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Primary and secondary VTE Prophylaxis in Palliative care patients: A Case Report

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ABSTRACT:

Venous thromboembolism (VTE) in cancer patients is a distressing problem for the patient and a difficult area for the physician to manage. There is lack of evidence-based clinical guidelines for the prophylaxis and management of venous thromboembolism in cancer patients receiving palliative care. This case reflection is an account of what we learnt from critical incidents experienced by four patients in our program in Saudi Arabia.

INTRODUCTION:

This reflection follows the "What? So what? Now what?" model of reflective practice proposed by Rolfe et al.[1]

Critical Incident 1 :

A 66-year-old female with adenocarcinoma of the endometrium, who had completed all active management and was under palliative care since 1 year, presented recently with documented increase in para-aortic and pelvic node metastases. An increase in pain had made her bed-bound for over 2 weeks and she was admitted under the oncology service and then transferred to the palliative care ward. The patient had a ureteric stent inserted 3 months previously. She was on

megestrol acetate 160mg/day for anorexia. She was on enoxaparin 40mg subcutaneously daily for primary VTE prophylaxis. A month later, she developed hematuria and enoxaparin was discontinued. She continued on megestrol acetate. The hematuria resolved and the ureteric stents were also removed and enoxaparin was not restarted. She was assessed as having a palliative performance status (PPS) of 40% (mainly confined to bed, Unable to do most activity, Extensive disease, assisted self-care, reduced oral intake, fully conscious and oriented), she received palliative radiation to the retroperitoneal lymph nodes and good pain relief was achieved with methadone. The critical incident happened when she developed left lower limb partial deep vein thrombosis, two weeks after enoxaparin was stopped.

Secondary prophylactic enoxaparin was started at 70mg subcutaneously every 12 Hours and the DVT resolved clinically. No pulmonary embolism occurred.

Critical Incident 2:

A 60-year-old female with gastric adenocarcinoma with brain metastasis and PPS 30% (totally bedbound, reduced oral intake) had been recently discharged home on enoxaparin 40mg subcutaneously daily. She was re-admitted with hematuria and vaginal bleeding. The enoxaparin was stopped, however, the vaginal bleeding continued to be significant causing anemia and fatigue and a hemoglobin drop from 13gm% to 8gm% over a week. A CT showed malignant metastatic mass in pelvis invading bladder and uterus. A DVT of iliac and femoral vessels was seen on CT and Doppler. Contrast Enhanced CT of the Chest showed no evidence of pulmonary embolism. An Inferior Vena Cava (IVC) filter was inserted and she remained symptomatic as regards leg pain and swelling. Vaginal bleeding was significantly reduced although slight spotting continued during a period of slow deterioration in her performance status, until her death 2 months later.

Critical Incident 3:

A 17-year-old male, who had aggressive Glioblastoma Multiforme, quadriplegia, a Glasgow Coma Scale of 5/15, and a PPS 30%, was transferred to the palliative care service with no evidence of a DVT. He was on enoxaparin 40mg subcutaneously daily for primary prophylaxis of VTE. A critical incident occurred when he developed

hematuria and enoxaparin was stopped. The hematuria resolved but he continued to deteriorate, and died 2 months later due to progression of brain tumor.

Critical Incident 4:

An 81-year-old frail lady was transferred to palliative care from the oncology service with advanced poorly differentiated carcinoma of lung with bone and liver metastases. She had a right femur fracture and was not a candidate of any surgical fixation of the fracture. She was on prophylactic enoxaparin 40mg subcutaneously daily. Patient developed fresh bleeding per rectum a month after starting enoxaparin resulting in a drop in her hemoglobin level to 6.3 gm%. The enoxaparin was stopped, 2 units of RBC was transfused, and the rectal bleeding subsequently stopped. She refused colonoscopy. After about 2 weeks, bilateral leg swelling was noticed and Doppler ultrasound leg revealed an acute DVT of right and left superficial femoral and popliteal veins.

As patient was at a high risk for pulmonary embolism, and had a previous episode of significant rectal bleeding with prophylactic enoxaparin, the decision of anticoagulation with unfractionated heparin was made. She was started on subcutaneous unfractionated heparin with a 25% dose reduction from the recommended therapeutic dose. Patient tolerated it very well, with no recurrence of rectal bleeding. After 6 days, she was shifted to enoxaparin again with a 25% dose reduction as heparin requires frequent monitoring of coagulation profiles. The leg pain and swelling improved without any evidence of a pulmonary embolism or recurrence of rectal bleeding until she died a month later from progressive primary malignancy.

Discussion

The critical incidents referred to here are common day-to-day clinical scenarios in a palliative care unit. Robust guidelines exist for patients at risk for VTE in oncology, medical and surgical specialties (non-palliative). However, there is a lack of such guidelines for patients with advanced progressive cancers and typically have limited life expectancy (palliative).

Based on ESMO, NCCN, ASCO and NICE guidelines, the following are clear regarding VTE prophylaxis in (cancer and non-cancer) patients under active management (2,3,4,5) Hospitalised cancer patients are at risk of

developing VTE as are non-ambulatory cancer patients. Specific chemotherapy agents like Thalidomide increase the risk of VTE even in ambulatory patients necessitating thromboprophylaxis. Enoxaparin (Low molecular weight Heparin - LMWH) is the drug of choice for primary prophylaxis for prevention of VTE in those who need it. There is debate regarding primary VTE prophylaxis in brain tumor patients with regards to balancing the risk from tumor bleeding with prevention of VTE in bedbound patients with brain tumor. Unfractionated Heparin can be used for those with risk of bleeding and contraindications to use of LMWH.

A 25% dose reduction has been advocated for those with active or high risk of bleeding but require anticoagulation for primary or secondary prophylaxis in some literature as eluded in the discussion below.

IVC filters are recommended for those with risk of bleeding and contraindications to heparins. IVC filters are however a temporary measure and they have to be switched to heparins as early as possible. There is a positive role of peripheral sequential compressive stockings / pneumatic devices along with Heparins in VTE prophylaxis. Early ambulation is part of VTE prophylaxis and management in those patients who have a good prognosis and are on active treatment.

These patients received treatment for VTE prophylaxis and management, based on best evidence available for cancer patients on active cancer treatment– but, as seen, not without complications. It is obvious that the VTE prophylaxis guidelines for patients under active treatment cannot be extended to patients under palliative care without careful individual consideration. Questions regarding the impact on quality of life, symptom control and risk vs benefits still linger after considering the management options for the cases outlined above.

We undertook a reflective exercise to explore existing evidence, areas of lacunae in knowledge and scope for further improvement in our practice in the future; specifically, applicable to advanced cancer patients with limited life expectancy and not on active treatment.

What could have been done differently?

Symptomatic venous thromboembolism (VTE) occurs in approximately 15% of patient with advanced malignancy [6]. Palliative patients are probably at a higher

risk of VTE either secondary to worsening immobility, underlying advanced malignancy, cord compression, fracture, acute comorbid medical illness etc. [6, 7]. Primary thromboprophylaxis using low molecular weight heparin is supported by Level 1A evidence in cancer patients with good performance status (4,8,9,10). Our patients were all cancer patients with advanced, progressive disease under palliative care. We elected to treat them with enoxaparin 40mg subcutaneously daily as primary prophylaxis for VTE. This was consistent with guidelines followed in our hospital (2,3,4). LMWH is more effective with less bleeding risk than oral anticoagulation in cancer patients [8,9,10].

Nevertheless, it appears from the critical incidents above that the prophylaxis and management of VTE in palliative care patients creates many clinical dilemmas. A survey amongst experts in palliative care, oncology and intensive care about anticoagulation showed that primary prophylaxis was withdrawn by physicians in patients with PPS less than 40% [8]. But, because patients with DVT/PE and cancer are at increased risk of death from pulmonary thromboembolism, [10] there is an ethical dilemma to balance the intentions of beneficence and non-maleficence in palliative care patients. However, available literature suggests that the role of primary thromboprophylaxis in palliative care patients is still unclear and there are wide variations in practice, due to perceived differences in prevalence, lack of impact on quality of life, need for monitoring and risk of complications. The risk reduction of fatal VTE even in cancer patients on active treatment is around 2% (NNT ranging 40 - 60) [11]. Thus, primary VTE prophylaxis in palliative care cancer patients with only a limited survival is of questionable benefit.

In critical incident 1, the patient developed DVT but she was also on megesterol which is known to increase VTE. Megesterol could have been replaced with dexamethasone with a lower incidence of VTE. Physical therapy and sequential compressive pneumatic stockings could have been used without enoxaparin in view of a poor PPS of 40%(8). The hematuria was attributed to enoxaparin but it could have been due to the ureteric stent or UTI. This could have been investigated before stopping enoxaparin. Overall, it appears that not stopping Enoxaparin could have prevented the DVT in this patient.

In critical incident 2, the primary prophylaxis with enoxaparin might have been avoided considering the PPS of 30% and the brain metastases. When she eventually developed DVT the options were LMWH, unfractionated Heparin or an IVC filter. We elected to use an IVC filter in view of the active vaginal bleeding and concerns regarding bleeding from gastric cancer and brain metastasis. This patient was clinically deteriorating and finally died in the hospital after a further 8 weeks, she remained symptomatic as regards leg pain and swelling. The impact of IVC filter on her quality of life, however, is questionable. Guidelines regarding IVC filter stating that this option is valid for those with reversible causes of bleeding, who can be switched to heparins at the earliest time (5). It should be noted that there is a risk of IVC filter dislocation, bleeding from procedure and contrast related complications. There is also evidence to suggest that an IVC filter alone might not be effective (12). It is pertinent to mention here that the decision to go ahead with IVC filter was made after a family meeting with the patient and her care-givers and a full discussion of the above issues.

In critical incident 3, it is clear from the previous discussion that primary VTE prophylaxis was not indicated in view of the primary brain tumor, a PPS of 30% and rapid clinical deterioration.

Regarding secondary VTE prophylaxis for those with DVT, there seems to be a reasonable agreement in literature that they should be treated even in palliative care patients. The dilemma arises when patients are considered to be at increased risk of bleeding. Literature suggests the use of LMWH in cancer patients who have a good performance status [13]. For fragile palliative patients who are not on any cancer directed therapy, have progressive disease and have a short life expectancy along with increased tendency for life-threatening bleed, the full dose of LMWH for long term could be very problematic. It is ideal to start them on full dose of LMWH for 7 days followed by a long term decreased fixed dose [10,13,14].

In our patient in critical incident 4, we decided on unfractionated heparin subcutaneously at 75% of recommended dose as she had just recovered from a recent rectal bleed. This approach allowed us to closely observe her for any re-bleeding and the option of quick reversal of heparin effects, in case of significant bleeding. Our

patient refused IVC filter and opted for medical management. She tolerated this adjusted heparin dose very well with no bleeding even after 6 days of anticoagulation which was then changed to LMWH at 75% of the recommended dose (2mg/kg = 80mg/day, 40kg. Final dose 30mg enoxaparin BID) long term (10,13,14). In non-cancer patients, the suggested duration of anticoagulation is 3-6 months. However, patients with advanced cancer, with disease progression, have a prothrombotic tendency [9]. There is no convincing data about the duration of anticoagulation in palliative care patients. In general, if anticoagulation is used long term in palliative care, consideration of discontinuation should occur in a framework of risk/benefit and futility. [15,16] In this case, we did not stop the anticoagulation until the patient was imminently dying with a PPS of 10%.

Conclusion:

Primary and secondary thromboprophylaxis of cancer patients with good performance status is well studied in literature. Primary and secondary prophylaxis of frail cancer patients in the care of palliative teams is an area for future research to help develop quality of life oriented guidelines. Available literature tends to support the idea that there is a sub-group of patients for whom any anticoagulation therapy could be futile and need careful risk-benefit assessment within an ethical framework.

In the imminently dying palliative patient (PPS10%), thromboprophylaxis can be stopped. In patients who have developed DVT, LMWH should be offered to prevent fatal pulmonary thromboembolic event. In those with DVT and risk of life-threatening bleeding a 75% dose reduction from the recommended daily dose of LMWH appears to be safe in those who are not imminently dying. IVC filters could also be of value in such patients. The evidence is unclear regarding VTEP for those with secondary (metastatic) brain tumors and at risk of thromboembolism. In our second patient, primary VTEP and the IVC filter after DVT was futile and we will be less inclined to anti-coagulate patients with brain metastases and PPS </= 30%.

The body of evidence in literature and the guidelines for VTEP for cancer patients on active oncological management and a good prognosis should not be applied to palliative patients without considering the individual

patient specific goals for improving quality of life and symptom control. The involvement of the patient and family members is crucial for an informed decision making process. Finally, further research toward identifying the sub group of palliative patients who will benefit from tailored VTEP interventions should guide clinical practice in the future.

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