clinical practice guidelines

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Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines

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introduction

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% [1]. 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 [1].

The increased risk of recurrent VTE in cancer patients is greatest in the first few months after malignancy is diagnosed [1] and can persist for many years after an initial episode of symptomatic VTE. While receiving chemotherapy, cancer patients have a 7-fold risk of developing VTE as compared with other patients without cancer.

Cancer patients, once hospitalized, are at an even higher risk of developing VTE. In a recent retrospective study involving >66 000 adults with cancer, 5.4% of patients developed VTE over the 8 years of the study [2].

Furthermore, in a retrospective study, cancer patients were found to have a 3-fold higher risk for recurrent VTE than patients who had an initial VTE in the absence of malignancy [3]. The probability of readmission for recurrent VTE within 183 days was 22% for cancer patients compared with 6.5% for those without malignancy [3].

The interrelationship between cancer and haemostasis is well known. From a clinical point of view the evidence of this association is based on the increased incidence of VTE in cancer patients, principally in metastatic cancer patients. VTE development has serious clinical consequences and impact on the clinical course of the disease, increasing both morbidity and mortality. The poor prognosis of VTE may reflect both a combination of fatal complications [e.g. pulmonary embolism (PE)] and a higher disease aggressiveness [4].

A recent study reported the results of a retrospective analysis in 227 pancreatic cancer patients who had received gemcitabine (GEM)-based chemotherapy for locally advanced or metastatic disease [4]. The clinical occurrence of symptomatic VTE conferred a worse response rate, progression-free survival and overall survival. Since the authors did not retrieve from medical charts acute death due to PE, it seems unlikely that complications of VTE can account entirely for the increased mortality among the patients evaluated in their retrospective analysis. Hence, these data suggest that in these patients the development of VTE may reflect the presence of a biologically more aggressive cancer that in turn leads to a worse prognosis.

Albeit that VTE commonly occurs in patients with cancer, most oncologists underestimate the prevalence of VTE and its negative impact on their patients [5, 6]. With this background in mind, the European Society for Medical Oncology (ESMO) decided to draft recommendations for clinical practice in order to improve perceptions about the magnitude of VTE risk in patients with malignancy and to improve prophylaxis and treatment of VTE in cancer patients.

methodology

ESMO selected two expert physicians in clinical oncology, clinical research and clinical haematology: one medical oncologist (M. Mandalà) and one haematology specialist with experience in thrombotic complications (A. Falanga). They used a systematic review of the evidence as the foundation for making recommendations. This process included a systematic weighting of the level of evidence and a systematic grading of the evidence for making a recommendation. In order to design a hierarchical grading system, they gave greater weight to well-designed randomized controlled trials and meta-analyses and progressively less weight to studies with weaker internal validity. Furthermore, the concordant findings of controlled studies that have not been subject to meta-analysis were highly considered in order to score the levels of evidence. When evidence was lacking, the expert physicians determined

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Conflict of interest: Professor Roila has reported that he is conducting research on prevention of venous thromboembolism sponsored by Sanofi-Aventis. Dr Mandalà has reported membership of Advisory Board and Speakers' Bureau for Sanofi, Clinical trials for thromboprophylaxis by Italfarmaco. Dr. Falanga has reported the following activities in the past two years: member of Pfizer Virtual Advisory board on Fragmin and member of the Adjudication Committee of Sanofi-Aventis Registry Master Oncology.

that it was appropriate to reach conclusions based on expert opinion.

An extensive 'Medline' and Cancerlit literature review (1996–2010) to produce evidence-based recommendations has been performed. Various combinations of search terms were used depending on the requirements of the database being searched. These terms included: 'Thrombosis', 'Thromb*', 'Venous Thrombosis', 'Coagulation', 'Cancer', 'Tumor', 'Treatment', 'Prophylaxis*', 'Therapy', 'Surgery', 'Chemotherapy', 'Hormonotherapy', 'Occult Cancer', 'Prognosis', 'Survival', 'Heparin', 'Coumarin', 'Warfarin*', 'Low molecular weight heparin*', 'LMWH' and 'Catheter'. Relevant references in each article were scanned and manual searches of abstracts from the annual meetings of the American Society of Hematology (1993–2010), American Society of Clinical Oncology, ESMO (1993–2010) and European Haematology Association (1993–2010) were also performed. Finally, the abstracts presented during ECCO, ASCO and ECCO-ESMO have been taken into consideration.

The draft was reviewed by the editor in chief and the section editor, who selected a panel of five experts designated by the ESMO guidelines task force. The ESMO-designated reviewers extensively and critically reviewed the manuscript to improve the scientific quality of the manuscript and to help the authors to give evidence-based recommendations.

clinical risk factors

Since VTE is a multifactorial event, the absolute risk depends on several factors including: tumour type, stage of disease, the administration of chemotherapy and/or hormone therapy, surgical interventions, length of anaesthesia, the presence of an indwelling central venous catheter, age, immobilization and previous history of VTE [7]. One of the most important factors promoting VTE may be the use of cytotoxic drugs. Chemotherapy can increase the risk of VTE by at least four mechanisms: (i) acute damage to vessel walls; (ii) non-acute damage of the endothelium; (iii) a decrease in natural coagulation inhibitors (reduced level of C and S proteins or antithrombin III); and (iv) platelet activation [7].

Antiangiogenic agents such as bevacizumab, thalidomide and lenalidomide also contribute to thrombosis, through endothelial cell and platelet activation and damage to the vascular endothelium. The thrombogenic effect of antiangiogenic agents is amplified by the co-administration of chemotherapy and steroids. In a recent meta-analysis of clinical trials of bevacizumab administered concomitantly with chemotherapy, the use of bevacizumab was associated with a 33% relative increase of VTE [8]. Among patients receiving bevacizumab, the overall incidence of any-grade and high-grade VTE was 11.9 and 6.3%, respectively. With regards to multiple myeloma, the highest incidence of VTE was observed in patients treated with thalidomide- and doxorubicin-containing chemotherapy (VTE rate of up to 34%) [9] and in patients with relapsed myeloma treated with lenalidomide and high-dose dexamethasone [10].

A predictive model, recently validated, is able to discriminate between ambulatory patients with low (score 0), intermediate (score 1 or 2) and high risk (score ≥3) of chemotherapy-associated thrombosis [11] (Table 1). 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) prechemotherapy platelet count of ≥350 × 10^9/l (risk score 1); (iii) haemoglobin level <10 g/dl or use of erythropoiesis-stimulating agents, or both (risk score 1); (iv) leukocyte count >11 × 10^9/l (risk score 1); and (iv) 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 a 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 (II, B).

Table 1. Predictive model for chemotherapy-associated VTE in ambulatory cancer patients

	Risk score
Cancer-related risk factors	
Site of cancer and tumour histotype	
Very high risk (stomach adenocarcinoma, pancreas adenocarcinoma)	2
High risk (lung, lymphoma, gynaecological, bladder, testicular)	1
Haematological risk factors	
Prechemotherapy platelet count ≥350 000/μl	1
Haemoglobin <10 g/dl or use of ESA growth factors	1
Prechemotherapy leukocyte count >11 000/μl	1
Patient-related risk factor	
Body mass index ≥35 kg/m^2	1

The rates of VTE were as follows: low-risk category (score = 0), 0.5%; intermediate-risk category (score = 1–2), 2%; high-risk category (score ≥3), 7%. ESA, erythropoiesis-stimulating agents VTE, venous thromboembolism.

The derivation and validation cohort of the above-described predictive model did not include certain cancers known to be strongly associated with VTE, such as brain tumours, furthermore poor performance status patients were underrepresented in the study population.

diagnosis of VTE in occult malignancy

There is general agreement that patients with idiopathic thrombosis present a higher risk of occult cancer [12]. Part of these malignancies can be identified by routine assessments at the time of the thrombotic event.

A prospective trial (SOMIT, Screening for Occult Malignancy in Patients with Symptomatic Idiopathic Venous Thromboembolism) has been performed in Italy in order to assess if an extensive screening programme is able to identify early stage, treatable cancers in order to improve treatment possibilities and prognosis [13]. The results show that extensive screening is able to detect most of the hidden malignancies with a high degree of sensitivity. The extensive screening led not only to an early detection of malignancies, but also to the identification of malignancies at an early stage. However, there was no improvement in overall survival, which was the primary endpoint of the study.

recommendation

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 faecal blood test, chest X-ray, urological visit in men and gynaecological visit in women. The request for more expensive examinations such as computed 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 general considerations. Cancer patients who undergo surgery are at high risk of developing a VTE complication. It has been reported that cancer patients undergoing a surgical procedure have twice the risk of postoperative VTE and more than three times the risk of fatal PE than patients who undergo surgery for benign diseases [14]. In addition to the cancer-associated risk, a large group of patients presents with additional risk factors for thrombosis, such as increasing age, prolonged immobility, obesity and indwelling central venous catheters.

The role of prophylaxis is unquestionable (I, A).

pharmacological thromboprophylaxis. A meta-analysis of perioperative prophylaxis demonstrated a reduced incidence of VTE in patients who received heparin prophylaxis (13.6%) compared with patients with no prophylaxis (30.6%) [15]. The therapeutic approaches used for the prevention of postsurgical VTE include compression stockings, subcutaneous (s.c.) low-dose unfractionated heparin (UFH) (5000 IU given daily every 8–12 h starting 1–2 h before the operation), and more recently the low molecular weight heparins (LMWHs) at a fixed single s.c. daily dose

Several studies suggest that in cancer patients LMWH and UFH appear to be equally effective and safe [16–20]. These results have been confirmed by at least three studies [21–23], one of them specifically designed for surgical cancer patients [21]. There are important advantages of LMWH because they can be administered once daily, have a better pharmacokinetic profile and are less likely to cause heparin-induced thrombocytopenia. For these reasons it would seem reasonable to consider LMWH as the first choice in this setting.

Fondaparinux was found to be at least as effective as LMWH in preventing VTE in a prospective, double-blind, randomized trial, which included high-risk abdominal surgery patients, most of them with malignant disease. However, this was only a *post hoc* subgroup analysis, hence that finding requires confirmation in future studies [24].

mechanical thromboprophylaxis. A number of mechanical thromboprophylactic modalities are available, including graduated compression stockings and intermittent pneumatic compression devices. There is no evidence from prospective, randomized studies that these devises may be used as monotherapy, without an adjunct to medical thromboprophylaxis.

recommendation

In cancer patients undergoing major cancer surgery, prophylaxis with LMWHs or UFH 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 a prospective, randomized, double-blind, multicentre trial, the efficacy and the safety of two different s.c. daily doses of the LMWH dalteparin (2500 and 5000 UI anti-Xa) have been tested in patients undergoing elective general surgery for malignant and benign abdominal disease [25]. This study clearly demonstrated that a high prophylactic dosage of LMWH increases the efficacy without enhancing the bleeding risk. In surgical cancer patients, high-dose s.c. LMWH (e.g. enoxaparin 4000 U of anti-Xa activity, dalteparin 5000 U of anti-Xa activity) once daily, or s.c.UFH 5000 U (three times daily) are recommended [I, A].

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

Two randomized controlled, prospective trials have shown that, in cancer patients undergoing elective major abdominal or pelvic surgery, continuing prophylaxis with a LMWH up to 30 days postoperatively can reduce the risk of VTE by 60% without increasing the risk of bleeding [26, 27].

recommendation

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

medical treatments

prophylaxis in hospitalized cancer patients. Three large, high-quality clinical trials, in hospitalized 'medical patients', which included cancer patients, have demonstrated that prophylaxis leads to a lower VTE incidence compared with placebo, without increasing major bleeding [28–30].

The low bleeding rates observed with LMWH and fondaparinux prophylaxis in the three major medical trials strongly support the safety of thromboprophylaxis in hospitalized cancer patients. One potential caveat may be that none of these studies has published bleeding rates specifically for the cancer subgroups of their populations.

recommendation

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 locally advanced or metastatic disease. In a prospective randomized clinical trial, Levine *et al.* [31] demonstrated that the use of very low dose warfarin, maintaining the international normalized ratio (INR) between 1.3 and 1.9, significantly reduced the VTE rate in metastatic breast cancer patients who received chemotherapy compared with those who received placebo. Prophylaxis with warfarin was effective, with no increase in major bleeding Nevertheless, the event rate in the study was low (4.4% vs 0.6%, in the study and

control group, respectively); in addition, drug interactions, malnutrition and liver dysfunction can lead to unpredictable levels of anticoagulation.

Recently two prospective studies have been reported in abstract form. A UK group conducted a randomized prospective phase IIb study specifically in advanced pancreatic cancer patients [32].

Patients received GEM 1000 mg/m^2 weekly in combination or not with daily dalteparin injections for 12 weeks at a therapeutic dose (200 U/kg once a day for the first month and then 80% of the initial dose for 5 months). The primary endpoint was to reduce VTE. In this study 123 patients were randomized; the incidence of VTE, during the first 3 months, was 25% vs 3.5% in the standard and the experimental group, respectively. Lethal VTE and sudden deaths were seen only in the standard arm (9%), with none in the experimental arm.

A second prospective, randomized clinical study has been performed by a German group [33]. Patients were randomized to receive GEM-based chemotherapy either in combination with or without enoxaparin 1 mg/kg daily s.c. Enoxaparin decreased the rate of symptomatic VTE after 3 months (observation, 9.87%; enoxaparin, 1.25%) and 12 months (observation, 15%; enoxaparin, 5%).

Recently the PROTECHT study has been reported [34]. In this trial 1150 patients were randomized to receive nadroparin or placebo; among those, 53 patients had locally advanced or metastatic pancreatic cancer. The primary endpoint was the composite of symptomatic venous or arterial thromboembolic events. Thromboembolic events occurred in 2.0 and 3.9% of patients treated with nadroparin and placebo, respectively, without increasing major or minor bleeding. This trial, by using a LMWH, demonstrated for the first time a statistically significant reduction of thromboembolic events in ambulatory cancer patients receiving chemotherapy for locally advancer or metastatic cancer.

Patients with lung or pancreatic cancer were more likely to experience thromboembolic events than were patients with breast, gastrointestinal, ovarian, or head and neck cancers, which suggested that these patient groups may benefit from LMWH prophylaxis.

recommendation

Extensive, routine prophylaxis for advanced cancer patients receiving chemotherapy is not recommended, but may be considered in high-risk ambulatory cancer patients [II, C].

Consider LMWH, aspirin or adjusted-dose warfarin (INR ~1.5) in myeloma patients receiving thalidomide plus dexamethasone or thalidomide plus chemotherapy [35, 36] [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). In the last two decades, two open-label randomized clinical trials suggested a role for prophylaxis with warfarin or a LMWH in patients with a CVC [37, 38].

Four recent studies have assessed that the incidence of symptomatic CVC-related VTE is in general low, ~3–4%, and that there is no statistically significant difference between patients undergoing and patients not undergoing prophylaxis [39–42].

recommendation

Extensive, routine prophylaxis to prevent CVC-related VTE is not recommended [I, A].

treatment of VTE in patients with solid tumours

acute treatment: LMWH and UFH

The aim of VTE treatment can be summarized as follows:

- To prevent fatal PE
- To prevent recurrent VTE
- To prevent long-term VTE and PE complication such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension,

The standard initial treatment of an acute episode of VTE in cancer and non-cancer patients consists of the administration of s.c. LMWH at a dose adjusted to body weight: 200 U/kg once daily (200 U of anti-Xa activity per kg of body weight administered once a day) (e.g. dalteparin) or 100 U/kg (100 U 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.

It is well known that LMWH is cleared only by the kidneys and has a significant accumulative effect in patients with impaired renal function (creatinine clearance <30 ml/min).

Patients with a creatinine clearance of ≤30 ml/min who are treated with standard therapeutic doses of enoxaparin have elevated levels of anti-Xa and an increased risk for major bleeding.

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 PE 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 from 2 to 3. VKAs are 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 two 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 VKAs and a higher anticoagulation-associated haemorrhagic risk as compared with non-cancer patients.

In cancer patients, the possible benefit of LMWH for prevention of recurrent VTE has been studied in two randomized clinical trials [43, 44]. In the largest trial, 676 patients with cancer and acute symptomatic VTE, after the initial treatment with the LMWH dalteparin at a dose of 200 IU/kg of body weight s.c. once daily for 5–7 days, were randomly assigned to continue with the same dose dalteparin for 1 month, followed by 75–80% of the initial dalteparin dose for another 5 months, or to receive a coumarin derivative for 6 months (target INR 2.5) [43]. The rate of recurrent VTE at 6 months was 17% in the oral anticoagulant group and 9% in the dalteparin group. There was no significant increase in the rate of major bleeding between the two arms. This trial has clearly demonstrated that dalteparin is more effective than oral anticoagulant with VKAs in reducing the risk of recurrent VTE without increasing the risk of bleeding.

Another small trial confirmed that the LMWH is more effective for the prevention of recurrent VTE as compared with warfarin [45].

The results from all the above-mentioned randomized clinical trials demonstrate that in these patients long-term treatment for 6 months with 75–80% (i.e. 150 U/kg once daily) of the initial dose of LMWH is safe and more effective than treatment with a VKA. This schedule is recommended for long-term anticoagulant therapy in cancer patients [I, A].

duration of therapy

The optimal duration of anticoagulant therapy for the prevention of VTE recurrence has not been specifically studied.

There are al least four clinical scenarios:

- Breast cancer patients treated with tamoxifen in the adjuvant setting
- Cancer patients treated with chemotherapy in the adjuvant setting
- Cancer patients treated with a potentially curative strategy for the metastatic disease (i.e. patients with metastatic germinal cancer)
- Cancer patients treated with palliative chemotherapy in the metastatic setting.

scenario 1. For breast cancer patients receiving tamoxifen in the adjuvant setting it is recommended to substitute tamoxifen with an aromatase inhibitor. In these patients a long-term treatment for 6 months with 75–80% (i.e. 150 U/kg once daily) of the initial dose of LMWH should be considered [II, B].

scenario 2. For cancer patients receiving chemotherapy in the adjuvant setting, a long-term treatment for 6 months with 75–80% (i.e. 150 U/kg once daily) of the initial dose of LMWH should be adopted [43] [II, A].

scenario 3. For cancer patients achieving a complete remission of a potentially curative disease (i.e. germinal cancer) a long-term treatment for 6 months with 75–80% (i.e. 150 U/kg once daily) of the initial dose of LMWH may be considered [III, C].

For patients receiving chemotherapy in a metastatic setting but with a neoadjuvant approach (colorectal cancer patients with potentially resectable liver metastases) the risk of recurrent cancer and/or VTE should be individually assessed [III, C].

scenario 4. For cancer patients receiving chemotherapy in a palliative setting, also for those achieving a complete remission but with a very high risk of recurrence, an indefinite treatment should be discussed with the patient [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 3-fold risk of recurrent VTE and a 3- to 6-fold risk of major bleeding while receiving anticoagulant treatment with a VKA, as compared with patients without cancer [46].

Patients on long-term anticoagulation with VKA who develop VTE when their INR is in the subtherapeutic range can be retreated with UFH or LMWH until VKA anticoagulation achieves a stable INR 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 s.c. UFH maintaining a therapeutic aPTT (aPTT ratio from 1.5 to 2.5), or LMWH at a weight-adjusted dose; or (ii) or increase the INR (to a target of 3.5). Full-dose LMWH (200 U/kg once daily) can be resumed in patients with a VTE recurrence while receiving a reduced dose of LMWH or VKA anticoagulation as a 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 [47] [II, B].

use of a vena cava filter

In the largest trial evaluating the effectiveness of vena cava filters, after 2 years of follow-up there was no significant difference in survival or symptomatic PE rate in patients ($n = 400$) randomly treated with either standard anticoagulation alone or anticoagulation plus a vena cava filter [48].

recommendation

The use of an inferior vena cava filter should be considered in patients with recurrent PE 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 [II, A].

contraindication to anticoagulation

Relative contraindications to anticoagulation include active, uncontrollable bleeding; active cerebrovascular haemorrhage; intracranial or spinal lesions at high risk for 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/ml); severe platelet dysfunction; or recent operation at high risk for bleeding.

anticoagulation and prognosis of cancer patients

The occurrence of VTE has several clinical consequences due to patient morbidity, interruption of chemotherapy and cost of hospitalization. It has been demonstrated that cancer, when diagnosed at the same time or within 1 year of an episode of VTE, is associated with an advanced stage and a 3-fold lower survival at 1 year. Two large population-based studies investigated the prognostic relevance of VTE in cancer patients [1, 49]. However, these studies may have several limitations because they do not provide information on chemotherapy and performance status, which may have an impact on overall survival.

A recent meta-analysis demonstrated that heparins confer a survival benefit in cancer patients in general, and in patients with limited stage small-cell lung cancer in particular. Furthermore heparins were found to be more beneficial in cancer patients with limited cancer or a longer life expectancy [50].

Another recent meta-analysis evaluated the impact of anticoagulants on survival and safety in cancer patients without VTE [51]. The authors found a significant reduction in overall mortality with anticoagulant therapy in cancer patients without VTE. The clinical effect was most pronounced for LMWH, which produced a relative risk reduction in mortality of 13.3% compared with a non-significant reduction with warfarin of 5.8%.

Recently two prospective randomized, placebo-controlled trials have been reported, specifically evaluating LMWHs for survival in cancer patients. In both studies the survival of patients with a good prognosis was significantly in favour of LMWH vs placebo [52, 53]. However, one of these trials [52] failed to reach its primary endpoint, and specifically to detect a difference in terms of survival at 1 year in patients with locally advanced or metastatic cancer who received dalteparin vs placebo. Only a *post hoc* analysis suggested a benefit for patients with a more indolent disease. This analysis was not previously planned as the primary or secondary endpoint of the study and no previous stratification was made according to expected prognosis.

Recently Sideras *et al.* found no survival benefit with use of LMWH in patients with advanced cancer [54]. Similarly, no effect on overall survival was observed in the TOPIC 1 and TOPIC 2 trials [55]. These trials have been reported, so far, only in abstract form, hence details of the clinical results and potentially flaws are not available to better understand the reason for these negative results. Similarly, no effect was demonstrated by the INPACT study, which used the approach of the MALT study [56].

The studies so far published have several limitations, which can be summarized as follows:

- The TNM staging of the disease, the performance status and other clinical prognostic factors are not reported in all studies. Several authors have reported the clinical results by considering two group of patients: those with limited and those with metastatic disease. This type of classification is not informative and the TNM or the AJCC staging system should be used to compare patients with basal similar outcome. This may be an important confounding factor since the performance status and the stage of the disease by themselves are prognostic in cancer patients.
- The schedule of chemotherapy is not documented in all published trials and this introduces a potential bias in the interpretation of the clinical results, since for head and neck, colorectal cancer, gastric cancer, pancreatic and biliary tract cancer patients preferred regimens may improve prognosis.
- The dose of heparin is heterogeneous in the reported trials and the clinical interpretation of the results is problematic, because the heterogeneous dosage cannot be considered as a single entity.
- The duration of treatment is different and this complicates the timing of administration and the best schedule to be administered.

recommendation

There is no evidence to recommend the use of anticoagulation to influence prognosis of cancer [I, B].

note

Levels of evidence [I–V] and grades of recommendations [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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