Factor XI inhibitors: a new option for the prevention and treatment of cancer-associated thrombosis

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ABSTRACT

Venous thromboembolism (VTE) is a relatively common complication in cancer patients with potentially dire consequences. Anticoaguants are the mainstay of treatment of cancer-associated VTE. The anticoagulants most often used are low-molecular-weight heparin (LMWH) and direct oral factor (F) Xa inhibitors, which include apixaban, edoxaban, and rivaroxaban. Most guidelines recommend primary VTE prophylaxis with LMWH, apixaban, or rivaroxaban after abdominal or pelvic cancer surgery, or in high-risk ambulatory cancer patients. Both oral FXa inhibitors and LMWH have limitations. LMWH requires daily subcutaneous injections, and because of its renal clearance, its use may be problematic in patients with severe kidney disease. The risk of bleeding with oral FXa inhibitors may be higher than with LMWH in patients with intraluminal gastrointestinal or genitourinary cancers. Other problems with oral FXa inhibitors include potential drug-drug interactions and dosing issues in patients with thrombocytopenia or severe kidney or liver disease. Therefore, there remains a need for convenient and safer anticoagulants for VTE treatment in cancer patients. FXI has emerged as a potentially safer target for anticoagulants than FXa because FXI is essential for thrombosis, but mostly dispensable for hemostasis. This review summarizes the currently available therapeutic options for cancer-associated VTE, highlights knowledge gaps, and discusses the potential of FXI inhibitors to address key unmet clinical needs in this vulnerable patient population.

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Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism, is relatively common in patients with cancer.1 Over the last few decades, the incidence of VTE has remained relatively stable in the general population, whereas it has progressively increased in cancer patients.2 In a large population-based study, the 6-month VTE risk in patients with cancer was 12-fold higher than that in subjects without cancer, and up to 23-fold higher among those receiving chemotherapy or targeted treatments.3

Cancer-associated thrombosis (CAT) represents the second most common cause of death in cancer patients after tumor progression,1 and it’s associated with substantial morbidity including repeated hospitalizations and delays or interruptions in potentially curative cancer-directed treatments.3,4 CAT is a distressing experience for patients and their relatives, increasing the psychological burden on vulnerable individuals already overwhelmed by the cancer diagnosis and its treatment.4,5 Treatment of VTE in cancer patients is challenging because of their heightened risk of recurrence and bleeding compared with patients without cancer.6,7 Both recurrent VTE and bleeding are associated with poorer quality of life, deferral or disruption of cancer treatments, and increased healthcare costs.8

The purpose of this review is to summarize the current therapeutic options for CAT, highlight current knowledge gaps, and explain how the new generation of factor (F) XI inhibitors may address unmet clinical needs.
Current treatment of cancer-associated thrombosis

Low molecular-weight heparin (LMWH) and direct oral FXa inhibitors, which include apixaban, edoxaban, and rivaroxaban are the current standards of care for CAT. In patients with CAT, studies have shown that oral FXa inhibitors are at least as effective as LMWH, and associated with a non-significant increase in major bleeding.9-14 Recent clinical guidelines suggest oral FXa inhibitors as an alternative to LMWH for most patients with CAT.15-18 Oral FXa inhibitors are more convenient to administer than LMWH, but their use may be problematic in patients with impaired gastrointestinal absorption secondary to vomiting, diarrhea, or upper gastrointestinal surgery. Patients with gastroesophageal or genitourinary cancers, especially those with unresected luminal tumors, had a higher risk of bleeding with edoxaban or rivaroxaban than with dalteparin.9,10,19,20 Although the risk of bleeding with apixaban was similar to that with dalteparin,13 recent guidelines suggest the use of LMWH rather than oral FXa inhibitors in patients with unresected gastrointestinal or genitourinary cancers.15-18 All oral FXa inhibitors are substrates of P-glycoprotein, and apixaban and rivaroxaban are metabolized by cytochrome (CYP) 3A4. Consequently, the concomitant use of drugs that affect these pathways could influence drug concentrations and increase the risk of bleeding or thrombotic complications.21,22 Most guidelines endorse the preferential use of LMWH in cancer patients receiving strong inducers or inhibitors of P-glycoprotein or CYP3A4.21 Oral FXa inhibitors are cleared in part by the kidneys and are metabolized in the liver, which limits their utility in patients with severe kidney or liver disease. In addition, since patients with brain cancer, hematological malignancies, or severe thrombocytopenia were excluded or underrepresented in the trials comparing the oral FXa inhibitors with dalteparin for the treatment of CAT, adjusted-dose LMWH is often the preferred option in these patients.

Limitations of current cancer-associated thrombosis treatments

Bleeding remains the major concern with both oral FXa inhibitors and LMWH.20 The risk of bleeding with current anticoagulants is related to their inhibitory effects on both thrombosis and hemostasis because they target FXa and thrombin, which are implicated in the common coagulation pathway.23 Preclinical and clinical evidence suggests that thrombosis can be uncoupled from hemostasis by targeting FXI, which is situated upstream to FXa in the intrinsic pathway of coagulation and is essential for thrombosis, but mostly dispensable for hemostasis.23 Therefore, anticoagulants that target FXI have the potential to be safer than the currently available agents.

Role of factor XI in cancer-associated thrombosis

FXI can be activated by FXIIa or by thrombin. Regardless of the activator, FXIa is likely to play a central role in the pathophysiology of CAT (Figure 1).24 The extrinsic coagulation pathway is initiated by tissue factor (TF) exposed at the site of blood vessel injury, or expressed on leukocytes or microvesicles that become tethered to activated endothelial cells. This pathway is particularly important in patients with cancer because some cancer cell types constitutively express TF and release extracellular vesicles bearing TF.25,26 In addition, increased expression of TF by monocytes has been reported in cancer patients.1 TF binds FVII or FVIIa to form the TF-FVIIa complex, which activates FX and FIX. FIXa together with FVIIIa assemble on the surface of activated platelets to form intrinsic tenase, which amplifies and sustains FXa and thrombin generation. Since the capability of the TF-FVIIa complex to propagate coagulation may be limited once the thrombus extends beyond the TF source, feedback activation of FXI by thrombin is thought to be essential for thrombus growth.23

Activation of FXI by FXIIa may also contribute to CAT. FXII activation can be triggered by negatively charged polyanions including neutrophil extracellular traps released by activated neutrophils, DNA or RNA released from cancer cells, or by polyphosphate released from activated platelets or from bacteria during infections.27-31 Central venous catheters (CVCs) are often used in patients with cancer for the administration of chemotherapy or other medications, or for blood product transfusion. Contact of the blood with CVCs triggers FXII activation (Figure 1).32 The relevance of FXII and FXI to catheter thrombosis is highlighted by studies in rabbits that revealed attenuation of catheter-related thrombosis with reduction in the levels of FXII or FXI with target-specific antisense oligonucleotides (ASOs).32

Figure 1. Role of factor XI in the pathophysiology of cancer-associated thrombosis.
Preclinical and epidemiological evidence supporting factor XI as a safer target than factor Xa

Mice deficient in FXI or FXII exhibited defective thrombus formation at sites of arterial or venous injury without evidence of increased bleeding.34-41 Likewise, antibodies against FXI inhibited thrombosis in rodent models without affecting bleeding, and a reduction in the level of FXI with ASOs reduced shunt thrombosis in baboons.41 Studies comparing the effects of antibodies against factor FXI or FXII in non-human primates suggested more potent antithrombotic effects with FXI-directed antibodies.34,42-44

Epidemiological data support the relevance of FXI in thrombosis. Elevated FXI levels were associated with increased VTE risk,51-57 and congenital deficiency protected against VTE and ischemic stroke with little or no bleeding.46-52 The evidence that FXI deficiency is protective against myocardial infarction is less consistent.48,49 In Mendelian randomization studies, lower FXI levels were associated with reduced risks of VTE and ischemic stroke without an increased risk of major bleeding.47 whereas high FXI levels were associated with a higher risk of VTE and ischemic stroke.52,53 These findings align with the observations that subjects with congenital FXI deficiency rarely have spontaneous bleeding and do not experience the muscle, joint, or intracranial bleeding that often occurs in persons with hemophilia A or B.48,50,54-56 Although spontaneous bleeding is rare in patients with congenital FXI deficiency, bleeding can occur after trauma or surgery, often at anatomic regions with increased fibrinolytic activity such as the gastrointestinal and genitourinary tract, and the nasopharynx.48-50,54-56

In contrast to FXI, the epidemiological evidence linking FXII with thrombosis is weaker. Despite robust data showing that FXII deficiency or inhibition attenuates arterial and venous thrombosis in animal models, epidemiologic studies failed to demonstrate protection from thrombosis in patients with FXII deficiency and reported an inconsistent association between higher FXII levels and thrombotic risk.46,57,58 FXII inhibition may also potentially be of limited benefit in settings such as cancer where TF is the major driver of thrombin generation because feedback activation of FXI by thrombin can bypass FXII inhibition.57,59 Because of the uncertain role of FXII in thrombosis, FXI has gained attention as the more attractive target.32

Pharmacological strategies targeting factor XI

As shown in Table 1, multiple pharmacologic strategies to inhibit FXI are under clinical development. These include: i) ASOs (e.g., fesomersen) that reduce the hepatic synthesis of FXI; ii) monoclonal antibodies (e.g., gruticibart, osocimab, abelacimab) that inhibit FXI activation, FXIa activity, or both; iii) small molecules (e.g., asundexian, milvexian) that block the active site of FXIa (Figure 2). Each strategy has its strengths and weaknesses. ASOs and monoclonal antibodies require parenteral administration, while small molecules are given orally. ASOs have a slow onset of action requiring 3-4 weeks of subcutaneous administration to lower FXI levels within therapeutic ranges, which limits their usefulness for the initial treatment of thrombosis or immediate thromboprophylaxis.52 Although second-generation ligand-conjugated ASOs like fesomersen have a more rapid onset of action of 1-2 weeks, this is still too slow to enable their use for acute VTE treatment. Small molecules have a rapid onset of action as do monoclonal antibodies if they are given intravenously, achieving maximum plasma concentrations 2-4 hours after administration, and thus enabling their use for acute

Table 1. Pharmacological features of factor XI-directed strategies.

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Antisense oligonucleotides (fesomersen)</th>
<th>Monoclonal antibodies (abelacimab, gruticibart, osocimab)</th>
<th>Small molecules (asundexian, milvexian)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration route</td>
<td>Subcutaneous</td>
<td>Intravenous or subcutaneous</td>
<td>Oral</td>
</tr>
<tr>
<td>Administration frequency</td>
<td>Weekly to monthly</td>
<td>Monthly</td>
<td>Daily</td>
</tr>
<tr>
<td>Onset of action</td>
<td>Slow (weeks)</td>
<td>Rapid (hours to days)</td>
<td>Rapid (1 to 4 hours)</td>
</tr>
<tr>
<td>Offset of action</td>
<td>Slow (weeks)</td>
<td>Slow (weeks)</td>
<td>Rapid (12 to 24 hours)</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>No</td>
<td>No</td>
<td>Yes*</td>
</tr>
<tr>
<td>CYP450 metabolism</td>
<td>No</td>
<td>No</td>
<td>Yes*</td>
</tr>
<tr>
<td>Potential for drug-drug interactions</td>
<td>No</td>
<td>No</td>
<td>Yes*</td>
</tr>
</tbody>
</table>

*Asundexian is not metabolized via the CYP system. CYP, cytochrome.
management. Small molecules have a short half-life and require once- or twice-daily administration, whereas ASOs and monoclonal antibodies have a long half-life allowing once-monthly subcutaneous dosing. While more convenient, the long half-life of ASOs and monoclonal antibodies could be problematic in case of serious bleeding or trauma, or in patients requiring urgent surgery. Small molecules are partly cleared by the kidneys, and milvexian is metabolized to a small extent by CYP3A4, thus there is a potential for accumulation of asundexian and milvexian in patients with kidney failure and for drug-drug interactions with milvexian.60-62

Clinical studies with factor XI inhibitors

The clinical evaluation of new anticoagulants usually starts in patients undergoing major orthopedic surgery because such patients are at risk for postoperative DVT that can be efficiently detected by venography. Although DVT is often asymptomatic in such patients, its presence or absence can help to inform dose selection. Following this drug development pathway, fesoterien, osocimab, abelacimab, and milvexian were compared with enoxaparin for VTE thromboprophylaxis after elective knee replacement surgery.63-66 A meta-analysis of these studies showed a 40-50% reduction in post-operative VTE and a 59% reduction in clinically relevant bleeding with FXI inhibitors compared with enoxaparin.67

The safety of long-term FXI inhibition with abelacimab was highlighted by the results of the phase II AZALEA study that compared monthly subcutaneous abelacimab in doses of 90 mg or 150 mg with rivaroxaban (20 mg once daily) in 1282 patients with atrial fibrillation and a median CHA2DS2-V ASc score of 5.67

Table 2. Completed and ongoing studies of factor XI inhibitors in patients with cancer.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Route</th>
<th>Study (NCT number)</th>
<th>Indication</th>
<th>N</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abelacimab</td>
<td>Monoclonal antibody against FXI and FXIa</td>
<td>Intravenous followed by subcutaneous</td>
<td>ASTER NCT05171049</td>
<td>CAT</td>
<td>1655</td>
<td>Apixaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MAGNOLIA NCT05171075</td>
<td>GI/GU</td>
<td>1020</td>
<td>Dalteparin</td>
</tr>
<tr>
<td>Gruticibart</td>
<td>Monoclonal antibody that blocks FXI activation</td>
<td>Intravenous</td>
<td>NCT04465760</td>
<td>Prophylaxis for CVC-related thrombosis in cancer</td>
<td>22</td>
<td>None (single arm)</td>
</tr>
</tbody>
</table>

Conclusions and future directions

Robust preclinical and clinical data in patients with atrial fibrillation and patients undergoing orthopedic surgery support FXI inhibition as a potential paradigm shift in the prevention and treatment of CAT. Abelacimab, a monoclonal antibody tar-
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geting both FXI and FXIa, holds promise for reducing bleeding risk compared with current anticoagulants and overcoming some of the limitations of the oral FXa inhibitors by eliminating the potential for drug-drug interactions and concerns about kidney or hepatic dysfunction. The reduction in gastrointestinal bleeding with abelacimab compared with rivaroxaban observed in the AZALEA trial suggests that eliminating active drugs in the gut may reduce local bleeding, which could provide abelacimab with an advantage over oral FXa inhibitors for CAT treatment in patients with gastrointestinal cancers.

With its long half-life, abelacimab may be an ideal agent for primary prophylaxis in high-risk cancer patients receiving chemotherapy or for postoperative thromboprophylaxis after major cancer surgery. FXI inhibitors may also have a role in the prevention of catheter-related thrombosis, as suggested by a small phase 2 study with gruticibart.69 The results of theASTER and MAGNOLIA trials, whose completion is expected in 2025, will establish the safety and efficacy of abelacimab in this highly challenging clinical scenario and may prompt investigation into the utility of the oral FXIa for the prevention and treatment of CAT.

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