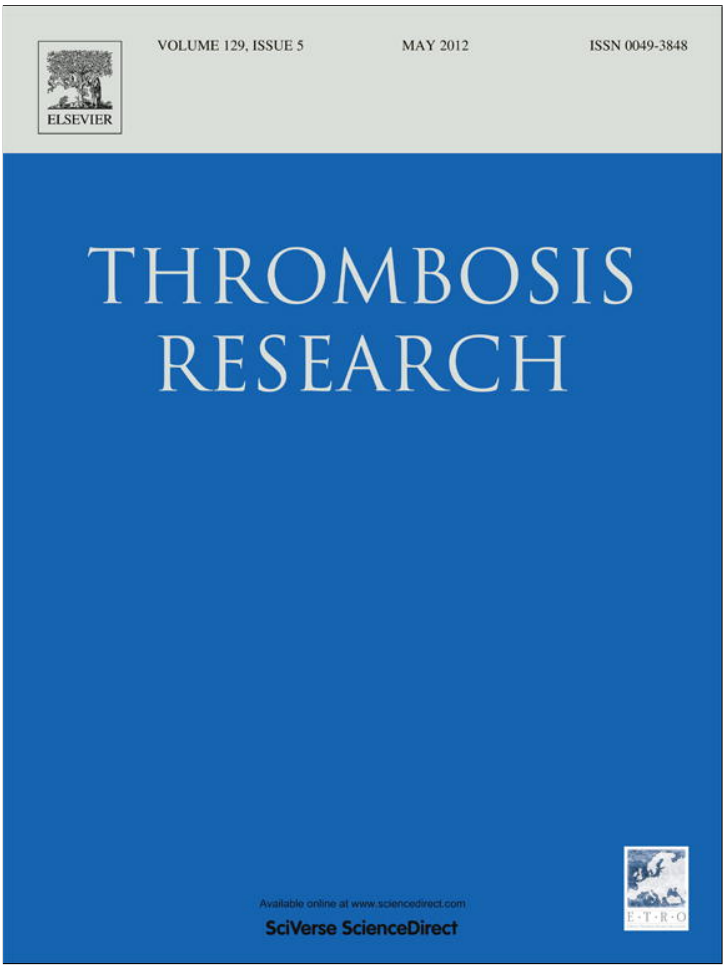

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Regular Article

Prevention of venous thromboembolism in patients with cancer: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET)[1]

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ABSTRACT

Background: Prevention of venous thromboembolism (VTE) in cancer patients remains controversial in most clinical settings.
Purpose: The Italian Society for Haemostasis and Thrombosis (SISET) commissioned a project to develop clinical practice guidelines for the prevention of VTE in patients with malignancy.
Methods: Key questions concerning the prevention of VTE in patients with malignancy were formulated by a multidisciplinary working group consisting of experts in clinical medicine and research. After a systematic review and discussion of the literature, recommendations were formulated and graded according to the supporting evidence. For those questions for which the literature search did not find any definitive answers (due to absence of evidence, low quality evidence and/or contradictory evidence), a formal consensus method was used instead to issue clinical recommendations.
Results: The search for "VTE prevention" resulted in 1021 citations; 69 articles were selected and 24 were used for drafting clinical recommendations. Four areas were graded A to C: 1) Need of prevention (pharmacological and/or mechanical) in cancer patients undergoing major abdominal or pelvic surgery and in 2) those with an acute medical disease requiring hospitalization and who are bedridden. Avoid prevention in 3) cancer patients with a central venous catheter and 4) those on chemotherapy, radiotherapy or hormonal therapy, except patients with multiple myeloma treated with thalidomide/lenalidomide plus high-dose dexamethasone, and those with gastrointestinal or lung cancer. Six areas were considered to be clinically important, but lacked evidence from the literature and thus required a formal consensus (grade D): 1) need of prevention during chemo- radiotherapy or hormonal therapy in patients with previous VTE; 2) optimal duration of pharmacological prevention in patients who are hospitalized/bedridden for acute medical illness; 3) optimal duration of pharmacological prevention in patients undergoing major surgery other than abdominal and pelvic; 4) optimal duration of pharmacological prevention in myeloma patients receiving thalidomide plus dexamethasone; 5) presence of cerebral metastasis as a contraindication to pharmacological prevention; 6) prevention in cancer patients undergoing surgery by laparoscopic procedures lasting>30 min.
Conclusion: Results of the systematic literature review and an explicit approach to consensus techniques have led to recommendations for the most clinically important issues in the prevention of VTE in cancer patients.

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Introduction

Venous thromboembolism (VTE) occurs in up to 20% of cancer patients, and is one of the leading causes of death in patients with cancer [1,2]. Cancer cells can promote the activation of blood coagulation directly by generating thrombin, or indirectly by stimulating endothelial cells and circulating mononuclear cells to synthesise and express several procoagulant factors [3–5].

The risk of thrombosis differs across various cancer subgroups and over the natural history of the disease. The risk of VTE is highest in the initial period after the diagnosis of malignancy [6], but varies according to the type of malignancy and stage of disease. This risk is also high even in patients who may suffer from thrombocytopenia; indeed, recent studies suggest a strong association with haematologic malignancies, particularly lymphomas [6,7].

Cancer chemotherapy has been shown to amplify the procoagulant effect of cancer cells thus increasing the risk for thromboembolic complications [8,9]. Patients with cancer undergoing surgery have a two-fold increased risk of postoperative deep vein thrombosis (DVT) and a three-fold greater risk of developing a fatal pulmonary embolism (PE) compared with patients who do not have cancer having similar surgery [10]. Results from numerous studies have identified the presence of a central venous catheter (CVC) as a risk factor for developing upper-extremity DVT [11], although discrepancies exist concerning the incidence of CVC-related DVT and the efficacy of pharmacological prophylaxis [12].

Unfortunately, the efficacy and safety of the various prophylaxis methods in these categories, as well as the need for prophylaxis among particular patient groups, are not supported by adequate evidence in different contexts, and there are considerably different approaches in clinical practice.

Considering this, the Italian Society for Haemostasis and Thrombosis (SISET) commissioned a project to develop clinical practice guidelines for the prevention of VTE in patients with malignancies. The recommendations were generated through a systematic literature search and formulated accordingly with explicit methods for consensus development.

The objective of the present guidelines was to provide recommendations for the prevention of VTE in cancer patients with particular attention to the topic of chemotherapy-associated thrombosis and areas of uncertainty.

Design and Methods

Methods

These guidelines were issued following a methodology previously defined by the SISET Guidelines Program Steering Group and approved by the SISET Executive Committee. Details on the methodology have been published [13]. The first literature search was performed in December 2005, and updated searches were continued until December 2010. The grading system adopted is the one designed by the Scottish Intercollegiate Guideline Network (SIGN) [14]. The draft recommendations were reviewed by an external panel of two internationally recognized experts in the field and the SISET Executive Committee.

Panel composition

The SISET Executive Committee convened a multidisciplinary working group consisting of experts in clinical medicine and research relevant to the treatment of VTE in patients with cancer, including medical and surgical oncologists.

The executive committee of SISET appointed one chairman (SS) for the development of the present guidelines, and invited an expert panel of 9 members from the society selected for their expertise in research and clinical practice in the prevention of VTE (UA, MC, AF, DI, ACM, DP, MS, MV, AV), one expert oncologist (FF) and one medical practitioner (RL). The panel members are listed in Appendix 1.

The present guidelines focus on adult patients with active, solid and haematological cancers, requiring chemo- radio- or surgical therapy or in any other state that would potentially increase the risk for VTE (such as being bedridden, insertion of CVC). The literature search was performed using the MEDLINE (1966 to 2010) and EMBASE (1980 to 2010) electronic databases. For each topic, two reviewers selected studies independently, with disagreements resolved through discussion and with the opinion of a third reviewer, if necessary. Detailed information on search strategies and results are available upon request. Selected articles were ranked according to a hierarchy of evidence levels, including systematic reviews, controlled clinical trials, uncontrolled clinical trials and case series. In the absence of evidence, a formal consensus method was applied. A detailed description of the organization and methodology of the SISET guidelines is reported elsewhere [13].

Results

Searching for "VTE prevention" resulted in 1021 citations; 69 articles were selected and 24 were used for drafting clinical recommendations.

Recommendations

1. Hospitalized patients with malignancies and concomitant acute medical illness should receive prophylactic doses of LMWH or fondaparinux (grade A)
2. For those at a high risk of bleeding, or others with contraindications to pharmacological prophylaxis, mechanical prophylaxis with intermittent leg compression or graduated stockings should be provided (grade C)
3. In patients undergoing surgery for cancer, pharmacological prophylaxis with UFH, LMWH or fondaparinux should be given for at least 7 days (grade A)
4. In patients undergoing surgery for cancer, mechanical prophylaxis can be given in addition to pharmacological prophylaxis (grade C)
5. In cancer patients undergoing surgery, pharmacological prophylaxis with unfractionated heparin (UFH) or LMWH should be administered preoperatively (grade C)
6. In cancer patients undergoing surgery with major abdominal or pelvic surgery, pharmacological prophylaxis with heparin or fondaparinux should be continued for 4 weeks (grade A)
7. In cancer patients with CVC, routine prophylaxis is not indicated (grade A)
8. Mechanical prophylaxis is indicated in patients with an increased risk of bleeding (grade C)
9. Pharmacological prophylaxis is not routinely recommended in patients undergoing chemotherapy or radiotherapy or hormonal therapy (grade C) except in the following cases:
   - patients with lung or gastrointestinal cancer should receive nadroparin (3,800 U anti-FXa daily) for no more than 4 months (grade A)
   - patients with multiple myeloma treated with thalidomide or lenalidomide plus high-dose dexamethasone should receive LMWH or aspirin or warfarin (Grade C)

Areas of uncertainty

Some areas of uncertainty have been discussed among experts who defined the following consensus grade:

1. Antithrombotic prophylaxis is appropriate in patients with previous VTE who must receive chemotherapy, radiotherapy or hormone therapy (grade D)
2. In cancer patients with concomitant acute medical illness, pharmacological prophylaxis up to 4 weeks is uncertain (grade D)

3. In cancer patients undergoing surgery other than abdominal or pelvic procedures, pharmacological prophylaxis for up to 4 weeks is appropriate (grade D)
4. In patients receiving thalidomide/lenalidomide plus high dose dexamethasone, pharmacological prophylaxis for up to 6 months is appropriate (grade D)
5. In patients with cerebral cancer, pharmacological prophylaxis (when needed) is appropriate (grade D)
6. Pharmacological or mechanical prophylaxis is appropriate in cancer patients undergoing laparoscopic procedures lasting>30 min. (Grade D)

Literature review and analysis

Hospitalized patients

The reported frequency of VTE in hospitalized patients with cancer ranges from 0.6% to 18% [7, 8]. Patients at a particularly high risk for VTE include older patients, patients with cancers of the brain, pancreas, ovary, kidney, bladder, lung, GI tract, or with haematologic malignancies, patients with metastatic disease, and those who are immobilized, neutropenic, or infected. The risk of VTE increases significantly when patients with cancer are hospitalized [8].

Unfortunately, data regarding the efficacy of primary prophylaxis for reducing VTE in this group of cancer patients are lacking since most of the information comes from non-cancer patients [15–19]. Three randomized, multicentre studies investigating pharmacological prophylaxis using either LMWH or fondaparinux in acutely-ill hospitalized patients have been reported [15–17]. In all studies, patients with cancer constituted a minority of the population, and only one provided outcome data for the cancer subset. Previous studies on medical prophylaxis using UFH (5,000 IU given twice daily) in acutely-ill medical patients failed to demonstrate a significant reduction in fatal PE [19], while in other studies UFH given three times daily (5,000 IU) had the same efficacy of LMWH [20]. Recent guidelines on VTE prevention in cancer patients (ACCP guidelines, NCCN, ASCO, AIOM) strongly recommend (1A) pharmacologic prophylaxis with either low-dose UFH or LMWH for bedridden patients with active cancer, although these recommendations are based on clinical trials in which only a minority of patients had cancer [21–25]. However, the low complication rates observed with prophylaxis in the major medical trials appear to justify the use of pharmacologic prophylaxis in hospitalized patients with cancer, even if compliance with thromboprophylaxis is low [25].

Surgical Patients

The presence of malignant disease doubles the risk for DVT [26] with reported incidences of asymptomatic calf vein thrombi of 40% to 80%, proximal-vein thrombi 10% to 20%, PE 4% to 10% and fatal PE 1% to 5% without perioperative thromboprophylaxis. The only factor influencing the risk of VTE, other than those found in non-cancer patients (age = OR 2.6; duration of anaesthesia OR = 4.5; prolonged postoperative immobilization = OR 4.4, and history of a previous episode of VTE = OR 6.0), is advanced stage of disease (OR 2.7) [26]. All patients undergoing major surgical interventions for malignant disease (laparotomy, laparoscopy, or thoracotomy lasting longer than 30 minutes) are considered to be at a high risk for developing VTE; thrombo-prophylaxis in the surgical setting includes pharmacologic and mechanical methods [27]. Pharmacologic methods of thromboprophylaxis include UFH, LMWHs, fondaparinux (an indirect inhibitor of activated factor Xa) and vitamin K antagonists. Potential advantages favouring LMWHs over UFH in cancer surgery prophylaxis include once-daily versus t.i.d. injections and a lower risk of heparin-induced thrombocytopenia [27]. Fondaparinux was found to be at least as effective as dalteparin in preventing VTE in a RCT (randomized clinical trial) of high-risk abdominal surgery patients (68% of the entire study population had cancer). A post-hoc analysis suggested improved efficacy in reducing VTE for fondaparinux versus dalteparin in this large subgroup of patients with cancer [28].

Two recent randomized studies suggest that prolonging the duration of prophylaxis up to 4 weeks is more effective than a shorter duration therapy in reducing postoperative VTE [29, 30]. In a RCT, VTE rates were 4.8% in patients receiving enoxaparin for 4 weeks after surgery for abdominal or pelvic cancer versus 12% in patients receiving enoxaparin for 1 week after surgery ($p<0.02$) [29]. In a second randomized study, patients undergoing major abdominal surgery were randomly assigned to receive either 4 weeks or 1 week of dalteparin prophylaxis. VTE rates were 16.3% in the 1-week arm compared with 7.3% in the 4-week prophylaxis arm ($p<0.012$) [30]. More than half of patients in each arm in this second study underwent cancer surgery. There was no increase in bleeding complications associated with prolonged prophylaxis in either study.

Regarding specific settings, there is little data regarding the benefit of thromboprophylaxis in patients undergoing laparoscopic surgery, and none in the cancer population. In a large retrospective study of patients with prostate cancer undergoing laparoscopic radical prostatectomy, the rate of symptomatic VTE was low (0.5%) [31]. In the absence of prospective data, however, standard prophylactic regimens may be tailored to individual patient risk factors.

Mechanical methods can overcome venous stasis either passively with graduated compression stockings, or actively with intermittent pneumatic calf compression (IPC) or mechanical foot pumps. Recent pooled analyses of studies of all three mechanical methods of thromboprophylaxis, evaluated in different patient populations, indicate that as monotherapy these methods for VTE prevention reduce the frequency of DVT by 66%, but only achieve a modest and insignificant reduction of 31% in the frequency of PE [32]. A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in patients with the highest risk. A Cochrane review of 19 studies showed that low-dose UFH combined with graduated compression stockings was four-times more effective for VTE prevention than low-dose UFH alone [33].

Chemotherapy-associated thrombosis

There is limited data available regarding the prevention of VTE in outpatients with cancer during chemotherapy.

In one study, Levine et al showed that low-dose warfarin is effective in reducing the rate of thrombosis during chemotherapy. In a double-blind randomized trial, 311 patients with metastatic breast cancer were given either very low dose warfarin (1 mg for 6 weeks, subsequently adjusted to achieve a target INR of 1.3 to 1.9) or placebo while receiving chemotherapy. The rate of thrombosis was 0.65% in the warfarin arm and 4.4% in the placebo arm, a statistically-significant 85% risk reduction in the rate of VTE with no increase in bleeding [34]. European investigators presented data in abstract form from two double-blind, placebo-controlled RCTs (TOPIC-1 and TOPIC-2) in patients with metastatic breast cancer or stage III or IV non–small-cell lung carcinoma. Patients were randomly assigned to receive either 6 months of the LMWH, certoparin (3,000 anti-factor Xa units daily) or placebo for the primary prevention of chemotherapy-associated VTE. In patients with breast cancer, there was no observed difference in the rates of VTE (4%), whereas rates of major bleeding complications during the 6 months of treatment were 1.7% for the LMWH arm and 0%for the placebo arm. In patients with lung cancer, there was a non-significant trend toward effectiveness of LMWH prophylaxis, with VTE rates of 4.5% for the LMWH arm and 8.3% for the placebo arm ($p=0.07$). Major bleeding in patients with lung cancer occurred in 3.7% of LMWH treated patients versus 2.2% in the placebo group. In a post-hoc analysis, rates of VTE in patients with stage IV lung cancer who received LMWH were 3.5% compared with 10.1% for those receiving placebo ($p=0.03$) [35].

The risk of VTE in patients receiving thalidomide for multiple myeloma (MM) has been found to range from 17% to 26% in combination with dexamethasone [36,37] and from 12% to 28% in combination with other chemotherapy agents including anthracyclines [38, 39]. Recent prospective studies of thalidomide-containing regimens in patients with MM have suggested the efficacy of LMWH, warfarin at low fixed doses and aspirin for prophylactic anticoagulation. [38–44]. Palumbo et al evaluated the safety and the efficacy of LMWH or low-dose aspirin (ASA) or low-fixed dose warfarin as anticoagulant prophylaxis in a subanalysis of 991 newly-diagnosed MM patients [42]. End-points were: incidence of VTE, acute cardiovascular events, sudden death and major and minor bleeding. Patients receiving thalidomide-containing regimens were randomly assigned to receive LMWH (enoxaparin 40 mg/d, N = 223) or ASA (aspirin 100 mg/d, N = 227) or low-dose warfarin (1.25 mg/d, N = 223) for the duration of induction therapy, while those receiving other anti-myeloma compounds were used as controls. The incidence of VTE was 5% in the LMWH group, 6% in the ASA group and 8% in the warfarin group (p = not significant). VTEs were 2% in the control group. Median time to onset of VTE for patients who received LMWH or ASA or warfarin was 4.7, 2.4 and 2.4 months, respectively. Cavallo et al evaluated the efficacy of LMWH or low-dose ASA as antithrombotic prophylaxis in 402 MM patients receiving lenalidomide and low-dose dexamethasone [45]. End-points were: incidence of VTE, acute cardiovascular events, death, major and minor bleeding. All eligible patients were randomly assigned to receive LMWH (Enoxaparin 40 mg/d, n = 166) or ASA (Aspirin 100 mg/d, n = 176) for the duration of the induction. During the induction phase, the overall incidence of any thrombotic events was 1% in the LMWH group and 2,4% in the ASA group (p = 0.45). Median time to the onset of thrombotic events for patients who received LMWH or ASA was 2.1 and 1 month, respectively.

Agnelli et al. evaluated ambulatory patients with lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer, who were randomly assigned in a double-blind manner to receive subcutaneous injections of nadroparin (3,800 IU anti-Xa once a day, n = 779) or placebo (n = 387) [46]. Study treatment was given for the duration of the chemotherapy for a maximum of 4 months. The primary outcome was the composite of symptomatic venous or arterial thromboembolic events, as assessed by an independent adjudication committee. All randomised patients who received at least one dose of study treatment were included in the efficacy and safety analyses (modified intention-to-treat population). A total of 1150 patients were included in the primary efficacy and safety analyses: 769 patients in the nadroparin group and 381 patients in the placebo group. 15 (2.0%) of 769 patients treated with nadroparin and 15 (3.9%) of 381 patients treated with placebo had a thromboembolic event (single-sided, p = 0.02). Five (0.7%) of 769 patients in the nadroparin group and no patient in the placebo group had a major bleeding event (two-sided, p = 0.18). The incidences of minor bleeding were 7.4% (57 of 769) with nadroparin and 7.9% (30 of 381) with placebo. There were 121 (15.7%) serious adverse events in the nadroparin goup and 67 (17.6%) serious adverse events in the placebo group.

CVC associated-thrombosis

The presence of a central venous catheter (CVC) predisposes cancer patients to upper-extremity DVT [47–51]. In a recent meta-analysis, nine RCTs were evaluated [52]. The use of heparin in cancer patients with CVC was associated with a trend towards a reduction in symptomatic DVT [relative risk (RR) = 0.43; 95% confidence interval (CI): 0.18 to 1.06], but the data did not show any statistically significant effect on mortality (RR = 0.74; 95% CI: 0.40 to 1.36), infection (RR = 0.91; 95% CI: 0.36 to 2.28), major bleeding (RR = 0.68; 95% CI: 0.10 to 4.78) or thrombocytopenia (RR = 0.85; 95% CI: 0.49 to 1.46). The effect of warfarin on symptomatic DVT was not statistically significant (RR = 0.62; 95% CI: 0.30 to 1.27). When studies assessing different types of anticoagulants were pooled, symptomatic DVT rates were significantly reduced (RR = 0.56; 95% CI: 0.34 to 0.92) [53]. Although this area remains controversial, prophylactic doses of LMWH cannot be recommended as thromboprophylaxis for cancer patients with indwelling CVCs, except in particular situations (such as previous thrombosis or additional known individual risk factors) [12,53].

Discussion

Patients with cancer represent a high-risk population for VTE although its prevention remains a challenge in terms of both treatment-associated toxicities and scarcely-available evidence. Notwithstanding these limits, in the last years at least three guidelines have been published addressing VTE prevention in cancer patients. The ACCP guidelines on antithrombotic and thrombolytic therapy included chapters on the prevention and treatment of VTE [21–25], but did not focus specifically on cancer patients, even if selected issues related to patients with cancer were discussed. The National Comprehensive Cancer Network (NCCN) VTE Panel was convened in 2005, and its most recent guidelines were published in 2008 [21]. All aspects of VTE (prophylaxis, treatment and related-complications) were discussed and presented in flow-charts; some issues, however, were not discussed but left to further evidence from clinical trials (such as VTE prophylaxis in patients with prolonged thrombocytopenia, VTE prophylaxis in patients with history of CVC-related DVT and extended VTE prophylaxis in medical oncology patients). The ASCO committed a comprehensive systematic review of the medical literature on the prevention and treatment of VTE in cancer patients; the comprehensive search included the use of electronic databases through the end of 2006. These guidelines focused the need of antithrombotic prophylaxis in selected settings: 1) hospitalized patients with cancer, 2) those receiving systemic chemotherapy, 3) those undergoing surgery and, finally, 4) the impact of anticoagulants on cancer patient survival [24]. The Italian Association of Medical Oncology (AIOM) has published recommendations to instruct clinical practice in the management of VTE in patients with cancer [23]. These recommendations are comprehensive and focus on six different aspects, including VTE associated with occult cancer, prophylaxis of VTE in cancer surgery, prophylaxis of VTE during chemotherapy or hormonal therapy, prophylaxis of VTE associated with central venous catheters, treatment of VTE in patients with cancer, and anticoagulation and prognosis of cancer. A recent update of the AIOM guidelines has been published, but it contains only a few recommendations regarding VTE prophylaxis [22,23].

Our guideline offers explicit recommendations for the use of anticoagulation and other measures for the prevention of VTE in hospitalized patients with cancer and those receiving cancer chemotherapy on an ambulatory basis, patients with cancer in the perioperative and postoperative period and those with recent VTE. We also give recommendations on areas of uncertainty that meet clinically important issues, such as patients with previous VTE who are eligible for chemotherapy, radiotherapy or hormone therapy, duration of VTE prophylaxis in medical cancer patients, subgroups of cancer patients who are candidates for low-risk surgical approaches, or those with cerebral cancer who require pharmacological antithrombotic prophylaxis. Nevertheless, the available data addressing these and related issues are limited, and there still remains the need for additional research, particularly in the form of large, well-designed, randomized, controlled clinical trials.

In conclusion, hospitalized patients with cancer should be considered candidates for VTE prophylaxis in the absence of specific contraindications, such as active bleeding, even if the recommendations for VTE prophylaxis are based on clinical trials that enrolled, in most cases, only a small proportion of patients with cancer. There is little data available regarding the prevention of VTE in outpatients with cancer. Additional studies are needed to further evaluate the potential risk of VTE and the value of primary prophylaxis in patients receiving novel targeted therapies, particularly the class of antiangiogenic agents.

Regarding major surgical intervention for malignant disease, all patients should be considered for thromboprophylaxis for at least 7 days postoperatively; prolonged prophylaxis for up to 4 weeks may be considered in high-risk patients, even if additional studies are needed to better define the risk-benefit profile of prolonged anticoagulation.

Conflict of interest statement

Nothing declared.

Appendix 1

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