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

1. Introduction ..................................................................................................................... 93
2. Methods .......................................................................................................................... 93
   2.1. Case reports ............................................................................................................. 93
   2.2. Literature review ..................................................................................................... 93
3. Case reports .................................................................................................................. 94
   3.1. Case 1 ....................................................................................................................... 94
   3.2. Case 2 ....................................................................................................................... 94
   3.3. Case 3 ....................................................................................................................... 94
   3.4. Case 4 ....................................................................................................................... 94
   3.5. Case 5 ....................................................................................................................... 94
4. Results .......................................................................................................................... 94
5. Literature review .......................................................................................................... 95
   5.1. Prophylaxis .............................................................................................................. 95
      5.1.1. Thromboprophylaxis in patients with haematological malignancies and central venous catheters .......................................................... 95
      5.1.2. Use of low molecular weight heparin in the prevention of veno-occlusive disease in patients undergoing haematopoietic stem cell transplantation ............................................................. 97
   5.2. Treatment ............................................................................................................... 97
      5.2.1. Treatment of venous thromboembolism in the patients undergoing haematopoietic stem cell transplantation .......................................................... 97
      5.2.2. Treatment of venous thromboembolism in severely thrombocytopenic patients with haematological malignancies ......................................................... 97
6. Discussion ...................................................................................................................... 97
7. Conclusion ..................................................................................................................... 98
Conflict of interest ........................................................................................................... 98
Authorship ....................................................................................................................... 98
References ....................................................................................................................... 98

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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 are 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
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 leukemias 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 haematological 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 and an established VTE. In cancer patients with thrombocytopenia, it is interesting to note that both ASCO and ISTH apply a threshold of 50 x 10^9/L below which therapeutic anticoagulation is relatively contraindicated. Additionally, when the platelet count is <50 x 10^9/L, BSHC also recommends the use of platelet transfusions to elevate the count to >50 x 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.

<table>
<thead>
<tr>
<th>Cancer Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site- Pancreas, stomach, brain, kidney, lung, ovary, haematological malignancies</td>
</tr>
<tr>
<td>Advanced Stage</td>
</tr>
<tr>
<td>Initial period after diagnosis (highest first 3–6 months)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Erythropoiesis stimulating agents</td>
</tr>
<tr>
<td>Hormonal therapy</td>
</tr>
<tr>
<td>Immunomodulatory drugs- Thalidomide, lenalidomide</td>
</tr>
<tr>
<td>Central venous Catheters</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Race: (Higher in African Americans, lower in Asians)</td>
</tr>
<tr>
<td>BMI (Obesity)</td>
</tr>
<tr>
<td>Comorbidities (renal disease, infection, pulmonary disease)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated D Dimer</td>
</tr>
<tr>
<td>Platelet count (≥350 x 10^9/L)</td>
</tr>
<tr>
<td>Leucocyte count (≥11 x 10^9/L)</td>
</tr>
<tr>
<td>Hb (&lt;100 g/L)</td>
</tr>
<tr>
<td>Elevated tissue factor</td>
</tr>
</tbody>
</table>

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 x 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.
3. Case reports

3.1. Case 1

A 19 year old Caucasian male presented with general lethargy and nausea. He was found to be anaemic and thrombocytopenic (Hb 84 g/L platelets 52 × 10^9/L). Circulating blasts were observed on the blood film and a bone marrow biopsy was performed which confirmed the diagnosis of B Acute Lymphoblastic Leukaemia (B ALL). He had been diagnosed with an unprovoked right lower limb deep venous thrombosis (DVT) 3 months prior and was on warfarin. Warfarin was ceased and he was switched to enoxaparin with a 50% dose reduction in view of his thrombocytopenia. He was commenced on induction chemotherapy using the Berlin Frankfert Munster (BFM) 2000 protocol. During induction, his mean and median platelet count until platelet recovery was 65 × 10^9/L and 51 × 10^9/L with a nadir of 23 × 10^9/L. Platelet transfusions were given to maintain a platelet count above 20 × 10^9/L. Further dose adjustments were made to enoxaparin according to his platelet count. Enoxaparin was withheld for 12 h prior to lumbar punctures for administration of intrathecal chemotherapy. Cyro-precipitate infusions were given for hypofibrinogenemia (<20 g/L) secondary to asparaginase therapy. No major or minor bleeding was noted throughout induction and consolidation chemotherapy. He was switched to a prophylactic dose of enoxaparin (40 mg daily) 6 months post diagnosis of his DVT and currently remains on maintenance chemotherapy.

3.2. Case 2

A 61 year old Caucasian female was referred with a 1 week history of increasing shortness of breath on exertion, spontaneous bruising, epistaxis, gum bleeding and haemoptysis. On presentation, she was thrombocytopenic with a platelet count of 18 × 10^9/L. An urgent bone marrow biopsy with FISH panel was performed and a diagnosis of acute myeloid leukaemia (not otherwise specified) was made. She was on warfarin following an unprovoked extensive left lower limb deep venous thrombosis involving the left iliac and femoral veins and bilateral pulmonary emboli (PE) 2 months ago. Warfarin was ceased and she was switched to full dose therapeutic enoxaparin. She was commenced on standard induction chemotherapy with cytarabine/idarubicin (7-3 regimen). Mean and median platelet count from induction until platelet recovery were 41 × 10^9/L and 37.5 × 10^9/L respectively with a nadir of 24 × 10^9/L. Platelet transfusions were given to maintain a platelet count above 50 × 10^9/L. Minor bleeding occurred (oozing around intravenous cannula insertion sites) during induction but no major bleeding complications were noted. She did not have any major bleeding at the time of completion of first consolidation chemotherapy.

3.3. Case 3

A 67 year old Caucasian male presented to hospital with a fall complicated by a right subdural haematoma. Platelet count at the time of presentation was 13 × 10^9/L. Coagulation profile including APTT (Activated Partial Thromboplastin Time) and PT (Prothrombin Time) were in the normal range. Fibrinogen was not done at time of bleed but was normal when performed 7 months prior. He had a diagnosis of transformed myelofibrosis on a background of JAK2 positive Essential Thrombocytopsisis. He was receiving dose adjusted enoxaparin (40 mg twice daily) for a right upper lobe pulmonary embolus which was diagnosed 1 month prior to this presentation. Platelet transfusions were given to maintain a platelet count >25 × 10^9/L. Mean and median platelet count from diagnosis of pulmonary embolus to subdural bleed were 24 × 10^9/L and 41.5 × 10^9/L respectively with a nadir of 13 × 10^9/L. Enoxaparin was ceased on upon detection of the subdural haematoma. The patient developed seizures with decreased level of consciousness and was admitted to the intensive care unit. Unfortunately the patient’s condition deteriorated and was palliated.

3.4. Case 4

A 58 year old Caucasian male receiving chemotherapy on the Cancer and Leukaemia Group B (CALGB) protocol for Acute Lymphoblastic Leukaemia was diagnosed with pulmonary embolus (PE) during the late intensification phase and was started on a daily dose of therapeutic enoxaparin (50% reduction). This occurred on a background of previous pulmonary embolus 3 years ago. He developed rectal bleeding and was admitted 1 month later with pancytopenia (Haemoglobin 78 g/L white cell count 0.2 × 10^9/L and platelet count 15 × 10^9/L) in the setting of ongoing chemotherapy. Mean and median platelet count from time of admission until platelet recovery were 32 × 10^9/L and 30 × 10^9/L respectively with a nadir of 15 × 10^9/L. Platelet transfusions were given to maintain a platelet count of >20 × 10^9/L. Enoxaparin was withheld on admission when the platelet count was <20 × 10^9/L but continued for the rest of his admission. No surgical intervention was required for his rectal bleeding. He was discharged after the bleeding had settled and platelet count at time of discharge was 30 × 10^9/L. He was switched to rivaroxaban 20 mg daily during maintenance phase of chemotherapy. No other minor or major bleeding was noted on follow up until completion of chemotherapy.

3.5. Case 5

A 69 year old Caucasian female with history of Mantle cell Lymphoma previously treated with 6 cycles of Rituximab, Cyclophosphamide, Vincristine and Prednisolone (RCHOP) was diagnosed with relapse 15 months after completion of RCHOP and while on maintenance Rituximab. This was complicated by proximal vein deep venous thrombosis for which she was on warfarin. Warfarin was ceased and switched to enoxaparin at a dose of 1.5 mg/kg. She was commenced on second line chemotherapy Rituximab, Etoposide, Methylprednisolone and Carabine (RESHAC). She received 3 cycles of R RESHAC in total as an outpatient. Twice weekly full blood counts were performed. No thrombocytopenia was noted during her first cycle. In her second cycle, she was first noted to be thrombocytopenic from day 10 post chemotherapy with a platelet count of 130 × 10^9/L. Mean and median platelet count until platelet recovery were 76 × 10^9/L and 58 × 10^9/L respectively with a nadir of 23 × 10^9/L and duration of thrombocytopenia for about 10 days. Enoxaparin was continued at full dose throughout the second cycle and no platelet transfusion was given. During cycle 3, her platelet count was 88 × 10^9/L on day 10. Mean and median platelet count until platelet recovery were 41 × 10^9/L and 34 × 10^9/L respectively with a nadir of 9 × 10^9/L and thrombocytopenia lasted for at least 10 days. Platelet transfusions were given for platelet counts <20 × 10^9/L and enoxaparin was withheld if platelet count was <50 × 10^9/L. No major or minor bleeding complications were noted throughout all 2 cycles of chemotherapy.

4. Results

5 patients with different haematological malignancies are presented in this review. The patient characteristics are shown in Table 2. VTE preceded the diagnosis of haematological malignancy in 2 patients (1 and 2). All received enoxaparin as treatment for VTE (2 lower limb DVTs, 3 PEs). Platelet transfusions were given for platelet counts <20 × 10^9/L and enoxaparin dose reduced for platelet counts <50 × 10^9/L in accordance to recommended
guidelines. Four patients (1, 2, 4, and 5) were receiving chemotherapy while treated for their VTE. Two patients (1 and 2) received treatment for VTE as inpatients while undergoing induction chemotherapy for acute leukaemia. Patient 4 was admitted post chemotherapy for acute leukaemia in the setting of significant cytopenias and received treatment for VTE while as an inpatient. Patient 3 and 5 were treated for their VTE as outpatients. A summary of the platelet counts (mean, median and nadir) and bleeding outcomes is shown in Table 3. There were two major bleeds (3 and 4), and one minor bleed (2). One major bleed was fatal (patient 3). None of the patients had recurrent or new VTE. In one patient (4), enoxaparin was switched to rivaroxaban during maintenance chemotherapy during which his platelet count was maintained above 100 \times 10^9/L.

5. Literature review

A summary of studies evaluating the safety of anticoagulation for VTE in patients with haematological malignancies is shown in Table 4. Majority of the studies evaluated the safety of thromboprophylaxis rather than treatment of VTE and most of these were based on catheter related thrombosis. When defined, catheter related thrombosis in these studies was defined as thrombosis of the vein(s) in which the catheter was placed and/or a contiguous vein. Most studies included patients with thrombocytopenia, 2 of which reported on a cohort of patients who received anticoagulation in the setting of severe thrombocytopenia (platelet count <20 \times 10^9/L). Low molecular weight heparin was the most common antithrombotic agent used. We found only 2 retrospective studies and no prospective or randomised controlled trials (RCTs) evaluating the safety of anticoagulation for the treatment of VTE in thrombocytopenic patients with haematological malignancies.

5.1. Prophylaxis

5.1.1. Thromboprophylaxis in patients with haematological malignancies and central venous catheters

Couban et al. conducted a randomised controlled trial which compared warfarin at a dose of 1 mg and placebo as thromboprophylaxis in 255 patients with central venous catheters, 80% of whom had haematological malignancies (Couban, 2005). In this study, the incidence of thrombocytopenia was not recorded and the study drug was withheld in patients with a platelet count below 20 \times 10^9/L. No significant difference in bleeding complications occurred in the arm receiving warfarin compared to placebo. In the CATHEM study, Cortelezzi et al. reported on 416 patients with haematological malignancies undergoing CVC insertion who were prospectively followed up to assess the incidence and risk factors for thrombotic complications (Cortelezzi et al., 2005). 14% of patients received thromboprophylaxis with low molecular heparin (majority), unfractionated heparin, warfarin or aspirin. The incidence of VTE (DVT and/or PE) was 3.2% and 80% of the patients were severely thrombocytopenic. 1.5% of the 416 patients were catheter related thrombosis. The authors concluded that antithrombotic prophylaxis was not associated with an increased risk of bleeding although the study was not designed for this indication.
Table 4
Studies evaluating the use of antithrombotics in the treatment/prophylaxis of VTE in patients with haematological malignancies and bleeding complications.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Study Design</th>
<th>Indication/antithrombotic agent</th>
<th>Bleeding severity/incidence</th>
<th>Study Conclusion</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couban et al JCO 2005 (Couban et al., 2005)</td>
<td>Cancer patients (80% haematological malignancy) with CVC n = 215</td>
<td>Prospective</td>
<td>Thromboprophylaxis; Warfarin 1 mg</td>
<td>Major bleeding* 0% Minor bleeding 4%</td>
<td>No increased risk of major bleeding</td>
<td>Anti thrombotic withheld below platelet count 20 × 10^9/L.</td>
</tr>
<tr>
<td>Cortelazzi BJH 2005 (Cortelazzi et al., 2005)</td>
<td>Patients with haematological malignancy and CVC n = 416</td>
<td>RCT</td>
<td>Thromboprophylaxis; LMWH (majority), UFH, aspirin, warfarin</td>
<td>Severe bleeding 0%</td>
<td>No increased risk of major bleeding</td>
<td>Only 14.2% received Antithrombotic prophylaxis. Thrombocytopenia (&lt;50 × 10^9/L) was present in 81% of patients. Study not designed to look at safety and efficacy of antithrombotic prophylaxis. 5 patients in LMWH group and 8 patients in placebo group withdrawn due to major bleeding</td>
</tr>
<tr>
<td>Or et al Transplantation 1996 (Or et al., 1996)</td>
<td>HSCT recipients n = 61</td>
<td>RCT</td>
<td>Prevention of Veno-occlusive Disease; LMWH</td>
<td>Bleeding events (events/pt) 2.3 ± 2.5 vs 5.3 ± 6 P = 0.025 Duration of bleeding (days/pt) 2.3 ± 2.6 ± 5.8 ± 6 P &lt; 0.06</td>
<td>LMWH associated with decreased risk of bleeding</td>
<td></td>
</tr>
<tr>
<td>Simon M et al, Bone marrow transplant 2001 (Simon and Hahn, 2001)</td>
<td>HSCT recipients n = 462</td>
<td>Retrospective</td>
<td>Prevention of Veno-occlusive Disease; UFH, UFH + PGE1, LMWH</td>
<td>Death due to hemorrhagic events 3% (total)</td>
<td>No significant difference in death due to hemorrhagic events in groups receiving prophylaxis vs no prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Forrest et al, Bone marrow transplant 2003 (Forrest et al., 2003)</td>
<td>HSCT recipients n = 40</td>
<td>Prospective</td>
<td>Prevention of Veno-occlusive Disease; LMWH</td>
<td>Clinically significant bleeding* (≥ Grade 2.75%) Minor bleeding (Grade 1) 60%</td>
<td>No significant increase in clinically significant bleeding</td>
<td>Platelet transfusion if &lt;10 × 10^9/L or &lt;30 × 10^9/L with clinically significant bleeding</td>
</tr>
<tr>
<td>Gonsalves et al, JTH 2008 (Gonsalves et al., 2008)</td>
<td>HSCT recipients n = 589</td>
<td>Retrospective</td>
<td>Treatment of VTE (n = 22); LMWH+/- Warfarin</td>
<td>No significant bleeding complications recorded</td>
<td>No significant bleeding complications</td>
<td></td>
</tr>
<tr>
<td>Gerber et al, Blood 2008 (Gerber et al., 2008)</td>
<td>HSCT recipients n = 1514</td>
<td>Retrospective</td>
<td>Treatment of VTE (n = 62); Type of antithrombotic not stated</td>
<td>Clinically significant bleeding* 37% (n = 23) Fatal bleeding 5% (n = 3)</td>
<td>Bleeding associated with anticoagulation (OR 3.1; 95% CI, 1.8-5.5), No significant increase in clinically significant bleeding</td>
<td>Median platelet count at the time of VTE events overall 75 × 10^9/L (IQR, 42–150 × 10^9/L).</td>
</tr>
<tr>
<td>Herishanu et al, Leukaemia Lymphoma 2004 (Herishanu et al., 2004)</td>
<td>Patients with haematological malignancy and severe thrombocytopenia n = 10</td>
<td>Retrospective</td>
<td>Treatment of CVC related VTE (n = 10); LMWH</td>
<td>Major Bleeding 0%</td>
<td>No increased risk of major bleeding</td>
<td></td>
</tr>
<tr>
<td>Imberti et al, Tumori 2004 (Imberti et al., 2004)</td>
<td>Acute Leukaemia n = 4</td>
<td>Retrospective</td>
<td>Treatment of VTE (n = 4)</td>
<td>No haemorrhagic complications</td>
<td>No haemorrhagic complications</td>
<td>Dose reduced by 50% if platelets &lt;20 × 10^9/L.</td>
</tr>
</tbody>
</table>

* Major bleeding: CNS bleeding, bleeding with hypotension (systolic blood pressure <80 mmHg or a > 30-mmHg decrease in systolic blood pressure), bleeding associated with the transfusion of more than 2 units of red cells in any 24-h period, or a decrease in haemoglobin by 20 g/L or more in any 24-h period.

grade 0 = no bleeding; grade 1 = minor mucosal bleeding or petechiae not requiring packed red blood cell (PRBC) transfusion; grade 2 = any bleeding episode requiring transfusion of 1–2U of PRBCs/episode in a 24-h period; grade 3 = any bleeding episode requiring transfusion of >2U of PRBCs/episode, but < 4U in a 24-h period or retroperitoneal bleeding; grade 4 = any bleeding causing hemodynamic instability or requiring transfusion of >4U of PRBCs in a 24-h period or any CNS bleeding.

# Clinically significant bleeding: a bleeding event between HSCT admission and HSCT day 180 that led to a specific clinical intervention. Interventions included but were not limited to hospitalization, transfusion, endoscopy, bronchoscopy, intubation, or continuous bladder irrigation. Bleeding episodes not requiring intervention (e.g., most mucosal and soft tissue bleeding, microscopic hematuria) were not recorded.
5.2. Use of low molecular weight heparin in the prevention of veno-occlusive disease in patients undergoing haematopoietic stem cell transplantation

Several studies have evaluated the safety of low molecular weight heparin in patients undergoing haematopoietic stem cell transplant for the prevention of veno-occlusive disease (Or et al., 1996; Simon and Hahn, 2001; Forrest et al., 2003). The results of these studies indicated that the use of low molecular heparin is safe with no increased risk of bleeding. In one study, the mean number and duration of severe haemorrhagic occurrences per patient were significantly lower in the LMWH group (P = 0.025 and P = 0.006, respectively compared to placebo).

5.2. Treatment

5.2.1. Treatment of venous thromboembolism in the patients undergoing haematopoietic stem cell transplantation

Gonsalves et al. (2008) performed a retrospective study on the incidence of symptomatic VTE in ambulatory patients in the transplant setting (n = 589, 382 autologous, 207 allogeneic). The incidence of VTE was 3.7%. Non catheter related venous thrombosis occurred in 7 patients (1.2%). The mean platelet count was 121 (range 50–174). Three patients had platelet counts below normal. All seven patients were treated with full-dose anticoagulation using low molecular weight heparin, but in two cases, low molecular weight heparin therapy was switched to treatment with warfarin. No significant bleeding complications developed during anticoagulant therapy in these seven patients. In contrast, a study of 1514 inpatients admitted for haematopoietic stem cell transplant (928 autologous 586 allogeneic) found anticoagulation (type not stated) to be associated with an increased risk of bleeding (OR3.1: 95% CI, 1.8–5.5) (Gerber et al., 2008). In this study, the total incidence of VTE was 4.6%. 13% (n = 20) were non catheter related venous thrombosis. 34% of VTE occurred at a platelet count <50 x 10^9/L and platelet transfusions were given to maintain a platelet count above this threshold in patients receiving anticoagulation. The reason for the different results obtained in the 2 studies is unclear. However, this may be related to the timing of VTE during the transplant.

5.2.2. Treatment of venous thromboembolism in severely thrombocytopenic patients with haematological malignancies

Herishanu et al. (2004) reported a retrospective cohort of 10 patients undergoing intensive chemotherapy for haematological malignancies who received low molecular weight heparin as thromboprophylaxis or treatment of CVC related thrombosis while severely thrombocytopenic. No major bleeding occurred in these patients. In another study (Imberti et al., 2004), 4 patients diagnosed with acute leukaemia and VTE were treated with low molecular weight heparin (enoxaparin) dose adjusted according to their platelet count (Mean platelet count was 55,750 x 10^9/L; range, 12,000–121,000 x 10^9/L). No VTE recurrences or haemorrhagic complications were reported. Although these were small studies, the results suggested that low molecular weight heparin could be used safely in this group.

6. Discussion

There are no randomised controlled trials evaluating the safety of anticoagulation for VTE in thrombocytopenic patients with haematological malignancies. In our literature review, 2 small retrospective studies (Herishanu et al., 2004; Imberti et al., 2004) concluded that low molecular weight heparin could be used safely in the treatment of VTE in the setting of thrombocytopenia whereas another large retrospective study demonstrated that anticoagulation for the treatment and prophylaxis of VTE in haematopoietic stem cell recipients was associated with a higher risk of bleeding although the type of anticoagulation was not stated (Gerber et al., 2008). In our case series of 5 patients, major bleeding (intracranial haemorrhage, gastrointestinal bleeding) occurred in 2 patients with the former being fatal while minor bleeding occurred in 1 patient.

The risk of bleeding in patients with VTE on anticoagulation has been evaluated in a meta-analysis by Linkins et al. (2003). Major bleeding was estimated at 7.2 events per 100 person-years, and the risk of fatal bleeding 1.31 per 100 person-years, with a case fatality rate of 13.4% from major bleeding. Intracranial bleeding occurred at a rate of 1.15 per 100 patient-years and accounted for 8.7% of all major bleeding episodes. Eleven of 24 intracranial bleeding episodes were fatal (Linkins et al., 2003). In another meta-analysis which compared the safety and efficacy of unfractionated heparin to enoxaparin in patients with VTE, the adjusted incidence of major bleeding at 3 months in patients on enoxaparin was 2.9% (Mismetti et al., 2005). In a pooled analysis of the bleeding risk of LMWH and VKA in patients with cancer, major bleeding occurred in about 6% of patients (Kamphuisen and Beyer-Westendorf, 2014). These studies did not report on the incidence of major bleeding in patients with haematological malignancies.

The highest risk of bleeding occurs in the initial period after starting anticoagulant therapy. Risk factors include age older age (>65 years and particularly >75 years), recent major bleeding (<15 days prior to VTE), comorbidities (previous gastrointestinal bleeding, stroke, chronic renal disease, metastatic malignancy, alcohol-related disease, or diabetes), thrombocytopenia, anaemia, concomitant antplatelet therapy, recent surgery, frequent falls, alcohol abuse, and reduced functional capacity (Prandoni et al., 2002; Shoeb and Fang, 2013; White et al., 1999; Palareti et al., 1996; Kuijer et al., 1999). A bleeding risk assessment scores based on findings from the RIETE registry (Ruiz-Giménez et al., 2008) and other similar scores have been developed (Shoeb and Fang, 2013; Kearon et al., 2012; Beyth et al., 1998). However, these studies have primarily been based on the use of oral Vitamin K antagonist warfarin and no bleeding scores to assess the risk of bleeding in the subgroup of patients with haematological malignancies have been developed.

Risk factors in our patient with JAK 2 positive myelofibrosis and fatal bleeding included age, comorbidities in particular history of previous stroke, thrombocytopenia and underlying haematological malignancy. Acquired platelet function abnormalities are well recognised in myeloproliferative disorders. Unfortunately baseline platelet function evaluation was not performed in this patient. While this could be a contributing factor to bleeding risk, this usually occurs in the setting of a very high platelet count, typically >1000 x 10^9/L (Alvarez-larran et al., 2013) which was not the case in our patient. Coexisting coagulopathy and fibrinogen abnormalities can also occur in myelofibrosis secondary to liver dysfunction. However, Prothrombin time (16 s; normal range 12–16 s) and Activated Partial Thromboplastin Time (34 s; normal range 24–36 s) were in the normal range at time of bleed. Fibrinogen was not done at time of bleed but was normal when performed 7 months prior. It is interesting to note that the 2 patients with major bleeding also had the lowest platelet counts. Bleeding occurred at a median platelet count of 22 x 10^9/L in patient 3 with fatal bleeding and was 30 x 10^9/L in patient 2 with gastrointestinal bleeding. Platelet count per se was not shown to correlate with bleeding in a multivariate analysis performed by Friedmann et al. (2002) on thrombocytopenic oncology patients. However, this may not apply to patients on anticoagulants. Other factors such as duration of thrombocytopenia, the type of haematological malignancy, and concomitant chemotherapy may also be important. More studies evaluating the risk factors of bleeding in thrombocytopenic patients with haematological malignancies on anticoagulation for VTE are therefore required which would be important in deciding which patients to anticoagulate based on their risk benefit profile.
Another controversial issue is the effectiveness of the use of prophylactic transfusions to prevent bleeding and what threshold to transfuse. Current recommendations suggest transfusion to maintain a platelet count greater than 20 × 10^9/L in patients not actively bleeding and above 50 × 10^9/L in those with active bleeding. These are based on supportive care in patients with acute promyelocytic leukemia and are expert opinion rather than evidence based. In the TOPPS trial, a randomised trial of 600 patients receiving chemotherapy or undergoing stem cell transplantation, prophylactic platelet transfusions resulted in less WHO grade 2–4 bleeding except in the population undergoing autologous stem cell transplantation (Stanworth et al., 2013). However it remains to be seen whether this can be also applied to patients with haematological malignancies on anticoagulation for VTE. Although our patient with fatal bleeding received prophylactic, platelet transfusions to maintain his platelet count above 20 × 10^9/L, the logistics of this was difficult as he was managed in an ambulatory care setting. Thus, more studies are required to investigate the role and indication of prophylactic platelet transfusions, as well as the safety of such a strategy in the ambulatory setting compared to inpatient setting.

Finally further studies to evaluate the dosing, duration and type of anticoagulation in such patients are needed. Current recommendations suggest full anticoagulation with low molecular weight heparin for patients with platelet counts >50 × 10^9/L and dose reducing if <50 × 10^9/L. The availability of direct oral anticoagulants provides an alternative attractive choice of anticoagulation with the advantage of convenience, tolerability and less drug interactions. However the safety and efficacy of these agents in this population of patients is not known and current guidelines do not support their use in this setting.

7. Conclusion

In summary, 5 cases of patients with haematological malignancies treated with low molecular weight heparin for non-catheter related venous thromboembolism while severely thrombocytopenic are discussed. A summary of literature is presented with discussion on various challenges around treating VTE in severely thrombocytopenic patients. Unlike previous case series, major bleeding occurred in 2 patients. Limitations of our study include its retrospective design and the small number of patients analysed. More studies are required to evaluate risk factors for bleeding, the safety and efficacy of anticoagulation for treatment and prophylaxis of venous thromboembolism, efficacy and indications for prophylactic platelet transfusions in thrombocytopenic patients, as well as the dosing, duration and type of anticoagulation used.

Conflict of interest

The authors disclose no conflicts of interest.

Authorship

MSL was responsible for design of study, acquisition of data and drafting the article. AKE was responsible for the conception of the study and critical revision of the article. Both MSL and AKE analysed and interpreted the data and gave final approval of the version to be submitted.

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