Wspolczesna Onkol 2012; 16 (5): 416–419

DOI: 10.5114/wo.2012.31771

Original paper

Can LMWH improve the outcome of patients with inoperable stage III non-small cell lung cancer?

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Aim of the study: Lung cancer is the most common malignancy, accounting for one-third of all deaths from cancer. Some studies have shown that low molecular weight heparin (LMWH) significantly prolongs the survival of patients with non-small cell lung cancer (NSCLC).

The aim of this study was to determine the effects of treating inoperable stage III NSCLC with LMWH in addition to concurrent chemoradiotherapy.

Material and methods: Eighty-two patients with inoperable stage III NSCLC were evaluated at Dicle University's Medical Oncology Department between 2005 and 2010. All patients were treated with concurrent chemoradiotherapy (CRT) with or without LMWH (enoxaparin 4000 IU/day) depending on the patient's risk of thrombosis. The primary objectives were to determine disease-free survival (DFS) and overall survival (OS) for patients treated with LMWH.

Results: A total of 38 patients in the LMWH negative group and 44 patients in the LMWH positive group were included in the study. The median OS was 11.2 months for the enoxaparin recipients and 12.7 months for the non-enoxaparin group ($p = 0.4$). The median DFS was 9.3 months with CRT alone and 10.0 months with CRT plus enoxaparin ($p = 0.9$). The one-year OS rates were 47% and 34% for groups treated with CRT and enoxaparin plus CRT, respectively, while the two-year OS rates were 23% and 21%, respectively. No significant difference was noted between the two groups in terms of grade 3–4 hematologic toxicity and mucositis ($p = 0.3$).

Conclusions: This study did not demonstrate improvements in survival for patients with NSCLC treated with enoxaparin. LMWH's positive contribution is still controversial.

Key words: non-small cell lung cancer, low molecular weight heparin, chemoradiotherapy.

Introduction

Lung cancer is one of the most common cancers and a major cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) comprises 85% of all lung cancers [1]. Stage IIIA and IIIB lung cancers include patients with locally advanced disease and without distant metastases [2]. Five-year survival rates for stage IIIA and IIIB NSCLC treated with standard concurrent chemoradiotherapy (CRT) are 19% and 7%, respectively, and the median survival times are 22 and 13 months, respectively. In the past, the standard treatment for NSCLC was radiotherapy or surgery, alone, which provided a median survival of approximately 10 months [3]. CRT is now the standard treatment [4].

Thromboembolism is the most common complication in patients with cancer. Cancer has been identified as an independent risk factor for the development of venous thromboembolism (VTE) [5]. Activation of the coagulation system occurs frequently in patients with cancer. Recent studies have shown that the pathogenesis of thromboembolism in malignancy is associated with the hemostatic alterations induced by cancer cells, the activation of blood coagulation and the inhibition of anticoagulant function. Although thromboembolism is commonly observed in patients with advanced cancer, it may occur in patients with occult cancer [6].

Anticoagulants may, therefore, have an important role in treating the thromboembolic complications of cancer and preventing their recurrence [6]. VTE in cancer patients is treated with LMWH or, less commonly, unfractionated heparin, whereas oral anticoagulants, principally warfarin, are commonly used for long-term prophylaxis [7]. Anticoagulation therapy decreases the incidence of VTE in patients with cancer [5]. Heparins have been reported to interfere with tumor progression and, in particular, with the occurrence and development of metastases in laboratory animals [8, 9]. The positive effects of LMWH on disease-free survival and overall survival have been shown in some different cancer studies [5, 10, 11]. However, in studies of patients with NSCLC, this positive response has not been observed [12, 13]. The potential survival benefits of heparin therapy for patients with cancer need to be evaluated in further clinical research. There are not adequate studies on the effect of LMWH on the survival of patients with NSCLC.

In our clinic, we detected a decreased risk of thrombosis in patients who were given LMWH prophylaxis, and these patients had good clinical courses. The goal of this study was to determine whether the addition of LMWH to CRT would improve NSCLC patient outcomes compared with CRT alone. There is no conflict of interest between the authors.

Material and methods

Patients

Patients diagnosed with NSCLC who presented to the Radiation and Medical Oncology Department of Dicle University Medicine Faculty between January 2005 and October 2010 were included in the study. All patients in this study had histologically confirmed medically inoperable or unresectable stage IIIA and IIIB NSCLC. Each patient had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of less than two and normal hematological, renal and hepatic function tests. Data were collected retrospectively from patient files. The patients' age, sex, stage, histological subtypes, performance status, and treatment responses were reviewed, and patients treated with LMWH due to risk of thrombosis were analyzed. The time periods from the diagnosis to progression and to death were recorded. Disease-free survival (DFS) and overall survival (OS) and treatment toxicities were compared.

Treatment regimen

In this study, 82 patients were treated with concurrent CRT. As a clinical practice, patients with a risk factor for thrombosis (cancer, old age, impaired mobility, and/or cardiac and pulmonary diseases) were given LMWH [14]. The patients were divided into two groups: patients treated with concurrent CRT (60 Gy RT in 30 fractions plus weekly docetaxel 25 mg/m^2 and cisplatin 25 mg/m^2; n = 38) and patients treated with low molecular weight heparin (enoxaparin 4000 IU/day) in addition to concurrent CRT (n = 44). When hemoptysis and other hemorrhages into organs were seen, the LMWH was stopped. If a partial response or stable disease response was observed in patients who received concurrent CRT, four additional cycles of chemotherapy were administered. Treatment toxicities were assessed according to the National Cancer Institute (NCI) guidelines [15]. All patients received conventional fractionated external radiotherapy (2D) five days a week (from Monday to Friday), for a total dose of 60 Gy in 30 fractions (2 Gy per day) administered over six weeks. A Simulix Oldef HP model simulator (Nucletron) was used to perform conventional simulation. For treatment of patients, a 6 MV photon beam was used with an Alcyone II model Co60 (General Electric) radioactive source teletherapy machine or a Saturn 43 F model Linear Accelerator (General Electric).

Statistical analysis

DFS was accepted as the period from the date of diagnosis to progression or recurrence and OS was accepted as the period from the date of diagnosis to death. Statistical analyses were carried out using SPSS 11.5 software. Fisher's test and the independent samples test were used to compare the groups. Survival analyses were completed according to the Kaplan-Meier method with two-sided log rank statistics.

Results

A total of 82 patients were included in the study. Thirty-eight patients were in the LMWH negative group and 44 patients were in the LMWH positive group. The median age was 60 years (range 28–79). Of the patients, 4 were female (4.9%) and 78 were male (95.1%). Statistical analysis showed no significant difference between the two groups in terms of age, gender, pathologic type or stage ($p > 0.05$). Patient characteristics are summarized in Table 1. Thirty-four patients (42%) had stage IIIA NSCLC, and 47 patients (58%) had stage IIIB. During this study, 67 (81.7%) of the 82 patients died from their disease, and the remaining 15 patients are still alive at the time of writing.

Median follow-up time was 12.5 months (range 1.1–87.3 months). Evaluation of survival results showed that the median DFS was 9.3 months for the enoxaparin negative group (95% CI: 7.4–11.2) and 10.0 months for the enoxaparin positive group (95% CI: 5.8–14.2; $p = 0.9$) (Fig. 1A). The median OS was 12.7 months in the enoxaparin negative group (95% CI: 7.4–18.0) and 11.2 months in the enoxaparin positive group (95% CI: 7.1–15.3; $p = 0.4$) (Fig. 1B). One- and two-year overall survival rates were 47% and 23% (n = 38), respectively, for the enoxaparin negative group, and 34% and 21% (n = 38), respectively, for the enoxaparin positive group (n = 44). The one- and two-year DFS rates were 37% and 15%, respectively, and the median survival was 9.3 months (95% CI: 7.4–11.2) for patients treated with CRT alone. The one- and two-year DFS rates were 32% and 12%, respectively, and the median survival was 10.0 months (95% CI: 5.8–14.2) for patients treated with CRT plus LMWH. These differences between treatment groups were not statistically significant ($p = 0.9$). The one- and two-year OS rates were 47% and 23%, respectively, and the median survival time was 12.7 months (95% CI: 7.4–18.0) for patients treated with CRT alone. The one- and two-year OS rates were 34% and 21%, respectively, and the median survival time was 11.2 months (95% CI: 7.1–15.3) for patients treated with CRT plus LMWH ($p = 0.4$). These results are summarized in Table 2 and Fig. 1. Overall tumor response rates were 88.5% with CRT alone (n = 35) and 82% with CRT plus LMWH (n = 39) ($p = 0.001$).

Table 1. Characteristics of patients

Characteristic	CRT n (%)	CRT + LMWH n (%)	P value
Median age (range)	60 (28–77)	63 (40–79)	0.05
Sex			
male	35 (92.1)	43 (95.1)	0.1
female	3 (7.9)	1 (4.9)	
Pathologic type			
squamous	14 (38.9)	21 (50.0)	0.1
adenocarcinoma	7 (19.4)	5 (11.9)	
non-subtype	15 (41.7)	16 (38.1)	
Stage			
IIIA	19 (51.4)	15 (34.1)	0.1
IIIB	18 (48.6)	29 (65.9)	
Treatment response			
stable	7 (20)	9 (23.1)	0.001
partial	21 (60)	20 (51.3)	
complete	3 (8.6)	3 (7.7)	
progression	4 (11.4)	7 (17.9)	
Metastasis			
local	6 (40)	5 (71.4)	0.01
distant	9 (60)	2 (28.6)	

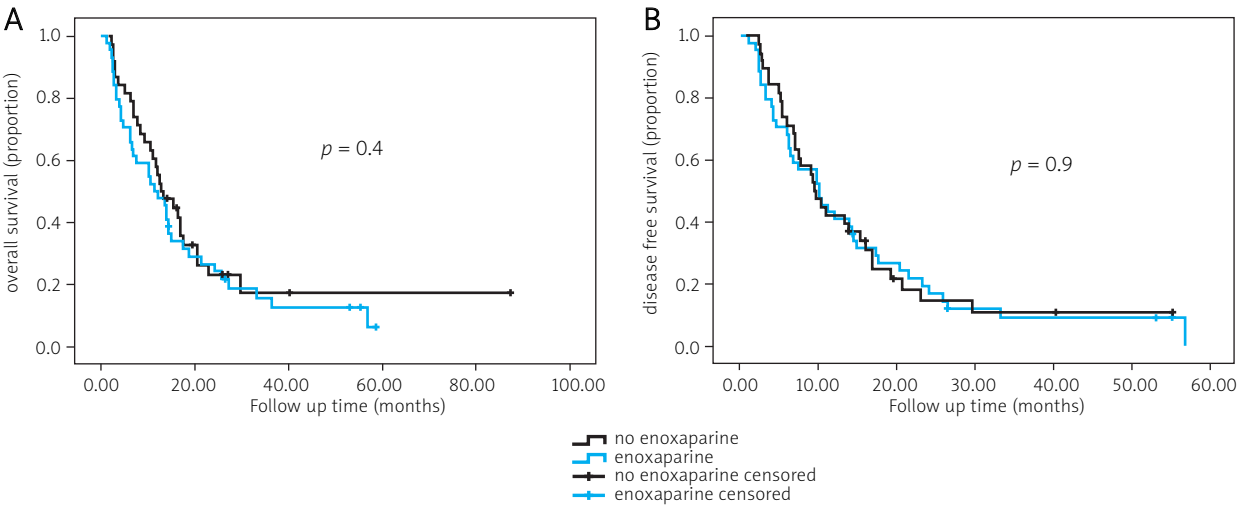

Fig. 1. Kaplan-Meier estimates of overall survival and disease free survival according to treament group

Table 2. Overview of survival data

Variable	Enoxaparin Median months (range)	No enoxaparin Median months (range)	*P* value
Disease-free survival	10 (5.8–14.2)	9.3 (7.4–11.2)	0.9
Overall survival	11.2 (7.1–15.3)	12.7 (7.4–18.0)	0.4

The patients were examined for the development of toxicity. Grade 3, 4 neutropenia was detected in 3 patients (7%) in the CRT plus LMWH group and 6 patients (16.7%) in the CRT-only group (p = 0.3). Grade 3, 4 mucositis and/or esophageal mucositis was detected in 5 patients (11.4%) in the CRT plus LMWH group and 4 patients (10.5%) in the CRT-only group (p = 0.7). One patient in the CRT plus LMWH group died as a result of hemoptysis. No deep vein thromboses developed in any patients.

Discussion

For stage IIIA and IIIB NSCLC, the survival rate is low in spite of aggressive treatments [16]. Stage III NSCLC affects a heterogeneous group of patients who are generally offered combined treatments including surgery and/or chemotherapy and/or radiotherapy. For patients with inoperable stage III NSCLC, the standard treatment is platinum-based chemotherapy with radiotherapy (CRT).

In cancer patients, thromboembolic complications are frequently observed. Anticoagulant treatments, especially LMWH, have been used to improve the survival in cancer patients with thromboembolic events. However, the effect of LMWH prophylaxis on cancer survival is controversial. There are some studies in the published literature reporting the antitumor activity of anticoagulant agents. These studies frequently focus on heparin, as an anticoagulant. Studies have demonstrated regression in the primary tumor [17, 18], as well as a reduced likelihood of developing metastases [19].

We observed a good clinical course in cancer patients using LMWH. Therefore, we noted in our retrospective study the positive effects of LMWH for cancer patients [20]. The aim of this study was to determine whether the addition of LMWH to CRT would improve NSCLC patient outcomes compared with CRT alone.

This study on the effects of the LMWH enoxaparin on the survival of patients with NSCLC and without other indications for anticoagulation demonstrated no overall survival advantage for those treated with enoxaparin. The median survival was 11.2 months among enoxaparin recipients, and 12.7 months among the non-enoxaparin group (p = 0.4). Even the median survival was better in the non-enoxaparin group. The low median survival time could be due to the larger number of patients with stage IIIB NSCLC in the enoxaparin group. However, DFS was better (10.0 vs. 9.3 months) for the enoxaparin group. In a randomized trial on the survival effects of LMWH for patients with stage IIIB NSCLC, the median survival was 12.1 months in the LMWH group and 10.3 months in the control group (p = 0.63) [13]. There were also other similar studies in the literature [21].

In our study, metastases were generally local rather than distant metastases in the LMWH group (p = 0.01). The regression of NSCLC metastases after LMWH use has been reported in a study [22]. In the studies, heparin was used for a period one and three months, during chemotherapy [13, 18]. In our study, heparin was used for one month during the CRT treatment period. Periods of LMWH use differ from study to study. If heparin use was prolonged, it could positively affect survival.

Consequently, no benefits of LMWH use were identified for patients with stage III NSCLC. However, the effect of LMWH on patient survival continues to be controversial.

The authors declare no conflict of interest.

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Submitted: 22.01.2012
Accepted: 31.07.2012