Are New Oral Anticoagulants Ready for Use in Patients With Cancer?

Paul C. Hendrie, MD, PhD, and David A. Garcia, MD

Abstract

Patients with cancer have long been an important and enigmatic part of basic science and clinical research in thromboembolic disease. The reciprocal deleterious effects on outcomes of a cancer diagnosis on patients with thrombosis and a thrombotic event on patients with cancer have been observed and documented for more than a century. Patients with cancer continue to be one of the more difficult populations to manage using the available unfractionated and low-molecular-weight heparins and the oral vitamin K antagonists. High rates of failure and bleeding complications have made researchers and practitioners alike seek newer more effective anticoagulation agents. The novel oral direct thrombin and activated factor Xa inhibitors have been shown in large clinical trials to be safe and efficacious in many prophylaxis and treatment settings. However, practitioners who treat patients with cancer should be cautious using these agents until more studies are specifically performed in this thrombophilic patient population. (JNCCN 2013;11:1446–1449)

Cancer and venous thromboembolism (VTE) have strong associations. According to the Computerized Registry of Patients with Venous Thromboembolism (RIETE), cancer was present in 20% of patients with venous thrombosis.1 Furthermore, patients with cancer seem to have a more aggressive form of VTE and tend to experience a higher rate of anticoagulant-associated bleeding.2,3 Patients with cancer who develop VTE also have a higher risk of death, only partly explained by recurrent thrombosis.4,5 Better strategies to treat and prevent VTE in patients with cancer are needed.

Until recently, anticoagulation for the prevention and treatment of VTE has been limited to oral vitamin K antagonists (eg, warfarin) and parenteral agents derived from heparin with anti–factor Xa and antithrombin activity. Unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) have been the mainstay for in-hospital–based prophylaxis, both postsurgically and on medicine floors, and for the acute management of deep vein thrombosis and pulmonary embolisms.6 The agents are given intravenously or subcutaneously and offer the advantages of quick pharmacologic effects. UFH is inexpensive and can be reversed with protamine sulfate, but, compared with LMWH,7,8 UFH has less predictable bioavailability. Whether UFH confers a greater risk of heparin-induced thrombocytopenia in patients with cancer is uncertain.7,8 LMWHs offer the advantage of more convenient dosing, administration, and more predictable anticoagulant effects; however, the anticoagulant effect of LMWH is incompletely reversed with protamine sulfate.9 Other parenteral factor Xa inhibitors and direct thrombin inhibitors have been used less frequently.10

For most patients with VTE, warfarin is a highly effective therapy and has several advantages, including oral administration and reversibility with vitamin K and fresh frozen plasma or prothrombin complex concentrates.11,12 The disadvantages of warfarin are a slow onset of anticoagulation, a long pharmacodynamic half-life, and interactions with diet and concomitant medications that require regular monitoring and dose adjustment. Although warfarin can virtually eliminate the risk of VTE progression/recurrence for most patients, individuals with cancer-associated VTE have a distur-
ingly high risk of recurrent thrombosis when treated with warfarin.\textsuperscript{13} Citing several studies\textsuperscript{14–16} that show a reduction in VTE recurrence, NCCN and other organizations recommend LMWH over warfarin in patients with cancer for at least the first 6 months of VTE treatment.\textsuperscript{6,17}

Although LMWHs have become the preferred VTE treatment for patients with cancer, problems with its use have prompted clinicians to seek newer antithrombotic agents. The biggest disadvantage of LMWH is that it cannot be given orally. Repeated needle injections can be cumbersome and occasionally painful for patients already dealing with the emotional and physical effects of malignancy. In addition to the storage and disposal of the needles, other disadvantages include the cost of LMWH and its inefficient reversibility. Finally, the efficacy of the LMWHs in this setting, although better than that of the vitamin K antagonists, leaves significant room for improvement; the landmark trial that forms the basis of current recommendations reported that almost 9\% of patients assigned to LMWH were diagnosed with recurrent VTE during 6 months of follow-up versus 17\% in the oral anticoagulation group.\textsuperscript{15} The ideal anticoagulant agent would be oral and have predictable pharmacologic effects, rare or insignificant interactions with other medications, low need for monitoring, and a favorable safety profile. A rapid onset of action, reversibility, and affordability would be welcome.

The available new oral direct thrombin inhibitors and factor Xa inhibitors fulfill some of these expectations. The new agents are dabigatran, a direct thrombin inhibitor, and rivaroxaban and apixaban, activated factor X inhibitors.\textsuperscript{18} First, they offer an oral alternative to the parenteral heparins. This is desirable for most patients with cancer, but may not be useful in patients whose gastrointestinal tract is unavailable because of disease involvement, surgery, radiation, or nausea. These agents also have easy dosing schedules without monitoring requirements in most patients, and all 3 have a rapid onset of pharmacologic effect.\textsuperscript{19} Their relatively low potential for drug-drug interactions would be useful for patients with cancer who are often receiving numerous other treatments. In large studies of surgical and medical patients, these agents have been shown to be as effective as more traditional strategies for VTE prophylaxis and treatment.\textsuperscript{20–24} Safety end points were equivalent for the VTE treatment studies; however, for VTE prophylaxis in the acutely ill medical patients, more bleeding events occurred in the rivaroxaban group than in the enoxaparin group (2.8\% vs 1.2\%).\textsuperscript{20–24}

Although subgroup analyses of patients with cancer in the large VTE treatment trials have been performed, they are of limited value because the number of patients with cancer and VTE events are very small, and the comparator in these studies has been warfarin, not LMWH. At least one preliminary study compared a novel oral agent, apixaban, with placebo for primary VTE prophylaxis in patients with cancer. This phase II feasibility study suggested that apixaban could be used safely in patients with cancer, but the number of thrombosis and bleeding events was too small for definitive conclusions.\textsuperscript{25}

Although the new oral anticoagulants have the potential to eliminate the inconvenience and discomfort of subcutaneous injections, clinicians who treat patients with cancer should be cautious before adopting the novel agents for widespread use. First, limited experience has been published with these target-specific agents in patients with cancer.\textsuperscript{26} Second, they have not been compared with LMWH, the current gold standard for the long-term treatment of cancer-associated VTE. Thrombosis associated with cancer has been recognized as unique since Armand Trousseau’s description in 1865.\textsuperscript{27} Recent studies have identified involvement of tissue factor and vascular endothelial growth factor in the pathophysiology of cancer-associated hypercoagulability.\textsuperscript{28–30} Mucin-producing cancers, those with the highest rates of thrombosis, have been shown to activate neutrophils and platelets through the adhesion molecules P- and L-selectin.\textsuperscript{31} It has been postulated that heparins, which are glycosaminoglycans of varying molecular weight, may directly interfere with one or more of these mucin-mediated interactions. If this explains all or part of the clinical effectiveness observed with heparin therapy, small molecules such as the new oral anticoagulants may be less able to antagonize thrombosis.

A recent meta-analysis of primary prevention trials using LMWH suggests a possible survival benefit of LMWH in patients with malignancies.\textsuperscript{32} Whether the novel oral inhibitors would have a similar impact on cancer mortality is not known. Other factors, such as venous stasis from vessel compression, immobility,
central venous catheters (CVC), and thrombogenic anticancer therapies, such as tamoxifen and thalidomide, play a role in some patients. The new agents have not been evaluated with specific chemotherapy regimens and have not been shown to reduce CVC-associated thrombosis. Given the incomplete understanding (and complexity) of the mechanisms and factors underlying the cancer-thrombosis association, extrapolating the conclusions from trials involving unselected patients with VTE to patients with active malignancy would be unwise.

The lack of an antidote or evidence-based reversal strategy for the new anticoagulants is especially problematic for patients with cancer, because they commonly develop significant thrombocytopenia. Although the short half-life of the new oral agents seems attractive for patients who require elective procedures, little is known about the safety of interrupting and restarting these drugs around the time of surgery. Finally, for patients with advanced renal insufficiency, the newer oral anticoagulants are contraindicated. Among individuals with cancer, this subgroup is particularly challenging, because LMWHs also depend heavily on renal clearance mechanisms.

The biology of venous thrombosis in the setting of an active malignancy seems to be different from VTE in other settings. Insufficient evidence exists to recommend the new oral anticoagulants for patients with (or at risk for) cancer-associated VTE. Although several pharmacologic characteristics of the new anticoagulant agents make them attractive, dedicated clinical trials will be necessary to define the safety and efficacy of these drugs in patients with cancer.

References

Oral Anticoagulants and Cancer


