Annals of Oncology 21 (Supplement 5): v274–v276, 2010
doi:10.1093/annonc/mdq199

Venous thromboembolism in cancer patients: ESMO Clinical Practice Guidelines for the management

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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 between 0.8% and 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 to 13 times higher among patients with metastatic disease as compared with those with localized disease.

risk factors

The absolute risk depends on tumour 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. The use of bevacizumab increases the risk of developing VTE.

A predictive model, recently validated, is able to discriminate between ambulatory patients with low (score 0), intermediate (score 1 or 2) or high risk (score ≥3) of chemotherapy-associated thrombosis. Five variables have been included: (i) site of cancer: cancer sites at very high risk (stomach, pancreas: risk score 2), high risk (lung, lymphoma, gynaecological, genitourinary: risk score 1) and low risk (breast, colorectal, head and neck: risk score 1); (ii) pre-chemotherapy platelet count of $\geq 350 \times 10^9$/l (risk score 1); (iii) haemoglobin level <10 g/dl, use of erythropoiesis-stimulating agents or both (risk score 1); (iv) leukocyte count $>11\times10^9$/l (risk score 1); (v) body mass index of ≥35 kg/m^2 (risk score 1). The incidence of VTE is 0.3%, 2% and 6.7% in patients with low-, intermediate- and high-risk score, respectively. This model might be used to identify ambulatory cancer patients who are clinically at high risk for VTE.

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, faecal occult blood test, chest X-ray, urological visit in men, gynaecological visit in women. The request for more expensive examinations such as computerized tomography (CT) scan, digestive endoscopy or tumour 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 pharmacological prophylaxis but should not be used as monotherapy unless pharmacological 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].

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Approved by the ESMO Guidelines Working Group: August 2008, last update December 2009. This publication supercedes the previously published version—Ann Oncol 2009; 20 (Suppl 4): iv182–iv184.

Conflict of interest: Dr Mandalà and Dr Falanga have reported no conflicts of interest; Prof. Roila has reported that he is conducting research on prevention of venous thromboembolism sponsored by Sanofi-Aventis.

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 (CVC). 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 tumours

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 of 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 from 2 to 3. VKA is started within 24 h from initiating 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 recurrence during oral anticoagulant therapy with VKA and a higher anticoagulation-associated haemorrhagic 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 VKA. This schedule is recommended for long-term anticoagulant therapy in cancer patients [I, A].

duration of therapy

It is recommended that anticoagulant therapy be continued 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.

Cancer patients have a threefold risk of recurrent VTE and a threefold to sixfold risk of major bleeding while receiving anticoagulant treatment with a VKA, as compared with patients without cancer.

Patients on long-term anticoagulation with VKA, who develop VTE when INR is in the subtherapeutic range can be retreated with UFH or LMWH until VKA anticoagulation has achieved a stable INR of between 2.0 and 3.0. If 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 subcutaneous 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 or VKA anticoagulation as long-term therapy. Escalating the dose of LMWH results in a second recurrent VTE rate of 9%, it is well tolerated, with few bleeding complications [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 a 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].

contraindication to anticoagulation

Relative contraindications to anticoagulation include active, uncontrollable bleeding; active cerebrovascular haemorrhage; intracranial or spinal lesions at high risk of bleeding; pericarditis, active peptic or other gastrointestinal ulceration; severe, uncontrolled or malignant hypertension; active bleeding (>2 units transfused in 24 h); chronic, clinically significant measurable bleeding; thrombocytopenia (<50 000/mm^3); severe platelet dysfunction; recent operation at high risk of bleeding.

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.

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