CLINICAL PRACTICE

Compliance with recommendations of clinical practice in the management of venous thromboembolism in cancer: The CARMEN study

Adhésion aux recommandations de bonne pratique clinique pour le traitement de la maladie thromboembolique veineuse en cas de cancer : l’étude Carmen

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Received 9 January 2014; accepted 28 February 2014
Available online 18 April 2014

KEYWORDS
Neoplasms;

Summary Cancer is associated with venous thromboembolism in 20% of patients. In such patients, thrombosis is difficult to treat, associated with bleeding, recurrence, and death. Specific treatments for venous thromboembolism in cancer are recommended. Guidelines have been implemented in many countries and international guidelines have been recently

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http://dx.doi.org/10.1016/j.jmv.2014.03.001

developed. We evaluated the adhesion to national French guidelines via a survey of cancer patients treated for venous thromboembolism.

**Methods.** — A national cross-sectional observational study evaluated the adhesion to guidelines in hospitalized patients. Good clinical practice was defined as initial 10-day treatment with injectable molecules followed by long-term treatment with low molecular weight heparin for at least 3 months. Demographic data, cancer type, stage, treatment, risk factors and type of thrombosis, were recorded.

**Results.** — Five patients were included in 47 centers. Overall adhesion to guidelines was present in 59% (55–63) of patients (295/500). During initial treatment, adhesion was high (487/496; 98%) but dropped (296/486; 62%) during the long-term maintenance. In patients with renal insufficiency, only a fourth of them received the adequate treatment. A majority of patients had metastatic disease (64%). Cancer sites were gastro-intestinal (25%), gynecologic (23%), pulmonary (21%), hematological (14%), urologic (10%), or other (8%). Lung and hematological malignancies were significantly associated with the highest and lowest rates of adhesion.

**Conclusion.** — Adhesion to national guidelines for treatment of venous thromboembolism in cancer is not optimal. Good compliance is observed during initial treatment, but drops after 10 days, underlying the need for further education to achieve a better implementation on a national level.

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Introduction

Patients with cancer face an increased risk of venous thromboembolism (VTE), up to 7-fold and beyond in some malignancies, as compared to non-cancer patients [1,2]. VTE, defined as pulmonary embolism (PE) and deep vein thrombosis (DVT) including catheter associated thrombosis, affects 15 to 20% of this patient population and represents the second leading cause of death in cancer patients [3–5]. This disease is best treated with low molecular weight heparins (LMWH), during the initial treatment (first 10 days), and also on a long-term period (at least 3 months). Indeed, three randomized clinical trials (Canthaxan, Clot and Lite) have demonstrated the superiority of LMWH during 3 months and in one of 6 months of treatment as compared with VKA in the treatment of cancer-related established VTE [6–8]. These results have been completed and analyzed in a meta-analysis on the subject [9]. Based on these data, clinical practice guidelines (CPG) have been elaborated in many countries using different methodologies. The Italian Association of Medical Oncology (AIOM) in 2006, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) in 2007 and the French "National Cancer Institute" INCA (www.sor-cancer.fr) in 2009 firstly issued specific CPG to treat patients with cancer and VTE including for the first time dedicated CPG on catheter related thrombosis [10–14]. These CPG were produced at the national level within the health cancer plan in order to provide effective tools of reference to improve cancer patient care and to guide clinicians with tools to be regularly updated. General recommendations for prevention and treatment of VTE in cancer and non-cancer populations were also provided via the American College of Chest Physicians (ACCP) and the French Agency for Securité Sanitaire and the product of health (AFSSaPS).

All CPG guidelines recommend the use of initial unfractionated heparin, LMWH or fondaparinux for initial treatment (first 10 days) of established VTE to be followed by at least 3 months up to 6 months of LMWH treatment according to individual evaluation of risk/benefit, tolerability, patients' preference and cancer activity. In France, as in most European countries, these therapies were made available and reimbursed for patients in this indication.

Several difficulties may interfere with a good application of prophylaxis guidelines: fear of bleeding, little knowledge about the clinical benefit for the patient, cost-effectiveness, lack of multidisciplinary approach and organizational barriers.

In view of this issue, we aimed to assess whether in France recommendations for the treatment of symptomatic VTE were correctly applied to cancer patients. We therefore carried out a survey on behalf of the Group Francophone on Thrombosis and Cancer (GFTC). The aim of our study was to evaluate the proportion of patients with VTE and cancer who received a prescription of anticoagulant treatment compliant with the established French CPG.

Material and methods

We performed a cross-sectional non-interventional non-randomized survey in hospitalized patients at the free voluntary participating hospitals. Centers contacted belonged to the Group Francophone on Thrombosis and Cancer (GFTC) including oncologists and vascular physicians. Centers that are members of a cancer national network (CNLCC) were also contacted as well as centers that are members of the vascular medicine network (AMEVAH). Most oncology departments of French university hospitals were contacted. French hospitals were eligible for participation if they provided medical care for cancer and VTE. All cancer patients aged ≥ 18 who had been diagnosed with VTE were to be included in the study. VTE had to be diagnosed during the six previous months in order to comply with the guidelines recommending treating cancer patients with established VTE by LMWH for at least 3 months up to 6 months. Patients were considered to fulfill the recommendations when receiving at least three months of LMWH at therapeutic doses. Patients already participating in a study on an antithrombotic drug or unable to answer the study questionnaire were not eligible for inclusion. Usual clinical practice and patient management in each center remained unmodified. Centers were asked to participate for one or several given days in the survey including all consecutive patients fulfilling the inclusion criteria in order to avoid a biased selection. Centers were asked to include consecutive patients: the number of patients per center was 10.6 (1–48) with a median of 8 and the number of days of inclusion was 4.7 (1–17) with a median of 4. No center interaction was noted. Investigators had to fill out a questionnaire about cancer diagnosis and VTE including: diagnosis, localization, spreading, histological type and treatment of cancer. Characteristics of VTE, date of diagnosis, type, treatment and risk factors were recorded.

Study findings

Compliance with recommendations (CPG+) was defined as applying initial 10-day treatment with unfractionated heparin (UFH) or LMWH or injectable anti-Xa agent followed by long-term LMWH for at least 3 months, avoiding LMWH in patients with severe renal insufficiency (SRI) defined as Cockcroft creatinin clearance inferior to 30 mL/min and heparins in case of thrombocytopenia when inferior to 50,000/mm³. Recommended long-term use of LMWH included daily doses of enoxaparin (150 IU/kg), dalteparin (200 IU/kg for one month then 150 IU/kg) or tinzaparin (175 IU/kg).

Other analyzed variables included:

- demographical data;
- cancer characteristics as defined by cancer site, histological type, cancer extension or staging (TNM classification), time to diagnosis, VTE prevention therapy, anti-cancer therapy;
- VTE type and site;
- pulmonary embolism (PE), deep vein thrombosis (DVT), or superficial vein thrombosis (SVT), risk factors for VTE, preventive anticoagulant therapy, time to diagnosis of VTE;
- platelets level, hemoglobin level and serum creatinin at the moment of the study.
Risk factors for VTE included: immobilization, previous VTE, surgery, radiotherapy, chemotherapy, central venous catheter, obesity, thrombophilia, acute infection, varicose veins, recent heart failure and recent respiratory failure.

Sample size and statistical analysis

Assuming a normal distribution of patients and relying on the hypothesis that only 50% of patients will receive a prescription compliant with recommendations, 500 patients were needed to conclude with ± 4% precision and 5% risk error. The descriptive analysis was based on all collected variables expressed as a number and frequency for qualitative variables and a mean and standard deviation for continuous variables (or median and interquartile range according to data distribution). The main study outcome (rate of prescriptions compliant with recommendations) was presented with the corresponding 95% confidence interval.

The Chi square test for qualitative variables was used when validity conditions were respected (otherwise the Fischer exact test was used) and the Student test was used for continuous variables.

A univariate analysis was also performed to investigate the relationship between the type of VTE and each explicative variable (Chi square test for qualitative variables and ANOVA for continuous variables).

The Stata 11.0 software (Stata Corp, College Station, Texas, USA) was used for the overall analysis.

Role of the funding source

The study protocol was written by an independent scientific committee. Data collection and statistical analyses were carried out at the Clinical Investigational Center (CIC) of Grenoble, France.

The study was declared at clinicaltrials.gov: NCT 01362933.

Results

From October 2010 to May 2011, 500 cancer patients from 47 centers were included in the study. A median of 8 (1–48) cancer patients per center was included by investigators during an average period of 4 (1–17) days. A total of 26 centers participated for less than 5 days and included 187 patients while 21 centers participated for 5 days or more and included 313 patients. On average, 10.6 patients per center were included in the study. All patients were hospitalized. Patient characteristics are summarized in Table 1. Patients had a mean age of 63.6 ± 13.7 years with the same proportion of males and females.

Anti-cancer therapies included surgery 60/500 (12%), chemotherapy 278/500 (56%), radiotherapy 43/500 (9%), hormonotherapy 25/500 (5%), tyrosine-kinase inhibitors 9/500 (2%), anti-angiogenic drugs 21/500 (4%), thalidomide or lenalidomide 10/500 (2%), erythropoietin (EPO) or granulocyte-colony stimulating factor (G-CSF) 55/500 (11%) and biotherapies 32/500 (7%). Therapies were prescribed alone or in combination: half of the patients received at least two types of anti-cancer therapies, whereas one third had no treatment at the time of the study.

Main VTE risk factors are presented in Table 1. The most common VTE risk factors were distributed as follows: 284/456 (62%) of patients had a central venous catheter, 113/500 (23%) were immobilized or confined to bed, 83/500 (17%) had surgery in the last 3 months and 64/500 (13%) had a history of previous VTE. Analysis of cases showed that in 64% of VTE cases occurred in patients with a metastatic disease (Table 2).

Compliance with guidelines

Out of the 500 cancer patients included in the study, 295 received a treatment of VTE compliant with guidelines

Table 1 Patients characteristics and VTE risk factors.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>VTE risk factors [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>63.6 ± 13.7</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>242 (49)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>255 (51)</td>
</tr>
<tr>
<td>Body mass index (kg/m² ± SD)</td>
<td>24.7 ± 4.9</td>
</tr>
</tbody>
</table>

Table 1: Patients characteristics and VTE risk factors.

Conformité aux recommandations en fonction du type de cancer.
Table 2 Overall compliance with recommendations (n [%]).
Conformité globale aux recommandations.

<table>
<thead>
<tr>
<th>Treatment period</th>
<th>Treatment</th>
<th>CPG+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial 10 days (n = 496)</td>
<td>UFH, LMWH or anti-Xa</td>
<td>487 (98)</td>
</tr>
<tr>
<td>Mid and long-term Non-SRI patients (n = 474)</td>
<td>LMWH ≥ 3 months</td>
<td>293 (62)</td>
</tr>
<tr>
<td></td>
<td>LMWH for 3 to 6 months</td>
<td>173 (37)</td>
</tr>
<tr>
<td></td>
<td>LMWH ≥ 6 months</td>
<td>120 (25)</td>
</tr>
<tr>
<td>SRI patients (n = 12)</td>
<td>VKA ≥ 3 months</td>
<td>3 (25)</td>
</tr>
<tr>
<td></td>
<td>VKA for 3 to 6 months</td>
<td>2 (17)</td>
</tr>
<tr>
<td></td>
<td>VKA &gt; 6 months</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

* CPG+: compliance with recommendations.

Table 3 Compliance according to cancer description, anti-cancer therapy and VTE site.
Conformité en fonction du type de cancer, de son traitement et de la localisation de la thrombose.

<table>
<thead>
<tr>
<th>Cancer description</th>
<th>n (%)</th>
<th>CPG+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tumor site (n = 500)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>106 (21)</td>
<td>67.9</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>92 (18)</td>
<td>56.5</td>
</tr>
<tr>
<td>Hematological</td>
<td>67 (13)</td>
<td>37.3</td>
</tr>
<tr>
<td>Breast</td>
<td>63 (13)</td>
<td>57.1</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>52 (10)</td>
<td>65.4</td>
</tr>
<tr>
<td>Urologic</td>
<td>48 (10)</td>
<td>64.6</td>
</tr>
<tr>
<td>Pancreas</td>
<td>32 (6)</td>
<td>50.0</td>
</tr>
<tr>
<td>Others</td>
<td>40 (8)</td>
<td>72.5</td>
</tr>
<tr>
<td><strong>Cancer stage at time of onset of VTE (n = 451)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local (T +)</td>
<td>81 (18)</td>
<td>63</td>
</tr>
<tr>
<td>Loco-regional (N +)</td>
<td>83 (18)</td>
<td>59.0</td>
</tr>
<tr>
<td>Metastatic (M +)</td>
<td>287 (64)</td>
<td>61.3</td>
</tr>
<tr>
<td><strong>Anti-cancer therapy at time of onset of VTE (n = 500)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>278 (56)</td>
<td>58.6</td>
</tr>
<tr>
<td>Surgery</td>
<td>60 (12)</td>
<td>61.7</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>43 (9)</td>
<td>67.4</td>
</tr>
<tr>
<td>EPO &amp; G-CSF*</td>
<td>55 (11)</td>
<td>60.0</td>
</tr>
<tr>
<td>Hormonotherapy</td>
<td>25 (5)</td>
<td>52.0</td>
</tr>
<tr>
<td>Other*</td>
<td>40 (8)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>VTE site (n = 498)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>149 (30)</td>
<td>59.7</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>315 (63)</td>
<td>61.2</td>
</tr>
<tr>
<td>Upper limb and catheter related</td>
<td>131 (26)</td>
<td>61.0</td>
</tr>
<tr>
<td>Lower limb</td>
<td>184 (37)</td>
<td>61.4</td>
</tr>
<tr>
<td>Superficial thrombosis</td>
<td>16 (3)</td>
<td>25</td>
</tr>
<tr>
<td>Other</td>
<td>18 (4)</td>
<td>NA</td>
</tr>
</tbody>
</table>

* EPO: erythropoietin, G-CSF: granulocyte-colony stimulating factor.
* Other includes anti-angiogenics, thalidomide, lenalidomide, tyrosin-kinase inhibitors and biotherapy.

(Fig. 1), showing an overall compliance rate of 59% (95% CI 55%–63%). Prescriptions during the initial 10-day treatment period were associated with a high compliance rate of 98%, whereas early 10-day to 3-month and long-term (> 3 months to 6 months) prescriptions were compliant with guidelines in 293 (62%) patients without SRI. Out of the 12 patients with SRI, only 3 (25%) had received an adequate prescription of VKA (Table 3).

The distribution of treatments outside recommendations is presented in Table 2. Other included few patients treated with injectable anti-X (0.09%), unfractionned heparin and therapeutic abstention.

Cancer type and status and CPG+ adherence

CPG+ did not vary according to the primary tumor location (Table 3) except in hematological malignancies (37.3%) compared to non-hematological cancers (62.4%, *P < 0.01*). The highest rate of VTE was found in patients suffering
from metastatic disease 287/451 (64%). Lung cancer was the most common primary tumor site in the study (106/500, 21%).

VTE type and adherence to guidelines

A comparable distribution between PE (149/498 [30%]), upper limb DVT (131/498 [26%]) and lower limb DVT (106/498 [21%]) was found among the studied cancer patients.

With the exception of superficial VTE, prescription compliance did not differ according to cancer extension, anti-cancer therapy or VTE diagnosis as shown in Table 3.

VTE, cancer spreading and therapy

The relationship between cancer stage and type of VTE is presented in Table 4. VTE description was not specific to any type of cancer. As previously noted, metastatic disease was associated with VTE in general and upper limb thrombosis related to chemotherapy given through indwelling catheters.

Other therapies were not associated with a high rate of VTE in the study (Table 4).

Discussion

The Carmen study provides a description of adhesion to CPG among French hospitals 3 years after the previous release recommendations of the French National Cancer Institute, endorsed by the French drug agency, which had recommended treating VTE in cancer patients with long-term LMWH for at least 3 months [13]. The aim of this study was to assess the respect of these recommendations on a daily routine clinical practice. The overall CPG+ of 59% (key finding) appears clearly insufficient with regard to the cancer-related VTE high risk. However, prescriptions were quite compliant with recommendations for the initial 10-day treatment period with a 98% CPG+ whereas the CPG+ fell down to 62% in the patient population eligible for LMWH therapy. This finding shows that physicians are aware of the importance of treating VTE initially, but do not follow the recommendations for long-term treatment.

Prescriptions were not significantly influenced by the primary tumor site with the notable exception of hematological malignancies associated with a CPG+ of 37.3%, significantly lower compared to CPG+ in non-hematological cancers (62.4%, p < 0.01). This may be attributed to concerns regarding the increased bleeding risk specific to hematological malignancies and related to thrombocytopenia. However, there was no evidence of such relationship in our
The CARMEN study

Observational study. Evidence-based guidelines are available for the prevention of thromboembolic complications in hematological malignancies, such as multiple myeloma patients treated with thalidomide or lenalidomide. In this instance, ASCO guidelines suggest to use either VKA, anti-aggregants or LMWH for VTE prophylaxis [15]. In other types of cancer, VKA is not used in prevention. There might be confusion in the use of VKA to prevent VTE in this population.

CPG+ was higher in patients with lung cancer (67.9%) and lower in patients with pancreatic cancer (50%) even though this malignancy is known to be associated with a particularly high VTE risk [16]. Otherwise, CPG+ was not statistically different across other items such as cancer spreading, anti-cancer therapy or VTE location. A striking finding, although present in the small subgroup of 12 patients with renal insufficiency, was that only 3 of them received long-term VKA whereas 7 patients were treated with LMWH despite the contra-indication of heparins in this patient population.

Similar observations were made from a previous retrospective, longitudinal cohort study in 1089 cancer patients with diagnosed VTE showing that the proportion of cancer patients receiving LMWH as a first-line therapy for the prevention of VTE recurrence had increased from 8% in 2000 to 31% in 2008 even though this remains insufficient [17]. Furthermore, another study in Switzerland has shown that only 39% of cancer patients with VTE were planned for long-term treatment with LMWH [18].

Our results show a poor compliance (25%) in patients with superficial vein thrombosis (SVT). However, numbers were small (n = 16 i.e. 3%) and the scarcity of data for the treatment of SVT make it difficult to draw relevant conclusions since the bleeding risk may offset the modest expected therapeutic benefit. The Carmen study shows that VTE localization does not modify the suggested treatment and the adhesion to CPG; physicians treat a distal calf venous thrombosis and a PE exactly the same way. This observation is of importance as the quality and duration of anticoagulant treatment in distal thrombosis is questioned and is thus the subject of ongoing trials. The Carmen study included a substantial proportion of patients with a clinical history of VTE before entering the study that underlines the importance of VTE recurrence in cancer and the necessity to apply CPG to the patients.

The Carmen study gives information on the application of guidelines in French clinical practice. The insufficient compliance of existing prescriptions with current guidelines despite the demonstrated usefulness of LMWH is an important issue. Whether our observations correspond to a similar or even lower patient compliance to long-term LMWH therapy remains to be addressed. Academic institutions have developed efforts to integrate current guidelines in the clinical practice. The value of international consensus groups followed by educational and active implementation of treatment guidelines has been outlined.

Limitation of CPG+ might be explained by several causes. The limitations due to the physician include:

- lack of information about mortality associated with VTE in cancer patients as the second cause of death;
- a low awareness of the medical importance of VTE in cancer patients defined as the morbidity due to pulmonary embolism and DVT leading to patient’s altered quality of life, serious clinical complications, delay in diagnosis and therapy such as surgery, chemotherapy or radiotherapy;
- little knowledge of the medical benefits for the cancer patient if VTE is treated according to GCP in terms of recurrence and hemorrhages;
- questions about the pertinence of the guidelines;
- the feeling of an increased obligation for the patient to receive daily injections compared to oral treatment not balanced by a clinical benefit;
- the question about cost-effectiveness of this strategy.

The limitations due to the patient depend greatly on the awareness of the physician and his knowledge and confidence in CPG to be able to convince the patient, but there are some limitations specific to the patient that include:

- the fear of receiving daily injections or to be able to perform auto-injections,
- the ignorance about re-imbursement of this strategy including nurse’s interventions for daily injections,
- the ignorance about benefit of CPG+ balanced by the potential morbidity and mortality due to VTE in cancer including death, disability, necessity to delay the treatment of cancer or to take off or replace in-dwelling venous catheters.

There are limitations due to healthcare networks not designed for this population. Inside the hospital, there are also, discrepancies between physicians that are able to work together in programs dedicated to education for clinicians, nurses and patients.

A dialogue between oncologists, thrombosis specialists, surgeons and general practitioners appears to be a key element for efficient implementation.

Recent publication of international clinical practice guidelines for treatment of VTE in cancer patients should help to improve an overall implementation [19,20].

Conclusion

The optimal duration of anticoagulation in cancer patients with VTE remains unknown, but a minimum of at least 3 months of LMWH has been shown to decrease relapse in 50% of cases with no increased risk of bleeding in three major pivotal trials in this setting. The recommended treatment with LMWH is the current preferred option, but different studies have consistently reported a significant underuse of LMWH and insufficient compliance to established guidelines in this patient population. Treatment efficiency is based on two levels of compliance. First, prescription compliance with established guidelines needs drastic improvement and requires enhanced collaboration between oncologists and thrombosis specialists. Second, patient compliance has to be based on motivation and appropriate information. Further observational studies with adequate follow-up are needed to better document these compliance-related issues.

Disclosure of interest

M.-A. Sevestre and F. Cajfinger have received honoraria from Leo Pharma.
The other authors declare that they have no conflicts of interest concerning this article.

Acknowledgement

The authors are indebted to C. Rolland and C. Genty for monitoring the study and statistical analysis.

Funding: This work received a grant from Leo Pharma

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