Cancer and Thrombosis: Managing the Risks and Approaches to Thromboprophylaxis

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Summary

Patients with cancer are at increased risk of venous thromboembolism (VTE) compared with patients without cancer. This results from both the prothrombotic effects of the cancer itself and iatrogenic factors, such as chemotherapy, radiotherapy, indwelling central venous devices and surgery, that further increase the risk of VTE. Although cancer-associated thrombosis remains an important cause of morbidity and mortality, it is often underdiagnosed and undertreated. However, evidence is accumulating to support the use of low-molecular-weight heparins (LMWHs) in the secondary prevention of VTE in patients with cancer. Not only have LMWHs been shown to be at least as effective as coumarin derivatives in this setting, but they have a lower incidence of complications, including bleeding, and are not associated with the practical problems of warfarin therapy. Furthermore, a growing number of studies indicate that LMWHs may improve survival among patients with cancer due to a possible antitumor effect. Current evidence suggests that LMWHs should increasingly be considered for the long-term management of VTE in patients with cancer.

Zusammenfassung

Krebspatienten unterliegen im Vergleich zu Patienten ohne Krebs einem erhöhten Risiko, venöse Thromboembolien (VTE) zu erleiden. Gründe dafür sind die prothrombotischen Effekte der Krebserkrankung selbst, aber zusätzlich erhöhen auch iatrogene Faktoren wie Chemotherapie, Strahlentherapie, zentrale Venenkatheter und operative Eingriffe das VTE-Risiko. Obwohl die krebsassoziierte Thrombose häufig ursächlich für Morbidität und Mortalität ist, wird sie oft zu wenig diagnostiziert und nicht adäquat behandelt. Es gibt zunehmende Hinweise dafür, dass niedermolekulare Heparine (NMHs) in der sekundären Thromboseprophylaxe von Krebspatienten von Vorteil sind. Sie sind nicht nur den Cumarinderivaten in dieser Indikation mindestens ebenbürtig, sondern führen auch zu weniger Komplikationen, insbesondere, was Blutungen anbelangt, und sind auch nicht mit den praktischen Problemen der Warfarintherapie belastet. Darüber hinaus gibt es basierend auf Studien zunehmend Hinweise, das NMHs durch mögliche Antitumor-Effekte das Leben von Krebspatienten verlängern könnten. Aufgrund der gegenwärtigen Datenlage sprechen einige Fakten dafür, NMHs zunehmend in der Langzeittherapie von Krebspatienten mit VTE einzusetzen.

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Frequency of Venous Thromboembolism in Cancer Patients

Venous thromboembolic disease (VTE) is a common and often underdiagnosed condition in cancer patients. It may be a presenting feature of occult malignancy, a life-threatening complication of early or advanced cancer, or a sequela of cancer therapy. Most clinical studies designed to determine the true incidence of VTE in cancer patients have been neither prospective nor have they included untreated patients. In the 1980s, the incidence of VTE in malignant disease was estimated to be approximately 15%, ranging from 7 to 30% depending on the tumor site [1]. However, more recently, incidence rates of 8% have been reported which may reflect the more widespread use of thromboprophylaxis in modern practice [2]. Cancer patients undergoing surgery have at least twice the risk of postoperative deep venous thrombosis (DVT) and more than three times the risk of fatal pulmonary embolism (PE) than noncancer patients undergoing similar procedures [3]. Only a few clinical studies have estimated the prevalence of asymptomatic DVT in cancer patients. One study screened 298 hospice patients, and DVT was detected in 52% of the patients, mainly those with poor mobility [4]. The clinical importance of asymptomatic VTE is that it can evolve into symptomatic DVT and even life-threatening PE. Furthermore, VTE is the second most common cause of death in patients hospitalized for solid tumors. This may also explain the fact that VTE detection rates at autopsy may be as high as 50% [5].

Pathogenic mechanisms accounting for the development of VTE in cancer patients include hypercoagulability due to tumor cell activation of clotting, vessel wall injury, and stasis [1, 6, 7]. Non-tumor-derived factors leading to an additional risk of VTE in cancer patients include advanced age, immobility, venous stasis, previous VTE and hereditary thrombophilia [7]. In addition, several iatrogenic factors can also increase the risk of thrombosis, including surgical procedures, chemotherapy, radiotherapy and indwelling central venous devices [8].

Thromboprophylaxis in Cancer Patients

Patients with cancer who undergo surgery have a much higher risk of postoperative VTE than non-cancer patients [8]. A series of trials has shown that low-dose unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) reduce the frequency of postoperative VTE [9–12]. In many of these studies, cancer patients have been included but not separately analyzed. In one large trial of patients undergoing surgery for intra-abdominal and pelvic malignancies, administration of 5,000 units of dalteparin was shown to be significantly more effective than 2,500 units, without increasing the risk of bleeding [13]. In another study of 631 patients who underwent venographic assessment following elective abdominal or pelvic cancer surgery, enoxaparin, 40 mg once daily, was as ef-

fective as UFH, with DVT occurring in 14.7 and 18.2% of patients, respectively [14]. Thus, current evidence indicates that LMWHs are at least as effective as UFH in reducing postoperative DVT and PE, with additional advantages due to the convenience of once-daily dosing.

The optimal duration of initial postoperative thromboprophylaxis in cancer patients is still under consideration. Bergqvist et al. [15] studied the effect of a prolonged prophylaxis (21 days) with enoxaparin 40 mg or placebo after initial treatment with enoxaparin for 7 days in patients with surgery for abdominal or pelvic cancer. The rate of VTE after 4 weeks was significantly higher in the placebo group (12%) than in the enoxaparin group (4.8%). Similar results were shown by Rasmussen et al. [16] in the FAME study in which 590 patients received 5,000 units of dalteparin daily for 1 week and were then randomized to receive a further 3 weeks of dalteparin therapy or no further thromboprophylaxis. Prolonged thromboprophylaxis was associated with a significant reduction in the incidence of VTE from 19.6 to 8.8%.

Non-surgical cancer therapies also increase the risk of VTE. Cancer patients receiving chemotherapy account for 13% of the overall prevalence of VTE in the population [17]. Further studies are required before recommendations can be made regarding the use of thromboprophylaxis in cancer patients receiving chemotherapy. However, in its 2004 consensus document, the American College of Chest Physicians (ACCP) made a Grade 1A recommendation that thromboprophylaxis appropriate for the current risk state should be routinely administered to hospitalized cancer patients who are bedridden with acute illness [8].

The incidence of catheter-related thrombosis (CRT) in cancer patients with long-term indwelling central venous catheters (CVCs) is highly variable. In a large study of 439 cancer patients undergoing chemotherapy for at least 12 weeks, the administration of dalteparin (5,000 units) did not reduce the frequency of CRT compared with placebo (3.7 vs. 3.4%, respectively; p = 0.88) [18]. Given the low incidence of CRT in cancer patients with CVCs, routine thromboprophylaxis cannot be recommended [8].

Treatment of VTE in Cancer Patients

The current standard for initial treatment of patients with VTE consists of intravenous UFH or subcutaneous LMWH. Recently, large clinical trials have shown that LMWHs have equivalent efficacy and safety to UFH, and may even be administered in an outpatient setting [19–21]. LMWHs have several pharmacological advantages compared with UFH, which include once- or twice-daily subcutaneous dosing without routine laboratory monitoring [22].

Anticoagulant regimens are generally the same for patients with or without cancer. Although standard therapy for acute VTE is highly effective in many patients, cancer patients have

Table 1. Cancer patients at low risk of bleeding who should receive full-dose anticoagulant therapy, and patients requiring reduced intensity anticoagulation

Low risk of bleeding – standard anticoagulant therapy
Patients considered to be cured from cancer, or in complete remission
Hodgkin's and non-Hodgkin's lymphomas
Primary tumor without high bleeding risk (e.g. cancer of breast, lung, pancreas, ovary)
Tumor with only bone metastases
Tumor with only lymph node metastases, or few and small metastases of visceral organs (e.g. lung, liver)

Increased risk of bleeding – reduced intensity of anticoagulation
Tumor or metastases in the brain
Tumors that involve ulceration into the lumen of an organ (e.g. stomach, bowel, bladder)
Macrohematuria in renal cancer
Currently bleeding tumor
Hereditary or acquired coagulopathy
Thrombocytopenia (< 50,000 / µl)

a 3- to 6-fold increased risk of bleeding and/or recurrent thrombosis during oral anticoagulant therapy, compared with non-cancer patients [23–25]. Furthermore, oral anticoagulant therapy may be problematic in cancer patients because of drug interactions, malnutrition, vomiting and liver dysfunction, all of which may lead to unpredictable levels of anticoagulation. Standard treatment with heparins (UFH or LMWH) and oral anticoagulants should only be administered in the absence of obvious bleeding risks, and reduced doses should be used in patients at risk of bleeding (table 1). Cancer patients with acute DVT and active bleeding cannot generally receive anticoagulant therapy, and there are no standardized antithrombotic regimens in this setting. In some institutions, inferior vena cava filters are inserted in patients with a high risk of PE, but this approach can be problematical as secondary thrombosis of the filter leading to recurrent DVT and fatal PE has been reported [26, 27]. However, in patients with active bleeding, inferior cava filter insertion may be the only option. After hemostasis is achieved, reduced-dose LMWH therapy should be commenced.

Treatment of Recurrent Thrombosis

Cancer patients have a 2- to 3-fold higher risk of recurrent VTE despite conventional anticoagulant therapy, compared with non-cancer patients [25, 28]. In the first large-scale study of the prevention of recurrent VTE in patients with cancer, the CLOT trial (Comparison of Low-molecular weight heparin versus Oral anticoagulant Therapy for the prevention of venous thromboembolism in patients with cancer), the efficacy of the LMWH, dalteparin, was compared with coumarin [29]. Patients with acute, symptomatic proximal DVT, PE or both were randomized to receive once-daily dalteparin, 200 units/kg, for 5–7 days, then a coumarin derivative for 6 months, or dalteparin alone for 1 month, and a lower dose of 150 units/kg for a further 5 months. During the 6-month study period, the risk of VTE was approximately halved in the dalteparin group (9%) compared with the oral anticoagulant group (17%; p = 0.002), with no increase in the risk of major bleeding (6 vs. 4%; p = 0.27). The long-term administration of tinzaparin has also been evaluated in the management of DVT [30]. Tinzaparin, 175 units/kg once daily, was as effective as a warfarin-based regimen in the prevention of recurrent VTE, with a lower risk of bleeding. The ACCP guidelines on VTE prevention highlight the dalteparin and tinzaparin regimens as approaches that have been shown to be effective [31].

LMWH and Survival in Cancer

Recent years have seen increasing interest in the possible survival benefits of LMWHs [32–34]. However, these data arise from studies that were not primarily designed to assess cancer mortality, and prognostic variables were not evenly distributed among the treatment groups. The Fragmin Advanced Malignancy Study (FAMOUS) was the first randomized, double-blind trial to evaluate the effect of long-term LMWH therapy (dalteparin) on survival in cancer patients with no underlying VTE [35]. Patients received either once-daily dalteparin, 5,000 units, or placebo for 1 year. The study did not demonstrate improved 1-year survival rates in patients with advanced malignancy, but post-hoc analysis showed a survival advantage at 17 months in a subgroup of patients with a 'better prognosis' (i.e. those surviving 17 months after randomization). Similarly, post-hoc analysis of the CLOT study demonstrated a survival benefit among patients without metastatic disease at entry into the study who received dalteparin (probability of death, 20%) compared with oral anticoagulant (36%) [36].

In the Malignancy and Low Molecular-Weight Heparin Therapy (MALT) study, a survival benefit was shown among patients with advanced cancer who received a 6-week administration of nadroparin, compared with placebo [37]. Several different tumor types were included in this study, and a significant survival advantage was observed with LMWH, for both the study population as a whole and the subgroup of 'better prognosis' patients. Similar findings were reported in an earlier trial of patients with small-cell lung cancer: those treated with UFH for 5 weeks had a higher 1-year survival rate (40%) than untreated patients (30%) [38]. In another trial of patients with small-cell lung cancer, standard combination chemotherapy was administered alone or in combination with dalteparin for 18 weeks. Median overall survival increased from 8.0 months with chemotherapy alone to 13.0 months with combined therapy [39]. Similar survival benefits were observed in patients with both limited and extensive disease who received LMWH. In contrast, 2 recent studies of certoparin administra-

tion in patients with advanced breast cancer or non-small cell lung cancer did not show a survival benefit of LMWH administration, compared with placebo [40].

Although some of these observations arise from post-hoc analyses, together these data suggest that LMWHs may have a modifying effect on tumor biology, especially in patients with non-metastatic disease. It is unlikely that the effect simply arises due to a reduced frequency of fatal PE because there was no obvious survival benefit during the acute treatment period, and the benefits of LMWH therapy were observed for several months afterwards [36–38]. Thus, a mechanism that is independent of the antithrombotic effects of heparins may be responsible. LMWHs have been shown to modify tumor growth by mechanisms that include inhibition of angiogenesis, tumor growth factors, heparinase and thrombin generation [41, 42]. An antiangiogenic effect is an appealing possibility [43, 44] and is consistent with the observations of the FAMOUS and CLOT studies [35, 36] where a survival benefit was evident in patients with limited disease and persisted beyond the treatment period. Heparins may also have direct effects on tumor cell activity, influencing tumor cell invasion and metastasis [44].

Recommendations for Routine Thromboprophylaxis with LMWH

Surgery in cancer patients is associated with a high risk of VTE, and the administered dose of LMWH should take into account the high-risk situation. There are several LMWHs on the market, and manufacturers generally provide information on the dose appropriate for high-risk patients. Although several studies demonstrate the benefit of prolonged prophylaxis, the optimal duration of postoperative thromboprophylaxis remains unclear.

The ACCP recommend the use of thromboprophylaxis in acutely ill medical patients, including patients with active cancer who are confined to bed with acute illness [8]. These patients are considered to be high-risk, and currently enoxaparin and dalteparin are licensed in Germany for this situation. While some studies have shown a survival benefit for cancer patients who have received short-term LMWH, there is currently no evidence to support their routine use in cancer patients to increase survival.

Conclusion

Compared with non-cancer patients, patients with cancer have a higher risk of VTE and recurrent VTE, in addition to increased bleeding rates following oral anticoagulant therapy, and some degree of resistance to therapy with UFH. Several LMWHs have demonstrated superior efficacy to UFH or oral anticoagulant therapy in the prevention or treatment of VTE, without increasing the risk of bleeding. These clinical benefits and the well-documented disadvantages of older therapies in cancer patients suggest that LMWH should be increasingly considered for the management of cancer-associated thrombosis.

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