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REVIEW

Management of venous thromboembolism in cancer patients and the role of the new oral anticoagulants

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ABSTRACT

Patients with cancer are at high risk for venous thromboembolism (VTE). Most clinical guidelines agree that low-molecular-weight heparins (LMWHs) are the preferred anticoagulants for the prevention and treatment of VTE in cancer patients. However, LMWHs require daily injections, weight-adjustment of dose, and can be associated with heparin-induced thrombocytopenia; all of which are important considerations in managing cancer-associated VTE. Comparatively, the new oral anticoagulants offer a more attractive option because of their oral administration, fixed-dose, and lack of routine laboratory monitoring. The results of phase III trials support the efficacy and safety of the new oral anticoagulants in the management of VTE. However, generalizing these findings to cancer patients with VTE is difficult since very few cancer patients were included. In this comprehensive review, we provide an overview of the current treatment of VTE, explore anticoagulant thromboprophylaxis in ambulatory cancer patients, and summarize existing evidence on the efficacy and safety of the new oral anticoagulants for the management of VTE in both non-cancer and cancer populations.

1. Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication of cancer patients. Approximately 15–20% of all VTE cases occur in patients with cancer [1,2]. In general, patients with cancer have a 4–7 fold increased risk for VTE as compared to non-cancer patients, and between 5 and 20% of patients diagnosed with cancer will develop VTE [3,4]. The risk of thrombosis is especially high during hospitalization, active chemotherapy, and following major cancer surgery. Patient characteristics, including advanced age, history of VTE, and poor performance status, as well as cancer-related factors, such as cancer type and disease stage, have been associated with an increased risk of VTE [3,5,6]. Furthermore, VTE in cancer patients is associated with important complications, including an 8–10% annual risk of bleeding with anticoagulant therapy and an annual 21–27% risk of VTE recurrence [3]. In addition, the occurrence of VTE may interfere with delivery of chemotherapy, reduce patient quality of life, and increase healthcare resource utilization [7,8]. Finally, cancer patients who develop VTE have an increased risk of death; combined arterial and venous thrombotic events are the second leading cause of death in cancer patients, accounting for 9% of cancer-related deaths [9–11].

In general, patients with VTE require anticoagulation to prevent thrombus extension and death acutely, and to prevent VTE recurrence in the long-term. In cancer patients, low molecular weight heparins (LMWHs) are the preferred anticoagulants, although vitamin K antagonists (VKAs) are used in patients where LMWH use is limited by severe renal dysfunction or cost. The inconvenience of daily injections, weight-adjustment of dose, and risk of heparin induced thrombocytopenia with LMWH and the frequent international normalized ratio (INR) monitoring and numerous food and drug interactions with VKAs, like warfarin, are important challenges in the care of the cancer patient with VTE. Of late, attention has turned to the new oral anticoagulants (NOACs) which include dabigatran, a direct thrombin inhibitor, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. The published trials to date, which are largely in non-cancer patient populations, have shown that these new agents are as efficacious and safe as standard anticoagulant therapies for the acute and the long-term treatment of VTE. Although data in cancer patients are sparse, these new agents are potentially attractive for use in patients with cancer because of their oral administration, fixed-dose, lack of a requirement for routine coagulation blood tests, and very little drug or food interactions. This review will briefly describe the management and prevention of VTE in cancer patients and summarize the published literature to date on the new oral anticoagulants and their potential role in the treatment and prevention of cancer-associated VTE.

2. Current treatment of venous thromboembolism in cancer patients

The initial treatment of acute VTE in cancer patients is similar to the treatment of VTE in non-cancer patients, with short-duration, weight-adjusted LMWH once or twice daily having largely replaced intravenous unfractionated heparin (UFH). The efficacy of parenteral anticoagulants

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for the initial treatment of VTE in cancer patients was assessed in a recent Cochrane review that incorporated data from 16 randomized controlled trials (RCTs) [12]. Meta-analysis showed a statistically significant reduction in mortality at three months follow-up with LWMH when compared to UFH (relative risk [RR] 0.71, 95% CI (0.52–0.98)), with a non-statistically significant advantage of LMWH over UFH in reduction of VTE recurrence (RR 0.78, 95% CI (0.29–2.08)). The reason for the survival benefit is unclear but may be secondary to antineoplastic effects of LMWH in certain cancer subgroups. Data on risk of bleeding and heparin-induced thrombocytopenia was insufficient to determine safety. Nonetheless, most clinical guidelines recommend LMWH over UFH for the initial treatment of acute VTE in cancer patients [13–16].

LMWH is also uniformly recommended across all guidelines for the long-term management of VTE in cancer patients [13–16]. A recent Cochrane review [17] included three open-label RCTs for a total of 1022 cancer patients comparing long-term LMWH (dalteparin, enoxaparin, and tinzaparin) to VKA for the treatment of cancer-associated VTE. In these trials, cancer patients with VTE were randomized to either weight-adjusted LMWH for 3–6 months or LMWH/UFH with VKA (dose adjusted to maintain an INR of 2–3) for 4–7 days, followed by VKA alone for 3–6 months [18–20]. There was a significant reduction in the incidence of recurrent VTE in patients receiving LMWH compared to VKA (hazard ratio [HR] 0.47, 95% CI (0.32–0.71)), with no significant differences in bleeding, thrombocytopenia or survival between the two groups. Each of the LMWHs has been studied in randomized controlled trials, however, only dalteparin is supported by the highest quality of evidence, and to date is the only LMWH with regulatory approval for the long-term treatment of cancer-associated VTE. Nonetheless, the three LMWHs are often considered therapeutically equivalent and many clinicians use them interchangeably. As a result, most major clinical guidelines do not recommend one LMWH over another for the treatment of thrombosis in cancer patients [13–16,21]. In addition to the superior efficacy of LMWH over VKAs, clinicians in general prefer LMWH because of its practical advantages over VKAs. These include the lack of food and few drug interactions, especially with chemotherapeutic agents; the avoidance of frequent venipunctures for monitoring of the anticoagulant effect; reliable delivery in patients with nausea, vomiting, and diarrhea; and a shorter half-life allowing for flexibility during invasive procedures and thrombocytopenia. However, the high cost and dependence on renal clearance may preclude use of LMWH in patients with renal insufficiency, and in these patients, VKAs are recommended [22].

3. The new oral anticoagulants and the treatment of venous thromboembolism

To date, results for dabigatran, rivaroxaban, apixaban, and, most recently, edoxaban for the treatment of acute VTE have been published. They hold promise of simplifying the management of VTE, including cancer-associated VTE. With predictable pharmacological profiles these agents are attractive alternatives to LMWH and VKAs. In particular, they are associated with minimal food and drug interactions, and can be taken orally in fixed-doses without the need for routine coagulation laboratory monitoring. Moreover, unlike VKAs, they have a shorter half-life and reach peak serum therapeutic levels within 2 to 4 h (Table 1). However, there are important considerations including their dependence on renal clearance, the lack of an antidote to reverse their anticoagulant effect in cases of bleeding, and the lack of a readily available assay to measure their anticoagulant effect if treatment failure or non-compliance is suspected.

3.1. Dabigatran for the acute and the long-term treatment of venous thromboembolism

Dabigatran has been compared with warfarin for the treatment of acute VTE in two phase III clinical trials: the RE-COVER [23] and RE-COVER II [24] trials. In both trials, patients were randomized to receive either fixed-dose dabigatran, 150 mg, twice-daily, or dose-adjusted warfarin (INR 2–3) for 6 months. The primary endpoint was non-inferiority in the 6-month incidence of recurrent VTE and VTE-related deaths. The results of both RE-COVER and RE-COVER II studies showed that dabigatran had similar efficacy as warfarin (HR 1.10, 95% CI (0.65–1.84) and HR 1.08, 95% CI (0.64–1.80), respectively) for the prevention of recurrent VTE with a similar safety profile (HR 0.82, 95% CI (0.45–1.48) and HR 0.69, 95% CI (0.36–1.32)) [23,24] (Table 2). Adverse events leading to drug discontinuation in RE-COVER were higher in the dabigatran group (7.9% vs. 6.5%, $p = 0.05$). However, there were no significant differences in the frequency of other adverse events, including number of deaths or acute coronary events, with the exception of dyspepsia (2.9% in the dabigatran group compared to 0.6% in the warfarin group, $p < 0.001$) [23].

Two complementary double-blind, randomized clinical trials were conducted to determine the efficacy and safety of dabigatran for the extended long-term treatment of VTE. These studies compared dabigatran (150 mg, twice daily) with warfarin (The RE-MEDY study [25]) or with placebo (The RE-SONATE study [25]) in patients with VTE after completing at least 3 months of initial treatment in the RE-COVER study. In the active-control study, dabigatran was shown to be non-inferior to warfarin in preventing recurrent VTE or VTE-related death (1.8% vs. 1.3%; HR 1.44, 95% CI (0.78–2.64), $p = 0.01$), with a trend toward a lower risk of bleeding compared to warfarin (0.9% vs. 1.8%; HR 0.52, 95% CI (0.27–1.02)). In the placebo-controlled study, recurrent VTE or VTE-related death occurred in 3 of 681 patients (0.4%) receiving dabigatran compared to 37 of 662 patients (5.6%) in the placebo group (HR 0.08, 95% CI (0.02–0.25), $p < 0.001$) and the risk of major bleeding with dabigatran was similar to that of placebo (0.3% vs. 0%). Although, there were more major or clinically relevant non-major bleeds in the dabigatran group compared to the placebo group (5.3% vs. 1.8%; HR 2.92, 95% CI (1.52–5.60), $p < 0.001$), there was no difference in the rate of acute coronary events among the groups.

It is worth mentioning, however brief, that there were significantly more cases of acute coronary events with dabigatran compared to warfarin (13 (0.9%) vs. 3 (0.2%), $p = 0.02$) in the RE-MEDY trial [25]. This lends support to the debate over whether use of dabigatran increases the risk of acute coronary events or if warfarin offers a cardioprotective effect through its multiple target effects on anticoagulation. When taking into consideration that dabigatran was not associated with a higher number of acute coronary events in the placebo-controlled RE-SONATE trial, it seems unlikely that dabigatran caused these events. Alternatively, the imbalance of baseline characteristics for cardiovascular risk factors (e.g., hypertension, diabetes), which favored the warfarin group, may have impacted the frequency of acute coronary events seen in the active-control study. Nonetheless, an

Table 1
Comparative pharmacology of the new oral anticoagulants and warfarin.

Characteristic	Rivaroxaban (Xarelto)	Dabigatran (Pradaxa)	Apixaban (Eliquis)	Warfarin (Coumadin)
Target	Factor Xa	Thrombin	Factor Xa	VKORC1
Type of inhibition	Direct	Direct	Direct	Indirect
Prodrug	No	Yes	No	No
Bioavailability	80-100%	6.5%	50%	100%
Dosing	q.d. (b.i.d.)	b.i.d.	b.i.d.	q.d.
Half-life	7–11 h	12–17 h	12 h	40 h[a]
T_{max}	2–4 h	1.5–3 h	3 h	2–8 h
Renal excretion	66%	80%	27%	None
Monitoring	No	No	No	Yes
Drug interactions	CYP-3A4/P-gp	P-gp	CYP-3A4	Multiple

Abbreviations: T_{max}, time to maximum plasma concentration; q.d., once daily; b.i.d., twice daily; VKORC1, C1 subunit of the vitamin K epoxide reductase enzyme; P-gp, P-glycoprotein; CYP-3A4, cytochrome P450 3A4 enzyme.
[a] Pharmacodynamic half-life of warfarin; half-life of NOACs is pharmacokinetic.