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New Drug Development and Clinical Pharmacology

New Oral Anticoagulants and the Cancer Patient

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Anticoagulants • Direct thrombin inhibitors • Factor Xa inhibitors • Venous thromboembolism • Cancer

Learning Objectives

Cite the current indications, basic clinical pharmacology, and rationale for development of the new oral anticoagulants.

Explain the potential risk for drug-drug interactions between the new oral anticoagulants and drugs commonly used in cancer patients.

Abstract

Indications for anticoagulation are common in patients with malignancy. Cancer patients have an increased risk of developing venous thromboembolic events or may have other indications for anticoagulation, such as atrial fibrillation. New oral anticoagulants (NOACs) are now available that offer increased options for anticoagulation beyond the traditional vitamin K antagonists and low molecular weight heparins that have long been the cornerstone of treatment. This review will focus on the three NOACs that are currently approved for use in the U.S.: the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors, apixaban and rivaroxaban. Oncologists are likely to encounter an increasing number of patients taking these agents at the time of their cancer diagnosis or to have patients who develop indications for anticoagulation during the course of their disease. The basic pharmacology, current clinical indications, and approach to the use of NOACs in the cancer patient will be reviewed. ***The Oncologist*** 2014; 19:82–93

Implications for Practice: The simplicity of oral administration without need for laboratory monitoring makes the new oral anticoagulants (NOACs) an attractive option for the prevention and management of thrombotic disorders. The increased baseline thrombotic and bleeding risk of cancer patients, their propensity to develop sudden changes in renal or hepatic function, and the lack of reliable reversal strategies for the NOACs raise concerns about the use of these agents in this high-risk group. Many chemotherapeutic agents have significant interactions with the CYP3A4 enzyme and/or P-glycoprotein transporter, which can alter the level of anticoagulation of the NOACs and predispose to bleeding or thrombotic complications. In absence of safety and efficacy data of the NOACs in cancer populations, these agents should be used with caution in patients with active malignancy only after careful evaluation of the risks and benefits for individual patients.

Introduction

Malignancy is a well-established hypercoagulable state that predisposes to venous thromboembolism (VTE). Large studies suggest that patients with active cancer experience a 4- to 8-fold increase in VTE compared with the general population [1, 2]. The relationship between cancer and thrombosis is complex and incompletely understood. Variables that increase thrombotic risk in the cancer patient include the following: expression and/or release of procoagulants by tumor cells, increased procoagulant activity of host cells in response to tumor, stasis (either from tumor compression or immobilization of the host), endothelial damage, advanced age, chemotherapy, and presence of central venous catheters. Despite anticoagulation, patients with malignancy have an approximately 3-fold increased risk of recurrent VTE [3, 4]. The presence of VTE in a patient with malignancy decreases survival up to 6-fold compared with patients without VTE [5, 6].

Since the landmark CLOT trial published in 2003 [7], low molecular weight heparin (LMWH) has supplanted vitamin K antagonists (VKAs) such as warfarin as the preferred treatment for acute VTE in cancer patients [8–11]. This study compared acute VTE treatment with dalteparin, an LMWH, with a VKA in patients with malignancy, most of whom were undergoing active treatment. Patients treated with dalteparin had a 52% reduction in recurrent VTE without significant differences in major bleeding or overall mortality. A recent Cochrane review of seven randomized clinical trials comparing LMWH versus VKA therapy for cancer patients with VTE also showed an approximately 50% reduction in recurrent VTE with LMWH with minimal differences in major bleeding [12]. The most

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Table 1. Randomized controlled trials of NOACs for acute VTE treatment

				Efficacy outcome Symptomatic recurrent VTE				Safety outcome Major bleeding				Safety outcome Major bleeding + clinically relevant nonmajor bleeding			
NOAC	Trial	Population	Dosing	NOAC	VKA	HR	*p* value[a]	NOAC	VKA	HR	*p* value	NOAC	VKA	HR	*p* value
Dabigatran	RE-COVER [15]	DVT or PE	150 mg twice daily[b]	2.4%	2.1%	1.10	<.001	1.6%	1.9%	0.82	.38	4.3%	9.7%	0.44	<.001
Rivaroxaban	EINSTEIN [16]	DVT only	15 mg daily for 3 weeks, then 20 mg daily	2.1%	3.0%	0.68	<.001 .08 for superiority	0.8%	1.2%	0.65	.21	8.1%	8.1%	0.97	.77
	EINSTEIN-PE [17]	PE only	15 mg daily for 3 weeks, then 20 mg daily	2.1%	1.8%	1.12	.003	1.1%	2.2%	0.49	.003	10.3%	11.4%	0.90	.23
Apixaban	AMPLIFY [18]	DVT or PE	10 mg daily for 7 days, then 5 mg daily	2.3%	2.7%	0.84 (RR)[c]	<.001	0.6%	1.8%	0.31 (RR)	<.001	4.3%	9.7%	0.44 (RR)	<.001
Edoxaban[d]	Hokusai-VTE [19]	DVT or PE	30 mg or 60 mg daily[b,e]	3.2%	3.5%	0.89	<.001	1.4%	1.6%	0.84	.35	8.5%	10.3%	0.81	.004

[a]All listed *p* values for the efficacy outcome are for noninferiority, unless otherwise specified.
[b]Patients in the RE-COVER and Hokusai-VTE trials received at least 5 days of parenteral anticoagulation with unfractionated heparin or low molecular weight heparin before initiation of NOAC or VKA therapy.
[c]All analysis in the AMPLIFY trial was reported as relative risk, rather than hazard ratio as in the other studies listed.
[d]Only one phase III trial has been published on edoxaban, an oral factor Xa inhibitor. Edoxaban is not currently available in the U.S.
[e]Patients with creatinine clearance >50 mL/min received 60 mg daily of edoxaban, and patients with creatinine clearance 30–50 mL/min received 30 mg daily of edoxaban.
Abbreviations: DVT, deep vein thrombosis; HR, hazard ratio; NOAC, new oral anticoagulant; PE, pulmonary embolism; RR, relative risk; VKA, vitamin K antagonist; VTE, venous thromboembolism.

significant factor for decreased efficacy of VKAs in cancer patients is difficulty maintaining a stable international normalized ratio (INR) in the setting of concomitant use of chemotherapy agents that affect VKA metabolism, inconsistent dietary intake due to anorexia, nausea or vomiting, low body weight, and low albumin [13, 14].

New Oral Anticoagulant Use in VTE and Atrial Fibrillation in the General Population

Dabigatran, rivaroxaban, and apixaban are NOACs that have been studied in large phase III clinical trials for the treatment of acute VTE [15–18]. Trial designs were different as dabigatran was started after initial short duration of treatment with LMWH, whereas rivaroxaban and apixaban were started immediately without LMWH. All three agents were found to be noninferior to VKA therapy for the primary efficacy outcome of recurrent symptomatic VTE (Table 1). Patients treated with dabigatran did not experience a significant difference in major bleeding episodes compared with the VKA control [15]. In pooled analysis of the two rivaroxaban trials for VTE, a statistically significant 46% reduction in major bleeding was noted in the rivaroxaban arm [16, 17, 19]. In patients with deep vein thrombosis or pulmonary embolism, apixaban also demonstrated a 69% reduction in major bleeding in a similarly designed trial [18]. In November 2012, rivaroxaban was granted approval by the Food and Drug Administration (FDA) for the treatment of acute pulmonary embolism or deep vein thrombosis and is the only NOAC currently approved for these indications in the U.S.

Atrial fibrillation (AF) is the most common indication for anticoagulation in the general population. It is also commonly found among cancer patients, as the incidence of both malignancy and AF increases with age [20, 21]. VKAs had long been the only oral anticoagulants available; as such, they were the first-line agents for stroke prevention in nonvalvular AF. In recent years, dabigatran [22], apixaban [23], and rivaroxaban [24] have been studied in large clinical trials enrolling thousands of patients, with all three agents demonstrating noninferior efficacy and safety. Some doses and agents conferred superior thromboembolic stroke prevention and significantly lower rates of intracranial hemorrhage compared with VKA therapy. In light of these promising results, the FDA approved these three agents between 2010 and 2012 for prevention of stroke in patients with nonvalvular AF. In the 2012 guidelines from the American College of Chest Physicians, dabigatran was recommended over a VKA for the prevention of stroke in select patients with AF [25], whereas the European Society of Cardiology recommends consideration of a NOAC rather than a VKA for most patients with nonvalvular AF [26]. NOACs are being increasingly prescribed by physicians for patients with AF, and it is expected that a growing number of patients with newly diagnosed malignancy will be taking one of these NOACs. Oncologists will be increasingly faced with the question of whether they may safely continue NOACs in their patients with newly diagnosed cancer.

Rationale for the Development of the NOACs

The NOACs were developed as alternatives to traditional anticoagulants, particularly VKAs and LMWH, both of which have their own disadvantages. The advantages and disadvantages of each of these anticoagulants are summarized in Table 2. The major drawback to treatment with LMWH is the need for daily or twice daily subcutaneous injections. Many patients are uncomfortable with self-injections (almost one third in one series [27]), and for some patients the out-of-pocket costs of LMWH are prohibitive, making LWMH a difficult option.

The challenges of treating a patient with VKAs are numerous. VKAs do not directly inhibit activated coagulation factors but rather work by inhibiting the posttranslational modification (γ-carboxylation) of vitamin K-dependent factors, an alteration that renders the factors unable to be activated. The onset and recovery of anticoagulant activity are therefore dependent on hepatic synthesis of factors II, VII, IX, and X. Bridging with an agent that has immediate anticoagulant

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Table 2. Advantages and disadvantages of anticoagulants

	VKA	LMWH	NOAC
Advantages	Oral agent Extensive clinical experience Reliable laboratory measure of anticoagulant activity (i.e., INR) Efficacious reversal agents (e.g., vitamin K, FFP, PCC) Safe in renal insufficiency	Rapid onset and offset Few drug-drug interactions Extensive clinical experience Reliable laboratory measure of anticoagulant activity (i.e., anti-Xa) Laboratory monitoring not routinely needed	Oral agent Rapid onset and offset Few drug-drug interactions Laboratory monitoring not needed
Disadvantages	Delayed onset and offset Many drug-drug and drug-food interactions Unpredictable dose requirements Narrow therapeutic window Requires frequent laboratory monitoring	Parenteral agent Lack of reliable reversal agent[a] Caution advised in renal insufficiency Need for high level of adherence	Limited clinical experience Lack of validated laboratory testing of anticoagulant effect Lack of reversal agent Caution advised in renal insufficiency Need for high level of adherence

[a]Protamine sulfate only partially reverses the anticoagulant effects of LMWH.
Abbreviations: FFP, fresh frozen plasma; INR, international normalized ratio; LMWH, low molecular weight heparin; NOAC, new oral anticoagulant; PCC, prothrombin complex concentrate; VKA, vitamin K antagonist.

activity such as unfractionated heparin, LMWH, or fondaparinux is required if rapid anticoagulation is needed. Conversely, patients may remain anticoagulated for days after stopping a VKA.

Interindividual differences in VKA metabolism can be significant. These differences are mediated in part by specific genetic polymorphisms, particularly in the VKORC1 and CYP2C9 alleles [28, 29]. Using these polymorphisms as a means to determine optimal dosing strategies has shown mixed results in clinical trials, and testing is therefore not recommended in routine clinical practice [30–32].

The biggest challenge with VKA therapy is an increasing number of drug-drug and drug-food interactions. The extensive metabolism of VKAs by multiple cytochrome P-450 isozymes can be affected by other drugs and foods metabolized by the same enzymes, leading to alterations in anticoagulant effect. VKAs are also highly bound by plasma proteins and can be displaced by other drugs. These factors in combination with the narrow therapeutic window of VKA necessitate frequent laboratory monitoring, especially during initiation of VKA therapy when a stable dose is being established [33]. Frequent blood draws and dose titrations are burdensome to patients and their caregivers [34], and they are costly for both the patient and health care system [35, 36].

Pharmacology of the NOACs

The pharmacologic properties of the NOACs overcome many of the disadvantages of traditional anticoagulants but also carry their own challenges (Table 3). In contrast to VKAs, the NOACs directly inhibit coagulant proteins in a dose-dependent manner by binding to their catalytic sites. Apixaban and rivaroxaban are direct factor Xa inhibitors, whereas dabigatran is a direct thrombin inhibitor. This direct effect on coagulation proteins gives the NOACs rapid onset of activity, with dabigatran, apixaban, and rivaroxaban each reaching peak plasma concentration within 2–4 hours [37], allowing patients with an urgent need for anticoagulation (e.g., a patient with a new diagnosis of VTE) to be treated upfront without the need for parenteral agent. Rivaroxaban and apixaban, but not dabigatran, have been studied in this setting [15–18] and can effectively provide rapid onset of anticoagulation with only oral treatment. Conversely, the half-lives of the NOACs are short—on the order of hours, rather than days as with VKAs. The anticoagulant effects more quickly dissipate when therapy is stopped. Plasma elimination half-lives are 12–14 hours for rivaroxaban, 12 hours for apixaban, and 9–13 hours for dabigatran [37]. This is beneficial when anticoagulation must be reversed for an elective invasive procedure [38] but also makes the NOACs less forgiving drugs in patients who are inconsistently compliant with therapy.

Laboratory monitoring is not required with the NOACs due to their wide therapeutic window creating a more consistent relationship between dose and pharmacodynamic effect in most patients. Whereas the NOACs prolong many coagulation assays, there are currently no validated tests to monitor activity of the NOACs [39]. Some assays show promise in measuring the in vivo anticoagulant activity of these agents (e.g., ecarin clotting time or dilute thrombin time for dabigatran or anti-factor Xa levels for rivaroxaban and apixaban), but no established target ranges have been established, and experience with their interpretation is limited [40].

One concern about the use of NOACs is the inability to rapidly reverse the anticoagulant activity in the setting of overdose, bleeding, or other urgent indication for reversal. VKA-related bleeding is easily reversed with infusion of fresh frozen plasma or prothrombin complex concentrates (PCCs) as the VKAs cannot inhibit transfused factors. Dabigatran can be at least partially removed with hemodialysis as only 35% is bound to plasma proteins [41]. PCC, factor eight inhibitor-bypassing activity (FEIBA), and recombinant factor VIIa (rFVIIA) have all been studied as potential reversal agents for the NOACs in laboratory assays or experimental situations. In vitro data on the efficacy of PCC, FEIBA, and rFVIIa have all yielded variable results, and clinical experience to guide their use is limited [42–44]. The lack of standardized laboratory measurement of the NOACs' anticoagulant activity makes it difficult to measure the benefit of these reversal agents and to determine when adequate reversal has occurred. Both animal and human studies are ongoing with potential "antidotes" for reversing the NOACs [45–47]. At this time no methods for rapid reversal of the NOACs have been validated.

Table 3. Pharmacology and FDA-approved indications of the new oral anticoagulants

	Dabigatran	Apixaban	Rivaroxaban
Target	Factor II (thrombin)	Factor Xa	Factor Xa
Protein binding	35%	87%	92%–95%
t_{max}	0.5–2 hours	3–4 hours	2–4 hours
$t_{1/2}$	12–17 hours	8–15 hours	5–9 hours (healthy) 11–13 hours (elderly)
Renal elimination	80%	25%	66%
Drug interactions	P-glycoprotein	CYP3A4 P-glycoprotein	CYP3A4 P-glycoprotein
FDA-approved indications	Nonvalvular AF	Nonvalvular AF	Nonvalvular AF DVT and PE VTE prevention after hip or knee replacement surgery

Abbreviations: AF, atrial fibrillation; DVT, deep vein thrombosis; FDA, Food and Drug Administration; PE, pulmonary embolism; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; VTE, venous thromboembolism.

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The NOACs differ in their renal clearance. Serious and fatal bleeding complications can occur in the setting of renal insufficiency or sudden decline in renal function. Eighty percent of dabigatran, 66% of rivaroxaban, and 25% of apixaban are excreted by the kidneys, with corresponding risk of increased plasma drug concentration with decreased renal function. The plasma concentration area under the curve (AUC) of dabigatran is increased by approximately 3-fold in patients with a creatinine clearance A)rCl) 30–50 mL/min and more than 6-fold in patients with a CrCl <30 mL/min [48]. Product labeling for dabigatran recommends dose reduction for patients with a CrCl 15–30 mL/min and avoidance of its use in patients with a CrCl <15 mL/min and in those on hemodialysis [49]. The plasma concentration AUC of rivaroxaban is increased by up to two thirds in patients with severe renal impairment (e.g., CrCl <30 mL/min) [50]. For VTE treatment in patients with a CrCl <30 mg/mL, product labeling for rivaroxaban recommends its use be avoided [51]. For stroke prevention in patients with AF, dose reduction is recommended for patients with CrCl between 15 and 50 mL/min; it should not be used in patients with a CrCl <15 mL/min or in patients requiring hemodialysis. The pharmacokinetic effects of apixaban are not strongly influenced by renal function. Product labeling advises dose reduction for patients with a serum creatinine >1.5 mg/dL only if the patient is either ≥80 years of age or weighs ≤60 kg [52]. Data are not available for apixaban in patients with a CrCl <15 mg/mL or on hemodialysis, and use in these patients is not advised.

The use of NOACs in patients with hepatic insufficiency is not well-studied. It is recommended to avoid use of all three drugs in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment. This recommendation stems not only from the impact of liver disease on drug concentration and metabolism [53], but also because of the associated coagulopathy often seen with hepatic impairment that may increase the risk of bleeding.

Drug-Drug Interactions of the NOACs

Although the NOACs have significantly fewer drug-drug interactions than VKAs, drugs that strongly affect the CYP3A4 enzyme and/or P-glycoprotein can alter the plasma concentration of the NOACs and can lead to clinically significant alterations in their anticoagulant effects. CYP3A4 is a member of the hepatic cytochrome P450 enzyme system and is responsible for oxidative metabolism of both apixaban and rivaroxaban. In contrast, dabigatran etexilate, the prodrug, is metabolized by esterases in the plasma and liver without significant involvement of CYP3A4 [37]. As substrates of CYP3A4, rivaroxaban and apixaban are vulnerable to both inducers and inhibitors of this enzyme when given concomitantly, leading to potential increased toxicity or decreased efficacy (54).

P-glycoprotein is an ATP-dependent efflux transporter belonging to the ATP-binding cassette transporter superfamily. It mediates drug absorption and excretion and is one mechanism of chemotherapy resistance, as its activity decreases uptake of chemotherapeutic agents in some cancer cells [55, 56]. P-glycoprotein is present in many normal human tissues, most notably the luminal membrane of enterocytes and the apical membrane of both hepatocytes and renal tubular cells [57]. In the intestines, it causes efflux of absorbed substances and drugs back into the intestinal lumen, decreasing net gut absorption. P-glycoprotein is responsible for efflux of drugs into the biliary canaliculi and renal tubules, decreasing net absorption via increased excretion of drug into the bile and urine. Inhibitors of P-glycoprotein increase plasma levels of its substrates, whereas inducers decrease levels. Dabigatran etexilate and, to varying degrees, rivaroxaban and apixaban, are substrates of P-glycoprotein and are therefore susceptible to strong inhibitors or inducers of this transporter [49, 51, 58–60].

Figure 1 lists strong inhibitors and inducers of CYP3A4 and/or P-glycoprotein. In human studies, the concomitant use of the NOACs with ketoconazole, a strong CYP3A4 and P-glycoprotein inhibitor, resulted in significant increases in the mean plasma

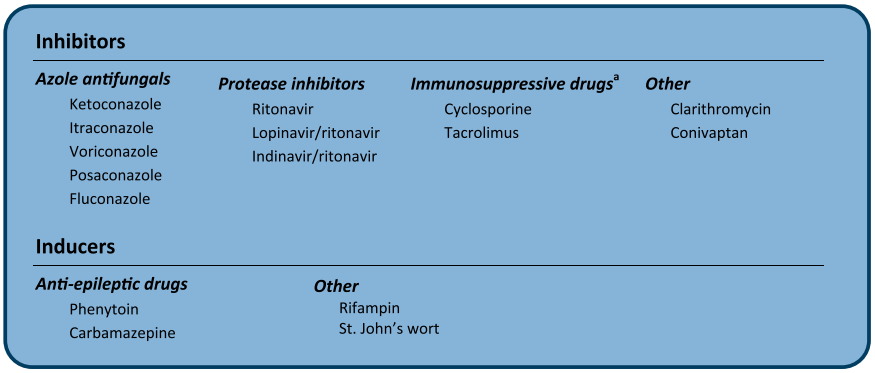

Figure 1. List is compiled from U.S. Food and Drug Administration-approved package inserts and European Medicines Agency-approved package leaflets.

[a]The European Medicines Agency recommends against concomitant use of dabigatran with cyclosporine and tacrolimus, which are strong P-glycoprotein inhibitors. There are no published recommendations against their use with rivaroxaban or apixaban.

concentration AUC of the NOACs from 2- to 2.6-fold with parallel increases in maximum plasma concentration [49, 58, 59]. Conversely, combination of the NOACs with rifampicin, a strong CYP3A4 and P-glycoprotein inducer, decreased the mean AUC by 50%–66%, also with parallel reduction in maximum plasma concentration [49, 51, 60].

The clinical impact of these drug interactions with the NOACs is not known. The following recommendations are based on FDA-approved drug labeling. Apixaban should be dose reduced by half or its use avoided in patients taking a strong dual inhibitor of CYP3A4 and P-glycoprotein, and use of apixaban with a strong inducer of CYP3A4 and P-glycoprotein is not recommended [52]. Dabigatran should be dose reduced in patients with moderate renal impairment taking a strong P-glycoprotein inhibitor and its use avoided in patients with severe renal impairment taking a strong P-glycoprotein inhibitor. Use of dabigatran with a strong P-glycoprotein inducer is not recommended [49]. Rivaroxaban should be used with caution in patients with CrCl between 15 and 50 mL/min taking a weak or moderate dual inhibitor of CYP3A4 and P-glycoprotein. Use of rivaroxaban with a strong dual inhibitor or inducer of CYP3A4 and P-glycoprotein is not recommended [51].

Drug-Drug Interactions of NOACs in Cancer Patients

Many chemotherapy drugs induce or inhibit the activity of CYP3A4, the P-glycoprotein transporter, or both. Table 4 lists agents commonly used by oncologists and their effects on CYP3A4 and P-glycoprotein. This information was obtained from FDA-approved package inserts and large drug databases [61–66]. The interactions listed below are theoretical, as data for combined use of any of the NOACs and specific chemotherapy agents do not exist.

Although this is an incomplete list of chemotherapeutic agents, some general class effects are worth noting. Some classes of chemotherapy appear to nearly universally interact with CYP3A4, P-glycoprotein, or both. These include the antimitotic microtubule inhibitors (e.g., vinca alkaloids and taxanes), tyrosine kinase inhibitors (with the exception of erlotinib, gefitinib, and sorafenib), and the immune-modulating agents, including glucocorticoids and mammalian target of rapamycin (mTOR) inhibitors (with the exception of everolimus). Conversely, none of the frequently used antimetabolites, platinum-based agents, intercalating agents, or monoclonal antibodies have significant inhibitory or inducing effects on CYP3A4 or P-glycoprotein. No clear class effect is noted among the topoisomerase inhibitors, anthracyclines, alkylating agents, or anticancer hormonal agents; significant heterogeneity in drug interaction potential is noted within each of these medication classes.

The list of supportive care agents in Table 4 represents some of the most common nonchemotherapy drugs used in cancer patients. Notably, aprepitant and fosaprepitant, neurokinin 1 receptor antagonists that are used in many highly emetogenic chemotherapy regimens, may cause either moderate inhibition or moderate induction of CYP3A4 depending on the duration of their use. Most other supportive care agents have little drug interaction potential, with the exception of some of the pain palliation agents (e.g., fentanyl, methadone, and acetaminophen).

Strong and moderate modulators of the CYP3A4 enzyme—especially those that also interact with P-glycoprotein—carry the highest relative risk for significant drug interactions with the NOACs [37]. Two strong inhibitors of CYP3A4 were identified: enzalutamide, an androgen receptor antagonist used to treat castration-resistant prostate cancer, and dexamethasone, a glucocorticoid used for its antitumor effects in many lymphoid malignancies and for the treatment and palliation of various cancer-related complications, including nausea and vomiting. No strong inducers of CYP3A4 were identified. Four moderate inhibitors of both CYP3A4 and P-glycoprotein activity were identified: imatinib, crizotinib, abiraterone, and cyclosporine. Use of these drugs in combination with any of the three NOACs could result in increased plasma concentrations of the NOAC. Drugs that exert moderate induction of CYP3A4 activity without significant influence on the P-glycoprotein transporter include paclitaxel, vemurafenib, prednisone, and bexarotene. Use of these agents in combination with rivaroxaban or apixaban could lead to decreased plasma concentration of either drug but would have no impact on dabigatran concentration. Bicalutamide moderately inhibits CYP3A4 and could potentially increase the plasma concentration of rivaroxaban or apixaban if used in combination. The neurokinin receptor 1 antagonists, aprepitant and fosaprepitant, can

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Table 4. Oncology drugs with CYP3A4 and P-glycoprotein interactions

	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Antimitotic agents						
Vinca alkaloids						
Vinblastine	+++		+	●	●	
Vincristine	+++		+	●		
Vinorelbine	+++		+			
Taxanes						
Docetaxel	+++		+	●		
Paclitaxel	**+++**	**++**		●		
Antimetabolites						
Antifolates						
Methotrexate				●		
Pemetrexed						
Purine analogs						
Mercaptopurine						
Thioguanine						
Pentostatin						
Cladribine						
Clofarabine						
Fludarabine						
Pyrimidine analogs						
Fluorouracil						
Capecitabine						
Cytarabine						
Gemcitabine						
Azacitadine						
Decitabine						
Topoisomerase inhibitors						
Topotecan						
Irinotecan	+++			●		
Etoposide	+++		+	●		
Anthracyclines/ anthracenediones						
Doxorubicin	+++		+	●	●	
Daunorubicin				●		
Idarubicin			+	●		
Mitoxantrone						
Alkylating agents						
Cyclophosphamide	+		+			
Ifosfamide	+++		+			
Chlorambucil						
Melphalan						
Bendamustine				●		
Carmustine						
Lomustine			+			
Busulfan	+++					
Procarbazine						
Dacarbazine						
Temozolomide						

(continued)

Table 4. (continued)

	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Platinum-based agents						
Cisplatin						
Carboplatin						
Oxaliplatin						
Intercalating agents						
Bleomycin						
Mitomycin C				●		
Dactinomycin						
Tyrosine kinase inhibitors						
Imatinib	+++		++	●		●
Dasatinib	+++		+			
Nilotinib	+++		+	●		●
Erlotinib	+++					
Gefitinib	+++					
Lapatinib	+++		+	●		●
Sunitinib	+++					●
Sorafenib	+					
Crizotinib	+++		++	●		●
Vemurafenib	+	++		●		
Vandetanib	+++					●
Monoclonal antibodies						
Rituximab						
Brentuximab	+++					
Alemtuzumab						
Cetuximab						
Trastuzumab						
Bevacizumab						
Hormonal agents						
Tamoxifen	+++		+			●
Raloxifene						
Anastrozole			+			
Letrozole	+					
Fulvestrant	+					
Leuprolide						
Flutamide	+++					
Bicalutamide			++			
Enzalutamide	+++	+++				●
Abiraterone	+++		++			●
Mitotane						
Immune-modulating agents						
Cyclosporine	+++		++	●		●
Sirolimus	+++		+	●		
Everolimus	+++			●		
Temsirolimus	+++		+	●		
Tacrolimus	+++		+	●		●
Dexamethasone	+++	+++		●	●	●
Prednisone	+	++				

(continued)

Table 4. (continued)

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Miscellaneous						
Lenalidomide				●		
Bortezomib	+++		+			
Bexarotene	+	++				
Supportive care						
Prochlorperazine						
Ondansetron	+++			●		
Palonosetron	+					
Metoclopramide						
Aprepitant	+++	++	++			
Fosaprepitant	+++	++	++			
Oxycodone	+++					
Hydromorphone						
Morphine						
Fentanyl	+++		+			
Methadone	+++		+			
Acetaminophen	+		+			
Lorazepam						
Clonazepam	+++					
Filgrastim						
Epoetin alfa						
Darbepoetin alfa						

[a]+++, strong interaction; ++, moderate interaction; +, weak interaction.
[b]Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c]Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

both moderately induce and inhibit CYP3A4 activity; effects on rivaroxaban and apixaban plasma concentrations are not clear.

Many other drugs were identified that are mild inducers or inhibitors of the CYP3A4 enzyme or that are inducers or inhibitors of P-glycoprotein but do not affect CYP3A4. These drugs with mild CYP3A4 interactions or that affect P-glycoprotein in isolation have a relatively low propensity for clinically significant drug interactions with the NOACs. However, chemotherapeutic agents are often used in combination, and the clinical relevance of these combined weak or moderate interactions is unknown. Data are limited on the relative magnitude of P-glycoprotein interactions, so stratification of these agents by potential risk of drug-drug interaction with the NOACs could not be performed.

Additional Concerns About NOAC Use in Cancer Patients

Data for the use of NOACs in cancer patients receiving chemotherapy are sparse. No phase III trials of the NOACs have studied their safety or efficacy in cancer patients. The large clinical trials of dabigatran, apixaban, and rivaroxaban for stroke prevention in AF excluded patients at high risk for bleeding complications or with life expectancies of less than 3 years, 2 years, and 1 year, respectively, effectively excluding many patients with active cancer [22–24]. In VTE trials, patients with active malignancy were either excluded or the number enrolled was small, ranging from 2.6% to 6% [16–18, 67]. Type of malignancy, stage, and concomitant use of chemotherapy were not reported. Subgroup analyses suggest no significant difference in recurrent VTE between the NOAC and VKA arms; however, the number of cancer patients included in these analyses is too small to draw any meaningful conclusions.

The only cancer-specific study using a NOAC is a phase II randomized placebo-controlled study of prophylactic dose apixiban for VTE prophylaxis in ambulatory patients with advanced or metastatic cancer [68]. Ninety-three patients were treated during a 12-week period while receiving chemotherapy. Apixaban was well-tolerated with minimal increase in major bleeding; however, the number of patients was too small to draw any statistically significant conclusions. The role of VTE prophylaxis in ambulatory cancer patients has yet to be defined.

It is well established that cancer patients carry a higher thrombotic risk than the general population [1–4]. Malignancy is a strong thrombotic risk, and it is not clear that the doses of NOACs used for AF or VTE in the general population will provide the same protection against thromboembolic events in patients with active malignancy. The RE-ALIGN trial, a phase II study of dabigatran versus warfarin for thromboembolism prophylaxis in patients with mechanical aortic valves, was

terminated early due to increased thrombotic and bleeding events in the dabigatran arm, despite using a dabigatran dose two times higher than that used for AF [69]. Based on these results, use of dabigatran is contraindicated in patients with mechanical heart valves [70]. These results have also prompted heightened concern for use of the NOACs in patients with high thrombotic potential, including patients with cancer.

The increased risk of bleeding in patients with active malignancy also raises concerns about the safety of the NOACs in this population. Cancer patients are at 2- to 6-fold higher risk for bleeding events while on anticoagulation [3, 4]. Oncology patients determined to have the highest risk for VTE have also been found to have the highest bleeding risk [71]. Factors increasing bleeding risk in cancer patients include surgery, tissue damage from radiation, mucosal bleeding from visceral malignancies (e.g., hemoptysis with lung cancer, gastrointestinal bleeding with gastric or colon cancer, hematuria with bladder cancer, etc.), thrombocytopenia from myelosuppressive chemotherapy, and abrupt fluctuations in hepatic or renal function. Although some of the NOACs have decreased rates of bleeding compared with VKAs in carefully selected study populations, the presence of the above risk factors in the cancer patient may offset these decreased bleeding rates. Age over 75 years is a risk factor for bleeding in the anticoagulated general population, whether the anticoagulant is warfarin, LMWH, or a NOAC [72–74]. Proposed reasons for increased bleeding in the elderly include more fragile blood vessels, decreased renal function not adequately reflected by calculated CrCl, more labile renal function, and multiple drug-drug interactions. In the older patient with cancer, bleeding risk with any anticoagulant may be substantially higher not only because of age, but also because of the added increased risk of side effects from cancer therapy.

There are also theoretical mechanistic reasons that the NOACs might not be as effective as LMWH for the treatment of VTE in cancer patients. Heparins exert a variety of antithrombotic effects that are not shared by VKAs and may be of significance in preventing recurrent VTE in the cancer patient [75, 76]. These effects of heparin products include decreased binding of L- and P-selectins to their ligands, release of tissue factor pathway inhibitor, and neutralization of various cytokines and chemokines that may modulate the prothrombotic effects of malignancy [76]. The relative role that these mechanisms play in the anticoagulant effects of heparins in malignancy is not currently known. As these mechanisms are not known to be shared by the NOACs, it is unclear whether the NOACs will have the same efficacy in cancer patients with VTE as do heparin products.

Evaluation of the Cancer Patient for NOAC Use

The risks and benefits of anticoagulation as well as the type of agent used need to be weighed for any patient starting anticoagulation, yet for those with malignancy the magnitude of risk is often greater than in the general population. Consideration of the use of a NOAC makes this evaluation even more complex. The following are factors that need to be considered when prescribing any anticoagulant in a patient with cancer, with some factors unique to the NOACs.

Table 5. Criteria for NOAC use in cancer patients requiring anticoagulation

Patient assessment
Risk factors for bleeding No major bleeding events in the past 2 months Absence of intracranial or visceral tumor at high risk for major bleeding
Platelets Platelet count >50,000 per μL No anticipated decrease due to disease or chemotherapy
Coagulation studies Normal PT, PTT, and fibrinogen
Liver function tests No significant hepatic impairment (e.g., Child-Pugh B or C, cirrhosis)
Renal function CrCl >30 mL/min (rivaroxaban) CrCl >15 mL/min (dabigatran and apixaban) No anticipated fluctuations due to nephrotoxic chemotherapy or other drugs
Medications No concomitant use of drugs with strong effect on CYP3A4 and/or P-glycoprotein Fig. 1 lists strong CYP3A4 and/or P-glycoprotein inhibitors and inducers Table 4 lists chemotherapy drugs that modulate CYP3A4 and/or P-glycoprotein Good medication compliance

Abbreviations: CrCl, creatinine clearance; NOAC, new oral anticoagulant; PT, prothrombin time; PTT, partial thromboplastin time.

In cancer patients with either a new or pre-existing diagnosis of AF who require anticoagulation, consultation from a cardiologist should be sought. In some patients, the risk of bleeding from anticoagulation may be significantly higher than the risk of thromboembolic stroke from AF, and discussion with the patient's cardiologist may be necessary to determine whether anticoagulation is needed. Initiation or continuation of one of the three NOACs can then be considered in select patients, as outlined below.

In those cancer patients with active disease getting chemotherapy who present with a new VTE event, a parenteral agent, such as LMWH or fondaparinux, is first-line therapy and should be continued for at least 3–6 months if possible. After this time point many decisions are required, including duration of anticoagulant therapy and choice of anticoagulant. Many guidelines exist to aid in decision making regarding duration of anticoagulation and anticoagulant choice for extended treatment of VTE in cancer patients based on expert and consensus opinion [10, 11, 77]. It is generally accepted that the majority of patients with metastatic disease and history of VTE should remain on anticoagulation indefinitely, but management of patients in remission after 3–6 months of anticoagulation for a VTE with no other VTE risk factors has not been studied.

For some cancer patients, use of a parenteral agent is not possible. VKAs may be used with careful INR monitoring, especially if the patient is not being treated with chemotherapy that affects VKA metabolism. Rivaroxaban, the only NOAC currently FDA-approved for treatment of VTE, can be considered in select patients. Table 5 summarizes general criteria for selecting potential candidates for NOAC therapy based on the authors' clinical experience and currently available studies.

Pharmacokinetic and pharmacodynamic studies of the effect of chemotherapy agents on NOAC plasma concentrations have not been published.

Assessment of bleeding risk should be performed when considering use of a NOAC. Patients with recent major bleeding events are poor candidates for NOAC therapy. NOAC use should also be avoided in patients with coagulopathy, significant thrombocytopenia, or impaired hepatic function. Patients with a CrCl <30 mL/min should not receive rivaroxaban, and patients with a CrCl <15 mL/min or on hemodialysis should not receive any of the NOACs. For patients with mild or moderate renal insufficiency, a NOAC may be used but should be dose-adjusted according to the package insert. Elderly patients appear to have increased risk of bleeding complications with NOACs [74]; they should be used in this population with caution.

Patients with recent major bleeding events are poor candidates for NOAC therapy. NOAC use should also be avoided in patients with coagulopathy, significant thrombocytopenia, or impaired hepatic function. Patients with a CrCl <30 mL/min should not receive rivaroxaban, and patients with a CrCl <15 mL/min or on hemodialysis should not receive any of the NOACs.

Medications, including plans for chemotherapy, should be evaluated for potential of myelosuppression and nephrotoxicity, as well as for interactions with CYP3A4 and P-glycoprotein. NOACs should be avoided in oncology patients with potential for development of significant thrombocytopenia or nephrotoxicity and in those taking strong CYP3A4 and P-glycoprotein modulators, as listed in Figure 1 and Table 4.

The lack of data for use in oncology patients and specific risks of the NOACs should be discussed with the patient. Medication compliance should be emphasized, as missed doses or variation in timing of doses significantly affects efficacy. Factors unique to use of the individual NOAC should be reviewed. For example, the 20 mg dose of rivaroxaban should be taken with a heavy meal to ensure adequate absorption, whereas dabigatran has an associated side effect of severe dyspepsia necessitating discontinuation in 3%–11% of patients [78]. To avoid delays in drug initiation, drug availability and insurance coverage should be assessed. NOACs have the reputation of being expensive; however, most copays can be significantly less for patients than out-of-pocket costs for LMWH.

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