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The Effect of LMWH (Nadroparin) on Tumor Progression

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Abstract Recent clinical studies on patients with malignancies, who were treated with UHF and LMWHs raised the possibility, that these agents may possess an inhibitory effect on tumor progression. Further studies supported that this effect is independent from the anticoagulant and antithrombotic action. In this retrospective study oncological patients with an increased risk for thromboembolism were choosen, who received prophylactic treatment with an LMWH (nadroparin) at least for 6 months. Comparing with the control group, in some subgroups (T3 and T4, as well as M1) the LMWH-treated patients showed a significantly increased survival.

Keywords LMWH · Nadroparin · Tumor progression · Survival

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Introduction

It is well established that malignant tumors are frequently accompanied by an increased risk for thromboembolism. To prevent this complication many patients receive anticoagulant prophylaxis, moreover, recent guidelines emphasize the importance of extended prophylaxis. Experimental and clinical data suggest that the administration of LMWH (low molecular weight heparin) to oncological patients influences the progression of the disease decreasing the risk for hematogenous metastases [1–6].

The clinical use of LMWHs is simple, safe and convenient. The drug is administered s.c. once a day in a dose adjusted to the body mass of the patient. The advantage of the LMWHs vs. unfractionated heparin (UFH) is the unnecessity of regular laboratory controll and the possibility of self-treatment at home [7].

In randomized clinical studies the effect of UFH and LMWHs was compared, and the tumorous patients treated with LMWH had a prolonged life-time in average of 3 months vs. to that treated with UFH [8]. Since the occurrence of thrombosis and the bleeding complications were almost identical in both groups, these results suggested that LMWHs may have antitumor activity, besides and independently from their anticogulant effect.

The anticoagulant effect of UFH and LMWHs is due to the increase of rate of complex formation of the physiological inhibitors of coagulation, i.e. antithrombin-III and the activated clotting enzymes (mainly thrombin and Xa), by several thousands. Out of the binding of heparins to antithrombin, due to their strong negative charge, they may bind to numerous regulatory molecules, modifying their activity as well [9]. These interactions depend on the special physicochemical characteristics of heparin-chains

Table 1 Comparison of the survival times in the LMWH-treated and control groups in the T3 and T4 stages

			LMWH	Control
T3	No of patients		33	16
	Survival time (mo)	Mean	***82,55***	***37,2***
		Median	71,93	21,27
	95% CI	Mean	[56,13; 108,96]	[23,95; 50,46]
		Median	[26,83; 117,03]	[6,11; 36,42]
T4	No of patients		23	6
	Survival time (mo)	Mean	49,31	58,87
		Median	***58,9***	***28,6***
	95% CI	Mean	[39,76; 58,85]	[11,31; 106,44]
		Median	[50,91; 66,89]	[0; 63,8]

and fragments resulting in a large variety of other biological effects next to anticoagulation. The antiproliferative effect of heparins and its derivatives on the malignant cell lines is achieved by the inhibition of the protein kinase C-dependent signaling pathway activating transcription factors as cFos and cMyc [10]. The immunomodulatory effect of heparins and their derivatives could be the consequence of the decreased adhesion of leukocytes to endothelial cells, and the same mechanism could work against the extravasation of the tumor cells. Heparins also exert an antiangiogenic effect with the modulation/inhibition of the angiogenic growth factors and their antagonists. As the UFH and the high molecular weigh fragments enhance the binding of the angiogenic growth factors to their receptors, the LMWHs and the small fragments inhibit this binding. Furthermore, heparins modulate other mechanisms of the angiogenesis as well (fibrin formation, migration of endothelial cells, matrix degradation by endothelial cell [11].

The migration of the cells has an important role in the formation of metastases and angiogenesis. Some heparins are able to modulate several steps of invasion by inhibiting the adhesion of the cells to the proteins of the extracellular matrix and also by inhibiting the activity of different proteolytic enzymes, they may modulate the invasion as well [9]. The thrombin generation is important regarding the protection of the circulating malignant cells. Without defending fibrin network the tumor cells become vulnerable and the intravascular arrest and extravasation will be less successful or inhibited [10–12].

The main aim of our study was to follow the survival of the oncologic patients having solid tumors, while treating them with nadroparin. The malignant tumors were in different stages at the start of the treatment. The patients in the LMWH-treated and in the control groups were monitored at the 6-monthly repeated visits.

Methods

Patients, selected for this retrospective, open-labeled study, were treated and monitored for solid tumors (almost exclusively colonic or breast cancer) in the Clinical Oncology Department of St. Imre Hospital, Budapest. The *treated group* of the patients (96 patients—62 breast cancer, 29 colorectal cancer and 5 ovarian cancer) had a demonstrable higher risk for thrombosis with activated clotting system and required long-term prophylactic anticoagulation. Each patient subscribed an informed consent and

Table 2 Comparison of the survival times in the LMWH-treated and control groups in the M0 and M1 stages

			LMWH	Control
M0	No of patients		44	55
	Survival time (mo)	mean	117,66	135,32
		median	79,17	163,87
	95% CI	mean	[53,72; 181,59]	[114,89; 155,75]
		median	[60,6; 97,74]	[16,81; 310,92]
M1	No of patients		52	13
	Survival time (mo)	mean	***75,38***	***33,85***
		median	66,7	27,13
	95% CI	mean	[58,66; 92,10]	[18,99; 48,72]
		meadian	[55,12; 78,28]	[6,13; 48,14]

Table 3 Comparison of the survival times in the LMWH-treated and control groups in the T3N0M1 and T3N1M1 stages

			LMWH	Control
T3N0M1	No of patients		9	4
	Survival time (mo)	mean	***66.1***	***42.4***
		median	38.8	27.1
	95% CI	mean	[28.57; 103.7]	[12.46; 72.37]
		median	[3.29; 74.31]	–
T3N1M1	No of patients		11	4
	Survival time (mo)	mean	***65.04***	***34.43***
		median	–	15.7
	95% CI	mean	[47.9;82.1]	[13.1;55.8]
		meadian	–	[0; 40.27]

agreed that instead of oral anticoagulation they receive nadroparin (partly by Sanofi-Aventis, partly by GlaxoSmith Kline) during and between the cycles of chemotherapy for at least 6 months. Patients received various chemotherapeutic protocols: FEC (5-fluorouracil, epirubicin, cyclophosphamid) for breast cancer, mainly de Gramont (5-fluorouracil, Leucovorin) for colorectal cancer and paclitaxel plus carboplatin for ovarian cancer. Nadroparin was given according to the protocol, briefly: <50 kg 0.2 ml/three postop days, daily/0.3 ml thereafter, 50–69 kg 0.3 ml/0.4 ml, and >70 kg 0.4 ml/0.6 ml.The patients were educated for s.c. self-administration of LMWH. The *control grou*p (68 patients) did not receive anticoagulant. Patients were monitored by imaging techniques, and by tumor markers during the 6 monthly visits. At the time of the first clinical examination none of the patients showed sign or symptom of CNS metastasis or deep venous thrombosis (DVT).

The primary aim of the study was to determine the progression free and survival time of the patients (the interval between the time of diagnosis of the tumor and the death of the patients or the time of the last control). The survival times were calculated in function of TNM staging. The differences were estimated with a Kaplan-Meier survival analysis, the significance of results were controlled by Logrank, Tarone-Ware and Breslow tests. We used SPSS 15.0 program package to the data management and statistics.

Results

Table 1 shows that the LMWH treatment increased the odds for increased survival in T3 and T4 stages. In order to enforce the differences we performed the Logrank, Tarone-Ware and Breslow probes. On that basis we can state that the distribution of the survival times in cases of T3 and T4 significantly differ in the LMWH-treated and control groups. Next, the two groups were compared at N stage level, but the results did not show any differences.

Both groups contained cases either in M0 or in M1 stage. As a suprise, those patients, who had metastases at the time of diagnosis did much better when received LMWH prophylaxis (Table 2). The frequency of thrombosis or severe bleeding were similar is these groups.

The Kaplan-Meier analysis of survival were performed on each variations of TNM staging, but reasonable number (still very low) of patients were only in T3N0M1 and in T3N1M1 groups. Data from this comparison showed again that the mean and median values of the survival was longer after LMWH treatment (Table 3).

The starting clinical state was determined at the time of the diagnosis. The average follow-up was 4.9 years. The changes in the clinical status of the patients—regression, progression, or steady state—were evaluated using imaging techniques and the levels of tumor markers (Table 4). At the end of the evaluation period (which was the time of the last visit or the death of the patient) progression was observed in 32.3% of the LMWH-treated patients, whereas it was 50.7% in the control group. The interval until the appearence of progression (progression free survival, PFS) was 35 months in average in the LMWH group, whereas 26 months in the control. Regression (total tumor burden was decreased by more than 25%) was observed in 12.5% of the LMWH treated group, while only in 3.1% in the control group. The duration of regression (which reflects the observation period) was 34 months in average in the LMWH-treated group and 17 months in the control. No

Table 4 The clinical status of the patients at the last control visit

		LMWH	Control
Regression	No of patients	12	2
		12.5%	3.1%
Progression	No of patients	31	35
		32.3%	50.7%
No change	No of patients	53	31
		55.2%	46.2%

clinical change occurred in 55.2% of LMWH-treated patients and in 46.2% of control patients.

Discussion

This study performed with the enrollment of 164 patients retrospectively was a "pilot" one, where we studied the effect of LMWH (here nadroparin) on the survival of patients with malignancies and risk for DVT. It is important to emphasize that neither thromboembolic nor severe bleeding complications were observed.

According to our observations the odds of longer survival was higher in the LMWH-treated group in T3 and T4 and in M1 stages. The analysis of the N stages showed no difference between the two clinical groups.

The finding that the probability for longer survival was significantly better for patients who already had metastasis is somewhat contradictory to some previous studies [5, 6], which found a longer survival in patients with a better prognosis. However, the suggested and observed antitumor effect of continuous nadroparin treatment could be more effective in patients with primary and metastatic tumor, because more steps of progression are provided as targets for LMWH action. (In that case malignant cells can be released into the circulation from any tumorous foci and an attack on angiogenesis is also feasible.) In case of no metastasis (which has definitely better prognosis) the therapeutic window for LMWH is much narrower. This can explain why the antitumor effect was missed in the M0 group.

The beneficial effect of nadroparin was obvious at the end of the observation period, i.e. at the time of the last control. More regression and less progression happened in the LMWH-treated group. Although, these results support those views which are in favour of the antitumor effect of LMWH, and even trying to develop LMWH or ULMWH agents with less antithrombotic and more powerful anticancer activity [13], our pilot study has been performed on a mixed oncological patient population. Further prospective trials are necessary on more selected cases to accept LMWHs or ULMWHs as antitumor agents with clearly defined indications.

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