PALLIATIVE PEARLS
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Oral Anticoagulant Use in Hospice
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Patient Case

OM is a 60-year-old female with a primary diagnosis of lung cancer and a history of HTN, depression, type II diabetes, myocardial infarction 5 years ago and deep vein thrombosis (DVT) 1 year ago. She weighs 160 pounds (72 kg), is ambulatory and has a good appetite. OM administers all of her own medication. She is allergic to penicillin and Bactrim DS® from which she develops a mild case of hives. She lives at home with her husband and has just been admitted to hospice.

Current Medications:

- Morphine 20m/ml: 0.25ml (5mg) PO every 3 hours as needed for pain or shortness of breath
- Morphine SR 60mg PO BID for pain
- Bisacodyl 10mg PR daily as needed for constipation
- Prochlorperazine 10mg PO every 6 hours as needed for nausea and vomiting
- Lorazepam 0.5mg PO every 6 hours as needed for anxiety
- Lovenox® (enoxaparin) 80mg/0.8ml syringe: inject 0.7ml (70mg) subcut. every 12 hours for prevention of blood clots
- Furosemide 40mg PO every day for fluid retention
- Potassium 20meq PO every day for low potassium
- Metoprolol tartrate 25mg PO twice daily for blood pressure and the heart
- Metformin 500mg PO twice daily for diabetes
- Citalopram 20mg PO every day for depression
- Senna 8.8mg PO twice daily as needed for constipation
- Albuterol-ipratropium 0.5-3mg/3ml neb. Solution: 1 amp. INH every 6 hours for shortness of breath
- Albuterol 90mcg HFA Inhaler: 2 puffs INH every 4 hours as needed

OM was prescribed Lovenox® 1 year ago when she was hospitalized for a DVT in her right leg at the same time she was diagnosed with lung cancer. OM states that she is tired of giving herself the twice daily injections, describing them as painful and irritating at the injection site. Lovenox®, due to its high cost is not part of the hospice formulary, however oral warfarin is a formulary alternative. OM is familiar with warfarin as her sister takes it and she used to drive her to the lab once a month for blood tests. A friend takes Pradaxa® who loves that she doesn't have to go to the lab. OM asks if Pradaxa® is an option.

Why are hospice patients at increased risk for Venous Thromboembolism (VTE)?

There are a number of factors that place patients in hospice and palliative care at increased risk for venous thromboembolism (VTE) including age, reduced mobility and cancer, which induces a hypercoagulable state.[1-3] When a blood clot, or thrombus, originates in the deep veins of the legs (usually calf or thigh) or the pelvis, it is called a deep vein thrombus (DVT). The thrombus may dislodge

from its original site and travel to the lung, resulting in a pulmonary embolism (PE). DVT and PE are collectively categorized as VTE, which ranks high among the leading causes of mortality in patients with cancer.[4,5] The reported incidence of VTE in palliative care patients is 1-5%, which may reflect an underestimation of VTE risk in advanced cancer and associated underreporting.[6]

What are the risks of anticoagulation?

Prior to reviewing an alternative agent, it's important to consider current bleeding risk and whether the benefit of anticoagulation therapy and prevention of VTE still outweighs its risk.

Bleeding risk increases with the number of risk factors present. From the list below, if patient has 0 factors present their risk of bleeding is low. One factor equates to a moderate risk and ≥ 2 factors represents high risk.[9]

- Age > 65 years
- Previous bleeding
- Conditions: Cancer, renal failure, liver failure, thrombocytopenia, previous stroke, diabetes, anemia
- Medications: Antiplatelet therapy, NSAID therapy
- Poor anticoagulant control
- Comorbidity and reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol abuse

How do warfarin, parenteral and direct oral anticoagulants (DOACs) compare in managing VTE in patients with active cancer?

Warfarin (Coumadin®, Jantoven®) is a widely familiar anticoagulant treatment for the long-term management of VTE in the general population.[7-12] However, despite its common use and low cost, its use in patients with cancer poses more problems than in patients without cancer.[13] Bleeding rates in cancer patients prescribed warfarin have been reported as high as 21.6%, and could be even higher in the palliative care population.[6] Other disadvantages include the need for international normalized ratio (INR) lab monitoring, dose adjustments, and numerous drug-drug, drug-food and drug-herbal interactions. Changes in patient's condition (e.g., poor nutrition intake, liver metastases) may also make it more challenging to maintain a therapeutic INR.[6,13]

LMWHs are fragments of heparin that inhibit the clotting cascade by binding specifically to clotting factors Xa and IIa and contribute to a more predictable therapeutic response and longer duration compared to unfractionated heparin (UFH). Compared to UFH, LMWHs are dosed once or twice daily and unlike warfarin, require no routine laboratory monitoring.[14] The two LMWHs marketed in the U.S.

are enoxaparin (Lovenox®) and dalteparin (Fragmin®).[15] Another available parenteral product, fondaparinux (Arixtra®), unrelated to heparin products, is useful for patients with a history of heparin-induced thrombocytopenia (HIT). In the CHEST Guidelines, LMWHs are recommended over warfarin therapy in active cancer patients with DVT of the leg or PE.[9]

The emergence of a new class of anticoagulants, the direct oral anticoagulants (DOACs) (rivaroxaban (Xarelto®), apixaban (Eliquis®), dabigatran (Pradaxa®), edoxaban (Savaysa®)) has led many to postulate their place in therapy. These products, although costly compared to warfarin, are taken orally and require no laboratory monitoring. Treatment of VTE with DOACs may be less burdensome and may be associated with better clinical outcomes compared to warfarin and LMWH therapy, however, postmarketing safety studies of DOACs were not available when guidelines were published. Due to the lack of currently available DOAC data, a weak recommendation is provided in favor of warfarin and LMWH therapy over DOACs in this patient population.[9,14]

The recommended duration of anticoagulation therapy for patients with DVT of the leg or PE and **active cancer** is ongoing, with **no end date**, regardless of medication choice.

What is the recommended duration of therapy for non- cancer diagnoses that require anticoagulation?

A 3-month duration is recommended in the below situations. The decision to extend therapy beyond 3 months depends on patient-specific factors.[9] For example, patients with a high bleeding risk should not be extended past 3 months of therapy. Patients with recurrent VTE may have therapy extended.

- Proximal DVT of the leg or PE provoked by surgery
- Proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor
- Isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor
- Unprovoked DVT of the leg (isolated distal or proximal) or PE

What are the costs of anticoagulation therapy?

The cost of 15-day supply of medication averages $11, $225, $350 and over $2000 for warfarin, DOACs, unfractionated heparin and LMWH/Arixtra®, respectively. Labor and costs associated with drawing labs to monitor warfarin therapy should also be considered.

Pharmacist assessment:

Hospice formularies promote cost-effective symptom management, however, they do not include all medications encountered in hospice care. When a medication is not formulary, the hospice should balance the needs of the patient with available formulary alternatives and the cost of non-formulary medications deemed necessary. DOACs are oral therapies effective for managing VTE but they are not

on the hospice's formulary, nor is Lovenox®. UFH intermittent injection and oral Warfarin are on formulary.

OM finds that the Lovenox® injections are painful and cause irritation at the injection site. UFH is not a feasible alternative for OM especially considering the "every 8 hour" injections required. Warfarin is an oral anticoagulant that typically requires monthly INR lab monitoring once therapy is stable. OM and her husband are ambulatory and currently do not require assistance to get to lab appointments. Warfarin would alleviate OMs twice daily injections and may be more tolerable. OM's appetite is normal at this time, eating 3 balanced meals a day –also making her a good candidate for warfarin therapy.

OM is at moderate risk of bleeding due to her history of cancer and diabetes. DOACs are less costly compared to LMWH/Arixtra® therapy. In patients similar to OM, with low to moderate risk of bleeding, in which anticoagulation is being continued, DOACs could be considered for patients with inconsistent diets who have difficulty traveling to a lab or in which lab draws are inconsistent with their goals of care.

Recommendation:

After review, the hospice interdisciplinary team determined that continuation of anticoagulation therapy is appropriate based on her moderate risk of bleeding and overall stability status. They recommended changing from Lovenox® to warfarin.

Instructions: Initiate warfarin at 5mg PO daily while continuing the current Lovenox® dose of 70mg subcut. every 12 hours. This overlap should occur for at least 5 days and until the INR is within therapeutic range for 24 hours.[21] Labs should be repeated weekly until INR is stable for 4 weeks, then frequency can be changed to monthly. The therapeutic INR range for OM is between 2 and 3.[22,23]

It's important that OM follow her warfarin regimen as prescribed and continue her current eating habits. Hospice will need to perform frequent blood draws at first, followed by monthly blood draws to monitor the warfarin regimen. OM should be monitored for changes in compliance, eating habits, or health status. Risk versus benefit of continuing anticoagulant therapy should be reevaluated when OM's condition declines.

For additional information on this topic, please review these references:

Enclara Pharmacia's educational resource, "Managing Cancer and VTE in Hospice and Palliative Care". Click here to log in

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