

The Role of Heparin in Lung Cancer

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Abstract:

Non-small cell lung cancer is a major health problem worldwide. Surgery is still the mainstay of treatment especially in early stages of the disease. Despite the fact that surgery is the potentially curative treatment, the recurrence and mortality rates are still high specifically with more advanced stages of cancer. Heparin has been suggested to have a positive impact on the outcome of various cancers through its anticoagulants properties and; in some instances; due to their antitumor activity. Recently, the molecular mechanisms of tumor cell spreading have been recognised. Metastasis is a complex process that could be therapeutically affected wherever certain extra-cellular matrix proteins could play an important role in prevention of tumor cell migration and invasion. Experimental studies have shown decreased metastases development after heparin use in rat models.

We have reviewed the literature to study the role of anticoagulants in cancer patients in general and in patients with Non Small Cell Lung Cancer (NSCLC) specifically.

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Running title: Heparin & lung cancer

Key words: Heparin, lung cancer, NSCLC, anticoagulants, cancer, LMWH, anticoagulants.

Received: March 23, 2017;

Accepted: May 10, 2017;

Published: Jul 23, 2017;

Introduction

Haematological complications especially coagulation problems are more frequent in cancer patients. The association between cancer and venous thrombo-embolic events is well established (1, 2). Cancer cells can produce activators that can initiate the coagulation cascade. This relationship between anticoagulants and cancer disclosed the potential beneficial effects of the use of anticoagulants in the prevention or treatment of cancer (2, 3).

The main cause of diminished survival in different types of cancer is tumor recurrence or tumor metastases. Several studies showed methods to reduce tumor progression (3- 5). Although an optimized surgical technique is the main determining factor (5), the application of various drugs for preventive strategy is also another important factor (6).

Recently, the molecular mechanisms of tumor cell spreading have been recognized. Metastasis is a complex process that could be therapeutically affected. Certain extra-cellular matrix proteins could play an important role in prevention of tumor cell migration and invasion (7, 8, 9). Cell adhesion is an important factor in cancer invasion. Experimental studies have shown decreased colorectal metastases after heparin use in rat models (10).

The objective of this article is to review the literature for the role of anticoagulants in cancer patients in general and particularly in patients with Non Small Cell Lung Cancer (NSCLC). The study will evaluate the effects of the anticoagulants and specifically Low Molecular Weight Heparin (LMWH) on the control of NSCLC recurrence and metastases and consequently survival in those patients.

History

Unfractionated heparin was developed during 1930s. Since that time it has been used by injections for more than sixty years. It requires coagulation monitor-

ing, and it can be associated with heparin-induced thrombocytopenia (HIT) and osteopenia (11-13).

Vitamin K Antagonists (VKAs), as warfarin and acenocoumarol, were the first oral anticoagulants introduced into the market during 1950s. Warfarin has been the drug of choice for prevention and treatment of arterial and venous thrombotic disorders for more than 40 years. It was initially marketed as pesticide against rats and mice and is still popular for this purpose. Although, VKAs are highly effective, they are difficult to manage well (14). These therapies require frequent monitoring and dose adjustment to limit adverse consequences and they have multiple food and drug interactions. Moreover, these factors may contribute to the frequent underuse of warfarin, especially in elderly patients, and low patient satisfaction (15). In addition, VKAs have a slow onset of action, and when used for Venous Thrombo-Embolic (VTE) treatment, bridging therapy with injected anticoagulants with a fast onset of action is required.

Ximelagatran was the first oral direct thrombin inhibitor and had proven efficacy for prevention and treatment of (VTE), stroke prevention with AF and recurrent coronary events after acute myocardial infarction (16, 17). Its use was initially approved for short term prevention of (VTE) in patients who will undergo orthopedic surgery in Europe. Then, it was drawn by AstraZeneca in 2006 due to laboratory work that confirmed the significant liver damage related to its use (17, 18).

During the 1980s, Low Molecular Weight Heparin (LMWH) had been developed to overcome the drawbacks of unfractionated heparin. LMWHs do not require monitoring and have a lower risk of HIT (19, 20) but they must be administered by injection, and can accumulate in patients with kidney impairment (16).

Since then, LMWH has been used extensively for treatment and prevention of many arterial and venous thrombo-embolisms. Moreover, the pharmaceutical

companies and researches are going fast for more advances in these drugs.

Magnitude of the NSCLC Problem

During 2012, it was found that there were about 1.82 new lung cancer cases and around 1.59 million lung cancer deaths worldwide (21). Approximately four out of five cases are men. Although the incidence is decreasing in men, it is still the most important cause of cancer death. In women, the incidence is increasing. More than 85% of lung cancers are associated with smoking. The median survival following diagnosis is eight months, and 13% of patients are still alive after five years (22). Only 25% of patients are eligible for an intentionally curative treatment, such as tumour resection. In this group, the cure rate is about 25%. The remaining patients are not eligible for resection due to locoregional or metastatic spread of disease, or their overall state of health (23). Despite diagnostic and therapeutic advances, the stage distribution and survival rate for patients with NSCLC has not improved substantially in accordance with this advancement (24).

Survival in different Stages of NSCLC

Non-small cell lung cancer (NSCLC) is a major health problem all over the world (25, 26). Surgery represents the mainstay treatment in stages I-II, and in some patients with stage IIIA (*i.e.* patients with minimal N2 or T3N1 disease). Stage IIIA, includes a heterogeneous group of patients who are usually offered a multimodal approach including surgery and/or chemotherapy and/or radiotherapy. The 5-year survival rates after surgery are satisfactory only in pT1N0 disease, 70 to 90% (20, 21), whereas they fall in more advanced stages: values of 57%, 55%, 39%, and 38% have been reported in T2N0, T1N1, T2N1, and T3N0 disease, respectively (27). In stages IIIA-B, the survival rate is even lower in spite of aggressive treatments (27, 29, 30).

Impact of Adjuvant Radiation on Survival of NSCLC

Adjuvant radiation therapy failed to demonstrate any significant improvement in survival rates: although radiotherapy would increase the rate of local control of the disease, there is no convincing evidence that it increases the distant control or the survival. In addition it was associated with a significant increase of death. The real impact on survival of adjuvant chemotherapy remains unclear in spite of several randomized clinical trials (31).

Impact of Neo-Adjuvant Chemotherapy on Survival of NSCLC

The impact of neo-adjuvant chemotherapy remains controversial. A Spanish study (32) and a US randomized study (33) on neo-adjuvant chemotherapy in N2 disease showed an increased survival in the study arm of combined treatment. However, the survival rate of patients undergoing surgery alone was extremely poor in both studies. In another study conducted in France (34) the administration of two courses of chemotherapy followed by surgery was compared to surgery alone in resectable stage I-IIIa NSCLC; a trend toward a survival advantage not reaching significance ($p = 0.11$) was observed. In addition, when the data were analyzed according to the nodal status, the survival advantage was significant in N0-N1 disease but not in patients with N2 disease.

Impact of Anticancer Agent on Survival in Patients with NSCLC

Over time, new anticancer agents, molecular-targeted agents became available for clinical studies. In particular, monoclonal antibodies and small molecules targeted to epidermal growth factor receptor were evaluated in a randomized setting of patients with advanced disease; but no survival advantage could be achieved by using these biological agents, combined with standard chemotherapy, in the whole group of enrolled patients (35).

Failure of Treatment in Patients with NSCLC

Local recurrence and distant metastasis have to be considered as the leading cause of treatment failure in resected NSCLC. The failure pattern in operated NSCLC depends on the stage of the disease; while the local control is very satisfactory in stages IA-B (28, 36). It is not the case in more advanced stages as they have a higher risk of local recurrence. In particular, the recurrence rate is relatively low in stage II (37), but increases in stage IIIA, especially in N2 disease (38). Overall, distant metastasis has to be considered as the leading cause of treatment failure in resected NSCLC. As a consequence, it is reasonable to hypothesize that the prevention of the metastatic spread (preoperatively, peri-operatively, and postoperatively) could represent the mainstay of improvement in chances of cure in those patients. Blood clotting components in micro vessels were found to play a significant role in the process of metastasis (39).

Venous Thrombo-Embolism in NSCLC patients

It has been recognised that venous thrombo-embolism (VTE) represents a common complication of malignancy. It was shown that the relative risk of VTE is increased about 4-6 folds in patients with cancer, compared to sex and age matched control (40). Previous studies have also showed that the development of symptomatic VTE in a cancer patient is associated with significant reduction of the overall survival (41).

The clinical importance of anticoagulant therapy in patients with cancer is readily apparent, in view of the prevalence of VTE in cancer patients, and its associated morbidity and mortality. Generally, in non-cancer patients, the acute VTE is treated with anticoagulants starting by using the unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for a period ranging from 5 to 7 days followed by oral anticoagulation via warfarin for at least 3 months (42).

The use of LMWH has particular advantages over UFH, many of which are of great importance to cancer patients (43). Firstly, The LMWH has a

significantly longer half-life than UFH, so can be administered once daily as subcutaneous injection. Secondly, due to its more predictable pharmacokinetics, it could be used without frequent laboratory monitoring (44). Finally, both heparin-induced thrombocytopenia (HIT), and heparin-induced osteoporosis are both less common with LMWH compared with UFH (43). Consequently, LMWH have become widely used as the treatment of choice for the management of acute VTE in cancer (45). However, it remains unclear whether different LMWH preparations are equally efficacious and also the optimal dose of LMWH dosage regimen should be defined in this setting (46).

The use of warfarin therapy in patients with cancer could be associated with important clinical problems like gastrointestinal disturbances, or hepatic dysfunction. Moreover, the concurrent chemotherapy can lead to significant fluctuation in International Normalized Ratio (INR). Consequently, establishing a stable INR within the target therapeutic range is more difficult. The risk of warfarin induced major bleeding will also be further exacerbated during any period of chemotherapy induced thrombocytopenia (47). In view of inherent difficulties associated with warfarin use in oncology patients, recent studies have evaluated the efficacy and safety of long term LMWH as an alternative to warfarin. All trials performed with different types of LMWH demonstrated a comparable long term efficacy in comparison to warfarin in cancer patients (48).

The pathogenesis of cancer related VTE is complex, involving multiple interactions between malignant cells, endothelial cells and coagulation cascades. Tumours can significantly impact upon all three components of Virchow's triad. These different mechanisms have been comprehensively discussed in another published review (49). One of the most important mechanisms through which cancer induced coagulation cascade activation is due to apparent tissue factor (TF) expression on tumour cell surfaces (including

pancreatic cancer, non small cell lung cancer, and leukemia) (50).

Link between Cancer and Coagulation Process

Platelet aggregation or fibrin coagulation may facilitate the tumor cell evasion of destruction by natural killer cells. Heparin increases the clearance of the tumor cells from the blood in mice and has an anti-metastatic effect (51) through making tumor cells more susceptible to NK lymphocytes (52). Moreover, there is clear evidence that the arrest of the tumor cells in capillaries is related to the development of micro-thrombi (53). Meanwhile, the thrombin affects directly the tumor cells to become more adhesive.

Tilley R. *et al.* demonstrated that activated coagulation proteases interact with protease activated receptors (PARs) on tumour and host vascular cells, leading to induction of genes involved in apoptosis, angiogenesis, and metastasis (50). The role for TF expression was reported in determining the progression of tumour growth and angiogenesis (54). The studies performed on animal models (rats inoculated with Walker 256 carcinosarcoma cells plus warfarin therapy for ten days), suggested that oral vitamin K antagonists could significantly reduce pulmonary metastases (98% vs. 85.8%; $p < 0.001$) and improved overall survival. Same results were encountered with other different malignant cell lines including B16 melanoma cells, KHT tumour transplant (55). In contrast, warfarin therapy was found not to enhance the cytotoxic or anti metastatic effects of 5-fluorouracil in murine models of adenocarcinoma or L210 leukemia, respectively (56).

Warfarin and Survival in Cancer Patients

In a study conducted by Zacharski *et al.* (56) to test the effects of warfarin effect on survival of cancer patient (head and neck, prostate, colorectal and lung), Warfarin therapy did not improve overall survival for patients with colorectal, prostatic, or head and neck tumours. However, subgroup analysis demonstrates a significant effect of warfarin on overall survival in

patients with small cell lung cancer (SCLC).

UFH and Survival in Cancer Patients

Several randomized clinical studies have tested the effect of heparin on survival in different types of cancer (small cell lung cancer "SCLC", breast, GIT, pancreas, gut, ovary, uterus, renal, colorectal and prostate). One study conducted by Lebeau *et al.* on survival in patients with both, limited and extensive SCLC who received UFH documented better complete response rates (37% vs. 23%; $p = 0.004$) and better median survival (317 days vs. 261 days; $p = 0.01$). A subgroup analysis demonstrated that a significant beneficial effects of UFH in patients with limited stage SCLC rather than those with more extensive disease ($p = 0.03$) (57-61).

LMWH and Survival in Cancer Patients

In order to investigate whether the LMWH influences survival in cancer patients without VTE, the FAMOUS (Fragmin Advanced Malignancy Outcome Study) trial enrolled 385 patients with histologically confirmed advanced (stage III and IV) malignant disease of different types of cancer (59). All patients had a minimum predicted life expectancy of three months, and received chemotherapy (32%) and or radiotherapy (8%) at the discretion of the treating physician. Moreover, patients were randomized to receive LMWH (Dalteparin) 5000 IU daily or placebo for 12 months. A non significant trend towards a survival advantage was observed in the group of patients treated with Dalteparin. In MALT (Malignancy And Low molecular weight heparin Therapy) study, there was a significant improvement in overall survival in those patients randomized to receive Nadroparin therapy compared to control group. Furthermore, the beneficial effects of LMWH therapy were again higher in the subgroup of patients who had longer life expectancy (more or equals to 6 months) at enrolment (60). A third study conducted by Sideras *et al.* has further investigated the effects of LMWH on survival in patients with advanced solid

tumours (61). In contrast to the previous two studies, this study did not show any effects of LMWH on overall survival even in the subgroup that had better prognosis.

Effect of Heparin on different Steps in Cancer Progression

Different coordinated steps are essential to evolve cancer and its metastases (62). These steps include 1) cell cancer proliferation; 2) establishment of a defence against attacks of the immune system; 3) angiogenesis; 4) cancer cell migration after detachment from their original site; 5) adhesion and invasion of surrounding tissues; 6) access of cancer cells to blood and lymph vessels with consequent adhesion and invasion of the lining endothelium giving the opportunity for colonisation at distant sites (62, 63).

Effects of Heparin on Cancer Cell Proliferation

Heparin can inhibit proliferation of different cell types. The anti-proliferative effects of heparin were attributed to their inhibitory effects on the proto-oncogenes as *c-fos* and *c-myc* through alterations of the protein kinase C-dependant signal transduction pathway (62, 64). It was shown that heparin inhibits phosphorylation of the mitogen activated protein kinase (MAPK), which is an intermediate kinase in the protein kinase C-signaling cascade (65, 66). However, the results of the few studies that evaluated the effect of heparin on proliferation of cancer cells were inconclusive (61, 66, 67).

Effects of Heparin on Immune System

Heparin can affect adhesion of leucocytes to endothelium at sites of inflammation or tumor invasion; hence it can interfere with the immune reactions. Moreover, heparin can inhibit leukocyte activation and affect complement activation (68). In addition to the direct effect of heparin on the immune system, Gorelik *et al.* (51) has suggested that heparin inhibits metastasis by rendering cancer cells more vulnerable to cytotoxic effects of natural killers (NK) cells.

In short, heparin could affect the immune system directly by inhibiting the complement system and extra-vasation of the leukocytes. Consequently, it enhances the susceptibility of cancer cells to immunological attacks (62).

Effects of Heparin on Angiogenesis

Angiogenesis is important step for further development of the tumors and even for facilitation of the tumor cells from the primary site to distant ones (62, 69). Angiogenesis is a complex process that involves many steps like endothelial cell activation, controlled proteolytic activation and other molecular mechanisms (70). In vitro and in vivo studies have shown that heparin interferes with the angiogenesis by other ways unrelated to its anticoagulant prosperities (62). Suppressing effects of heparin on angiogenesis were attributed mainly to their interference with activity of angiogenic growth factors but heparin could also modulate the angiogenesis process through its anticoagulant effects (71). In addition, heparin may affect angiogenesis via inhibition of proliferation and migration of pericytes (63, 72). Finally, various experimental studies have reported that angiogenesis can be inhibited by treatment with combinations of UFH and corticosteroids but the mechanisms have not been explained yet (62, 73).

Effects of Heparin on Cancer Cells and Endothelial Cells Migration

Cell migration is important for both metastasis and angiogenesis. Heparin was found to affect the cancer cell migration. It may restrain migration of cells through adhesion inhibition of the cells to the ECM proteins. Moreover, heparin can either stimulate or inhibit synthesis of the ECM proteins which may indirectly modulate migration of cells (62).

Effects of Heparin on Invasion of Cancer Cells and Endothelial Cells

Cancer cells and endothelial cells use specific

proteolytic enzymes during invasion of the extracellular matrix (ECM) (74). Heparin may affect cellular invasion by modifying the activity of the various proteolytic enzymes like plasmin. They potentially stimulate u-PA activity and plasminogen activation, but inhibit heparanases and Matrix metalloproteinase (MMPs) (62).

Effects of Heparin on Cancer Cell Adhesion and Vascular Endothelium

The arrest of cancer cells in small vessels is an essential step in the metastatic process. Cancer cells first attach loosely to the endothelium using selectins which binds to the carbohydrates-ligands such as sialyl-Lewis^x and sialyl-Lewis^a (75). Expression of these ligands correlates with the metastatic potential of the cancer cells (76). Heparin can interfere with the binding of selectin to their carbohydrate ligands (62, 77). Moreover, heparin and other anticoagulants may inhibit adhesion of the cancer cells to the endothelium by inactivation of thrombin or inhibition of platelets aggregation and thrombus formation (78).

Experimental Studies on Heparin and Cancer Cells

It was postulated that heparins can influence the cancer progression. Moreover, this is supported by numerous experimental studies (79 - 81). These studies have shown that heparins do not only affect cancer by their interaction with the coagulation cascade; but also by various other ways. Heparins are members of a family of polysaccharides, the glycosaminoglycans. Additional members of this family include heparan sulfate, chondroitin 4-sulfate, chondroitin 6-sulfate, dermatan sulfate, and hyaluronic acid. Glycosaminoglycans are linear carbohydrate polymers, which are composed of alternating uronate and hexosamine saccharides that are linked by glycosidic linkages. UFH is a mixture of glycosaminoglycan chains, each containing 200 to 300 saccharide units. LMWH consists of low molecular weight fragments of UFH produced by controlled enzymatic or chemical depolymerization, which yields chains that are less than 18 saccharide

units long with a mean molecular mass of approximately 5000 Da. UFH and LMWH exert their anticoagulant effects by activating the physiological coagulation inhibitor antithrombin, which neutralizes many of the serine proteases involved in the coagulation system. Particularly thrombin and activated factor X (Xa) (82). Besides binding to antithrombin, UFH and to a lesser extent LMWH bind to a wide range of proteins and molecules via electrostatic interactions with the polyanionic groups of the polyaminoglycan chains. Consequently, UFH and LMWH have a wide variety of biological activities other than their anticoagulant effects. Thus far, numerous mechanisms by which heparins potentially affect tumor development and/or metastasis have been described, but the ultimate effects of either UFH or LMWH on cancer progression are still poorly understood.

Heparin and Lung Cancer

As previously mentioned the anticoagulants have been proved to exert anti-tumor and anti-metastatic effects either as a part of their anti-coagulation function or through other direct or indirect ways that are not fully explored until now. The effect of heparin could be different depending on the type of the tumor cells (1). This variability in the effects of heparin on different types of tumor cells have enforced several researches (83, 84) to assess for its effects on lung cancer and more specifically on NSCLC.

Recently, Abu Arab *et al.* (85) have documented that LMWH has a potential suppressor effect on A495 adenocarcinoma cells in vitro. They have found that LMWH has inhibitory effects on NSCLC cells proliferation as documented by diminished cell count and decreased expression of c-Myc oncoprotein which is involved in proliferation, differentiation and apoptosis (85, 86). Moreover, this group (85) has documented that LMWH has a potential anti-metastatic effects on NSCLC away from its anticoagulation properties. It was found that LMWH decreases the expression of CD44 (85) which is

an important surface receptor involved in cell adhesion and metastasis formation (87). Moreover, these inhibitory effects were found to be dose and time dependant (85).

Clinical Trials

Several clinical studies have been conducted to reveal the effect of the heparin on survival of patient with cancer. Most important clinical trials are enlisted in Table 1. Lebeau *et al.* (57) have recruited 277 patients with both limited and extensive SCLC. Patients were randomised to receive along with their chemotherapy a prophylactic dose of UFH for five weeks or no intervention. The study showed a significant increase in median survival (317 days versus 261 days; $p = 0.01$).

Kakkar *et al.* (59) (FAMOUS group) recruited 385 patients with advanced (stage III or IV) malignant disease of breast, lung, gastro-intestinal tract (GIT), pancreas, liver, genitor-urinary tract (GU), ovary or uterus. Patients were randomised to receive a prophylactic dose of LMWH (dalteparin) or placebo for 12 months. This group also has showed an improved survival of the use of LMWH in those patients with cancer (44 months versus 24 months; $p = 0.03$).

Whereas 302 patients with different types of solid malignant tumors were included in the study conducted by Klerk *et al.* (60) (MALT trail). Those patients had different types of cancer that include: colorectal, breast, lung, gastric, oesophageal, liver, gall bladder, kaskin, prostatic, pancreatic, urothelial, cervical, renal, ovarian, melanoma, endometrial and other cancer. Patients were given a therapeutic dose of LMWH (Nadroparin) for two weeks followed by a prophylactic dose for a period of four weeks or a placebo for six weeks without any concomitant chemotherapy or radiotherapy. This study showed also a significant increase in median survival (8 months versus 6.6 months; $p = 0.02$).

In a randomised clinical study conducted by Altinbas *et al.* (58), 84 patients with both limited and

extensive SCLC were included. A prophylactic dose of LMWH (dalteparin) or placebo for 18 weeks or less in combination with chemotherapy in case of disease progression. It was noted also that there is an increase in median survival (13 months versus 8 months; $p = 0.01$).

On the other hand, Sideras *et al.* (61) have included 141 patients with different types of advanced cancer in his study. Types of included cancers are breast, lung, colorectal and prostate cancers. Patients were randomised either to a prophylactic dose of LMWH (Dalteparin) or to placebo or no intervention. In contrast to the previously mentioned trials, he has not found any significant effect on median survival. It is important to mention here that subgroup analysis in two studies conducted by Lebeau *et al.* (57) and Altinbas *et al.* (58) showed beneficial effect to small cell lung cancer (SCLC).

All of the previous studies have evaluated the effects of heparin on different types of cancers including SCLC but none has evaluated its effects on survival of NSCLC patients. Loyens *et al.* (88) has documented regression in NSCLC in one patient with the use of LMWH. We could not find a large randomised clinical trial that study the effects of heparin on lung cancer either SCLC or NSCLC. In addition most of the previously mentioned studies have involved small numbers of patients with heterogeneous types and stages of cancer.

Future directions

It is well known that heparin; especially LMWH; has a role in cancer patients, not only in treatment of thrombo-embolic events but also in potential enhancement of median survival. As previously discussed, heparin effects could differ according to the type of cancer. Further evaluation should study their effects on each cancer cell type specifically. Larger clinical trials focusing on specific tumor types and cancer stages should be planned to precisely detect the effect of heparin on patient survivals and quality of life.

Table 1: Different randomised clinical trials assessing the effects of heparin on cancer patients' survival

Study	Year	Type of cancer	Patient	Treatment	Outcome
Lebeau et al.	1994	SCLC	227	Prophylactic dose of UFH for five weeks	An increase in median survival (317 days versus 261 days; p = 0.01).
Kakkar et al. (FAMOUS trial)	2004	Breast, lung, GIT, pancreas, GUT, ovary,	385	A prophylactic dose of LMWH (dalteparin)	An improved survival (44 months versus 24 months; p = 0.03).
Klerk et al. (MALT trial)	2005	Breast, lung, GIT, pancreas, renal, ovary, uterus	84	A therapeutic dose of LMWH (nadroparin) for two weeks followed by a prophylactic dose for a period of four weeks	A significant increase in median survival (8 months versus 6.6 months; p = 0.02).
Altinbas et al.	2004	SCLC	302	A prophylactic dose of LMWH (dalteparin) or placebo for 18 weeks or less in combination with chemotherapy in case of disease progression.	An increase in median survival (13 months versus 8 months; p = 0.01).
Sideras et al.	2006	Beast, lung, colorectal,	138	A prophylactic dose of LMWH (dalteparin)	No significant effect on median survival.

The optimal time frame and the dose of heparin to be used to treat or to prevent cancer recurrence or metastases should be determined. Should its use be limited to certain stages of cancer? Or should it be used with chemotherapy or radiotherapy? These are important questions that should be answered before employment of its use in patients.

Recent researches are now to develop chemically modified non anticoagulant heparin that could be used in treatment of cancer with limitation of the adverse effects of anticoagulation. Stevenson *et al.* have documented the success of chemically modified, non anti-coagulant heparins in reduction of metastases through inhibition of P- and L-selectin (89). Further studies should be performed to assess its efficacy and clinical application.

Conclusion

In conclusion, heparin was found to have positive effects on different types of cancer in laboratory experiments including NSCLC where it was shown to decrease proliferation and metastasis. Heparin exerts its effects on cancer cells through its anticoagulant and non anticoagulants properties; either directly or indirectly. The exploration of the mechanisms underlying the effects of heparin on cancer cells are of utmost importance for identifying new potential therapeutic targets. Moreover, further large clinical trials specified for certain cancer types should be performed to precisely determine the effects of heparin on survival in those patients with cancer.

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