Treatment of Venous Thromboembolism in Ambulatory Cancer Patients in Germany: A Prospective Non-Interventional Study

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Introduction

Venous thromboembolism (VTE) is a frequent and serious complication of cancer. The overall risk in cancer patients is 4–7-fold higher than in non-cancer patients. 10–20% of cancer patients develop VTE during the course of their disease [1, 2]. This high incidence is a result of the multitude of risk factors in cancer patients, including frequent surgeries, immobility, advanced age, and prothrombotic medications (e.g. hormonal therapies, angiogenesis inhibitors, thalidomide and derivatives). In addition, some tumors can activate coagulation factors and platelets, while activated factors and platelets support growth and spread of the tumor, thereby creating a positive feedback loop [3, 4]. VTE in cancer patients is associated with a poorer prognosis compared to cancer patients without VTE [5–7].

Non-cancer patients with VTE are usually treated with a rapidly acting parenteral anticoagulant (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], or fondaparinux), overlapping with and followed by an oral vitamin K antagonist (VKA). In 2003, the CLOT study showed that treatment of VTE in cancer patients with LMWH decreases the risk of recurrent VTE by almost 50% relative to the standard treatment with VKA [8]. A few smaller studies and meta-analyses subsequently confirmed the superior efficacy of LMWH to VKA in cancer patients [9–12]. Although these studies were all conducted more than 10 years ago, the actual CATCH study still confirms the superiority of LMWH [13, 14]. Accordingly, practice guidelines recommend LMWH over oral anticoagulants in cancer patients with VTE [15–17].

Recently, direct oral anticoagulants (DOACs) have been introduced into clinical practice (apixaban, dabigatran, edoxaban, rivaroxaban, etc.). With regard to DOACs, guidelines still recommend LMWH to VKA in cancer patients [9–12]. Although these studies were all conducted more than 10 years ago, the actual CATCH study still confirms the superiority of LMWH [13, 14]. Accordingly, practice guidelines recommend LMWH over VKA for secondary prophylaxis and long-term therapy in cancer-associated VTE [15–17].

Keywords

Cancer-associated venous thromboembolism · Health services research

Summary

Background: Venous thromboembolism (VTE) is a serious threat for all cancer patients. This study was aimed to assess the VTE treatment of cancer patients in the ambulatory care setting. Patients and Methods: This is a prospective non-interventional study, which includes ambulatory cancer patients from office-based oncologists. A standardized case report form was used to obtain data on patient characteristics, treatment regimens, duration of treatment, and side effects. Results: Specialists from 34 centers included data from 76 patients. The median patient age was 62 years (range 33–81 years). The 4 most common cancer types were breast cancer (32%), colorectal cancer (18%), lymphoma and lung cancer (each 8%). 18% of the acute VTE cases were treated as inpatients, 80% as outpatients, and 99% with low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), or fondaparinux. After the acute phase, secondary prophylaxis with LMWH/UFH/fondaparinux was planned in 61% of the patients, with oral anticoagulation in 39%. During acute-phase treatment and secondary prophylaxis, no patient had recurrent VTE. 4 patients (5%) experienced minor bleedings. Conclusions: This study shows that many ambulatory cancer patients with VTE have early tumors, no metastases, and an excellent performance score. Most patients receive LMWHs for secondary prophylaxis, as recommended by the national and international guidelines. Still, a relevant percentage is switched to oral anticoagulants.
Within the last 20 years there has been a worldwide effort to decrease medical costs, particularly in cancer treatment. This was achieved by shortening the hospital stays and shifting diagnostic procedures and therapeutic interventions from the inpatient to the ambulatory care setting. Today, cancer patients are discharged earlier after surgery. Most cancer chemotherapies are administered in outpatient clinics or prescribed to be taken orally at home. With this shift to outpatient care, VTE has become a major issue in ambulatory oncology [18]. Guidelines recommend heightened vigilance for signs and symptoms of VTE and provide detailed advice on prophylaxis and therapy in the outpatient setting [15–17].

At the same time, several studies indicate that the impact of the VTE guidelines on the clinical practice is limited [19, 20]. This is particularly true for the use of LMWHs in the treatment of cancer-associated VTE. Many patients still continue to receive VKAs, and if LMWHs are given, they are often underdosed or terminated prematurely [21–31]. With the advent of the DOACs, the preference of the guidelines for LMWHs over any of these newer agents will be challenged. Despite the absence of data on the safety and efficacy of DOACs in cancer-associated VTE, it is likely that many patients and their physicians will prefer taking a pill that does not require further blood testing over a VKA or daily subcutaneous (s.c.) injections.

For any future recommendations, it is important to know the answers to the following questions: Who diagnoses cancer-associated VTE and who directs anticoagulant treatment in the outpatient setting? What side effects are seen and how many ambulatory cancer patients with VTE are still alive after 12 months? Have guideline recommendations been implemented in real-world oncology care and, if not, why? The purpose of this study was to assess all these different aspects of VTE treatment in ambulatory cancer patients in Germany.

Patients and Methods

This was a prospective cohort study. Physicians specialized in hematology/oncology in the ambulatory sector of the German health care system were invited to participate. Each physician was asked to include a maximum of 3 consecutive patients with objectively confirmed VTE between February and December 2012. Patients had to be ambulatory, 18 years or older, and had to carry the diagnosis of cancer or of a malignant hematological disorder. Patients had to be included within 1 week after diagnosis of VTE. Patients with a life expectancy of < 6 months and with no secondary prophylaxis planned were excluded.

A questionnaire on the patient and cancer characteristics, anticoagulant treatment regimens, duration of treatment, and adverse events at baseline, after 3 months and after 12 months, had been drafted by the authors. To avoid ambiguities, the questions had been pretested with a number of practice-based oncologists not specialized in VTE treatment.

Descriptive analysis of the data was carried out according to a pre-established analysis plan. The collected data were analyzed with epidemiological methods, using the SPSS for Windows program package (version 15.0), for descriptive analysis. Not all respondents answered each question. In cases where the respondent left a question blank, relative percentages were calculated based on the number of evaluable answers.

The study was approved by the ethics committee of the Saarland Medical Council. From all patients, written informed consent was obtained per the Declaration of Helsinki.

Results

A total of approximately 85 physicians were invited, of whom 34 participated and included 78 patients, of whom 76 were evaluable. The patients’ progress through the phases of this prospective non-interventional trial, i.e. enrolment, follow-up, and data analysis, is shown in figure 1.

By hematologists/oncologists, 66 patients (86.8%) were included, 4 (5.3%) by angiologists/phlebologists, and 6 (7.9%) by other specialties or not specified. 15 practices included 3 patients each, 12 practices 2 patients, and 7 practices 1 patient. The mean patient age was 62 years and 72% had a good performance status
The VTEs were diagnosed by hematologists/oncologists, 33.8% by angiologists/phlebologists, and 14.9% by other specialists (2.6% specialty not stated). None of the specialists used the Wells score. Many patients had a VTE within 3 months after surgery. The next most common risk factor was prior venous thrombosis or pulmonary embolism, while thrombophilia was not reported in any of the patients (table 3). Venous thrombosis was localized to the lower extremity in 69.7% of the cases while 23.7% had upper-extremity thromboses (table 4).

For acute-phase treatment, 98.7% of the patients received therapeutic-dose LMWH, UFH, or fondaparinux and were managed as outpatients by their office-based hematologists/oncologists (table 5). Only 5 patients received a reduced LMWH dose during the acute phase. The stated reasons were risk of bleeding, thrombocytopenia, and surgery. 81% of the patients were planned to receive at least 6 months of anticoagulation treatment. Many practices did not give a definitive answer as to whether they would continue anticoagulation as an injection or switch to an oral agent. Most patients self-injected the anticoagulant while the percentages of patients who depended on relatives or nurses were 10% and 6%, respectively (table 6). After 3 months, 11 patients had terminated the anticoagulant treatment; 5 terminations were pre-planned and 6 were unplanned (4 deaths, 1 on patient’s request, 1 because of nose and urethral bleeding). After 12 months, 29 additional patients had terminated treatment, 16 pre-planned and 13 unplanned (11 deaths, 1 on patient’s request, 1 after central vein catheter removal). During the study, a total of 8 patients were
Side effects reported during anticoagulant treatment

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding (not specified)</td>
<td>4 (5.3%)</td>
</tr>
<tr>
<td>Urethral and nose bleed</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Activated Partial Thromboplastin Time</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Other (surgery for lower-leg fracture, afterwards switch to rivaroxaban)</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>0</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>0</td>
</tr>
</tbody>
</table>

Physicians' response to the question as to which criteria were relevant for their choice of anticoagulant (multiple answers allowed)

| Criteria                                                        | Count (Percentage) |
|                                                               |--------------------|
| Risk of bleeding                                               | 27 (35.5%)         |
| Risk of recurrent VTE                                          | 25 (32.9%)         |
| Heparin-induced thrombocytopenia                               | 9 (11.8%)          |
| Type of cancer                                                 | 23 (30.3%)         |
| Risk with low creatinine clearance                             | 13 (17.1%)         |
| Contraindications                                              | 16 (21.1%)         |
| Economic reasons                                               | 13 (17.1%)         |
| Personal experience                                            | 20 (26.3%)         |
| Risk-benefit ratio                                             | 22 (28.9%)         |
| Other                                                           | 1 (1.3%)           |

Initial treatment of VTE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute treatment</td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>70 (92.1%)</td>
</tr>
<tr>
<td>UFH</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>VKA</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>4 (5.3%)</td>
</tr>
</tbody>
</table>

Patients were initially treated as

- Inpatients: 14 (18.4%)
- Outpatients: 61 (80.3%)
- Not stated: 1 (1.3%)

Who prescribed first dose of anticoagulant?

- Hospital-based physician: 16 (21.9%)
- Hematologist/oncologist practice: 39 (53.4%)
- Angiologist/phlebologist: 16 (21.9%)
- General practitioner: 0
- Other specialty: 2
- Data not provided: 3

Secondary prophylaxis after the initial phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Projected duration</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>13 (18.6%)</td>
</tr>
<tr>
<td>6 months</td>
<td>29 (41.4%)</td>
</tr>
<tr>
<td>Longer</td>
<td>28 (40.0%)</td>
</tr>
<tr>
<td>Not stated</td>
<td>6</td>
</tr>
</tbody>
</table>

Planned type of anticoagulation

- Parenteral only: 17 (60.7%)
- Switch to oral anticoagulant: 11 (39.3%)
- Not stated: 48

Who gives the anticoagulant?

- Patient self-injects: 58 (84.1%)
- Relative: 7 (10.1%)
- Community nurse: 4 (5.8%)
- Not stated: 7

Switched to a VKA and 5 patients to rivaroxaban (fig. 2). The median duration on secondary prophylaxis (all anticoagulants) was 166 days.

Side effects from anticoagulant treatment were mostly minor (table 7). 15 patients (19%) died during this observational study. None of the deaths was related to the anticoagulant treatment. The physicians' primary parameters for their choice of anticoagulant were risk of bleeding and risk of recurrent thrombosis (table 8).
Discussion

This study was designed to compare guideline recommendations and the daily practice of VTE treatment in cancer outpatients in Germany. Guidelines recommend LMWH for initial treatment of cancer-associated VTE, for secondary prophylaxis, and for long-term therapy. These recommendations are based on studies that had been initiated more than 10 years ago [8–11] but the recent CATCH study still supports the superiority of LMWH [13, 14]. For initial treatment, 98.7% of the patients in this study received LMWH, UFH, or fondaparinux. This confirms a high observance of the guidelines. Most patients received standard therapeutic doses. Only 5 patients had a reduced dose. The reasons were higher bleeding risk from thrombocytopenia, elevated creatinine levels, planned surgery, or chemotherapy (not further specified). This underscores the need for specific recommendations on anticoagulant treatment of cancer-associated VTE in patients with low platelet counts or low creatinine clearance.

While serum creatinine was documented in 96% of the patients, creatinine clearance was documented in only 4%. This is surprising because LMWH dosing should be guided by creatinine clearance rather than serum creatinine. Apparently, creatinine clearance is not perceived as a routine parameter for LMWH therapy, like blood counts for chemotherapy.

While initial treatment was in line with the guideline recommendations, the type of anticoagulant chosen for secondary prophylaxis and long-term treatment varied substantially. Even though the guidelines recommend LMWH over VKAs or DOACs, many patients were switched to oral agents within 3 months. The reason could be that VKAs/DOACs avoid the discomfort of injections. After 12 months, as many patients were on VKAs/DOACs as on LMWH. It is still unknown whether DOACs are as safe as LMWH in cancer patients. A study on the safety and efficacy of DOACs in patients who receive chemotherapy (comparable to the patients in CLOT or CATCH) is urgently needed.

In most patients, secondary prophylaxis was intended for 3 or 6 months, which is in accordance with the guideline recommendations. The mean duration of anticoagulant treatment in this study was 167 days (~5.5 months), which is longer than the 3.5–4 months in the CLOT study [8]. It is therefore interesting to look at how many patients stopped prematurely, and why. 19 patients stopped secondary prophylaxis earlier than intended. The most common reason was death (15 patients). None of the deaths was considered due to the anticoagulant therapy. In 2 patients, anticoagulation was stopped at the patient’s request, and in only 1 patient because of side effects (mild bleeding from nose and urethra, see below). The death rate in this study (19%) is only half of that in the CLOT study (40%) and also much lower than in other studies on cancer patients with VTE [5, 6, 32]. It is not realistic to attribute this low death rate only to progress in cancer care over the last 10 years since the most actual CATCH study has survival rates similar to CLOT. It is more likely that cancer patients treated in outpatient practice have a better overall health status and better prognosis.

The risk of bleeding and recurrent thrombosis is highest during the first month of treatment [32, 33]. In this study, no patient had a recurrent thrombosis and only 4 patients reported bleeding. This bleeding rate is much lower than the numbers from previous studies (e.g. CLOT) and more actual ones (CATCH study) and supports the aforementioned assumption: Cancer patients who are treated as outpatients have a generally better status and lower risk for complications.

Another question was: Who diagnoses VTE in cancer patients and who is in charge of secondary prophylaxis and long-term treatment? The survey confirms that most VTE patients received their initial treatment from their oncologists/hematologists in ambulatory practice, but still a considerable percentage was seen initially by angiologists or hospital-based physicians. We do not know whether these hospital-based physicians were also hematologists/oncologists or general internists. Guidelines on VTE treatment in cancer patients have been published in hemostasis and hematology/oncology journals and may escape the educational focus of other specialties. It is the opinion of the authors that, whenever a cancer patient develops VTE, his hematologist/oncologist should assume primary responsibility for the anticoagulant management, initially and in the long term. The oncologist/hematologist knows best about his patient’s cancer, the bleeding risk, and co-operations with the potential to interact with anticoagulation.

The study reveals another interesting aspect of clinical practice: Neither the Wells score nor the Geneva score played a role in the initial assessment of cancer outpatient VTEs. An explanation could be that neither the Wells nor the Geneva score are well known in the hematology/oncology community. Most VTEs were diagnosed after the patient had reported symptoms. This makes it important to regularly ask cancer patients for signs of VTE. With an increasing number of patients taking their oral cancer therapies at home, with the concentration of oncology services in specialized centers, and the need to travel longer distances to these centers, patients might be less likely to see their hematologists/oncologists when they develop symptoms of VTE. Therefore all oncology professionals should provide patient education about the signs of VTE and instruct the patients to immediately call the practice when noticing the first symptoms.

This study is limited by the small number of patients. In addition, the patients were younger and had a better health status than the general cancer patient population. A reason could be that old and multimorbid patients were not included by the physicians or not treated in ambulatory practices. Also the spectrum of cancer and hematologic disorders is not representative. Prostate cancer patients are under- and lymphoma patients are overrepresented. This can be explained by the patient spectrum of ambulatory cancer care in Germany where many prostate cancer patients are seen by urologists and most breast cancer patients are seen by gynecologists. This underscores the need to disseminate knowledge on cancer-associated VTE not only among oncologists but in all specialties.

In conclusion, this study shows that the initial treatment of cancer-associated VTE in ambulatory patients follows the guideline recommendations while secondary prophylaxis and long-term therapy vary substantially. In this study, ambulatory cancer pa-
patients with VTE were younger, had a better general health status and experienced less complications. The hematologist/oncologist should always be in charge of the VTE management in all his/her patients.

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Disclosure Statement
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