

Quality of Life in Patients With Cancer Under Prolonged Anticoagulation for High-Risk Deep Vein Thrombosis: a Long-Term Follow-Up

Clinical and Applied
Thrombosis/Hemostasis
Volume 26: 1-5
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DOI: 10.1177/1076029620918290
journals.sagepub.com/home/cat



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Abstract

Current guidelines recommend to prolong anticoagulant treatment in patients with cancer with venous thromboembolism (VTE); only few studies evaluated other parameters than cancer itself for selecting patients at higher risk of recurrent VTE. Long-term management of VTE is thus challenged by several controversies mainly for patients compliance. We here report results of a long-term follow-up in patients with deep vein thrombosis under anticoagulant treatment with low-molecular-weight heparin (LMWH) for residual vein thrombosis (RVT) detected at compression ultrasonography (CUS), 6 months after standard anticoagulant treatment. Patients with RVT were deemed at high risk of recurrences and included in the current observational study. They continued LMWH (reduced at 75% standard dose) for further additional 2 years after enrolment or until death. Patients were followed up every 3 months or earlier, if needed. Among ancillary study end points, there was the assessment of patients' quality of life during daily treatment with subcutaneous injections. Quality of life was determined by the EORTC-C30 questionnaire, administered by a skilled psychologist at enrolment and every 6 months follow-up visits. Overall, 128 patients were evaluated during follow-up. Mean global EORTC-C30 score at enrollment and at 6, 12 and 24 months follow-up were 52.1, 51.4, 50.8 and 50.1, respectively. There were no statistically significant differences between scores at enrolment and at the last available follow-up ($P = .1$). Long-term treatment with LMWH resulted, effective and safe, it was globally well tolerated and exempt of negative impact on quality of life of the enrolled patients. Reported results support long-term anticoagulant treatment with LMWH in cancer patients at risk of recurrent VTE.

Keywords

residual vein thrombosis, low-molecular-weight heparin, cancer, recurrences, bleeding

Date received: 17 November 2019; revised: 26 February 2020; accepted: 19 March 2020.

Introduction

The optimal duration of anticoagulation after cancer-associated venous thromboembolism (VTE) is still debated even if current guidelines suggest prolonging treatment until cancer is active.¹⁻³ However, treatment decisions are challenged by risk of adverse events, patient compliance, and costs. American Society of Clinical Oncology (ASCO) guidelines suggest continuation of anticoagulant treatment only for selected patient categories, such as those with metastatic cancer or under active treatment.⁴ Moreover, only few studies evaluated other parameters than cancer itself for selecting patients at higher risk of recurrent VTE. Even regarding the bleeding risk, in comparison to the general population, patients with cancer treated for VTE have an incidence of major bleeding up to 18%, not always related to over

anticoagulation.^{5,6} Finally, thrombotic burden varies in patients with cancer since it may be related to type and extension of neoplasm or other variables. Therefore, owing to the lack of

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properly designed studies in this patient population, the treatment of cancer-associated VTE beyond the initial 6 months after diagnosis is still debated. The optimal choice of anticoagulant treatment in patients with cancer after a first episode of VTE is still debated. Although available recent studies have shown the efficacy and safety of direct oral anticoagulants (DOACs) in the context of cancer,⁷⁻¹⁰ low-molecular-weight heparin (LMWH) still remains the most suitable therapy for high-risk patients (ie, participants with platelets count below $10 \times 10^6/L$, renal impairment or under treatments known to interfere with DOACs metabolism).¹¹⁻¹³ We have recently demonstrated, in a randomized trial, that detection of residual vein thrombosis (RVT) after 6 months of treatment identifies patients with cancer requiring extension of anticoagulant treatment.¹⁴ According to results from the Cancer-DACUS, patients with RVT need prolonged anticoagulation while those without RVT can safely stop anticoagulants.¹⁴ An additional critical issue is that, although the indication for a prolonged anticoagulation, no data are available about the safety (and efficacy) on such approach in patients with cancer treated with anticoagulants for longer than 12 months. Quality of life (QoL) in long-term therapy with daily subcutaneous injections needs furthermore to be accurately evaluated and possibly preserved.¹⁵ In conclusion, at the present, data evaluating safety and QoL in prolonged anticoagulation with LMWH in high-risk patients with cancer with VTE are lacking. We here report results of an observational study of patients treated with LMWH up to 2 and half years from the first episode of proximal symptomatic deep vein thrombosis (DVT) of the lower limbs.

Methods

Patients Population

Patients with cancer at high risk for recurrent DVT treated with long-term anticoagulation. High-risk patients were defined according to the presence of RVT, detected after 6 months of LMWH administered for a first episode of DVT. Symptomatic proximal DVT was detected by compression ultrasonography (CUS); and active cancer was defined as metastatic or locally advanced lung, gastrointestinal (GI; stomach, colon, or rectum), pancreatic, breast, ovarian, or head and neck cancer or blood cancer diagnosed and objectively confirmed at the time of DVT diagnosis or up to 6 months before DVT. Symptomatic proximal DVT was treated with LMWH for 6 months after the index event.

Study Design

Patients, with a first episode of cancer-related DVT of the lower limbs, were evaluated after 6 months of LMWH, administered at therapeutic dosage (nadroparine, approximately 100 UI anti-FXa bid) for the first month, then reduced at 75% for the following 5 months. At this time, RVT was assessed by CUS as previously described.¹⁶ Patients with RVT were deemed at high risk of recurrences and included in the current observational study. They continued LMWH (reduced

at 75% standard dose) for further additional 2 years after enrollment or until death. Patients with RVT were treated with LMWH up to 2 and half years from the first episode of proximal symptomatic DVT of the lower limbs. Patients without RVT were deemed at low risk for recurrences and stopped LMWH (population not evaluated in the current study).

Such RVT-based approach is currently part of our standard of care in treating patients with cancer with DVT of the lower limbs. At our institution, graduated compression stockings are also recommended after diagnosis of DVT; however, the current study has not evaluated compliance to this indication and information on this has not been included in the current analysis. Patients with upper extremity or distal DVT were not included in the current study.

Additional inclusion criteria were age ≥ 18 years; active cancer defined as metastatic or locally advanced lung, GI (stomach, colon, or rectum), pancreatic, breast, ovarian, or head and neck cancer or blood cancer. Exclusion criteria were Eastern Cooperative Oncology Group performance status more than 2; previous VTE; conditions that required prolonged anticoagulation other than RVT, such as antiphospholipid syndrome; active bleeding or bleeding requiring hospitalization, transfusion, or surgery; intracranial bleeding over the past 6 months; high risk of bleeding (international normalized ratio or activated partial thromboplastin time ratio = 1.3 or a platelet count $\leq 50 \times 10^9/L$); active gastric or duodenal ulcer; severe and uncontrolled hypertension; creatinine clearance less than 30 mL/min; severe liver insufficiency; and unavailability for follow-up. Patients underwent clinical follow-up visits every 3 months.

Definition of Outcomes

Primary outcomes were (1) to determine the incidence rates of recurrent DVT and major hemorrhage during prolonged anticoagulant treatment and (2) to evaluate the QoL.

In cases of suspicion of DVT recurrence, CUS was performed by an independent investigator, blinded to the baseline CUS, and test results were compared with baseline. Diagnosis of recurrent DVT was made if a previously fully compressible segment became no longer compressible or if an increase of more than 4 mm in the diameter of the residual thrombus during compression was detected.¹⁶ In undetermined cases, repetition of the test (after 5-7 days) or contrast venography was performed. In patients symptomatic for pulmonary embolism (PE), diagnosis was based on objective algorithms with the use of clinical probability, ventilation-perfusion lung scanning, or helical computed tomography.¹⁴ Pulmonary embolism as a cause of death was excluded for the absence of clinical symptoms or normal imaging results.

Major bleeding was defined according to the International Society of Thrombosis and Hemostasis criteria.¹⁷ A QoL questionnaire (EORTC-C30)¹⁸ was administered to each patient at enrollment and during follow-up visits.

Cancer remission, progression, or relapse were diagnosed on clinical, instrumental, and histological evaluation. The study

Table 1. Cancer Site in Patients With RVT.

Cancer (%)	Patients With RVT (n = 230)
Lung	36 (15.6)
Other GI	15 (6.5)
Colon	47 (20.4)
Rectum	8 (3.4)
Breast	40 (17.3)
Genitourinary	10 (4.3)
Head and neck	5 (2.1)
Blood	69 (30)
HL	7 (3)
NHL	20 (8.6)
CLL	17 (7.3)
MM	25 (10.8)

Abbreviations: CLL, chronic lymphocytic leukemia; GI, gastrointestinal (gastric, pancreatic); HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; RVT, residual vein thrombosis.

Table 2. Characteristics of Patients at RVT Assessment.

Patient characteristics	RVT (n = 230)
Mean age (years; SD)	61.1 (14.2)
Sex (male), n (%)	125 (54.3)
Mean body mass index (kg/m ² ; SD)	23.8 (2.8)
Recent cancer surgery, n (%)	52 (22.6)
Chemotherapy, n (%)	128 (55.6)
Radiotherapy, n (%)	55 (23.9)
Hormone therapy, n (%) ^a	30 (13)
Central venous catheter, n (%)	48 (20.8)
Metastasis, n (%)	77 (33.4)
Site of DVT	
DVT at one site (popliteal or common femoral), n (%)	137 (59.5)
DVT at 2 sites (popliteal and common femoral), n (%)	93 (40.4)
Left side, n (%)	127 (55.2)

Abbreviations: DVT, deep vein thrombosis; RVT, residual vein thrombosis; SD, standard deviation.

^aHormone therapy for breast cancer: tamoxifen (n = 10), raloxifen (n = 3).

was carried out in accordance with the provisions of the Declaration of Helsinki and local regulations. The local institutional review board (Policlinico “P. Giaccone”, approval no: 112010) approved the protocol, and written informed consent was obtained from all patients. Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all the items. Frequency analysis was performed with χ^2 test and Fisher exact test, as needed. Data were analyzed using SPSS version 20 (SPSS Inc, Chicago, Illinois).

Results

Between January 2011 and December 2013, we evaluated 380 consecutive patients with cancer and a first episode of DVT. After 6 months of standard anticoagulation (prestudy period), 106 patients died for cancer progression; the remaining 274 patients were alive and underwent CUS.

Among them, 230 patients had RVT; they were deemed at high risk for recurrences and included in the current analysis (Tables 1 and 2). Forty-four patients without RVT stopped treatment (data not reported). Enrolled patients received specific recommended treatments for the underlying cancer. Median follow-up lasted¹⁹ months (range: 12-27).

During the follow-up, recurrent DVT was clinically suspected in 43 patients but it was instrumentally confirmed in 31 cases (13.4%): 27 DVT (20 ipsilateral, 7 contralateral site), 4 PE. In 1 case of DVT, diagnosis was undetermined and it needed 2 consecutive CUS (one week after) to be confirmed.

After VTE recurrences, LMWH was continued but adjunctive anticoagulant treatments were not administered for the following reasons: low platelet count (platelet count ≥ 50 but $\leq 100 \times 10^9/L$; n = 2), contemporary active cancer treatments (n = 18), patient compliance (n = 7), and cachexia (n = 4).

Three major bleeding events (2 gastrointestinal and 1 intracerebral bleeding) occurred at 12, 15, and 18 months follow-up, respectively. Patients with major bleeding discontinued treatment.

At 24-month follow-up, 84 (36.5%) patients with RVT died as a result of cancer progression. Low-molecular-weight heparin was discontinued after 2 years in 18 (7.8%) patients with RVT for cured cancer. Quality of life was evaluated at each-follow-up visit among 128 patients with RVT under treatment.

Mean global scores for QoL questionnaires (EORTC-C30) at enrollment and 24-year follow-up were 52.1 and 50.1, respectively (Table 3). No significant differences between scores for QoL questionnaires in patients at RVT assessment and 24-month follow-up ($P = .1$) were recorded.

Discussion

Anticoagulant treatment of VTE, though effective in patients with cancer, is jeopardized by a higher morbidity related to bleeding and recurrent thrombosis.^{1,20} The choice to prolong anticoagulation is patient based and additional factors such as QoL, costs, patient preferences, and life expectancy must be taken into account beyond potential benefits. To the best of our knowledge, this is the first report to describe outcomes of an anticoagulant treatment with LMWH for DVT in cancer lasting more than 18 months. Results from Registry of Patients With Venous Thromboembolism (RIETE) defined as “long-term” the acute treatment of VTE²¹ after the first 7 days from diagnosis, while the study from Prandoni et al⁵ reported a 12-month follow-up in patients with cancer treated with warfarin and the Dalteparin sodium for the long-term management of venous thromboembolism in cancer patients (DALTECAN) study evaluated treatment with dalteparin for 12 months.²² During prolonged anticoagulant treatment, the rate of a major hemorrhage has been reported to be higher than that of a recurrent VTE,²³ thus in the evaluation of treatment duration, the expected clinical impact of major bleeding should be at least comparable to that of recurrent VTE. A recent retrospective chart review study has confirmed the adequacy of standard

Table 3. EORTC-30 Global Scores During Follow-Up.

Follow-Up	T1	T2	T3	T4
EORTC-C30, mean (range)	52.1 (48-54)	51.4 (47-55)	50.8 (45-54)	50.1 ± 4.4 (44-53)

Abbreviations: T1, 6 months follow-up; T2, 12 months follow-up; T3, 18 months follow-up; T4, 24 months follow-up.

anticoagulant treatment (not only with LMWH) for VTE in patients with a cured cancer and showed an increased risk of DVT recurrence in cases of cancer relapse.²⁴ In the management of cancer-related DVT, adherence to patients informed wishes is crucial, in particular when continuous injections are proposed as the best currently available anticoagulation strategy. Cancer-associated DVT determines a non-negligible psychological burden on patients.²⁵ In the Cancer-DACUS study, we have validated RVT as a feasible approach in the management of patients with cancer-related DVT, we here show the safety of prolonging LMWH therapy while preserving QoL in a subgroup of high-risk patients with cancer with DVT. Treatment decisions are here based on an individualized approach not influenced by cancer status. One of the limits of the current study relays on the reproducibility of RVT detection; however, we have previously shown a small inter and intravariability²⁶ of the test, thus making such approach widely applicable. We have furthermore not evaluated in the current study recurrent DVT in patients with cancer without RVT. In patients with unprovoked DVT, the role of RVT as a predictor of recurrence has been shown stronger when detected early,²⁷ that is, at 3 months after DVT (hazard ratio = 2.17; 95% confidence interval: 1.11-4.25), we however here focused on patients with active cancer. Although the reported follow-up lasted only 24 months, this period is considered as long enough to detect recurrences and it remains the longest reported up to date. It could be argued that RVT persistence may mirror a more aggressive cancer biology, the correlation between molecular cancer characteristics and clinical outcome is however not a goal of the current study, although we cannot exclude such hypothesis. In conclusion, our data try to partly fill the gap in the management of patients with cancer at high risk of DVT recurrences.

Conclusions

The low incidence of recurrent VTE in high-risk patients with cancer under prolonged treatment with LMWH, associated with an acceptable risk of major bleeding and a stable QoL, supports a clinical management based on thrombotic burden and RVT detection.

Authors' Note

M.N. and S.S. designed the research and wrote the preliminary draft of the article. M.F.M. administered questionnaires and interpreted results. S.R. and M.N. enrolled patients and collected data. S.S. managed database and performed the statistical analysis. All authors have critically revised and approved the current version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.N. acted as a consultant for: Novonordisk, Sobi, Bayer, BIOFVIIIx, Amgen. S.S. acted as a consultant for Novonordisk, Sobi, Bayer, BIOFVIIIx, Amgen, Pfizer, CSL-Behring, Novartis.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: M.N. received speaker fee by Kedrion, Octapharma, Baxalta, Bayer, Novonordisk, Pfizer, CSL-Behring.

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References

1. Farge D, Frere C, Connors JM, et al.; International Initiative on Thrombosis and Cancer (ITAC) advisory panel. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2019;20(10):e566-e581.
2. Kearon C, Akl E, Horneles J, et al. Antithrombotic therapy for VTE disease. *Chest* 2016;149(2):315-352.
3. Engman CA, Zachariah LR. Low molecular weight heparins as extended prophylaxis against recurrent thrombosis in cancer patients. *J Natl Compr Canc Netw*. 2008;6(7):637-645.
4. Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2013;31(17):2189-2204.
5. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002;100(10):3484-3488.
6. Santos JT, Nieto JA, Tiberio G, et al. Predicting recurrences or major bleeding in cancer patients with venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost*. 2008;100(3):435-439.
7. Young AM, Marshall A, Thirlwall J., et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol* 2018;36(20):2017-2023.
8. Agnelli G, Becattini C, Bauersachs R., et al. Apixaban versus dalteparin for the treatment of acute venous thromboembolism in patients with cancer: the Caravaggio Study. *Thromb Haemost* 2018;118(9):1668-1678.

9. McBane RD, Wysokinski WE, Rademacher JL, et al. Apixaban, dalteparin, in active cancer associated venous thromboembolism, the ADAM VTE trial. *Blood* 2018;132(suppl 1):421.
10. Kraaijpoel N, Nisio MD, Mulder FL, et al. Clinical impact of bleeding in cancer-associated venous thromboembolism: results from the Hokusai VTE Cancer Study. *Thromb Haemost* 2018; 118(8):1439-1449.
11. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003; 349(2):146-153.
12. Akl EA, Kahale L, Sperati F, et al. Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer. *Cochrane Database Syst Rev*. 2014; (6):CD009447.
13. Lee AY, Kamphuisen PW, Meyer G, et al. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA*. 2015;314(7): 677-686.
14. Napolitano M, Saccullo G, Malato A, et al. Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the Cancer-DACUS Study. *J Clin Oncol*. 2014;32(32):3607-3612.
15. Noble SF, Finlay IG. Is long-term low-molecular-weight heparin acceptable to palliative care patients in the treatment of cancer related venous thromboembolism? a qualitative study. *Palliat Med*. 2005;19(3):197-201.
16. Siragusa S, Malato A, Saccullo G, et al. Residual vein thrombosis for assessing duration of anticoagulation after unprovoked deep vein thrombosis of the lower limbs: the extended DACUS study. *Am J Hematol*. 2011;86(11):914-917.
17. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.
18. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
19. Lee AY. Management of thrombosis in cancer: primary prevention and secondary prophylaxis. *Br J Haematol*. 2005;128(3): 291-302.
20. Napolitano M, Siragusa S. Prolonged anticoagulant treatment in patients with cancer: where do we stand? *Thromb Res*. 2017;158: 152-153.
21. Mahe I, Sterpu R, Bertoletti L, et al. Long-term anticoagulant therapy of patients with venous thromboembolism. What are the practices? *PLoS One*. 2015;10(6):e0128741.
22. Francis CW, Kessler CM, Goldhaber SZ, et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN study. *J Thromb Haemost*. 2015; 13(6):1028-1035.
23. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med*. 2003;139(11): 893-900.
24. Van der Hulle T, den Exter PL, Van den Hoven P, et al. Cohort study on the management of cancer-associated venous thromboembolism aimed at the safety of stopping anticoagulant therapy in patients cured from cancer. *Chest*. 2016;149(5): 1245-1251.
25. Seaman S, Nelson A, Noble S. Cancer-associated thrombosis, low-molecular-weight heparin, and the patient experience: a qualitative study. *Patient Prefer Adherence*. 2014;8:453-461.
26. Siragusa S, Malato A, Anastasio R, et al. Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: the Duration of Anticoagulation based on Compression Ultrasonography (DACUS) study. *Blood*. 2008; 112(3):511-515.
27. Donadini MP, Ageno W, Antonucci E, et al. Prognostic significance of residual venous obstruction in patients with treated unprovoked deep vein thrombosis: a patient-level meta-analysis. *Thromb Haemost*. 2014;111(1):172-179.