Venous thrombosis in cancer patients: Prediction, diagnosis and management
Kleinjan, A.
Anticoagulant treatment of cancer patients with pulmonary embolism in the real world

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Submitted
| ABSTRACT |

Introduction
Since 2004, guidelines provide specific recommendations for patients with cancer and pulmonary embolism (PE), namely long-term treatment with low-molecular-weight heparin (LMWH).

Objectives
We aimed to assess the proportion of cancer patients with PE actually treated with LMWH and the duration of treatment in the real world.

Methods
This was a retrospective cohort study. Patients with PE were selected from national hospital discharge records, after linkage to a large national pharmacy database. Cancer patients with PE were identified and matched to subjects with PE without cancer; for age, sex and year of diagnosis of PE.

Results
Six-hundred cancer patients with PE and 1200 patients with PE without cancer were identified. Long-term LMWH was prescribed in 82 (13.7%) of the cancer patients and in 8 (0.7%) of the cancer free patients (p<0.001). From 1998 to 2008, there was an increase in the use of LMWH in cancer patients, but not in controls (p<0.001 and p=0.76, respectively).

In patients with cancer and PE in 2007/2008, LMWH was prescribed in 42 (32%) cases, compared to 1 (1.7%) of the cancer patients with PE in 1998/1999. Median duration of treatment was 5.8 months (interquartile range 3.1-8.8) in cancer patients, compared to 7.0 months (4.9-11) in patients without cancer (p<0.001).

Conclusions
Although the use of LMWH in patients with cancer and PE is increasing, in 2008, patients are still mostly treated with VKA, and not with LMWH as recommended by guidelines. Cancer patients with PE on average receive shorter treatment than matched patients without cancer.
INTRODUCTION

Almost two centuries ago Bouillaud associated the presence of cancer to the development of venous thromboembolism (VTE) (1). Since then, many studies have confirmed that malignancy increases the risk of VTE, and to a lesser extent also of arterial thrombosis (2-5). The consequences of VTE in cancer patients cannot be underestimated, since it causes morbidity and pulmonary embolism (PE) related mortality (6;7).

While patients with VTE are usually treated with vitamin K antagonists (VKA) for 3 to 12 months, since 2004, international guidelines provide specific recommendations for patients with cancer and VTE, namely long-term treatment with low-molecular-weight heparin (LMWH) (8-10). These recommendations are based primarily on the results of the pivotal Clot study, which showed a 50% reduction in the risk for recurrent VTE in the LMWH group, when compared to the VKA group (11). Other smaller studies and two meta-analyses confirmed these findings (12-15). Next to the superior efficacy, there are other advantages of LMWH use in cancer patients, including the more stable anticoagulant effect and the lack of need for monitoring, when compared to VKA. However, it is unclear whether the bleeding risk is lower with LMWH compared to VKA, as most studies are relatively underpowered to adequately assess this clinically important question. In general, VKA-associated bleeding risk is twofold increased in cancer patients as compared to patients without cancer (16-18).

Although the recommendations regarding LMWH date from 8 years ago, recent studies indicate that the use of LMWH mono-therapy in cancer patients is far from optimal. Using the medical records of four hospitals in the United States, Delate and colleagues showed that the use of LMWH – although increasing over the years – is still as low as 31% for cancer patients diagnosed with VTE in 2008 (19). Recent data from a cohort of 144 cancer patients with PE suggested that the use of LMWH is not much higher in Europe (20).

An important area of uncertainty in the management of PE in cancer patients is the duration of the anticoagulant treatment. Guidelines - based on expert opinion - advice to continue treatment as long as the cancer is active (10;21). However, no study has specifically evaluated the use of anticoagulants in cancer patients beyond 6 months. In the absence of supporting evidence, the choice on the duration and type of anticoagulants is left to the treating physicians who are often posed with the dilemma of a patient in the terminal phase, with a high risk for both bleeding and recurrent VTE.

The aim of this study was to evaluate the type and duration of anticoagulant treatment used in the real world in cancer patients with PE relative to PE patients without cancer.

MATERIALS AND METHODS

Study design and population

Data for this retrospective cohort study were derived from the Pharmo Record Linkage System (Pharmo Institute, Utrecht, The Netherlands; available at www.pharmo.nl). The
registry includes demographic details and complete medical histories of more than 2 million Dutch patients based on data from community pharmacies. These medication histories were linked to hospital admission and discharge records from the Dutch National Medical register (LMR). Drugs were coded according to the Anatomic Therapeutic Chemical (ATC) classification. The hospital admission and discharge codes were coded according to the International Classification of Diseases Ninth Revision Clinical Modification (ICD9 CM). Data on all-cause mortality was retrieved from the Dutch registry for mortality, coordinated by the Central Bureau for Genealogy (www.cbg.nl).

All subjects with a first hospitalization for PE (ICD 415.1) between 1998 and 2008 were identified. In a previous study which used the same patient data set, 10% of all PEs had been randomly verified, by checking whether the diagnosis had been objectively confirmed, which was the case in more than 95% of the events (22). We excluded patients without a prescription for anticoagulants after the PE diagnosis.

Among patients with PE, cancer patients were identified based on at least one hospitalization for cancer in the time period of 2 years prior to the PE and 1 year after the PE. Hospitalization for cancer was retrieved with ICD9 codes: 140-199 (excluding code 176 and 181) and 200-208, including all admissions for solid and hematological cancer and melanoma and excluding all other skin cancers. Data were manually checked for all patients with a diagnosis of cancer outside the defined time range, to see if they received chemotherapeutic agents around the time of PE (2 years before to 1 year after PE). If so, these patients were also considered as cancer patients. Information on chemotherapy agents was available if prescribed via the local pharmacy. This included drugs under the classification ‘hormones and hormone antagonists’ (ATC L02...) and the anti-neoplastic agents (ATC L01...).

For every patient with PE and cancer, two PE patients without cancer were matched for age (± 1 year), sex and year of diagnosis of PE. The last moment of follow-up was defined as either the last date of hospitalization in the database, or two months after the last prescription (for any indication), or the date of death, whichever date came last.

**Study objectives**

The primary objective was to assess the type and duration of outpatient anticoagulant treatment for PE. Anticoagulants were divided into LMWH (enoxaparin, tinzaparin, dalteparin and nadroparin) and VKA (acenocoumarol and phenprocoumon), based on ATC codes B01AA07, B01AA04, B01AB05, B01AB04, B01AB10 and B01AB06. Warfarin is not approved for use in the Netherlands and the new anticoagulants were not approved yet at the time of the study. For LMWH prescriptions, we checked each dose to see whether it was indeed therapeutic, i.e. more than 5500 anti-Xa units per day.

Normally, the duration of a medication prescription is approximately 2-3 months, therefore, conservatively; a patient was considered treated until 2 months after the last prescription. Subsequently, the duration of treatment was calculated by subtracting the
date of PE from this date. The treatment was considered (temporarily) stopped, if the time period between two prescriptions for anticoagulants exceeded 4 months.

The secondary objective of the study was to evaluate the incidence of hospitalizations for bleeding during the entire follow-up. Bleeding was defined with ICD codes 430-432, 578, 362.81, 379.23, 599.7, 786.3, 784.7, 459, 569.3, 929.92, 998.11, 719.1 and 287.9. Unadjusted rates of bleeding were calculated, and then expressed as incidence rate per 1000 patient-years of follow-up. Furthermore, rates were assessed for untreated, LMWH-treated and VKA-treated patient-years.

**Data analysis**

The analyses were performed with PASW statistics version 19 (IBM) statistical software. Groups were described using means and standard deviations for normally distributed continuous type of variables, and medians and interquartile ranges (IQR) for the non-normally distributed data. Differences between groups were tested using the t-test for data with a normal distribution or the Mann-Whitney test for non-normally distributed data. Chi-square tests were applied for comparing dichotomous and nominal data. A p-value of less than 0.05 was considered to be statistically significant.

**RESULTS**

Between January 1998 and August 2008, 6988 patients were diagnosed with PE, of which 947 with cancer at the time of PE. After excluding patients for whom no prescription for anticoagulants was present in the database, 600 cancer patients with PE were eligible for the analyses, 306 women and 294 men (Figure 1 and Table 1). These patients suffered from the following types of cancer: genital/urinary tract cancer (n=114; 19%), gastro-intestinal cancer (n=106; 18%), lung/bronchus cancer (n=106; 18%), breast cancer (n=99; 17%), hematological cancer (n=51; 8.5%), brain cancer (n=21; 3.5%), cancer of the gallbladder/pancreas/liver (n=17; 2.8%) malignant melanoma (n=10; 1.7%), and cancer of the bone and soft tissue (n=6; 1.0%). Lastly, in 11 patients (1.8%) the cancer type was unspecified, or rare (lip, adrenal, conjunctivae), and 59 patients (9.8%) suffered from metastases of a non-specified or unknown primary tumor.

For comparison, 1200 PE patients without cancer, 612 women and 588 men, were enrolled. The median duration between the index PE event and the end of the follow-up was 14 months (IQR 6.1-36) for the cancer patients and 40 months (IQR 19-69) for those without cancer (p<0.001).

**Type of treatment prescribed for the first episode of PE**

Long-term treatment of PE in cancer patients consisted of therapeutic doses of LMWH in 13.7% (82/600) of the cases, whereas this was 0.7% (8/1200) of the non-cancer patients (p<0.001). All other PE patients were treated with VKA. When the year of diagnosis of PE was taken into
Table 1. Characteristics of cancer patients with PE and control subjects with PE and without cancer

<table>
<thead>
<tr>
<th>Year of diagnosis pulmonary embolism (n, %)</th>
<th>Cancer (n=600)</th>
<th>No cancer (n=1200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>27 (4.5%)</td>
<td>49 (4.1%)</td>
</tr>
<tr>
<td>1999</td>
<td>31 (5.2%)</td>
<td>71 (5.9%)</td>
</tr>
<tr>
<td>2000</td>
<td>39 (6.5%)</td>
<td>76 (6.3%)</td>
</tr>
<tr>
<td>2001</td>
<td>39 (6.5%)</td>
<td>76 (6.3%)</td>
</tr>
<tr>
<td>2002</td>
<td>48 (8.0%)</td>
<td>100 (8.3%)</td>
</tr>
<tr>
<td>2003</td>
<td>62 (10%)</td>
<td>118 (9.8%)</td>
</tr>
<tr>
<td>2004</td>
<td>78 (13%)</td>
<td>158 (13%)</td>
</tr>
<tr>
<td>2005</td>
<td>67 (11%)</td>
<td>134 (11%)</td>
</tr>
<tr>
<td>2006</td>
<td>76 (13%)</td>
<td>150 (13%)</td>
</tr>
<tr>
<td>2007</td>
<td>75 (13%)</td>
<td>150 (13%)</td>
</tr>
<tr>
<td>2008</td>
<td>58 (9.7%)</td>
<td>118 (9.8%)</td>
</tr>
</tbody>
</table>

*Age in years; SD standard deviation

account, there was a clear increase in the use of LMWH in cancer patients in the more recent years (Figure 2; p<0.001), but not for the patients without cancer (p=0.76). In 2007/2008, 42/133 (32%) of the patients with cancer and PE were treated with LMWH monotherapy, compared to 1/58 (1.7%) of the cancer patients with PE in 1998/1999. Of all 82 cancer patients with a first prescription of LMWH, 14 (17%) switched to VKA, after a median time of 3.7 months (0.0-6.1),
after which they were treated with VKA for a median of 2.2 months (1.9-2.4). Of the 518 cancer patients treated with VKA, 40 (7.7%) switched to LMWH after a median of 3.9 months (3.1-5.9); subsequently they were treated with LMWH for 3.2 months (2.2-6.0).

**Duration**

The median duration of treatment for PE was 5.8 months (3.1-8.8) in the patients with cancer, compared to 7.0 months (4.9-11) in the patients without cancer (p<0.001). One-hundred and sixteen (19%) cancer patients died after a median time of 4.9 months (IQR: 2.2-12), compared to 81 (7%) patients in the control population after a median time of 26 months (9-40; p<0.001). Of all cancer patients who died, 69 (59%) died while using anticoagulant treatment. When patients who died during anticoagulant treatment were excluded from the analysis, the median duration of treatment did not significantly change (6.1 months for cancer patients vs. 7.0 months for patients without cancer, respectively).

Cancer patients on long-term LMWH were treated for a median duration of 5.1 (3.4-9.7) months, compared to 5.9 months (3.0-8.7) in the cancer patients treated with long-term VKA (p=0.36). The year of PE diagnosis did not affect the treatment duration, neither in the cancer patients, nor in the control patients (p=0.98).

**Bleeding**

Patients with cancer were hospitalized for 29 bleeding episodes during a median follow-up of 14 months (IQR: 6.1-36), i.e. 22 hospitalizations for bleeding per 1000 patient-years of follow-up, compared to 43 bleedings in the control population during a median follow-up of 40 months (IQR: 19-69), i.e. 11 hospitalizations for bleeding per 1000 patient-years of follow-up (Table 2), corresponding with a twofold increased risk of major bleeding in
patients with cancer (OR 1.9, 95% CI 1.2-3.1). Also, these major bleedings occurred after a median of 5.3 months (IQR 1.3-19) in cancer patients, compared to a median of 11 months (4.4-47) in the controls (p=0.026). Of the 29 major bleeding episodes in cancer patients, 18 occurred during treatment with VKA, and subsequently these patients were switched to LMWH in 5 cases (28%), anticoagulants were stopped in 7 patients (39%) and in the remaining 6 patients (33%) VKA treatment was continued. Another six bleeding episodes occurred during LMWH treatment; 2 of these patients were switched to VKA, in 1 patient anticoagulants were stopped and 3 patients continued LMWH therapy. The remaining 5 hospitalizations for bleeding occurred while off anticoagulant treatment.

When excluding those patients who bled during anticoagulant treatment, the treatment duration remained unaffected, i.e. 5.7 months in the cancer patients versus 7.0 months in the controls.

**Table 2. Rates of hospitalizations for bleeding in patients with and without cancer**

<table>
<thead>
<tr>
<th></th>
<th>Cancer</th>
<th>No cancer</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per 1000 patient-years, overall</td>
<td>22</td>
<td>11</td>
<td>0.0049</td>
</tr>
<tr>
<td>Per 1000 untreated-patient years</td>
<td>6.9</td>
<td>4.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Per 1000 VKA treated patient-years</td>
<td>36</td>
<td>18</td>
<td>0.011</td>
</tr>
<tr>
<td>Per 1000 LMWH treated patient-years</td>
<td>68</td>
<td>0</td>
<td>0.018</td>
</tr>
</tbody>
</table>

VKA vitamin K antagonists; LMWH low-molecular-weight heparin

**DISCUSSION**

In this study, we evaluated the real world practice of anticoagulant treatment in a large cohort of cancer patients with PE, and found that the use of LMWH in cancer patients, although increasing significantly during the years 1998 to 2008, was still as low as 32% in 2008. Our findings are consistent with those of Delate and colleagues in a cohort of American patients. They found that in 2008, 31% of the cancer patients, received LMWH (19). Also, our results are in line with a recent cohort of 141 European cancer patients with PE in which 40% received LMWH (20).

The question arises why LMWH is underused in cancer patients despite clear recommendations in guidelines which date from already 9 years ago. Barriers for LMWH long-term use were studied in a small cohort of North American patients which found that in 49% of the cases the problem was represented by the insurance coverage (23). Financial reimbursement is very unlikely to be the reason of LMWH prescription in our cohort as there is universal coverage of LMWH by insurance companies in the Netherlands. Another explanation could be that not all treating physicians are aware of the specific treatment guidelines for cancer patients with VTE, especially as these patients are treated by a large variety of medical specialists. Alternatively, patients might have a preference for oral VKA
instead of subcutaneous LMWH administration, which is not supported by evidence from qualitative studies in patients with terminal cancer, which showed that LMWH is more acceptable for these patients than VKA (24;25). Unfortunately, the impact of long-term LMWH on the quality of life in non-terminal cancer patients has not been investigated.

The present data indicate that, unexpectedly, the duration of anticoagulant treatment in cancer patients is not longer, but on average one month shorter than matched non-cancer patients with PE, which cannot be explained by a higher mortality of cancer patients while still on anticoagulants. Information on the stage of cancer and chemotherapeutic treatment was not available from the dataset, which precluded assessing whether anticoagulant treatment was stopped while patients were still receiving active oncological treatment or still had active cancer (10). Our findings appear, however, in line with those from previous studies reporting a median duration of treatment of 200 days (19), with up to 77% of cancer patients with PE being treated for 6 months or shorter (20). In the latter cohort of hospitalized patients, the reason for stopping in 41% of the patients was death, which is much higher than in our cohort of ambulant patients. In parallel with the relatively low observance of the guidelines with respect to LMWH long-term treatment, physicians might not be aware of the specific advices with regard to the duration of treatment in cancer patients, or possibly, they might feel that the beneficial effects of anticoagulants do not outweigh the bleeding risk after 6 months. Until now, no studies have assessed the benefits of prolonging anticoagulant therapy in cancer patients beyond 6 months.

We confirmed the increased risk for major bleeding in cancer patients compared with age and sex matched patients without cancer, in agreement with earlier reports (16;18). Bleeding rates for cancer patients in our study were higher during LMWH compared to during VKA treatment, although this might be due to confounding by indication with patients with the highest perceived bleeding risk receiving preferably LMWH.

Several aspects of the present study design and results require comment. First, we were only able to include patients with pulmonary embolism in the present analysis, and no patients with deep vein thrombosis. Patients with DVT nowadays are often treated at home, while in the Netherlands most patients with PE before 2009 were treated in the hospital, according to the Dutch guideline on thrombosis treatment (26;27). Delate and colleagues in their study looked into differences between the treatment of patients with cancer and DVT or PE, and did not find any (19). Second, the use of hospital discharge codes may lead to misclassification of patients. However, in a previous study with the same cohort, the validity of the ICD code for PE was confirmed (22). To identify cancer patients, we used the definition of a hospitalization for cancer within a time frame of 2 years prior to and 1 year after the PE. This time window was chosen to reduce the chance of missing or falsely identifying cancer patients. The approach is dependent on a hospitalization for cancer, and therefore, cannot give precise information on the date when the cancer diagnosis was made. In the present study, all patients with ICD codes for malignancy were manually checked to see whether they also received chemotherapy or had a hospitalization
for chemotherapy, and/or whether the description of the hospitalization supported the diagnosis of cancer. Third, some patients with PE were excluded from the analyses as no anticoagulants were started after the PE diagnosis. The reason for this is unclear. The date of death was available; therefore, these patients did not die before anticoagulant treatment could be started. Fourth, we were not able to relate the use of LMWH to the stage of disease. Lastly, the efficacy of anticoagulant treatment in cancer patients could not reliably be established in the present dataset, because of the lack of information about the occurrence of recurrent DVT and recurrent PE as possible cause of death.

In conclusion, although the use of LMWH in patients with cancer and PE is increasing, patients in 2008 are still mostly treated with VKA rather than with LMWH as recommended by major guidelines. Moreover, more than 50% of cancer patients are not treated indefinitely, instead receive anticoagulants for 6 months or shorter.

| REFERENCE LIST |