

# ADMINISTRATION OF LOW MOLECULAR WEIGHT HEPARINS FOR PROLONGING THE SURVIVAL OF PATIENTS WITH CANCER

Eugeniusz Majewski<sup>1</sup>, Marian Simka<sup>2</sup>

<sup>1</sup>Medical University of Silesia, School of Health Sciences in Katowice, Poland

<sup>2</sup>Department of Nursing, College of Applied Sciences, Ruda Śląska, Poland

## ABSTRACT

Thromboembolism represents one of the most common causes of mortality and morbidity in cancer patients, and thromboembolic events occur more often in patients with biologically more aggressive malignant disease. Therefore, low molecular weight heparins (LMWHs) are routinely administered to cancer patients. Importantly, in addition to the prophylactic activity against thromboembolism, LMWHs seem to decrease mortality in these patients. Improved clinical prognosis is independent of the antithrombotic efficacy, since vitamin K antagonists do not improve patient survival, and non-anticoagulant heparins exhibit a similar anti-cancer effect. This protective effect is primarily related to the prevention of spreading of the cancer through metastases. The mechanisms responsible for heparin-dependent inhibition of metastases comprise: inhibition of integrins, restraint of P- and L-selectin-mediated interactions of the platelets with circulating neoplastic cells, silencing of the chemokine CXCL12/CXCR4 axis, inhibition of heparanase activity, inhibition of neoangiogenesis within the tumour, and reduced local generation of thrombin. A combined effect of the above-described mechanisms is also possible. Although at the moment cancer patients are not recommended routine administration of LMWHs for survival improvement, such a recommendation might be expected in the future. It is possible that for this purpose, instead of currently available agents, some novel heparins or similarly structured chemical compounds will be used.

**Key words:** cancer, metastasis, heparin, patient survival.

The association of malignant tumours with thrombosis is a well-known phenomenon, especially in cancer patients with metastatic disease. Not only is venous thromboembolism (VTE) very often seen among cancer patients, but also these patients are more likely to have recurrent venous thrombosis: a three-fold higher risk for recurrent VTE compared to patients without malignancy [1–4]. Although VTE represents one of the most common causes of mortality and morbidity in cancer patients, it is unclear whether this increased mortality of cancer patients with thromboembolism is directly linked to such fatal events as pulmonary embolism. Rather, VTE occurs in the case of biologically more aggressive malignant disease [5, 6]. Currently it is believed that this procoagulant attribute of cancer is an indispensable phenomenon of its malignant nature. By activating coagulation through the autocrine system the neoplastic tumour augments its malignant phenotype, which is why venous thrombosis is associated with a higher aggressiveness of cancer [7].

Currently it is recommended that cancer patients receive antithrombotic prophylaxis with anticoagulants – heparin, fondaparinux, or semuloparin – in several

clinical situations: as a perioperative and post-discharge prophylaxis in patients undergoing surgical procedures, in hospitalised patients who are confined to bed, and in high-risk ambulatory cancer patients receiving chemotherapy [2, 8–12]. Heparins, low molecular weight heparins (LMWHs) in particular, are regarded the first-line therapy for VTE in cancer patients, and these pharmaceutical agents are increasingly used for this purpose [1, 4, 13–15]. The LMWHs are produced from unfractionated heparin by either chemical or enzymatic depolymerisation, with a mean molecular mass of a final product of about 5000 Da. There are important advantages of LMWHs over unfractionated heparin: the drug can be administered once daily, it exhibits a more favourable pharmacokinetic profile, and it is less likely to evoke heparin-induced thrombocytopenia and osteoporosis.

Importantly, in addition to the prophylactic activity against thromboembolism, LMWHs seem to decrease mortality in cancer patients [16–21]. This phenomenon of improved survival of cancer patients associated with administration of LMWHs has been attracting attention for many years [22–28]. The list of clinical trials in cancer

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## ADDRESS FOR CORRESPONDENCE

Marian Simka  
Department of Nursing  
College of Applied Sciences  
Królównej Jadwigi 18  
41-704 Ruda Śląska, Poland  
e-mail: mariansimka@poczta.onet.pl

patients that have demonstrated such a decreased mortality in patients receiving LMWHs are as follows: the FAMOUS (Fragmin Advanced Malignancy Outcome Study) study, in which prophylactic doses of LMWH dalteparin were compared to placebo and the main endpoint of the study was the efficacy of primary thromboembolic prophylaxis [17]; the MALT (Malignancy and Low Molecular Weight Heparin) study, in which LMWH nadroparin was administered to patients with advanced malignancy [29]; the CLOT (Comparison of Low-Molecular-Weight Heparin vs. Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) study, which assessed the efficacy of secondary prophylaxis against thromboembolism with LMWH dalteparin in cancer patients with good clinical prognosis [19]; and the PROTECHT (Prophylaxis of Thromboembolism During Chemotherapy) study on thromboembolic prophylaxis with LMWH nadroparin in patients receiving chemotherapy for advanced cancers [30].

In the FAMOUS trial, carried out on a subgroup of patients with good clinical prognosis, administration of LMWH significantly improved their survival [17]. In the MALT study, administration of LMWH resulted in improved survival in cancer patients with advanced malignancy with a life expectancy of more than six months [29]. Similarly, cancer patients with good clinical prognosis benefited from LMWH administration in the CLOT study [19]. Also, a post-hoc analysis of the results of the PROTECHT study revealed improved survival, but only in patients responding to chemotherapy [30], while this beneficial effect was not seen in those not responding to the treatment [31]. On the other hand, such an anti-cancer protective effect was not found in other clinical trials assessing the survival benefit of LMWH administration. However, these trials examined patients with an advanced malignancy and poor clinical prognosis [32, 33].

Analysis of the above-mentioned trials suggests that in selected groups of cancer patients LMWHs improve survival irrespective of the antithrombotic efficacy of the drug, since vitamin K antagonists did not improve clinical prognosis [19]. Besides, this anti-cancer effect did not result from an inhibition of primary tumours, but rather from anti-metastatic activity [34, 35]. Consequently, two published meta-analyses [36, 37] suggest that LMWHs can improve the survival of cancer patients, primarily those with non-metastatic disease. It is also possible that at least some patients with advanced tumours can also benefit from LMWH administration. However, detailed clinical characteristics of such patients who could particularly benefit from LMWH administration, as well as optimal dosing of the drug for this purpose, remain to be discovered by future research. Although the protective effect of LMWHs was primarily seen in some kinds of malignancy, for example small-cell lung cancer, a complete list of heparin-susceptible cancers must still be established [36, 37].

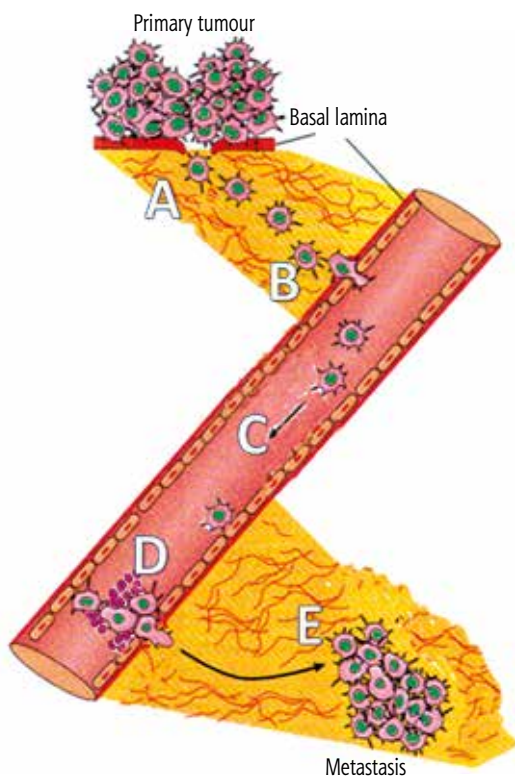
The anti-metastatic properties of LMWHs were also demonstrated in animal and *in vitro* experiments. For example, in an animal experiment the LMWH enoxaparin significantly suppressed the formation of hepatic metastases of colon cancer. This inhibition of metastases was probably dependent on the disruption of interactions between chemokines CXCR4 and CXCL12 [38]. In another animal experiment, LMWH administered together with adriamycin (antineoplastic agent) reduced the growth of breast cancer [39]. This anti-tumour effect was likely to be associated with the induction of apoptosis of cancerous cells and inhibition of angiogenesis within the tumour. Another animal study revealed that anticoagulation with the LMWH enoxaparin attenuated growth of osteosarcoma cells *in vivo* [7]. Similarly to the results of clinical trials, animal experiments suggest that the anti-cancer activity of LMWHs is independent of the antithrombotic activity. For example, a chemically modified non-anticoagulant heparin: SST0001 inhibited myeloma growth [40]. In addition to growth inhibition of the tumour, in this experiment SST0001 reduced angiogenesis. In another paper researchers reported that SST0001 inhibited growth of sarcoma tumours, which was probably associated with the anti-angiogenic activity of this chemically modified heparin [41]. An orally active LMWH conjugate, LHTD4, exhibited anti-cancer activity, which was probably associated with the anti-angiogenic properties of LHTD4 [42], and a similar anti-metastatic activity was also revealed by some selectin-specific heparin derivatives [26, 43]. Another animal experiment on orally absorbable heparin derivative demonstrated a significant attenuation of experimentally induced metastases of murine melanoma and human lung carcinoma cells [44]. In this animal model metastatic activity was primarily attributed to the interruption of the interactions between neoplastic cells and activated platelets.

Similar conclusions came from *in vitro* studies. One such experiment demonstrated that the LMWH suppressed proliferation and migration of hepatocellular cancer cells. Of note, these antiproliferative and antimigratory properties of LMWH were further augmented by simultaneous treatment with an antineoplastic agent: doxorubicin [45]. In another *in vitro* study LMWH enoxaparin diminished osteosarcoma (human and murine neoplastic cells) growth. This anti-neoplastic effect was related to reduced local thrombin generation [7]. Another *in vitro* study demonstrated that LMWH fraxiparine in a dose-dependent manner significantly inhibited migratory and adhesive properties of lung cancer cells. It was found that this LMWH affected cytoskeleton re-arrangement of neoplastic cells through prevention of F-actin polymerisation. Also, LMWH fraxiparine inhibited CXCL12-mediated migration of these cells and disrupted the CXCL12-CXCR4 chemokine axis [46, 47].

Metastasis of a cancer is an active multistep process of migration of neoplastic cells, which is very similar to

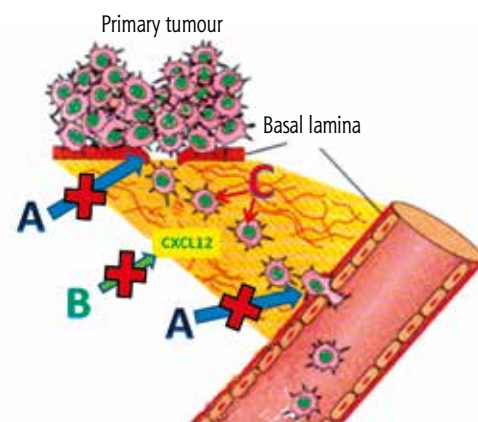
the homing of normal cells, such as leukocytes. Different populations of leukocytes and other migratory cells precisely home to their target organs and tissues because they are equipped with specialised sets of adhesion molecules, chemokines, and their receptors. By the same token, metastasis of cancer consists of the shedding of neoplastic cells from the primary tumour, entering of these cells into the circulation, and docking to the endothelium in the target organ (such as the liver, lung, brain, or bone) followed by extravasation into the surrounding tissue (Fig. 1) [16, 48, 49]. For the time being, the mechanisms behind anti-metastatic activity of LMWHs remains elusive, even if the above-cited studies have shed some light on possible pathways responsible for this phenomenon. LMWHs are the group of pleiotropic pharmaceutical agents. They can interact with a large number of biologically active compounds, primarily glycans and glycopeptides [50]. Importantly, these chemical compounds are thought to participate in cancer progression and metastasising.

Research suggests that the anti-metastatic protective activity of LMWHs is unlikely to be a by-product of their antithrombotic properties. Rather, this attenuation of metastases is secondary to the restraint of P- and L-selectin-mediated interactions of the platelets with circu-

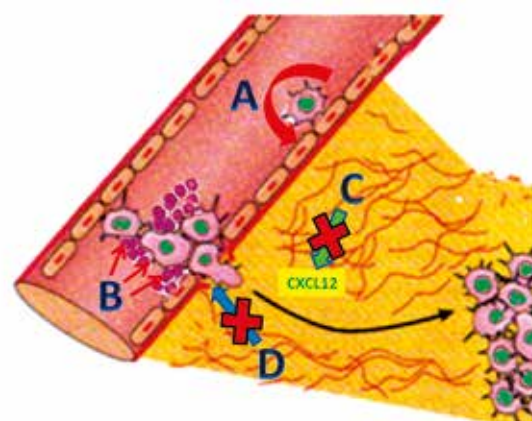


**Fig. 1.** Metastasis of a cancer: A) shedding of neoplastic cells from primary tumour and their transmigration through the basal lamina; B) active migration of neoplastic cells towards blood vessels and entering the circulation; C) passive migration via blood vessels to the target organ; D) docking to the endothelium and extravasation of neoplastic cells into the surrounding tissue; E) forming a metastasis in the target organ

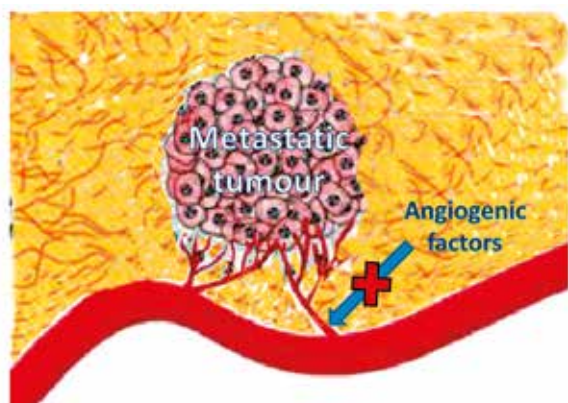
lating neoplastic cells [16, 43, 51–55], modulation of the chemokine CXCL12/CXCR4 axis [16, 37, 38, 46, 47, 56, 57], inhibition of heparanase activity [58–61], and inhibition of neoangiogenesis within the tumour (Figs. 2, 3, and 4) [39, 40, 50, 62–65]. LMWHs can also interfere with the activity of another class of adhesion molecules: integrins. Integrins are transmembrane glycoproteins that are ubiquitously expressed by endothelial cells, different kinds of leukocytes, and cancerous cells. They play an important role in cell motility and migration. These complex molecules mediate cell adhesion and bind components of the extracellular matrix. Also, since the internal part of an integrin is linked to the cytoskeletal structures, binding of its extracellular receptor may result in a change of intracellular metabolism. This signalling is mediated,



**Fig. 2.** Mechanisms by which heparins attenuate the initiation of cancer metastasis: A) inhibition of heparanase-dependent degrading of basement membrane; B) inhibition of chemotaxis mediated by the chemokine CXCL12; C) inhibition of migration of neoplastic cells through re-arrangement of their cytoskeleton



**Fig. 3.** Mechanisms by which heparins attenuate formation of metastasis: A) inhibition of selectin-dependent rolling of neoplastic cells; B) inhibition of selectin- and thrombin-dependent formation of complexes composed of neoplastic cells and platelets; C) inhibition of chemotaxis mediated by the chemokine CXCL12; D) inhibition of heparanase-dependent degrading of basement membrane



**Fig. 4.** Inhibition of neoangiogenesis through blocking the angiogenic growth factors

among others, by activation of kinases, GTPases, and Ras/Rho pathway signalling [66]. Silencing of integrins results in diminished aggressiveness of a number of some neoplasms, especially of malignant melanoma [66].

It is also possible that at least in some cases an anti-neoplastic effect of LMWHs is associated with reduced local generation of thrombin [7]. Thrombin may promote malignant transformation through several mechanisms: via direct activation of thrombin receptors on the cell surface - which in turn leads to cell proliferation, via increased release of VEGF, and via enhanced interaction between platelets and neoplastic cells. In addition, fibrin that develops after pro-coagulant action of the thrombin is an ideal milieu for tumour growth. Moreover, fibrin enhances adhesion of neoplastic cells to the platelets, which further promotes malignancy. All of these effects associated with thrombin formation can be attenuated by LMWHs [7]. Probably a combination of all the above-mentioned mechanisms plays a role in protecting patients from cancer progression [67].

Although at the moment cancer patients are not recommended an administration of LMWHs for survival improvement, such a recommendation might be expected in the future. It is possible that for this purpose, instead of currently available LMWHs, some novel LMWHs or similarly structured chemical compounds will be used. Besides, their clinical use would be part of a more complex treatment, such as multidrug chemotherapy combined with the administration of the drugs modifying the interaction of host tissues with the tumour. Perhaps these new heparins recommended for anti-cancer therapy would be deprived of anti-thrombotic activity [26, 67]. Although administration of standard LMWHs is beneficial in terms of thromboembolic prophylaxis, there is also a risk of bleeding, especially with high doses or prolonged administration of these pharmaceutical agents. In addition, it cannot be ruled out that anti-cancer doses of standard LMWHs should actually be much higher than those used for the prophylaxis against thromboembol-

ic events. Still, because of the risk of bleeding, in many patients heparins exhibiting antithrombotic effect would be of limited use for long-term anti-metastatic prophylaxis. On the contrary, non-antithrombotic heparin derivatives seem to be natural candidates for future trials on high-dose and long-term prophylaxis against cancer metastases and progression.

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