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The Role of Direct Oral Anticoagulants in Treatment of Cancer-Associated Thrombosis

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Abstract: Venous thromboembolism (VTE) complicates the clinical course of approximately 5-10% of all cancer patients. Anticoagulation of the cancer patient often presents unique challenges as these patients have both a higher risk of recurrent VTE and a higher risk of bleeding than patients without cancer. Although low molecular weight heparins (LMWH) are the standard of care for the management of cancer-associated VTE, their use requires once or twice daily subcutaneous injections, which can be a significant burden for many cancer patients who often require a long duration of anticoagulation. The direct oral anticoagulants (DOACs) are attractive options for patients with malignancy. DOACs offer immediate onset of action and short half-lives, properties similar to LMWH, but the oral route of administration is a significant advantage. Given the higher risks of recurrent VTE and bleeding, there has been concern about the efficacy and safety of DOACs in this patient population. Data are now emerging for the use of DOACs in the cancer patient population from dedicated clinical trials. While recently published data suggest that DOACs hold promise for the treatment of cancer associated VTE, additional studies are needed to establish DOACs as the standard-of-care treatment. Many such studies are currently underway. The available data for the use of DOACs in the treatment of cancer-associated VTE will be reviewed, focusing on efficacy, safety, and other considerations relevant to the cancer patient.

Keywords: Direct oral anticoagulant, cancer-associated thrombosis, VTE, venous thromboembolism, malignancy, low molecular weight heparin, dalteparin, edoxaban, rivaroxaban

1. Introduction

Malignancy is a known risk factor for venous and arterial thrombosis. Venous thromboembolism (VTE) occurs in approximately 5-10% of cancer patients, a 4 to 7-fold increased risk over patients without cancer [1]. It is the second leading cause of death in cancer patients [2] and occurrence of VTE increases the likelihood of death from cancer by approximately 2 to 4-fold [3-5]. Beyond the increased VTE risk from the malignancy itself, the treatments for cancer—cytotoxic chemotherapy, certain targeted therapies, hormonal therapy and radiation therapy—further increase risk [2]. While standard-of-care management of cancer-associated VTE for over a decade has been therapeutic anticoagulation with low molecular weight heparin (LMWH), this field is rapidly evolving, with recent evidence suggesting noninferiority of oral direct factor Xa inhibitors to prevent cancer-associated VTE recurrence [6,7]. Determination of optimal anticoagulation management in cancer patients is often challenging. While direct oral anticoagulants (DOACs) are an
attractive option given their oral bioavailability, a critical analysis suggests that they may not be optimal in several cancer patient populations. The risk of bleeding may be elevated in certain tumor types, cancer-directed therapies may interact with DOAC metabolism, and advanced age and frailty in this population may increase risk of complications. In this review, we explore the challenges of anticoagulation in the cancer population, the options for treating these patients, and offer evidence-based recommendations regarding the use of DOACs in the cancer patient.

2. Thromboembolic and Bleeding Risk in the Cancer Population

Venous thromboembolic risk is remarkably heterogeneous in the cancer patient, a major consideration when making clinical decisions concerning the length, intensity, and type of anticoagulation. Tumor site of origin is a major factor, with the highest risk associated with pancreatic ductal adenocarcinoma and gastric adenocarcinoma [8] and other tumor types considered high risk including lung, gynecologic, hematologic, testicular, and bladder cancers [8-10]. Disease stage is clearly important, as metastatic cancer patients have a dramatically increased risk of first VTE, a risk approximately 20-fold higher than those cancer patients without cancer [1]. As for VTE in the general population, risk for VTE in the cancer population also increases with age, body mass index (BMI), and following surgery [8].

Anticoagulation of the cancer patient is complicated by both recurrent thrombosis and bleeding at higher rates than those without cancer. The rate of recurrent VTE in the cancer patient is 3 to 4-fold that of patients without cancer [11,12], occurring in approximately 20% of patients. Similarly, the rate of major bleeding in the anticoagulated cancer patient is approximately 2 to 3-fold that of the anticoagulated patient without cancer [12,13], with one large cohort reporting a 12-month major bleeding rate of 12.4% (versus 4.9% in patients without cancer) [12]. Both recurrence and bleeding rate appear to be related to cancer severity independent of under- or over-anticoagulation [12]. This finding is of significant consequence when evaluating the trials examining treatment for cancer-associated VTE, as the cancer patient population is dramatically heterogeneous and enrichment of a given trial population with high or low severity patients may have a considerable impact on the trial results.

3. Vitamin K Antagonists and Low Molecular Weight Heparins for Cancer-Associated VTE

The current standard of care for management of cancer-associated VTE as recommended by numerous guidelines and professional societies is LMWH [14-17]. The body of evidence on which this recommendation is based is formed primarily by five major randomized, controlled, open-label, multicenter trials that each compared a LMWH agent to vitamin K antagonists (VKAs) in the initial management of cancer-associated VTE:

- The CANTHANOX trial compared enoxaparin 1.5 mg/kg once daily to warfarin over a 3-month treatment period in 146 patients with cancer-associated thrombosis [18]. The trial was ended early due to poor accrual. Risk of recurrent VTE was lower in those receiving LMWH (10.5% versus 21.1%) and rate of fatal hemorrhage was higher in patients receiving warfarin (8.5% versus 0%), but none of these findings were statistically significant.
• The LITE trial compared tinzaparin (175 anti-Xa units/kg once daily) with usual care VKA management over a 3-month treatment period in 200 patients with cancer-associated thrombosis (PE or proximal DVT) [19]. At 12 months from randomization, the tinzaparin group had a significantly lower rate of recurrent VTE than the VKA group (7% versus 16%). The rate of major bleeding was similar in the two groups.

• The ONCENOX trial randomized 102 cancer patients to receive enoxaparin 1 mg/kg once daily, enoxaparin 1.5 mg/kg once daily, or warfarin for 6 months after a 5-day enoxaparin 1 mg/kg twice daily lead-in [20]. The trial did not fully accrue, and there were no differences in rates of recurrent VTE or bleeding between the three groups.

• The CATCH trial, considered to be the most definitive because of the number of patients enrolled, compared 6 months of dalteparin (200 IU/kg once daily for 1 month followed by 150 IU/kg once daily for 5 months) with 6 months of VKA therapy (following a 5-7 day dalteparin bridge) in 672 cancer patients [6]. At 6 months, the dalteparin group had a significantly lower rate of recurrent VTE than the VKA group (17% versus 9%). There were no differences in the rates of major bleeding between the two groups. While the trial did not find a mortality difference in the two groups, a post-hoc analysis did find a benefit for dalteparin in patients with localized cancer (20% mortality in the dalteparin group vs. 36% in the VKA group at 12 months from randomization) [21].

• The CATCH trial, published 12 years after the CLOT trial, compared 6 months of tinzaparin (175 anti-Xa units/kg once daily) with warfarin in 900 cancer patients with a life expectancy of greater than 6 months. The rates of VTE recurrence (7.2% for the tinzaparin group and 10.5% for the warfarin group) and major bleeding (12 patients in the tinzaparin group and 11 in the warfarin group) were not significantly different, though clinically-relevant non-major bleeding was lower in the tinzaparin group.

While it is possible that some of the smaller trials were not adequately powered to detect the difference in recurrent VTE risk between the treatment arms, the disparate findings of CLOT and CATCH, the two largest trials, suggest that this explanation may not be adequate. Review of baseline patient characteristics from these trials (Table 1) suggests that the disparate findings may be related to differences in these characteristics. Comparison of the CLOT and CATCH trials reveals considerably higher rates of mortality, metastatic solid tumors, and receipt of cancer-directed therapy in CLOT (Table 1). Previous to these trials, it was well-established that VKA therapy was challenging in the more advanced cancer patient receiving anti-cancer therapy, with lower times in therapeutic range (TTR) than the non-cancer population [22]. Treatment with chemotherapeutics that can interact with warfarin, inconsistent dietary intake of vitamin K, and nausea presenting a barrier to swallowing pills all contribute to the increased challenge of VKA management [23]. It is quite possible that the disparate outcomes of CLOT and CATCH represent a failure of VKA management, known to be more challenging in more advanced cancer patients on active cancer therapy, rather than inferiority of the anticoagulant effect of VKAs. Indeed, in CLOT, most warfarin failures were in the first month of therapy during establishment of a stable dose and 37.7% of recurrent thrombotic events occurred when the INR was <2.0. The differences in severity of cancer stage and associated complications may have also lead to a lower event rate in the VKA arm in CATCH, resulting in an underpowered study. Improved VKA management could potentially overcome these issues, as demonstrated by a published retrospective study demonstrating equivalence of warfarin and LMWH for
Table 1. Comparison of trials comparing VKAs with LMWH. CT, chemotherapy; RT, radiation therapy.

<table>
<thead>
<tr>
<th></th>
<th>CANTHANOX</th>
<th>LITE</th>
<th>ONCENOX</th>
<th>CLOT</th>
<th>CATCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA Mortality (%)</td>
<td>22.7 (3 months)</td>
<td>47.0 (1 year)</td>
<td>32.4 (7 months)</td>
<td>39 (6 months)</td>
<td>32.2 (6 months)</td>
</tr>
<tr>
<td>LMWH Mortality (%)</td>
<td>11.3 (3 months)</td>
<td>47.0 (1 year)</td>
<td>32.8 (7 months)</td>
<td>41 (6 months)</td>
<td>34.7 (6 months)</td>
</tr>
<tr>
<td>Receiving cancer therapy (%)</td>
<td>72.6</td>
<td>NR</td>
<td>45.5 (CT)</td>
<td>34.3 (RT)</td>
<td>77.7</td>
</tr>
<tr>
<td>Metastatic solid tumors (%)</td>
<td>52.7</td>
<td>41.5</td>
<td>58.4</td>
<td>67.3</td>
<td>54.7</td>
</tr>
<tr>
<td>VKA TTR (%)</td>
<td>41</td>
<td>NR</td>
<td>NR</td>
<td>46</td>
<td>47</td>
</tr>
</tbody>
</table>

Another consideration is the type of statistical analysis used. While the CLOT trial found a 52% relative risk reduction and 9% absolute risk reduction in the rate of recurrent VTE for dalteparin versus VKA therapy according to the Kaplan-Meier method, this analysis does not consider the competing risk of death, which is clearly sizeable in these trials [25]. A re-analysis of CLOT using the competing risk analysis of Fine and Gray found that the risk of recurrent VTE in both treatment groups was overestimated by approximately 30% [26]. When considering the competing risk of death, LMWH still imparted a significantly lower risk of recurrent VTE but with a lower absolute risk reduction (6%).

Even as these trials established LMWH as the standard of care in cancer-associated thrombosis, numerous issues remained. Guidelines favor continuing anticoagulation indefinitely as long as active cancer remains, yet this is supported by little data and optimal duration of therapy in cancer patients remains unclear [14-17]. As an injectable agent that can result in pain, anxiety, unsightly bruising, and painful subcutaneous hematoma formation, indefinite use of LMWH presents a clear burden to patients. This burden may be judged to be excessive by patients or providers, especially in the terminally ill. An analysis of 2941 patients from a large insurer database supports these concerns, finding median treatment durations for LMWH, warfarin, and rivaroxaban for cancer-associated VTE to be 3.3, 7.9, and 7.9 months, respectively [27]. Another large database analysis of 964 cancer patients found that rates of recurrent VTE, major bleeding, and non-major bleeding were similar in patients receiving indefinite LMWH to those completing 6 months of LMWH who were then transitioned to warfarin by providers [28]. The accumulated evidence suggests poor adherence to guidelines for use of an injectable anticoagulant by patients and providers, and supports the notion that indefinite LMWH may be unnecessary. There is a need for other satisfactory options for these patients. The DOACs, if sufficiently safe and effective, would alleviate many of the issues that hinder treatment with LMWH (route of administration) and warfarin (achieving and maintaining a therapeutic level).
4. Direct Oral Anticoagulants for Treatment of Cancer-Associated VTE

The direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban have already replaced warfarin as the preferred agents for treatment of venous thromboembolism in patients without cancer based on the results of multiple large, randomized controlled trials [29-33] demonstrating non-inferiority for preventing recurrent VTE. Meta-analyses of these trials have confirmed non-inferiority of the efficacy of DOACs, with lower rates of intracranial bleeding, fatal bleeding, and clinically-relevant non-major bleeding than warfarin [34].

Each of the pivotal trials of a DOAC versus warfarin for VTE included a small subset of cancer patients. One meta-analysis of 6 pivotal phase III trials included a subgroup analysis of those identified as cancer patients (1581 cancer patients out of a total of 27,023 enrolled patients) [34]. Those treated with DOACs had a lower VTE recurrence rate than those treated with VKAs, with similar rates of bleeding. Another meta-analysis selecting 1132 active cancer patients from these same trials found similar rates of recurrent VTE and major bleeding for DOACs and VKAs [35]. These findings may not be generalizable to the entire cancer population, however. Several of the pivotal trials excluded active cancer patients or excluded certain groups of cancer patients. No data on the types of cancer, extent of disease, or use or type of chemotherapy are available. For example, the Hokusai-VTE trial of edoxaban vs. VKAs directly excluded cancer patients in whom long-term treatment with LMWH was anticipated [30]. The most appropriate conclusions to draw from this data are that DOACs may have similar efficacy and safety as VKAs in a highly-selected cancer patient population. Similarly, a single-center prospective cohort study of 200 highly-selected patients with cancer-associated VTE treated with rivaroxaban demonstrated rates of recurrent VTE and bleeding similar to the cancer patient subgroups receiving rivaroxaban in the EINSTEIN trials [36]. As for the two meta-analyses, the results of this study may not be generalizable to the cancer population as a whole, especially those with advanced-stage disease actively receiving chemotherapy and those with complicated comorbid conditions.

The results of two multicenter, open-label, randomized, controlled trials of direct factor Xa inhibitors with LMWH for the initial therapy of cancer-associated VTE have been published:

- The Hokusai VTE Cancer trial enrolled 1050 cancer patients with acute symptomatic or incidental PE or proximal VTE to receive LMWH for 5 days followed by edoxaban 60 mg daily or dalteparin 200 IU/kg daily for one month followed by 150 IU/kg daily [37]. Patients were treated for 6-12 months on study. For the composite primary outcome of recurrent VTE or major bleeding during the 12 months after randomization (regardless of actual duration of anticoagulation), edoxaban was non-inferior to dalteparin (HR 0.97, $P=0.006$ for noninferiority). Rates of recurrent VTE were not significantly different in each arm [41 (7.9%), edoxaban arm; 59 (11.3%), dalteparin arm; $P=0.09$]. Rates of major bleeding were higher in the edoxaban arm [36 (6.9%), edoxaban arm; 21 (4.0%), dalteparin arm; $P=0.04$]. There was no difference in overall survival.

- The SELECT-D trial enrolled 406 cancer patients with acute symptomatic or incidental PE or proximal VTE to receive rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily for a total of 6 months) or dalteparin (200 IU/kg daily for 1 month followed by 150 IU/kg daily for 5 months) [38]. The primary efficacy outcome of rate of recurrent VTE was lower in the rivaroxaban
arm (4% versus 11%, HR 0.43, 95% CI, 0.19-0.99), while the major safety outcomes found that major bleeding was similar (6% rivaroxaban arm, 4% dalteparin arm, HR 1.83, 95% CI, 0.68-4.96), and clinically relevant non-major bleeding was significantly higher in the rivaroxaban arm (13% vs. 4%, HR 3.76, 95% CI, 1.63 to 8.69). There was no difference in overall survival.

Baseline cancer-related characteristics, such as the fraction actively receiving cancer-directed therapies and the fraction with metastatic disease (Table 2) are similar to the trials comparing LMWH with VKAs (Table 1), suggesting a representative active cancer population. All patients in the SELECT-D trial and approximately 98% in the Hokusai VTE Cancer trial had active cancer at the time of enrollment, a major contrast with the patients classified as cancer patients in the EINSTEIN trials [32,33] or the Hokusai VTE trial [30]. These trials appear to suggest that DOACs are as good as or better than LMWH for the prevention of recurrent VTE, albeit with increased bleeding risk.

### Table 2. Comparison of trials comparing DOACs with LMWH.

<table>
<thead>
<tr>
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<th>Hokusai VTE Cancer (12-month study duration)</th>
<th>SELECT-D (6-month study duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOAC</td>
<td>LMWH</td>
<td>DOAC</td>
</tr>
<tr>
<td>Recurrent VTE (%)</td>
<td>7.9</td>
<td>11.3</td>
</tr>
<tr>
<td>Major Bleeding (%)</td>
<td>6.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Clinically-relevant non-major bleeding (%)</td>
<td>14.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>39.5</td>
<td>36.6</td>
</tr>
<tr>
<td>Receiving cancer treatment (%)</td>
<td>71.6</td>
<td>73.1</td>
</tr>
<tr>
<td>Metastatic disease (%)</td>
<td>52.5</td>
<td>53.4</td>
</tr>
</tbody>
</table>

In the Hokusai Cancer VTE trial, patients were required to complete at least 6 months of therapy per protocol, although they remained on study (analyzed by modified intention to treat analysis) for 12 months. While treatment adherence rates to in both groups were similar, median duration of anticoagulation was 211 days in the edoxaban group versus 184 in the dalteparin group, a significant difference ($P=0.01$) which may have contributed to numerically lower rates of VTE recurrence in the edoxaban arm. The major disparity between the two arms in the reason for discontinuation was in patient decision to discontinue due to inconvenience of dosing, resulting in 21 treatment discontinuations (4%) in the edoxaban arm compared with 78 treatment discontinuations (14.9%) in the dalteparin arm. While such a disparity may not be unexpected given the known compliance issues with long-term injectable anticoagulants [27], it suggests that the difference in VTE recurrence between LMWH and DOACs may be a difference in effectiveness, not efficacy. The median duration of treatment in the SELECT-D trial was less disparate (5.9 months for rivaroxaban and 5.8 months for dalteparin). Detailed data for discontinuation reasons were not given. In the motivated patient who accepts injectable therapy, LMWH may have equal efficacy to DOAC treatment with reduced bleeding risk.

Both trials reported higher rates of gastrointestinal bleeding in patients receiving DOACs. This is consistent with several prior trials of DOACs for stroke prevention in atrial fibrillation that demonstrated an approximately 1.5-fold increased risk of GI bleeding in patients receiving a DOAC compared with
warfarin [39-41]. While the large DOAC VTE trials did not demonstrate this increased risk [34], the higher overall bleeding risk of the cancer population [12,13] may have manifest the risk more clearly in SELECT-D and Hokusai Cancer VTE. Additionally, the GI bleeding risk may be particularly high in patients with esophageal or gastric cancer. A safety analysis performed following enrollment of the first 220 patients in the SELECT-D trial noted a nonsignificant difference in major bleeding between the rivaroxaban and dalteparin arms in 19 patients with esophageal or gastroesophageal junction cancers (more detailed information as to this difference was not published) [38]. As a result, the Data Safety Monitoring Committee recommended modification of the study protocol to exclude patients with these types of cancers. Similarly, in a subgroup analysis of the Hokusai VTE Cancer trial, patients with GI malignancies had a substantially increased risk of major bleeding. Of the 1050 patients enrolled, 261 had a GI malignancy (approximately 40% upper GI cancers and 60% lower GI cancers). The major bleeding rate in GI malignancy patients randomized to dalteparin was 2.4% (3/125) versus 13.2% (18/136) in those randomized to edoxaban, a significant difference (P=0.0224). Approximately 1 in 7 patients with a GI malignancy treated with edoxaban for 6-12 months developed major bleeding according to the ISTH definition (≥2 g/dL hemoglobin drop, required transfusion of ≥2 units of blood, occurred in a critical site, or contributed to death) [42]. Given the available evidence, DOAC use in patients with certain gastrointestinal malignancies may have an unacceptably high bleeding risk and a LMWH or VKA may be more appropriate for these patients.

Other trials of DOACs for the treatment of cancer-associated VTE are under way. The CARAVAGGIO study (NCT03045406), a phase IIIb randomized, controlled, open-label trial with an estimated enrollment of 1168 participants, is an international trial comparing apixaban with dalteparin for a 6-month treatment period. The CANVAS study (NCT02744092), a pragmatic clinical effectiveness randomized open-label trial in the US with an estimated enrollment of 940 participants, compares DOAC therapy (rivaroxaban, apixaban, edoxaban, or dabigatran, by investigator’s choice) with LMWH with or without a transition to warfarin. Lastly, a phase III of the safety of apixaban versus dalteparin in cancer-associated VTE (NCT02585713) has completed enrollment of 315 patients but has not yet been analyzed. These trials and others will be crucial in confirming and further defining the role of DOACs in the treatment of cancer associated VTE.

5. Personalization of Therapy and Future Directions

Many questions about treatment of cancer-associated VTE remain unanswered. In addition to deciding which anticoagulant to use for acute VTE treatment, the duration of therapy required in cancer patients is a major unanswered question, with the current general consensus and guidelines suggesting continuing anticoagulation if cancer is still present after 3-6 months or in patients actively receiving treatment [16,43]. The intensity of anticoagulation needed after the acute treatment period is also unclear. With the AMPLIFY-EXT [44] and EINSTEIN CHOICE [45] trials demonstrating benefit of reduced-dose anticoagulation with apixaban or rivaroxaban beyond 6 months in the general VTE population with only modest additional bleeding risk, many providers will look to extrapolate this data to DOAC-treated cancer patients. As many patients with cancer-associated VTE have incurable malignancy and with it a strong non-transient procoagulant state, it is critical that future trials address the efficacy and safety of reduced-dose extended-duration DOAC treatment in the cancer population.
While DOAC treatment may not be optimal for all cancer patients, the addition of these agents to our armamentarium for the treatment of cancer-associated VTE provides a much-needed additional option. Modern treatment must eschew the one-size-fits-all approach, which for over a decade has been LMWH for treatment of all cancer-associated VTE. Personalization of care for each patient is now warranted. Assessment of all of the relevant factors—concomitant systemic therapies, aversion to injectable medications, type of malignancy, and others—allows for identification of optimal cancer patient populations for each of the three primary classes of anticoagulants (Table 3). These factors can guide therapy at this time until more data are available that identify the benefits and risks of using DOACs for VTE treatment in the many different subsets of patients with cancer.

**Table 3.** Recommended ideal and non-ideal candidates for each type of anticoagulant for treatment of cancer-associated VTE.

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Optimal</th>
<th>Avoid</th>
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</table>
| VKA | - Any situation in which close anticoagulant monitoring is necessary  
- Advanced chronic kidney disease  
- Extremes of weight (<50 kg or >150 kg) | - Lack of access to dedicated anticoagulation monitoring service with experience caring for cancer patients |
| LMWH | - Frequent emetogenic chemotherapy, difficulty with oral intake  
- Concerns for GI absorption (feeding tubes, gastric or bowel resections)  
- Systemic therapy with known VKA and/or DOAC drug-drug interactions  
- Motivated patient  
- Known increased bleeding risk  
- Recurrent cancer-associated VTE | - Strong aversion to injectable therapy  
- Extremes of weight (<50 kg or >150 kg) |
| DOAC | - Low baseline bleeding risk in a patient without GI malignancy  
- Ease of treatment for patient is a priority  
- No strong drug-drug interactions | - Active GI malignancy (especially esophageal, gastroesophageal junction, or gastric cancer)  
- History of GI bleeding  
- Extremes of weight (<50 kg or >150 kg) |

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