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Incidence of venous thromboembolism and use of anticoagulation in hematological malignancies: Critical review of the literature

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ABSTRACT

Venous Thromboembolism (VTE) frequently complicates the course of hematologic malignancies (HM) and its incidence is similar to that observed in high-risk solid tumors. Despite that, pharmacologic prophylaxis and treatment of VTE in patients with HM is challenging, mainly because a severe thrombocytopenia frequently complicates the course of treatments or may be present since diagnosis, thus increasing the risk of bleeding. Therefore, in this setting, safe and effective methods of VTE prophylaxis and treatment have not been well defined and hematologists generally refer to guidelines produced for cancer patients that give indications on anticoagulation in patients with thrombocytopenia. In this review, besides to summarize the incidence and the available data on prophylaxis and treatment of VTE in HM, we give some advices on how to use antithrombotic drugs in patients with HM according to platelets count.

1. Introduction

Venous Thromboembolism (VTE) frequently complicates the course of hematologic malignancies (HM) with a significant impact on morbidity and mortality; its incidence is similar to that observed in high-risk solid tumors (Falanga and Marchetti, 2009; Castelli et al., 2010a). Pathogenesis of VTE, also in HM, is as usual multifactorial depending on: a) type and burden of hematological malignancy, b) type of chemotherapy, c) patients related factors and d) other risk factors such as: platelet and leukocyte count, presence of infections or central venous catheter (CVC), interventional procedures (Prandoni et al., 2005). Moreover, as in solid tumor, neoplastic blood cells and/or leukemic stem cells may release procoagulant, proinflammatory and angiogenic factors including tissue factor, cancer procoagulant (Gale and Gordon, 2001) and tumor necrosis factor alpha (Grignani and Maiolo, 2000). Furthermore, the use of high-dose steroids, erythropoietic and myeloid growth factors contribute to enhance the risk of thrombosis (Wun and White, 2010; Falanga and Marchetti, 2012; Lee and Levine, 1999). In addition, chemotherapy may damage the endothelial wall and determine liver function impairment with reduction in circulating physiological anticoagulants (Falanga and Marchetti, 2012; Lee and Levine, 1999). Finally, thrombosis can also be found incidentally during the diagnostic work up or follow-up for malignancies (den Exter et al., 2012).

Despite the above evidence, prophylaxis and pharmacologic treatment of VTE in patients with HM is challenging mainly because a severe thrombocytopenia frequently complicates the course of treatments or is present since diagnosis. In this particular setting, safe and effective methods of VTE prophylaxis are challenging and mainly based on retrospective data and expert opinions. The lack of prospective studies or evidence-based guidelines in the field of VTE in HM leads hematologists to refer to guidelines produced for patients with solid cancers, not or only partially focused on anticoagulation in patients with thrombocytopenia (Carrier et al., 2013). Taking into account this premise, we performed a systematic review on incidence, prophyaxis and treatment of VTE in HM, particularly highlighting the “gray zones” in the management of frail patients, with thrombocytopenia and at high risk of bleeding

2. Methods

To identify all available studies, a detailed search related to the occurrence of thrombotic complications during hematological malignancies was performed according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Moher et al., 2009). A systematic search was conducted in the electronic databases (PubMed, Web of Science, Scopus, EMBASE), using the following search terms in all possible combinations: Thrombosis, Venous

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Thromboembolism, Pulmonary Embolism, Deep Vein Thrombosis, Atypical site thrombosis, Mesenteric vein thrombosis, Cerebral sinus vein thrombosis, Acute leukemia, Acute myeloid leukemia, Acute lymphoblastic leukemia, Chronic myeloproliferative neoplasms (MPNs), Polycythemia Vera, Essential Thrombocythemia, Primary Myelofibrosis, Jak-2 (V617F) gene mutated MPN, Lymphoma, Lymphoproliferative disease, Multiple Myeloma,Chemotherapy, Radiotherapy, Anticoagulant treatment, Low Molecular Weight Heparin, Oral anticoagulants.

The search strategy was developed with the following language and publication year restrictions: abstracts written in English, with the following timeframe limit: from 1st January 1980 to 31st January 2017. Furthermore, the reference lists of all retrieved articles were manually reviewed. Two independent authors (MN and OA) analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted (GA). Discrepancies were resolved by consensus. The primary endpoint was to evaluate characteristics and duration of anticoagulant treatment after VTE in patients with hematological malignancies; secondary endpoints were the occurrence and management of recurrent VTE after or during treatment for a first VTE and bleeding.

The main parameters evaluated referred to: indication to anticoagulant treatment in patients with hematological malignancies; anticoagulant treatment schedules adopted, hemorrhagic risk evaluation; efficacy measures of anticoagulant treatment; safety of anticoagulant treatment. In detail, VTE recurrence and bleeding episodes during anticoagulant treatment were evaluated, if available. The inclusion criteria required a confirmed diagnosis of hematological malignancy and VTE. Among available data, particular attention was given to frail patients at high bleeding risk due to severe thrombocytopenia (platelets count < 30.000/μL). In detail, frail subjects were considered all the patients with VTE and hematological malignancies under active chemotherapy treatment and expected or overt severe thrombocytopenia.

Major bleeding was defined as a decrease in hemoglobin of more than 2.0 g/dL, intracranial or retroperitoneal bleeding requiring surgery or blood transfusion, or any other bleeding necessitating suspension of anticoagulation and hemostatic approaches. Minor bleeds comprised all other events. All patient ages were considered.

2.1. Data extraction and quality assessment

According to the pre-specified criteria, all studies related to venous thrombosis in the course of HM were included. Single case-reports, abstract from conferences and animal studies were excluded. To be included in the analysis, a study had to provide data on venous thrombosis (clinically suspected and instrumentally diagnosed), their management, any underlying hematological malignancies and treatment. Because of the wide variability in the outcomes considered, neither formal study quality assessment nor meta-analytic evaluation were performed.

3. Results

The search provided 556 results, of which 480 were excluded because they were single case reports or judged off the topic after scanning the title and the abstract (articles related to biological and laboratory aspects of VTE in cancer, N = 75; articles and reviews not referring to hematological malignancies, N = 297; papers reporting VTE secondary to surgical procedures or medical illness other than blood cancer, N = 108). In addition, seven studies were excluded after evaluation of the full-length paper (Fig. 1). Only three studies specifically evaluated the safety of LMWH in frail thrombocytopenic patients with hematological malignancies (Khanal et al., 2016; Lim and Enjeti, 2016; Imberti et al., 2004). However, these studies do not reach a statistical power to be considered useful.

Before the publication of the CATCH study (Lee et al., 2015a), we have identified only 5 randomized clinical studies dealing with anticoagulant treatment of VTE in cancer patients (Meyer et al., 2002; Hull et al., 2006; Lee et al., 2003; Deitcher et al., 2006; Romera et al., 2009). Only 2 of these studies (Meyer et al., 2002; Hull et al., 2006) accrued patients with HM who are generically reported as hematologic cancer, without any detail on the type and characteristics of HM. The same is reported in the CATCH study, the last of these studies, where 94/900 (10.4%) patients had an unspecified hematologic tumor (Lee et al., 2015a). Therefore, we were unable to adopt these studies for the purpose of our review.

3.1. Acute leukemia

3.1.1. Reported incidences of VTE (Table 1)

VTE incidence in AL ranges from about 2% up to 12% (Ziegler et al., 2005; Ku et al., 2009; De Stefano et al., 2005; Melillo et al., 2007; Vu et al., 2015; Rickles et al., 2007). Ku et al. (2009) have observed a 2-year VTE cumulative incidence of 5.2% in AML and 4.5% in ALL, in a cohort study on 7876 patients with acute leukemia, mainly during the first month of diagnosis: age, comorbidities and CVC were reported as the most frequent associated risk factors for VTE.

De Stefano et al. (2005) evaluated the risk of VTE in a cohort of 379 adult patients with a newly diagnosed AL; overall, VTE episodes occurred in 19 (5%) patients and in 13 cases of entire population (3.4%), it was the presenting manifestation. In particular, VTE at diagnosis was observed in 1.4% of ALL, 9.6% of APL and 3.2% of other AML. Moreover, patients treated with L-asparaginase had a 4.9 fold increased risk of thrombosis (95%CI: 1.5–16). Death rate due to thrombosis was 0.8% and, differently from AML, in ALL the occurrence of VTE increased of 40% the risk of dying within 1 year.

Estimated incidence of VTE in children with ALL, derived from prospective studies, range from 3% to 36.7% (Shapiro et al., 1993; Mitchell et al., 1994; Athale and Chan, 2003). A meta-analysis of 17 studies showed a 5.2%, rate of thrombosis in pediatric patients with ALL mainly during induction therapy with L-asparaginase (Caruso et al., 2006). A similar trend (incidence rate of 5.9%) was observed in adults with ALL from 13 published prospective studies including 323 patients (Caruso et al., 2007).

A study performed by the GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) on 124 patients with acute promyelocytic leukemia (APL) treated with ATRA and Idarubicin showed an incidence rate of VTE of 8.8% (Breccia et al., 2007).

Vu et al. (2015) recently published a retrospective study on 1295 patients with AL reporting a prevalence of VTE of 10.7%. Most VTEs occurred within 3 months from diagnosis; however, most of them were upper extremity CVC related deep vein thrombosis and occurred mainly in ALL (Table 1).

3.1.2. Treatment options

Most of the reported VTE in AL are CVC-related (Oliver et al., 2015) and their anticoagulant treatment with Low Molecular Weight Heparin (LMWH) has been shown safe and effective when retrospectively compared with no treatment (Frere et al., 2014; van Doormaal et al., 2011).

Recently, in a multicenter study on 1461 patients with AL, our group has demonstrated the occurrence of non-CVC related VTE also in patients with severe thrombocytopenia (PLT < 30.000/μL). Treatment with LMWH, at a full dose for one month and adjusted regimens for the following 3 months resulted safe and effective in the reported cohort of patients with AL (Napolitano et al., 2016).

Treatment recommendations of VTE in children with ALL are extrapolated from adults. The American College of Chest Physicians (ACCP) Evidence based Clinical Practice Guidelines for children (9th edition) defines optimal strategies for the management of thrombosis in children, with and without cancer (Monagle et al., 2012). LMWH remains the most suitable treatment option also in the setting of ALL due