Critical Reviews in Oncology/Hematology 105 (2016) 92–99

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

# Safety of anticoagulation in the treatment of venous thromboembolism in patients with haematological malignancies and thrombocytopenia: Report of 5 cases and literature review

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**Contents**



ARTICLE INFO

*Article history:*
Received 22 November 2015
Received in revised form 26 May 2016
Accepted 16 June 2016

*Keywords:*
Anticoagulation
Venous thromboembolism
Haematological malignancies
Thrombocytopenia

ABSTRACT

Venous thromboembolism (VTE) is relatively common among patients with haematological malignancies. Management is challenging because many of these patients are also thrombocytopenic and at increased risk of bleeding. Current recommendations regarding the treatment of VTE in thrombocytopenic patients with haematological malignancies are limited as there only few studies evaluating the safety and efficacy of anticoagulation in this population of patient. A literature review on the safety of antithrombotic therapy for treatment or prophylaxis of VTE in patients with haematological malignancies was undertaken. This includes a report on 5 patients with haematological malignancies at our institute who received enoxaparin for treatment of VTE while thrombocytopenic. Unlike previous case series which

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http://dx.doi.org/10.1016/j.critrevonc.2016.06.011

Cont showed that the use of LMWH (low molecular weight heparin) is safe in this group of patients, major bleeding occurred in 2 patients, and was fatal in one case. More studies are required to evaluate the risk factors and safety of anticoagulation in these patients.



## 1. Introduction

Patients with haematological malignancies are at increased risk of venous thromboembolism (VTE). The reported incidence of VTE in the literature varies (2–12% in patients with acute leukaemias and 1.5–14.6% in patients with Lymphomas) (Falanga and Marchetti, 2009), with the highest incidence reported in CNS Lymphoma 59.5%. (Goldschmidt et al., 2003) Risk factors for cancer-associated thrombosis can broadly be classified into cancer-related, treatment related and patient related factors (Table 1). In addition, several biomarkers for increased risk of thrombosis have been proposed and a validated risk score based on a combination of the above risk factors and biomarkers has been developed (Khorana et al., 2008).

Treatment of VTE is challenging as patients with haematalogical malignancies are at increased risk of both bleeding and thrombosis recurrence (Levitan et al., 1999; Palareti et al., 2000; Prandoni et al., 2002; Trujillo-Santos et al., 2008). In particular, these patients are often thrombocytopenic due to disease and/or chemotherapy. Recommendations for treatment of VTE in patients with cancer have been published by the International Society of Thrombosis and Haemostasis (Farge et al., 2013), American Society of Clinical Oncology (Lyman et al., 2013), and British Committee for Standards in Haematology (Watson et al., 2015). However these clinical practice guidelines are limited due to lack of well-designed randomised controlled studies in the literature looking specifically at VTE in thrombocytopenic patients with haematological malignancies. According to these guidelines, low molecular heparin for initial treatment and maintenance for a period of 3–6 months is recommended for patients with cancer with an established VTE. In cancer patients with thrombocytopenia, it is interesting to note that both ASCO and ISTH apply a threshold of $50 \times 10^9$/L below which therapeutic anticoagulation is relatively contraindicated. Additionally, when the platelet count is $<50 \times 10^9$/L, BCSH also recommends the use of platelet transfusions to elevate the count to $>50 \times 10^9$/L to allow full dose anticoagulation especially in the immediate period following thrombosis development (Watson et al., 2015). This threshold is based on exclusion criteria used in clinical trials rather than evidence based. Furthermore, whether these recommendations can be applied to patients with haematological malignancies and VTE remains unclear and although this topic has been the focus of previous review articles (Falanga and Marchetti, 2009), there has been no significant progress in this area to date.

We report 5 cases of patients with haematological malignancies treated with low molecular weight heparin while thrombocytopenic together with a literature review of the safety of anticoagulation for treatment and prophylaxis of VTE in this patient population.

**Table 1**
Examples of risk factors for cancer associated thrombosis.

| |
|---|
| **Cancer Related** |
| Site- Pancreas, stomach, brain, kidney, lung, ovary, haematological malignancies |
| Advanced Stage |
| Initial period after diagnosis (highest first 3–6 months) |
| **Treatment related** |
| Chemotherapy |
| Erythropoiesis stimulating agents |
| Hormonal therapy |
| Immunomodulatory drugs- Thalidomide, lenalidomide |
| Central venous Catheters |
| **Patient Related** |
| Advanced age |
| Female sex |
| Race (Higher in African Americans, lower in Asians) |
| BMI (Obesity) |
| Comorbidities (renal disease, infection, pulmonary disease) |
| **Biomarkers** |
| Elevated D Dimer |
| Platelet count ($\geq 350 \times 10^9$/L) |
| Leucocyte count ($>11 \times 10^9$/L) |
| Hb (<100 g/L) |
| Elevated tissue factor |

## 2. Methods

### 2.1. Case reports

We retrospectively reviewed cases of patients with known or newly diagnosed haematological malignancies treated for concomitant VTE either as inpatients or outpatients at the Calvary Mater Hospital between 2013 and 2015 inclusively. Cases were selected if they met the following inclusion criteria (1) Thrombocytopenia (platelet count $<100 \times 10^9$/L) on at least 2 consecutive days during treatment for VTE (2) Non Catheter related VTE (3) Had follow up throughout period of thrombocytopenia and/or treatment for haematological malignancy. We excluded cases of catheter related thrombosis because this is relatively common in patients with malignancies and has been extensively reviewed in previously published guidelines (Farge et al., 2013). Major bleeding was defined as fatal bleeding, symptomatic bleeding in a crucial area or organ, or bleeding that caused a reduction in haemoglobin concentration of >2 g/dL or that necessitated transfusion of >2 units of whole blood or red blood cells (Schulman and Kearon, 2005). Minor bleeding comprised all bleeding events that did not meet the criteria for major bleeding.

### 2.2. Literature review

A search of MEDLINE, EMBASE, CINAHL databases, Cochrane Central Register of Controlled Trial, and Cochrane Database of Systemic Reviews for articles published in English between January 1996 and January 2015. References cited in the articles obtained from the above search and similar articles in MEDLINE were included. The search terms included venous thromboembolism (VTE), treatment, thromboprophylaxis, heparin, unfractionated heparin, low molecular heparin, warfarin, haematological malignancies and thrombocytopenia. As there were only very few studies evaluating the safety of anticoagulation in thrombocytopenic patients with haematological malignancies treated for venous thromboembolism, we expanded our search to include any article that evaluated the safety of anticoagulation as thromboprophylaxis or treatment of VTE in patients with haematological malignancies.