Palliative Care Review

Thrombosis and Bleeding Complications in the Seriously Ill

The prevalence of both symptomatic and undiagnosed venous thromboembolism (VTE) in patients with advanced disease is thought to be as high as 52%. Cancer patients in particular have an approximately sevenfold increased risk of this complication and its adverse consequences.

Patients who are diagnosed concurrently with malignancy and VTE have a 12% one-year survival rate. Risk of recurrent venous thromboembolism after stopping warfarin is 2%–10%. This high risk underscores the importance of treatment of VTE with anticoagulation. It must be recalled, however, that bleeding risk also may be high in patients with advanced illness (in cancer, it is as high as 6%–10%). Given this risk, applying current treatment guidelines to patients with advanced illness can be difficult. Evaluation of risk and benefit is essential when considering anticoagulation treatment options.

Anticoagulation

The goal of therapy for VTE is to prevent the extension of thrombus, acute pulmonary embolism (PE), recurrence of thrombosis, and the development of late complications, such as pulmonary hypertension and post-thrombotic syndromes.

Treatment of venous thromboembolism and the use of anticoagulants in patients with advanced illness can be challenging. Evidence and studies guiding recommendations for these indications excluded patients with poor prognosis or poor performance status, thrombocytopenia, bleeding, or brain metastases. The patients studied also were not the frail elderly..

Given the limitation of available studies, decisions regarding anticoagulation treatment need to be on a case-by-case basis.

Important considerations include the stage in illness trajectory, bleeding risk, patient's performance status, comorbidities, and nutritional status. These conversations should be conducted at regular intervals as patients advance in their illness. Care coordination with other health care providers and the interdisciplinary team is also essential.

The following are guidelines regarding anticoagulation use in this challenging population.

VTE Treatment in Cancer Patients

Given that patients with metastatic cancer remain at high risk of recurrent VTE despite 3 or 6 months of therapy, the general recommendation is for lifelong anticoagulation and/or as long as there is "active" cancer.

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Current clinical guidelines recommend low molecular weight heparin (LMWH) for the long-term treatment of cancer-related VTE. Warfarin is an alternative, but it is more difficult to monitor, and LMWH has shown to be superior in treatment of cancer patients with recurrent VTE in the CLOT trial. This study demonstrated that patients treated for VTE with LMWH have lower thrombo-embolism rates than VTE patients treated with warfarin, with relatively similar bleeding risk in both treatment arms.

For patients 65 and older, warfarin is the most common drug implicated in ED visits for adverse drug reactions. Its use in patients with advanced illness needs to be monitored closely, and indications for continuation of therapy should be reassessed at regular intervals. Studies have also shown that risk for bleeding on warfarin is especially high in the first 30 days of initiation, so this is a time when clinicians should be particularly vigilant for bleeding complications.

One of the more difficult complications to treat in the cancer population or patients with advanced illness is recurrent VTE despite use of anticoagulation. Treatment strategies include: increasing the dose of LMWH (if sub-therapeutic), changing to twice-daily injections to minimize trough levels, or switching to intravenous or subcutaneous unfractionated heparin (UFH), where direct thrombin activation is suspected or rapid reversal prior to surgery is needed.

Non-vitamin K oral anticoagulants (NOACs) have now become another option in the anticoagulation armamentarium. While they offer the ease of less monitoring and oral use, cautions regarding the use of these drugs include the paucity of reversal agents and the need for dose adjustments in renal insufficiency. There is also limited evidence for their use in patients with mechanical heart valves, so their use is not recommend-ed in this population. Recently, the U.S. FDA did approve idarucizumab [Praxbind®] as a reversal agent for dabigatran, one of the NOACs that is a thrombin inhibitor.

When deciding on treatment, it is important to know that certain tumors are more thrombogenic than others. Among these are ovarian, primary brain tumors, pancreatic, gastric, and colorectal. Its particularly important for clinicians to have a high index of suspicion for VTE in these patients.

Anticoagulation in Patients with Mechanical Heart Valves

Anticoagulation in patients with mechanical heart valves typically employs warfarin. Guidelines recommend continuing use of warfarin if the INR is relatively stable and infrequent monitoring is required. However, in the case of patients with difficult-to-control INR, or patients with contraindications to warfarin, there are very limited treatment options. Other options include the use of LMWH; however, it is important to watch the weight and renal function in these patients, as dose adjustments may be required. If there is a contraindication or severe bleeding risk, then a discussion with the patient and family regarding possibly stopping anticoagulant may need to be conducted. Included in this discussion should be the benefits, risks, burden, alternatives, and patient and family preferences about this decision.

Non-valvular Atrial Fibrillation and Stroke

For primary prevention of stroke in non-valvular atrial fibrillation (NVAF), risk stratification tools can be used. The CHADS2-VASc score is used to determine risk of stroke. The HASBLED score profiles bleeding risk.

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NVAF Risk Stratification Tools

CHADS2-VASc
(Score of ≥2 changes management)

Feature	Score if present
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Age between 65 and 74 years	1
Stroke/TIA/TE	2
Vascular disease (previous MI, peripheral arterial disease, or aortic plaque)	1
Diabetes mellitus	1
Female	1

HASBLED (Score ≥3 considered high risk)

	Condition	Points
H	**H**ypertension: (uncontrolled, >160 mmHg systolic)	1
A	**A**bnormal renal function: Dialysis, transplant, Cr >2.26 mg/dL or >200 µmol/L	1
	Abnormal liver function: Cirrhosis or Bilirubin >2x Normal or AST/ALT/AP >3x Normal	1
S	**S**troke: Prior history of stroke	1
B	**B**leeding: Prior Major Bleeding or Predisposition to Bleeding	1
L	**L**abile INR: (Unstable/high INR), Time in Therapeutic Range < 60%	1
E	**E**lderly: Age > 65 years	1
D	Prior Alcohol or **D**rug Usage History (≥ 8 drinks/week)	1
	Medication Usage Predisposing to Bleeding: (Antiplatelet agents, NSAIDs)	1

For primary stroke prevention, treatment is recommended with warfarin if the CHADS2-VASc score is ≥ 2. For patients that have one or no risk factors, treatment with aspirin 75 mg-325 mg is generally recommended.

For secondary stroke prevention, the risk stratification tools are not needed, and oral anticoagulant should be the treatment of choice if the patient is a candidate. Warfarin or an approved NOAC are options in these patients. NOACs are approved for treatment of atrial fibrillation, but they are not recommended in patients with prosthetic heart valves, severe renal failure (Cr Cl < 15 ml/min), or advanced liver disease.

The American College of Chest Physicians (ACCP) has specific guidelines for the prevention of embolism due to atrial fibrillation. They indicate the following:

- Low-risk patients (i.e., those with only atrial fibrillation without other risk factors) and patients younger than age 65 years should be treated with aspirin. (CHADS2-VASc score of 0)
- Patients aged 65-75 years without risk factors may or may not be given warfarin at the discretion of the treating clinician, as their condition may be based on other underlying disorders (e.g., valvular disease, prosthetic valve replacement). Aspirin and NOACs are alternatives for these moderate risk patients. (CHADS2-VASc score of 1)
- Warfarin or a NOAC should be used for all high risk patients and for all patients older than age 75 years regardless of risk. (CHADS2-VASc score of 2 or above)

Use of Inferior Vena Cava Filters (IVCF)

Typically, IVCF filters are used in patients with lower-body VTE who have contra-indications to anticoagulation, have failed anticoagulation, or are hemodynamically

unstable as an adjunct to anticoagulation. There is relatively little known about the use of IVCF in patients with serious chronic illness. Some data suggest that they offer no mortality benefit. Again, the risks and benefits need to be weighed.

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