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Treatment of venous thromboembolism in acute leukemia: A systematic review

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ABSTRACT

Background: The safety and efficacy of venous thromboembolism (VTE) treatment in patients with acute leukemia (AL) are not well understood and the optimal treatment strategy is unclear.
Methods: We conducted a systematic review of the literature aiming to identify observational studies and randomized trials describing treatment of VTE in the setting of AL including, acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), and acute lymphoblastic leukemia (ALL). Due to the heterogeneity of findings, no meta-analysis was attempted.
Results: A total of 13 observational studies (11 cohorts and 2 case-control) totaling 5359 participants were included. The number of patients with VTE among the total population was 304 (5.7%; 95% CI 5.1–6.3). In patients with VTE, 221 patients received treatment with anticoagulation using either of low-molecular-weight heparin, unfractionated heparin, and/or vitamin K antagonists. Most studies adjusted the anticoagulant dose based on platelet count. The reported recurrence rate ranged from 0 to 29% among different studies and varied according to the duration of anticoagulant treatment and follow up. Bleeding events were not uniformly reported but the total number was low among anti-coagulated patients.
Conclusion: There is a significant lack of data in this area with a high degree of heterogeneity in the choice of anticoagulant, dose adjustments for thrombocytopenia, and duration of anticoagulation. Further studies are required to develop guidelines and suggestions for treatment of VTE in AL.

1. Introduction

Patients with acute leukemia (AL) are prone to developing venous thromboembolism (VTE) as a result of alterations in hemostasis. In addition to the risks intrinsic to the malignant cells, other risk factors such as the presence of central venous catheters (CVC), chemotherapy, and hospitalizations make this population prone to VTE complications. Although the real incidence of VTE is unclear in AL patients, the incidence of VTE in hematological malignancies is reported up to 10% with these patients being up to 26 times more likely to develop VTE compared to the general population [1].

Standard treatment for VTE is anticoagulation; however, treatment of VTE in AL patients is challenging due to the presence of thrombocytopenia and coagulopathy in many of these patients which leads to a subsequent increased risk of hemorrhage. The safety and efficacy of anticoagulation has not been formally evaluated in AL patients. Low molecular weight heparin (LMWH), unfractionated heparin (UFH), vitamin K antagonist (VKA) and direct oral anticoagulants (DOACs) are routinely used to treat VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE). However, information regarding the safety and efficacy of AC treatment in AL patients is largely unknown [2–6]. We conducted a systematic review of the literature aiming to identify observational studies and randomized trials describing the treatment of VTE in the setting of AL.

2. Methods

2.1. Search strategy and data sources

We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7].

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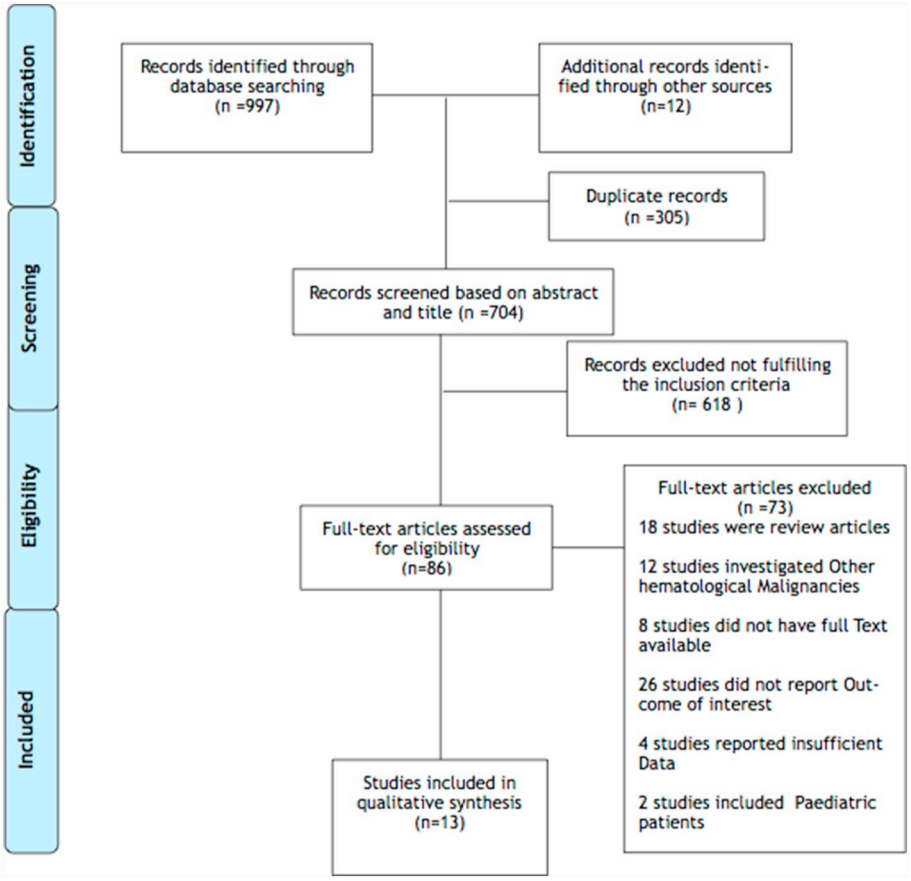

Fig. 1. Flow diagram summarizing the identification process of relevant clinical trials.

The search was conducted in MEDLINE®, using both Ovid and PubMed search interfaces, and Embase® electronic bibliographic databases. The search terms were a combination of keywords and medical subject headings, including “acute myeloid leukemia”, “precursor cell lymphoblastic leukemia-lymphoma”, “venous thromboembolism”, “thromboembolism”, “thrombosis”, “VTE”, “DVT” and “pulmonary embolism”. A detailed description of our search strategy can be found in the Appendix. Citations were supplemented by cross checking the reference lists of the eligible studies to identify additional published data.

2.2. Eligibility criteria

We aimed to include observational studies, randomized controlled trials and case series with > 20 patients published from January 1994 through April 2017, and describing VTE treatment in adult patients (older than 16 years of age) with AL including acute myeloid leukemia (AML) including acute promyelocytic leukemia (APL), and acute lymphoblastic leukemia (ALL). The outcomes of the review included treatment for different subtypes of VTE events including anticoagulation agent, dose of anticoagulant, duration of treatment, associated bleeding events, and rate of recurrence of VTE. Studies that included patients with superficial phlebitis, patients younger than 16 years of age, or patients who received fresh frozen plasma (FFP) for VTE prophylaxis were excluded.

2.3. Study selection and data collection

Potentially relevant studies were independently assessed by two reviewers. A third reviewer resolved any discrepancies. Level 1 screen was based on article titles and/or abstracts. A liberal accelerated process was adopted for Level 1 screening. One reviewer was required to include a study and two were required to exclude it. The full-text of all articles passing Level 1 screening was retrieved for Level 2 screening and to confirm final eligibility. Discrepancies were resolved by a third reviewer. Two investigators independently and separately performed the data extraction according to PRISMA guidelines [7]. Using a standard form, the information that was extracted from each study included the first author, year and country of publication, the Newcastle-Ottawa scale for assessing quality of observational studies, number of patients studied, patients' mean age and gender, type of leukemia, number of patients with central venous catheters placed, chemotherapy regimen, number of patients with VTE and sub-types of VTE, thromboprophylaxis, anticoagulation agent, dose used for VTE treatment, duration of anticoagulation, rate of bleeding, rate of recurrence, and any deaths related to bleeding or VTE. Outcome data was then reviewed by the team and discrepancies were resolved by consensus or a third investigator if necessary [29]. Authors were to be contacted if necessary in cases in which details of study design or descriptive statistics for outcomes were not presented in the original paper.

2.4. Assessment of quality and risk of bias in included studies

Internal validity of study design and conduct was assessed by two reviewers. For non-randomized observational studies, the Newcastle-Ottawa Quality Assessment tool and the risk of bias in non-randomized studies-of interventions (ROBINS-I) were utilized.

2.5. Study outcomes

The principal summary measures included anticoagulation agents and dose, duration of treatment, and the efficacy and safety of anticoagulation therapy including VTE recurrence rate and bleeding events

on follow up. Although a meta-analysis of proportions was originally planned, due to the heterogeneity of the findings it was not conducted. Instead, a qualitative synthesis of the studies was employed to integrate study results.

3. Results

3.1. Included studies

The study selection process is shown in Fig. 1. A total of 1009 potentially relevant studies were initially identified and after removing 305 duplicated citations, 704 articles were screened. After the Level 1 screen by two reviewers, 618 reports were excluded (e.g. letters, studies where other hematological malignancies were included in addition to AL, studies that included patients younger than 16 years of age, studies in which FFP was used for VTE prophylaxis, and articles that were not in English). There were 86 articles that fulfilled the inclusion criteria and were fully reviewed and 13 were included in the final review as all other studies did not report treatment regimen used in VTE [8–20].

Among the 13 studies selected, there were seven retrospective studies and six prospective studies: 11 studies were cohort studies, and two were case control studies. Among the studies, nine were conducted in Europe, 1 report in Asia, and 3 in America. All articles were published between 2004 and 2015. Table 1 summarizes the details of included studies as well as their quality assessed by the Newcastle-Ottawa Scale (NOS). The number of subjects in each study ranged from 35 to 1461 patients and included patients with ALL, AML and APL. Median age of the patients ranged from 33 to 58 years with age range of 16 to 84. There was no evidence of publication bias.

3.2. Venous thromboembolism in acute leukemia

Patients' characteristics are shown in Table 2. In all included studies, there were 5359 patients with AL, and 304 (5.7%; 95% CI 5.1–6.3) VTE events that were distributed as follows: 14% deep vein thrombosis of upper limb (DVT-UL) unrelated to central venous catheters (CVC), 24% deep vein thrombosis in the lower limb (DVT-LL), 9% pulmonary embolism (PE) and concomitant PE and DVT, 50% catheter-related thrombosis, 5% cerebral venous thrombosis (CVT), and one case of central retinal vein occlusion (CRVO) [13]. In the retrospective cohort review by Vu et al., venous thromboembolic events related to CVC were the most frequent subtype of VTE accounting for 77.9% of VTE cases in AML patients and 83% of VTE cases in ALL patients [18].

The studies' outcomes were reported at different follow up periods: 2 studies reported VTE events from the diagnosis of acute leukemia up to 6 month follow up [10,15], 5 studies reported VTE events during induction [8,9,13,14,20], and the follow up was not specified in the 6 remaining studies [11,12,16–19].

3.3. Treatment algorithms and VTE outcomes

The choice of anticoagulant, dose, duration of therapy, and outcomes are summarized in Table 2. Among the 304 patients who developed VTE and had treatment information, 221 patients received anticoagulation for treatment of VTE. Treatment strategies included full or reduced dose anticoagulation or no anticoagulation and this was variable among different studies. For example, Chang et al. reported 5 cases of catheter-related thrombosis (CRT) in their patient population. In all cases the central venous catheter (CVC) or peripherally inserted central catheters (PICC) was removed; however, only 2 patients received anti-thrombotic therapy with low molecular weight heparin. Dose of LMWH was not reported. None of the cases had progression of the thrombus and the overall outcome was good [8]. On the other hand, a retrospective cohort study by Morano et al. published in 2015, studied 138 patients with AL. They reported five cases of catheter-related thrombosis. None of the catheters were removed due to thrombotic episodes and all patients were treated with LMWH while the catheter remained in place. There were no fatal events related to thrombosis [15]. In many other reports, up to 90% of patients diagnosed with a clinically significant VTE received anticoagulation for treatment [9–16,19]. In a prospective study by Napolitano et al., among the 22 patients with acute clinically relevant unprovoked VTE, 20 received anticoagulation. Two patients did not receive anticoagulation due to platelet counts $< 10 \times 10^9$/L that were refractory to transfusions [16]. Similarly, in a prospective cohort study by Imberti et al., all patients with VTE received anticoagulation with LMWH [12]. A retrospective comparative cohort study by Oliver et al. included 35 patients with acute leukemia and catheter-related thrombosis and measured the safety and efficacy of low molecular weight heparin for DVT treatment in two groups, one of which received anticoagulation whereas the other one did not. Among 21 patients who received anticoagulation, enoxaparin was used at either full or reduced doses. This study showed that the improvement of catheter-related thrombosis was higher in the anticoagulated group although this was not statistically significant [17].

Heparin and LMWH were predominantly used as the anticoagulation agent of choice in all studies. However, three studies also used vitamin K antagonists, in a subset of patients [10,11,19]. Reasons for choosing oral anticoagulants were not discussed in these studies. Appropriate dose adjustments were made to achieve an INR of 2–3. Unlike LMWH use, INR targets did not differ for patients with thrombocytopenia.

Most studies utilized similar doses of LMWH (100 units/kg q12h for Dalteparin) with a duration of 3 to 6 months [10,16]. Imberti et al. used

Table 1
Study characteristics of 13 included studies on treatment of VTE in AL.

Author, year	Country of publication	Study design	Risk of bias (ROBINS-I)	Study quality (NOS)	AL group	Sample size
Chang H, 2013	Taiwan	Single center retrospective case control	Serious risk	**/*/*[1]	APL	127
Couturier, 2015	France	Single center prospective cohort	Moderate risk	**/*/*[1]	ALL	572
De Stefano, 2005	Italy	Single center prospective cohort	Moderate risk	***/*/*[1]	AML, APL, ALL	379
Guzman-Uribe, 2013	Mexico	Single center retrospective cohort	Low risk	**/*/**[1]	AML, APL, ALL	181
Imberti, 2004	Italy	Single center prospective cohort	Serious risk	*/*/*[1]	ALL, AML	35
Mellilo, 2007	Italy	Single center prospective cohort	Low risk	**/*/**[1]	AML, APL, ALL	114
Mitrovic, 2015	Serbia	Single center retrospective cohort	Moderate risk	***/*/**[1]	APL	63
Morano, 2015	Italy	Single center retrospective cohort	Serious risk	*/*/*[1]	ALL, AML	138
Napolitano, 2016	Italy	Multi-center prospective cohort	Moderate risk	*/*/*[1]	AML, APL, ALL	1461
Oliver, 2015	USA	Single center retrospective cohort	Serious risk	*/ /*[1]	AML, APL, ALL	35
Vu K, 2014	USA	Single center retrospective cohort	Low risk	***/*/**[1]	AML, APL, ALL	1295
Ziegler, 2005	Austria	Single center retrospective cohort	Moderate risk	**/*/*[1]	AML, APL, ALL	719
Zuurbier, 2015	The Netherlands	Multi center prospective nested case control	Low risk	**/*/**[2]	ALL	240

[1] Newcastle-Ottawa quality assessment scale cohort studies (Selection/Comparability/Outcome).
[2] Newcastle-Ottawa quality assessment scale case control studies (Selection/Comparability/Exposure).

Table 2
Population characteristics and study outcomes. NA: not applicable.

Author, year	Population	Age range (year)	Median age (year)	Types of AL (%)	Patients with VTE (%)	Types of VTE (%)	Treatment with AC (%)	Treatment	Duration of Treatment (months)	Recurrence Rate %
Chang, 2013	127	22–67	55	APL (100)	5 (3.9)[a]	CRT (100)	2 (40)	LMWH	NA	NA
Couturie, 2015	572	NA	33	ALL (100)	16 (2.8)[a]	DVT-UL (30), DVT-LL (50), PE (15)	16 (100)	LMWH, UFH	6	20
De Stefano, 2005	379	14–89	60	ALL (18.2), AML (73.6), APL (8.1)	19 (5)[b]	DVT-LL (41.67), PE (16.67), CRT (4.17), CVT (8.33)	19 (100)	LMWH, UFH, VKA	6	21
Guzman-Uribe, 2013	181	15–86	33	ALL (45.8), AML (39.2), APL (10.5)	13 (7.1)[c]	DVT-LL (30.77), PE (7.69), CRT (61.53)	13 (100)	UFH or LMWH followed by VKA	6–12 or duration of CT	0
Imberti, 2004	35	22–77	55.7	ALL (31.4), AML (68.6)	4 (11.4)[c]	DVT-LL (75), PE (25)	4 (100)	LMWH	6 or duration of CT	0
Mellilo, 2007	114	16–67	39	ALL (38.6), AML (49.1), APL (12.3)	11 (9.6)[a]	DVT-LL (45.45), DVT-UL (18.18), CRT(9.09), CVT (18.18)	10 (91)	LMWH, UFH, VKA	NA	NA
Mitrovic, 2015	63	19–78	44	APL (100)	9 (14.3)[a]	DVT-LL (44.44), CRT (33.33), CRVO (11.11), Budd-Chiari (11.11)	9 (100)	LMWH	3–6	0
Morano, 2015	138	NA	54.5	ALL (24.6), AML (75.4)	5 (3.6)[b]	CRT (100)	5 (100)	LMWH	While CVC in situ	0
Napolitano, 2016	1461	19–84	54.6	ALL, AML APL	22 (1.4)[c]	DVT-UL, DVT-LL, PE, CVT	20 (91)	LMWH	3–6	0
Oliver, 2015	35	NA	58, 52	ALL, AML, APL	35 (100)[*,c]	CRT (100)	21 (60)	LMWH, UFH	NA	0% recurrence, 11% non-resolving
Vu K, 2014	1295	14–89	NA	ALL (23.1), AML (71.3), APL (5.6)	126 (10.4)[c]	DVT-LL (21.01), DVT-UL (10.15), PE(10.14), CRT (58.70)	80 (58)	LMWH	1–6	21–29
Zeigler, 2005	719	NA	55	ALL (25.7), AML (67.5), APL (6.8)	15 (2)[c]	DVT-LL, PE, CRT	14 (93.3)	LMWH, VKA	0.5–6	0
Zuurbier, 2015	240	16–59	33	ALL	24 (10)[a]	VT-UL, DVT-LL, PE, CVT	8 (33.3)	LMWH	NA	8

AL, acute leukemia; APL, acute promyelocytic leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; VTE, venous thromboembolism; CVT, cerebral venous thrombosis; CRT, catheter related thrombosis; DVT-LL, deep vein thrombosis of the lower limb; DVT-UL, deep vein thrombosis of the upper limb; PE, pulmonary embolism; AC, anticoagulation; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKE, vitamin K antagonist; CVC, central venous catheter; NA not available.

[*] Inclusion criteria for this study was presence of VTE.

[a] VTE reported from diagnosis up to 6 months of follow up.

[b] VTE reported during leukemia induction.

[c] Reporting period not specified.

dalteparin at a dose of 100 units/kg every 12 h for one month followed by 150 units/kg daily for 5 months or as long as patient was receiving chemotherapy [12]. Another study used enoxaparin at a dose of 1 mg/kg q12h or 1.5 mg/kg daily [17]. In general dose adjustments were made for patients with thrombocytopenia but the definition of thrombocytopenia was variable among different studies. However, the majority of authors reduced the dose of LMWH by half when the platelet count was $< 50 \times 10^9$/L [10,12,14–16]. Others held anticoagulation when the platelet count was $< 30 \times 10^9$/L [14,19]. In one study, the dose of anticoagulation was reduced by half if the platelet count was $< 20 \times 10^9$/L. [12] Overall, in studies where the bleeding events were reported [9–12,14,16,17,19,20], anticoagulant therapy seemed to be safe for treatment of VTE and was associated with very few or no bleeding events. This information however, is limited by poor reporting and lack of standardized definitions.

4. Discussion

Understanding the efficacy and risks associated with different VTE therapeutic strategies in AL patients can improve clinical care. Unfortunately, there is scarce data regarding the efficacy and safety of standard antithrombotic treatment in these patients as they have previously been excluded from studies and trials assessing treatment of VTE [28,2,3] given the increased risk of hemorrhagic complications associated to thrombocytopenia and coagulopathies in this group.

The present work showed that VTE is common in AL patients and that VTE related to CVC might be the most common subtype [18]. Although most patients with VTE received anticoagulation, the choice of treatment and dose of anticoagulation was very variable. Unfractionated heparin and LMWH were the most commonly used anticoagulants. Similar doses of LMWH were used in different reports for durations of 3 to 6 months. Dose adjustments were made in the presence of thrombocytopenia. The most challenging issue in AL patients with VTE is starting anticoagulant therapy in the context of severe thrombocytopenia. An updated guideline specifically addressing anticoagulant management in patients with severe, cancer-related thrombocytopenia has been recently published [30]. The guideline suggests adjusting the anticoagulant dose according to the platelet level and the risk of thrombotic recurrence, which is usually higher in the first 30 days after a VTE diagnosis. In general, if the platelet count is $> 50 \times 10^9$/L full anticoagulant doses can be used. If the patient has a platelet count $< 50 \times 10^9$/L and a high risk of recurrence, treatment can be done using therapeutic anticoagulant doses with transfusion support targeting a platelet count $>$ 40–50 $\times 10^9$/L. Otherwise physicians can consider reducing the anticoagulant dose by 50% or using prophylactic doses. After the initial 30 days, reducing the doses of anticoagulants and in some cases withholding them is preferred. Finally, the use of retrievable inferior vena cava filters should only be considered in patients with an acute VTE and an absolute contraindication to anticoagulation. However, these recommendations are largely based on consensus given the paucity of information and, as our review showed, the use of different platelet thresholds and adjustment strategies.

Furthermore, we found that a standard practice was not followed for catheter-related thrombosis with some studies reporting removal of the CVC and others only receiving anticoagulation with LMWH and CVC in situ. There were no fatal events reported attributed to catheter-related thromboses [15,8].

Our study has several limitations, mostly related to the fact that most of the studies selected in this systematic review were limited by study design and did not allow for conclusive interpretation. All studies were observational and many had small study populations. Furthermore, due to the paucity of data on this topic this review was limited to only 13 studies, 3 of which reported on catheter-related thrombosis only, the information should be interpreted with caution. Despite these limitations this study provides a comprehensive overview of the current literature on the treatment of VTE events in AL. Our search strategy and use of PRISMA guidelines allowed for effective appraisal of studies and independent reviews by authors decrease the risk of introducing any selection or information bias.

The risk of VTE is four to seven times higher in cancer patients than in patients without cancer, including leukemia [21,22]. In leukemia patients the pathogenesis of VTE is complex and reflects the action of different mechanisms including activation of blood coagulation via procoagulant pathways, damage to the endothelium and a thrombogenic state [23,24]. Exogenous factors like immobility, infections, indwelling venous catheters, and chemotherapy also contribute to increased incidence of VTE in AL [19,25–27]. Given the prevalence of VTE and the challenges posed by its treatment among AL patients, developing treatment guidelines is necessary, with special attention to the treatment of catheter-related thrombosis, duration of anticoagulation, and anticoagulation in the context of thrombocytopenia.

In conclusion, this study provides a review of the current literature regarding the treatment strategies for patients with acute leukemia and VTE. The existing evidence is scarce and low quality; however it does suggest that treatment with LMWH is efficacious and may be associated with low rates of bleeding and recurrence. Dose reduction of LMWH in the setting of thrombocytopenia is varied but commonly reported by the published literature, but an optimal approach is unknown. Future studies are required to determine the safest and most efficacious treatment for VTE events in AL patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.03.014.

Declaration of conflict of interest

Authors do not have any financial and personal relationships with other people or organizations that could inappropriately influence or bias this work.

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