Deep vein thromboembolism in malignant diseases

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SUMMARY

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Tumourous diseases are associated with haemorrhagic as well as thrombotic complications. Trousseau described in 1865 a mutual association between tumourous diseases and venous thromboembolism. As many as 15–20 % patients with venous thromboembolism have an undetected malignity, which equals a prevalence of 2–3 % in the population. From this ensues the relative risk of a newly diagnosed malignity which is higher during the first year after venous thromboembolism. Migrating thrombophlebitis is a relatively specific sign in tumours, in particular in pancreatic tumours. In the pathogenesis of venous thromboembolisms in tumourous diseases, the following factors play a significant part: elevated coagulation parameters, reduced fibrinolysis, frequent immobilization, surgical operations in the case history, chemotherapy, hormonal therapy and central venous catheters. Conventional long term management of VTE involves the use of vitamin K antagonists, such as warfarin, to reduce the risk of recurrence. Recent evidence-based approach in long term management of VTE in patients with tumorous disease shows that the use of LMWH offers an effective alternative to VKAs with higher efficacy, without a significantly increased risk of bleeding, and without the need for regular laboratory monitoring.
Key words: haemostasis – deep venous thrombosis – tumourous diseases – pathogenesis – treatment – unfractionated/low molecular weight heparin – warfarin

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SOUHRN

Žilní tromboembolizmus u maligních onemocnění

Nádorová onemocnění jsou provázena jak krvácivými, tak i trombotickými komplikacemi. Trousseau popsal v roce 1865 vzájemnou souvislost mezi nádorovými onemocněními a žilními tromboembolizmy. Až 15–20 % pacientů s žilním tromboembolizmem má nepoznanou malignitu,

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což představuje prevalenci 2–3 % v populaci. Z toho vyplývá relativní riziko nově diagnostikované malignity, které je vyšší během prvního roku po žilním tromboembolizmu. Migrující tromboflebitidy jsou poměrně specifickou známkou u nádorů, především u nádorů pankreatu. V patogenezi žilních tromboembolizmů u nádorových onemocnění hrají roli především tyto faktory: zvýšené koagulační parametry, snížená fibrinolýza, častější imobilizace, prodělané operace, chemoterapie, hormonální terapie a centrální žilní katetry. Konvenční dlouhodobá léčba VTE snižující riziko recidiv spočívá v užití antagonistů vitaminu K, nejčastěji warfarinu. Recentní, na důkazech založený přístup v dlouhodobé léčbě VTE u nemocných s nádorovým onemocněním ukazuje, že užití nízkomolekulárního heparinu nabízí účinnou alternativu k warfarinu, s vyšší účinností, bez signifikantně zvýšeného rizika krvácení a bez potřeby pravidelného laboratorního monitorování.
Klíčová slova: hemostáza – žilní tromboembolism – nádorová onemocnění – patogeneze – léčba – nefrakciovaný/nízkomolekulární heparin – warfarin

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An association between venous thromboembolism (VTE) and malignant disease has been recognised for over 100 years. Nevertheless, VTE remains under-diagnosed and under-treated in patients with malignant disease [1, 2], although VTE significantly affects the morbidity and mortality associated with malignant disease [3, 4]. The relationship between malignant disease and thrombosis is further supported by the observation that presentation with VTE might precede the development or diagnosis of malignant disease [5].

Patients with VTE are generally managed with anticoagulant therapy with the aim of treating an acute event and preventing death due to pulmonary embolism (PE), in addition to minimising the risk of postthrombotic symptoms and recurrent VTE [6]. However, traditional approaches to anticoagulant therapy are often hampered by the presence of malignant disease and its treatment [6]. In addition, patients with malignant disease are at increased risk of recurrent VTE and anticoagulant-associated bleeding [3]. Thus, the management of VTE may be complex in patients with malignant disease, and VTE can further compromise the quality of life.

In this article the authors review the clinical significance of VTE in patients with malignant disease and the strategies for the management of VTE in these patients, including the potential role of low molecular weigh heparins (LMWHs).

The epidemiology of VTE in patients with malignant disease

Thrombosis is a common complication in patients with malignant disease [6]. VTE is found at autopsy in more than 50 % of patients with malignant disease [7, 8]. However, the assessment of the true incidence of VTE in patients with malignant disease is difficult because most of these patients receive chemotherapy or hormonal therapy, both of which can precipitate VTE [9]. In addition, many patients with malignant disease have indwelling central venous lines, which can also initiate thrombotic events to the catheter [10].

It is not certain whether particular types of malignant disease are associated with an increased risk of VTE or whether the distribution of cancer type in patients with thrombosis simply reflects the prevalence of malignant disease in the general population. Nevertheless, given the presence of a range of risk factors for VTE in patients with malignant disease, it may be prudent to anticipate that all patients with malignant disease are at a higher risk of VTE than the general population.

Risk factors for VTE in malignant disease

The presence of sub-clinical activation of the coagulation system is widely recognised in untreated patients with malignant disease [11, 12]. This hypercoagulable state associated with malignant disease is thought to arise from direct activation of the clotting system by neoplastic cells, leading to the production of thrombin [12, 13]. In addition, neoplastic cells may activate the coagulation system indirectly by stimulating a procoagulant phenotype on host cells, including monocytes, platelets, and endothelial cells [12, 13]. Although alterations in biochemical markers of haemostatic abnormalities among patients presenting with malignant disease are common, these changes are not useful for predicting subsequent development of thrombosis [14]. However, the presence of hypercoagulability might predict the presence of advanced disease in cancer patients. Likewise, patients with advanced malignant disease might be at a higher risk of VTE than those with an early stage of disease [4].

Chemotherapy with oncolytic drugs further increases the risk of VTE associated with malignant disease [9]. This phenomenon has been extensively investigated in patients receiving treatment for breast cancer. In a prospective trial of 205 women with stage II breast cancer who received 12 or 36 weeks of chemotherapy plus hormonal therapy, the overall thrombosis rate was 6.8 % [15]. All thrombotic events were recorded during the periods in which chemotherapy was administered, and these findings clearly demonstrate that chemotherapy with oncolytic drugs contributes to a heightened risk of thrombosis in patients with malignant disease.

Similar findings were reported in a review of 2673 patients with breast cancer in trials organised by the Eastern Cooperative Oncology Group [16]. Venous and

arterial thromboses were significantly more common among women receiving chemotherapy plus hormonal therapy than in controls (5.4 % versus 1.6 %, P=0.0002). The addition of tamoxifen to chemotherapy regimens increased the incidence of VTE from 0.8 % to 2.8 % (P=0.03) in pre-menopausal women, and from 2.3 % to 8.0 % in post-menopausal women (P=0.03). Another study has shown that the addition of chemotherapy to tamoxifen therapy also increases the risk of arterial and venous thromboembolic events in patients with breast cancer [17]. Thromboembolic events were observed in 13.6 % of women receiving combination therapy, compared with 2.6 % of those randomised to tamoxifen therapy alone (P<0.0001). Importantly, thromboembolic complications resulted in more days in hospital and more deaths than any other complication of therapy, including infection, in this study. In fact, it was concluded that these events may outweighed any benefits of the chemotherapy. Thus, the clinical impact of VTE should not be underestimated. A high incidence of VTE (11 % at 1 year) following chemotherapy has also been reported recently in other cancer types [18].

The risk of postoperative VTE is approximately twice as high in cancer patients as in patients without cancer undergoing comparable surgery [19, 20]. Immobilisation due to prolonged bed-rest in debilitated patients with malignant disease further increases the risk of VTE [21, 22].

Patients with malignant disease who survive an initial thrombotic event are also at increased risk of recurrent VTE. A cohort study of 355 patients with symptomatic deep vein thrombosis (DVT) estimated that the presence of malignant disease was associated with a hazard ratio of 1.72 for the risk of recurrent VTE, compared with patients without malignant disease [3]. Furthermore, the risk of death after VTE was shown to be greater in the presence of malignant disease (hazard ratio 8.1) compared with non-cancer patients and is consistent with the view that VTE in patients with malignant disease is a predictor of poor survival.

The heightened risk of recurrent VTE among patients with malignant disease persists for many years after the initial event. A prospective cohort study of patients presenting with symptomatic DVT revealed a cumulative incidence of recurrent VTE of 17.5 % after 2 years, 24.6 % after 5 years and 30.3 % after 8 years [3]. The presence of malignant disease increased the risk of recurrent VTE by a factor of 1.72. Furthermore, the cumulative incidence of the post-thrombotic syndrome was 22.8 % after 2 years, 28 % after 5 years and 29.1 % after 8 years. These findings challenge the conventional short-term approach to antithrombotic therapy and indicate that extended thromboprophylaxis may be necessary in patients with malignant disease.

The relationship between VTE and malignant disease

In view of the well-recognized risk of VTE in patients with malignant disease, it has been suggested that idiopathic VTE might predict the presence of occult cancer. This could lead to the recommendation of screening of very early (i.e. treatable) cancer in patients presenting with idiopathic VTE. Large prospective studies yield an incidence of previously undiagnosed malignant disease of 4 % – 5 % in patients presenting with VTE [23–25]. Other, smaller, studies have detected malignant disease in as many as 7 % – 12 % of patients with idiopathic VTE, compared with only 2 % – 3 % of patients with VTE associated with identifiable risk factors [5, 26, 27]. In two studies in which patients presenting with VTE underwent investigation for malignant disease, the occurrence of occult cancer was detected in up to 25 % [27–29].

In view of these findings, it has been suggested that an underlying malignant disease should always be considered in patients presenting with VTE, especially if there is no identifiable risk factor. A careful medical history and thorough physical examination, plus standard laboratory tests and a chest radiograph have been suggested as routine screening for underlying malignant disease in patients with idiopathic VTE [30]. A prospective study of extensive screening in patients with idiopathic DVT was completed recently, although the study was not sufficiently powerful to demonstrate an effect of extensive screening on cancer survival [31]. The value of screening for malignant disease in patients with idiopathic DVT remains unclear and further trials are needed.

The development of VTE in patients with established malignant disease is associated with a poor prognosis. The findings of two prospective studies indicate that cancer patients have a four to eight-fold higher risk of death after an acute thrombotic event than patients without malignant disease [3, 4]. Although patients with malignant disease would be expected to have a lower survival rate than those without malignant disease, the occurrence of VTE in cancer patients further reduces patient survival rates. In another study, 44 % of patients with malignant disease presenting with VTE were found to have metastatic cancer at presentation, compared with 35 % of age-matched controls with comparable malignant disease but no VTE [4]. Furthermore, 1-year survival was only 12 % in the group with cancer and VTE compared with 36 % in the control group. Malignant disease associated with VTE tends to be more advanced and have a poorer prognosis than malignant disease without VTE.

Current management strategies for VTE in patients with malignant disease

In general, the management of deep vein thrombosis and pulmonary embolism are similar, since the two conditions have stemmed from the same pathological process. Standard thrombosis management involves the initial administration of weight–adjusted LMWH by subcutaneous injection (once daily with dalteparin, twice daily with enoxaparin or nadroparin) or unfractionated heparin (UFH) by intravenous injection or infusion, for 5–7 days. If UFH is used, patients are generally required to remain in hospital for this period and the dose of UFH administered is adjusted to maintain an activated partial thromboplastin time of approximately 1.5–2.5 times the

normal. Treatment with a vitamin K antagonist (VKA), e.g. warfarin or another coumarone, is usually commenced on day 1 during initial LMWH/UFH therapy, adjusted to achieve an international normalized ratio (INR) of 2–3, and continued for 3–6 months, in order to reduce the risk of recurrent VTE [32]. Current guidelines from the American College of Chest Physicians (ACCP) recommend the use of LMWH for the long-term treatment of acute VTE, and should be continued for minimum of 3–6 months (Grade 1A) [32].

Because of the high risk of VTE in patients with malignant disease, the role of primary thromboprophylaxis is being evaluated in prospective randomised trials. At present, the current ACCP guidelines recommend that primary prevention is considered for patients with malignant disease in the presence of additional risk factors for thrombosis: chemotherapy with oncolytic drugs, or surgery, during periods of immobilisation, and in the presence of central venous catheters (Grade 1A) [6, 32].

Challenges of antithrombotic therapy in patients with malignant disease

Patients with malignant disease and VTE, including those treated with VKAs, are more likely to have recurrent episodes of VTE than non-cancer patients [32]. The use of VKAs is associated with practical difficulties in all patients, due to the narrow therapeutic window of these agents and the need for regular laboratory monitoring. However, this is particularly problematic in patients with malignant disease because of frequent changes in nutritional status, multiple drug interactions and alterations in liver metabolism, arising both from the disease itself and increased prothrombotic treatment. In addition, there is a delay of several days between the initiation of treatment with a VKA and the appearance of a full anticoagulant effect because this depends on the clearance of clotting factors from plasma. This adds to the inconvenience associated with interruption in therapy that might be required in patients with malignant disease due to chemotherapy-induced thrombocytopenia, or prior to surgery or other invasive procedures.

The principal problem with VKAs is the risk of bleeding, which is considerably greater in patients with malignant disease than without [7]. The risk of bleeding appears to correlate with the extent of the disease; one study found that the risk of major bleeding was increased by a factor of 2–3 in patients with moderately extensive cancer, and by a factor of 5 in patients with extensive cancer [33]. It has been suggested that these findings may result from bleeding at the site of the cancer.

VKAs are known to interact with a wide range of drugs, and the use of concomitant therapies may produce an increased anticoagulant effect. For example, the anticoagulant action of warfarin is augmented by many drugs including several non-steroidal antiinflammatory drugs, antibacterial agents, antipeptic agents such as cimetidine and omeprazole, and anticancer therapies including ifosfamide and tamoxifen [34].

Surgery is also more hazardous for patients with malignant disease than in non-cancer patients. Surgery for malignant disease is associated with an approximately two-fold higher risk of VTE than similar surgery in patients without malignant disease [6]. One study that evaluated the risk of postoperative PE found that the presence of malignant disease markedly increased the risk of developing PE after surgery among patients with cancer compared with those without cancer (odds ratio 6.7) [35]. Furthermore, patients with malignant disease are at increased risk of per-operative bleeding [36]. This adds to the difficulties of ensuring adequate thromboprophylaxis in these patients.

However, in view of the high risk of VTE in surgical patients with malignant disease, recent guidelines published by the ACCP recommend the use of primary prophylactic treatment with UFH or LMWH [6]. The thromboprophylactic efficacy of the LMWH has been compared with that of UFH in patients undergoing elective abdominal surgery (63 % with malignant disease) [37]. The study showed that 5 to 8 days treatment with LMWH reduced the incidence of DVT in all patients (from 9.2 % to 5.0 %, P=0.02) with a similar, although non-significant, reduction in the subgroup of patients with malignant disease (from 11.2 % to 6.4 %; P=0.06). Importantly, there was no difference in bleeding rate for each treatment in the cancer subgroup (3.2 % for LMWH and 2.8 % for UFH; P=0.28). Results from the ENOXACAN II study [38], and the recently completed Fragmin after Major Abdominal Surgery (FAME) study indicate that extending thromboprophylactic therapy with enoxaparin 40 mg once daily or dalteparin 5000 IU once daily to 4 weeks duration provides additional benefit in patients undergoing surgery for abdominal malignancy [39]. Notably, the FAME study demonstrated that the reduction in VTE achieved with LMWH was driven by a reduction in proximal DVT.

Improving VTE management in malignant disease

In view of the difficulties associated with standard thromboprophylactic regimens in patients with malignant disease, alternatives to long-term VKA therapy are being investigated. Secondary prophylaxis with a LMWH may offer an alternative to long-term treatment with VKAs, although until recently no large randomised trials had been conducted in this patient population. The CLOT (Comparison of Low Molecular Weigh Heparin versus Oral Anticoagulant Therapy) trial is the first large-scale study to compare the safety and efficacy of LMWH and VKA therapy in the prevention of recurrent VTE in cancer patients. The trial showed that, in cancer patients with acute VTE, long-term treatment with LMWH was more effective in reducing the risk of recurrent VTE than treatment with a VKA, which increased the risk of bleeding [40]. Patients with malignant disease, in addition to symptomatic proximal DVT, PE or both were randomised to receive initial treatment with LMWH (dalteparin (200IU/kg body weigh) once daily for 5–7 days followed by a VKA (warfarin or acenocoumarol) for 6 months (target INR 2.5). The second, experimental group of patients

received LMWH alone for 6 months (dalteparin 200 IU/kg once daily for 1 month, then a daily dose of approximately 150 IU/kg for 5 months). This new LMWH dosing regimen was designed to provide initial intensive anticoagulation, followed by a period of reduced-dose therapy, with the aim of reducing the long-term risk of anticoagulant-related bleeding. Over the 6-month study period, the probability of recurrent VTE was 17.4 % in the VKA group, compared with 9 % in the LMWH group. Importantly, the efficacy advantage of this new LMWH regimen was not achieved at the expense of an increase of bleeding risk compared with VKA therapy: there was no significant difference in the incidence of major bleeding in the two groups (4 % in the VKA group and 6 % in the LMWH group). This is likely to reflect the new LMWH dosing regimen that was used in the CLOT study. This regimen was well tolerated by the patients in the study.

Prior to the CLOT study, there was no clear evidence to suggest that LMWH therapy was more effective or had a superior safety profile compared with VKAs in the prevention of recurrent VTE in patients with malignant disease [41]. Several small trials that included both cancer and non-cancer patients failed to demonstrate a substantial advantage of LMWH therapy over VKAs in the secondary prevention of VTE [42–44]. In a more recent randomised trial of 146 patients with VTE and malignant disease, 3-month treatment with LMWH was compared with warfarin and a combined outcome of haemorrhage plus recurrent VTE was evaluated [45]. Of the 71 evaluable patients assigned to receive warfarin, 15 (21.1 %) had a major haemorrhage or recurrent VTE, compared with 7 (10.5 %) of the 67 patients allocated to LMWH (P=0.09).

LMWH have several practical advantages over VKAs. First, LMWHs exhibit predictable bioavailability after subcutaneous administration and dose-independent renal clearance and, as a consequence, therapy does not require monitoring of coagulation tests. These agents can, therefore, be used in the geographical areas without access to laboratories capable of determining INR values, and in patients in whom repeated blood sampling is difficult or inconvenient. Secondly, LMWHs have a rapid onset and offset of action, which offers greater flexibility than that which is possible with VKAs when treatment needs to be interrupted; for example, before invasive procedures. Furthermore, the predictable anticoagulant response achieved with LMWHs means that the initiation of treatment with LMWHs does not require patients to be hospitalised [46]. Not only is this more convenient for the patient but economic analyses suggest that outpatient treatment with LMWHs could reduce the duration of inpatient stay by an average 5 to 6 days per patient, and could significantly affect the total cost of medical care for these patients.

LMWHs are readily bioavailable after subcutaneous administration and their long half-lives permit a twice daily treatment regimen; some LMWHs require only once daily administration. In contrast, UFH generally requires continuous intravenous infusion during treatment initiation. An additional advantage over UFH is that the dose of LMWHs can be calculated on the basis of body weight, and laboratory-based tests and subsequent dosage adjustment are not necessary. Furthermore, LMWHs are at least as effective as UFH for the treatment of acute DVT and are associated with less bleeding compared with UFH [47, 48] and a lower total mortality rate [49].

CONCLUSION

Patients with malignant disease have long been recognized to be at high risk of venous thromboembolism (VTE), although the condition remains under–diagnosed and under-treated in these patients. As a consequence, the morbidity and mortality due to deep vein thrombosis and pulmonary embolism remains unacceptably high in this group. Furthermore, the management of VTE in the presence of malignancy is complex, due both to the effects of the cancer itself and its treatments. Patients with malignant disease present a number of major challenges in the treatment and prevention of initial thrombotic events and subsequent thromboprophylaxis. Cancer–associated hypercoagulability increases the risk of complications associated with surgery and other invasive procedures. Conventional long-term management of VTE involves the use of vitamin K antagonists (VKAs), such as warfarin, to reduce the risk of recurrence. However, this approach is associated with a range of practical difficulties including the need for regular laboratory monitoring, and the potential for drug interactions, in addition to the risk of treatment resistance and bleeding in patients with malignant disease. Recent research indicates that the use of low molecular weight heparin (LMWH) therapy instead of VKAs is beneficial in these patients. Evidence–based approach to the long-term management of VTE, in particular the use of LMWH, indicates that these agents offer an effective alternative to VKAs with predictable anticoagulant effect, thus avoiding the need for regular monitoring, in addition to superior efficacy to VKAs without a significantly increased risk of bleeding.

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