

# The challenges of managing cancer related venous thromboembolism in the palliative care setting

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*Postgrad Med J* 2007;**83**:671–674. doi: 10.1136/pgmj.2007.061622

Cancer patients with venous thromboembolism (VTE) pose particular management challenges since they have an increased risk of bleeding and recurrent thrombosis compared to the non-cancer population. Also, as the disease progresses so do the hazards of anticoagulation, and patients in the palliative stages of their cancer could be viewed as a separate disease group with respect to diagnosis and management. As the focus from curative treatment moves towards symptom control, physicians face several challenges in providing the most appropriate care. Palliative care patients have rarely been included in research on VTE and the supporting evidence needs to be extrapolated cautiously. Quality of life aspects of VTE and their management may be a more appropriate outcome measure in this stage of disease than radiological end points. This paper looks at the challenges facing professionals in the management of VTE in the advanced cancer patient.

## CHALLENGE 1: DEFINING THE POPULATION

Palliative care patients are not solely looked after by palliative care teams. The majority will come under the acute care of the admitting physician, surgeon or oncologist. Decision making for palliative care patients will need to weigh up the burden or benefit of investigations and treatments against the decision to treat solely symptomatically. Nevertheless, the nihilistic view that “a large PE might be a nice way to go” is not supported by the evidence. Cancer deaths from a PE are rarely sudden, quick and symptom-free. Postmortem studies of cancer patients who died of PE suggest most patients were symptomatic for an average of 2 h before death.<sup>4,5</sup> In addition, symptoms due to fatal PE, such as dyspnoea, anxiety and pain, are difficult to remedy in the ensuing cardiovascular collapse and diminished perfusion which impairs the delivery of necessary symptom control medicines in the terminal stages.

The original model of palliative care, founded around the hospice movement, looked after patients at the end of life in a predominantly inpatient population. The model of palliative care has changed and many services integrate their involvement earlier in the patient’s cancer journey when symptoms first become problematic. They will therefore be involved with patients of better performance status. There is no agreed definition of a palliative care patient although various suggestions have been made.<sup>7</sup> Defining a patient as palliative, based on predicted prognosis, is one possibility—for example, accepting involvement of patients with an estimated prognosis <6 months. However, doctors are known to be over optimistic in their estimation of survival and this method would lead to referrals too late in life.<sup>8</sup> In addition, patients are living longer with advanced disease and consequently have symptom control needs for longer.

Another possible definition is based on the presence of metastatic disease which would suggest that the cancer was incurable. In practice, as oncology develops more treatments for patients with metastases, they will remain under the main care of oncology and may do so for years. Considering the World Health Organization’s

The association between venous thromboembolism (VTE) and cancer has been recognised since the 19th century and was first described by Armand Trousseau.<sup>1</sup> Patients with cancer have a higher risk of developing deep vein thrombosis (DVT) and pulmonary embolus (PE) than the non-cancer population due to secretion of cancer related procoagulants and an increased activation of coagulation factors such as tissue factor, thrombin anti-thrombin complex and factor VIIa. The prevalence of clinically apparent VTE in cancer patients is up to 15%, yet as the cancer progresses so does the prothrombotic tendency.<sup>2</sup> Studies in the advanced cancer population have shown an incidence of asymptomatic VTE in up to 52% of inpatients.<sup>3</sup> This figure is similar to postmortem studies which show evidence of PE in 50% of cancer patients.<sup>4,5</sup> The management of cancer associated VTE is different to that of the non-cancer population. Emerging evidence has demonstrated the advantages of low molecular weight heparin (LMWH) over warfarin with respect to VTE recurrence, drug–drug interactions, absorption and safety.<sup>6</sup> Within the palliative care cancer population, the management of VTE needs to be based on quality of life as much as clinical efficacy. Available existing evidence, extrapolated from a healthier study population, needs to be applied in the context of a poor performance status, non-homogeneous patient group. To do this one needs to appreciate the fundamental challenges of managing cancer related VTE in the palliative care setting.

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Received 14 May 2007  
Accepted 18 July 2007

**Abbreviations:** CTPA, computed tomographic pulmonary angiography; DVT, deep vein thrombosis; INR, international normalised ratio; LITE, Long-term Innohep Treatment evaluation; LMWH, low molecular weight heparin; PE, pulmonary embolus; SPCU, Specialist palliative care unit; VTE, venous thromboembolism; V/Q scan, ventilation/perfusion lung scintigraphy

definition of palliative care, the speciality looks after “patients facing problems associated with life threatening illness”. By this definition, not every patient with terminal disease needs palliative care and the service will focus on those with the most complex needs.

For the purpose of this paper a palliative care patient will be defined as someone with incurable cancer whose specialist care is predominantly under the care of the palliative care service. This definition, although not perfect, defines a heterogeneous group of varied performance status, prognosis and degree of metastatic disease. It will include those who, despite having liver or brain metastases, may still have good performance status, as well as those who are asymptomatic but of performance status 3 or 4.

### CHALLENGE 2: RECOGNITION OF THE VTE

Despite a suggested incidence of asymptomatic VTE in over 50% of palliative care patients, the reported incidence is considerably smaller at around 1–5%.<sup>9</sup> There may be several reasons for this. First, the true natural history of asymptomatic VTE in the palliative care patient is not known. It is possible that not all thrombi will progress to symptoms and, therefore, cause no problems. Secondly, the reported incidence may represent an under appreciation of the risk factors of advanced malignancy among palliative care physicians. The practice of VTE management varies worldwide and over 25% of British oncologists were unaware of the associated risks of VTE with cancer.<sup>10–11</sup> Finally, the common presenting symptoms of VTE are similar to those of other common pathologies experienced by patients with advanced cancer—for example, a painful swollen leg raises a high index of suspicion in a non-cancer patient while there are several causes to consider in the palliative care setting (box 1). Likewise dyspnoea, the most common symptom associated with PE, is seen in many common conditions associated with advanced cancer (box 2). It is important to recognise that although many conditions may mimic VTE, the presence of one such diagnosis does not negate the concurrent diagnosis of thrombosis. Acute conditions such as infection, heart failure and local venous obstruction will increase the prothrombotic state and likelihood of undiagnosed VTE.<sup>12</sup>

### CHALLENGE 3: CONFIRMATION OF VTE

#### Use of D-dimers

Plasma D-dimers are specific cross-linked fibrin derivatives produced when fibrin is degraded by plasmin. Concentrations are therefore raised by thrombolysis, making them a highly sensitive indicator for VTE. Although sensitive for VTE, high D-dimer concentrations also occur in infection, malignancy and postoperative states, thus being insufficiently specific for making a positive diagnosis.<sup>13–14</sup>

D-dimer values are now widely recognised as being an important exclusary test for the diagnosis of VTE, with a negative predictive value of close to 100%. However, their use in cancer patients is limited since they may have increased concentrations due to their underlying malignant disease. They currently have no role in the diagnosis of VTE in the palliative care setting.

#### Confirmation of suspected DVT

There are a number of techniques available for the detection of lower limb DVT. Each has advantages and disadvantages including different degrees of sensitivity, specificity, operator dependence, cost, accessibility and invasiveness. Radiological diagnosis will depend upon local practice and availability of investigations.

Doppler ultrasonography is the most widely available, cheap, non-invasive test and has largely replaced venography as the first choice for symptomatic DVT. A recent meta-analysis suggested the sensitivity of ultrasonography to be 89% overall

### Box 1: Common causes of swollen legs in the palliative care patient

#### Unilateral

- Deep vein thrombosis
- Cellulitis
- Nodal disease in groin
- Lymphoedema

#### Bilateral

- Deep vein thrombosis
- Hypoalbuminaemia
- Heart failure
- Medicines—for example, steroids, nifedipine
- Lymphoedema
- Pelvic disease causing reduced venous outflow

### Box 2: Common causes of dyspnoea in advanced cancer

- Pneumonia
- Pulmonary oedema
- Pleural effusion
- Anaemia
- Lung metastases
- Lymphangitis
- Muscle fatigue
- Concurrent pulmonary illness
  - chronic obstructive pulmonary disease
  - emphysema
  - interstitial lung disease
  - congestive cardiac failure

for symptomatic DVT and 97% for above knee thrombus. Problems with ultrasonography include a poor sensitivity for asymptomatic disease, difficulties in diagnosing DVT recurrence, and limited visualisation in the pelvis.<sup>15–16</sup>

Impedance plethysmography is also commonly used but has similar limitations in the setting of recurrent thrombosis, asymptomatic DVT and DVT below the knee or in the pelvis.<sup>15–16</sup>

Venography is the reference standard diagnostic test but has in large been replaced by non-invasive tests. In practice it is the most reliable test for the diagnosis of asymptomatic thrombus and thrombus located within the calf or pelvis. However, this involves injecting intravenous contrast and has largely been replaced by less invasive tests in most hospitals.<sup>15–17</sup>

#### Confirmation of suspected pulmonary embolus

Confirmation of suspected PE first requires the diagnosis to be considered. Secondly the clinician must decide whether a positive diagnosis of PE would alter the patient’s management. In a specialty where the balance of quality of life and active treatment is paramount, one must consider the burden of obtaining radiological confirmation which may need to be done on a site away from the specialist palliative care unit (SPCU). In addition to considering the burden of diagnosis on the patient, one must also consider whether the treatment of a confirmed PE is safe and feasible. The anticoagulation of someone

at high risk of haemorrhage would be inappropriate, as would someone who is entering the terminal phase of their condition, where other symptom control measures could be instigated. It is clear that decision making must therefore take into account quality of life aspects of treatment and investigation and individualisation of care which considers the patient's wishes.

Imaging tests available for the diagnosis of PE include ventilation/perfusion lung scintigraphy (V/Q scan), pulmonary angiography, and spiral computed tomographic pulmonary angiography (CTPA) (table 1). Unfortunately all of the imaging techniques have limitations and access to each may vary between SPCUs.

Pulmonary angiography remains the reference standard but is technically demanding and invasive.<sup>18 19</sup> For this reason it is unlikely to be the investigation of choice in the palliative care setting, unless the patient is robust enough to undergo the test. It is also associated with a major complication rate of 0.5% and a mortality rate of 0.1%.

V/Q scans are relatively simple to perform and non-invasive, but when used in isolation can be non-diagnostic in up to 70% of suspected PEs.<sup>20</sup> Within the advanced cancer population, concurrent lung pathology makes interpretation even more challenging. Better results have been obtained combining clinical probability with V/Q scan interpretation, but its role in the palliative care setting is likely to be limited.<sup>21</sup>

CTPA is gaining wider acceptance and popularity since it is readily available in most hospitals and is well tolerated by patients. Although this technique is excellent for diagnosing central or lobar PEs, it is unable to rule out isolated subsegmental PEs. Meta-analyses suggest CTPA has a sensitivity of about 70% and a specificity of 90% in the diagnosis of PE.<sup>22</sup> For this reason a negative result does not exclude a diagnosis in 30% of patients. Despite these limitations, CTPA is likely to be the most appropriate diagnostic tool in the investigation of PE in the palliative care setting.

#### CHALLENGE 4: TREATMENT OF VTE

Although warfarin is the mainstay of long term anticoagulation for VTE, several studies have demonstrated significant increases in rates of bleeding among cancer patients receiving oral anticoagulation (as high as 21.6% in one study).<sup>23 24</sup> The bleeding risk in palliative care patients is even greater. An audit of anticoagulation in a Scottish SPCU reported 15 bleeding episodes in 17 patients, which was improved to 11 episodes in 18 patients by stringent international normalised ratio (INR) monitoring.<sup>25</sup> Although these numbers are small, other palliative care physicians share these findings and there is a tendency to maintain the INR at subtherapeutic levels in advanced cancer.<sup>9</sup>

In addition to an increased risk of bleeding, cancer patients are more likely to develop further thrombotic events on warfarin than non-cancer patients.<sup>18 22</sup> Studies have shown that up to 27% of cancer patients will develop secondary VTE despite therapeutic warfarin administration, and the incidence is likely to be higher in advanced malignancy since:

- patients become more pro-thrombotic as the malignancy advances
- patients tend to be anticoagulated at subtherapeutic levels to minimise the risk of bleeding.

There is increasing evidence to suggest that LMWH is the drug of choice in the long term management of VTE.<sup>26</sup> One qualitative study suggests that LMWH is an acceptable intervention in the palliative care setting and, for some patients, preferable to warfarin.<sup>27</sup> LMWH has been shown to have several benefits over warfarin in cancer patients, which are listed below.

**Table 1** Imaging tests available for the diagnosis of pulmonary embolus

Investigation	Accuracy in diagnosing PE	Burden on patient	Usefulness in palliative care
Pulmonary angiography	+++	+++	++
V/Q scan	++	+	+
CTPA	+++	+	+++

CTPA, computed tomographic pulmonary angiography; PE, pulmonary embolus; V/Q scan, ventilation/perfusion lung scintigraphy

- Dose is calculated according to patient weight and so there is no need to monitor anticoagulation
- Efficacy is not altered by changes in nutritional status
- Not affected by absorption problems or poor oral intake
- Efficacy not altered by new medicines.

Although several trials have addressed long term treatment for VTE with oral anticoagulant versus LMWH, only three have looked at patients with cancer. Meyer and associates randomised patients with cancer and VTE to 3 months of treatment with either LMWH enoxaparin (1 mg/kg) or warfarin.<sup>28</sup> The composite outcome of major bleeding and recurrent VTE was observed in 15 out of 71 (21.1%) patients receiving warfarin, compared to 7 of the 67 (10.5%) receiving LMWH ( $p = 0.09$ ). The Long-term Innohep Treatment evaluation (LITE) trial randomised 200 patients with acute VTE and cancer to receive either unfractionated heparin followed by warfarin for 84 days at a targeted INR of 2.5, or the LMWH tinzaparin (175 IU/kg) for 85 days.<sup>29</sup> The rate of recurrent VTE at 3 months was 6% in the LMWH group compared to 10% in the warfarin group, and at 1 year 7% and 16%, respectively ( $p = 0.044$ ).

Lee and associates reported the results of the CLOT trial, which was a large multicentre trial comparing treatment with the LMWH dalteparin with oral anticoagulant treatment in patients with active cancer presenting with acute VTE.<sup>26</sup> A total of 338 patients were enrolled into each arm and were well matched for gender, age, outpatient treatment and performance status. Twenty-seven patients in the LMWH group experienced recurrent VTE compared with 53 in the oral anticoagulant group. Patients receiving long term LMWH treatment had a significantly lower cumulative risk of recurrent VTE at 6 months than those who received long term oral anticoagulant treatment (8.8% vs 17.4%, 52% risk reduction;  $p = 0.0017$ ). Major bleeding was seen in 19/338 (5.6%) patients receiving LMWH compared with 12/338 (3.6%) in the oral anticoagulant group ( $p = 0.27$ ). Corresponding data for any bleeding were 13.6% and 18.5%, respectively ( $p = 0.09$ ).

These three studies clearly establish a case for LMWH as the first line treatment of cancer related VTE, and the acknowledged hazards of warfarin in palliative care support its use in the advanced cancer patient. The CLOT study excluded patients of performance status 3 or 4, while the LITE and Myers study populations included 47% and 50% patients with metastatic disease, respectively. Myers recorded that 40% of patients were no longer receiving active treatment.

Although no studies have been conducted specifically in the palliative care environment, one prospective cohort study in patients with metastatic cancer (brain or liver) and VTE investigated the effect of using low dose dalteparin. Two hundred and three patients received a 7 day course of dalteparin according to body weight followed by a fixed dose of 10 000 IU dalteparin once daily for at least 3 months.<sup>30</sup> Eleven patients (5.4%) developed major bleeding complications (six fatal) during the 3 month study period, and 18 patients (8.9%) developed VTE recurrences (two patients died). There

## Learning points

- Venous thromboembolism (VTE) is common in advanced cancer patients.
- The management of VTE in this patient group needs to take into account the impact of investigations and treatments on their overall quality of life.
- Involvement of patients in the decision making process is essential.
- Anticoagulated patients are at high risk of bleeding complications and recurrent thromboses.
- Low molecular weight heparins are more efficacious and have a better impact on quality of life than warfarin in the advanced cancer patient.
- Warfarin is not advised in the treatment of VTE in the advanced cancer patient.

were no higher complication rates in patients with either liver or brain metastases.

## CHALLENGE 5: HOW LONG TO CONTINUE ANTICOAGULATION?

In the non-cancer population, anticoagulation should be continued for 3–6 months.<sup>31</sup> This is based on the clinical knowledge that the prothrombotic risk factor that precipitated the initial event (stasis, surgery, etc) has now resolved and cessation of anticoagulation will have no sequelae. The prothrombotic tendency, in the advanced cancer patient, will by definition be ongoing and, if anything, increase as the disease progresses. None of the cancer VTE studies were continued past 6 months so there are no clinical trial data supporting anticoagulation past this period of time. However, a recent case series of 62 palliative care patients with VTE reported patients receiving LMWH for up to 243 days. Interestingly, of the seven patients who had their anticoagulation stopped at 6 months, three (43%) had recurrence of their thrombus and recommenced anticoagulation. If one is to consider anticoagulation long term, there will still come a time when the continuation of LMWH offers no symptomatic benefit or improvement in quality of life. In the case series reported, most patients continued anticoagulation until they entered the last few days of life.<sup>32</sup> These data, while shedding light on how long we should continue anticoagulation, also suggest that the majority of palliative care patients are appropriate for investigation and treatment of suspected VTE. Sometimes the biggest danger faced by the palliative care patient is not a complication of the disease process but rather the paternalistic nihilism inflicted on them by the attending clinician.

## CONCLUSION

While the evidence favouring the use of LMWH versus warfarin in the management of VTE is encouraging, there is a need for a robust clinical study in the palliative care population to look at the best way to treat and prevent VTE. In particular, a comparison of the CLOT protocol with the lower dose regimen described by Monreal is clearly needed. Careful consideration will need to be given to measurable end points that are relevant to the advanced cancer population. In a patient group where time is precious, quality of life outcomes are as important as radiological ones.

Competing interests: None

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