

Platelet cut-off for anticoagulant therapy in thrombocytopenic patients with blood cancer and venous thromboembolism: an expert consensus

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Background. Management of venous thromboembolism (VTE) in patients with haematologic malignancies and thrombocytopenia is clinically challenging due to the related risks. No prospective studies or clinical trials have been carried out and, therefore, no solid evidence on this compelling issue is available.

Methods. Given this, an expert panel endorsed by the *Gruppo Italiano Malattie Ematologiche dell'Adulto* Working Party on Thrombosis and Haemostasis was set up to produce a formal consensus, according to the RAND method, in order to issue clinical recommendations about the platelet (PLT) cut-off for safe administration of low molecular weight heparin (LMWH) in thrombocytopenic (PLT <100×10⁹/L) adult patients with haematologic malignancies affected by acute (<1 month) or non-acute VTE.

Results. In acute VTE, the panel suggests safe anticoagulation with LMWH at therapeutic doses for PLT between ≥50<100×10⁹/L and at 50% dose reduction for PLT ≥30<50×10⁹/L. In acute VTE for PLT <30×10⁹/L, the following interventions are recommended: positioning of an inferior vena cava (IVC) filter with prophylactic LMWH administration and platelet transfusion. In non-acute VTE, anticoagulation with LMWH at therapeutic doses for PLT between ≥50<100×10⁹/L or over and at 50% dose reduction for PLT ≥30<50×10⁹/L is considered appropriate. The discontinuation of full or reduced therapeutic dose of LMWH is recommended for PLT <30×10⁹/L, both in acute and non-acute VTE.

Discussion. We suggest using dose-adjusted LMWH according to PLT to optimise anticoagulant treatment in patients at high bleeding risk.

Keywords: venous thrombosis, thrombocytopenia, blood cancer, anticoagulant treatment, consensus.

Introduction

Cancer is an independent and major risk factor for venous thromboembolism (VTE)¹⁻³. Cancer-related VTE challenges clinicians as it determines an increased risk

of recurrent VTE, bleeding complications, morbidity, and hospital admissions^{4,5}. In particular, haematologic malignancies are often associated with thrombocytopenia secondary to bone marrow infiltration at disease onset

and/or myelotoxic effects of treatments, thus increasing the risk of bleeding⁶⁻⁹.

Standard oral anticoagulation with anti-vitamin K drugs (VKA) cannot be considered a valid option in patients with cancer-related VTE⁴.

Studies comparing low molecular weight heparin (LMWH) to VKA treatment for cancer-associated VTE reported a reduced rate of major bleeding episodes in patients treated with LMWH¹⁰⁻¹³. Therefore, current guidelines recommend the use of LMWH rather than VKA for the treatment of cancer-related VTE¹⁴⁻¹⁸. Although promising, the role of direct oral anticoagulants (DOACs) for the treatment of VTE in cancer has still not been well defined in the setting of haematologic malignancies; recent studies on this issue have excluded patients with a platelet count (PLT) $<50 \times 10^9/L$ ¹⁹⁻²¹.

There is still a relevant risk of major bleeding associated with LMWH treatment for cancer-related VTE²² (around 4%) because of neoplasm characteristics (extent, site, histological features), as well as the need for surgery and invasive procedures. Overall, a reliable assessment of the bleeding risk in severely thrombocytopenic patients receiving therapeutic dose of LMWH is not available because PLT $<30-50 \times 10^9/L$ was an exclusion criterion from randomised clinical trials (RCTs). However, PLT was shown to be the most important independent predictor factor of bleeding in a recent trial on critically ill patients²³.

Similarly, in a population of patients undergoing stem cell transplantation for haematologic malignancies, the risk of bleeding was reported to be directly proportional to the PLT²⁴.

Full-dose anticoagulant treatment is usually considered unsafe for PLT $<50 \times 10^9/L$. It has been suggested that temporarily withholding anticoagulant treatment of VTE in patients with haematologic malignancies and severe thrombocytopenia might reduce adverse outcomes, thereby balancing bleeding risk and VTE recurrence^{25,26}.

In detail, only two retrospective cohort studies and two case series specifically evaluated the safety of LMWH in severe thrombocytopenic patients (PLT $<30 \times 10^9/L$) with haematologic malignancies^{9,27-29}. Data on lowering doses of anticoagulants in the treatment of VTE with PLT $<50 \times 10^9/L$ in the setting of haematologic cancer have been reported only in two small observational studies^{27,29}, thus, good-quality evidence on this compelling clinical issue is lacking²⁹⁻³³.

The aim of the current study was to produce a formal consensus, according to the RAND method, focused on the PLT cut-off for safe administration of LMWH in thrombocytopenic (PLT $<100 \times 10^9/L$) adult patients with haematologic malignancy affected by acute (<1 month) or non-acute VTE.

Materials and methods

Guideline focus and target population

Platelet cut-off levels to establish LMWH treatment schedules or to avoid anticoagulation vary widely, as they are based primarily on unstructured expert opinions^{14,15,17}.

For non-pharmacological approaches, such as positioning of a retrievable vena cava filter in cancer patients, the only well-defined indication is the presence of an acute proximal DVT and/or PE, and a contraindication to anticoagulation^{18,34}. The focus of the current consensus is on the PLT cut-off for safely administering LMWH in adult patients with haematologic malignancies, acute (no later than 1 month) or non-acute VTE and thrombocytopenia (PLT $<100 \times 10^9/L$).

Consensus development process

Panel composition

The Italian scientific foundation of the *Gruppo Italiano Malattie Ematologiche dell'Adulto* (GIMEMA) has, on the basis of scientific proficiency, officially elected a Working Party on Haemostasis and Thrombosis (WPHT-GIMEMA) with the aim of improving scientific co-operative research in the field. The WPHT-GIMEMA endorsed a working group (WG) on the reported topic. This working group includes 11 haematologists expert in thrombosis and haemostasis (MN, MC, LC, GC, AC, AF, ABF, MM, ER, RS, and SS), two methodologists (GS and MM), one study co-ordinator (SS), and the WPHT co-ordinator (VDS).

PICO framework questions

The co-ordinator of the WG (SS) had the primary responsibility of defining the scope of the clinical questions concerning the appropriate dosage of LMWH in patients affected by haematologic malignancies and VTE. For each question, the co-ordinator, together with the 2 methodologists (GS and MM), defined the relevant population, alternative management strategies (intervention and comparator), and outcomes (i.e., population, intervention, comparator, and outcome [PICO] format). Each clinical question provided the framework within which to formulate study inclusion and exclusion criteria, and guided the search for relevant evidence (systematic reviews and original studies).

The study population that went forward for analysis consisted of adult patients with haematologic malignancies, VTE, and a stable thrombocytopenia (>3 days). Catheter-related thrombosis was also proposed and discussed separately. Since cancer patients with VTE may have symptoms that are masked by the underlying malignancy, with diagnostic delays, acute VTE was identified as a diagnosis made no later than one month earlier³⁵.

The interventions considered were the administration of different doses of LMWH (therapeutic, reduced dose at 50% of full therapeutic dose, prophylactic dose, and discontinuation of LMWH treatment) according to different cut-off values of PLT: $\geq 50 < 100 \times 10^9/L$; $\geq 30 < 50 \times 10^9/L$; $< 30 \times 10^9/L$. LMWH doses were defined according to the datasheet for each LMWH molecule. Standard LMWH treatment was considered as full dose LMWH for the first month of treatment, followed by 75% of the full dose¹⁰. PLT cut-off values were chosen on the basis of literature results, expert opinion, and common clinical practice.

The proposed treatment scenario was considered in comparison to the standard anticoagulant treatment approach for VTE.

The main outcomes considered were: rates of VTE (first event, recurrence, and catheter-related DVT), major and minor bleeding, thrombocytopenia, and death. Major bleeding was defined as fatal bleeding, bleeding into a critical organ, or clinically overt bleeding associated with a decrease in haemoglobin levels of more than 2 g/dL or leading to the transfusion of two or more units of packed red blood cells³⁶. Minor bleeding was defined as all other bleedings. VTE referred to the following conditions: symptomatic or asymptomatic DVT of the proximal or distal upper and lower limbs; symptomatic or asymptomatic pulmonary embolism (PE); symptomatic or asymptomatic atypical-site thrombosis (i.e., splanchnic vein thrombosis and cerebral sinus vein thrombosis); and catheter-related VTE. Haematologic malignancies refer to any type of haematologic cancer (acute, chronic, and either undergoing active treatment or not). Management of heparin-induced thrombocytopenia (HIT) was not included in the current consensus.

The panelists were instructed to consider only the clinical perspective, and to disregard financial costs and other potential constraints to the availability of the treatment. A list of questions is provided in the *Online Supplementary Content, Table SI*.

Literature analysis and data extraction

A systematic review of the literature was performed via electronic databases (MEDLINE, EMBASE, and Cochrane Library Central Registry) by 2 methodologists (GS and MM), and disagreements were resolved by a third expert (VDS). Topics and research terms included: blood cancer, haematologic malignancy (acute leukaemia, acute myeloid leukaemia, acute lymphoblastic leukaemia, chronic myeloproliferative neoplasms, polycythemia vera, essential thrombocytemia, primary myelofibrosis, lymphoma, lymphoproliferative disease, multiple myeloma), venous thromboembolism, PLT, risk of bleeding, anticoagulant drugs, LMWH, and

treatments. First, the review was conducted to shape the research questions and to define the study design. Second, a comprehensive overview of clinical studies was provided to the panelists. Reference lists of selected papers and narrative reviews, editorials, guidelines, and direct inquiries to field experts were identified. For the literature search, all publications were considered regardless of publication date. Not many results were found regarding guidelines, systematic reviews, and controlled clinical trials. Therefore, an unfiltered search approach was also adopted to include uncontrolled clinical trials, case series, retrospective studies, and expert opinions. Editorials, letters to the editor, case reports, publications without an abstract, press releases, and animal studies were excluded. Abstracts were included only when data had subsequently been reported in full in an article published in a peer-reviewed medical journal. When specific studies on patients with haematologic malignancies could not be retrieved, studies on the general population of VTE patients, but including patients with cancer, were also analysed; in this case, the results were extrapolated to cancer patients and methodological biases were considered. For inclusion in the analysis, studies had to focus on the therapeutic management (including initial treatment, early maintenance and long-term treatment of established VTE, as well as treatment to prevent VTE recurrence) of confirmed VTE in haematologic cancer patients. Studies on patients with catheter-related thrombosis were also reported and were evaluated separately.

The quality of available studies underwent double-blind evaluation by two methodologists using validated critical appraisal (methodological and clinical relevance) and data extraction grids³⁷. Discrepancies in opinion between the two methodologists were resolved by discussion and, in the event of persisting disagreement, by a third expert. All the working group members subsequently validated the data separately.

Methods to define consensus and rating structure

The RAND/UCLA Appropriateness Method (RAM)³⁸ was adopted to produce formal consensus and thereby issue clinical recommendations. The RAND method is designed to facilitate agreement among expert groups about the appropriateness of the level of health care interventions, particularly when scientific evidence is absent, scarce, and/or heterogeneous. The study design is shown in Figure 1.

The RAND method has been extensively described elsewhere³⁸. Briefly, the results of the literature review and a list of indications were sent to all members of the WG. A form was prepared for each clinical scenario represented by a defined PICO question. Each member of the WG scored the appropriateness of a proposed

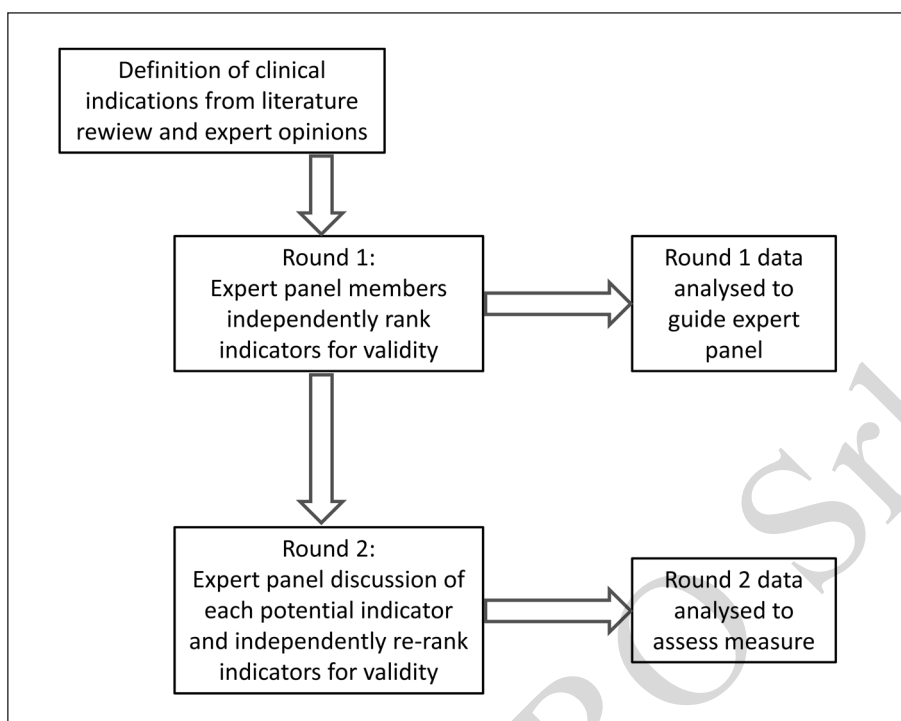


Figure 1 - Summary of consensus steps according to the RAND method.

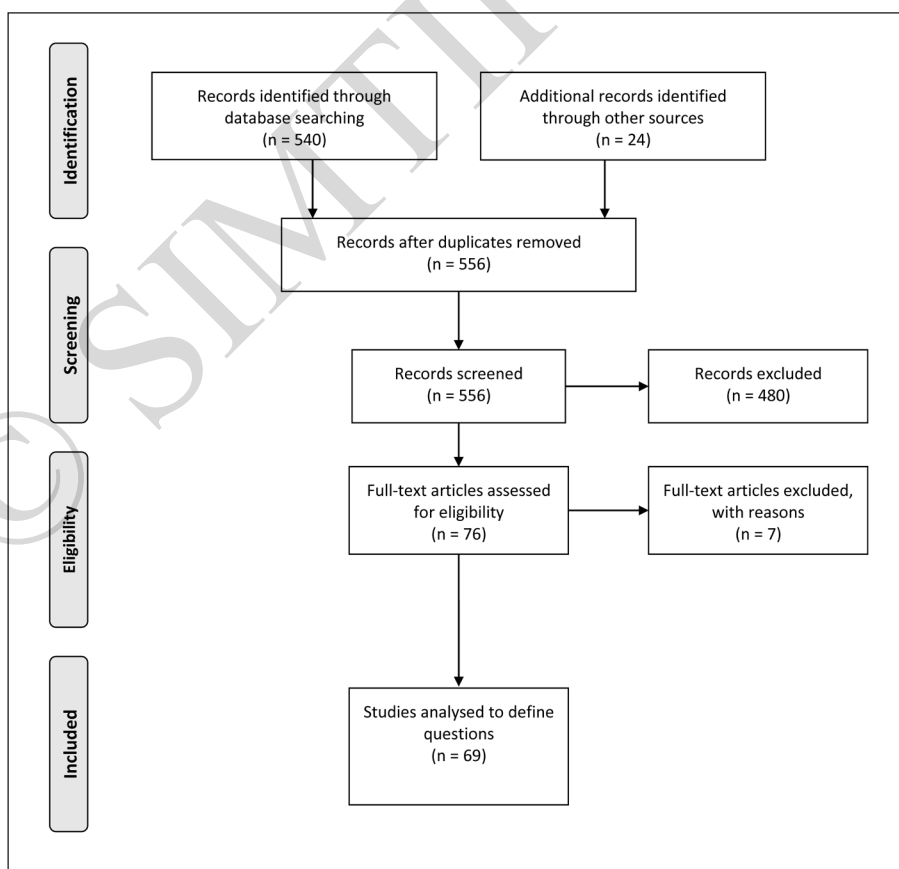


Figure 2 - Summary of evaluated studies, according to the PRISMA Flow Diagram³⁹.

recommendation on a graded scale, from completely inappropriate (scoring 1) to fully appropriate (scoring 9). All scored ballots were collected in such a way that members did not know each other's scores. The extreme scores (highest and lowest) were discarded, and the area containing the majority of the ballots then defined the classification of the intervention as inappropriate, uncertain, or appropriate.

For each indication, the panel members rated the benefit-to-harm ratio of the indication on a scale of 1 to 9, where 1 means that the expected harm greatly outweighs the expected benefits, and 9 means that the expected benefits greatly outweigh the expected harm. A middle rating of 5 can mean either that the harm and benefits are fairly equal or that the rater cannot make any judgment for the clinical scenario described in the indication.

For each range of PLT, questions of appropriateness of LMWH administration were proposed, both in acute and non-acute VTE and in catheter-related thrombosis. Fourteen questions were administered to the panel. Each member of the panel responded to the questionnaire individually. All members then met during a meeting organised to discuss the ratings. Focusing on panel results falling in the areas of uncertainty for PLT cut-off values that were $\geq 30 < 50 \times 10^9/L$, a second list of 6 indications was proposed considering three therapeutic approaches: LMWH administration reduced to 50% of full dosage, administration of LMWH at prophylactic dosage, and discontinuation of LMWH administration. Subsequently, a second round of individual rating was performed. Final recommendations were established during a second panel meeting.

Statistical analysis

The translation of ratings was based on the mathematical rules normally applied in the RAM method. Agreement was defined by the presence, for each question, of at least 7 of the 9 ratings in the same section of the 9-point scale (1-3, 4-6, 7-9). An indication was defined as appropriate if the median panel score was between 7 and 9 and as inappropriate if the median was between 1 and 3, both without disagreement. All other results were labelled "uncertain".

Results

The literature search provided 556 results, of which 480 were excluded because, after scanning the title and/or the abstract, they were not considered to be on the topic in question: articles related to biological and laboratory aspects of VTE in cancer ($n=75$); articles and reviews not specifically referring to the issue in question ($n=297$); papers reporting VTE secondary to surgical procedures or medical illness other than haematologic malignancies ($n=108$). In addition, seven studies were excluded after evaluation of the full-length paper. Available studies (Figure 2) generically related to VTE in cancer ($n=69$) were: prospective studies ($n=26$), consensus papers/expert opinions ($n=5$), cohort trials ($n=1$), meta-analyses ($n=2$), reviews ($n=2$), retrospective studies ($n=35$). Overall, only four studies on VTE in haematologic malignancies (two retrospective cohort studies and two case series) specifically evaluated the safety of LMWH in patients with severe thrombocytopenia^{9,27,28,29}. Based on the critical revision of the available data (Table I), and on expert clinical practice, the panel elaborated and debated 20 questions to highlight the critical issues and areas of uncertainty in the management of haematologic cancer patients with VTE and thrombocytopenia. The results relating to the degree of agreement on applicability of each treatment are reported in Table II.

Recommendations

For acute (including catheter-related) VTE, the panel recommends treatment with a therapeutic dose of LMWH for $PLT \geq 50 < 100 \times 10^9/L$, a reduced dose to 50% of LMWH for $PLT \geq 30 < 50 \times 10^9/L$, and discontinuation of therapy for $PLT < 30 \times 10^9/L$. In acute VTE with $PLT < 30 \times 10^9/L$, insertion of an IVC filter, treatment with a prophylactic dose of LMWH and platelet transfusions to allow for any kind of anticoagulant treatment are also recommended.

For non-acute VTE, the panel recommends treatment with a therapeutic dose of LMWH for $PLT \geq 50 < 100 \times 10^9/L$, a reduced dose to 50% of LMWH for $PLT \geq 30 < 50 \times 10^9/L$, and discontinuation of therapy for $PLT < 30 \times 10^9/L$.

For non-acute, catheter-related VTE, the panel agrees on the administration of a therapeutic dose of LMWH

Table I - Studies evaluated for consensus development.

Haematologic malignancy	N. of available studies evaluated for consensus	Anticoagulant treatments adopted for VTE	Outcomes reported
Acute leukaemias	11	LMWH	Bleeding, VTE recurrences
Chronic myeloproliferative neoplasms	24	LMWH, ASA	Bleeding, VTE recurrences, safety
Lymphoproliferative neoplasms	18	LMWH, ASA	Bleeding, VTE recurrences,
MGUS and multiple myeloma	15	LMWH, vitamin K antagonists	Bleeding, VTE recurrences

LMWH: low molecular weight heparin; ASA: acetylsalicylic acid; VTE: venous thromboembolism; MGUS: monoclonal gammopathy of undetermined significance; N: number.

Table II - Degree of agreement on treatment with low molecular weight heparin according to expert consensus.

Clinical scenario	PLT $\geq 50 < 100 \times 10^9/L$	PLT $\geq 30 < 50 \times 10^9/L$	PLT $< 30 \times 10^9/L$
Acute VTE			
Therapeutic dose of LMWH	Appropriate (11/11)	Uncertain (6/11)	Inappropriate (9/11)
Reduced dose to 50% of LMWH	Inappropriate (11/11)	Appropriate (8/11)	Inappropriate (9/11)
Prophylactic dose of LMWH	Inappropriate (10/11)	Uncertain (6/11)	Uncertain (6/11)
Discontinuation of LMWH	Inappropriate (11/11)	Inappropriate (9/11)	Appropriate (8/11)
IVC filter and prophylactic LMWH	Inappropriate (10/11)	Inappropriate (10/11)	Appropriate (8/11)
PLT transfusion	Inappropriate (11/11)	Inappropriate (11/11)	Appropriate (8/11)
Non-acute VTE			
Therapeutic dose of LMWH	Appropriate (9/11)	Uncertain (6/11)	Inappropriate (11/11)
Reduced dose to 50% of LMWH	Inappropriate (10/11)	Appropriate (8/11)	Uncertain (6/11)
Prophylactic dose of LMWH	Inappropriate (10/11)	Uncertain (6/11)	Inappropriate (8/11)
Discontinuation of LMWH	Inappropriate (10/11)	Inappropriate (8/11)	Appropriate (11/11)
IVC filter and prophylactic LMWH	Inappropriate (9/11)	Inappropriate (8/11)	Inappropriate (8/11)
PLT transfusion	Inappropriate (11/11)	Inappropriate (8/11)	Inappropriate (8/11)
Acute catheter-related VTE			
Therapeutic dose of LMWH	Appropriate (11/11)	Uncertain (6/11)	Inappropriate (10/11)
Reduced dose to 50% of LMWH	Inappropriate (11/11)	Uncertain (6/11)	Inappropriate (10/11)
Prophylactic dose of LMWH	Inappropriate (11/11)	Uncertain (6/11)	Uncertain (6/11)
Discontinuation of LMWH	Inappropriate (11/11)	Inappropriate (9/11)	Appropriate (9/11)
IVC filter and prophylactic LMWH	Inappropriate (11/11)	Inappropriate (9/11)	Appropriate (8/11)
PLT transfusion	Inappropriate (11/11)	Inappropriate (8/11)	Uncertain (6/11)
Non-acute catheter-related VTE			
Therapeutic dose of LMWH	Appropriate (8/11)	Inappropriate (8/11)	Inappropriate (9/11)
Reduced dose to 50% of LMWH	Inappropriate (11/11)	Uncertain (6/11)	Inappropriate (10/11)
Prophylactic dose of LMWH	Inappropriate (10/11)	Uncertain (5/11)	Inappropriate (9/11)
Discontinuation of LMWH	Inappropriate (10/11)	Uncertain (6/11)	Appropriate (8/11)
IVC filter and prophylactic LMWH	Inappropriate (9/11)	Uncertain (6/11)	Inappropriate (9/11)
PLT transfusion	Inappropriate (11/11)	Inappropriate (11/11)	Uncertain (6/11)

LMWH: low molecular weight heparin; IVC: inferior vena cava filter; VTE: venous thromboembolism; PLT: platelet count.

for PLT $\geq 50 < 100 \times 10^9/L$ and discontinuation of therapy for PLT $< 30 \times 10^9/L$; consensus was not reached for PLT $\geq 30 < 50 \times 10^9/L$.

For catheter-related VTE (either acute or non-acute), a consensus was not reached on the indication of platelet transfusion to allow for any kind of treatment with PLT $\geq 30 < 50 \times 10^9/L$.

Good clinical practice points

An accurate monitoring of platelet counts is mandatory for haematologic cancer patients who require treatment of VTE. The working group identified three cut-off points for PLT and distinguished acute from non-acute VTE to define the best treatment approach in each clinical scenario. The discontinuation of

LMWH treatment is deemed appropriate in cases of severe thrombocytopenia ($PLT < 30 \times 10^9/L$) both in acute and non-acute VTE. Platelet transfusion may support the administration of LMWH in acute VTE with severe thrombocytopenia. However, repeated platelet transfusions in patients with haematologic malignancies could lead to immune refractoriness and carefully managed. Therefore, for acute VTE, the positioning of a retrievable IVC filter followed by prophylactic administration of LMWH should also be considered. In patients with $PLT \geq 30 < 50 \times 10^9/L$, half-dose LMWH treatment may be discussed on an individual basis according to the clinical risk of recurrences and bleeding.

Discussion

Venous thromboembolism is the second cause of mortality in patients with cancer. Thrombocytopenia challenges clinicians in the management of antithrombotic therapy, often determining an inappropriate treatment discontinuation and increasing the risk of bleeding, particularly in subjects with haematologic malignancies⁴⁰. Available data are insufficient for the development of evidence-based guidelines^{41–50}; however, several studies have reported on the administration of reduced doses of LMWH according to PLT in cancer patients with VTE and thrombocytopenia^{7,9,25,27,28,41,42}.

Lim *et al.* reported 5 cases of thrombocytopenic patients with haematologic cancer⁹. This retrospective study defined thrombocytopenia by $PLT < 100 \times 10^9/L$ on at least two consecutive days during treatment of VTE. However, at disease onset or during chemotherapy, $PLT < 30 \times 10^9/L$ was documented in all reported cases. VTE treatment was based on dose-adjusted LMWH (for $PLT < 50 \times 10^9/L$). Platelet transfusions to maintain $PLT > 20–50 \times 10^9/L$ were administered to all subjects in case of active bleeding and thrombocytopenia. Khanal *et al.* retrospectively reported 47 patients with $PLT < 50 \times 10^9/L$ within a timeframe of perceived need for new or prolonged anticoagulation (e.g., acute VTE) compared to haematologic cancer patients with $PLT > 50 \times 10^9/L$ ($n=81$) secondary to chemotherapy²⁷. Two major bleeding events were reported during anticoagulant treatment; one subdural bleeding resulted fatal. Imberti *et al.* reported 4 cases of VTE treatment in severe thrombocytopenic patients with acute leukaemia²⁸. Treatment was based on dose-adjusted LMWH (for $PLT < 50 \times 10^9/L$) and resulted safe and effective in the absence of major bleeding or VTE recurrences.

Herishanu *et al.* reported 10 cases of central venous catheter (CVC)-associated VTE in frail thrombocytopenic patients with haematologic cancer after intensive chemotherapy²⁹. All subjects received dose-adjusted LMWH; no major bleedings were observed.

The risks of recurrent VTE are highest in the acute setting^{10,11}. Consequently, the administration of appropriate anticoagulant therapeutic doses is crucial. For haematologic patients with acute cancer-associated thrombosis and $PLT \geq 50 \times 10^9/L$, full therapeutic anticoagulation is appropriate. However, in patients with $PLT < 50 \times 10^9/L$, the optimal treatment remains unknown even though therapeutic anticoagulation should be evaluated^{24,40}. The PLT cut-off of $50 \times 10^9/L$ is empirical and based on the consensus of having a low risk of spontaneous bleeding above this level. In cases of acute VTE and severe thrombocytopenia, some authors suggest using platelet transfusions to increase PLT to $> 50 \times 10^9/L$, a cut-off value considered safe for anticoagulation¹⁷. When this option is not feasible, the positioning of a retrievable IVC filter, to be removed when PLT counts are $> 50 \times 10^9/L$ and when anticoagulation reaches a safe level, has been suggested⁴⁸. Our panel has confirmed the indication to transfuse platelets in acute settings for $PLT < 30 \times 10^9/L$. However, in haematologic patients with expected prolonged periods of thrombocytopenia, the risk of developing a reaction to platelet infusion and the impaired response to multiple transfusions over a short time interval may compromise the efficacy of this approach⁵¹. Furthermore, in cases of severe thrombocytopenia ($PLT < 30 \times 10^9/L$), insertion of an IVC filter, even if this is an invasive approach and not without risk, was deemed appropriate in acute VTE.

In the sub-acute or chronic treatment periods, when the risk of VTE recurrence is reduced, published data provide weak support for LMWH dose reduction in patients with thrombocytopenia^{42,43}. According to these results, in patients with $PLT < 50 \times 10^9/L$, a reasonable approach is the use of a half or a prophylactic dose of LMWH, depending on individual patient characteristics (e.g., tumour burden, clot burden, and risk factors for bleeding)^{27,43,44}. In patients with $PLT < 25 \times 10^9/L$, withholding anticoagulant therapy might be prudent. However, prophylactic doses of LMWH have been safely used even in patients with severe thrombocytopenia and symptomatic relief has been observed²⁸. In a large series of 379 patients with acute leukaemia, 20 patients who had one ($n=16$) or two ($n=4$) VTE events were treated with enoxaparin 100 U/kg bid; in the case of $PLT < 50 \times 10^9/L$, or an increased risk of bleeding, the dose was reduced to 100 U/kg qd or 50 U/kg bid⁴⁶. In another series of 26 patients (21 with haematologic malignancies) undergoing haematopoietic stem cell transplantation (HSCT), enoxaparin was administered for the treatment of VTE. Twenty-five VTE events were recorded (4 patients had two events at different sites), and 11 cases had upper extremity CVC-related deep venous thrombosis. During phases of thrombocytopenia ($< 55 \times 10^9/L$), enoxaparin administration was reduced to

a median value of 49 U/kg/day (range 34-75), and it was withdrawn in some instances for PLT $<20 \times 10^9/L$. Two major bleeding events (8%) occurred and one event was fatal⁴⁷. We have recently performed a multicentre study with a population of 1,461 patients with acute leukaemia at an increased risk of bleeding and demonstrated that treatment with LMWH was not affected by PLT during the treatment course; however, basal PLT was an important co-factor in determining decisions regarding treatment administration and schedules⁵². In 2007, the *Associazione Italiana Ematologia Oncologia Pediatrica* (AIEOP) suggested that the first two weeks of treatment of an acute VTE should be based on the administration of full-dose LMWH (anti-factor Xa level 0.5-1 U/mL), maintaining PLT $>50 \times 10^9/L$ ⁴⁹.

Direct oral anticoagulants are now emerging as a valid therapeutic option for cancer-associated thrombosis (CAT); fixed-dosing regimen, few drug interactions, absence of laboratory monitoring, and oral administration support their prescription in the context of cancer, especially when long-term treatment is needed. The Hokusai-VTE-Cancer and SELECT-D randomised trials^{20,21} have respectively compared edoxaban and rivaroxaban to dalteparin for the treatment of CAT. However, only approximately 10%²⁰ and 3%²¹ of the enrolled patients suffered from haematologic malignancies. The available up-to-date data on DOACs *versus* LMWH in CAT have shown that at six months, DOACs have lower rates of recurrent VTE but more major bleeding events^{20,21}. Recently released guidelines suggest the administration of DOACs in patients with stable cancer, not under active chemotherapy treatment¹⁹, while still supporting the administration of LMWH in patients at high bleeding risk⁵³. For the moment, the perceived bleeding risks and scarce evidence available mean that the use of DOACs in the target population of the current consensus (haematologic cancer patients with thrombocytopenia) cannot be suggested.

Conclusions

To the best of our knowledge, this is the first expert consensus on RAM to establish the safe PLT cut-off for LMWH therapy in patients with acute and non-acute VTE secondary to haematologic malignancies. It suggests the use of dose-adjusted LMWH according to PLT and identifies several clinical scenarios to optimise LMWH treatment administration in high-risk patients. However, further investigation is needed to establish the best management of haematologic cancer-related VTE in patients with thrombocytopenia, according to progressive reductions of PLT and established cut-off values. *Ad hoc* studies are currently ongoing and will hopefully fill the current gaps in the clinical setting.

Authorship contributions

MN wrote the paper and helped define study aims. GS and MM developed the questions and analysed results. SS conceived the study. GC, MC, EC, AC, LC, AF, ABF, ER and RS collected and interpreted data. VDS co-ordinated the GIMEMA-WPHT. All the members of GIMEMA-WPHT made a significant contribution to the discussion, critically revised the paper, and approved the final version for publication (see Appendix 1).

The Authors declare no conflicts of interest.

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Appendix 1

Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) Working Party on Thrombosis and Hemostasis:

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