Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study

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Summary

Background Clinical trials are needed to assess the clinical benefit of antithrombotic prophylaxis in patients with cancer who are receiving chemotherapy, since these patients are at an increased risk of developing a thromboembolism. We did a trial to assess the clinical benefit of the low-molecular-weight heparin nadroparin for the prophylaxis of thromboembolic events in ambulatory patients receiving chemotherapy for metastatic or locally advanced solid cancer.

Methods Between October, 2003, and May, 2007, ambulatory patients with lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer were randomly assigned in a double-blind manner to receive subcutaneous injections of nadroparin (3800 IU anti-Xa once a day, n=779) or placebo (n=387), in a 2:1 ratio. Study treatment was given for the duration of chemotherapy up to a maximum of 4 months. The primary study 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). The study is registered with ClinicalTrials.gov, NCT 00951574.

Findings 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 patients 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.

Interpretation Nadroparin reduces the incidence of thromboembolic events in ambulatory patients with metastatic or locally advanced cancer who are receiving chemotherapy. Future studies should focus on patients who are at a high risk for thromboembolic events.

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Introduction

Thromboembolic events are common in patients with cancer,[1,2] make patient management more complicated, and are associated with increased mortality.[3,4] 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.[5] The risk of thromboembolic events in cancer patients varies according to the type of malignancy and its disease stage, and it is increased by surgical and non-surgical cancer treatments.[6] Cancer chemotherapy has been shown to both amplify the prothrombotic effect of cancer cells[5] and to damage vessel walls directly, and is increasingly recognised as a risk factor for thromboembolic complications.[7,8]

Thromboembolism is a frequent complication in hospitalised and bedridden patients with cancer,[9] but fewer data are available for ambulatory patients with cancer. A pivotal study by Levine and colleagues[10] showed warfarin prophylaxis was effective at reducing the risk of thromboembolism in patients with advanced breast cancer who were receiving chemotherapy. The clinical benefit was also assessed in patients with advanced lung cancer.[11] However, there is a paucity of evidence from randomised studies regarding the clinical benefit of antithrombotic prophylaxis in patients with cancer who are undergoing chemotherapy. Consequently, the most recent guidelines of the American Society of Clinical Oncology[12] and the Conference on Antithrombotic Therapy of the American College of Chest Physicians[13] state that clinical trials are required before any recommendations can be made about the use of antithrombotic prophylaxis in ambulatory patients receiving chemotherapy for cancer, although the

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guidelines do recommend antithrombotic prophylaxis in hospitalised and bedridden patients with cancer.

The PROTECHT (PROphylaxis of ThromboEmbolism during CHemoTherapy) was a randomised, placebo-controlled, multicentre study aimed at assessing the efficacy of the low-molecular-weight heparin nadroparin for the prophylaxis of thromboembolic events in ambulatory patients receiving chemotherapy for metastatic or locally advanced solid cancer.

Methods

Patients

Ambulatory patients older than 18 years of age who were receiving chemotherapy for metastatic or locally advanced lung, gastrointestinal (stomach, colon, or rectum), pancreatic, breast, ovarian, or head and neck cancer were recruited to the study at 62 centres across Italy between October, 2003, and May, 2007.

Patients on adjuvant or neoadjuvant chemotherapy were excluded from the study. Other exclusion criteria were: objectively confirmed venous or arterial thromboembolism in the past 3 months; antithrombotic treatment for any indication; life expectancy of less than 3 months; Eastern Cooperative Oncology Group score greater than 2; active bleeding or bleeding requiring hospitalisation or transfusion or surgical intervention in the past 4 weeks; intracranial bleeding in the past 6 months; high risk of bleeding (international normalised ratio or activated partial thromboplastin time ratio above 1·3, or platelet count lower than 50×10^9/L); known active gastric or duodenal ulcer; known cerebral metastasis; severe and uncontrolled hypertension; renal impairment (creatinine concentration >0·025 mg/mL); substantial liver insufficiency; and known hypersensitivity to heparin and derivates.

The study was done in accordance with the provisions of the Declaration of Helsinki and local regulations. The protocol was approved by the institutional review board at each study centre, and written informed consent was obtained from all patients before randomisation.

Procedures

Eligible patients were randomly assigned to receive either subcutaneous injections of nadroparin (3800 IU anti-Xa once a day) or placebo in a 2:1 ratio. The 2:1 randomisation ratio was chosen to minimise the number of patients exposed to parenteral placebo. The dose of low-molecular-weight heparin was chosen as recommended for the prophylaxis of venous thromboembolism in high-risk patients.

Study treatment was started on the same day as chemotherapy (the first cycle or a new course), and was given for the duration of chemotherapy or up to a maximum of 120 days (±10 days). If the duration of chemotherapy was less than 4 months, study treatment was given after the last cycle of chemotherapy for a period of time equal to the duration of the last cycle. Antiplatelet agents, oral anticoagulants, fibrinolytic agents, unfractionated heparin or low-molecular-weight heparin other than nadroparin were not allowed during the study period. The administration of non-steroidal anti-inflammatory drugs was allowed with caution if considered necessary, and was monitored closely. Paracetamol was recommended as the first step for analgesic or anti-inflammatory treatment. All concomitant therapies were fully reported in case-report forms along with their daily dosage, duration, and reason for administration.

The primary efficacy outcome was the composite of symptomatic deep-vein thrombosis of lower or upper limbs, pulmonary embolism, visceral or cerebral venous thrombosis, acute myocardial infarction, ischaemic stroke, acute peripheral arterial thromboembolism, and unexplained death of possible thromboembolic origin occurring during the study treatment plus 10 days. The secondary efficacy outcomes were asymptomatic thromboembolic events incidentally diagnosed, survival at the end of study treatment and at 12 months, superficial thrombophlebitis of the lower limbs, response to chemotherapy and, for patients with central venous catheters, central-venous-catheter-related complications of possible thrombotic origin. In a subgroup of patients, biological markers of activation of blood coagulation were collected before and at the end of study treatment; the results of these assays will be reported elsewhere.

Major bleeding that occurred between randomisation and 48 h after the last injection of the study drug was the main safety outcome. A bleeding event was defined as major if it was fatal or clinically overt and associated with a decrease in haemoglobin concentration of at least 0·02 g/mL over a 48-h period, or with transfusion of two or more units of whole blood or red cells, or occurred in a critical organ (brain, spine, pericardium, retroperitoneum, or eye), or required an invasive intervention.[14] All other overt bleeding events were considered to be minor.

All study outcomes were assessed by a central independent adjudication committee whose members were unaware of patients' study-group allocation. The adjudication committee reviewed all cases of death that occurred during the study period.

Patients were seen regularly at their scheduled chemotherapy visits. Additional study visits were done at the occurrence of clinically suspected thromboembolic events. If patients had symptoms of venous or arterial thromboembolism, they underwent confirmative diagnostic work-up. Patients were followed up for survival at 12 months after study inclusion.

A data and safety monitoring board was responsible for the assessment of safety and efficacy during the course of this clinical trial. This was done at pre-specified meetings to review interim analyses.

Randomisation and masking

The randomisation list was generated by an independent statistician who used a standard permuted block of six

without stratification. The list was generated with SAS version 8.2. The allocation sequence was available online to the investigators using the Hypernet web-based system. At the time the investigator accessed the web-based system with personal codes (user ID and password) and requested the treatment allocation for a new patient who fulfilled the eligibility criteria, the system assigned the next free number in accordance with the randomisation sequence. Patients and investigators did not know whether study drug or placebo was being given, since pre-filled syringes were used which were identical in appearance. Treatment assignments were masked from all study personnel and participants for the duration of the study. The planned interim analysis was done by an independent data and safety monitoring board to maintain the masking of treatment assignments from the people involved in the trial. For the final analysis, the treatment code was opened after the database was locked.

Statistical analysis

It was assumed that 8% of patients in the placebo group would have a primary efficacy outcome,[7] compared with 4% of patients in the nadroparin group. Using the one-sided Pampallona-Tsiatis group sequential design with a shape parameter of 0, type I error rate of 0·05 and type II error rate of 0·20, a total sample size of 1080 patients randomised in a 2:1 allocation ratio was estimated, considering the normal approximation to the binomial proportion (*Z*-pooled statistic), and two interim analyses at a third and two-thirds of the total enrolment.[15] At each interim analysis, the study could be stopped for efficacy or futility, as well as for safety issues. A sequential design with predefined interim analyses was used to minimise the exposure of patients to the parenteral placebo.

All randomised patients who received at least one dose of the study treatment were included in the efficacy and safety analyses. The empirical error spending approach[15] for both α and β spending was used to approximate the planned Pampallona-Tsiatis boundaries during the interim and final analyses while allowing, under specified conditions, the accommodation of irregular or unscheduled interim looks or the elimination of planned analyses. Consistent with the sequential nature of the trial, the stage-wise ordering approach was used to compute the final p-value and the point estimate of the treatment difference with associated one-sided 95% CI at the end of the study. Patients' characteristics were compared by means of the χ^2 test or the Student's *t* test as appropriate. Cumulative rates for thromboembolic events were estimated by the Kaplan–Meier method. Secondary efficacy and safety analyses were performed only on the final study data set.

The software program East version 5.1 was used to plan and perform the interim and final analyses; SAS version 9.1 was used for all other analyses.

The study was registered at the Drug Agency (AIFA) of the Italian Ministry of Health with the code DS/Sele/01, May 2003. The study is registered at ClinicalTrials.gov, number NCT00951574.

Role of the funding source

The study was designed and supervised by a steering committee. Data were collected and analysed by Hyperphar Group, Milan, Italy. The sponsor gave advice on the preparation of the protocol and the interpretation of the results. The sponsor had no role in data collection and data analysis. All authors had access to all data. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

Results

Between October, 2003, and May, 2007, 1166 patients were recruited to the study at 62 study centres in Italy. 1150 patients received at least one dose of the study treatment and were included in the efficacy and safety analyses (figure 1). Patient characteristics, thromboembolic risk factors, cancer site, and chemotherapy regimens were well balanced between the two treatment groups (tables 1 and 2).

The median duration of follow-up was 111 and 113 days in the nadroparin and placebo groups, respectively. 766 (66·6%) of 1150 patients completed the study treatment as defined by the protocol: 496 (64·5%) of 769 patients in the nadroparin group and 270 (70·9%) of 381 patients in the placebo group. The main reasons for not completing the study are shown in figure 1.

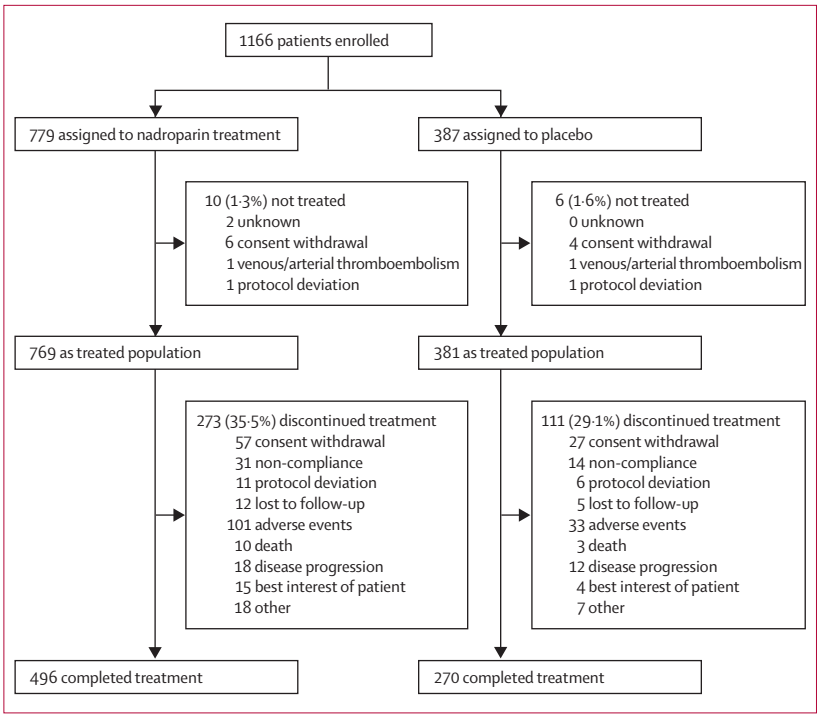

Figure 1: **Trial profile**

Adverse events were the cause of not completing the study in 13·1% (101 of 769 patients) and 8·7% (33 of 381 patients) in the nadroparin and placebo group, respectively.

Only one of the two planned interim analyses was done. The second interim analysis was omitted because its results would not have been available before the conclusion of patient enrolment. For this reason, the steering committee accepted the opportunity offered by the flexible monitoring approach to spend all the remaining type I and type II error rates in the final analysis.

At the interim analysis, which was done with 394 patients, the *Z*-pooled statistic comparing the nadroparin and placebo groups was 1·80. This value crossed neither the lower boundary for accepting the null hypothesis (–0·02), nor the upper boundary for rejecting the null hypothesis (2·74), so the trial was allowed to continue.

	Nadroparin (N=769)	Placebo (N=381)
Mean age (years; SD)	62·1 (10·3)	63·7 (9·2)
Sex (male)	372 (48·4)	183 (48·0)
Mean body mass index (kg/m^2; SD)	25·4 (4·4)	25·2 (4·2)
Recent cancer surgery*	170 (22·1)	87 (22·8)
Bed rest†	30 (3·9)	14 (3·7)
Previous venous thromboembolism	12 (1·6)	6 (1·6)
Previous cancer surgery	511 (66·4)	253 (66·4)
Previous chemotherapy	364 (47·3)	168 (44·1)
Previous radiotherapy	162 (21·1)	78 (20·5)
Previous hormone therapy	95 (12·4)	53 (13·9)
Central venous catheter	322 (41·9)	147 (38·6)

Data are n (%) unless otherwise stated. *In the past 3 months. †At least 7 days in the last 4 weeks.

Table 1: **Baseline characteristics and risk factors for thromboembolic events by treatment group**

	Nadroparin (N=769)	Placebo (N=381)
Cancer site		
Lung	199 (25·9)	80 (21·0)
Gastrointestinal	272 (35·4)	148 (38·8)
Stomach	58 (7·5)	40 (10·5)
Colon	156 (20·3)	79 (20·7)
Rectum	58 (7·5)	29 (7·6)
Pancreas	36 (4·7)	17 (4·5)
Breast	110 (14·3)	55 (14·4)
Ovary	96 (12·5)	47 (12·3)
Head and neck	19 (2·5)	17 (4·5)
Other	37 (4·8)	17 (4·5)
Chemotherapy		
Pyrimidine analogues	485 (63·1)	258 (67·7)
Platinum compounds	432 (56·2)	225 (59·1)
Anthracyclines (and related)	109 (14·2)	58 (15·2)
Nitrogen mustard analogues	38 (4·9)	18 (4·7)
Monoclonal antibodies	27 (3·5)	11 (2·9)

Data are n (%).

Table 2: **Cancer site and chemotherapy by treatment group**

At the final analysis, 15 of the 769 patients treated with nadroparin (2·0%) and 15 of the 381 patients treated with placebo (3·9%) were judged to have had a thromboembolic event (table 3). The null hypothesis was rejected as the final *Z* score was 2·0, and therefore crossed the upper boundary of 1·62 with a final one-sided p value of 0·02, point estimate of treatment difference of 2·00% and associated one-sided 95% CI of 0·303%. The time course of the thromboembolic events is shown in figure 2. Venous thromboembolism accounted for 22 events, with rates of 1·4% (11 of 769 patients) in the nadroparin group and 2·9% (11 of 381 patients) in the placebo group, respectively. Of note, 14 thromboembolic events occurred in patients with lung cancer: 3·5% (seven of 199) in patients treated with nadroparin and 8·8% (seven of 80) in patients treated with placebo (one-sided p value=0·07 at post-hoc analysis.)

Six (0·8%) of 769 patients in the nadroparin group and four (1·0%) of 381 patients in the placebo group were incidentally diagnosed with an asymptomatic thromboembolic event. These events were not counted in the primary analysis. Superficial thrombophlebitis occurred in 1·3% (10 of 769) of patients in the nadroparin group and 1·6% (six of 381) of patients in the placebo group. No difference was found in complete or partial response to chemotherapy, which was reported in 20·5% (158 of 769) of patients in the nadroparin group and 23·6% (90 of 381) of patients in the placebo group. The proportion of patients with a central venous catheter was 41·9% (322 of 769) in the nadroparin group and 38·6% (147 of 381) in the placebo group (table 1). Among these patients, central-venous-catheter-related complications of possible thrombotic origin occurred in 1·6% (five of 322) of patients in the nadroparin group and 2·0% (three of 147) of patients in the placebo group.

Five of 769 patients in the nadroparin group (0·7%) and none in the placebo group had major bleeding (p=0·18, two-sided test). One 58-year-old man with small-cell lung carcinoma developed haemoptysis and died as a result; one 75-year-old man with head and neck cancer developed melaena and recovered; one 68-year-old man with lung adenocarcinoma developed haemoptysis and recovered; one 74-year-old man with pancreatic cancer developed melaena and recovered; and one 81-year-old woman with rectal cancer developed intracranial bleeding and recovered. The incidence of minor bleeding was similar in the two treatment groups: 77 events in 57 (7·4%) of 769 patients given nadroparin, and 38 events in 30 (7·9%) of 381 patients given placebo.

A serious adverse event, comprehensive or major bleeding, was reported in 121 (15·7%) of 769 patients given nadroparin and 67 (17·6%) of 381 patients given placebo. Serious adverse events were considered to be

related to the study treatment by the investigators in 1·2% (nine of 769) of patients given nadroparin and in 1·6% (six of 381) of patients given placebo (table 4). 33 (4·3%) of 769 patients in the nadroparin group and 16 (4·2%) of 381 patients in the placebo group had died by the end of the study treatment. Overall, 48 of these deaths were judged to be related to disease progression, and one death in the nadroparin group to severe haemoptysis in a patient with lung cancer. 1 year after randomisation, 488 patients had died: 333 (43·3%) of 769 patients in the nadroparin group and 155 (40·7%) of 381 patients in the placebo group.

Discussion

This study shows that the low-molecular-weight heparin nadroparin almost halves the absolute rate of thromboembolic complications in ambulatory patients receiving chemotherapy for cancer (from 3·9% to 2·0%). This reduction in symptomatic outcomes is consistent with reductions attributable to low-molecular-weight heparin in the prevention of venous thromboembolism in several other clinical settings.[13] The antithrombotic effect was most evident for deep-vein thrombosis and pulmonary embolism, and was most apparent in patients with lung or gastrointestinal cancer.

In this study, the event rate in untreated patients was lower than expected compared with the rates seen in observational studies.[1,2] This might be explained by the fact that this trial was designed in the absence of reliable data on the incidence of thromboembolic events during intervention studies in ambulatory patients receiving chemotherapy. It is not uncommon to observe a lower event rate in randomised clinical trials than in other experimental settings.[16] Most of the thromboembolic events occurred in patients with lung and gastrointestinal cancer, and the rate was unexpectedly low in patients with breast and ovarian cancer. A recently developed predictive model for chemotherapy-associated thrombosis could be used to identify high-risk patients.[17] Moreover, the median treatment duration in our study was less than 4 months, which could have precluded the observation of thromboembolic events that occurred after that period, especially in some types of cancer.[18,19]

Although less common than venous thromboembolism, the rate of arterial complications in cancer patients is not negligible. For this reason, and for the clinical relevance of arterial events, we included both venous and arterial complications as study endpoints. However, in our study the contribution of arterial events to the overall rate of thromboembolism was limited, possibly owing to the exclusion of patients chronically receiving antithrombotic or anticoagulant treatments. As a further finding, the proportion of patients with central venous catheters and the rate of central-venous-catheter-related thromboses were well balanced in the two treatment groups, and therefore did not significantly affect study outcomes.

	Nadroparin (N=769)	Placebo (N=381)
Overall thromboembolic events	15 (2·0)	15 (3·9)
Deep-vein thrombosis	8 (1·0)	8 (2·1)
Pulmonary embolism	3 (0·4)	3 (0·8)
Visceral venous thrombosis	1 (0·1)	1 (0·3)
Stroke and peripheral thrombosis	3 (0·4)	3 (0·8)
Thromboembolic event by cancer site		
Lung	7/199 (3·5)	7/80 (8·8)
Gastrointestinal	4/272 (1·5)	4/148 (2·7)
Pancreas	3/36 (8·3)	1/17 (5·9)
Other	1/262 (0·4)	3/136 (2·2)

Data are n (%).

Table 3: **Thromboembolic events by treatment group and cancer site**

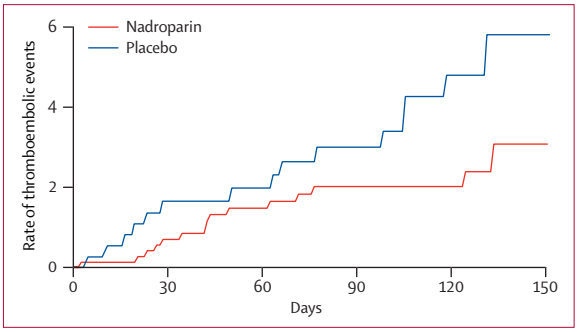

Figure 2: **Cumulative hazard of thromboembolic events by treatment**

	Nadroparin (N=769)	Placebo (N=381)
Serious adverse events (SAE)		
All SAE	121 (15·7)	67 (17·6)
SAE related to investigational drug	9 (1·2)	6 (1·6)
Type of SAE*		
Abdominal pain	2 (0·3)	3 (0·8)
Asthenia	3 (0·4)	3 (0·8)
Condition aggravated	5 (0·7)	2 (0·5)
Dyspnoea	11 (1·4)	3 (0·8)
Fever	4 (0·5)	4 (1·0)
Intestinal obstruction	7 (0·9)	2 (0·5)
Neutropenia	6 (0·8)	6 (1·6)

Data are n (%). *Serious adverse events with an incidence of more than 0·5% in at least one of the treatment groups were reported.

Table 4: **Serious adverse events by treatment group**

More patients who received nadroparin experienced a major bleeding event than did those who received placebo. However, the study was not powered to assess a difference in the bleeding rate between the two treatment groups. The rate of minor bleeding events was similar in the two groups, and this is somewhat reassuring, as minor bleeding is considered to be a surrogate for major bleeding. Overall, the rate of bleeding was low and

consistent with that seen in other studies of long-term prophylaxis comparing low-molecular-weight heparin with placebo in patients with cancer.[20,21]

It has recently been claimed that low-molecular-weight heparin can prolong survival in patients with cancer,[22–26] but no effect on patient survival was noted here. This lack of effect on survival could be due to several factors. First, the duration of treatment in our study was shorter than that of the trials focused on survival. Second, the dose of low-molecular-weight heparin was lower than the doses that have shown a favourable effect in terms of survival. And third, this study included patients with metastatic or locally advanced disease, whereas most of the benefit from low-molecular-weight heparin noted in the survival studies has been seen in patients with less advanced disease.

Preventing thromboembolic complications in patients with cancer has a substantial effect on patient care. Thromboembolic events can cause the interruption of chemotherapy and increase health expenditure. Thromboembolic complications require anticoagulant treatment that is particularly complicated in patients with cancer. Additionally, the rate of recurrence and bleeding is particularly high in patients with cancer and venous thromboembolism.[27]

To our knowledge, this is the first study since the pivotal trial of Levine and colleagues,[10] published 15 years ago, to show that antithrombotic prophylaxis during chemotherapy can have significant favourable effects in ambulatory patients with cancer. The study by Levine and colleagues showed that warfarin had a clinical benefit in patients with advanced breast cancer. However, despite that result, warfarin is not currently used for this indication because treatment with this agent is particularly problematic in patients with cancer due to monitoring difficulties and drug interaction.[28] These issues might be made easier to deal with by using a low-molecular-weight heparin.[29]

This study supports the concept that thromboembolic events can be prevented in ambulatory patients with cancer receiving chemotherapy. This has potential implications for future therapeutic scenarios. There is increasing evidence that the new angiogenesis inhibitors are associated with a particularly high risk of arterial and venous thromboembolic complications.[30–32] Furthermore, the availability of new oral antithrombotic agents that do not require monitoring and do not cause significant drug interactions could optimise our results by extending the use and duration of antithrombotic prophylaxis, once proved effective.

This study has several limitations. First, the duration of study treatment might have been too short to fully explore the clinical benefit of antithrombotic prophylaxis. Ethical concerns related to the use of a parenteral placebo were the main reason for choosing 4 months as the maximum study treatment duration. Furthermore, vascular mortality did not seem to contribute to the composite study outcome. This finding is not consistent with the concept that vascular mortality is the second cause of death in patients with cancer. Of note, patients in this study were ambulatory, and most of them died at home from disease progression. Therefore, the exact cause of death was difficult to assess.

However, this study also has several methodological strengths. This was a double-blind and placebo-controlled study that had confirmed symptomatic clinical events as study outcomes. Furthermore, all the study outcomes were assessed by an independent adjudication committee, whose members were unaware of the patients' study group allocation. Almost 99% of the randomised patients were included in the efficacy and safety analysis.

The heterogeneity of the study population concerning the sites of cancer and the chemotherapy regimens could be seen both as a limitation and a strength of the study. On the one hand, this heterogeneity might have caused the dilution of a beneficial effect from antithrombotic prophylaxis. On the other hand, the heterogeneity of study population allowed the burden of thromboembolic complications and the benefit of the intervention in different types of cancer to be estimated.

In conclusion, nadroparin reduces the incidence of thromboembolic events in ambulatory patients with metastatic or locally advanced cancer receiving chemotherapy. Future studies should focus on patients at high risk for thromboembolism, such as patients with lung cancer or patients identified through the use of scores that have recently been proposed to optimise patient risk stratification.[17]

Contributors

GA, GG, CB, MV, EB, and MT were responsible for the design of the study. EB planned and reviewed the statistical analysis. All authors contributed to the writing of the paper and vouch for the accuracy and completeness of the data and analysis.

Conflicts of interest

CB is the scientific director of Italfarmaco. All other authors declared that they had no conflicts of interest.

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