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Management patterns and outcomes in symptomatic non-catheter related venous thromboembolism following allogeneic hematopoietic stem cell transplantation --Manuscript Draft--

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Management patterns and outcomes in symptomatic non-catheter related venous thromboembolism following allogeneic hematopoietic stem cell transplantation.

Running short title

VTE after allogeneic HSCT

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Authorship Details:

J. R. Gonzalez-Porras and J. Labrador conceived the study; J. Labrador and J. Gonzalez-Rivero collected the data; J. Gonzalez-Rivero and J. R Gonzalez-Porras analysed the data; J. Labrador and J. R. González-Porras wrote the paper; F. S. Lozano, L. Lopez-Corral, M. D. Caballero and J. R. González-Porras provided the patients; all authors critically reviewed the paper and approved its final version.

DESIGN AND METHODS**Subjects**

Analyses were performed in accordance with the Declaration of Helsinki and the guidelines of the institutional review board of the Hospital Universitario de Salamanca. We conducted a retrospective cohort study of 23 consecutive patients (aged over 18 years) who had undergone allogeneic HSCT and had an episode of symptomatic non-catheter VTE. No patients received prophylaxis or therapeutic anticoagulation at the time of HSCT admission. VTE was classified as deep venous thrombosis (DVT) or pulmonary embolism (PE). The diagnosis of DVT was considered valid by compression ultrasonography or venography, according to standard methods. Pulmonary embolism was only accepted if it was demonstrated by perfusion lung scan or computerized tomography. In cases where DVT and PE occurred together, the events were classified as PE. Informed consent was obtained from all patients before HSCT. The main demographic and haematological features of the evaluable allogeneic HSCT recipients (median age, 55 years; 48% male) are shown in Table 1. The day of stem cell infusion was designated as day 0. Post-HSCT complications, such as GVHD was recorded. Any bleeding event after allogeneic HSCT was also included in the analysis, with the exception of mild petechiae. The number and location of bleeding sites were recorded. Bleeding was considered a major event if it conditioned a reduction in the haemoglobin level of at least 20 g/l, transfusion of at least two blood-pack units, or symptomatic bleeding in a critical area or organ. Major bleeding was considered to be life-threatening if it resulted in: fatality, symptomatic intracranial or pulmonary bleeding, bleeding with a decrease in the haemoglobin level of at least 50 g/l, or bleeding requiring transfusion of at least four red blood-cell units or inotropic agents, or if surgery was required. All other bleeding was considered to be minor.

Statistical analysis

Data were initially included in an Excel (Microsoft) spreadsheet and a descriptive statistical analysis performed. Results are expressed as percentages for categorical variables and as medians (and range) for continuous variables.

RESULTS

Twenty-three cases of symptomatic VTE following HSCT were identified. Eighteen patients had lower extremity DVT after allogeneic HSCT, whereas 5 patients had PE. The median time from HSC administration to diagnosis of venous VTE was 150 days (range, 17 – 3285 days). At the time of VTE diagnosis, the mean platelet

count was $128 \times 10^9/L$ (range 31–315). 21 out of 23 patients were treated with antithrombotic therapy. The median time of antithrombotic therapy was 93 days (range, 25 - 341). Eleven patients were treated with full-dose anticoagulation using low molecular weight heparin (LMWH) (enoxaparin 1 mg/kg/every 12 hours or bemparin 115 UI/kg/daily), but in one case, low molecular weight heparin therapy was switched to treatment with acenocumarol (INR target, 2-3). Ten patients with minor bleeding and/or relevant thrombocytopenia were managed using prophylactic-dose LMWH (enoxaparin 40 mg/ once daily or bemparin 3500 UI/once daily) on a best clinical judgment basis. In two patients with DVT and active intestinal haemorrhage, anticoagulation treatment was not initiated and an inferior vena cava (IVC) filter was inserted. Both cases died from intestinal transplant associated microangiopathy and leukaemia progression after 3 and 6 months of IVC placed, respectively. Rate of clinically relevant haemorrhage observed in our patients was 30% (7 patients). The median time until the first bleeding episode was 60 days (range, 2 - 3660 days). Two of the bleeding events were considered minor bleeding, 1 was major and 4 bleeding episodes were life-threatening events. The life-threatening bleedings affected either the GI tract (n = 2) lung (n = 1) or the central nervous system (n = 1). The life-threatening bleedings occurred in both full-dose LMWH (n = 2) and low-dose LMWH (n=2). All four patients discontinued LMWH permanently. Two deaths were directly attributable to bleeding. Rate of clot recurrence or extension was 17% (4 patients). At the time of clot recurrence or extension, three of four patients received low-dose LMWH and one patient full-dose LMWH. All four patients with recurrence VTE had extensive chronic GVHD.

DISCUSSION

This study illustrates a significant problem in patients with allogeneic HSCT; How to manage the anticoagulation in patients with venous thromboembolism following allogeneic HSCT? In this series, we have observed that antithrombotic management of symptomatic non-catheter related VTE following allogeneic HSCT is a complex task. Nearly half of the HSCT recipients who have a VTE may not be receive full-dose LMWH. Also, rates of clot recurrence or extension (17%) and clinically relevant haemorrhage (30%) observed in our patients were highly significant. Among patients with active cancer and acute symptomatic VTE, the use of full-dose tinzaparin was a safety and effective strategy on preventing recurrent VTE [5]. However, in allogeneic HSCT is difficult to maintain a full-dose LMWH. Prolonged severe thrombocytopenia and tissue damage, caused by conditioning regimen or post-transplant complications such as acute GVHD or thrombotic microangiopathy, are the best reasons of bleeding following allogeneic HSCT [3,4]. Even as low-dose LMWH

we have reported two cases of life-threatening bleeding complication. However, well-designed clinical trials to evaluate the risks and benefits of VTE anticoagulation treatment in this population are needed.

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