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Review

Treatment of cancer-associated venous thromboembolism in patients under palliative care

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ABSTRACT

Many patients with cancer require palliative care at some stage and the vast majority of people followed in palliative care are cancer patients. Patients with cancer are at high risk of venous thromboembolism (VTE), and this is particularly true during the advanced palliative phase when mobility is limited or absent. Patients with cancer in palliative cancer are at higher bleeding risk compared to non-cancer patients. Decisions to treat VTE or withhold anticoagulation for these patients have proven to be difficult and depend largely on an individual clinician's judgment. For this reason, we have developed a consensus proposal for appropriate management of cancer-associated thromboembolism (CAT) in patients in palliative care, which is presented in this article. The proposal was informed by the recent scientific literature retrieved through a systematic literature review. In cancer patients in advanced palliative care, the benefit-risk ratio of anticoagulation seems unfavourable with a higher haemorrhagic risk than the benefit associated with prevention of CAT recurrence and, above all, in the absence of any benefit on quality of life. For this reason, we recommend that patients should be prescribed anticoagulants on a case-by-case basis. The choice of whether to treat, and with which type of treatment, should take into account anticipated life expectancy and patient preferences, as well as clinical factors such as the estimated bleeding risk, the type of VTE experienced and the time since the VTE event.

1. Abbreviations

AC	Anticoagulants
ASCO	American Society of Clinical Oncology
CAT	Cancer-Associated Thrombosis
CRNMB	Clinically Relevant Non-Major Bleeding
DXI	Direct factor Xa Inhibitor
ECOG-PS	Ecog Performance Status
GCS	Graduated compression Stockings
LMWH	Low Molecular Weight Heparin
M1	Month 1
MajB	Major Bleeding
MinB	Minor Bleeding
NR	Not Reported
Pts	Patients

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[2] A full list of the INNOVTE CAT Working Group can be found at the end of the article, in Appendix A. INNOVTE CAT Reviewers are listed in Appendix B.

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PCU	Palliative Care Unit
PCP	Palliative Care Patients
PCU	Palliative Care Unit
TIH	Heparin-Induced Thrombocytopenia
US	Ultrasound
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

2. Introduction

In 2002, the World Health Organization defined palliative care as an approach that improves the quality of life of patients and their families who are facing problems associated with life-threatening illness [1]. In clinical practice, the vast majority of people followed in palliative care are cancer patients [2]. As the American Society of Clinical Oncology (ASCO) guidelines recommend early palliative care interventions [3], this definition can be applied to a large number of cancer patients, including both those at the beginning of their treatment and those close to the end of life. Venous thromboembolism (VTE) is most prevalent both during the initial months after cancer diagnosis, at the time of relapse and during the advanced palliative phase [4]. The true prevalence and clinical relevance of symptomatic VTE in the palliative setting remain unclear. In a recent narrative review of patients receiving specialist palliative or hospice care [5], the prevalence of VTE was estimated to be between 6 and 12% and the incidence was between 0.5 and 8%, these rates being higher in studies with a higher proportion of patients with cancer. Decisions to treat VTE or withhold anticoagulation for these patients have proven to be difficult and depend largely on an individual clinician's judgment [6]. Despite this great variability of practice, there are no specific guidelines for management of cancer-associated thrombosis (CAT) in the palliative care setting. Guidelines from the ASCO, however, state that anticoagulation at therapeutic doses is of uncertain benefit in patient receiving end-of-life or hospice care and in those with a very limited life expectancy with no benefit in terms of symptom mitigation or reduction [7]. The present article deals only with the treatment of VTE in cancer patient in palliative care, and not VTE prevention.

3. Influence of VTE on global survival and quality of life in palliative cancer patients in palliative care

In a retrospective study of 2,707 cancer patients followed in a palliative care unit (PCU), global survival was lower in patients who had experienced a VTE than in those who, had not (69 vs. 80 days, $P = 0.03$) [4]. In contrast, in the prospective HiDDen study, survival did not differ between patients with and without DVT (30.6 vs. 31.4 days) [8]. This difference in global survival between the two studies, whose clinical relevance is debatable,. can be probably explained by that the fact that the population in the retrospective study was much healthier and could be followed up for a mean duration of 1,003 days [4].

The HIDDen study has challenged many of the previous views about the clinical relevance of CAT in the PCU setting. Despite a high prevalence of DVT (34%), no association was found between the presence of DVT on admission and presenting symptoms, apart from the presence of leg oedema which is, in any case, very common in palliative care (Fig. 1) [8]. On the other hand, VTE can cause atypical or non-specific symptoms, which are not usually recognised as being associated with VTE. For example, cancer patients with unsuspected PE are significantly more likely than control patients to complain of fatigue and shortness of breath [9]. These symptoms can be explained by disease progression, lung metastases or anaemia. Like oedema, these are so frequent at end of life that they are included in the items of some survival estimation scales in palliative care [10].

4. Influence of anticoagulation on quality of life in cancer patients in palliative care

As quality of life and symptom relief are the main objectives of palliative care [7], the patient's view on anticoagulation must be considered. In this population with limited life expectancy, quality of life and symptom relief may be more important endpoints than survival and recurrent VTE. Two successive qualitative studies of 28 and 40 patients using semi-structured interviews showed LMWH to be acceptable to cancer in-patients receiving palliative care with a positive impact on overall quality of life [11,12]. In these surveys, many patients expressed a feeling of freedom by being treated by LMWH and that something active was being done [11,12]. Using the same methodology, the PELICAN study (20 cancer patients, 13 treated with a palliative intent) and a survey of 14 patients (9 palliative care patients) explored the experience of living with CAT: daily subcutaneous LMWH appeared to cause minimal distress or inconvenience and many patients expressed a preference for injections over a theoretical trade-off of reduced efficacy with oral anticoagulants [13,14]. The PELICAN study has since been replicated in several other countries, with published data available from France [15], Spain [16] and Canada [17]. The main lesson from these surveys is that the acceptability of LMWH is good because patients see themselves primarily as cancer patients and secondarily as thrombotic patients, although certain disparities were observed between countries, with a lower acceptability of LMWH in the French study [15]. Despite converging data, several points must be borne in mind in interpreting these studies. For example, they did not use validated quality-of-life measures, they only included small numbers of patients, and they only investigated treatment with LMWH. In addition, all these studies were conducted by the same team [13–17]. In order to facilitate treatment decisions regarding the appropriate use of anticoagulants in people with cancer at the end of life, the SERENITY study has been initiated with the aim of developing an information-driven shared decision support tool [18].

5. Treatment of VTE in cancer patients in palliative care

It is important to note that all trials evaluating anticoagulation in CAT conducted to date have excluded patients with a life expectancy of less than three months, and most studies excluded patients with poor performance status (ECOG-OMS PS > 2), increased bleeding risk, renal impairment, weight < 40 kg, thrombocytopenia, and other comorbidities common in palliative care patients. On the other hand, general guidelines for management of CAT (not specifically in the context of palliative care) recommend treating patients experiencing proximal DVT or PE with anticoagulants for at least six months [7,19].

Studies on cancer patients in palliative care treated with anticoagulants for CAT are summarised in Table 1. Based on the limited available data (three small studies), the rate of recurrence is difficult to assess, but appears to range from 0.5% to 8.5%. The rate of bleeding seems higher, between 6 and 11% with 2.7 to 5.6% of patients experiencing major bleeds. The RHESO study highlights a case fatality rate for bleeding of around 20%, although this observation should be interpreted with caution in a population with many patients in advanced palliative care who have a high

Table 1
Recurrence and bleeding rates in palliative care cancer patients.

Study	Design	Population	Recurrence	Bleeding	Death	Follow-up	Remarks
Noble 2018 [20]	Prospective study *n* = 214	PCP followed in a CAT center	No symptoms suggestive of VTE recurrence	CRNMB: 9/131 (7%) 131 = LMWH to death or 7 days up to death	100% within 2 years	Up to death	108 pts (50%) LMWH until death 23 pts (11%) LMWH up to 7 days prior to death No additional follow-up examination for VTE
Noble 2007 [21]	Prospective study *n* = 62	PCP treated with LMWH No active oncological treatment	No symptomatic VTE recurrence under LMWH 7 pts stopped LMWH → 3 (5%) with symptoms of recurrence → 1 (1.6%) VTE radiologically confirmed	MinB = 5 (8.1%) Bleeding attributable to LMWH = 1 (1.8%) MajB = 0	NR	NR	No TIH Median duration of LMWH = 97 days Additional follow-up examination for VTE NR
Soto-Cárdenas 2008 [22]	Retrospective study *n* = 71	PCP in PCU Therapeutic dose of enoxaparin	*n* = 6 (8.5%)	*n* = 8 (11.3%) MajB: 4 (5.6%)	M1: 64% M3: 20% M6: 15% VTE related death *n* = 11 15.5% Bleeding related death *n* = 3 (4.1%)	NR	VTE recurrence diagnostic procedures: NR
Johnson 1997 [23]	Retrospective study N = 17 (VTE = 12) Prospective study *n* = 18	PCP in hospices Treatment with VKAs (VTE = 13)	NR	Events *n* = 15, 11 pts (65%) Fatal bleeding *n* = 1 (5.9%) Events *n* = 11, 9 pts (50%) Fatal bleeding *n* = 0	NR	Study over a one-year period	Hemorrhagic events evaluated with the bleeding severity index but no grading
Tardy 2017 [24]	Prospective study *n* = 1199 Cancer: 91%	PCP in PCU VTE prophylaxis during PCU stay: 527 (32%) Primary end point: bleedings	Incidence at M3: Suspected clinical VTE 6 (0.5%) Objectively confirmed by US: 4 (0.3%)	Incidence M3: Total: 116 (9.7%) MajB: 32 (2.7%) Fatal MajB: 23 (1.9%) CRNMB: 89 (7.5%)	At M3: 1087 (91%) Case fatality rate: → Bleeding = 20% → MB = 72%	3 months	5 pts with MajB and CRNMB Risks associated with bleeding in multivariate analysis → cancer HR = 5.65 (1.40–22.9) → previous bleeding HR = 3.36 (2.28–4.97) → antiplatelet therapy HR = 1.67 (1.15–2.44) → AC prophylaxis HR = 1.48 (1.02–2.15) Main objective = bleeding not VTE recurrence

AC: anticoagulants; LMWH: low molecular weight heparin; CAT: cancer-associated thrombosis; CRNMB: clinically relevant non-major bleeding; M1: month 1; MinB: minor bleeding; MajB: major bleeding; NR: not reported; PCP: palliative care patients; PCU: palliative care unit; pts: patients; TIH: heparin-induced thrombocytopenia; US: ultrasound; VKA: Vitamin K antagonist; VTE: Venous thromboembolism.

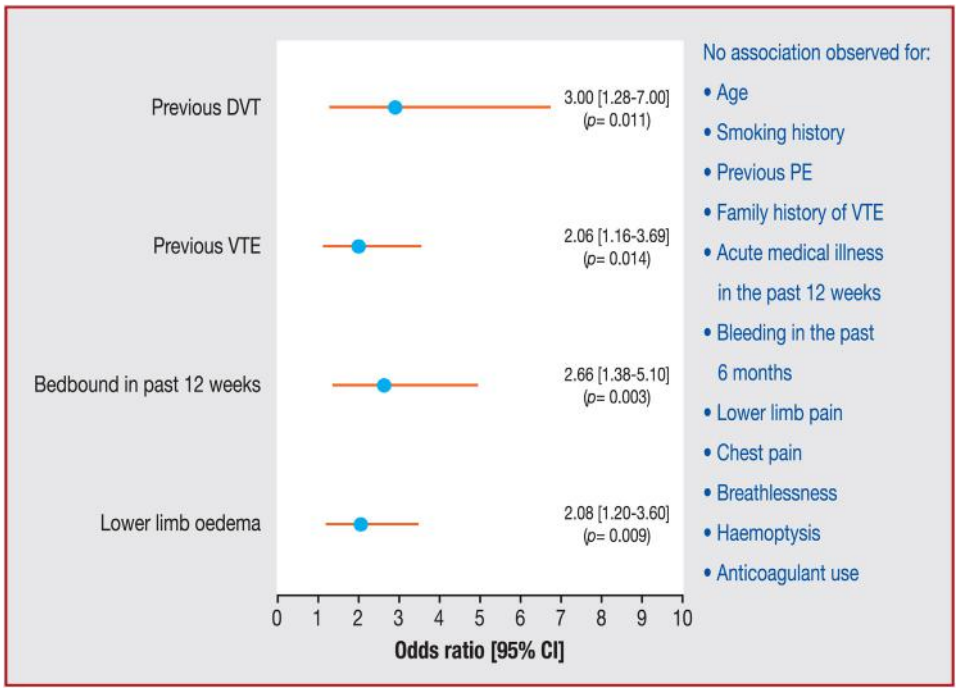


Fig. 1. Factors associated with the presence of DVT on admission to palliative care. Data are taken from the HIDDen study [8]. The data are presented as odds ratios with their 95% confidence intervals for each variable that was significantly associated with the presence of DVT on admission to palliative care.

mortality rate anyway [24]. This increased bleeding risk is well perceived by clinicians, who prescribe less antithrombotic therapy, both in the therapeutic and prophylactic setting [25].

In a retrospective cohort of 1,141 patients discharged from hospice care, Kowalewska et al. [25] reported an odds ratio of 0.38 (0.22–0.64) for the probability of being prescribed therapeutic or prophylactic antithrombotic treatment in patients with cancer compared to those with over chronic diseases. Previously, Johnson et al. [26] performed a clinical practice audit of 131 palliative care physicians and found that 60% of participants used subtherapeutic dosed of anticoagulants in patients with CAT in order to minimise the bleeding risk [23]. Twenty international academic experts (five intensive care physicians, five palliative care physicians, five coagulation specialists and five oncologists) were asked about their practice based on virtual cases [27]. Palliative care physicians were a little more reluctant to deliver secondary prophylaxis of VTE compared with the other physicians; however, none of the expert prescribed secondary prophylaxis to end-of-life patients [27].

Until recently, guidelines recommended LMWH for CAT treatment. There is no data on direct Factor Xa inhibitors (DXIs) in the palliative care setting. However, caution has been advised in using these anticoagulants in the frail and elderly, with hepatic dysfunction, impaired renal function (no DXIs when creatinine clearance < 30 mL/min) and with potential drug–drug interactions, all these clinical situations being common in cancer patients in palliative care. Clinical relevant non-major bleedings are more common with DXIs than with LMWH in patients with active cancer [28], which may have an impact on quality of life in cancer patients in palliative care. A meta-analysis of 336 patients with metastatic cancers showed LMWH to be more effective than warfarin in the prevention of VTE recurrence [RR = 0·51 (95% CI 0·35–0·74; $P = 0·0001$)] with no increase in the bleeding risk [RR = 1·10 (95% CI 0·77–1·58; $P = 0·60$)] [29].

Current evidence is insufficient to support the use of graduated compression stockings (GCS) for preventing DVT [30]. As oedema is common and sometimes disabling in cancer patients in palliative care, GCS should be prescribed on an individual basis, giving preference to quality of life.

6. Proposals of the expert group

6.1. General considerations

In patients with CAT in palliative care, we suggest individualising anticoagulant treatment on the basis of:

- patient preferences: no treatment, subcutaneous or oral anticoagulants;
- life expectancy: end-of-life anticipated within three months or beyond. For estimating 3-month survival in palliative care cancer patients, we recommend using the PRONOPALL score [31] (Appendix C);
- contra indications to anticoagulants: see Summary of Product Characteristics;
- evaluation of bleeding risk;
- the time since VTE diagnosis (over or under three months);
- the type of VTE: PE or DVT;
- expert panel ranking: 3.89 out of 4.00.

6.2. Specific recommendations and proposals

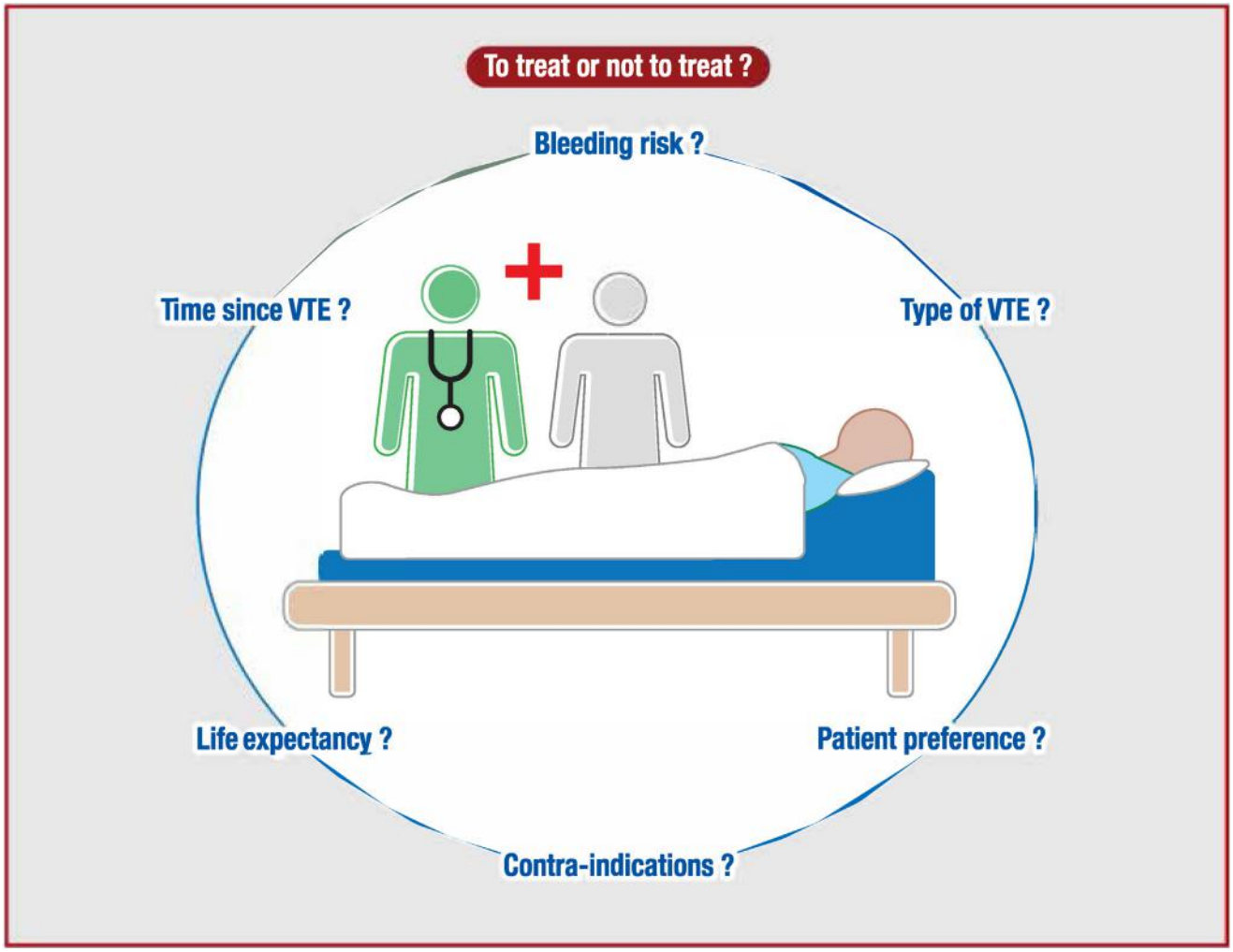
We recommend taking all decisions following discussion and agreement with the patient, family and carers (shared

medical decision-making). Expert panel ranking: 3.93 out of 4.00.

If a decision is made to initiate anticoagulant treatment, we recommend assessing the potential benefits and risks of LMWH and DXIs on an individual patient basis. Expert panel ranking: 3.93 out of 4.00.

The following considerations should be taken into account in the discussion with the patient:

- in patients with a life expectancy > 3 months, an ECOG-OMS performance status < 2 (Appendix C) and no contra indications to anticoagulants, we suggest standard care of CAT [32]. Expert panel ranking: 3.88 out of 4.00;
- in patients with a life expectancy < 3 months and with a history of proximal DVT or PE < 3 months previously, we suggest continuing anticoagulants for at least three months after the VTE event, or until the onset of a contra indication, a bleeding complication or the first signs of end-of-life. Expert panel ranking: 3.85 out of 4.00;
- in patients with a life expectancy < 3 months and a history of VTE > 3 months previously, we suggest discontinuing of anticoagulation, due to the lower risk of recurrence. Expert panel ranking: 3.70 out of 4.00;
- in end-of-life patients, we suggest withdrawing anticoagulants. Expert panel ranking: 3.81 out of 4.00.



Central Illustration.

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Appendix C.

PRONOPALL score

ITEM	RESPONSE	SCORE
ECOG performance status	0–1	0
	2–3	2
	4	4
Number of metastatic sites	< 2	0
	≥ 2	2
Albumin	< 33 g/L	3
	≥ 33 g/L	0
LDH	< 600	0
	≥ 600	1

SCORE	Median survival
8–10	35 days IC 95% [14–56]
4–7	78 days IC 95% [71–114]
0–3	301 days IC 95% [209–348]

ECOG Performance Status (ECOG-PS)

ECOG	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

Appendix D. Supplementary material

Supplementary material associated with this article can be found in the online version available at https://doi.org/10.1016/j.acvd.2023.11.008.

Disclosure of interest

PD reports personal fees or travelling expenses from Sanofi and Pfizer. LB reports personal fees and non-financial support from Bms/Pfizer, personal fees and non-financial support from Leo-Pharma, personal fees and non-financial support from Viatris, grants from Bayer, grants, personal fees and non-financial support from MSD, outside the submitted work. DM has received personal fees from Leo Pharma, Pfizer and BMS. PG reports personal fees or travelling expenses from Leo Pharma, BMS Pfizer and Bayer. FS reports consulting fees from Amgen, Roche, Chugai, Mylan, Mundi Pharma, Leo Pharma, Pierre Fabre Oncology, Helsinn, MSD, Pfizer and BMS, all outside the submitted work. OS reports grants, personal fees and non-financial support from Bayer, grants, personal fees and non-financial support from BMS Pfizer, grants and personal fees from Sanofi, grants from Daiichi Sankyo, grants, personal fees and non-financial support from Leo Pharma, personal fees and non-financial support from Viatris, grants and personal fees from Boeringher Ingelheim, during the conduct of the study. IM reports grants, personal fees and non-financial support from BMS-Pfizer Alliance, grants, personal fees and non-financial support from Leo Pharma, personal fees from Sanofi, personal fees and non-financial support from Astra-Zeneca, outside the submitted work.

The author MAS declares that she has no competing interest.

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