Venous thromboembolism: not as easy as it looks

Venous thromboembolism persists as a significant cause of death, much of which could be prevented. The symposium in this month's journal includes an overview of the UK perspective by Professor Kakkar, welcoming recent Department of Health policy developments which attempt to reduce hospital venous thromboembolism-related mortality. He highlights the considerable evidence base regarding risk factors, thrombophylaxis efficacy and outlines new advances in anticoagulation.

The practicalities of anticoagulation with heparin have changed dramatically with the advent of low molecular weight heparin. Low molecular weight heparin has been a welcome addition and is easier to manage than unfractionated heparin with its less predictable pharmacokinetics. However, unfractionated heparin is still required in certain circumstances, but now therefore is used by clinicians who are less familiar with unfractionated heparin than low molecular weight heparin. Dr Sado and colleagues' timely article recommends the use of standard weight-based nomograms to guide safe use of unfractionated heparin for both venous and arterial thromboses when indicated.

Venous thromboembolism and cancer

It is a widely accepted fact that cancer is a pro-thrombotic condition. The pathophysiology of cancer-related venous thromboembolism is well described and best practice guidelines for anticoagulation are published (Lyman et al, 2007; Noble et al, 2008). In spite of this, patients continue to suffer symptoms, or die from this preventable and treatable complication of malignant disease. In this symposium, Drs Noble and Jenkins discuss the factors contributing to this morbidity and mortality.

Level 1 evidence supports the recommendation for long-term treatment with low molecular weight heparin as secondary prevention in patients with cancer-related venous thromboembolism. However, the report from a UK database of venous thromboembolism management shows that only 9% of cancer patients received low molecular weight heparin for longer than 30 days and only 5% for longer than 90 days (VERITY Venous Thromboembolism Registry, 2007). Although this register may not be completely representative of all UK practice, in that it is a voluntary database, it could be expected that any clinician voluntarily entering details is likely to have an interest in management of venous thromboembolism. It is therefore possible that this gives a rosier picture rather than an under-estimate of good practice.

Sub-optimal management despite best evidence is a widespread issue throughout medical practice. Knowledge of research evidence is rarely enough to change management (NHS Centre for Reviews and Dissemination, 1999) and other factors affect clinical decision making, such as memory of last bad experience, access to resources and local prescribing policies and protocols.

Drs Noble and Jenkins also discuss the ambivalent and perhaps complacent attitude of many clinicians regarding patients with cancer-related venous thromboembolism. The perception that death from a pulmonary embolus is an easy 'way out' is not supported by published evidence (Havig, 1977) and runs in contradiction to an increasing emphasis on the importance of taking the patient's view into account during joint clinical decision making. Patient and clinician may have widely differing opinions about the risks and benefits of treatment. This attitude may colour the clinical index of suspicion, willingness to investigate and to initiate anticoagulation. Given that venous thromboembolism may be difficult to diagnose in patients with cancer anyway because it may be truly asymptomatic, or present with symptoms misattributed to the underlying cancer or its treatment, this attitude may cloud the situation even further.

The risk of a cancer patient developing venous thromboembolism is further increased by many anti-cancer chemotherapies. The ambivalent attitude towards cancer-related venous thromboembolism can even be seen here in the haphazard method of recording venous thromboembolism events in chemotherapy clinical trials (Maraveyas and Johnson, 2009). In addition, causality is rarely attributed to the chemotherapy itself.

Recording is essential

More stringent recording of venous thromboembolism in trials is a very recent thing, resulting from irrefutable evidence of increased risk of venous thromboembolism with thalidomide therapy in myeloma and with some of the newer targeted agents.

Part of the difficulty lies with the absence of any evidence-based clinically relevant grading tool for clinical trials. For example, the standard clinical trials classification of adverse events (CTCAE) tool for venous thromboembolism would classify both a small, asymptomatic, incidentally discovered pulmonary embolus, and a massive saddle embolus with cardiovascular collapse as grade 4 toxicity. Thus although it is accepted that chemotherapy raises the risk of venous thromboembolism, we still have insufficient evidence to recommend thromboprophylaxis except for myeloma patients receiving linalinomide or thalidomide (Lyman et al, 2007).

There is better development and application of evidence-based guidance for thromboprophylaxis for cancer patients undergoing surgery, perhaps because of the close scrutiny consequent to perioperative death.

Promoting quality of life

As cancer management has improved, so many more patients are living longer with the disease. Active cancer continues to pose a risk of venous thromboembolism, and clinical decision making can be difficult for those with a limited life span

where quality of life is key, but who are not imminently dying. The risks of anticoagulation in a group of patients who are more likely to bleed and have recurrent thrombosis produce management dilemmas.

Current recommendations are for long-term low molecular weight heparin, and although many patients find daily administration acceptable, some may not. However, it remains a superior option to the precarious business of anticoagulation with warfarin in a patient with potential liver dysfunction, changing medication regimens, variable dietary intake and absorption. The recent development of new anti-thrombotic oral agents is therefore most welcome and evaluation in cancer patients is eagerly awaited.

Conclusions

Venous thromboembolism has long been the clinical and research 'Cinderella' of oncology. A greater awareness of the complex interaction between cancer, its treatment and thrombosis is required in order to improve management for patients. **BJHM**

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KEY POINTS

- Venous thromboembolism persists as a significant cause of death, much of which could be prevented.
- Standard weight-based nomograms should be used to guide safe use of unfractionated heparin for both venous and arterial thromboses when indicated.
- A greater awareness of the complex interaction between cancer, its treatment and thrombosis is required in order to improve management for patients.
- Doctors of all specialties have a responsibility to patients to have a high index of suspicion for the risk of and presence of venous thromboembolism, and to give appropriate prophylaxis or treatment.