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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<sup>1</sup>. These reported rates are actually believed to be underestimated, as autopsy rates of VTE are as high as 50%<sup>2</sup>. Cancer patients account for approximately 15-20% of all VTE cases<sup>3</sup>. 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<sup>1</sup>. 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<sup>4</sup>. 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<sup>5</sup>. 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<sup>6</sup>. 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<sup>7</sup>. 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<sup>8</sup>. Specifically, certain antiangiogenic chemotherapies (thalidomide, lenalidomide, and bevacizumab) and hormonal therapies (tamoxifen) have been associated with an increased VTE risk<sup>9</sup>. 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<sup>11,12</sup>. 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 thromboprophylaxis? 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"<sup>13</sup>. 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<sup>14</sup>. 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<sup>14</sup>. 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<sup>15</sup>. 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<sup>13</sup>.

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<sup>16</sup>. 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<sup>17</sup>. 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<sup>18</sup>. This is particularly important with a recent observational study, showing 40% of VTE events occurred 21 days after surgery<sup>13</sup>. 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<sup>8</sup>. 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;  $P < .0001$ )<sup>5</sup>. 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,  $P = 0.4$ <sup>19</sup>. The PREVENT trial, another large randomized double-blind placebo-controlled trial, randomized 3,706 hospitalized patients to treatment with dalteparin versus placebo<sup>20</sup>. 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<sup>21</sup>. 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)<sup>21</sup>. 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<sup>22,23</sup>.

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<sup>8</sup>. In regards

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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<sup>24</sup>. 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<sup>25</sup>. 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<sup>26</sup>. 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<sup>30</sup>. 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<sup>31</sup>. 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<sup>9,32</sup>. 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<sup>33</sup>. 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<sup>34</sup>. 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<sup>35</sup>. 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<sup>36</sup>. 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<sup>36</sup>. 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%)<sup>37,38</sup>. 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 thromboprophylaxis for each patient.

#### REFERENCES

1. **Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH.** Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost.* 2007 Mar;5(3):632-4. PubMed PMID: 17319909.
2. **Gomes MP, Deitcher SR.** Diagnosis of venous thromboembolic disease in cancer patients. *Oncology* (Williston Park). 2003 Jan;17(1):126-35, 139; discussion 139-44. Review. PubMed PMID: 12599936.
3. **Deitcher SR.** Cancer-related deep venous thrombosis: clinical importance, treatment challenges, and management strategies. *Semin Thromb Hemost.* 2003 Jun;29(3):247-58. Review. PubMed PMID: 12888929.
4. **Sørensen HT, Mellekjaer L, Olsen JH, Baron JA.** Prognosis of cancers associated with venous thromboembolism. *N Engl J Med.* 2000 Dec 21;343(25):1846-50. PubMed PMID: 11117976.
5. **Khorana AA, Francis CW, Culakova E, Fisher RI, Kuderer NM, Lyman GH.** Thromboembolism in hospitalized neutropenic cancer patients. *J Clin Oncol.* 2006 Jan 20;24(3):484-90. PubMed PMID: 16421425.
6. **Elting LS, Escalante CP, Cooksley C, Avritscher EB, Kurtin D, Hamblin L, Khosla SG, Rivera E.** Outcomes and cost of deep venous thrombosis among patients with cancer. *Arch Intern Med.* 2004 Aug 9-23;164(15):1653-61. Erratum in: *Arch Intern Med.* 2008 Jun 9;168(11):1218. PubMed PMID: 15302635.
7. **Kahn SR, Panju A, Geerts W, Pineo GF, Desjardins L, Turpie AG, Glezer S, Thabane L, Sebaldt RJ;** CURVE study investigators. Multicenter evaluation of the use of venous thromboembolism prophylaxis in acutely ill medical patients in Canada. *Thromb Res.* 2007;119(2):145-55. Epub 2006 Mar 3. PubMed PMID: 16516275.
8. **Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd.** Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med.* 2000 Mar 27;160(6):809-15. PubMed PMID: 10737280.
9. **Cavo M, Zamagni E, Cellini C, Tosi P, Cangini D, Cini M, Valdrè L, Palareti G, Masini L, Tura S, Baccarani M.** Deep-vein thrombosis in patients with multiple myeloma receiving first-line thalidomide-dexamethasone therapy. *Blood.* 2002 Sep 15;100(6):2272-3. PubMed PMID: 12229885.
10. **Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, Olson RE.** Incidence of venous thromboembolism in patients hospitalized with cancer. *Am J Med.* 2006 Jan;119(1):60-8. PubMed PMID: 16431186.
11. **Khorana AA, Francis CW, Culakova E, Lyman GH.** Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. *Cancer.* 2005 Dec 15;104(12):2822-9. PubMed PMID: 16284987.
12. **Kröger K, Weiland D, Ose C, Neumann N, Weiss S, Hirsch C, Urbanski K, Seeber S, Scheulen ME.** Risk factors for venous thromboembolic events in cancer patients. *Ann Oncol.* 2006 Feb;17(2):297-303. Epub 2005 Nov 9. PubMed PMID: 16282243.
13. **Agnelli G, Bolis G, Capussotti L, Scarpa RM, Tonelli F, Bonizzoni E, Moia M, Parazzini F, Rossi R, Sonaglia F, Valarani B, Bianchini C, Gussoni G.** A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. *Ann Surg.* 2006 Jan;243(1):89-95. PubMed PMID: 16371741; PubMed Central PMCID: PMC1449979.
14. **Clagett GP, Reisch JS.** Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. *Ann Surg.* 1988 Aug;208(2):227-40. Review. PubMed PMID: 2456748; PubMed Central PMCID: PMC1493611.
15. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. ENOXACAN Study Group. *Br J Surg.* 1997 Aug;84(8):1099-103. PubMed PMID: 9278651.

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16. **Wille-Jørgensen P, Rasmussen MS, Andersen BR, Borly L.** Heparins and mechanical methods for thromboprophylaxis in colorectal surgery. *Cochrane Database Syst Rev.* 2003;(4):CD001217. Review. PubMed PMID: 14583929.
17. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, Dietrich-Neto F; ENOXACAN II Investigators. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med.* 2002 Mar 28;346(13):975-80. PubMed PMID: 11919306.
18. **Rasmussen MS, Jørgensen LN, Wille-Jørgensen P, Nielsen JD, Horn A, Mohn AC, Sømmod L, Olsen B;** FAME Investigators. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. *J Thromb Haemost.* 2006 Nov;4(11):2384-90. Epub 2006 Aug 1. PubMed PMID: 16881934.
19. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Nguyen H, Olsson CG, Turpie AG, **Weisslinger N.** A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med.* 1999 Sep 9;341(11):793-800. PubMed PMID: 10477777.
20. **Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ;** PREVENT Medical Thromboprophylaxis Study Group. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation.* 2004 Aug 17;110(7):874-9. Epub 2004 Aug 2. PubMed PMID: 15289368.
21. **Alikhan R, Cohen AT.** WITHDRAWN: Heparin for the prevention of venous thromboembolism in general medical patients (excluding stroke and myocardial infarction). *Cochrane Database Syst Rev.* 2010 Feb 17;(2):CD003747. doi: 10.1002/14651858.CD003747.pub3. Review. PubMed PMID: 20166070.
22. **Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, De Bon E, Tormene D, Pagnan A, Prandoni P.** A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost.* 2010 Nov;8(11):2450-7. doi: 10.1111/j.1538-7836.2010.04044.x. PubMed PMID: 20738765.
23. **Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, Cook DJ, Balekian AA, Klein RC, Le H, Schulman S, Murad MH;** American College of Chest Physicians. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012 Feb;141(2 Suppl):e195S-226S. doi:10.1378/chest.11-2296. PubMed PMID: 22315261; PubMed Central PMCID: PMC3278052.
24. **Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanga A, Samosh M, Bramwell V, Pritchard KI, Stewart D, et al.** Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. *Lancet.* 1994 Apr 9;343(8902):886-9. PubMed PMID: 7908358.
25. **Haas SK:** Prevention of venous thromboembolism with low molecular weight heparin in patients with metastatic breast and lung cancer: Results of TOPIC Studies. *J Thromb Haemost* 3, 2005 (suppl 1;abstr OR059).
26. **Agnelli G, Gussoni G, Bianchini C, Verso M, Mandalà M, Cavanna L, Barni S, Labianca R, Buzzi F, Scambia G, Passalacqua R, Ricci S, Gasparini G, Lorusso V, Bonizzoni E, Tonato M;** PROTECHT Investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol.* 2009 Oct;10(10):943-9. doi:10.1016/S1470-2045(09)70232-3. Epub 2009 Aug 31. PubMed PMID: 19726226.
27. **Reiss H, Pelzer U, Deutschnoff G, et al:** A prospective, randomized trial of chemotherapy with or without the low molecular weight heparin enoxaparin in patients with advanced pancreatic cancer (APC): results of the CONKO-004 trial. *J Clin Oncol* 2009 ASCO Annual meeting Proceedings 200927 (June 20 Suppl):LBA4506.
28. **Maraveyas MH, Lofts F, Garadi KK, et al.** Chemoanticoagulation versus chemotherapy in advanced pancreatic cancer: Results of the interim analysis of the FRAGEM trial. *J Clin Oncol* 2007 ASCO Annual Meeting Proceedings 2007;25(18S)(June 20 Suppl):4583.
29. **Maraveyas MH, Roy R, Propper D, et al.** Gemcitabine with or without prophylactic weight adjusted dalteparin in patients with advanced or metastatic pancreatic cancer: a multicentre, randomized phase IIB trial (the UK FRAGEM study). Poster presented at: National Cancer Research Institute Conference. 5<sup>th</sup> NCRI Cancer Conference; 2009 October 4-7; Birmingham, UK: LB112.
30. **Agnelli G, George DJ, Kakkar AK, Fisher W, Lassen MR, Mismetti P, Mouret P, Chaudhari U, Lawson F, Turpie AG;** SAVE-ONCO Investigators. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med.* 2012 Feb 16;366(7):601-9. doi: 10.1056/NEJMoa1108898. PubMed PMID: 22335737.
31. **Akl EA, Labedi N, Barba M, Terrenato I, Sperati F, Muti P, Schünemann H.** Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. *Cochrane Database Syst Rev.* 2011 Jun 15;(6):CD006650. doi:10.1002/14651858.CD006650.pub3. Review. PubMed PMID: 21678361.
32. **Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR;** Eastern Cooperative Oncology Group. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2006 Jan 20;24(3):431-6. Epub 2005 Dec 19. PubMed PMID: 16365178.
33. **Rajkumar SV, Hayman SR, Lacy MQ, Dispenzieri A, Geyer SM, Kabat B, Zeldenrust SR, Kumar S, Greipp PR, Fonseca R, Lust JA, Russell SJ, Kyle RA, Witzig TE, Gertz MA.** Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood.* 2005 Dec 15;106(13):4050-3. Epub 2005 Aug 23. PubMed

#

#

- PMID: 16118317; PubMed Central PMCID: PMC1895238.
34. **Palumbo A, Rus C, Zeldis JB, Rodeghiero F, Boccadoro M;** Italian Multiple Myeloma Network, Gimema. Enoxaparin or aspirin for the prevention of recurrent thromboembolism in newly diagnosed myeloma patients treated with melphalan and prednisone plus thalidomide or lenalidomide. *J Thromb Haemost.* 2006 Aug;4(8):1842-5. PubMed PMID: 16879233.
  35. **Tagalakis V, Wharin C, Kahn SR.** Comprehensive update on the prevention and treatment of venous thromboembolism in cancer patients. *Semin Thromb Hemost.* 2013 Mar;39(2):127-40. doi: 10.1055/s-0032-1333537. Epub 2013 Feb 5. PubMed PMID: 23386467.
  36. **Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW.** Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood.* 2008 May 15;111(10):4902-7. doi: 10.1182/blood-2007-10-116327. Epub 2008 Jan 23. PubMed PMID: 18216292; PubMed Central PMCID: PMC2384124.
  37. **Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, Quehenberger P, Zielinski C, Pabinger I.** Prediction of venous thromboembolism in cancer patients. *Blood.* 2010 Dec 9;116(24):5377-82. doi: 10.1182/blood-2010-02-270116. Epub 2010 Sep 9. PubMed PMID: 20829374.
  38. **Mandala M, Clerici M, Corradino I, Vitalini C, Colombini S, Torri V, De Pascale A, Marsoni S.** Incidence, risk factors and clinical implications of venous thromboembolism in cancer patients treated within the context of phase I studies: the 'SENDO experience'. *Ann Oncol.* 2012 Jun;23(6):1416-21. doi:10.1093/annonc/mdr524. Epub 2011 Nov 2. PubMed PMID: 22052988.

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