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CLINICAL VIGNETTE

Thromboprophylaxis in Cancer Patients

by
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Venous thromboembolism (VTE) is one of the leading causes of death in cancer patients, reported in 4-20% of patients diagnosed with cancer[1]. These reported rates are actually believed to be underestimated, as autopsy rates of VTE are as high as 50%[2]. Cancer patients account for approximately 15-20% of all VTE cases[3]. A recent analysis of more than 66,000 patients from US academic medical centers found 5.4% of patients developed VTE per hospitalization with this number increasing by 36% from 1995 to 2002[1]. This rise in the incidence of VTE is largely accounted for by newer prothrombotic chemotherapeutic agents, improved cancer patient survival, more advanced high-resolution imaging, and the increased utilization of central venous catheters. The diagnosis of VTE has important clinical and economic implications.

There is three-fold greater mortality rate when VTE develops at the same time or within one year of a cancer diagnosis[4]. Additionally, the recurrence of VTE is three-fold more frequent in cancer patients, requiring long-term anticoagulation and consequently, a two-fold greater risk of bleeding complications[5]. Each VTE diagnosis is associated with increased use of health care resources. A retrospective analysis found an average cost of a DVT-attributable hospitalization was $20,065 with a mean length of stay of 11 days[6]. Despite robust evidence of the high-risk of VTE in the cancer population, VTE prophylaxis remains largely underused. Ironically, cancer patients have a lower likelihood of receiving VTE prophylaxis on admission to the hospital[7]. This may be due to the fear of bleeding complications in cancer patients, the lack of awareness among physicians regarding VTE management strategies, and underestimation of risk for VTE in cancer patients. There is a move to identify thrombotic risk factors that will stratify cancer patients and assess their need for thromboprophylaxis in ambulatory care settings. For instance, patients receiving active chemotherapy have a 6.5-fold increased risk of VTE[8]. Specifically, certain antiangiogenic chemotherapies (thalidomide, lenalidomide, and bevacizumab) and hormonal therapies (tamoxifen) have been associated with an increased VTE risk[9]. The type of cancer also poses a risk for VTE with malignant brain tumors, hematologic malignancies (particularly lymphomas), and certain adenocarcinomas posing the greatest risk (5,10). Other risk factors include hospitalization, undergoing a surgical procedure, platelet counts >350,000, and prothrombotic mutations[11,12]. This review will provide a comprehensive update on the recommendations for thromboprophylaxis in cancer patients in various inpatient and outpatient settings, including prophylaxis in cancer patients undergoing surgery, hospitalizations, and active chemotherapy.

Should patients undergoing surgery receive pre-operative and post-operative thrombo-prophylaxis? VTE is a common yet preventable complication in cancer patients undergoing surgery. One observational study cited “40% of VTE events occurred 21 days after surgery” and “VTE was responsible for 46% of deaths within 30 days after surgery”[13]. This was attributed to prolonged anesthesia, postoperative inactivity, and advanced cancer stage in patients requiring surgery. Most major guidelines, such as ASCO, NCCN, and ACCP, recommend in-hospital thromboprophylaxis in cancer patients undergoing surgery. In regards to mechanical prophylaxis, a small study of 355 patients that randomly assigned cancer patients to compression stockings versus control showed DVT rates of 12.8% in the pneumatic compression stocking group versus 21% in the control group[14]. The use of unfractionated heparin (UFH) has also been evaluated extensively in the surgical cancer population. A meta-analysis of 10 trials with 919 patients showed administration of UFH 5,000 units 2

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hours preoperatively and every 8 hours postoperatively significantly reduced DVT rates from 30.6% in the control group to 13.6% in the UFH group[14]. Studies comparing UFH to low molecular-weight heparin (LMWH) have demonstrated similar efficacy in regards to VTE prophylaxis. A large double-blind multicenter trial of 600 cancer patients undergoing pelvic or abdominal surgery randomized patients to receive LMWH enoxaparin 40mg daily or UFH 5,000 units three times a day with venographic assessment at day 28 of their hospital stay. The outcome suggested that the two treatments had equal efficacy in VTE prophylaxis with no difference in bleeding events[15]. Multiple subsequent studies have confirmed these results in regards to efficacy; however, possible advantages of using LMWH versus UFH include once daily injections as opposed to three times a day and a lower risk of heparin-induced thrombocytopenia. Similarly, a randomized controlled trial of patients undergoing abdominal surgery found fondaparinux as effective as dalteparin for VTE prophylaxis[13].

Better outcomes have been documented with combined mechanical and pharmacologic prophylaxis in a Cochrane review of 19 studies, showing that UFH or LMWH and compression stockings were four times more effective in VTE prophylaxis compared to either alone[16]. As far as the duration of prophylactic pharmacologic treatment, two randomized control trials suggest that extending the duration of treatment to 4 weeks reduces the rates of VTE[17]. The FAME study randomized patients undergoing major abdominal surgery into daily dalteparin for 4 weeks versus dalteparin for 1 week, and showed a reduction in VTE rates from 16.3% in the 1-week arm to 7.3% in the 4-week arm along with a relative risk reduction of 55% (95% CI, 0.15 to 0.76) without an increased risk of bleeding[18]. This is particularly important with a recent observational study, showing 40% of VTE events occurred 21 days after surgery[13]. Most guidelines have established that cancer patients undergoing surgery should be treated with UFH or LMWH for at least 7-10 days (with the option of combining mechanical prophylaxis) and that this duration should be extended to one month in those patients undergoing major abdominal surgery.

Should hospitalized cancer patients receive thromboprophylaxis? Hospitalization is one of the greatest risk factors for VTE development with hospitalized patients having an 8-fold increased risk of VTE[8]. The implications on morbidity and mortality are substantial: hospitalized patients with VTE have greater in-hospital mortality (odds ratio, 2.01;95% CI 1.83 to 2.22; P<.0001)[5]. The MEDENOX trial, a double-blind placebo-controlled multicenter study, randomized 579 patients to receive enoxaparin versus placebo during hospitalization (19). There was a decrease in VTE events in the treatment group (5.5%) versus the control group (14.9%) (95% CI, 0.22 to 0.63, P<.001). However, only 72 of the 579 patients were cancer patients, and the outcomes for the cancer subset (19.5% VTE events in placebo arm vs 9.7% in treatment arm) was not statistically significant, P= 0.4[19]. The PREVENT trial, another large randomized double-blind placebo-controlled trial, randomized 3,706 hospitalized patients to treatment with dalteparin versus placebo[20]. There was a reduction in VTE events in the treatment arm (2.77%) versus the control arm (4.96%) (95% CI, 0.38 to 0.8, P=.0015). However, this trial, like the MEDENOX trial, only had a small subset of cancer patients (5.1%) (20). Recently, a review of 13 RCTs with a total of 22,141 hospitalized patients found patients randomized to receive UFH or LMWH experienced a 60% risk reduction in DVT events (RR, 0.40; 95% CI, 0.31 to 0.53) and a 42% risk reduction in PE events (RR, 0.58, 95% CI, 0.43 to 0.58) compared with placebo or no intervention[21]. Again, however, only a small subset of these patients had a cancer diagnosis, and no outcome data for the cancer subset were included. Patients receiving UFH had an increased risk of bleeding (RR, 1.28, 95% CI, 1.28 to 3.72)[21]. There is an obvious need for more RCTs looking at pharmacologic thromboprophylaxis in hospitalized cancer patients. At this time, given that active cancer patients are amongst the most prothrombotic inpatients, general consensus is to use prophylaxis, as long as there is not an active contraindication[22,23].

The more interesting question is whether ambulatory cancer patients should receive thromboprophylaxis during systemic chemotherapy. The diagnosis of cancer itself carries a substantial risk of VTE; with the addition of active chemotherapy, this risk increases 6.5-fold, especially concerning in those with metastatic or advanced cancer[8]. In regards

to low-dose warfarin, a double-blind trial randomized 311 patients receiving chemotherapy with metastatic breast cancer to be given either 1mg of warfarin for 6 weeks with target INR of 1.3-1.9 versus placebo. There was a significant 85% risk reduction with a 0.65% rate of VTE in the warfarin arm versus 4.4% rate of VTE in the placebo arm[24]. The TOPIC-1 and TOPIC-2 trials examining the efficacy of LMWH have not been as successful with inconclusive evidence on whether administration of LMWH during chemotherapy infusions is beneficial in advanced stages of breast and lung cancers[25]. Furthermore, the PROTECT trial randomized 1,166 ambulatory patients receiving chemotherapy with metastatic or locally advanced cancers to receive either nadroparin or placebo. The VTE incidence was 3.9% in the control group versus 2% in the treatment group with no significant survival benefit[26]. In contrast, the CONKO-004 study and the FRAGEM study randomized advanced pancreatic cancer patients receiving gemcitabine chemotherapy to be given LMWH (enoxaparin/dalteparin) versus placebo and found that patients receiving LMWH had a significant reduction in VTE events (5% in enoxaparin arm versus 14.5% in placebo arm in CONKO-004 and 12% in dalteparin arm versus 31% in placebo arm in FRAGEM) (27-29). Most recently, the SAVE-ONCO study, a double-blind multicenter trial, randomized 3,212 patients with metastatic or locally advanced solid tumors receiving chemotherapy to receive subcutaneous LMWH semuloparin 20mg once daily versus placebo. VTE occurred in 1.2% of the semuloparin arm versus 3.4% of the placebo arm (hazard ratio 1.40; 95% CI, 0.89 to 2.21) with the conclusion that semuloparin reduces the incidence of VTE events without an increased risk of major bleeding in patients receiving chemotherapy[30]. However, the FDA in 2012 did not approve semuloparin for the purpose of preventing VTE in cancer patients receiving chemotherapy for cited reasons, such as a small absolute risk reduction (2.2%), a suboptimal target population, and a modest benefit in its application. A recent Cochrane Collaboration systematic review looked at 9 RCTS with 2,857 cancer patients with metastatic or locally advanced solid cancers receiving chemotherapy and concluded that prophylaxis with LMWH or UFH reduced VTE event rate (RR 0.55; 95% CI, 0.37 to 0.82) and mortality at 48 months[31]. However, conclusions could not be made from this systematic review because it lacked statistical power. Myeloma patients being treated with antiangiogenic agents, such as thalidomide and its derivatives, are another story. The risk of VTE in these patients has ranged from 17-26% in combination with dexamethasone[9,32]. A phase II trial by Rajkumar et al reported a lower observed rate of VTE in cancer patients receiving lenalidomide plus dexamethasone who were given 80 to 325mg of aspirin versus placebo[33]. Another retrospective study looked at the rates of VTE in three groups of multiple myeloma patients treated with melphalan, prednisone, and thalidomide: those without prophylaxis, those treated with enoxaparin 40 mg daily, and or those treated with aspirin daily. The incidence of VTE was 18.5% in the group without prophylaxis, 5.2% in the group treated with enoxaparin, and 2.1% in the aspirin group[34]. This study pushed ASCO, ESMO, NCCN, and other groups to support the use of LMWH or warfarin in multiple myeloma patients receiving antiangiogenic therapy in the outpatient setting. Overall, the consensus is that myeloma patients and advanced pancreatic cancer would benefit from thromboprophylaxis in the ambulatory setting given the high rates of VTE[35]. However, there is inconclusive evidence from trials regarding non-myeloma and non-pancreatic cancer patients receiving chemotherapy. For these patients, the recommendation is to risk stratify.

Khorana et al developed a risk score for VTE from a cohort of 2,701 solid cancer patients receiving chemotherapy[36]. The patient characteristics included in the predictive model include: site of cancer (2 points for stomach and pancreas; 1 point for lung, lymphoma, and GU cancers), prechemotherapy platelet count of >350,000 (1 point), hemoglobin <10 or use of EPO agents (1 point), prechemotherapy leukocyte count >11,000 (1 point), and a body mass index of >35 (1 point). Patients receiving a total score of 0 are considered low-risk with a VTE risk of 0.3-0.8%, whereas patients receiving a total score of 1-2 are considered intermediate-risk with a VTE risk of 1.8-2.0%. Patients in the high-risk category received a total score of 3 or higher with a VTE risk of 6.7-7.1%. They recommended only high risk category patients should receive ambulatory thromboprophylaxis[36]. The Khorana model has been validated by numerous studies. More specifically, the Vienna Cancer and Thrombosis Study (CATS) expanded the Khorana score to

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include two biomarkers: D-dimer and P-selectin. This modification has more distinctly separated the low-risk patients (VTE risk 1%) from the intermediate (VTE risk 10.3%) and high (VTE risk 35%)[37,38]. Until more RCTs are undertaken to show substantial benefit from thromboprophylaxis in ambulatory cancer patients receiving chemotherapy, the onus falls on the awareness and judgment of health-care providers to appropriately risk stratify patients using the predictive models that are available.

Cancer patients are high-risk patients for the development of venous thromboembolic disease, which has significant clinical and economic implications for this population. Despite recognition of VTE being a major complication of oncologic patients, there is profound underutilization of pharmacologic and non-pharmacologic prophylactic measures. This may be due to lack of physician awareness of consensus recommendations, but also may reflect inconclusive evidence regarding thromboprophylaxis in both the inpatient and outpatient setting for cancer patients. It is vital for this gap to narrow because it is only promoting the morbidity and mortality of our cancer patients. There are established evidence-based guidelines recommending prophylactic anticoagulation therapy in cancer patients (without any contraindications) undergoing surgery and hospitalized cancer patients who are acutely ill. Strategies need to be implemented to raise awareness. As far as outpatient cancer patients receiving chemotherapy, there remains a pronounced need for more randomized controlled trials to offer more conclusive evidence. In the meantime, risk stratification models need to be used with physicians individualizing thrombophylaxis for each patient.

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