ed heparin for initial treatment of acute venous thromboembolism.[13] The study included 261 patients with malignancy and 1,038 without cancer. The rates of recurrent VTE were 27% per year versus 9% per year, respectively, $p = 0.003$. These data are supported by the results of a recent population-based cohort study, which compared the outcome of anticoagulation courses in 95 patients with malignancy with the outcome of 733 patients without malignancy.[14] The rate of recurrent thrombosis in cancer patients was 6.8% compared to 2.5% in non-cancer patients, $p = 0.06$. An important contribution to this particular aspect has been given very recently by a prospective trial published by Prandoni and colleagues.[15] Clinical trials have been initiated to test alternative anticoagulation strategies for the prevention of recurrent VTE in patients with cancer.

Conclusions

In conclusion, analysis of the literature shows that the risk of occult cancer in patients with idiopathic VTE is approximately 4-7 fold higher, as determined by prospective trials designed to compare the cancer risk in patients with well-defined idiopathic VTE with that in patients with secondary VTE (i.e. due to known causes). This odds ratio rises to perhaps 9 fold when data are examined from patients with *recurrent*, idiopathic VTE. Thus, patients with idiopathic VTE in whom all other causes have been carefully excluded should be followed closely for the development of cancer, particularly during the 6-12 months immediately following the episode of VTE.

It is equally well established that the odds ratio is approximately 2, when comparing the risk for postoperative VTE in cancer patients with that in non-cancer patients undergoing the same surgical procedures, and comparing recurrence of VTE in cancer patients and non-cancer patients.

At present, further studies are needed to collect data prospectively to address the incidence of thrombosis in different types of cancers.

Quantification of the magnitude of the thrombotic risk associated with malignancy and with anticancer interventions is indispensable in order to develop the optimum anticoagulant strategies to protect cancer patients from thromboembolism.

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The treatment of venous thromboembolic disorders: new challenges and opportunities

The aim of treating patients with venous thromboembolism (VTE) is to improve outcomes by preventing extension of the thrombosis, embolization to the lungs, and the development of late complications, such as recurrences, post-thrombotic syndrome, and chronic pulmonary hypertension.

The large majority of patients with VTE are currently treated with full doses of unfractionated (UFH) or low-molecular-weight heparin (LMWH) followed by at least three months of oral anticoagulant therapy.[1] Selected patients with critical manifestations of pulmonary embolism (PE) are administered thrombolytic drugs, while intravenal cava filters are confined to patients with either deep vein thrombosis (DVT) or PE who present with serious contraindications to conventional anticoagulation.[1]

Although considerable progress has been made in the treatment of venous thromboembolic disorders, many unanswered questions remain and await proper solution. Furthermore, new opportunities are

emerging, which have the potential to modify the therapeutic scenario substantially in the near future. The topics that are worth exploring include home treatment of selected patients with DVT, the treatment of cancer patients with venous thrombosis, renewed interest in thrombolytic drugs in patients with PE, the optimal duration of oral anticoagulant therapy, and the potential of new drug categories in the initial treatment and secondary prevention of VTE.

Home treatment of DVT

The observation that LMWHs are at least as effective and safe as UFH when administered by fixed-dose subcutaneous injections stimulated the hypothesis that it might be possible to use LMWH preparations to treat selected patients with DVT in an out-of-hospital setting. To test this fascinating hypothesis, two multicenter clinical trials were performed in the second half of the 1990s: one used nadroparin, the other enoxaparin.[2,3] Their conclusions consistently supported the feasibility, efficacy and safety of home treatment of patients with uncomplicated DVT with subcutaneous fixed doses of LMWHs. Furthermore, this strategy was associated with an improvement of quality of life, and a relevant reduction of health care costs. A number of prospective cohort studies have been subsequently performed, supporting the feasibility and safety of home treatment of DVT.[4]

Home treatment of DVT has become daily clinical practice in many countries. There are, however, essential requirements for the success of a home treatment program. Patients need to be educated about what venous thrombosis is, its possible complications and side effects, and need to be instructed on self-injecting the drug or nursing support. Initiation and monitoring of oral anticoagulant therapy are performed entirely on an outpatient basis; thus community facilities should be prepared for this task. A few aspects of home treatment still await appropriate clarification: when and how intensively can patients ambulate? Does the platelet count need to be determined? Might selected patients benefit from drug monitoring ?

The treatment of cancer patients with venous thrombosis

Patients with DVT who also have cancer have a higher risk of recurrent thromboembolism and major bleeding during anticoagulation.[5,6] In a recent prospective cohort study in a wide series of patients with venous thrombosis with or without cancer, the 12-month cumulative incidence of both recurrent thromboembolism and major bleeding during anticoagulation was significantly higher in patients with cancer than in those without cancer.[7] Recurrence and bleeding were both related to cancer severity, occurred predominantly during the first month of anticoagulant therapy but could not be explained by sub- or overanticoagulation.[7] Possibilities for improvement using the current paradigms of anticoagulation seem, therefore, limited and new treatment strategies should be developed. The long-term use of LMWH has recently been shown to be significantly more effective than and as safe as warfarin for the initial treatment and secondary prevention of VTE in cancer patients with venous thrombosis.[8]

The treatment of pulmonary embolism

Recent studies have put into question the systematic use of anticoagulants alone in the initial treatment of patients with submassive PE. The risk of an unfavourable outcome seems definitely higher in patients with right ventricular dysfunction, as shown by echocardiography.[9,10] The use of thrombolytic drugs, which promptly restore the patency of the pulmonary arterial vessels, has the potential to improve the outcome of patients with PE. Recently, two meta-analyses of comparative studies between thrombolysis and heparin in the treatment of acute PE have been published.[11,12] The results of these meta-analyses consistently showed that patients treated with thrombolytic drugs had a more favorable outcome, in terms of prevention of short-term recurrent episodes of PE, than those treated with heparin alone. The difference became statistically significant when a composite end-point consisting of death/recurrence was calculated.[11] However, patients treated with thrombolytic drugs had a definitely higher risk of hemorrhage.[11,12] In a recent prospective controlled study, a wide series of patients with submassive PE and contemporary right ventricular dysfunction were randomized to receive heparin alone or in combination with alteplase.[13] Patients treated with the combination of heparin with alteplase had a significantly lower rate of in-hospital death and clinical deterioration, while the hemorrhagic risk was similarly low in the two treatment groups. The results of this study have the potential to expand the use of thrombolysis in patients with acute PE, at least in those with right ventricular dysfunction.

The optimal duration of anticoagulant treatment

After the publication of an impressive series of prospective cohort studies,[14,15] population-based studies,[16] and randomized clinical trials,[17-20] we know that:

- 5-10% of patients with secondary DVT from transient risk factors have a recurrent VTE after three months of oral anticoagulant therapy;
- 15-30% of patients with idiopathic DVT have a recurrent VTE after three months. This rate will not change by prolonging OAT up to 6-12-24 months;
- The role of thrombophilia is controversial.

— The annual incidence of major bleeding from oral anticoagulant therapy is 1.5-2.0%. The *case-fatality rate* of an episode of major bleeding is four times as high as that observed in patients with recurrent VTE.

To optimize the long-term treatment of VTE, new strategies and new drugs are currently under investigation. Recent studies suggest that low-intensity warfarin therapy, after an initial three to six-month period of conventional anticoagulation, may confer an additional protection without an excessive bleeding risk.[21] Furthermore, recent studies suggest that the risk of late recurrences can be carefully predicted on an individual basis by strategies that include the ultrasound assessment of thrombotic burden[22,23] or the laboratory evaluation of D-dimer.[24,25] Finally, new categories of drugs are emerging, which have the potential to simplify the long-term treatment of patients with VTE by obviating the need for periodic laboratory monitoring, while being associated with a favorable benefit-to-risk ratio (*see below*).

Beyond heparins

Selective factor Xa inhibitors. Fondaparinux, a pentasaccharide, is the first of a new class of synthetic antithrombotic agents designed specifically for a single physiologic target in the coagulation cascade. This compound is identical to the pentasaccharide sequence in heparin with high affinity for antithrombin. It selectively binds to antithrombin and induces a conformational change of its molecule that increases the anti-Xa activity of antithrombin by almost 300 times. This compound has recently been approved for prophylaxis of VTE in patients undergoing major orthopedic surgery.

In a phase II study published in 2000, this compound appeared to be as effective and safe as dalteparin across a wide range of doses also for the treatment of established DVT.[26] According to the results of two large phase III multicenter clinical trials, the once daily subcutaneous administration of 7.5 mg of fondaparinux is as effective and safe as enoxaparin for the treatment of DVT, and as least as effective and safe as UFH for the treatment of PE.[27] Furthermore, the once weekly administration of 2.5 mg of a long-active formulation of pentasaccharide (idraparinux) has recently been shown in a phase II study to be at least as effective and safe as warfarin for the secondary prevention of DVT.[28]

Direct thrombin inhibitors

The direct thrombin inhibitors include hirudin, bivalirudin, and active-site inhibitors (such as argatroban and melagatran). Agents that directly inhibit thrombin have several advantages over (LMW)heparins, including the inhibition of fibrin-bound thrombin, a dose response that is more predictable because there is no binding to plasma proteins, and a lack of potential to produce immune thrombocytopenia. Among these preparations, ximelagatran (an oral prodrug that is converted to melagatran and does not require laboratory monitoring) show promise for the prophylaxis and treatment of VTE. According to the results of a recent, randomized clinical trial, the oral administration of fixed doses of ximelagatran is more effective than and as safe as placebo for the prevention of recurrent VTE following the administration of six months of warfarin in patients with DVT.[29] A phase III clinical trial of ximelagatran for the initial treatment of DVT has recently completed recruitment.

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