Practice Patterns for Prophylaxis and Treatment of Venous Thromboembolism in German Cancer Patients

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Keywords

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Summary

Background: Venous thromboembolism (VTE) is a serious threat for cancer patients. Guidelines recommend low-molecular-weight heparin (LMWH) for prophylaxis and treatment, but it is unknown to what extent specialists adhere to these recommendations. This survey assesses the current approach to patients with cancer-associated VTE in Germany. **Materials and Methods:** A questionnaire was sent out to members of the DGHO (Deutsche Gesellschaft für Hämatologie und Onkologie), the BNHO (Berufsverband Niedergelassener Hämatologen und Onkologen) and the DGP (Deutsche Gesellschaft für Phlebologie). For most questions, more than 1 answer was possible; therefore, the total sum of percentages may exceed 100%. **Results:** 275 specialists responded. 76% of them treat acute VTE with LMWH while 22% switch to oral treatments (vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs)) during the acute phase. For the next 3–6 months, 55% of the specialists continue LMWH, while 31% switch to VKAs and 33% to NOACs. Among those who continue LMWH for 3–6 months, 37% continue at the full dose, 26% reduce to 75% of the initial dose, and 40% even to 50%. Important factors guiding treatment decisions were the need for injections and the availability of a partner/spouse (LMWH), the need for laboratory controls (VKAs), and the number of other oral medications (NOACs). **Conclusion:** This survey reveals that practice patterns often do not follow the guideline recommendations with respect to the use of LMWH for long-term treatment of VTE in cancer patients.

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Introduction

Venous thromboembolism (VTE) is a frequent and serious complication of cancer. Without prophylaxis, up to 8% of ambulatory [1] and almost 20% of hospitalized cancer patients develop VTE [2]. The overall risk is 4–7-fold higher than in non-cancer patients. This high incidence comes from a multitude of risk factors in cancer patients, including frequent surgeries, immobility, advanced age, and prothrombotic medications (e.g., hormonal therapies, angiogenesis inhibitors, thalidomide and its derivatives). In addition, tumors activate coagulation factors and platelets to a variable degree, which supports the growth and spread of tumor cells, 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].

The prevention and treatment of cancer-associated VTE has become an important issue in the daily care of cancer patients. Several national and international evidence-based guidelines on the prevention and treatment of cancer-associated VTE have been published to support clinicians working in the field [8–11]. These guidelines uniformly recommend thromboprophylaxis for hospitalized cancer patients, while routine thromboprophylaxis is not recommended for ambulatory patients. If VTE occurs, treatment recommendations differ between non-cancer and cancer patients. The former usually receive a rapid-acting, parenteral anticoagulant (unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux) overlapping with and followed by an oral vitamin K antagonist (VKA). The new non-VKA oral anticoagulants (NOACs) have also been approved for this indication. The treatment of cancer-associated VTE is different in the way that LMWHs should be given initially and as long-term treatment because of their improved efficacy over VKAs.

The use of NOACs is currently not recommended for patients with malignancy and VTE.

This preference for LMWH is based on 4 studies that date back to the 1990s or early 2000s. The LITE study started in 1994 [12], CANTHANOX in 1995 [13], CLOT in 1999 [14], and the ONCENOX study in 2001 [15]. The treatment of cancer patients has changed fundamentally since then. Today, the majority of cancer patients are treated in the ambulatory care setting. Patients survive longer and quality of life and convenience of treatment are major issues in daily care. Several studies indicate that the impact of VTE guidelines on clinical practice is limited [16, 17]. This is particularly true for the use of LMWHs in the long-term treatment of cancer-associated VTE. Many patients receive VKAs instead, and if LMWHs are given, they are often underdosed or terminated prematurely [18–29]. With the advent of NOACs, the preference of the guidelines for LMWHs over any of these newer agents will be further challenged. It is likely that many patients will prefer taking a pill that does not require frequent blood testing (international normalized ratio (INR) in case of VKA) or daily subcutaneous (s.c.) injections (LMWH) [30].

For any future recommendations, it is important to know: Which cancer patients already receive thromboprophylaxis and which of them do not? Who diagnoses VTE when it occurs and who is in charge of the anticoagulant treatment? Which guideline recommendations have already been implemented in real-world oncology care, which of them have not, and why? The purpose of this study was to assess all these different aspects of VTE treatment in cancer patients in Germany.

Materials and Methods

This was a cross-sectional survey on the attitudes of physicians towards the prophylaxis and treatment of cancer-associated VTE.

In a first step, a questionnaire was drafted by the authors. This questionnaire was discussed with specialists in hematology/oncology and VTE treatment in several meetings and further adapted to the clinical practice. The final questionnaire contained mainly multiple-choice questions and is available as an online supplement.

In January 2014, the questionnaire was sent out by mail or electronically to all members of the DGHO (Deutsche Gesellschaft für Hämatologie und Onkologie), the BNHO (Berufsverband Niedergelassener Hämatologen und Onkologen), and the DGP (Deutsche Gesellschaft für Phlebologie). Data lock was April 1.

Descriptive analysis of the data was carried out according to a pre-established analysis plan. The collected data were analyzed using the Statistical Package for the Social Sciences software (SPSS version 22.0). In case of single-choice questions, a Chi squared (χ^2) test was carried out to assess the independence of the distribution of the answers relative to the participant subgroups. For multiple-choice questions, each answer was assessed independently by means of Fisher's exact test on a 2×2 contingency table. All tests were 2-sided at a 5% level of significance.

For most questions, more than 1 answer was possible. In these cases, the sum of percentages may exceed 100%. Not all respondents answered each question. When the sum of answers was smaller than the number of completed questionnaires, relative percentages were calculated based on the number of evaluable answers.

Table 1. Characteristics of the responding physicians

	n	%
Physician's specialty		
Internal medicine, hematology, oncology	214	78.4
Internal medicine (not hematologists/oncologists)	27	9.9
Angiology	7	2.6
Phlebology	27	9.9
Additional qualification in hemostasis	22	8.1
Other specialties	49	17.9
Physician's primary location of medical service		
Hospital	107	39.1
Practice	136	59.5
Other	9	3.3
Start of practicing medicine		
Before 1980	18	6.6
1980–1990	117	43.0
1991–2000	100	36.8
2001–2010	36	13.2
After 2010	1	0.4

Results

A total of 4,627 questionnaires were sent out between January and February 2014. 275 (5.9%) of them were completed and available for analysis. Most of the responding physicians were hematologists/oncologists or angiologists/phlebologists. The majority worked in ambulatory patient care and had been practicing medicine for more than 20 years (table 1). 58.3% stated to see between 1 case of cancer-associated VTE per month and 1 case per week; 28.4% see even more than 1 case per week. 38.3% of the hematologists/oncologists reported that they routinely educate their patients about the risk and symptoms of VTE (this is the only analysis where non-hematologists/oncologists were censored because non-hematologists/oncologists usually do not educate patients with regard to oncology treatments).

Prophylaxis of VTE

For hospitalized cancer patients, 67.8% of the physicians routinely offer thromboprophylaxis unless contraindicated. In the ambulatory care setting, 5.3% offer thromboprophylaxis routinely. Among those physicians who offer thromboprophylaxis only to ambulatory patients with risk factors, 58.6% give it to multiple myeloma patients, 45.0% to pancreatic cancer patients, and 35.1% base their decision on a combination of tumor type and performance status. Only 13% of the respondents utilized the Khorana score [1], a prediction score that assesses the risk of VTE in ambulatory patients with cancer. Most physicians felt that a history of prior VTE was the most relevant risk factor for VTE in cancer patients, followed by tumor type and mobility/performance status (table 2).

Table 2. Factors considered relevant for VTE risk in cancer patients (more than 1 answer allowed)

	n	%
Age	155	57.4
Tumor type	242	89.6
Tumor stage	146	57.8
Mobility/ECOG	242	89.6
Recent surgery	209	77.4
Medication	230	85.2
Social factors (education, occupation)	22	8.1
History of VTE	259	95.9

ECOG = Eastern Cooperative Oncology Group,
VTE = venous thromboembolism.

Table 3. Who performs diagnostic workup in cancer patients with suspected VTE (more than 1 answer allowed)?

	n	%
Physician himself	100	37.2
Patient is sent to a hospital with in- and outpatient diagnostic facilities	86	32.0
Patient is referred to a vascular care specialist	91	33.8
Patient is referred to a radiologist (ambulatory care)	49	18.2
Patient is referred to a hematologist/oncologist	1	0.4
Patient is referred to another specialist (not specified)	16	5.9

Table 4. Initial treatment (more than 1 answer allowed)

For the initial treatment of newly diagnosed VTE, ...	n	%
I give only LMWH	206	76.3
I initially give LMWH and switch to an oral anticoagulant soon	60	22.2
I refer my patient to another physician who decides	7	2.6

Diagnosis and Acute Treatment of VTE

When a patient has symptoms of VTE, most of the treating physicians perform the diagnostic workup themselves, followed by sending the patient to a hospital with special in- and outpatient diagnostic facilities, or to a vascular care specialist (table 3). The diagnostic workup is triggered by symptoms in 85% of patients; thus, 15% of the patients are asymptomatic and VTE is an incidental finding. The Wells score, a clinical prediction score that assesses the probability of VTE [31], is used in 9% of symptomatic patients. For initial treatment, 76.3% of the physicians give LMWH only; 22.2% start with an LMWH but switch to an oral anticoagulant within 3–4 weeks (table 4). After the initial diagnosis and therapy, 68.6% of the responding physicians stay in charge of the VTE management, which means that they are responsible for prescribing, monitoring, and dosing the anticoagulants; 39.0% refer their patients to the family physician and 15.2% to another specialist.

Table 5. Duration, dose, and type of secondary prophylaxis (more than 1 answer allowed)

	n	%
How long do you give secondary prophylaxis? (all types of anticoagulants)		
Less than 1 month	8	3.1
Up to 3 months	71	27.5
Up to 6 months	145	56.2
More than 6 months	187	72.5
I am not in charge of therapy	35	13.6
Do you switch your patient to OAs for secondary prophylaxis?		
I do not give OAs	127	55.0
I switch to VKAs	71	30.7
I switch to NOACs	77	33.3
When do you switch to OA?		
After 1 month	41	36.9
After 3 months	26	23.4
After 6 months	21	18.9
In case you give LMWHs for secondary prophylaxis: which dose?		
I give full dose (100%)	79	37.1
I reduce to 75%	55	25.8
I reduce to 50%	86	40.4
When do you reduce the LMWH dose?		
I do not reduce the dose	86	38.6
After 1 month	50	22.4
After 3 months	70	31.4
Other	28	12.6

OA = Oral anticoagulant, VKA = vitamin K antagonist, NOAC = non-VKA oral anticoagulant, LMWH = low-molecular-weight heparin.

Table 6. Type of prolonged secondary prophylaxis (more than 1 answer allowed)

Long-term anticoagulation beyond secondary prophylaxis (after 6–12 months)	n	%
LMWH alone	78	38.0
VKA	93	45.4
NOAC	81	39.5

LMWH = Low-molecular-weight heparin, VKA = vitamin K antagonist,
NOAC = non-VKA oral anticoagulant.

Secondary Prophylaxis (Anticoagulation after Acute Phase for 3–6 Months)

Most physicians offer anticoagulation for 3–6 months. When using an LMWH, 40.4% reduce the dose to 50% of the initial full therapeutic dose. 30.7% of the respondents switch to a VKA, 33.3% to a NOAC (table 5).

Long-Term Anticoagulation beyond 3–6 Months

69% of the physicians responded that they offer long-term anticoagulant treatment for as long as cancer is active; most patients are then switched to a VKA or a NOAC (table 6).

Fig. 1. Factors considered relevant for prescribing LMWH vs. VKA vs. NOAC. VTE = Venous thromboembolism, INR = international normalized ratio, LMWH = low-molecular-weight heparin, VKA = vitamin K antagonist, NOAC = non-VKA oral anticoagulant.

Adherence

Factors considered by physicians as relevant for treatment adherence of their patients differed between LMWH, VKAs, and NOACs (fig. 1). For LMWH, the need of injections and the availability of a partner to perform the injections were considered most relevant, while the need for blood tests and fear of bleeding dominated in case of the VKAs and the number of comedications and fear of bleeding in case of NOACs. Fear of serious hemorrhage was more than 2 times higher with VKAs and NOACs than with LMWH.

Discussion

This study was designed to assess the daily practice of VTE prophylaxis and treatment in cancer patients in Germany. A questionnaire was sent out to German hematologists/oncologists and vascular medicine specialists. The results show that VTE prophylaxis and initial treatment with LMWH follow the guideline recommendations while the dose and type of the anticoagulant for secondary prophylaxis and long-term treatment varied substantially.

Did the Survey Reach Its Intended Target Group?

In Germany, cancer care is divided between hospital-based and ambulatory practice-based hematologists/oncologists. In addition, many patients with cancer-associated VTE are treated by vascular medicine specialists (angiologists, phlebologists). Almost all Ger-

man hematologists/oncologists are members of either the DGHO or the BNHO (or both) and many vascular medicine specialists are members of the DGP. By sending the questionnaire to all members of these 3 organizations, we hoped to reach the intended target group. Other medical subspecialties (e.g. vascular surgeons and general internists) were not addressed in order to limit the survey to those physicians with the highest likelihood to see cancer-associated VTE.

A limitation of this survey is the low response rate (5.9%), which is lower than the usual rate for oncology surveys [32]. The survey results might therefore not be representative, but they are still hypothesis generating. One explanation might be that members of these organizations who work in research, in health administration, or in other fields not involved in daily patient care did not respond. It is also possible that prophylaxis and treatment of VTE is not perceived as a primarily hemato-oncological problem but that it is more of an issue for general internists or family physicians, or some cancer specialists did not feel competent in issues of hemostasis and therefore did not answer. With 275 completed questionnaires, this is still the largest survey on the management of cancer-associated VTE in Germany. Almost 50% of the respondents had started to practice medicine before 1990 and 60% work in the ambulatory sector. These characteristics suggest that they were more likely to be senior physicians in charge of treatment decisions and not physicians still in training. This can be interpreted as a particular strength of this survey.

VTE Prophylaxis

Guidelines recommend thromboprophylaxis for most patients with cancer throughout hospitalization. This recommendation has been extrapolated from studies in general internal medicine patients [2]. There is uncertainty whether really *all* hospitalized cancer patients should be offered prophylaxis. The recent American Society of Clinical Oncology (ASCO) guideline update reflects this discussion and concedes that there is inadequate support for routine thromboprophylaxis in cancer patients admitted for minor procedures or short chemotherapy infusion [9, 10]. The discomfort with uniform thromboprophylaxis is also reflected in our survey. Almost one-third of the respondents do not routinely offer thromboprophylaxis to hospitalized cancer patients.

In ambulatory patients, guidelines advise against routine thromboprophylaxis except for selected high-risk patients. The results of this survey are again in line with this recommendation in that many hematologists/oncologists only offer prophylactic anticoagulation to ambulatory patients with pancreatic cancer or multiple myeloma, as recommended by the ASCO or the National Comprehensive Cancer Network (NCCN) [10, 11]. Some also provide prophylaxis for ambulatory lung cancer patients, as has been recommended by the International Society on Thrombosis and Haemostasis (ISTH) [8].

With regard to risk assessment, the respondents ranked a history of prior VTE highest, followed by performance status and tumor type. This is interesting because the Khorana score only utilizes the tumor type but not the other 2 criteria [1]. This might explain why only a minority of physicians use the Khorana score. More than 90% of the respondents stated that they would welcome another simple and more practical assessment tool.

Patient Education

Most cancer patients are nowadays treated as outpatients and usually receive specific instructions on what to do when side effects (e.g. fever) occur. One can assume that 100% of cancer patients undergoing chemotherapy have been told about the risk of infection because this is an integral part of all consent forms. In contrast, only 38% of hematologists/oncologists inform their patients routinely about signs and symptoms of VTE before starting cancer treatment. This percentage is surprisingly low considering how common thromboembolism is in cancer patients. Up to 8% of the ambulatory and 20% of the hospitalized cancer patients develop VTE [1, 2]. This number is comparable to the incidence of febrile neutropenia, and thromboembolism is a leading cause of death in cancer outpatients receiving chemotherapy [33]. Therefore, the ASCO 2013 guideline for the first time explicitly recommended that oncology professionals educate their patients about the signs and symptoms of VTE [9]. Apparently, the oncology community does not yet perceive VTE as an essential complication of cancer and thus an integral part of patient education, at least not as essential as neutropenic fever or infections. This misjudgment needs to be amended.

Diagnosis and Initial Treatment

Most respondents in this survey stated that they see 1 or more patients with cancer-associated VTE per month. Symptoms usually trigger diagnostic workup, but physicians also report a high number of incidental VTEs in their cancer patients. This may be explained by the frequent diagnostic imaging in cancer patients for reasons other than deep-vein thrombosis (DVT) or pulmonary embolism (PE) [34].

For initial treatment, most of the respondents give LMWH, which is in accordance with guideline recommendations. However, almost one-fifth switches to oral anticoagulants already during this initial treatment phase. We did not query the reasons for this deviation from the guideline recommendations, but we may speculate that convenience of oral anticoagulation is an important factor [30].

Secondary Prophylaxis

We wanted to know who is in charge of secondary prophylaxis for cancer-associated VTE after the initial phase. 69% of the physicians responded that they stay in charge of treatment. At the same time, 54% stated that they transfer treatment to the family physician or another specialist (the sum is > 100% because some respondents marked both options). Again, we did not query the specific reasons, but the following scenarios are possible:

Cancer patients with VTE are initially treated as inpatients, and after discharge from the hospital, they first go to see their family physician who then continues VTE treatment.

Many VTE patients might be too sick to receive any further cancer-specific therapy and are managed by their family physician or specialized palliative care physicians and no longer by their hematologist/oncologist.

Another reason might be that, in Germany, hematologists/oncologists receive a fixed lump sum payment for every cancer patient. Additional office visits for treatment and monitoring of VTE do not generate additional revenues. It is therefore attractive to transfer the VTE care to the family physician or another specialist.

Whatever the reason, it shows that cancer patients see different doctors for closely related medical problems. It is therefore important to disseminate knowledge on the prophylaxis and treatment of cancer-associated VTE not only among hematologists/oncologists but among all physicians involved in the care of these patients.

Most of the respondents give secondary prophylaxis for 3 months or longer employing LMWH, 37% of them with 100% therapeutic dose; some reduce to 75% of the initial therapeutic dose and 40% stated that they even reduce to 50%. Most physicians reduce the heparin dose after 3 months or later (table 5). Again, we did not query the reasons, but from the authors' experience, several scenarios are likely:

Many patients have initially received therapeutic LMWH as twice daily (BID) injections (e.g., in Germany, therapeutic-dose enoxaparin is licensed only for BID administration), and it is more convenient to give only 1 injection.

A dose reduction to 75% of the initial dose for secondary prophylaxis after the acute phase is recommended for cancer-associated VTE treated with dalteparin. It is possible that many physicians follow the same approach when they use other LMWHs although this dose reduction has only been tested for dalteparin. Still, neither dalteparin nor any of the other LMWHs has an approval for 50% (half-therapeutic) dosing.

The risk of recurrent thrombosis is perceived as highest during the first 3 months, and lower thereafter [35]. Therefore oncologists may find a half-therapeutic dose more acceptable after 3 months.

Oncology professionals are concerned about the risk of bleeding because this is significantly higher in cancer than in non-cancer patients. Half-therapeutic dosing 'feels' safer.

Regimens with a dose intermediate in anticoagulant intensity between high- and low-dose regimens (half-therapeutic dose) are commonly used for perioperative bridging of non-cancer patients, and many physicians have personal experience with half-therapeutic dosing [36, 37].

In this survey, 55% of the respondents stated that they would continue LMWH for secondary prophylaxis. But 31% stated that they would also give VKAs, and 33%, NOACs (again some of the respondents marked 2 or all 3 options). In the 2003 FRONTLINE survey, 66–88% of the respondents switched to oral anticoagulants [18]. Thus, the guideline recommendations have achieved some change, but the high percentage of VKA/NOAC use is still surprising. One has to keep in mind that, at the time of this survey, rivaroxaban was the only NOAC approved for VTE treatment (market approval in Germany in December 2011). Within 2 years of market introduction, already one-third of the physicians felt comfortable with giving these agents to oncology patients, despite the fact that there are no studies showing the efficacy and safety of NOACs in cancer patients in a head-to-head comparison with LMWH. In addition, NOACs might interfere with anticancer agents [38]. An important reason could be that VTE treatment with NOACs is almost 4 times cheaper than with LMWH. While the German health care system covers all medications, it also urges the physicians to choose the most cost-effective treatment. Most practices have a cap on prescription costs, and in the daily practice, cost considerations factor into treatment decisions.

Another common argument is that VKAs and NOACs have market approval for all patients with VTE and that cancer patients are not excluded from this approval. From a medicolegal standpoint, it is therefore 'safe' to prescribe VKAs or NOACs to cancer patients. This discrepancy between market approval and guideline recommendations underlines the urgent need for more studies on anticoagulation in cancer patients.

Long-Term Treatment beyond 6 Months

Prospective trials of anticoagulation in cancer patients beyond 6 months are rare [39], but long-term anticoagulation is recommended by most guidelines, at least when cancer is still present. 69% of the respondents offer long-term anticoagulant treatment to their patients with active cancer. For this long-term treatment beyond the initial 6–12 months, oral agents are preferred over LMWH.

We asked which reasons are considered relevant in deciding for or against LMWHs, VKAs, or NOACs. In case of LMWH, practical issues like the need for injections and the availability of a partner to perform injections ranked highest. This suggests that the capability of cancer patients to accept long-term injectable anticoagulant treatment is probably underestimated. Studies have shown that injections are per se no barrier to good compliance [40]. Patients with cancer-associated VTE are much more willing to continue long-term injections, as long as this does not interfere with their cancer treatment [41, 42]. In case of VKAs, the need for INR measurements and the fear of bleeding were important factors. Fear of bleeding was also important with NOACs. This is not surprising because cancer patients have a particularly high bleeding rate, and at the time of this survey, no antidote was available. Another issue with NOACs was the number of comedications. This is important not only because of potential interactions between NOACs and anticancer agents but also because oncologists are very aware of decreasing adherence when they prescribe more oral medications [43].

In conclusion, this study shows that prophylaxis and initial treatment of VTE in cancer patients follows guideline recommendations while secondary prophylaxis and long-term therapy varies substantially. Economic and convenience factors may play a major role in treatment decisions. Patients with cancer-associated VTE are managed not only by their hematologist/oncologist but also by family physicians and other specialists. Our survey underlines the need to disseminate knowledge of and improve adherence to guidelines on the treatment of cancer-associated VTE among all physicians who participate in the care of cancer patients.

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