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Clinical outcomes of venous thromboembolism with dalteparin therapy in multiple myeloma patients

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ABSTRACT

This study focused on the clinical outcomes in multiple myeloma (MM) patients with venous thromboembolism (VTE) who received low-molecular-weight heparin (dalteparin) therapy. Changes in D-dimer levels before and after VTE were also evaluated. Among 549 patients treated with various chemotherapeutic agents, a total of 52 (9.47%) patients including 32 newly diagnosed with MM and 16 with relapsed/refractory MM developed VTE, 48 of whom received dalteparin. Among the 48 treated patients, 37 (77%) had proximal deep vein thrombosis (DVT), four had (8%) pulmonary embolism (PE), and seven (15%) had both DVT and PE. In 32 patients with available paired samples (at baseline and VTE occurrence), significant conversion of D-dimer levels from 2.2 ± 0.4 mg/L to 11.8 ± 1.6 mg/L ($P < 0.001$) was observed, which decreased from 10.9 ± 0.4 mg/L to 1.9 ± 0.6 mg/L one month after initiating dalteparin therapy. A total of 44 patients received dalteparin with a median duration of 4.2 months (range, 2.7–9.4), and four patients were discontinued early due to death ($n = 3$) and major bleeding ($n = 1$). After a median follow-up of 9.0 months (range, 0.7–35.8) since the first VTE episode, five patients showed recurrence of VTE with a cumulative incidence of 17.5 ± 7.9%. Major bleeding occurred in three patients. In summary, dalteparin seems to be a promising drug for the treatment of VTE in MM. In addition, the significant difference in D-dimer levels observed before occurrence of VTE and after dalteparin treatment may suggest the usefulness of D-dimer testing as a surrogate marker for VTE in MM patients.

1. Introduction

Patients with multiple myeloma (MM) are at a higher risk for developing venous thromboembolism (VTE) as a result of the monoclonal protein and the procoagulant activity. Although the risk of VTE in the first 4 months following a diagnosis of MM is approximately 3–4% in patients receiving either dexamethasone alone [1] or melphalan plus prednisone therapy [2,3], the use of novel agents, especially immunomodulatory drugs (IMiDs), has led to an increased incidence of VTE. Currently, therapy type is the primary determining factor for VTE risk. In addition, patient characteristics such as age, obesity, immobility, comorbidity, and factors derived from disease such as hyperviscosity, procoagulant antibody formation, paraprotein interference with fibrin structure, activated protein C resistance, and decreased protein S levels may also contribute to the pathogenesis of VTE [4]. Furthermore, increased secretion of proinflammatory cytokines (interleukin-6 and tumor necrosis factor) can activate coagulation pathways [5].

Due to the increased risk of VTE in patients treated with thalidomide and lenalidomide, the International Myeloma Working Group has proposed several recommendations with the aim of lowering the incidence of VTE to <10%, namely, low-dose aspirin prophylaxis for low-risk patients and low-molecular-weight heparin (LMWH) or full-dose warfarin for patients with two or more individual or myeloma-related risk factors. In addition, it has been recommended that LMWH or full-dose warfarin should be considered in all patients receiving high-dose dexamethasone, doxorubicin, or multiagent chemotherapy, regardless of individual risk factors [6]. Indeed, based on the results of a phase 3 prospective randomized clinical trial comparing different antithrombotic prophylaxis in newly diagnosed MM patients treated with IMiDs containing regimens [7,8], prophylaxis with either LMWH or low-dose aspirin to prevent VTE is the accepted treatment for patients receiving IMiDs and/or dexamethasone.

VTE treatment and second prophylaxis with LMWH may be a more effective and practical alternative to oral anticoagulant therapy. Unlike vitamin K antagonists (VKA), LMWH have predictable pharmacokinetic properties and drug interactions [9], and they can be effective in

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patients with cancer who have recurrent VTE while receiving warfarin [10,11]. Poor gastrointestinal absorption is not a concern with subcutaneously injected LMWH. The therapeutic dosage is based on the patient's weight, and laboratory monitoring is not routinely required [12]. Although VTE is treated in a similar manner as cancer-related thrombosis [13], there have been few studies focusing on the clinical outcomes of VTE with LMWH therapy in MM patients. In a single-center study, the rate of VTE recurrence in MM patients with thalidomide-associated VTE was 13.8% for re-exposure to thalidomide and 5% for no retreatment [14]. Therefore, we retrospectively investigated clinical outcomes of MM patients who had developed VTE during active anti-cancer treatments including various novel agents and then received dalteparin therapy. In addition, we evaluated changes in D-dimer levels before and after VTE, as this may be an important predictor.

2. Materials and methods

2.1. Patients

Between August 2012 and February 2015, 549 MM patients received chemotherapy at our institution. Among these patients, 52 developed VTE during the period of first line therapy (n = 35) and therapy for refractory or relapsed MM (n = 17). Four patients treated with warfarin (n = 1) and rivaroxaban (n = 3) were excluded and 48 patients who were treated with dalteparin were included in our analysis. A first episode of objectively documented symptomatic VTE, either deep vein thrombosis (DVT) and/or pulmonary embolism (PE) was evaluated. The patient population for this study is summarized in Fig. 1. The Institutional Review Board of The Catholic University of Korea approved the research protocol for data analysis and this study was conducted in accordance with the Declaration of Helsinki.

2.2. Evaluation and management of VTE

All patients with MM who were treated with IMiDs received thromboprophylaxis with low-dose aspirin (100 mg daily). In patients with suspected VTE, the presence and localization of the VTE was confirmed by ultrasonography and/or CT scan according to established diagnostic criteria [6]. When the patients had acute symptomatic proximal DVT, PE, or both, dalteparin (200 IU/kg/day) was administered subcutaneously for the first 1 month, followed by 150 IU/kg subcutaneously once a day for up to 3–6 months [12]. If concomitant thrombocytopenia $<50 \times 10^9$/L was maintained, dalteparin was held until recovery above 50×10^9/L. Decisions regarding the continuation of dalteparin beyond the first 3 months of treatment were based on relief of symptoms, continuation of thalidomide or lenalidomide therapy, and follow-up imaging results.

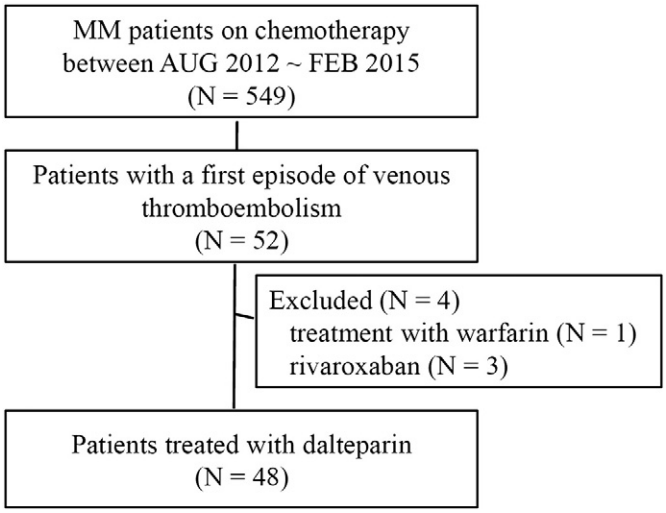

Fig. 1. Schematic diagram of the patient selection protocol.

2.3. Statistical analysis

The main purpose of this study was to assess recurrence of VTE and bleeding in MM patients who received dalteparin anticoagulant therapy. In addition, we evaluated the change in D-dimer levels at the initiation of chemotherapy (baseline) and when VTE occurred. In addition, D-dimer levels were also monitored in 1-month intervals after starting anticoagulant therapy. To identify risk factors for recurrence of VTE, the following clinical factors before beginning dalteparin were assessed: gender, age, body mass index (BMI), type of M-protein, performance status (PS), use of recombinant erythropoietin (EPO), hemoglobin (Hb), creatinine, lactate dehydrogenase (LDH), high-sensitivity C-reactive protein (hsCRP), D-dimer level, renal dysfunction, and treatment regimens. Cumulative incidence was used to estimate the probability of recurrence of VTE, treating death as a respective competing risk. Covariates with a *P* value less than 0.1 in the logistic regression were added to the multivariate analysis model.

3. Results

3.1. Patient characteristics

Patient characteristics are summarized in Table 1. A total of 48 VTE patients (24 men and 24 women) treated with dalteparin were analyzed. With a median age of 63 years (range, 33–76 years), the distribution of patients with I, II, and III international staging were 21%, 33% and 38%, respectively, with 8% at an unknown risk. The median time from diagnosis to VTE occurrence was 5.1 months (range, 0.3–198.5 months). At the time of VTE occurrence, 32 patients were in first line chemotherapy consisting of bortezomib-based (n = 15), thalidomide-based (n = 13), or other treatment (n = 4). In addition, 16 refractory or relapsed myeloma patients were in bortezomib-based (n = 3), thalidomide-based (n = 3), lenalidomide-based (n = 9), or other chemotherapy (n = 1). As shown in Table 2, 37 (77%) patients had lower extremity DVT and 4 (8%) patients had PE without DVT. PE with lower extremity DVT or upper extremity DVT was observed in 6 (13%) and 1 (2%) patients, respectively.

3.2. Overall outcomes of dalteparin therapy

Forty-four patients received dalteparin therapy with a median duration of 4.2 months (range, 2.7–9.4), and 4 patients discontinued treatment early due to death (n = 3) and major bleeding (n = 1). After a median follow-up of 9.0 months (range, 0.7–35.8 months) following the first VTE episode, 5 patients had a recurrence of VTE: 2 episodes of PE occurred in 2 patients who continued dalteparin after 0.7 and 4.6 months from the first DVT episode, respectively. In addition, there were 3 recurrent DVT patients who discontinued dalteparin 8.9, 13.2, and 14.7 months after first episode of PE (n = 1) or DVT (n = 2), respectively (Table 3). The cumulative incidence of VTE recurrence was 17.5 ± 7.9% (Fig. 2). Major bleeding were observed in 3 patients (1 intracranial bleeding and 2 gastrointestinal bleeding requiring transfusions), as well as one patient with a nonfatal intracranial bleeding followed by permanent discontinuation of dalteparin therapy. The characteristics of the patients who experienced hemorrhage are summarized in Supplementary Table 1.

3.3. Evaluation of D-dimer levels

D-dimer test results at the time of VTE occurrence were available for 46 patients. Among these patients, 43 had an increased D-dimer level with a median of 9.02 mg/ml (range 0.99–35.2, reference <0.80 mg/ml) at the time of VTE occurrence and 3 patients had a normal D-