 14% ($n = 3$) somewhat agreed, 5% ($n = 1$) strongly disagreed]

Statement 16: In patients with catheter-related thrombosis started on anticoagulation, we strongly recommend that the catheter stay in place as long as symptoms improve and the catheter is needed, working, and not infected. [Level of evidence: IIB; Level of agreement: 100% ($n = 21$) strongly agreed]

Statement 17: We recommend that catheter-related cancer-associated thrombosis in patients with cancer should ideally be treated with anticoagulation for at least 3 months. Consideration can be given to extending the duration of anticoagulation as long as the catheter remains *in situ*. [Level of evidence: IIB–V; Level of agreement: 71% ($n = 15$) strongly agreed, 24% ($n = 5$) somewhat agreed, 5% ($n = 1$) neutral]

Statement 18: We do not recommend primary thromboprophylaxis for patients with an indwelling catheter and cancer. [Level of evidence: IA; Level of agreement: 95% ($n = 20$) strongly agreed, 5% ($n = 1$) neutral]

Catheter-related upper extremity DVT is a frequent complication in cancer patients. Although the clinician might find it appealing to consider primary thromboprophylaxis, a systematic review of RCTs showed no clear benefit of primary thromboprophylaxis in patients with catheter-related cancer-associated DVT[20].

A diagnostic algorithm for the diagnosis of catheter-related upper-extremity DVT, including pretest probability assessments in combination with D-dimer, has recently been developed[21], but not validated in cancer patients. The algorithm is therefore of unknown value in that population. Ultrasonography is a sensitive (84%–97%) and specific (87%–96%) diagnostic modality that is noninvasive and readily available[22]. In cases in which ultrasonography is inconclusive, other modalities should be considered. Contrast venography can have better sensitivity than ultrasonography, but it is invasive, requires the administration of intravenous contrast, and should be reserved for complex cases. Although no studies of CT venography have been conducted in this setting, that modality might be more readily available than contrast venography.

The decision to initiate anticoagulation for catheter-related cancer-associated upper extremity DVT depends on the location and extent of the thrombus. The calibres of the brachial deep vein and the superficial veins are smaller, and anecdotal experience shows that thrombi in those locations are unlikely to extend or embolize, might not require anticoagulation, and are likely to resolve with conservative management in most cases. Standard anticoagulation therapy with LMWH and warfarin has been shown to be safe and effective for the management of proximal catheter-related cancer-associated upper extremity thrombosis[23]. The same prospective cohort study also demonstrated that the catheter can be kept in place as long as it was needed and working[23]. Monotherapy with LMWH might also be a reasonable alternative to LMWH overlapped with warfarin in cancer patients[24]. There is currently no evidence for the use of DOACs in the treatment of catheter-related thrombosis in patients with cancer, but studies are ongoing. Patients should be treated for a minimum of 3 months or until the catheter is removed. There could be a role for thrombolytics in the treatment of severe or refractory symptomatic catheter-associated DVT, but trials in this specific population are needed, given their significant risk of major bleeding.

3.5 Recurrent Cancer-Associated Thrombosis Despite Anticoagulation

Statement 19: In patients with active cancer and a history of VTE who develop an objectively confirmed VTE recurrence during active anticoagulation with warfarin, we recommend switching to a LMWH at full therapeutic dose for a minimum of 4 weeks; expert consensus would recommend long-term therapy. [Level of evidence: IIA; Level of agreement: 95% (n = 20) strongly agreed, 5% (n = 1) somewhat agreed]

Statement 20: In patients with active cancer and a history of VTE who develop an objectively confirmed VTE recurrence during active anticoagulation with a LMWH at a dose lower than the full therapeutic dose (for example, 75% or lower), we recommend increasing the dose to the full therapeutic dose for a minimum of 4 weeks; expert consensus would recommend long-term therapy. [Level of evidence: IIA; Level of agreement: 95% (n = 20) strongly agreed, 5% (n = 1) somewhat agreed]

Statement 21: In patients with active cancer and a history of VTE who develop an objectively confirmed VTE recurrence during active anticoagulation with a LMWH at full therapeutic weight-based dose, we recommend increasing the total dose by 20%–25% for a minimum of 4 weeks and considering twice-daily dosing. [Level of evidence: IIA; Level of agreement: 95% (n = 20) strongly agreed, 5% (n = 1) somewhat agreed]

Statement 22: In patients with active cancer and a history of VTE who develop an objectively confirmed VTE recurrence during active anticoagulation with a supratherapeutic dose of LMWH (that is, after dose escalation), expert consensus on the optimal treatment strategy is lacking. We suggest any one or a combination of these options:

- Further LMWH dose escalation with or without the use of anti–factor Xa monitoring
- Addition of an antiplatelet agent
- Consideration of changes to the antineoplastic treatment in consultation with the treating oncologist

[Level of evidence: V; Level of agreement: 81% (n = 17) strongly agreed, 9% (n = 2) somewhat agreed, 5% (n = 1) somewhat disagreed, 5% (n = 1) strongly disagreed]

Statement 23: In patients with active cancer and a history of VTE who develop an objectively confirmed VTE recurrence during active anticoagulation with a DOAC (for example, apixaban, dabigatran, rivaroxaban, edoxaban), we recommend switching to full-dose LMWH for a minimum of 4 weeks; expert consensus would recommend long-term therapy. [Level of evidence: V; Level of agreement: 95% (n = 20) strongly agreed, 5% (n = 1) somewhat agreed]

Statement 24: In patients with active cancer and a history of VTE who develop an objectively confirmed VTE recurrence during active anticoagulation with either LMWH or warfarin, we recommend against switching to DOACs or fondaparinux. [Level of evidence: IV; Level of agreement: 76% (n = 16) strongly agreed, 10% (n = 2) somewhat agreed, 10% (n = 2) neutral, 5% (n = 1) somewhat disagreed]

Compared with patients without cancer, patients with a malignancy who develop VTE are at higher risk of recurrence. In patients treated for cancer-associated thrombosis, the 6-month incidence of

recurrent VTE is 14% for those receiving warfarin and 7% for those receiving LMWH monotherapy[25]. Three retrospective cohort studies reported on the efficacy and safety of a full therapeutic dose of LMWH for the management of recurrent VTE despite anticoagulation with warfarin[20,26,27]. Similarly, two retrospective cohort studies assessed the use of LMWH dose escalation for patients with recurrent VTE despite treatment with LMWH[20,26]. Patients with recurrent cancer-associated thrombosis despite intermediate or prophylactic doses of LMWH were managed by increasing the dose to a therapeutic weight-adjusted LMWH dose. Similarly, in patients with recurrent events despite therapeutic doses of LMWH, the dose of LMWH was increased by 20%–25%. Those approaches seem to be safe and effective for treating recurrent cancer-associated thrombosis despite anticoagulation.

Only a very small number of patients successfully managed using further dose escalation of LMWH for additional recurrent events have been reported in the literature[20]. Although the use of plasma anti–factor Xa has been suggested to guide further dose escalation[28], our recommendation is based solely on expert opinion. It would, however, be reasonable to obtain a peak anti–factor Xa level to assess treatment compliance. Further studies are much needed in this area. Small retrospective cohort studies for patients with recurrent cancer-associated VTE despite LMWH treatment reported a higher rate of second recurrent VTE with fondaparinux (36%) than with LMWH dose escalation (8%)[29,30].

3.6 Thrombocytopenia Resulting from Chemotherapy or Marrow Infiltration by Cancer

Statement 25: We recommend that acute cancer-associated thrombosis be treated with a full therapeutic dose of LMWH if the platelet count exceeds 50×10^9/L. [Level of evidence: IIB–V; Level of agreement: 86% (n = 18) strongly agreed, 10% (n = 2) somewhat agreed, 5% (n = 1) neutral]

Statement 26: Expert consensus recommends an individualized approach for patients with new or recent (<1 month) cancer-associated thrombosis with a platelet count of $30–50\times10^9$/L. In that population, management options include

- dose-reduced LMWH (for example, 50% of full dose);
- if achievable, transfusion to a platelet count exceeding 50×10^9/L and treatment with full-dose LMWH; or
- if DVT is present and no anticoagulation is given, placement of an inferior vena cava (IVC) filter (preferably temporarily).

Once the patient's platelet count exceeds 50×10^9/L, a full therapeutic dose of LMWH should be resumed. [Level of evidence: Overall, V; for IVC filter and transfusion, IIB; Level of agreement: 86% (n = 18) strongly agreed, 10% (n = 2) somewhat agreed, 5% (n = 1) neutral]

Statement 27: We recommend that patients on anticoagulation treatment for cancer-associated thrombosis (≥1 month) with a platelet count of $30–50\times10^9$/L can be treated with reduced-dose LMWH (50% of full or prophylactic dose). Once the patient's platelet count exceeds 50×10^9/L, a full therapeutic dose of LMWH should be resumed. [Level of evidence: V; Level of agreement: 52% (n = 11) strongly agreed, 43% (n = 9) somewhat agreed, 5% (n = 1) neutral]

Statement 28: We suggest that patients on anticoagulation treatment (≥1 month) for cancer-associated thrombosis with severe thrombocytopenia ($<30\times10^9$/L) of expected short duration (≤7 days) should have LMWH held until the platelet count exceeds 30×10^9/L, at which point anticoagulation should be resumed. For patients on anticoagulation treatment (≥1 month) for cancer-associated thrombosis with severe thrombocytopenia ($<30\times10^9$/L) of expected long-term duration (>7 days), an IVC filter could be considered in selected circumstances (for example, proximal DVT, progressive VTE). [Level of evidence: Overall, V; for IVC filters, IIB; Level of agreement: 67% (n = 14) strongly agreed, 19% (n = 4) somewhat agreed, 5% (n = 1) neutral, 9% (n = 2) strongly disagreed]

Statement 29: Expert consensus suggests an individualized approach for patients with new or recent (<1 month) cancer-associated thrombosis with a platelet count below 30×10^9/L. In that population, management options include

- if achievable, transfusion to a platelet count exceeding 50×10^9/L and treatment with full-dose LMWH; or
- if DVT is present and no anticoagulation is given, placement of an IVC filter (preferable temporarily).

Once the patient's platelet count exceeds 30×10^9/L, anticoagulation should be resumed. [Level of evidence: Overall, V; for IVC filters, IIB; Level of agreement: 71% (n = 15) strongly agreed, 14% (n = 3) somewhat agreed, 5% (n = 1) neutral, 5% (n = 1) somewhat disagreed, 5% (n = 1) strongly disagreed]

It is important to note that the foregoing recommendation focuses on chemotherapy-induced thrombocytopenia or thrombocytopenia caused by marrow infiltration by cancer. In the setting of new-onset thrombocytopenia, it is important to rule out heparin-induced thrombocytopenia and microangiopathic processes (for example, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, etc.). There is general consensus among hematologists that a threshold of 50×10^9/L is safe for initiation of

therapeutic doses of anticoagulation, a recommendation that aligns with statements from the International Society on Thrombosis and Haemostasis guidelines[28] and the Italian RAND analysis[32]. Management of anticoagulation in patients with moderate ($30–50\times10^9$/L) and severe ($<30\times10^9$/L) thrombocytopenia has to be tailored based on time since diagnosis of the index VTE (<1 month, ≥1 month). In patients with new or recent cancer-related thrombosis (<1 month) and moderate or severe thrombocytopenia, management should be tailored case by case. Management options include transfusion to maintain a platelet count exceeding 50×10^9/L[33], LMWH dose reduction[32], or IVC filter placement in selected patients with proximal DVT[34]. In patients with chronic cancer-associated thrombosis (≥1 month) and temporary thrombocytopenia, LMWH can be dose-reduced (moderate thrombocytopenia) or interrupted (severe thrombocytopenia)[28,32]. Therapeutic doses of LMWH should be resumed (and the IVC filter retrieved, if inserted) once the thrombocytopenia resolves.

3.7 Moderate-to-Severe Renal Impairment

Statement 30: We recommend that renal function surveillance be exercised in all patients with calculated creatinine clearances below 50 mL/min and that therapeutic doses of LMWH be avoided in patients with severe renal disease (creatinine clearance < 30 mL/min) unless they are monitored using anti–factor Xa heparin levels. Compared with longer courses of LMWH, short courses (<7 days) are likely to be associated with less risk of major bleeding episodes and might be safe to administer without anti–factor Xa heparin level monitoring, particularly when using LMWHs with greater nonrenal clearance. Available evidence suggests that, at prophylactic doses, the risk of bioaccumulation is lower than it is at therapeutic doses. [Level of evidence: Overall, V; in some domains, IV; Level of agreement: 62% (n = 13) strongly agreed, 24% (n = 5) somewhat agreed, 14% (n = 3) somewhat disagreed]

Statement 31: Compared with smaller molecules, larger molecules are more likely to be cleared by extrarenal mechanisms and thus could have a lower risk of accumulation and bleeding. In patients with a creatinine clearance between 30 mL/min and 50 mL/min, full therapeutic doses of enoxaparin and fondaparinux are likely to bioaccumulate. [Level of evidence: V; Level of agreement: 43% (n = 9) strongly agreed, 43% (n = 9) somewhat agreed, 10% (n = 2) neutral, 5% (n = 1) strongly disagreed]

Statement 32: Extensive practical experience suggests that unfractionated heparin monitored by activated partial thromboplastin time and transitioned to warfarin with a target international normalized ratio of 2.0–3.0 is a practical approach for therapeutic anticoagulation in patients with renal insufficiency. [Level of evidence: V; Level of agreement: 81% (n = 17) strongly agreed, 14% (n = 3) somewhat agreed, 5% (n = 1) strongly disagreed]

Statement 33: Although anti–factor Xa monitoring makes sense based on experience with other medications for which levels are monitored and doses adjusted, little evidence has been developed to show that this practice improves outcomes when used to guide LMWH dosing. Additionally, there is reasonable-quality evidence of large variations in anti–factor Xa levels between reagents and laboratories, which leads to questions about the utility of the test. We suggest that if anti–factor Xa monitoring is used to assess bioaccumulation with therapeutic doses of once-daily LMWH, trough levels should be targeted to below 0.4 U/mL. [Level of evidence: V; Level of agreement: 47% (n = 10) strongly agreed, 48% (n = 10) somewhat agreed, 5% (n = 1) strongly disagreed]

Statement 34: We suggest that LMWH should be used with extreme care in patients with end-stage renal disease requiring dialysis. Use should ideally be confined to research studies in the setting of anti–factor Xa monitoring. [Level of evidence: V; Level of agreement: 52% (n = 11) strongly agreed, 38% (n = 8) somewhat agreed, 10% (n = 2) strongly disagreed]

Evidence for the management of cancer-associated thrombosis in patients with moderate (30–50 mL/min) to severe (<30 mL/min) renal dysfunction is extrapolated from the non-cancer literature. At prophylactic doses, dalteparin and tinzaparin do not seem to bioaccumulate[35–39]. One large RCT[36] and two smaller cohort studies[37,38] concluded that dalteparin at prophylactic doses was unlikely to contribute to bleeding in patients with renal impairment. Enoxaparin at prophylactic doses might bioaccumulate in patients with severe renal dysfunction, and dose reduction is recommended[39,40].

Therapeutic doses of LMWH should be used with extreme caution in patients with severe renal dysfunction. One small RCT comparing tinzaparin and dalteparin found that both drugs accumulated in hemodialysis patients at therapeutic doses[41]. Similarly, a meta-analysis found an increase in bleeding risk with enoxaparin in patients with renal impairment[40]. Compared with longer-course treatment, short-course therapeutic doses (up to 5 days) of dalteparin or tinzaparin are less likely to be associated with bioaccumulation and might be reasonable for initiating oral anticoagulation with warfarin therapy. However, extensive practical experience suggests that unfractionated heparin monitored by activated partial thromboplastin time and transitioned to warfarin with a target international normalized ratio of 2.0–3.0 is a practical approach for therapeutic anticoagulation in patients with renal insufficiency.

There is very limited and, to some degree, conflicting evidence regarding the level of renal impairment at which LMWH treatment should be modified. There is no evidence using comparative data to measure clinical outcomes. Although extensive experience of measuring anti–factor Xa levels and adjusting doses based on those levels has been reported, the relationship of anti–factor Xa levels during LMWH treatment with clinical outcomes is not clear. Only one small study linked anti–factor Xa levels with risk of bleeding in postoperative patients treated with prophylactic doses of LMWH[42]. Additionally, wide variability in heparin clearance is likely, depending on the mechanism of kidney injury, individual patient characteristics, and the particular drugs in use. Thus, the evidence is insufficient to establish a threshold at which the LMWH dose should be adjusted. Comparative data to allow conclusions to be drawn about the safety or efficacy of one LMWH over another are lacking. Very limited data and little practical comparative evidence are available about any potential differences between the various LMWHs. Given the extensive experience with unfractionated heparin in patients with renal failure, it seems logical that larger unfractionated heparin–like products would be preferable in that patient population; however, that supposition is largely conjectural.

4. ACKNOWLEDGMENTS

We thank Drs. Christine Demers, Jim Douketis, Blair D. Ernst, Jeannine Kassis, Michael Kovacs, Philip Kuruvilla, Gregoire Le Gal, Lori-Ann Linkins, André Roussin, Susan Solymoss, Axel Tosikyan, Christine Tremblay, and Cynthia Wu for serving on the validation committee, helping to select topics to cover in these recommendations, and reviewing and commenting on the proposed recommendations. Rebecca Cowan of MedPlan Communications Inc. is thanked for editorial support in the preparation of the manuscript.

5. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: MC has received research funding from Leo Pharma and Bristol–Myers Squibb. He has also participated on advisory boards for Pfizer, Bayer and Boehringer Ingelheim. ALL has received honoraria from Pfizer, Bayer, Leo Pharma, and Boehringer Ingelheim and has participated in studies sponsored by Pfizer, Leo Pharma, Bayer, Daiichi–Sankyo, Novartis, and Celgene. VT has received research funding from Sanofi and Pfizer Canada. She has also participated on advisory boards for Pfizer, Sanofi, and Bayer. SS has participated on advisory boards for Pfizer, Bayer and Boehringer Ingelheim. NB has received research funding from Pfizer Canada. He has also participated on advisory boards for Pfizer, Sanofi, Leo Pharma, Boehringer Ingelheim, and Bayer. MC has sat on advisory boards for Bayer, Boehringer Ingelheim, Pfizer, Leo Pharma, Portola, and AKP America, and holds a Career Investigator award from the Heart and Stroke Foundation of Ontario and the Leo Pharma Chair in Thromboembolism Research at McMaster University. MC's institution has received funding for research projects from Leo Pharma and Bayer, and MC has received funding for presentations from Bristol–Myers Squibb—Pfizer alliance, Leo Pharma, Bayer, Celgene, Shire, and CSL Behring.

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