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Original Article

LMWH Treatment in Patients with Cancer Diagnosed with Venous Thromboembolism

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Venous thromboembolism (VTE) is associated with increased mortality and morbidity in cancer patients, and VTE development is among the most frequent causes of death in cancer patients. In this study, we evaluated the efficacy of enoxaparin and tinzaparin on thrombosis development in 36 cancer patients. Of 36 the cases, 14 were given enoxaparin (single dose, 6000 anti-Xa/0.6 ml, s.c.), and 22 were given tinzaparin (single dose 20.000 IU/0.7 ml, s.c.). The improvement was observed following the treatment in Doppler ultrasonography and the resolution of VTE was clinically detectable. We did not observe any signs of a new thrombus development or bleeding in the patient group. We detected a longer survival time in patients with enoxaparin treatment ($p<0.05$). We conclude that low-molecular-weight heparins are an efficient treatment method for VTE in cancer patients.

Keywords: LMWH, cancer, venous thromboembolism, enoxaparin, tinzaparin
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INTRODUCTION

Venous thromboembolism (VTE) which includes events deep vein thrombosis (DVT) and pulmonary embolism (PE) is associated with increased mortality and morbidity in cancer patients.

Patients with malignant tumors experience VTE more likely when compared to an individual without a malign condition, and VTE development is among the most frequent causes of death in cancer patients.[1] Tumors are known to induce a hypercoagulable environment in the organism and increased thrombosis risk due to complex and not yet well-defined factors such as activation of coagulation pathways, stimulation of thrombus formation, altered vascular permeability, tumor-derived chemicals, stasis of blood, and antitumor therapies and drugs.[2-3] Besides, hematopoietic agents for bone marrow stimulation were also reported to be a cause of VTE in cancer.[4]

A VTE risk-assessment model for cancer patients taking chemotherapy reported five predictive variables as cancer site, platelet and white blood cell counts before the initiation of chemotherapy, hemoglobin levels or the use of erythropoiesis-stimulating agents, and body mass index (BMI).[5] The tumors with a higher risk of VTE during chemotherapy and radiotherapy are the malign lesions of the pancreas, stomach, lung, genitourinary tract and nervous system.[6]

Low-molecular-weight heparins (LMWHs) are synthetic heparin derivatives that bind and exaggerate the activity of the anticoagulant antithrombin (AT), thus inhibiting factor Xa activity.[7] LMWHs exhibit pharmacokinetic variations and have superiority on other heparin-derivatives in terms of a prolonged half-life, increased bioavailability, rapid onset of action, predictable clearance, subcutaneous bioavailability, and a lack of demand for therapy monitorization.[8] Besides their indications for the management of cardiological conditions including unstable angina, non-Q wave myocardial infarction, LMWHs were reported to reduce mortality in cancer patients, and also have an anti-cancer effect via their effect on angiogenesis and metastasis formation.[9]

In this study, we aimed to evaluate the efficacy of enoxaparin and tinzaparin on thrombosis development in cancer patients.

METHOD

The records of a total of 36 cancer patients with VTE admitted to a research hospital, and treated with either enoxaparin or tinzaparin were reviewed retrospectively. The diagnosis of VTE was confirmed by clinical and radiological evaluation.

The study was condeucting in accordance with the Declaration of Helsinki. 18 years or older patients with cancer who signed informed consent for LMWH therapy were included. Patients with active bleeding or at risk of bleeding, impaired hematological status, liver and/or kidney failure, active gastric, and/or duodenal ulcer, a history of the cerebrovascular event were excluded.

Thirty-one patients were receiving chemotherapy, and five patients were undergoing radiotherapy for gastrointestinal system tumors in 22 cases; genitourinary system tumors in five cases; breast cancer in 3 cases; lung cancer in four cases; lymphoma in one case and brain tumor for one case.

Of 36 affected cases, 14 were given enoxaparin (single dose, 6000 anti-Xa/0.6 ml, s.c.), and 22 were given tinzaparin (single dose 20.000 IU/0.7 ml, s.c.) of appropriate doses. Dosing regimen was regulated considering the age, BMI, liver and kidney function status of the patients. All function and clearance tests were performed in a regular base. Patients were closely motinorized for an early sign of bleeding. The data on tumor type, cancer treatment, localization of VTE, and vital status were recorded.

Table 1. The data on deceased patients and their treatment regimen.

Cases	Tumor type	VTE treatment	Survival after initiation of the therapy
Patient #1	Colorectal cancer	Enoxaparin	9 months
Patient #2	Colorectal cancer	Enoxaparin	16 months
Patient #3	Colorectal cancer	Tinzaparin	4 months
Patient #4	Colorectal cancer	Tinzaparin	5 months
Patient #5	Stomach cancer	Tinzaparin	1 month
Patient #6	Stomach cancer	Tinzaparin	3 months
Patient #7	Stomach cancer	Enoxaparin	7 months
Patient #8	Pancreas cancer	Enoxaparin	3 months
Patient #9	Pancreas cancer	Enoxaparin	3 months
Patient #10	Pancreas cancer	Tinzaparin	1 month

The complications and concomitant adverse effects were also scanned and evaluated.

The comparison of the survival time depending on the Enoxaparin or Tinzaparin treatment was performed using the student's t-test. A significance value of <0.05 was accepted as statistically significant.

RESULT

Of the 36 patients, ten died within the treatment period. Four of the deceased patients were treated for colon tumors, three for stomach tumors, and three for pancreas tumors. The LMWH type and survival duration following the initiation of treatment were summarized in Table 1. We detected a longer survival time in patients with Enoxaparin treatment (Table 2). The VTEs were mostly localized on the lower extremity vessels, 19 in the deep and 14 in the superficial veins.

The improvement was observed following the treatment in Doppler ultrasonography and the resolution of VTE was clinically detectable. We did not observe any signs of a new thrombus development or bleeding in the patient group.

DISCUSSION

Patients with different types of cancer have an increased thrombosis risk as a result of various inducing factors such as tumor- and/or treatment-related mechanisms, and supportive therapies. Tumor-related thrombus is a widely known phenomenon worldwide, and different management algorithms are suggested using anticoagulant and antithrombotic agents.[10] In this study, we aimed to evaluate the therapeutic efficacy of two different LMWHs, enoxaparin and tinzaparin in cancer patients with VTE, and the survival duration after the initiation of treatment. We observed that both agents are efficient in terms of thrombus control, new thrombi formation and hematological adverse effects such as bleeding. Besides, the overall survival in the patient group receiving enoxaparin was significantly longer than the tinzaparin group.

VTE is a frequent complication in patients with different types of tumors and has consequences as the delay of the treatment, loss of functions, impaired life quality and increased risk of mortality. Although pre-treatment of VTE is not possible due to the unpredictable nature of the condition, there are defined risk factors such as cancer site, platelet and leukocyte count and hemoglobin levels before the cancer therapy, and body mass index.[11]

LMWHs are derivatives of UFH with a mean molecular weight of 3-6 kDa and 12–18 saccharide units obtained by various synthetic production mechanisms and steps. Different LMWHs show specific structural variations and potency. LMWHs show their effect on the FXa activity rather than thrombin, facilitating a more controlled coagulation profile and predictable therapeutic efficiency.[12] There are a large number of studies reporting the superiority of LMWHs over the alternative treatment strategies for VTE, such as vitamin K antagonists and UFH. Also, the risk of VTE recurrence in cancer patients significantly reduced with LMWHs when compared to vitamin K antagonist therapy.[13,14]

Since the chemotherapy and radiotherapy procedures increase the risk of thrombocytopenia and bleeding in patients, the management strategies for VTE should be carefully defined and administered. Furthermore, in terms of drug intoxication and elimination, the condition of the kidney and liver should be carefully evaluated particularly in the late stages of the diseases. In such uncertain and ambiguous conditions, LMWHs are a better treatment-of-choice for these patients as a result of their predictable nature and clearance, immediate effect, and easier application. One advantage of LMWHs over UFH products is that their clearance is not affected by the dose administered. Bleeding is the most common side effect during the management of VTE.[9] However, we did not observe any signs of bleeding during the follow-up duration in our patient group.

Table 2. Mean survival between two treatment groups.

Treatment	Mean survival (months)	p value
Enoxaparin	7.6 ± 5.36	**<0.05**
Tinzaparin	2.8 ±1.78	

In patients with malignant tumors, secondary prophylaxis or long-term treatment results using LMWHs have been efficient. Cancer patients with contraindications for oral anticoagulant therapy can benefit from treatment with LMWHs. In most cases, LMWHs for the treatment of VTE might be given once a day at a fixed dose for a prolonged antithrombin activity without any side effects. The

efficacy and safety of LMWHs in comparison to UFH therapy in outpatient cases have been demonstrated in various studies. In summary, LMWHs have an established role for both inpatient and outpatient cases in the treatment of VTE and cancer patients.[15] There is evidence that DMAHs can help prolong life in cancer patients and avoid complications from acute coronary syndrome.[16]

Although LMWH thromboprophylaxis is a widely adopted approach for the patients undergoing major surgery procedures, a randomized cohort study reported that a dose of 40 mg enoxaparin reduced the VTE risk up to 40% in cancer patients when compared to the other randomization groups who received 20 mg enoxaparin or placebo. There is evidence suggesting that standard treatment doses of LMWHs are not adequate for thromboprophylaxis in cancer patients, and the beneficial effect is based on the tumor type.[17]

It has been reported with in vivo and in vitro studies that heparin and heparin-like products affect on with tumor progression via different tumor or angiogenesis dependent mechanisms. Particularly enoxaparin has been shown to prevent the endothelial cell capillary vessel formation through vascular endothelial growth factor and fibroblast growth factor-2 related mechanism in patients with breast cancer and leukemia.[18] In an ongoing randomized and placebo-controlled trial on non-small cell lung cancer patients receiving Tinzaparin (TILT) with a daily dose of 100 IU/kg for 12 weeks, a 10% absolute increase in the survival rate is expected.[9] In a multicenter trial to investigate a prophylactic 1 mg/kg dose of enoxaparin in patients with recently diagnosed small-cell lung cancer, although overall survival ratio and the mortality rate did not improve, however, there was a significantly lower incidence of VTE.[19]

In a recent Turkish study, on the efficacy and safety of LMWHs in cancer patients, bemiparin was reported to be more effective than enoxaparin in thrombosis resolution and has a similar tolerability profile. They also stated that there was no current treatment protocol for VTE.[20]

Three patients with pancreas cancer in our patient group deceased within three months following the treatment for VTE. The occurrence of VTE in the course of pancreatic cancer is a known increased mortality factor, and our data is consistent with the literature, independent of the type of LMWH. Although two out of three patients receiving Enoxaparin in our study group lived three months when compared to one patient treated with Tinzaparin, the sample size is too small to make a conclusion. Additionally, a risk stratification strategy depending on the age, stage, treatment strategies and duration, and comorbidities is required to further evaluate the anti-tumor effect of Enoxaparin in our patient group with pancreas cancer. The survival time with LMWH or UFH therapy depends on the limited or metastatic condition of the disease.

It should also be noted that different types of tumors show a distinct mechanism of action specific to their biology and the compounds they produce. Thus, significant differences in response to LMWH treatment between different patient groups is an appraisable consequence.

We observed the most definite difference in the colorectal cancer patients, and the enoxaparin arm had an overall survival of 9-16 months compared to the patients who received tinzaparin therapy and survived 4-5 months. Furthermore, one out of three patients receiving enoxaparin therapy survived longer when compared to two patients undergone tinzaparin treatment for the management of VTE.

CONCLUSION

This study indicates that enoxaparin and tinzaparin are effective in resolving thrombosis in cancer patients and have a favorable trying to safety.

CONFLICT OF INTEREST

The author states the original work, and there is no conflict of interest in doing this research.

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