Miriam J. Johnson[1], Simon I.R. Noble[2], Anthony Maraveyas[3]

[1]Senior Lecturer in Palliative Medicine, Hull and York Medical School, University of Hull
[2]Clinical Senior Lecturer in Palliative Medicine, Cardiff University
[3]Senior Lecturer and Consultant in Medical Oncology, Department Haematology & Oncology, Hull and York Medical School, University of Hull

Antithrombotic therapy in palliative care

Abstract

Management of venous thromboembolism (VTE) in patients in advanced cancer can be difficult due to the increased risk of recurrent and extending VTE despite therapeutic anticoagulation, and of bleeding due to or exacerbated by anticoagulation. Currently, best practice is long term administration of low molecular weight heparin (LMWH), but a recurrent VTE and bleeding rate remains, and some patients have contra-indications to anticoagulation. Newer anticoagulants such as oral anti-thrombin agents and biotinylated idrapurinux may have a role in the future.

Key words: palliative care, cancer, low molecular weight heparin, anticoagulation

Adv. Pall. Med. 2009; 8, 3: 95–100

Introduction

Cancer patients have an increased risk of VTE compared with patients without cancer due to the secretion of cancer-related procoagulants, which increase with advancing disease [1–5]. Up to 15% of cancer patients are estimated to develop clinically apparent VTE, although this is likely to be an underestimate of the problem [1, 4). The prevalence of both symptomatic and undiagnosed VTE in advanced disease is thought to be as high as 52%, which is in keeping with post-mortem studies [6–8]. Recent work with patients with advanced cancer of the pancreas — one of the most thrombogenic tumours — highlights the problem of "early death burden" in clinical trials, that is, death within 12 weeks, which affects nearly a quarter of participants [9]. The pilot work with chemo-anticoagulation in this highly thrombogenic cancer suggests that up to 75% of early death burden in pancreatic cancer patients could be due to hitherto unrecognised and unreported VTE. The coexistence of VTE with cancer has been shown in a number of studies to have significant negative impact on survival [10, 11].

Most of these data however pertain to the relatively fit ambulant patients with cancer. The data for the poor performance status patients (ECOG > 2 or Karnofsky < 60) which form the bulk of the conventional "palliative" caseload are much less robust. This review aims to summarise these and offer some insight into best practice and avenues of much needed further research.

Concerns regarding patients with advanced cancer

Management of patients with VTE and cancer, especially those with advanced disease, can be

Address for correspondence: Miriam J. Johnson
St. Catherine's Hospice, Throxenby Lane, Scarborough, N Yorks, YO12 5RE
Tel: 01723 351421, fax: 01723 356033
e-mail: miriam.johnson@hyms.ac.uk

Advances in Palliative Medicine 2009, 8, 95–100

fraught with difficulty as there is an increased risk of both bleeding with, and further episodes of VTE despite, anticoagulation, particularly with warfarin compared with non-cancer patients [12–24]. The risk becomes greater with progressive cancer [24] and thus clinical decision-making may not be easy in patients for whom the focus of treatment is palliative, but who are not imminently dying. The risk worsens with advanced disease not only because of increased risk of ulcerating lesions or tumour masses compressing venous return, but because of worsening disseminated intravascular coagulation (DIC) which results in increasing activation of the coagulation cascade and a tendency to bleed. In addition, thrombocytopenia, due to marrow invasion or as a complication of treatment, increases the risk of bleeding. This is also the patient group for whom even a relatively minor insult such as a small pulmonary embolus (PE) or minor deep vein thrombosis (DVT) may have a disproportionately large impact on quality of life at a time when time itself is precious.

Current guidance

Warfarin is less effective and may carry a higher risk of bleeding than LMWH in patients with advanced cancer. Four randomised controlled studies comparing warfarin and long-term low molecular weight heparin (LMWH) treatment indicate that LMWH is more effective at preventing recurrent VTE in cancer patients [15, 18, 20, 21]. One of these studies also showed LMWH to be safer in terms of bleeding complications [15]. It is difficult to judge the number of patients with advanced disease included in these studies, indeed, two excluded patients with poor performance status (ECOG 3 and 4) [18, 20]. However, over 40% of patients in each study were classed as having metastatic disease or were no longer receiving active treatments for their cancer. These studies did not show worse bleeding with warfarin. It is therefore hard to apply these results to a population with advanced cancer where clinicians may be so concerned about the risks of treatment that they are reluctant to treat at all, or to treat at a reduced dose in an attempt to minimise risk [25]. A recent systematic review and meta-analysis has attempted to apply this evidence base to patients with advanced disease [26], and a more in depth discussion of the particular issues facing patients with advanced disease and VTE is also available [27].

Application to advanced disease

A prospective cohort study of cancer patients with VTE treated with warfarin showed a clear increased risk of recurrent thrombosis with advanced disease; extensive disease — hazard ratio; 4.6, moderately extensive — hazard ratio; 5.3 and less extensive disease — hazard ratio; 1.9. For bleeding, the differential hazard ratios were: 4.8 for extensive disease, 2.5 for moderately extensive and 0.5 for less extensive [24]. Other prospective cohort and retrospective studies have shown a high risk of bleeding in cancer patients anticoagulated with warfarin. Thus treating with long-term LMWH seems to be the most effective and safe approach in patients with advanced disease for whom anticoagulation is deemed to be appropriate.

Monreal et al. published the results of a prospective cohort of 203 cancer patients with disseminated disease and VTE treated with a modified dose long-term LMWH regime [28]. This patient group therefore, does seem to match more closely the population of concern. In an attempt to reduce the risk of anticoagulant related bleeding, patients were treated with full weight adjusted treatment dose of Dalteparin for 7 days, and the dose reduced to 10,000 u daily thereafter. There was further dose reduction if the patient had thrombocytopenia. Major bleeding occurred in 5.4% which compares with 6–7% [20, 21] on full dose LMWH. 8.9% had recurrent VTE which compares with 2.8–8% [20, 21] on full dose LMWH.

Occasionally, patients with advanced disease may need to be considered for unfractionated heparin (UFH) therapy. This is usually in specific circumstances e.g. peri-operatively in a patient with cancer and VTE, in whom the risk of recurrent/progressive VTE is too high to risk stopping the LMWH for very long, and the flexibility of UFH's short half life and ability to completely reverse with protamine sulfate is useful. Another indication for UFH would be for patients with renal failure on haemodialysis. Occasionally, a cancer patient will have VTE resistant to LMWH because of tumour driven direct thrombin activation which will bypass the factor Xa inhibiting activity of LMWH. It is hoped that the new oral thrombin inhibitors would have a role to play in the future and this is discussed later in this article. However, it is unclear yet whether the theoretical benefit of direct thrombin inhibition will bring with it an increased risk of bleeding.

There is little published work specifically looking at patients with advanced cancer and no randomised

controlled trials. A survey of UK palliative physicians showed that only 20% thought that they would anticoagulate hospice out-patients with VTE, and only 6% would anticoagulate hospice in-patients [25]. Specific concerns raised were problems of drug interactions, INR control and bleeding with warfarin. Some would opt for using very low dose warfarin (1mg per day) thus providing less effective secondary VTE prevention and a continued risk of bleeding. The survey was carried out in the 1990s and is therefore now out of date, but even then there was a move to use LMWH in these patients in preference to warfarin, if anticoagulation was to be considered. Interestingly, for a single postal questionnaire survey, there was a high response rate (75%) indicating that this was considered an important area.

What about the patient who is bleeding?

There is no published evidence to guide the clinician in this particularly challenging situation and management should be tailored to the individual after full discussion of the risks of each treatment option [27]. A sensible first step is to try and stop the bleeding if possible. If this is not possible, then mild, nuisance bleeding such as mild epistaxis or haemoptysis should not prevent anticoagulation in patients with symptomatic proximal DVT or PE involving segmental or more central pulmonary arteries in whom the risk of clinically significant PE is high. If the bleeding is from a visible, easily monitored and unlikely life-threatening source then full anticoagulation should commence (or be continued) but be followed up carefully. If the bleeding is due to mucosal involvement by tumour, such as bowel, duodenal, bladder or vaginal disease a more cautious approach of reduced or even prophylactic doses should be used and the patient monitored closely. The haemostatic properties of a palliative course (usually a single or a couple of fractions) of radiation should not be forgotten as it tends not to be too onerous for the poor performance patient and rarely adds to the morbidity [29]. If haemoglobin remains stable and bleeding does not worsen, the dose can be slowly titrated up. A twice daily LMWH regime, rather than once daily, may smooth out peaks and troughs in anticoagulation level. If there is active bleeding of a more serious and potentially life threatening nature (intracranial, retroperitoneal or upper gastrointestinal bleeding), then anticoagulation is contraindicated. A vena caval filter may be considered for patients with proximal DVT.

Vena caval interruption

There is no evidence that insertion of a vena caval filter improves outcome for cancer patients with VTE who are bleeding and published studies are too small for useful conclusions [30–35]. However, for patients with contraindications to anticoagulation, or who continue to embolise despite therapeutic anticoagulation, there is little other option and individual patients may gain some benefit. Filter insertion does not suppress the underlying hypercoagulable state, and there is concern that its presence may even stimulate clot extension. In addition, fatal PE can still result from thrombus formation in the vena cava proximal to the filter, and this complication has been reported in cancer patients. Filters can be permanent, or if only a temporary cessation of anticoagulant therapy is needed, e.g. peri-operatively, retrievable ones may be used.

What about primary thromboprophylaxis?

Noble et al. [36] has published a telephone survey of palliative physician opinion and practice regarding VTE primary prophylaxis. They compared opinion and practice from 2000 (74% response) and 2005 (91% response). Over this time practice changed from 62% physicians in 2000 routinely stopping VTE prophylaxis even in high risk good prognosis patients, to only 18% in 2005. The authors suggest that there is a growing awareness of the problem of VTE in patients with advanced cancer amongst palliative physicians and a growing perception that LMWH is an acceptable form of anticoagulation — at least for primary prophylaxis [37].

What happens if the patient is not anticoagulated?

Untreated, the risk of further VTE, either extension or recurrence, is thought to be high, although hard to ascertain from the literature, and may range from no symptoms, to debilitating symptoms, to early death from catastrophic cardiovascular collapse. Post mortem studies show that 50% of proximal DVTs embolise to the lungs [38] but it is less easy to ascertain which of these are of clinical significance. VTE is a great mimic clinically and further post-mortem evidence suggests that it is poorly recognised; treated as pneumonia or myocardial infarction [38]. Havig [38] also showed that 25% of patients took over an hour to die, with two-thirds

of the abruptly dead having symptoms of "advertising emboli"; thus even fatal PE may be the cause of considerable morbidity that is potentially preventable or treatable.

Obtaining data in patients that have had a VTE and who have not been anticoagulated is difficult. The closest we can come to obtaining reasonable figures is to study patients with DVT who have had a vena caval filter inserted because of an absolute contraindication to systemic anticoagulation [39–43]. Such data suggests a thrombosis rate of 7–10% per month (of which approximately half will be symptomatic) during the first 3 months following insertion of a device. Further data can be obtained from the more modern retrievable filters that once again tend to be used without anticoagulants and are removed fairly quickly (usually recommended to be taken out before 3 months) [44, 45].

Clinicians may consider that for advanced cancer patients, a fatal PE is a "quick and easy" or "nice" way to go [46]. However, as described above, the evidence suggests that this is not necessarily so. As clinical decision making moves further away from the traditional paternalistic model to a patient-centred one, we need to understand, not only the RCT evidence based for management options, but also how the patient feels about them, and what risks are acceptable to them. We know from previous work in lung cancer patients, that a significant group would be prepared to accept a much higher risk from chemotherapy treatment for a smaller gain, than their clinicians [47].

We are also aware that cancer patients value being included in decisions regarding VTE primary prophylaxis, feeling that they were still being considered for the best treatment and not being "given up on" [37].

The unpredictable nature of recurrent VTE may also be a problem for a group of patients for whom "last goals" are important, such as family events and a relatively sudden, but unpleasant death can contribute to family distress in bereavement. In a recent study, Noble et al. demonstrated that patients wish to be included in treatment decisions and not treated with clinical paternalism with this regard, at least with VTE prophylaxis [37].

Future therapeutic options and indications

The release of new oral Xa inhibitors (e.g. Rivaroxaban) and direct thrombin inhibitors (e.g. Dabigatran, Apixaban) are a potentially exciting development in the prevention and treatment of VTE in the palliative care setting. Currently they are only licensed in the primary thromboprophylaxis of elective hip and knee surgery but are being evaluated for a breadth of primary and secondary thromboprophylaxis indications. If demonstrated to be as efficacious and safe as the LMWHs they will have a profound impact on the management of palliative care patients with respect to quality of life and health resource usage.

Other attractive options include idrapurinux which is a synthetic pentasaccharide with a very high affinity for antithrombin. It has a long half life which enables a once weekly injection which may be an attractive alternative for palliative care patients. However, concerns about major bleeding, of especial concern given its long half life, have limited its acceptance in patients with advanced disease. Recently, though, a biotinylated form of idrapurinux has been introduced into clinical trials which allow neutralisation of anticoagulant effect using avidin, providing a potentially useful way round this problem.

Anticancer effects of anticoagulants

There is small but developing research evidence of possible direct antineoplastic effects of anticoagulants. In vitro studies have shown that warfarin, heparin, fibrinolytics, and even antiplatelet agents inhibit tumor growth and metastasis [48]. Thrombin and fibrin have been found to contribute to the adhesion and implantation of tumor cells, so antifibrin or antithrombin agents might exert their effects by inhibiting this implantation. Furthermore, heparin has been found to inhibit vascular endothelial growth factor, tissue factor, and platelet-activating factor, each of which may contribute to angiogenesis. It has also been hypothesized that fibrin deposits around tumors may offer protection against immune surveillance, so that anticoagulants might aid in immune clearance of small deposits of cancer cells. More recently a major anti-neoplastic, anti-metastatic effect of the heparins has been shown to be mediated through anti P and E- selectin properties [49].

Although this is an exciting area, in the recent meeting at the American Society of Hematology (2008), major opinion leaders in the field (Zacharski, Varki) expressed the view that the effect of these agents is more likely to be relevant in the earlier stages of cancer (e.g adjuvant setting) or in the very fit population of cancer patients with small volume

disease that may have time for the impact of protection against further increase in tumour burden to have a practical, measurable impact on survival. It is for these reasons that the likelihood that the more end-stage spectrum of cancer patients seen with advanced disease may not be those who will experience significant improvement from direct antineoplastic effects of these agents as developed at present. Potentially however, combinations of nontoxic agents that can deliver tumour stasis through inhibition of complex mechanisms including those of the anticoagulation pathways without the need for concurrent aggressive anticancer treatment may benefit even the patients with advanced cancer in the future.

Future challenges

The holistic, individualised nature of palliative care makes it difficult to develop blanket guidelines that are applicable to a heterogeneous population covering a breadth of histology, stage, performance status and prognosis. Clearly not all palliative care patients will benefit from prophylaxis or treatment of an established VTE and the challenge remains for us to identify those that are likely to benefit without burdening those who will not.

Robust, properly powered studies with appropriate outcome measures are required, but the challenges of conducting such clinical trials in the palliative setting cannot be underestimated. To answer such questions will require wide collaboration from many clinical units if sufficient numbers are to be recruited to future palliative care VTE studies.

References

1. Bick R.L. Alterations of hemostasis associated with malignancy: etiology, pathophysiology, diagnosis and management. Semin. Thromb. Hemost. 1978; 5: 1–26.
2. Johnson M.J., Walker I.D., Sproule M.W., Conkie J. Abnormal coagulation and deep venous thrombosis in patients with advanced cancer. Clin. Lab. Haematol. 1999; 21: 51–54.
3. Kakkar A.K., DeRuvo N., Chinswangwatanakul V., Tebbutt S., Williamson R.C. Extrinsic-pathway activation in cancer with high factor VIIa and tissue factor. Lancet 1995; 346: 1004–1005.
4. Levitan N., Dowlati A., Remick S.C., Tahsildar H.I., Sivinski L.D., Beyth R. et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine (Baltimore) 1999; 78: 285––291.
5. Sampson M.T., Kakkar A.K. Coagulation proteases and human cancer. Biochem. Soc. Trans. 2002; 30: 201–207.
6. Ambrus J.L., Ambrus C.M., Mink I.B., Pickren J.W. Causes of death in cancer patients. J. Med. 1975; 6: 61–64.
7. Johnson M.J., Sproule M.W., Paul J. The prevalence and associated variables of deep venous thrombosis in patients with advanced cancer. Clin. Oncol. (R. Coll. Radiol.) 1999; 11: 105–110.
8. Sproul E.E. Carcinoma and venous thrombosis: the frequency of association of carcinoma in the body or tail of the pancreas with multiple venous thrombosis. Am. J. Cancer 1938; 34: 566–585.
9. Sgouros J., Maraveyas A. Excess premature (3-month) mortality in advanced pancreatic cancer could be related to fatal vascular thromboembolic events. A hypothesis based on a systematic review of phase III chemotherapy studies in advanced pancreatic cancer. Acta. Oncol. 2008; 47: 337–346.
10. Mandala M., Reni M., Cascinu S. et al. Venous thromboembolism predicts poor prognosis in irresectable pancreatic cancer patients. Ann. Oncol. 2007; 18: 1660–1665.
11. Alcalay A., Wun T., Khatri V. et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. J. Clin. Oncol. 2006; 24: 1112–1118.
12. Chan A., Woodruff R.K. Complications and failure of anticoagulation therapy in the treatment of venous thromboembolism in patients with disseminated malignancy. Aust. N. Z. J. Med. 1992; 22: 119–122.
13. Clarke-Pearson D. Anticoagulation therapy for VTE in patients with gynaecologic malignancy. Coleman R.E., Synan I.S., Hinshaw W., Creaseman W.T. (eds). Am. J. Obstet. Gynecol. 1987; 147: 369–375.
14. Debourdeau P., Meyer G., Sayeg H. et al. [Classical anticoagulant treatment of venous thromboembolic disease in cancer patients. Apropos of a retrospective study of 71 patients]. Rev. Med. Interne 1996; 17: 207–212.
15. Deitcher S.R., Kessler C.M., Merli G., Rigas J.R., Lyons R.M., Fareed J. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin. Appl. Thromb. Hemost. 2006; 12: 389–396.
16. Gitter M.J., Jaeger T.M., Petterson T.M., Gersh B.J., Silverstein M.D. Bleeding and thromboembolism during anticoagulant therapy: a population-based study in Rochester, Minnesota. Mayo Clin. Proc. 1995; 70: 725–733.
17. Harrington K.J., Bateman A.R., Syrigos K.N. et al. Cancer-related thromboembolic disease in patients with solid tumours: a retrospective analysis. Ann. Oncol. 1997; 8: 669–673.
18. Hull R.D., Pineo G.F., Brant R.F. et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am. J. Med. 2006; 119: 1062–1072.
19. Krauth D., Holden A., Knapic N., Liepman M., Ansell J. Safety and efficacy of long-term oral anticoagulation in cancer patients. Cancer 1987; 59: 983–985.
20. Lee A.Y., Levine M.N., Baker R.I. et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N. Engl. J. Med. 2003; 349: 146–153.
21. Meyer G., Marjanovic Z., Valcke J. et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch. Intern. Med. 2002; 162: 1729–1735.
22. Moore F.D., Jr., Osteen R.T., Karp D.D., Steele G., Jr., Wilson R.E. Anticoagulants, venous thromboembolism, and the cancer patient. Arch. Surg. 1981; 116: 405–407.
23. Paloretti G. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous thromboembolic disease in patients with or without malignan-

cy. Legnani C., Lee A. (eds.). Thromb. Haemost. 2000; 84: 805–810.
24. Prandoni P., Lensing A.W., Piccioli A. et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002; 100: 3484–3488.
25. Johnson M.J., Sherry K. How do palliative physicians manage venous thromboembolism? Palliat. Med. 1997; 11: 462–468.
26. Noble S.I., Shelley M.D., Coles B., Williams S.M., Wilcock A., Johnson M.J. Management of venous thromboembolism in patients with advanced cancer: a systematic review and meta-analysis. Lancet Oncol. 2008; 9: 577–584.
27. (AUTOR)Venous thromboembolism in advanced disease: a clinical guide. Oxford University Press, Oxford 2008.
28. Monreal M., Zacharski L., Jimenez J.A., Roncales J., Vilaseca B. Fixed-dose low-molecular-weight heparin for secondary prevention of venous thromboembolism in patients with disseminated cancer: a prospective cohort study. J. Thromb. Haemost. 2004; 2: 1311–1315.
29. Biswal B.M., Lal P., Rath G.K., Mohanti B.K. Hemostatic radiotherapy in carcinoma of the uterine cervix. Int. J. Gynaecol. Obstet. 1995; 50: 281–285.
30. Calligaro K.D., Bergen W.S., Haut M.J., Savarese R.P., DeLaurentis D.A. Thromboembolic complications in patients with advanced cancer: anticoagulation versus Greenfield filter placement. Ann. Vasc. Surg. 1991; 5: 186–189.
31. Cohen J.R., Tenenbaum N., Citron M. Greenfield filter as primary therapy for deep venous thrombosis and/or pulmonary embolism in patients with cancer. Surgery 1991; 109: 12–15.
32. Olin J.W., Young J.R., Graor R.A., Ruschhaupt W.F., Beven E.G., Bay J.W. Treatment of deep vein thrombosis and pulmonary emboli in patients with primary and metastatic brain tumors. Anticoagulants or inferior vena cava filter? Arch. Intern. Med. 1987; 147: 2177–2179.
33. Walsh D.B., Downing S., Nauta R., Gomes M.N. Metastatic cancer. A relative contraindication to vena cava filter placement. Cancer 1987; 59: 161–163.
34. Whitney B.A., Kerstein M.D. Thrombocytopenia and cancer: use of the Kim-Ray Greenfield filter to prevent thromboembolism. South Med. J. 1987; 80: 1246–1248.
35. Zerati A.E., Wolosker N., Yazbek G., Langer M., Nishinari K. Vena cava filters in cancer patients: experience with 50 patients. Clinics 2005; 60: 361–366.
36. Noble S.I., Finlay I.G. Have palliative care teams' attitudes toward venous thromboembolism changed? A survey of thromboprophylaxis practice across British specialist palliative care units in the years 2000 and 2005. J. Pain Symptom Manage 2006; 32: 38–43.
37. Noble S.I., Nelson A., Turner C., Finlay I.G. Acceptability of low molecular weight heparin thromboprophylaxis for inpatients receiving palliative care: qualitative study. BMJ 2006; 332: 577–580.
38. Havig O. Deep venous thrombosis and pulmonary embolism: An autopsy study with multiple regression analysis of possible risk factors (ADRES?) 1977.
39. Kolachalam R., Julian T. Clinical presentation of thrombosed Greenfield filters. Vascular Surgery 1990; 24: 666––670.
40. Tardy B., Mismetti P., Page Y. et al. Symptomatic inferior vena cava filter thrombosis: clinical study of 30 consecutive cases. Eur. Respir. J. 1996; 9: 2012–2016.
41. Murphy T.P., Dorfman G.S., Yedlicka J.W. et al. LGM vena cava filter: objective evaluation of early results. J. Vasc. Interv. Radiol. 1991; 2: 107–115.
42. Millward S.F., Marsh J.I., Peterson R.A. et al. LGM (Vena Tech) vena cava filter: clinical experience in 64 patients. J. Vasc. Interv. Radiol. 1991; 2: 429–433.
43. Streiff M.B. Vena caval filters: a comprehensive review. Blood 2000; 95: 3669–3677.
44. Asch M.R. Initial experience in humans with a new retrievable inferior vena cava filter. Radiology 2002; 225: 835–844.
45. Millward S.F., Oliva V.L., Bell S.D. et al. Gunther Tulip Retrievable Vena Cava Filter: results from the Registry of the Canadian Interventional Radiology Association. J. Vasc. Interv. Radiol. 2001; 12: 1053–1058.
46. Noble S.I., Nelson A., Finlay I.G. Factors influencing hospice thromboprophylaxis policy: a qualitative study. Palliat. Med. 2008; 22: 808–813.
47. Slevin M.L., Stubbs L., Plant H.J. et al. Attitudes to chemotherapy: comparing views of patients with cancer with those of doctors, nurses, and general public. BMJ 1990; 300: 1458–1460.
48. Hejna M., Raderer M., Zielinski C.C. Inhibition of metastases by anticoagulants. J. Natl. Cancer Inst. 1999; 91: 22––36.
49. Varki N.M., Varki A. Heparin inhibition of selectin-mediated interactions during the hematogenous phase of carcinoma metastasis: rationale for clinical studies in humans. Semin. Thromb. Hemost. 2002; 28: 53–66.