incidence
Venous thromboembolism (VTE) represents one of the most important causes of morbidity and mortality in cancer patients. According to population-based case–control studies, the 2-year cumulative incidence of VTE is 0.8–8%. Patients with the highest 1-year incidence rate of VTE are those with advanced disease of the brain, lung, uterus, bladder, pancreas, stomach and kidney. For these histotypes, the rate of VTE is 4–13 times higher among patients with metastatic disease as compared with those with localized disease.

risk factors
The absolute risk depends on tumor type, stage of disease, administration of chemotherapy and/or hormone therapy, surgical intervention, the presence of an indwelling central venous catheter, age, immobilization and previous history of VTE. Pre-chemotherapy platelet count of ≥350 × 10⁹/l, use of erythropoiesis-stimulating agents, leukocyte count >11 × 10⁹/l and body mass index of ≥35 kg/m² are associated with an increased risk of developing VTE in ambulatory cancer patients. The role of hereditary thrombophilia is still unclear. Screening for the most common polymorphisms is therefore not indicated.

diagnosis of VTE in occult malignancy
There is general agreement that patients with idiopathic thrombosis present a higher risk of occult cancer. Part of these malignancies can be identified by routine assessments at the time of the thrombotic event. To date, without definitive data to demonstrate an advantage in terms of overall survival using invasive diagnostic tests and intensive follow-up, patients should undergo only physical examination, occult fecal blood test, chest X-ray, urological visit in men, gynecological visit in women. The request for more expensive examinations such as computer tomography (CT) scan, digestive endoscopy or tumor markers should be addressed in the case of a strong clinical suspicion of occult cancer [II, C].

prevention of VTE
surgery:
Prevention in general surgical patients. In cancer patients undergoing major cancer surgery prophylaxis with low-molecular weight heparins (LMWH), unfractionated heparin (UFH) or fondaparinux is recommended. Mechanical methods such as pneumatic calf compression may be added to pharmacologic prophylaxis but should not be used as monotherapy unless pharmacologic prophylaxis is contraindicated because of active bleeding [I, A].

Dosing in the perioperative setting. In surgical cancer patients LMWH (e.g. enoxaparin 4000 units of anti-Xa activity, dalteparin 5000 units of anti-Xa activity) once daily (o.d.), UFH 5000 U (three times daily) (t.i.d.), fondaparinux 2.5 mg o.d. are recommended [I, A].

Duration of prophylaxis. For patients having a laparotomy, laparoscopy, thoracotomy or thoracoscopy lasting >30 min consider LMWH for at least 10 days postoperatively.

Cancer patients undergoing elective major abdominal or pelvic surgery should receive in hospital and post-discharge prophylaxis with LMWH for up to 1 month after surgery [I, A].

medical treatments
Prophylaxis in hospitalized cancer patients. Prophylaxis with UFH, LMWH or fondaparinux in hospitalized cancer patients confined to bed with an acute medical complication is recommended [I, A].

Prophylaxis in ambulatory patients receiving palliative chemotherapy for advanced disease. Extensive, routine prophylaxis for advanced cancer patients receiving chemotherapy is not recommended. Consider LMWH or adjusted-dose warfarin [International Normalized Ratio (INR) @ 1.5] in myeloma patients receiving thalidomide plus dexamethasone or thalidomide plus chemotherapy [II, B].

Prophylaxis in cancer patients receiving adjuvant chemotherapy and/or hormone therapy. Prophylaxis in cancer patients
receiving adjuvant chemotherapy and/or hormone therapy is not recommended [I, A].

Central venous catheters (CVCs). Extensive, routine prophylaxis to prevent CVC-related VTE is not recommended. To date prophylaxis might be tailored according to individual risk level [I, A].

treatment of VTE in patients with solid tumors

acute treatment: LMWH and UFH

The standard initial treatment of an acute episode of VTE in cancer and non-cancer patients consists in the administration of LMWH subcutaneously (s.c.) at a dose adjusted to body weight: 200 U/kg o.d. (200 units of anti-Xa activity per kg of body weight administered once daily) (e.g. dalteparin) or 100 U/kg (100 units of anti-Xa activity per kg of body weight) administered twice daily (e.g. enoxaparin) or UFH intravenously (i.v.) in continuous infusion. UFH is first administered as a bolus of 5000 IU, followed by continuous infusion, nearly 30 000 IU over 24 h, adjusted to achieve and maintain an activated partial thromboplastin time (aPTT) prolongation of 1.5–2.5 times the basal value. In patients with severe renal failure (creatinine clearance <25–30 ml) UFH i.v. or LMWH with anti-Xa activity monitoring is recommended [I, A].

acute treatment: thrombolytic therapy

Thrombolytic treatment should be considered for specific subgroups of patients such as those with pulmonary embolism presenting with severe right ventricular dysfunction, and for patients with massive ilio-femoral thrombosis at risk for limb gangrene, where rapid venous decompression and flow restoration may be desirable. Urokinase, streptokinase and tissue-type plasminogen activator are able to achieve a rapid lysis of fresh pulmonary emboli [II, A].

Long-term treatment. According to standard treatment, the initial phase is followed by treatment with oral anticoagulation with vitamin K antagonists (VKAs) administered for 3–6 months, at a therapeutic INR range of 2–3. VKAs are started within 24 h of initiation of heparin (UFH or LMWH) administration. A full dose of heparin is continued for at least 5 days and suspended when full anticoagulation by VKA (i.e. INR > 2.0) is achieved for at least 2 consecutive days.

However, oral anticoagulation with VKA may be problematic in patients with cancer. Drug interactions, malnutrition and liver dysfunction can lead to wide fluctuations in INR. Cancer patients have both a higher rate of VTE recurrences during oral anticoagulant therapy with VKA and a higher anticoagulation-associated hemorrhagic risk as compared with non-cancer patients.

Results from recent randomized clinical trials demonstrate that in these patients long-term treatment for 6 months with 75–80% (i.e. 150 U/kg o.d.) of the initial dose of LMWH is safe and more effective than treatment with VKAs. This schedule is recommended for long-term anticoagulant therapy in cancer patients [I, A].

Duration of therapy. It is recommended to continue anticoagulant therapy as long as there is clinical evidence of active malignant disease (e.g. chronic metastatic disease) [III, C].

Anticoagulant therapy in patients with recurrence of VTE.

Patients adequately anticoagulated who develop VTE recurrence should be checked for progression of their malignancy.

Patients on long-term anticoagulation with VKA, who develop VTE when INR is in the sub-therapeutic range can be retreated with UFH or LMWH until VKA anticoagulation achieves a stable INR between 2.0 and 3.0. If recurrent VTE recurrence occurs while the INR is in the therapeutic range there are two options: (i) either shift to another method of anticoagulation, such as s.c. UFH maintaining a therapeutic aPTT (aPTT ratio of 1.5–2.5) or LMWH at weight-adjusted dose; (ii) or increase the INR (to a target of 3.5). Full-dose LMWH (200 U/kg o.d.) can be resumed in patients with a VTE recurrence while receiving a reduced dose of LMWH as long-term therapy. Alternatively, patients may be shifted to VKA anticoagulation [II, B].

Use of a vena cava filter. The use of an inferior vena cava filter should be considered in patients with recurrent pulmonary embolism despite adequate anticoagulant treatment or with a contraindication to anticoagulant therapy (i.e. active bleeding and profound, prolonged thrombocytopenia). Once the risk of bleeding is reduced, patients with vena cava filter should receive or resume anticoagulant therapy in order to reduce the risk of recurrent deep vein thrombosis of the lower extremities [I, A].

anticoagulation and prognosis of cancer patients

Current information is too limited to recommend or not recommend the use of anticoagulation to influence prognosis of cancer [I, B].

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty.

literature


