Clinical Experience of Nadroparin in Patients with Cancer

a report by

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DOI: 10.17925/EOH.2008.04.1.34

Anticoagulant drugs represent an essential therapeutic class in patients with cancer, venous thromboembolism being one of the most common complications occurring during the evolution of this disease.[1] Among the available drugs, oral vitamin K antagonists are not ideally suited to this patient group owing to the presence of factors that may influence the stability of the anticoagulant effect (including drug interactions, malnutrition, vomiting and liver dysfunction). In contrast, due to their high level of efficacy and safety and their ease of use, low-molecular-weight heparins are particularly appropriate in patients with cancer. Therefore, the use of these drugs is recommended in a number of international guidelines on the prevention and treatment of venous thromboembolism in this group of patients.[2–4] Furthermore, a promising aspect of low-molecular-weight heparins in patients with cancer is that these drugs may prolong the survival of these patients independently of their therapeutic effect on thrombosis. Among the available low-molecular-weight heparins, nadroparin is one of the most studied for the prevention and treatment of venous thromboembolism in patients with cancer. Nadroparin is also the first low-molecular-weight heparin that has been shown to prolong the survival of cancer patients without venous thromboembolism.[5] In this manuscript, we review the nadroparin studies in order to present clinical evidence supporting the use of this drug in cancer patients.

Nadroparin and the Prevention of Venous Thromboembolism in Patients with Cancer

Cancer is a major risk factor for venous thromboembolism.[6] For example, the incidence of venous thromboembolism is about two times higher in patients hospitalised with cancer than in patients hospitalised without cancer.[7] Moreover, approximately 15% of patients with cancer develop symptomatic venous thromboembolism during the course of their disease.[8] The thrombotic risk varies according to cancer type, with the tumour sites most commonly associated with venous thromboembolism being the brain, ovary, digestive tract, pancreas, bone and lung.[7,9–12] Thrombotic risk is highest in the first few months after cancer diagnosis; it increases with advancing cancer stage and the presence of metastases.[11–15] Furthermore, cancer patient management involves procedures that favour the development of thrombosis, including surgery, the administration of chemotherapy or hormonal therapy, the use of invasive procedures and long-term placement of central venous catheters.[12,14,16,17] Due to the ageing population, rising incidence of cancer and increasing use of invasive procedures, venous thromboembolic events associated with cancer, particularly pulmonary embolism, are becoming more common.[12,18] The development of venous thromboembolism in the course of this disease adversely affects not only the quality of life of patients with cancer, but also the overall prognosis. The probability of death in cancer patients with venous thromboembolism is higher than that in patients with cancer alone or venous thromboembolism alone.[19–21] Thus, venous thromboembolism is the second cause of death in patients with cancer.[22] Furthermore, it is the most common cause of death at 30 days post-surgery.[23]

The efficacy and safety of nadroparin in the prevention of venous thromboembolism were investigated in a surgical and non-surgical setting (see *Table 1*).

Surgical Patients

The prevention of venous thromboembolism in cancer patients is challenging. First, cancer patients undergoing surgery have at least twice the risk of post-operative deep-vein thrombosis and more than three times the risk of fatal pulmonary embolism than non-cancer patients undergoing similar procedures.[2] Second, cancer is an independent predictor of lack of effect of thromboprophylaxis.[2] Third, cancer patients exhibit a higher risk of bleeding than non-cancer patients.[24,25] In a meta-analysis of studies comparing various low-molecular-weight heparins with unfractionated heparin in the prevention of deep-vein thrombosis after surgery, the two classes of drugs were shown to be equally safe and effective in terms of bleeding risk.[25] This result was confirmed in the subgroup of patients undergoing surgery for cancer.[25] Due to their ease of use, international guidelines favour the use of low-molecular-weight heparins over unfractionated heparin in this setting, including in cancer patients.[2–4]

An important point specific to the cancer patient population is that venous thromboembolic events may occur long after cancer surgery.[23] Thus, while the standard duration of thromboprophylaxis after surgery is seven to 10 days, international guidelines suggest administering of post-hospital discharge prophylaxis with low-molecular-weight heparins for up to four weeks after cancer surgery, notably after major abdominal/pelvic surgery with residual malignant disease, obesity or a previous history of venous thromboembolism.[2–4]

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Table 1: Nadroparin Studies in the Prevention of Venous Thromboembolism in Patients with Cancer

Study	Setting	Total Population	Cancer Patients (%)	Nadroparin	Comparator
Pezzuoli et al.[26]	General surgery	4,498	1,507 (33.5)	2,850 anti-Xa IU (0.3ml) once daily	Placebo
European Fraxiparin Study[27]	Abdominal surgery	1,896	694 (36.6)	2,850 anti-Xa IU (0.3ml) once daily	UFH 5,000U 3 times daily
Simonneau et al.[28]	Colorectal cancer surgery	1,288	1,288 (100)	2,850 anti-Xa IU (0.3ml) once daily	Enoxaparin: 4,000 anti-Xa IU (40mg) once daily
Bounameaux et al.[30]	Abdominal surgery	194	92 (47.4)	2,850 anti-Xa IU (0.3ml) once daily	Dalteparin: 2,500 anti-Xa IU once daily
Marassi et al.[32]	Abdominal surgery	61	61 (100)	2,850 anti-Xa IU (0.3ml) once daily	No treatment
Azorin et al.[36]	Lung surgery	150	150 (100)	2,850 anti-Xa IU (0.3ml) once daily	Nadroparin: 3,800 anti-Xa IU (0.4ml) between 40 and 70kg; 5,700 anti-Xa IU (0.5ml) between 71 and 110kg
Boncinelli et al.[37]	Urological surgery	50	50 (100)	2,850 anti-Xa IU (0.3ml) once daily	UFH 5,000U 3 times daily
Nurmohamed et al.[39]	Neurosurgery	485	400 (82.5 with brain or spinal cord tumour)	2,850 anti-Xa IU (0.3ml) once daily + graduated compression stockings	Graduated compression stockings
Harenberg et al.[42]	Bedridden medical patients	1,590	120 (7.5)	2,850 anti-Xa IU (0.3ml) once daily	UFH 5,000U three times daily
Weber et al.[43]	Cancer patients under palliative care	20	20 (100)	2,850 anti-Xa IU (0.3ml) once daily if <70kg 3,800 anti-Xa IU (0.4ml) once daily if >70kg	No treatment
Mismetti et al.[47]	Cancer patients with central venous catheters	59	59 (100)	2,850 anti-Xa IU (0.3ml) once daily	Warfarin 1mg once daily
Niers et al.[48]	Patients with a haematological cancer and a central venous catheter	113	113 (100)	2,850 anti-Xa IU (0.3ml) once daily	Placebo

General Surgery

Nadroparin is the only low-molecular-weight heparin demonstrated to reduce mortality in patients undergoing surgery. This was shown in a randomised, double-blind trial comparing the efficacy and safety of nadroparin versus placebo for preventing overall mortality and fatal pulmonary embolism in 4,498 patients undergoing general surgery; approximately 65% of surgical procedures were abdominal surgery, and 33% of patients were operated on for cancer.[26] Compared with placebo, nadroparin 2,850 anti-Xa IU or 0.3ml once daily significantly ($p<0.05$) reduced overall mortality by 55.7% (95% confidence interval [CI] 10.7–78). Nadroparin non-significantly reduced the incidence of pulmonary embolism by 50%, from 0.18 to 0.09%. During surgery, there was no significant difference in the number of patients requiring transfusions or in the number of transfused units between the two study groups. Bleeding as assessed by the surgeon and the total amount of blood loss were significantly lower ($p<0.05$) in the placebo group. Similarly, post-operative bleeding was significantly less frequent ($p<0.01$) in the placebo group. However, no fatal bleeding was reported, and bleeding complications did not result in a significant difference in the number of study treatment discontinuations. No subgroup analysis was performed in cancer patients.

Abdominal Surgery

Several studies have demonstrated the benefit of nadroparin in cancer patients undergoing abdominal surgery. A first randomised trial compared the efficacy and safety of nadroparin with those of unfractionated heparin in 1,896 patients undergoing elective abdominal surgery, with a subset of 694 (36.6%) patients undergoing surgery for cancer.[27] Nadroparin was given at a once-daily dose of 2,850 anti-Xa IU (0.3ml). Unfractionated heparin was administered at a dose of 5,000U three times daily, the thromboprophylactic regimen of choice in this context. Both drugs were initiated two hours pre-operatively, and treatment continued for seven days. Overall, nadroparin significantly ($p<0.01$) reduced the incidence of deep-vein thrombosis from 4.5% with unfractionated heparin to 2.8%. The incidence of deep-vein thrombosis was higher in cancer patients compared with non-cancer patients. Nevertheless, nadroparin also reduced the incidence of deep-vein thrombosis in patients with cancer. No pulmonary embolism was observed in these patients. They had a higher bleeding tendency than non-cancer patients, but nadroparin was as safe in terms of bleeding risk as unfractionated heparin, regardless of the presence of cancer.

A large randomised, double-blind study specifically performed in patients with colorectal cancer confirmed the value of nadroparin in this setting.[28] In this trial, nadroparin 2,850 anti-Xa IU once daily or 0.3ml was compared with enoxaparin 4,000 anti-Xa IU or 40mg once daily, both drugs being initiated two to four hours pre-operatively and administered for 9±2 days. In a total of 1,288 randomised patients, nadroparin was less effective for reducing asymptomatic distal deep-vein thrombosis, but more effective for reducing symptomatic venous thromboembolism (see *Table 2*). Nadroparin was also safer in terms of major bleeding ($p=0.012$); this increased safety was observed regardless of age or creatinine clearance.[29]

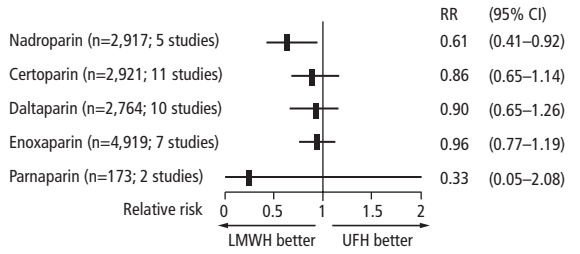
Other data obtained in a randomised, single-blind trial performed by Bounameaux et al.[30] support the high efficacy of nadroparin in abdominal surgery patients. Nadroparin 2,850 anti-Xa IU once daily or 0.3ml was

Table 2: Efficacy and Safety of Nadroparin versus Enoxaparin in Colorectal Cancer Surgery[28]

	Nadroparin n/N(%)	Enoxaparin n/N (%)	Relative risk (95% CI)
Venous thromboembolism (primary outcome)	74/464 (15.9)	61/486 (12.6)	1.27 (0.93–1.74)
Any proximal deep-vein thrombosis	15/503 (3)	14/515 (2.7)	
Distal deep-vein thrombosis only	58/503 (11.5)	42/515 (8.2)	
Symptomatic venous thromboembolism	1/643 (0.2)	9/628 (1.4)	
Symptomatic deep-vein thrombosis	1/643 (0.2)	5/628 (0.8)	
Symptomatic pulmonary embolism	0/643 (0)	5/628 (0.8)	
Major bleeding	47/643 (7.3)	72/628 (11.5)	0.64* (0.45–0.91)
Death from any cause	2/653 (0.3)	8/635 (1.3)	0.24** (0.05–1.15)

**p=0.012; **p=0.07.*

Figure 1: Low-molecular-weight Heparins versus Unfractionated Heparin in General Surgery (35 studies)



Meta-analysis comparing the efficacy for preventing the occurrence of deep-vein thrombosis of various low-molecular-weight heparins (LMWH) with that of unfractionated heparin (UFH) in patients undergoing general surgery.[25]

compared with dalteparin 2,500 anti-Xa IU once daily in 194 patients undergoing elective abdominal surgery; 92 patients had cancer (47.4%). The incidence of deep-vein thrombosis was 16.3% (95% CI 9–25) in the nadroparin group versus 32.3% (95% CI 23–43) in the dalteparin group. In a subsequent study, the incidence of deep-vein thrombosis with once-daily 5,000 IU dalteparin was 14.1% (95% CI 7–21).[31]

Another randomised trial specifically examined the risk–benefit ratio of nadroparin in 61 patients undergoing major abdominal surgery for cancer.[32] Nadroparin given at the same dosage regimen as in previous trials significantly ($p<0.01$) reduced the incidence of deep-vein thrombosis from 35.4% without thromboprophylaxis to 6.8%. The volume of intra-operative blood loss or transfused blood and the number of patients with blood transfusion or with wound haematomas were comparable in the two study groups. However, a higher ($p<0.05$) post-operative transfusion requirement was observed in the group receiving nadroparin.

These data all indicate that the same dosage regimen of nadroparin (i.e. 2,850 anti-Xa IU once daily, or 0.3ml) is effective and safe in the prevention of venous thromboembolism after surgery, irrespective of whether patients have cancer. This is a noteworthy distinction between nadroparin and other low-molecular-weight heparins. In a subpopulation of general surgery patients operated on for cancer, enoxaparin 20mg once daily (i.e. 2,000 anti-Xa IU) tended to be less effective than thrice-daily 5,000U unfractionated heparin.[33] A higher dose of enoxaparin (40mg once daily, or 4,000 anti-Xa IU) was required in order for this drug be as effective as unfractionated heparin; however, this result was obtained at the cost of a trend towards an increased risk of major bleeding.[34] Likewise, in a subgroup of abdominal surgery patients with cancer, once-daily 5,000 anti-Xa IU dalteparin was more effective than once-daily 2,500 anti-Xa IU dalteparin for preventing venous thromboembolism (8.5 versus 14.9%; $p<0.05$). The frequency of bleeding complications was not significantly different between the two arms (4.6 versus 3.6%).[35] Whether this reflects a true difference in efficacy between the various low-molecular-weight heparins and the nadroparin dosage regimen remains to be seen; however, in a meta-analysis of low-molecular-weight heparins in general surgery patients, the sole low-molecular-weight heparin shown to be statistically more effective than unfractionated heparin was nadroparin (see *Figure 1*). In this analysis, the safety of nadroparin in terms of bleeding risk was comparable to that of unfractionated heparin.[25]

The efficacy and safety of a similar dosage regimen of nadroparin 2,850 anti-Xa IU once daily or 0.3ml were shown in cancer patients undergoing other types of surgical procedures, as described below.

Lung Surgery

The efficacy and safety of nadroparin in 150 patients undergoing lung surgery for cancer were investigated in a randomised, open trial.[36] Nadroparin was given once daily either at a fixed dosage (2,850 anti-Xa IU or 0.3ml) or according to bodyweight (3,800 anti-Xa IU for those between 40 and 70kg, and 5,700 anti-Xa IU for those between 71 and 110kg). Treatment was initiated 12 hours before surgery and continued for eight days. No cases of symptomatic deep-vein thrombosis or pulmonary embolism were reported in either study group. There were two major bleeding episodes in the fixed-dosage group, and six in the bodyweight-adjustment group.

Urological Surgery

The efficacy and safety of nadroparin were compared with those of unfractionated heparin in cancer patients undergoing radical retropubic prostatectomy.[37] Fifty patients were randomly assigned to receive either once-daily 2,850 anti-Xa IU nadroparin (0.3ml) or thrice-daily 5,000U unfractionated heparin. Nadroparin and unfractionated heparin were initiated 12 and two hours before surgery, respectively. Treatment was maintained at least until hospital discharge. No patient in either group presented symptomatic deep-vein thrombosis or pulmonary embolism. There was one major bleeding event in a patient treated with unfractionated heparin. During the first post-operative week, 42% of nadroparin and 57% of unfractionated heparin patients required transfusion.

Neurosurgery

Craniotomy for brain neoplasm carries a high risk of venous thromboembolism.[38] Despite this, peri-operative anticoagulant prophylaxis for post-operative venous thromboembolism in neurosurgical patients has not gained wide acceptance because of the concern about intracranial haemorrhage; physical methods are favoured by neurosurgeons. A randomised, double-blind trial investigated the efficacy and safety of adding nadroparin post-operatively to graduated compression stockings for the prevention of venous thromboembolism in 485 patients, about 80% of

whom were undergoing neurosurgery for a brain or spinal cord tumour.[39] At day 10, nadroparin initiated 18–24 hours post-operatively reduced the incidence of venous thromboembolism by 28.9%, from 26.3 to 18.7% (p=0.047). The rates for proximal deep-vein thrombosis/pulmonary embolism were 6.9% in nadroparin plus compression stocking patients and 11.5% in compression stocking only patients (i.e. a relative risk reduction of 40.2%; p=0.065). At day 56, the rates of venous thromboembolism were 13.7 and 20.9%, respectively (p=0.018). Major bleeding complications during the treatment period occurred in six (2.5%) nadroparin patients and in two (0.8%) control patients (p=0.087). Mortality at day 56 was higher in the nadroparin group, but none of the deaths were judged by a blinded adjudication committee to be related to the study drug.

Non-surgical Patients

Although no specific studies have been performed to determine the benefit of anticoagulant therapy in hospitalised bedridden patients with active cancer, international guidelines recommend the use of unfractionated or low-molecular-weight heparins in these patients.[2–4] This recommendation was based on a number of trials performed in bedridden acutely ill medical patients at high risk of venous thromboembolism.[40,41] Concerning nadroparin, a first randomised, double-blind study was performed in 1,590 non-surgical bedridden patients, of whom 8% had cancer on admission.[42] Subcutaneous nadroparin at the once-daily dose of 2,850 anti-Xa IU (0.3ml) was compared with subcutaneous unfractionated heparin at the dose of 5,000U three times daily. The results showed efficacy equivalence of the two study treatments, with a venous thromboembolic event rate of 0.83 and 0.56% in the nadroparin and unfractionated heparin groups, respectively. Major haemorrhages were rare in both groups, none being fatal or requiring blood transfusions. There were more minor bleeding episodes in the unfractionated heparin group than in the nadroparin group. Likewise, the incidence of subcutaneous haematomas with a diameter greater than 2.5cm was significantly (p<0.001) higher in the unfractionated heparin group.

Another open, randomised study comparing the once-daily subcutaneous injection of nadroparin (2,850 anti-Xa IU or 0.3ml if bodyweight <70kg and 3,800 anti-Xa IU or 0.4ml if bodyweight >70kg) or no treatment was performed in 20 patients with advanced cancer and an estimated life expectancy of less than six months.[43] One venous thromboembolism and one major bleeding episode occurred in the group receiving nadroparin, whereas two minor bleeding episodes occurred in the control group. At three months, nine out of 10 patients (90%) had died in the control group versus five out of 10 (50%) in the group receiving nadroparin (p=0.141).

The benefit of anticoagulant therapy in ambulatory patients with cancer receiving chemotherapy is uncertain, as only one trial has been conducted. The trial studied 311 women with metastatic breast cancer receiving chemotherapy and randomised to low-dose warfarin (with a target international normalised ratio [INR] of between 1.3 and 1.9) or placebo.[44] Symptomatic venous thromboembolism was reduced from 4.5% in placebo-treated women to 0.8% in warfarin-treated women (p=0.038). Since the publication of this trial in 1994, no other randomised trial has assessed the value of anticoagulant therapy in non-surgical patients with cancer receiving chemotherapy. International guidelines do not recommend systemic thromboprophylaxis in these patients, except in women with advanced breast cancer receiving chemotherapy[3] and in patients with myeloma receiving thalidomide plus chemotherapy or dexamethasone.[4] However, it is noteworthy that the risk of venous thromboembolism in cancer patients receiving chemotherapy or other cancer-related medical treatments was recently highlighted in a literature review on this topic.[16] Furthermore, thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy.[22] The value of low-molecular-weight heparins in this context remains to be evaluated.

Patients with a Long-term Central Venous Catheter

Many cancer patients have a long-term central venous catheter inserted for chemotherapy. Without antithrombotic prophylaxis, the incidence of asymptomatic upper-limb deep-vein thrombosis related to central venous catheters ranges from 27 to 90%, and that of symptomatic thrombosis from 0 to 20%.[45] This is a serious event that may result in pulmonary embolism, favour sepsis and the loss of the venous access for infusion chemotherapy.[46]

Two trials evaluated the efficacy and safety of nadroparin in this setting. In a first randomised, open trial in 59 patients with non-haematological cancer scheduled to undergo placement of a long-term subclavian venous catheter, nadroparin was compared with warfarin.[47] Nadroparin was given subcutaneously at the once-daily dose of 2,850 anti-Xa IU (0.3ml). Warfarin was given orally at a fixed daily dose of 1mg. Both treatments were given for 90 days. At day 90, venographically documented upper-extremity thrombosis was reported in 28.6% of the patients in the nadroparin group and in 16.7% of the patients in the warfarin group (p=0.48). Safety was satisfactory and similar with both treatments.

A second placebo-controlled, double-blind randomised trial studied the efficacy and safety of nadroparin in patients with a haematological malignancy.[48] Nadroparin 2,850 anti-Xa IU (0.3ml) or placebo was given subcutaneously once daily for three weeks. Seven of the 41 (17%; 95% CI 0.06–0.28) patients in the nadroparin group and four of the 46 (9.0%; 95% CI 0.002–0.16) patients in the placebo group exhibited catheter-related central venous thrombosis (p=0.49). No major bleeding episodes were reported. Clinically relevant non-major bleeding events occurred in two patients (4%) in each group.

Overall, these studies confirmed the safety of nadroparin in terms of bleeding risk in cancer patients. However, they and others[49–51] also showed that in the general cancer patient population the risk of clinically pertinent venous thromboembolism related to the presence of a long-term central venous catheter appears to be too low to warrant routine thromboprophylaxis.[2,4] However, it is still unknown whether thromboprophylaxis in patients with a central venous catheter and a high risk of catheter-related thrombosis (e.g. patients with more than one insertion attempt, inadequate position of the catheter tip, ovarian cancer, distant metastases or chest radiotherapy or patients with a state of acquired or congenital thrombophilia) is beneficial.[52–54]

Nadroparin and the Treatment of Venous Thromboembolism in Patients with Cancer

Anticoagulant drugs are indicated for the short-term initial treatment and long-term secondary prevention of venous thromboembolism. The value of nadroparin has been studied in these two indications (see *Table 3*).

Short-term Initial Treatment

Venous thromboembolism appears to be more aggressive in cancer patients. Compared with non-cancer patients, deep-vein thrombosis is more frequently bilateral, located in the more proximal veins or at unusual sites.[8,55,56] Furthermore, antithrombotic drugs are less effective and their use

Table 3: Nadroparin Studies in the Treatment of Venous Thromboembolism in Patients with Cancer

Study	Setting	Total Population	Cancer Patients (%)	Nadroparin	Comparator
Prandoni et al.[63]	Treatment of proximal deep-vein thrombosis	170	33 (19.4)	Bodyweight adjusted twice daily	aPTT-adjusted intravenous UFH
Prandoni et al.[64]	Treatment of venous thromboembolism	720	157 (21.7)	Bodyweight adjusted twice daily	aPTT-adjusted subcutaneous UFH
Charbonnier et al.[65]	Treatment of proximal deep-vein thrombosis	651	91 (14)	Bodyweight adjusted once daily (double concentration)	Bodyweight adjusted twice daily (standard concentration)
Koopman et al.[70]	Outpatient treatment of proximal deep-vein thrombosis	400	70 (17.5)	Bodyweight adjusted twice daily	aPTT-adjusted intravenous UFH
Lopaciuk et al.[77]	Long-term treatment of proximal deep-vein thrombosis	193	12 (6.2)	Bodyweight adjusted once daily for 3 months	INR-adjusted acenocoumarol for 3 months
Lopez-Beret et al.[78]	Long-term treatment of proximal deep-vein thrombosis	158	35 (22.2)	Bodyweight adjusted twice daily for 3 months ± bodyweight adjusted once daily for 3 months	INR-adjusted acenocoumarol for 3–6 months

aPTT = activated partial thromboplastin time; UFH = unfractionated heparin; INR = international normalised ratio.

associated with more bleeding complications. Compared with patients without cancer, cancer patients have a two- to three-fold higher risk of recurrent thrombosis and a two- to six-fold higher risk of haemorrhagic complications.[57–59] Despite this, international guidelines on the initial treatment of venous thromboembolism in patients with cancer are not specific to this population.[2–4] A recent meta-analysis of clinical trials performed in the general population with venous thromboembolism showed that the risk–benefit ratio of low-molecular-weight heparins was better than that of unfractionated heparin, with a greater efficacy for reducing recurrence and overall death.[60] This greater efficacy of low-molecular-weight heparins was also confirmed in a group of patients with cancer.[61] In patients with pulmonary embolism, low-molecular-weight heparins were at least as effective and safe as unfractionated heparin.[62] As their use is also easier from a practical perspective, low-molecular-weight heparins are generally preferred for the initial five- to 10-day treatment of venous thromboembolism, including in patients with cancer.[2–4]

As for other low-molecular-weight heparins, no trial has specifically studied nadroparin in the initial treatment of venous thromboembolism in patients with cancer. In the nadroparin trials in this setting,[63–65] cancer patients represented a subgroup, varying between 14 and 22% (see *Table 3*). Overall, these trials showed that nadroparin administered once or twice daily was both efficacious and safe in terms of bleeding risk in the initial treatment of patients with venous thromboembolism. The once-daily regimen of nadroparin at double concentration is particularly attractive for patients with cancer who are already receiving a number of other drugs. Of note, the efficacy of such a once-daily regimen has not been demonstrated for all of the other available low-molecular-weight heparins.[66,67]

Several reports have shown that the outpatient treatment of venous thromboembolism in cancer patients was safe and effective,[68,69] a particularly interesting result in this population, who are frequently hospitalised for many other reasons. The benefit of nadroparin in the outpatient treatment of patients with venous thromboembolism has also been proved in several trials, which included 13–18% cancer patients.[70,71]

Long-term Secondary Prevention

The use of vitamin K antagonists is particularly problematic in patients with cancer, with a significantly greater risk of unpredictable levels of anticoagulation due to frequent drug interactions, malnutrition, vomiting or liver dysfunction. Their use also requires frequent laboratory monitoring.[72] Low-molecular-weight heparins do not have these drawbacks.[73] Furthermore, in the long-term secondary prevention of venous thromboembolism in patients with cancer, low-molecular-weight heparins were shown to be at least as effective and safe as vitamin K antagonists.[74,75] These drugs also improved the quality of life of palliative care cancer patients, who felt liberated from hospitals or clinics.[76] Thus, in international guidelines on the long-term treatment of venous thromboembolism in patients with cancer,[2–4] low-molecular-weight heparins are recommended for the first three to six months after the event; the consideration of anticoagulation for an indefinite period for patients with active cancer (metastatic disease or continuing chemotherapy) is also proposed.

Two clinical studies have shown the efficacy and safety of nadroparin compared with vitamin K antagonists in the long-term prevention of venous thromboembolism. The first trial was a randomised, open-label trial of 202 patients with proximal deep-vein thrombosis, with 6.2% of the 193 evaluable patients exhibiting cancer.[77] After initial therapy with nadroparin 0.1ml/10kg twice daily in all patients for 10 days, patients were randomised to nadroparin 0.1ml/10kg once daily or acenocoumarol, with both drugs being administered for three months. In the second randomised, open-label trial of 158 patients with deep-vein thrombosis, of whom 22.2% had cancer, nadroparin was again compared with acenocoumarol.[78] However, after initial therapy with nadroparin 0.1ml/10kg twice daily for at least three days in all patients, nadroparin was administered at 0.1ml/10kg twice daily for three months, then once daily for three additional months if necessary. In both studies, nadroparin and acenocoumarol were comparable in terms of recurrent venous thromboembolism, major bleeding and death, but there was a trend towards fewer events in favour of nadroparin.

Nadroparin and Prolonging the Survival of Patients with Cancer

The influence of anticoagulants on the spread of cancer and cancer mortality has been suspected for a long time. However, data on the potential antitumour effects of unfractionated heparin or vitamin K antagonists have been inconclusive.[79,80] In 1999, a systematic analysis of nine low-molecular-weight heparin trials showed that the three-month mortality rate in cancer patients with venous thromboembolism treated

Table 4: Nadroparin Studies in the Prolongation of Survival in Patients with Cancer

Study	Setting	Total Population	Type of Cancer	Nadroparin	Comparator
Klerk et al.[5]	Prolongation of survival	302	Various types	3,800 anti-Xa IU if <50kg 5,700 anti-Xa IU between 50 and 70kg 7,500 anti-Xa IU if >70kg Twice daily for 14 days then once daily for another 4 weeks	Placebo
Icli et al.[86]	Prolongation of survival	69	Pancreas cancer	2,850 anti-Xa IU Once daily for 8 days every 3 weeks for a median of 6 cycles	No treatment
INPACT (ongoing)[87]	Prolongation of survival	500	Lung, pancreas or prostate cancer	Therapeutic doses for 2 weeks followed by half therapeutic doses for 4 weeks After 4 weeks of wash-out, subsequent 2-week periods of therapeutic doses of nadroparin A total of 6 cycles, each separated by 4 weeks of wash-out	No treatment
NVALT-8b (ongoing)	Prolongation of recurrence-free survival	600	Resected non-small-cell lung cancer with a high risk of recurrence	Initiated 4–6 weeks after surgery Therapeutic doses for 2 weeks and half-therapeutic doses for 14 weeks	No treatment

with these drugs was 40% lower than that in patients treated with unfractionated heparin.[81] Moreover, this analysis revealed that the mortality reduction was present for various subtypes of malignancy; it was not due to differences in death related to venous thromboembolism or bleeding and persisted after adjustment for several prognostic variables. Another interesting fact was that in the treatment of venous thromboembolism, the benefit of low-molecular-weight heparins relative to unfractionated heparin on death reduction appeared to be specific to the subgroup of patients with cancer.[60] After this, two other meta-analyses and systematic reviews showed that anticoagulants, particularly low-molecular-weight heparins, significantly improved overall survival in cancer patients without venous thrombosis, suggesting that the beneficial effect of these drugs was partly independent of their antithrombotic effect.[82,83]

Nadroparin appears to be a very promising drug in this setting, as shown in various studies, both experimental and clinical (see *Table 4*). *In vitro*, it was shown that nadroparin may have antimetastatic activity by interfering with the adhesion and invasion of blood-borne metastatic cells: at equivalent concentrations in terms of anti-factor Xa units, nadroparin but not enoxaparin significantly inhibited P-selectin-dependent tumour cell interactions.[84] In a mouse experimental model, the dose (in anti-factor Xa units) of nadroparin required to inhibit lung metastases by 50% was five-fold lower than that of enoxaparin. The ability of nadroparin to inhibit P-selectin-dependent tumour cell interactions *in vitro* was positively correlated with their ability to inhibit experimental lung metastases *in vivo*. This study confirmed previous data showing the ability of nadroparin to inhibit experimental metastases.[85]

The clinical value of nadroparin in prolonging the survival of patients with cancer was first suspected in a nadroparin trial in cancer patients with deep-vein thrombosis, in which only 7% of nadroparin patients died compared with 44% of unfractionated heparin patients (p=0.021).[63] However, this study was not primarily designed to investigate the effect of nadroparin on cancer mortality. In addition, treatment lasted for only five to 10 days and the follow-up period was generally limited to three months. The prospective Malignancy And Low-molecular-weight heparin Therapy (MALT) trial was performed in order to clarify the value of nadroparin in prolonging the survival of cancer patients without thrombosis.[5] It was a randomised, double-blind, placebo-controlled study. Patients with metastasised or locally advanced solid tumours but without venous thromboembolism were randomly assigned to receive a six-week course of subcutaneous nadroparin or placebo. Nadroparin was administered according to patient weight: 3,800 anti-Xa IU (0.4ml) in patients below 50kg; 5,700 anti-Xa IU (0.6ml) in patients between 50 and 70kg; and 7,600 anti-Xa IU (0.8ml) in patients above 70kg. It was administered subcutaneously twice daily for the first 14 days of treatment, then once daily for another four weeks. In total, 148 patients were allocated to nadroparin and 154 patients to placebo. Mean follow-up was one year. The overall hazard ratio of mortality was 0.75 (95% CI 0.59–0.96), with a median survival of 8.0 months in the nadroparin recipients versus 6.6 months in the placebo group. After adjustment for potential confounders (life expectancy, World Health Organization [WHO] performance status, concomitant treatment, type and histology of cancer), the beneficial effect of nadroparin on survival remained significant (hazard ratio, 0.76; 95% CI 0.58–0.99). In the *a priori* specified subgroup of patients with a life expectancy of six months or above at enrolment, the hazard ratio of mortality was 0.64 (95% CI 0.45–0.90), with a median survival of 15.4 and 9.4 months in the nadroparin and placebo patients, respectively. For patients with a shorter life expectancy, the hazard ratio of mortality was 0.88 (95% CI 0.62–1.25). Major bleeding occurred in five nadroparin patients (3.4%) and in one placebo patient (0.6%; p=0.12). None of these events were fatal. Of the major bleeding episodes in the nadroparin group, three were spontaneous bleeds associated with the malignancy; another occurred during an intervention (drainage of ascites). This was the first randomised, placebo-controlled study that showed that a low-molecular-weight heparin may provide a survival benefit in the cancer population as a whole.

A second nadroparin trial in this context was performed to determine whether the addition of this drug to gemcitabine and cisplatinum improved the response rate and survival of 69 patients with advanced pancreatic cancer.[86] Gemcitabine 800mg/m^2 and cisplatinum 35mg/m^2 were given on days one and eight: this was repeated every 21 days. No additional treatment was given to a first control group. Nadroparin was administered subcutaneously at the once-daily dose of 2,850 anti-Xa IU (0.3ml) for each gemcitabine/cisplatinum cycle in a second group. Nadroparin-treated patients received a median of six (range: two to nine) cycles; control patients received a median of three (range: two to eight) cycles. The total response rate was 58.8% in patients treated with nadroparin and 12.1% in control patients (p<0.001). Median times to progression and overall survival times were 7.3±2.1 and 13.0±3.8 months, respectively, in the nadroparin group versus 4.0±0.3 (p<0.001)

and 5.5±1.3 months (p<0.001), respectively, in the control group. One-year survival rate was significantly (p=0.012) higher in the nadroparin group (58.6%) than in the control group (13.6%).

Other ongoing trials are currently being performed to further define the role of nadroparin in the survival of cancer patients. The Improving with Nadroparin the Prognosis in Advanced Cancer Treatment (INPACT) trial is a randomised trial of nadroparin versus placebo on survival in 500 patients with lung, pancreas or prostate cancer (i.e. three cancer types with similar prognosis) and a life expectancy of at least three months. Nadroparin patients are treated with two weeks of nadroparin at therapeutic doses and four weeks at half-therapeutic doses. The study was also designed to assess whether repeated treatment courses (six cycles of two-week periods of nadroparin every six weeks) may provide additional benefit.[87]

A randomised phase III study of adjuvant chemotherapy with or without low-molecular-weight heparin in completely resected non-small-cell lung cancer patients with high risk of recurrence (NVALT-8b) trial is a randomised clinical trial studying the value of nadroparin on the recurrence-free survival of 600 patients with resected non-small-cell lung cancer and a high risk of recurrence receiving adjuvant chemotherapy (Dingemans AC, personal communication). The administration of chemotherapy with or without nadroparin is initiated four to six weeks after surgery. In the group of patients randomised to nadroparin, the drug is administered for 16 weeks, at a therapeutic dose during the first two weeks, and thereafter at a half-therapeutic dose.

Conclusion

The benefit of low-molecular-weight heparins in the prevention and treatment of venous thromboembolism in patients with cancer should be emphasised in order to reduce the burden of this increasingly common severe disease. Concerning the prevention of venous thromboembolism, a significant proportion of cancer patients are not adequately treated.[88–90] Nadroparin may be valuable in this context because, in contrast to other low-molecular-weight heparins for which higher doses are required in cancer patients undergoing general surgery compared with non-cancer patients undergoing similar surgical procedures, a single dosage regimen of nadroparin 2,850 anti-Xa IU or 0.3ml once daily was effective and safe for preventing venous thromboembolism in both non-cancer and cancer patients. Furthermore, nadroparin is also the only low-molecular-weight heparin shown to reduce mortality in general surgery patients with or without cancer. It is important to highlight the importance of the long-term administration of low-molecular-weight heparins after the surgical procedure for cancer. In this regard, the good local tolerability of nadroparin appears to be particularly valuable.[91,92] Low-molecular-weight heparins, including nadroparin, were shown to be very effective and safe in terms of bleeding risk in the treatment of venous thromboembolism, including in an outpatient setting. In patients with cancer, low-molecular-weight heparins are particularly valuable for replacing vitamin K antagonists in the long-term prevention of recurrent venous thromboembolism. Finally, low-molecular-weight heparins may be particularly beneficial for prolonging the survival of patients with cancer.[83] The nadroparin experimental and clinical data in this setting are particularly compelling. It is not known whether this potential effect is specific to this drug or common to all low-molecular-weight heparins. However, although very promising, the trials that showed the benefit of nadroparin for prolonging the overall survival of patients with cancer are only hypothesis-generating. The ongoing trials should clarify the value of nadroparin in this setting. ■

Acknowledgements

Dr Piovella discloses that he has served on the speakers bureau of GlaxoSmithKline, Sanofi Aventis, Boehringer Ingelheim and Bayer, and has assisted advisory committees of the same companies. Dr Barone reveals no real or potential conflicts of interest or commitments. This article was funded by an unrestricted educational grant from GSK. The opinion of the authors does not necessarily reflect the position of GSK.

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