Warfarin remains the foundation for oral anticoagulation, and due to a narrow therapeutic window, serious complications can occur with its use. Adverse reactions with warfarin have been associated with hospital admissions, and inpatient medication errors are common with warfarin. Because of an astonishing number of factors, including genetic polymorphism, dietary intake, and drug and food interactions, warfarin may be difficult to dose, even in the seemingly uncomplicated patient.

Warfarin has been found to be safe and effective in cancer patients, but patients with advanced cancer have an increased risk of a supratherapeutic international normalized ratio (INR). Active cancer is a predictor of a lengthened time for a supratherapeutic INR to decrease to target levels. Additionally, maintaining an INR between 2 and 3 is more difficult in cancer patients than in patients without cancer.

Through the presentation of a brief case study

**Use of Warfarin in the Patient With Cancer**

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**Case Vignette: The Interplay Between Warfarin and Cancer**

AJ is a 53-year-old woman with stage IV colon cancer (T4N2M1), liver metastasis, and proximal deep vein thrombosis of the left leg who returned to the physician’s office for follow-up after completing a 3-month course of enoxaparin (Lovenox). Laboratory evaluations demonstrated that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were approximately twice the normal limit, and the alkaline phosphatase level was slightly elevated. The total bilirubin level was within normal limits, and the albumin level was 3.2 g/dL. The international normalized ratio (INR) was 1.2, and the prothrombin time was 12.7 seconds. Hemoglobin and leukocyte values were within normal limits. Long-term anticoagulation options were considered, including continued low-molecular-weight heparin (LMWH) or initiation of warfarin. Due to an estimated creatinine clearance (CrCl) of 40 mL/min and concern for worsening renal function, she was started on 3 mg of warfarin once daily (INR target, 2.5). Enoxaparin was discontinued after the INR was greater than 2.0 for 2 days.

After one month, AJ was due for a cycle of FOLFIRI (infusional fluorouracil, leucovorin, irinotecan [Camptosar]). At that time, her warfarin dose was stable with a therapeutic INR. Prior to the chemotherapy infusion, she received granisetron (Kytril), dexamethasone, and lorazepam for the intermediate emetogenic potential FOLFIRI regimen. Post infusion, she reported tolerable nausea and vomiting once daily, which were effectively treated with prochlorperazine. Two episodes of diarrhea daily were effectively treated with loperamide. A complete blood count revealed that the platelet count was 175,000/mm³, and the hemoglobin value was 10.1 g/dL. A repeat liver function test revealed stable hepatic function, and cardiovascular evaluation was within normal limits.

After reporting bone pain, AJ was started on hydrocodone/acetaminophen (5 mg/325 mg) She subsequently reported taking the maximum dose for 3 days and was asked to have her INR checked.

AJ asked about "calcium pills," danshen for her heart, and St. John’s wort for her mood. It was determined that 0.04 mg of phytonadione (vitamin K) was contained in the calcium product. She was instructed to take the calcium supplement consistently and avoid the herbal products.
(see boxed item), the authors address the numerous factors to consider when using warfarin in patients with cancer, exploring such topics as venous thromboembolism, dosing guidelines for warfarin, INR monitoring, concomitant use of other medications, gastrointestinal toxicity, risks related to chemotherapy-induced thrombocytopenia and/or anemia, and the effects of nutritional supplements and/or herbal preparations.

Questions

**WHY WAS WARFARIN CHOSEN FOR LONG-TERM ANTICOAGULATION IN THE CASE STUDY, AND WHAT GUIDELINES FOR MANAGING VTE IN CANCER PATIENTS ARE AVAILABLE?**

Warfarin is a vitamin K antagonist indicated for the prophylaxis and treatment of VTE. Warfarin inhibits the synthesis of the vitamin K-dependent clotting factors II, VII, IX, X, and anticoagulant proteins C and S. It is a racemic mixture in which the S-isomer is five-fold more active than the R-isomer. The major risk with warfarin use is hemorrhage, and uncommon side effects include necrosis and purple-toe syndrome. An overview of the pharmacokinetics of warfarin is found in Table 1.

The antithrombotic effect of warfarin occurs when prothrombin (factor II; half-life, ~60–70 hours) has been depleted. However, upon initiation of warfarin, a potential procoagulant state exists, primarily due to decreasing protein C (half-life, ~6 hours). Therefore, initial warfarin dosing, as in our case study, requires the co-administration of an immediate-acting anticoagulant (low-molecular weight heparin [LMWH] or unfractionated heparin concomitantly with warfarin) until the INR has been at least 2.0 for 48 hours. Bridging allows time for the warfarin dose to reach its antithrombotic effect. (VTE treatment guidelines are available from the American College of Chest Physicians [ACCP] and the National Comprehensive Cancer Network.)

The pivotal Comparison of Low-Molecular-Weight Hepa-rin Versus Oral Anticoagulation Therapy (CLOT) trial studied 6 months of the LMWH dalteparin (Fragmin) versus 5 to 7 days of dalteparin with 6 months of a coumarin in cancer patients with acute VTE. Patients receiving 6 months of dalteparin had less probability of VTE recurrence than the coumarin group (9% vs 17%). No differences in bleeding, major bleeding, or mortality were found. The ACCP recommends that cancer patients receive 3 to 6 months of LMWH initially for long-term anticoagulation of DVT followed by anticoagulant therapy indefinitely or until resolution of cancer.

Long-term warfarin was chosen for our patient due to concern for unstable renal function. Lim and colleagues studied LMWH use in non-dialysis patients with severe renal insufficiency (defined as a creatinine clearance [CrCl] of 30 mL/min or less). This meta-analysis revealed that patients with severe renal insufficiency who received fixed-dose enoxaparin (Lovenox) had higher anti-Xa levels and an increased risk for bleeding.

**WHAT CRITERIA DETERMINE INITIAL WARFARIN DOSING, AND WHEN SHOULD THE INR BE MONITORED?**

Initiating warfarin with a 5- or 10-mg dose is a topic of de-
The ACCP recommends that an initial warfarin dose of up to 5 mg be administered in elderly patients and patients who are malnourished, debilitated, or have liver disease or congestive heart failure. Table 2 lists factors to consider when initiating warfarin in the oncology patient. These factors are numerous and include patient characteristics, acute conditions, dietary status, comorbidities, and concomitant medications. Clinicians may decide to start the oncology patient on a substantially lower dose than 5 mg. Due to decreased dietary intake, low albumin levels, and liver involvement, our patient was started on 3 mg.

To our knowledge, no specific INR monitoring guidelines for the oncology patient have been published; however, monitoring suggestions for the general population exist. During warfarin initiation, Jaffer and Bragg recommend monitoring the INR daily or every other day until it is therapeutic for 48 hours; the INR should then be monitored every 3 to 5 days until it is stable for 1 week, at which time it can be monitored weekly. The ACCP recommends that no more than four weeks should elapse between INR evaluations.

HOW WILL THE ADDITION OF A CHEMOTHERAPY REGIMEN AFFECT THE INR?

Table 3 lists mechanisms by which warfarin can interact with other medications. Pharmacokinetic drug interactions may affect the absorption, distribution, metabolism, or elimination of warfarin. The most significant drug interactions are seen with medications that inhibit or induce the hepatic microsomal enzymes. Enzyme inhibitors increase the INR by decreasing the metabolism of warfarin, whereas enzyme inducers decrease the INR by increasing the metabolism of warfarin. Induction or inhibition of the 2C9 pathway is of particular concern due to interference with the more active S isomer.

Pharmacodynamic drug interactions occur when medications affecting clotting factor synthesis or catabolism or medications affecting hemostasis via alternative mechanisms are added to a warfarin regimen. For example, concomitant use of aspirin may increase the bleeding risk of warfarin due to its antiplatelet effect; the additive effect cannot be monitored via the INR.

Table 4 lists chemotherapeutic agents that may interact with warfarin. However, the majority of data on drug interactions are from case reports, retrospective reviews, and manufacturers’ information. In addition, the list is likely to increase due to the development of new chemotherapeutic agents.

Before adding a drug that might interact with warfarin, clinicians should consider therapeutic alternatives to either...
Use of Warfarin in the Patient With Cancer

Gastrointestinal (GI) toxicity can manifest as nausea, vomiting, mucositis, diarrhea, or constipation. Such toxicity may affect dietary intake of vitamin K. In addition, GI toxicity could alter the absorption of warfarin and dietary vitamin K. Therefore, clinicians should consider the emetogenic potential and GI side effects of chemotherapy regimens that are to be given to a patient receiving warfarin. Maximal prophylactic and breakthrough antiemetics should be prescribed. Clinicians should note, however, that aprepitant (Emend), approved for moderate or highly emetogenic potential chemotherapy, should be used with caution in patients on warfarin, as it could increase her INR.

An inducing drug can take 1 or more weeks to decrease plasma levels of the affected drug. The time line is determined, in part, by the half-life of the inducing drug. Therefore, clinicians should monitor the INR frequently for several weeks after addition, dose adjustment, or discontinuation of an inducing drug. In general, increased INR monitoring should be performed during the 2 weeks after any new drug is added or discontinued from a regimen containing warfarin. In the future, warfarin management may be guided by pharmacogenetic studies.

**WHY AND HOW SHOULD CHEMOTHERAPY-INDUCED GASTROINTESTINAL TOXICITY BE MANAGED?**

Because the oncology population frequently requires pain control, clinicians often prescribe an acetaminophen-containing product. Acetaminophen is commonly prescribed to patients on warfarin due to its lack of antiplatelet activity. However, acetaminophen can increase the INR.

Hylek and colleagues found that patients taking at least 9,100 mg weekly (~1,300 mg/d) of acetaminophen had a tenfold greater risk of their INR values exceeding 6.0 than did patients not taking acetaminophen. Although the mechanism of this interaction is not completely understood, Thijsen et al reported that the toxic metabolite of acetaminophen, N-acetyl-p-benzoquinone-imine (NAPQI), interacts with warfarin by interfering with vitamin K-dependent clotting factor...
Patients should be monitored if they ingest more than 2 g of acetaminophen daily or more than 1.3 g daily for more than 2 weeks. Patients should be advised to avoid other acetaminophen-containing products such as over-the-counter (OTC) cold medicine while taking acetaminophen-based pain medication.

The alternatives for pain management may have implications if given with warfarin. Non-steroidal anti-inflammatory agents can increase the risk of bleeding when given with warfarin because of their antiplatelet effect and potential for gastric mucosal injury. Cyclooxygenase-2 inhibitors increase the risk for GI hemorrhage when taken concomitantly with warfarin. High-dose salicylates may interfere with the production of clotting factor, thereby increasing bleeding times. Opiates, on the other hand, are not believed to interact with warfarin.

**HOW DO NUTRITIONAL SUPPLEMENTS TAKEN CONCOMITANTLY WITH WARFARIN AFFECT THE INR?**

Oncology patients often take vitamins, minerals, and nutritional supplements to improve their nutritional status. Some of these products contain phytonadione (vitamin K), which could counteract the mechanism of action of warfarin if taken in large doses. For example, certain calcium supplements also contain vitamins D and K. Whether the amount of vitamin K could affect the efficacy of warfarin is unclear. However, it is feasible that if such a calcium supplement were taken in conjunction with other vitamin K-containing multivitamins and/or nutritional supplements, an interaction could occur. The combination of vitamin K with the dietary vitamin K could act as a warfarin antagonist and render warfarin less effective. Patients on warfarin should eat a diet consistent in the vegetables high in dietary vitamin K, namely the leafy-green vegetables (eg, spinach, kale, collard greens). Patients should be instructed to review the contents of their multivitamins and nutritional supplements with healthcare professionals to determine the content of vitamin K. Patients should take these products consistently and contact their physician if they take any additional products. The INR should be monitored closely until the potential for interaction has lapsed.

**SHOULD CLINICIANS BE CONCERNED ABOUT COMPLEMENTARY AND ALTERNATIVE MEDICATION USE WITH WARFARIN?**

The use of complementary and alternative medicines (CAM) is common in the oncology population. A survey completed by patients with colorectal cancer found that 32% started CAM after diagnosis of cancer. Almost half of the CAM therapies were herbal preparations. Vitamins and medicinal teas were among other CAM therapies used. Ramsey and colleagues surveyed patients initiating warfarin therapy on their use of CAM; they found that almost 27% were taking CAM and that 58% of those patients were taking a product that could potentially interact with warfarin.

Approval from the US Food and Drug Administration (FDA) is not required for dietary supplements, including herbal products, prior to marketing. Thus, these products are not regulated for safety and efficacy. Many reports of interactions between warfarin and herbal preparations exist. Herbal products may contain coumarins, salicylates, or vitamin K derivatives or may have antiplatelet, anticoagulant, procoagulant, or fibrinolytic properties.

Danshen and St. John’s wort are two Chinese herbs that have been reported to interact with warfarin. Danshen, used to prevent cardiovascular and cerebrovascular atherosclerosis, has been reported to potentiate the anticoagulant effect of warfarin. St. John’s wort, used for depression, has been reported to decrease the effectiveness of warfarin. Therefore, patients using warfarin should avoid herbal preparations and should always consult with their physician before taking CAM. Additionally, clinicians should ask their patients specifically about the use of CAM.

**Conclusion**

The use of warfarin in the oncology patient is complex. As this population may require long-term or indefinite anticoagulation, warfarin complications could occur due to patient-specific factors, drug interactions, chemotherapeutic toxicity, or disease state. Clinicians should educate patients about the proper use of warfarin, precautions to take while on warfarin therapy, and when to alert healthcare professionals (Table 5). Frequent INR monitoring and patient education may potentially decrease complications in this medically complicated patient population.

**Table 5**

Reasons for Warfarin Patients to Alert Their Physician

<table>
<thead>
<tr>
<th>Signs and symptoms of unusual bruising or bleeding</th>
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</thead>
<tbody>
<tr>
<td>Significant nausea, vomiting, and/or diarrhea</td>
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<tr>
<td>Significant change in oral intake</td>
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<tr>
<td>New medication added to regimen (prescription, over the counter, complementary, or alternative)</td>
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<tr>
<td>Increased use of pain medication</td>
</tr>
<tr>
<td>Signs and symptoms of infection</td>
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</tbody>
</table>

**References**

PubMed ID in brackets


31. Thijssen HH, Souta BA, Vroovert ML, Calessens JG. Paracetamol (acetaminophen) warfarin interaction: NAPQI, the toxic metabolite of paracetamol, is an inhibitor of enzymes in the vitamin K cycle. Thromb Haemost 2004;92:797–802. [15467911]