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REVIEW ARTICLE

Low-molecular-weight heparins and cancer: Focus on antitumoral effect

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A close relationship between cancer and thrombosis does exist, documented by the fact that an overall 7-fold increased risk of venous thromboembolism (VTE) has been reported in patients with malignancy compared to non-malignancy. The potential impact of antithrombotic agents in cancer-associated VTE has long been recognized, and, in particular, several clinical trials in the last 20 years have reported the safety and efficacy of low-molecular-weight heparins (LMWHs) for treatment and prophylaxis of VTE in patients with various types of cancer. More recently, a number of preclinical and clinical studies have suggested that LMWHs may improve survival in cancer patients with mechanisms that are different from its antithrombotic effect but are linked to the ability of influencing directly the tumor biology. This paper reviews the evidence around the potential survival benefits of LMWHs by analyzing the suggested mechanisms and the available clinical data.

Key words: Cancer, low-molecular-weight heparin, prophylaxis, survival, therapy, venous thromboembolism

Key message

- Besides reducing mortality and morbidity related to venous thromboembolism, accumulating experimental and clinical data suggest that low-molecular-weight heparins may improve overall survival of cancer patients by influencing directly the tumor biology.

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication of malignancy (1). Patients with cancer have a 4- to 6-fold higher relative risk of VTE than age- and sex-matched controls (2,3), and the overall prevalence of cancer-associated thrombosis is 15%, with rates as high as 50% in advanced metastatic cancer patients (4). Vice versa, an underlying malignancy has been implicated in around 5%–7% of all new cases presenting with symptomatic VTE (5). VTE recurrence is also a major concern in cancer patients. A prospective analysis of more than 800 patients with VTE revealed that the 12-month cumulative incidence of recurrent VTE was significantly higher in cancer patients than in patients without cancer (20.7% versus 6.8%, hazard ratio [HR] 3.2; 95% confidence interval [CI] 1.9–5.4) (6). Previous studies have also clearly demonstrated that the development of symptomatic VTE and VTE recurrence in patients with cancer are associated with significantly reduced survival (7,8). In this clinical context, the potential importance of anticoagulant therapy can be easily recognized, and indeed a number of studies have assessed the role of anticoagulants (i.e. warfarin and heparin) for treatment or prevention of VTE in patients with cancers (9–11). In particular, thanks to their high efficacy and safety profile, low-molecular-weight heparins (LMWHs) are actually recommended as the treatment of choice for the acute and long-term management of cancer-associated VTE (12–16). Besides reducing mortality and morbidity related to VTE (17), accumulating clinical evidence suggests that LMWHs significantly improve overall survival by affecting the cancer itself (18,19). The molecular basis and the clinical evidence of the antitumoral effect of LMWH will be critically discussed in this narrative review.

Search strategy

We reviewed the medical literature for published studies evaluating the efficacy of LMWHs in patients with cancer. The PubMed electronic database was searched without temporal limits using an English language restriction. The key words used were: neoplasm, cancer, tumor, antitumoral, heparin, low-molecular-weight heparin, therapy, prophylaxis, thromboprophylaxis, venous thromboembolism, pulmonary embolism, deep vein thrombosis, survival, and death. References of the most recent review articles on thromboprophylaxis in cancer patients were also cross-referenced to identify potentially relevant papers not captured in our initial literature search. Search terms were also applied to abstracts from the latest international hematological and oncological congresses.

Mechanisms of LMWH-induced anti-cancer activity

Although the anti-cancer properties of unfractionated heparin (UFH) have been known for 60 years (20,21), recent experimental studies have investigated the mechanisms underlying the

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antitumor effect of LMWHs, which have replaced UFH in the treatment or prophylaxis of VTE (22). While a role for LMWHs in cancer treatment can be logically argued based on the well-known theories of fibrin and tumor implantation and dissemination (23), LMWHs may have important antitumor effects that are independent of their non-specific suppression of thrombin generation or activity. Indeed, accumulating *in vitro* evidence has demonstrated that LMWHs can influence cancer cell adhesion, tumor cell proliferation, tumor local growth and metastasis, and angiogenesis through a number of coagulation-independent mechanisms (24).

The LMWHs dalteparin, enoxaparin, and tinzaparin have been shown to inhibit the ERK kinase pathway (which plays a pivotal role for the activity of several anti-cancer drugs) in tumor-derived endothelial cells, and thus potentially the ability to interfere with cell proliferation (25). Interestingly, a LMWH was recently found to inhibit the receptor for advanced glycation end-products (RAGE), which is implicated in tumor cell proliferation and invasion (26). However, despite the finding that LMWHs may interfere with pathways crucial for cell proliferation, *in vitro* studies have shown no effect of LMWHs on cancer cell proliferation, with the exception of enoxaparin (27).

A number of *in vitro* and *in vivo* animal studies have examined the effect of LMWHs on tumor growth with conflicting results. In a study with subcutaneously inoculated lung carcinoma cells, tumor growth was significantly reduced by dalteparin (28). On the other hand, dalteparin did not influence *in vivo* growth of human melanoma cells (29), while preliminary data suggest that the LMWH tinzaparin possesses some inhibitory effects on the growth of primary tumors (30).

More convincing data are available on the anti-metastatic effect of LMWHs. Some studies have also shown that LMWHs inhibit metastasis from peritoneal administration of tumor cells (31,32), and in an experimental melanoma model of metastasis the LMWHs tinzaparin, dalteparin, nadroparin, and enoxaparin showed potent inhibition of lung and liver metastases and colony formation (33–35). Stevenson and colleagues found tinzaparin and UFH to have comparable efficacy regarding inhibition of lung metastases after intravenous injection of colon carcinoma and melanoma cells (36). The anti-metastatic properties of tinzaparin have also been shown in an *in vivo* model of metastasis using severe combined immunodeficiency mice inoculated with human breast cancer cells (37). Notably, anti-metastatic effects of LMWHs have been documented also for non-anticoagulant LMWHs, indicating that such effects are not directly related to effects on anti-Xa or anti-IIa activity (38). Rather, this non-coagulant fraction seems to be crucial for the anti-metastatic properties of LMWHs, as they exert an inhibitory effect on the cell adhesion molecules P- and L-selectin, essential for cancer cell dissemination (39).

Finally, most of the anti-cancer properties of LMWHs are due to the inhibition of angiogenesis, which plays a pivotal role for both local tumor growth and metastasis (40). LMWHs were shown to inhibit endothelial cell proliferation induced by vascular endothelium growth factor (VEGF) mainly through the release from endothelial cells of tissue factor pathway inhibitor (TFPI), a major down-regulator of pro-coagulant and pro-angiogenetic activity of tissue factor (24,41). LMWHs were found also to have an inhibitory effect on endothelial cell tube formation by affecting the structure of the fibrin matrix (42).

LMWHs and cancer survival: clinical studies

In addition to the previously mentioned clinical evidences on the efficacy of LMWHs for VTE treatment (43), several studies on the effect of LMWH on survival in cancer patients without VTE have been performed (16,19). With a practical purpose, in this section we analyze only the results from randomized trials (44–54) and meta-analyses (55–59).

Randomized trials

Altinbas and colleagues (44) randomized 84 patients with small-cell lung cancer to receive standard chemotherapy alone or in combination with dalteparin at a dose of 5,000 units once daily for up to 18 weeks and showed an improved tumor response rate, disease-free median survival, and overall survival associated with the LMWH therapy. The FAMOUS (Fragmin for Advanced Malignancy OUtcome Study) was a large, randomized, placebo-controlled trial designed to examine the effect of a low dose of this LMWH on survival in patients with cancer (45). In this study, 385 patients with advanced solid tumors were randomized to the LMWH dalteparin 5,000 U once daily or placebo for one year. According to an intention-to-treat analysis, a survival advantage at 1, 2, and 3 years, although not statistically significant, was observed in patients receiving dalteparin. However, in a *post hoc* analysis in the subgroup of patients with a relatively good prognosis at entry, there was a statistically significant improvement in survival in favor of the LMWH, thus suggesting a greater impact of this agent on survival in patients with early limited disease (45). Similarly, the MALT (Malignancy and Low molecular weight heparin Therapy) trial randomized 302 patients with advanced cancer to 6 weeks of the LMWH nadroparin versus placebo (46). There was a trend to an increased survival in patients treated with nadroparin versus controls, but again the beneficial effect was more evident in patients with a better prognosis at time of enrollment (expected life span $>$ 6 months). By contrast, a small trial of 141 patients with advanced breast, lung, or prostate cancers randomized to receive no anticoagulant or dalteparin at a dose of 5,000 units once daily failed to show any difference in survival (47). In the PROTECHT (PRophylaxis of ThromboEmbolism during CHemoTherapy) study 1,150 ambulatory patients with lung, gastrointestinal, pancreatic, breast, ovarian, and head and neck cancers were randomized to receive daily nadroparin 3,800 U or placebo for up to 4 months (48). Nadroparin was found to reduce by 50% the absolute rate of thromboembolism. However, this effect was not matched by a favorable effect on patient survival. Similarly, in the SAVE-ONCO study conducted on 3,212 patients with locally advanced or metastatic cancers no survival benefit was demonstrated for the LMWH semuloparin compared to placebo (51). Another open-label randomized phase III trial, which evaluated the effect of nadroparin on survival and disease progression in 503 patients with stage IIIb non-small-cell lung cancer, hormone-refractory prostate cancer, and locally advanced pancreatic cancer, failed to detect a survival advantage conferred by the addition of this LMWH to standard anti-cancer treatment (49). In the PRODIGE study 186 malignant glioma patients were randomized to dalteparin at 5,000 units daily versus placebo (50). Again, there was no statistically significant difference in the 12-month mortality rate between the LMWH and placebo arms. In the TOPIC-1 and TOPIC-II studies (52), 353 patients with disseminated metastatic breast carcinoma and 547 patients with stage III/IV non-small-cell lung carcinoma, respectively, were randomized to receive the LMWH certoparin 3,000 U or placebo once daily for 6 months. No difference in VTE occurrence and mortality rate were detected. Another trial randomized 123 patients with advanced pancreatic cancer to receive chemotherapy with gemcitabine alone or in combination with dalteparin (53). In spite of the fact that this LMWH was effective in reducing VTE

Table I. Summary of the randomized trials evaluating the role of LMWHs in cancer survival.

Study	Participants/controls (*n*)	Inclusion criteria	Type and dosage of LMWH	Duration of anticoagulation	Main results
Altinbas et al., 2004 (44)	84/42	SCLC (all stages)	Dalteparin 5000 U OD	18 weeks	Significant increase in median survival (13 months in LMWH group vs. 8 months in control group; $P = 0.01$)
Kakkar et al., 2004 (45)	374/184	Advanced stage cancers	Dalteparin 5000 U OD	One year or until death	Dalteparin significantly increased 2-year survival (78% in LMWH group vs. 55% in placebo group; $P = 0.03$) and 3-year survival (60% in LMWH group vs. 36% in placebo group; $P = 0.03$) in patients with better prognosis
Klerk et al., 2005 (46)	302/154	Advanced stage cancers	Nadroparin 9500 U BID; Nadroparin 9500 U OD	2 weeks; 4 weeks	Nadroparin was associated with a significant increased median survival (15.4 months in LMWH group vs. 9.4 months in placebo group; $P = 0.01$) in patients with better prognosis
Sideras et al., 2006 (47)	68/70	Advanced stage cancers	Dalteparin 5000 U OD	2 years or until death	No significant difference in median survival (7.3 months in LMWH group vs. 10.5 months in control group; $P = 0.46$)
Agnelli et al., 2009 (48)	1150/381	Advanced stage cancers	Nadroparin 3800 U OD	4 months	15 of 769 (2.0%) nadroparin-treated patients and 15 of 381 (3.9%) placebo-treated patients had a thromboembolic event ($P = 0.02$). No difference was observed in 1-year mortality (43.3% in LMWH group vs. 40.7% in the placebo group)
Perry et al., 2010 (50)	186/87	Malignant glioma	Dalteparin 5000 U OD	6 months	The 1-year mortality rate did not differ between LMWH group and placebo group (47.8% vs. 45.4%; HR 1.2, 95% CI 0.73–2.0; $P = 0.48$)
van Doormaal et al., 2011 (49)	503/259	NSCLC (stage IIIb), hormone-refractory prostate cancer, locally advanced pancreatic cancer	Nadroparin (2 weeks at the therapeutic dose and 4 weeks at half therapeutic dose)	6 weeks	No difference in median survival was observed in nadroparin group compared with no-treatment group (13.1 months versus 11.9 months; HR 0.94, 95% CI 0.75–1.18)
Agnelli et al., 2012 (51)	3212/1640	Advanced stage cancers	Semuloparin 20 mg OD	3.5 months	20 of 1608 (1.2%) semuloparin-treated patients and 55 of 1604 (3.4%) placebo-treated patients had a thromboembolic event (HR 0.36, 95% CI 0.21–0.60; $P < 0.0001$). No difference was observed in 1-year mortality (43.4% in LMWH group vs. 44.5% in the placebo group)
Haas et al., 2012 (52):					
TOPIC-I	353/179	Metastatic breast cancer	Certoparin 3000 U OD	6 months	Mortality rate: 8.6% with certoparin and 6.7% with placebo
TOPIC-II	547/274	Stage III/IV NSCLC	Certoparin 3000 U OD	6 months	Mortality rate: 20.2% with certoparin and 21.6% with placebo
Maraveyas et al., 2012 (53)	123/63	Advanced pancreatic cancer	Dalteparin 200 U/kg OD for 4 weeks followed by 150 U/kg for 8 weeks	12 weeks	100-day mortality was 11% in gemcitabine arm versus 7% in gemcitabine plus dalteparin arm
Lecumberri et al., 2013 (54)	38/18	Limited stage SCLC	Bemiparin 3500 U OD	26 weeks	Median overall survival was 345 days in the chemotherapy alone group and 1133 days in the bemiparin group (HR 2.96, 95% CI 1.22–7.21; $P = 0.017$)

BID = twice daily; CI = confidence interval; HR = hazard ratio; LMWH = low-molecular-weight heparin; NSCLC = non-small-cell lung cancer; OD = once daily; SCLC = small-cell lung cancer.

Table II. Summary of the systematic reviews and meta-analyses analyzing the survival effect of LMWHs in cancer.

Author, year (reference)	Studies included	Patients (*n*)	1-year overall mortality in the LMWH group versus placebo group, relative risk (95% CI)
Kuderer et al., 2007 (57)	11 RCT	2435	0.88 (0.79–0.98, $P = 0.015$)
Lazo-Langner et al., 2007 (58)	4 RCT	898	0.87 (0.77–0.99, $P = 0.04$)
Sanford et al., 2014 (59)	9 RCT	5987	0.94 (0.86–1.04, $P = 0.24$)
Che et al., 2013 (60)	11 RCT	7284	0.97 (0.92–1.02, $P = 0.27$)
Akl et al., 2011 (61)	9 RCT	2857	12 months: 0.93 (0.85–1.02, $P = 0.15$); 24 months: 0.92 (0.88–0.97, $P = 0.01$)

CI = confidence interval; LMWH = low-molecular-weight heparin; RCT = randomized controlled trials.

risk, the authors did not demonstrate a survival advantage in the dalteparin arm. Interestingly, a recent multicenter randomized trial on patients with limited-stage small-cell lung cancer found a survival benefit in the group receiving the LMWH bemiparin (54). Table I summarizes the randomized trials evaluating the effect of LMWHs on survival in cancer patients. The results of two ongoing randomized trials, TILT (Tinzaparin In Lung Tumors) and FRAGMATIC (55,56), assessing the effect of LMWHs tinzaparin and dalteparin, respectively, on survival of patients with lung cancer, are awaited.

Systematic reviews and meta-analyses

A number of systematic reviews and meta-analyses have analyzed the survival benefit of LMWHs in cancer patients (Table II). A meta-analysis including 11 studies with cancer patients who had no VTE treated with LMWHs found a 12% reduction in mortality risk at 1 year in patients treated with LMWHs compared to placebo (57). A similar survival advantage was observed in a meta-analysis of four randomized trials, including 898 patients, published in 2007 by Lazo-Langner and colleagues (58). However, an update of the same meta-analysis performed on a larger number of randomized trials and patients (nine trials with 5,987 patients) did not confirm the survival benefit of LMWHs in cancer patients (59). Another meta-analysis concomitantly published did show that the reduced VTE risk in cancer patients treated with LMWH did not translate into a significant reduction in the 1-year mortality (60). On the other hand, a Cochrane systematic review (61) evaluating the effect on survival of parenteral anticoagulation in patients with cancer who had no therapeutic or prophylactic indication for anticoagulation showed that heparins (both UFH and LMWHs) were associated with a significant reduction of deaths at 24 months but not at 12 months.

Conclusions

Thanks to the robust clinical evidence available, LMWHs are currently considered the mainstay of treatment and prevention of VTE in patients with cancer (13). Whether this clinical efficacy of LMWHs translates into a survival benefit in cancer patients is, however, still a matter of debate. Although a number mechanisms underlying the antitumoral effect of LMWH have been discovered in the last 20 years, the link between inhibition of hemostasis and tumor growth and dissemination is known only in part and needs to be further investigated by experimental studies. Also, the results from clinical trials are conflicting. Indeed, while some randomized controlled trials (44–46,54) and meta-analyses (57,58,61) observed a statistically significant effect of LMWHs on mortality, others (47–53,59,60) did not. The reasons for this discrepancy are multiple and lie essentially in the wide heterogeneity in terms of study design, patient status, type and stage of cancers, dosing, schedules, and duration of LMWH therapy, and chemotherapy regimens among different studies. Also the heterogeneity of the LMWH molecules utilized could have played a role in the observed inter-study inconsistency. As a consequence, all these confounding factors render any comparison or pooling very difficult to perform and interpret (62). In addition, as suggested by some authors (63), the anticancer effect of LMWHs is probably tumor type-, tumor stage-, and dose-dependent, being more evident in patients with limited stage lung cancer treated with LMWHs at prophylactic dose (44,45,54). In conclusion, further randomized controlled trials are needed on more homogeneous cancer patient populations in order better to identify those groups whose outcome would be improved by the addition of a LMWH to standard chemotherapy regimens.

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