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Symptom Management and Supportive Care

Warfarin Versus Low-Molecular-Weight Heparin Therapy in Cancer Patients

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Define characteristics of the interface between deep vein thrombosis and malignancy.

2. Evaluate patient factors that may complicate long-term warfarin use in patients with cancer.

3. List advantages that may be realized with low-molecular-weight heparin (versus warfarin) therapy in cancer patients.

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ABSTRACT

The association between cancer and venous thromboembolism (VTE) is well established. Importantly, VTE is a significant cause of mortality in cancer patients. Although long-term warfarin (Coumadin™; Bristol-Myers Squibb; New York, NY) therapy is the mainstay of treatment for cancer patients with VTE, there are many practical problems with its use in this population. In particular, achieving therapeutic drug levels is difficult in cancer patients due to the increased risk of drug interactions, malnutrition, vomiting, and liver dysfunction in these patients. Moreover, cancer patients are at an increased risk of adverse effects of warfarin therapy. In contrast, low-molecular-weight heparins (LMWHs) are associated with a lower risk of adverse events compared with warfarin in patients with cancer. These agents also offer practical advantages compared with warfarin, including more predictable anticoagulant effects and ease of administration in addition to possible antineoplastic effects. Several LMWHs have demonstrated superior efficacy to warfarin in the secondary prevention of VTE. In particular, the LMWH, dalteparin (Fragmin®; Pfizer; New York, NY), has recently been shown to have superior efficacy to warfarin in a large trial of patients with cancer and VTE without increasing the risk of bleeding. A randomized trial of dalteparin has also shown improved response rates and survival in patients with small cell lung cancer. In view of the availability of more effective and reliable alternatives to warfarin therapy in cancer patients, it is appropriate to reassess the role of warfarin therapy in patients with cancer and VTE. Further evaluation of the LMWHs for effects on cancer outcome is indicated. *The Oncologist* 2005;10:72-79

INTRODUCTION: CANCER AND VENOUS THROMBOEMBOLISM

Since Trousseau's initial observations, the association between venous thromboembolism (VTE) and cancer has been frequently observed. Although usually developing in advanced stages of the disease, VTE may also appear before the cancer has become symptomatic and may provide an opportunity for early diagnosis of cancer. Cohort studies of surgical patients have shown that the incidence of VTE is markedly higher in patients with cancer than in patients without cancer [1]. Postmortem studies have also demonstrated a higher incidence of VTE in patients with cancer [2, 3]. The association between cancer and VTE arises both as a direct consequence of tumor growth and host inflammatory responses and indirectly as a consequence of cancer treatment, venous stasis, and direct vessel trauma [4].

The development of VTE in cancer patients adversely affects their prognosis. One autopsy-based study showed that one of every seven hospitalized cancer patients did not die of cancer per se but of pulmonary embolism (PE), and that 60% of all patients who died of PE had localized cancer or limited metastatic disease, which would have allowed for reasonable survival in the absence of fatal PE [5]. Furthermore, two population-based studies have clearly shown a negative impact of VTE on patient outcome in cancer patients [6, 7].

Anticoagulants may, therefore, have an important role in treating the thromboembolic complications of cancer and preventing their recurrence. In addition, anticoagulants appear to have a direct and beneficial effect on the rate of tumor progression [8]. The purpose of this article is to review the therapeutic role of warfarin in cancer patients and to consider the alternative approaches that are now emerging at this challenging interface between oncology and coagulation medicine.

THE ROLE OF WARFARIN AS AN ORAL ANTICOAGULANT

In current clinical practice, the initial therapy of VTE in cancer patients is low-molecular-weight heparin (LMWH) or, less commonly, unfractionated heparin (UFH), whereas long-term prophylaxis is generally with oral anticoagulants, principally warfarin. Warfarin and related oral anticoagulants are coumarin derivatives that interfere with the cyclic interconversion of vitamin K and its 2,3 epoxide. This produces an anticoagulant effect by inducing hepatic production of partially decarboxylated coagulation factors II, VII, IX, and X with reduced activity. In addition, warfarin and other vitamin K antagonists inhibit carboxylation of the regulatory anticoagulant proteins C and S. These agents also have antithrombotic effects, which are distinct from their anticoagulant properties [9]. Indirect evidence from in vitro and in vivo studies of thrombosis indicates that, in contrast to conventional understanding, the anticoagulant and antithrombotic effects of warfarin can be dissociated. The reduction of prothrombin levels appears to be the key mechanism by which warfarin exerts its antithrombotic effects.

Warfarin is rapidly absorbed and has a long half-life of 36-42 hours [9]. There is considerable variation between the dose and response, dependent on both genetic and environmental factors and on both the pharmacokinetics of the drug, including drug interactions, and pharmacodynamic factors. The safety and efficacy of warfarin are critically dependent on maintaining the international normalized ratio (INR) within the target range continuously during long-term treatment. The pharmacokinetic profile of warfarin, coupled with its narrow therapeutic window, make dose adjustment problematic and require that its anticoagulant effect be carefully monitored. The prothrombin time is the most common test used to monitor warfarin therapy. During the initial phase of warfarin therapy, the INR is usually checked daily until the therapeutic range has been reached and sustained for 2 days, then less frequently, depending on results and on changes in patient status. This need for regular laboratory testing results in patient inconvenience and contributes to the cost of care.

WARFARIN THERAPY FOR SECONDARY PREVENTION OF VTE IN CANCER PATIENTS

Patients with VTE are usually treated with warfarin for several months after an initial VTE event. However, insufficient data are available specifically from cancer patients to determine the optimal duration of secondary prophylaxis. In the absence of data from clinical trials, the general view is that, following an initial VTE event, thromboprophylactic therapy should be continued indefinitely in patients with cancer, or certainly for as long as the cancer is active [10, 11].

Cancer patients with VTE are at an increased risk of recurrence compared with VTE patients without cancer. In an inception cohort study of patients enrolled in an anticoagulation clinic, who were receiving warfarin following VTE, the rate of recurrent thrombosis was approximately sixfold higher among the 104 patients with cancer (1.2% per month) than in the 208 patients without cancer (0.2% per month) [12]. Retrospective analysis of data from two multicenter, randomized clinical trials has also shown an increased risk of recurrent VTE among cancer patients [13]. In that analysis, the incidence of recurrent VTE among patients receiving oral anticoagulant therapy for 3 months was 27 per 100 patient-years for cancer patients, compared with 9 per 100 patient-years for patients without cancer ($p = 0.003$). This is consistent with the findings of a large population-based study of the outcome of anticoagulation therapy in 95 patients with cancer and 733 patients without cancer [14]. There was a

nonsignificant trend toward a higher rate of thrombotic complications in cancer patients than in those without cancer (6.8% versus 2.5%, respectively; $p = 0.058$). Similar findings were reported in a prospective follow-up study of outpatients receiving oral anticoagulant therapy for at least 3 months following thrombosis [15]. Recurrent thromboembolism was observed in 20.7% of cancer patients compared with 6.8% of those without cancer. Interestingly, the risk of recurrence in cancer patients appeared to be related to the extent of the disease: the risk of recurrence was increased by two- to threefold in patients with more localized cancer compared with an almost fivefold increased risk among those with extensive or moderately extensive disease.

Treatment of recurrent VTE in patients who are already receiving warfarin presents a difficult challenge. Treatment options include an increased warfarin dose, although this increases the risk of bleeding, the use of other antithrombotic agents, such as UFH or LMWH, or insertion of an inferior vena caval filter.

Although long-term warfarin therapy is the mainstay of treatment for cancer patients who develop VTE, several studies have reported a higher incidence of bleeding during treatment in this group of patients compared with non-cancer patients. This is important because the risk of major bleeding during warfarin administration is a crucial determinant of the risk-benefit ratio of therapy and is a critical variable in decisions on whether to initiate or continue treatment. A recent meta-analysis has highlighted the clinical impact of anticoagulant-related bleeding [16]. That analysis, of 33 studies of patients with VTE who received oral anticoagulant therapy (with a target INR of 2.0-3.0) for at least 3 months, demonstrated an overall case-fatality rate of 13.4% for anticoagulant-related major bleeding. After the initial 3 months of oral anticoagulant therapy, the case fatality rate for major bleeding was 9.1%. These findings indicate that the risk of oral anticoagulant-related bleeding may be higher than previously perceived, and this could have an important influence on decisions concerning the duration and intensity of treatment.

Patients with cancer are also at a greater risk of anticoagulant-associated bleeding than patients without cancer. A population-based study reported cumulative incidences of major hemorrhage at 12 and 24 months of 5.3% and 10.6%, respectively, among patients with VTE treated with warfarin. However, the presence of malignant disease was significantly associated with the risk of major bleeding, with a relative hazard ratio of 4.07 for cancer patients compared with patients without cancer [17]. Other studies have reported a three- to sixfold higher bleeding risk among cancer patients compared with patients without cancer receiving oral anticoagulation therapy [13-15].

A number of risk factors for bleeding have been identified during warfarin therapy, including duration of therapy, recent history of surgery or trauma, age above 65 years, presence of renal or hepatic insufficiency, high intensity therapy, history of gastrointestinal bleeding, and female gender [18]. Although these conditions increase the risk associated with anticoagulant therapy, they are not generally viewed as absolute contraindications. However, long-term warfarin therapy should generally be avoided in the presence of significant thrombocytopenia, cerebral metastases, or active bleeding. Although there is little published evidence to justify these concerns, anecdotal case reports and series suggest that alternatives to warfarin therapy should be considered for patients with VTE and these conditions.

Practical Problems: Warfarin Dosage and Monitoring

Achieving the target INR is especially problematic in cancer patients due to a high background risk of drug interactions, malnutrition, vomiting, and liver dysfunction in these patients. It is, for example, common practice to administer warfarin to cancer patients receiving chemotherapy infusions, which can result in interactions between chemotherapeutic drugs and warfarin. For instance, a high incidence of INR abnormalities has been reported in patients receiving 5-FU infusions due to an interaction between warfarin and fluorouracil [19]. Additional difficulties arise if the oral anticoagulant therapy needs to be interrupted for surgical procedures or in the event of chemotherapy-induced thrombocytopenia. Due to the delayed onset of action and slow clearance of warfarin, interruption of treatment is required several days in advance of invasive procedures, and therapeutic levels may not be reached for several days after treatment is recommended. This is an important limitation of warfarin therapy in all clinical settings, but it is particularly troublesome in cancer patients for whom invasive procedures are regularly undertaken, often at unpredictable times. In addition to the reduction in thromboprophylactic efficacy during treatment interruptions, this disruption of warfarin therapy adds to the difficulties of dose adjustment in cancer patients [11, 20].

As a consequence, cancer patients on warfarin generally require more regular monitoring of the prothrombin time than patients without cancer. This may be particularly problematic in cancer patients who frequently have limited and difficult venous access or who are geographically distant from their oncologist. In view of the inherent difficulties of maintaining therapeutic levels of warfarin, which are amplified in many cancer patients, alternative approaches to long-term thromboprophylaxis are being actively investigated.

Warfarin Therapy and Development of Malignancy

There is evidence that warfarin therapy may have an anti-neoplastic effect. This suggestion has been supported by the observation of an inhibitory effect of anticoagulants on tumor growth and metastasis [21, 22]. However, the findings of clinical trials are less conclusive. In the early 1980s, a large U.S. Veterans Administration Cooperative Study reported a doubling of the median survival time among patients with small cell lung cancer (SCLC) who received warfarin in addition to multiagent chemotherapy compared with those who received chemotherapy alone (50 weeks versus 24 weeks, $p = 0.03$) [23]. However, subsequent trials in which warfarin was used as an adjuvant therapy for SCLC have yielded somewhat different results [24–26]. A randomized trial of patients with extensive SCLC reported a significant improvement in tumor regression and an increased disease-free interval among patients who received warfarin in addition to chemotherapy compared with chemotherapy alone [24]. Similar findings were reported in a pilot study of 66 patients with limited SCLC in whom warfarin was added to a chemoradiotherapy regimen [25]. A further large randomized trial of patients with limited-stage SCLC failed to demonstrate an overall improvement in outcomes when warfarin was added to treatment with chemoradiotherapy, but a statistically significant improvement in long-term survival was observed on landmark analysis [26].

In addition to the possibility that antithrombotic therapy may improve outcomes in patients with diagnosed cancer, it has also been suggested that treatment may reduce the incidence of new cancers. In a prospective randomized trial of patients with VTE who were followed for a mean of 8.1 years, new cancer was diagnosed in 15.8% of patients who received warfarin prophylaxis for 6 weeks, compared with only 10.3% of patients who received warfarin for 6 months after the VTE event [27]. The difference only became evident after 2 years of follow-up and was limited to the incidence of urogenital cancers. However, there was no difference in overall survival between the two treatment groups. A more recent multicenter, prospective study of patients with a first episode of idiopathic VTE showed no difference in the incidence of newly diagnosed overt cancer between patients who received oral anticoagulant treatment for 3 months compared with 1 year [28]. It has been hypothesized that LMWHs may improve cancer outcome due to their antithrombotic effects, inhibition of coagulation proteases, and/or direct antitumor effects [29]. Clearly, further well-designed, prospective, randomized clinical trials are required to determine whether anticoagulant therapy has a clinically relevant antineoplastic effect.

COMPARISON OF LMWH AND WARFARIN THERAPY

Several trials have compared LMWHs with oral anticoagulants for the long-term prevention of VTE, but these were generally of short duration and did not focus primarily on patients with cancer [30–35]. The studies consistently found no difference in the rate of VTE between LMWH and oral anticoagulant therapy, but a nonsignificant trend toward increased bleeding in patients treated with oral anticoagulants [20]. Furthermore, a recent meta-analysis showed a reduction in the rate of recurrence of VTE (odds ratio: 0.66) and major bleeding complications (odds ratio: 0.45) in favor of LMWHs, although this did not reach statistical significance [36].

LMWHs have been reported to be associated with a lower risk of adverse events compared with warfarin. A study of 146 cancer patients with VTE and cancer [37] who received 3 months of treatment with LMWH or warfarin demonstrated a higher risk of major bleeding or recurrent VTE in the warfarin group (21.1% versus 10.5%, respectively), although this difference was not significant ($p = 0.09$). However, the study highlighted the difficulty of achieving and maintaining the target INR during warfarin therapy and underlined the need for careful monitoring and frequent dose adjustment of warfarin in cancer patients. Similar findings were reported in a more recent randomized trial in which 27.4% and 28.5% of patients entered into the two treatment groups had cancer [38]. In that study, long-term therapy with LMWH was shown to have equivalent efficacy and a superior safety profile compared with initial UFH plus long-term warfarin therapy in patients with proximal deep vein thrombosis (DVT). Another study, conducted in 102 patients with active malignancy and acute symptomatic DVT, PE, or both, demonstrated that treatment with LMWH for 180 days was associated with equivalent safety and efficacy compared with the standard approach of initial LMWH administration followed by long-term warfarin therapy [39]. Moreover, extended treatment with LMWH was associated with higher rates of patient compliance (97.6% and 94.1% for the two LMWH regimens studied) compared with long-term warfarin therapy (92.8%), suggesting that the former approach is at least as acceptable to patients as long-term warfarin therapy.

Few studies have compared LMWHs and warfarin for the prevention of thromboembolism associated with central venous catheters. This is an important consideration in view of the fact that a large proportion of cancer patients receive chemotherapy or parenteral nutrition via long-term indwelling central venous catheters. Two open-label, randomized studies have evaluated the role of venous thromboprophylaxis in patients with central venous catheters [40, 41]. A study of 84 cancer patients indicated that low-dose

warfarin produced a significant reduction in the incidence of thrombosis, compared with placebo, in patients with central venous catheters (10% versus 37%, $p < 0.001$), with similar risks of bleeding in the two groups [40]. In a further randomized study of similar design, the use of LMWH was associated with a lower incidence of catheter-related thrombosis compared with patients who received no prophylaxis (6% versus 62%, respectively, $p = 0.002$) [41]. Another recent study has reported similar risk:benefit ratios for low-dose warfarin and LMWH therapy in 59 cancer patients with a central venous catheter [42]. These findings suggest that LMWH may provide an alternative for patients in whom oral anticoagulant therapy is contraindicated.

In patients with cancer, secondary prophylaxis with a LMWH may be a useful alternative to long-term oral anticoagulant therapy, although no large randomized trials have been conducted in this patient population. The CLOT trial (Comparison of Low-molecular-weight heparin versus Oral anticoagulant Therapy for the prevention of recurrent venous thromboembolism in patients with cancer) was the first large-scale study to investigate this possibility [43]. CLOT was an open-label study of 676 patients with cancer and symptomatic proximal DVT, PE, or both. Patients were randomized to receive either once-daily dalteparin, 200 IU/kg body weight, for 5–7 days, followed by oral anticoagulant therapy (warfarin or acenocoumarol; target INR, 2.5) for 6 months, or dalteparin alone for 6 months (200 IU/kg once daily for 1 month, followed by a daily dose of approximately 150 IU/kg for 5 months). End points included the incidence of symptomatic recurrent VTE and major bleeding in addition to overall survival at 1 year. During the 6-month study period, the incidence of recurrent VTE in patients treated with dalteparin alone was about half that observed in patients allocated to long-term oral anticoagulant therapy (8.1% versus 16.0%, respectively). Importantly, the incidences of major bleeding in the two groups were not significantly different (6% in the dalteparin group versus 4% in the oral anticoagulant group). Furthermore, the risk of recurrent VTE at 6 months was only 9% in the dalteparin only group, compared with 17% in the oral anticoagulant group. Thus, the CLOT study demonstrated that 6-month treatment with dalteparin is more effective than oral anticoagulation in reducing the risk of recurrent VTE in patients with cancer, without increasing the risk of bleeding.

The potential antitumor effects of LMWHs are thought to have a greater impact on early cancer compared with more advanced, disseminated malignancy [27]. In view of this hypothesis, a post-hoc analysis of the CLOT results was performed to determine whether a treatment-related difference in mortality existed between patients with metastatic or nonmetastatic solid tumors at randomization [44]. At a 12-month follow-up, 70% of the subgroup of patients with metastatic disease had died, and there was no difference in mortality between the two treatment groups. In contrast, among those with nonmetastatic disease at entry to the study, the 12-month cumulative mortality was 20% for those in the dalteparin group compared with 35% in the oral anticoagulant group (hazard ratio 0.50, $p = 0.03$). This observed difference in mortality among patients with nonmetastatic disease at randomization could not be attributed to a difference in fatal PE between treatment groups and is consistent with the theory that LMWHs may exert clinically relevant antineoplastic effects in nonmetastatic cancer. Irrespective of the mechanism of action, the findings of the CLOT trial indicate that long-term thromboprophylaxis with dalteparin may reduce mortality in cancer patients with nonmetastatic disease and acute VTE.

The findings of the post-hoc analysis of the CLOT data are consistent with the results of a subanalysis of the FAMOUS (Fragmin Advanced Malignancy Outcome Study) trial that has recently been reported [45]. FAMOUS is the first randomized, placebo-controlled trial of LMWH therapy in patients with advanced solid tumors, without evidence of underlying thrombosis, with the aim of determining the effect of dalteparin on survival at 1 year. A total of 385 patients were randomized to receive either dalteparin, 5,000 anti-Xa units subcutaneously, or a matched placebo injection (0.9% normal saline), daily for 1 year. Among the subgroup of patients with a good prognosis (i.e., those who survived over 17 months from randomization), Kaplan-Meier survival estimates for 2 and 3 years after randomization were significantly higher in the dalteparin group than in the placebo group (78% and 55%, respectively, for dalteparin and 60% and 36%, respectively, for placebo; $p = 0.03$). There was no significant difference in bleeding rates between the two groups (4.7% dalteparin, 2.7% placebo). The findings from that trial suggest that dalteparin has a long-term favorable effect on tumor cell biology that results in improved survival of patients having a good prognosis. Altinbas and associates have recently reported significantly improved tumor response rates and survival in patients with SCLC randomized to receive dalteparin and combination chemotherapy compared with chemotherapy alone [46].

PRACTICAL ADVANTAGES OF LMWHs
Not only do some LMWHs demonstrate greater efficacy than warfarin, there are several practical advantages associated with the use of LMWHs in long-term therapy of VTE. First, LMWH therapy does not require regular laboratory monitoring of prothrombin time because of its more predictable bioavailability after subcutaneous injection and

dose-independent renal clearance [10, 11]. Furthermore, the anticoagulant response is not affected by changes in diet or the use of concomitant drugs [11]. Thus, outpatient management of thromboprophylaxis is feasible with LMWHs. This benefit is particularly attractive in cancer patients for whom quality of life and minimizing the requirement for hospital visits are particularly important.

LMWHs have a more rapid onset of action and more predictable clearance than warfarin. This provides not only a more consistent anticoagulant effect during treatment but also offers greater flexibility than is possible with warfarin when treatment needs to be interrupted for invasive procedures [11]. Another advantage of LMWHs is that they may be effective in patients who develop thrombosis in spite of therapeutic levels of warfarin anticoagulation, a situation that is more likely to occur in cancer patients than in those without cancer [10, 11, 47].

LMWHs are administered by subcutaneous injection rather than taken orally, and this avoids the difficulties of delivering an effective dose of oral anticoagulation in patients with anorexia or vomiting, a common consequence of cancer or its treatment. The potential inconvenience of subcutaneous administration of LMWHs may be compensated for by the use of self-injection techniques or home administration by a caregiver. In addition, the risk of injection site problems has been shown to be small, and self-administration of LMWHs has been associated with a low incidence of adverse effects and is well tolerated [48]. Moreover, the incidence of injection site hematomas is low; small hematomas were reported very rarely in one study of LMWH therapy following DVT in 187 patients [30]. A further study of outpatient management of acute DVT reported only one injection site hematoma in 152 patients (0.66%) [49].

Although warfarin is a relatively inexpensive drug compared with LMWHs or other antithrombotic drugs, the costs of hospitalization during dose establishment and the costs of regular monitoring, in addition to the management of complications such as bleeding episodes, must be considered in addition to the costs of the drug itself. Furthermore, patients can be taught to self-inject during initial inpatient treatment for DVT and thus may require a shorter hospital stay after initiation of long-term prophylactic therapy [31, 43]. This approach would be associated with lower costs than hospital-based treatments, including oral anticoagulant therapy.

As mentioned earlier, the results of meta-analyses and studies in particular tumor types suggested that LMWHs can inhibit tumor growth and metastatic spread by several possible mechanisms [8, 29]. The results from large clinical trials of cancer patients with [44] and without [45] VTE as well as in patients with SCLC [46] showing that LMWH therapy is associated with improved survival provide a starting point for future studies.

CONCLUSIONS

In view of the limitations of warfarin therapy in cancer patients and the availability of effective and convenient alternatives, it is reasonable to reassess the role of warfarin in the management of patients with cancer and VTE. Thus, the effectiveness of warfarin in preventing VTE recurrence is lower in patients with cancer than without cancer, while the risk of bleeding may be higher in patients with malignancy. Warfarin carries the further disadvantage of having substantial inter- and intraindividual variability in dose requirement and the need for frequent dose monitoring, a problem that is exaggerated in cancer patients.

The weight of clinical evidence available to date suggests that LMWHs should be given increased consideration for long-term thromboprophylaxis in patients with cancer. Several LMWHs have demonstrated superior efficacy to warfarin in the prevention of recurrent VTE. Specifically, dalteparin has demonstrated superior efficacy to warfarin in a large trial of patients with cancer and VTE without increasing the risk of bleeding [43]. Thus, compared to warfarin, the LMWHs exhibit a superior safety profile and more predictable antithrombotic effects and can usually be given once daily in a unit dose without the need for dose monitoring. Importantly, possible antineoplastic effects of LMWHs may alter the natural history of malignant disease [44-46].

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