Risk factors for venous thromboembolic events in cancer patients

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Background: Cancer patients of the Department of Internal Medicine (Cancer Research) of the Essen University Medical School (Tumor Clinics), Germany, were examined and questioned with the aim of identifying those who run a high risk of deep vein thrombosis (DVT).

Patients and methods: Between September 2002 and April 2003, cancer therapy and DVT risk factors of 507 cancer patients (53% males, 47% females, mean age 56 ± 12 years) were documented. During a mean follow-up of 8 ± 5 months, 60 patients (12%) suffered from new venous thromboembolic events (VTE): 28 at the lower limb, 25 at the upper limb and 13 pulmonary embolisms.

Results: The following factors were considered as predictive for an increased VTE risk: inpatient treatment (P < 0.0001), prior DVT in medical history (P = 0.0275), DVT in family (P = 0.0598), chemotherapy (P = 0.0080), fever (P = 0.0093) and CRP (P < 0.001). After combining factors in one variable (number of factors) the predicted VTE risk increased with the number of factors in both outpatients (OR 1.85, 95% CI 1.18–2.88, P = 0.0071) and inpatients (OR 2.34, 95% CI 1.63–3.36, P < 0.0001). In the absence of all these factors the predicted VTE risk was 2.3%, increasing to 72% if all were present.

Conclusions: In cancer patients the risk of VTE steadily increases with the number of risk factors, and identification of patients at high risk is possible.

Key words: deep vein thrombosis, risk assessment, cancer, chemotherapy

introduction

Patients with solid tumors or malignant hematological disorders (cancer patients) present a major clinical challenge in the era of oncologic awareness and more intensive care, which has led to prolonged survival and a longer time frame during which complications may develop. A frequent complication is the occurrence of venous thromboembolism (VTE), for which cancer is one of the most relevant risk factors. In a prospective register including 5451 patients with ultrasound-confirmed deep vein thrombosis (DVT), 32% of all patients suffered from cancer [1]. The overall incidence of postoperative DVT inpatients with cancer is about twice as high as that of patients free of malignancy [2]. Thus, in risk assessment scales for surgical patients, those with cancer are always assigned to the high-risk group.

For prophylaxis in the surgical setting, once-daily subcutaneous injections of low molecular weight heparin (LMWH) are as effective and safe as multiple doses of unfractionated heparin, and extending prophylaxis with LMWH beyond hospitalization can safely reduce the risk of postoperative thrombosis after abdominal surgery for cancer [3]. However, prevention of venous thromboembolism is less well studied in patients treated in medical departments. In the Medenox trial, enoxaparin in high prophylactic doses was an effective and safe measure of thromboprophylaxis in bedridden medical patients [4]. Risk assessment scales for medical patients are still a matter of discussion, but LMWH for VTE prophylaxis is already recommended in medical cancer patients today [5].

In oncological departments LMWHs are already established for DVT treatment and secondary prophylaxis [6–8] but their role in primary prophylaxis for cancer patients is still to be clarified. There is evidence that the absolute risk depends on tumor type, stage or extent of cancer, and cytotoxic treatment [9–11]. The general prophylactic use of intravenous unfractionated heparin, LMWH or low doses of oral warfarin, however, may not be optimal in the setting of active cancer and ongoing anticancer therapy and is not generally recommended by the Guidelines of the American College of Chest Physicians in cancer patients per se, but only for those undergoing surgery or who are bedridden [12].

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Patients with cancer may harbor many alterations of hemostasis. These are multifaceted and must be considered when trying to control hemorrhage or thrombosis in cancer patients [13]. The role of risk factors such as inpatient treatment, immobilization, obesity or varicose veins has never been investigated in cancer patients and there are insufficient data to assess the individual risk of thrombosis for cancer patients. Thus, we examined and questioned cancer patients at the Department of Internal Medicine (Cancer Research) of the Essen University Medical School (Tumor Clinics), with the aim of identifying those who run a high risk of DVT and to support future decisions about the individual necessity of prophylactic anticoagulation.

patients and methods

We established a prospective observational register at the Tumor Clinics in September 2002. At the Tumor Clinics, which comprises three wards with a total of 110 beds and two outpatients clinics, patients with all types of malignancy are treated. The Ethics Committee of the Essen University Medical School approved the prospective investigation and all patients gave their written informed consent before participating. Risk factors were grouped into those documented once at enrollment and those documented at subsequent visits (either in the outpatients clinics or on the wards). The project and its performance did not affect routine workflows in the Tumor Clinics and did not induce additional visits. Four doctoral candidates collected all project data. The workflows for recruitment, data collection and follow-up are shown in Figure 1.

The risk factors documented at enrollment are listed in Table 1. All patients were asked to report any thrombotic events in their own or their family history. A non-invasive physical examination was performed to look for signs and symptoms of chronic venous insufficiency in leg veins (edema, varicose veins, hemosiderosis, lipodermatosclerosis, active or healed ulcers). These clinical symptoms were classified according to the CEAP-classification (Clinical condition, Etiology, Anatomic location and Pathophysiology) into stages C1–C6 [14]. The CEAP score was not used to assess previous DVT. Patient records provided the date of first cancer diagnosis or recurrence as well as TNM classification or lymphoma staging, respectively.

The risk factors documented at each contact after enrollment are summarized in Table 2. Tumor therapy (cytotoxic treatment, operations or radiation therapy) was documented including therapy date and dosage. For analysis we classified cytotoxic treatment according to the ATC code [15] and therapy-associated toxicities (vomiting, diarrhea, fever and infection) considered relevant to the development of VTE according to the Common Toxicity Criteria [16]. We also documented whether patients were given heparin (for prophylactic or therapeutic reasons). Laboratory tests for parameters of interest [hematocrit, fibrinogen, C-reactive protein, antithrombin III, lactic acid dehydrogenase (LDH) and platelet count] were available during routine treatment and downloaded from the laboratory computer.

follow-up

For the planned 6 months follow-up according to informed consent, patients were either contacted during routine visits at the Tumor Clinics or phoned at home 6 months after enrollment. The total number of contacts per patient varied between one and 32. Each deep vein thrombosis (DVT) of the upper or lower limb and each pulmonary embolism (PE) occurring after enrollment was documented as a new event. Patients were not actively screened for DVT or PE, but if they became symptomatic, a sonography or venography was performed to prove the DVT. MR imaging or CT scan proved PE. Thus, the date of proven diagnosis was used as the relevant date for any new VTE.

patient population

Between September 2002 and April 2003, 564 patients were contacted, 507 of whom (representing 24% of all patients treated in the Tumor Clinics during this time) were finally enrolled. All patients who could be interviewed in the morning were asked to participate. There was no systematic selection beyond that. Those who did not participate mostly refused without giving further reasons. The disposition of patients is shown in Figure 2.

Accordingly, 53% of patients were male, 47% female, the mean age was 56 ± 12 years and the mean body mass index 25 ± 4. At enrollment 53% were treated as outpatients and 47% as inpatients. The most frequent malignancies were lung cancer (24%), cancer of the gastrointestinal tract (23%), malignant lymphomas (17%) and breast cancer (12%). Mean follow-up time was 8 ± 5 months and 60 patients (12% of our population) suffered from new VTE: 28 at the lower limb, 25 at the upper limb and 13 PE. A much higher number of asymptomatic VTEs can be supposed but patients were not actively screened. A total of 147 deaths were documented during follow-up. Population characteristics grouped for patients with and without new VTE are shown in Tables 1 and 2. During follow-up 459 patients were treated with chemotherapy. Forty-one patients were on heparin for prophylactic or therapeutic reasons during a 30 day-period before a new thromboembolic event (see below for details regarding this time-frame), 19 of them had a new VTE. Fifteen patients were on therapeutic heparin.
We included risk factors in the analysis either if they were present at enrollment or if they were documented within 30 days before the VTE was proven. For patients without new VTE a comparable time frame was calculated from the median time between enrollment and the first new VTE in the other group. This median of 72 days was used for calculation of the 30-day period. We differentiated between prophylactic and therapeutic heparin by using a 5-day period before the VTE was proven (or before the median in the other group). Independent from the dosages, patients who were given heparin during this 5-day period were counted for therapeutic heparin.

Continuous variables are presented with their mean, standard deviation and standard error of the mean, median and quartiles. Absolute and relative frequencies and odds ratios are given with confidence intervals and describe categorical variables. Group differences between patients with and without new VTE were analyzed using the chi-square or Fisher’s exact test. All P values are to be understood as strictly descriptive. Group differences were considered as statistically significant at a P value below 0.05.

Factors presumed clinically relevant (e.g. age, sex, body mass index (BMI)) and additional factors reaching the level of statistical significance in univariate analysis (e.g. fever) were included in exploratory multivariate logistic regression models using backward variable elimination. We did not include all factors concurrently in one model but used several models to limit model complexity in relation to the number of events. We also performed stepwise regression analyses. Furthermore, those factors included in the regression models were analyzed for correlation using the Spearman coefficient.

**results**

The results for univariate analysis of the potentially relevant factors are shown in Tables 1 and 2.
risk factors present at enrollment
This logistic regression model included the factors gender, age, BMI, inpatient treatment, CEAP score (maximum CEAP score for both legs), prior DVT in medical history and DVT in family history (Figure 3). The factors, gender ($P = 0.8647$), age ($P = 0.3549$), BMI ($P = 0.2867$) and CEAP score ($P = 0.8725$) did not reach statistical significance. The following factors were statistically significant: inpatient treatment ($P < 0.0001$), prior DVT in medical history ($P = 0.0275$) and DVT in family ($P = 0.0498$).

other risk factors
This logistic regression model included central venous lines, cytotoxic chemotherapy, fever, diarrhea, vomiting, infection and inpatient treatment (Figure 4). Except for inpatient treatment, gender and age, all data presented here were documented within the 30-day time frame described above. Fever, diarrhea, vomiting and infection were graded according to the Common Toxicity Criteria [15]. The factors, central venous catheter ($P = 0.5922$), diarrhea ($P = 0.2413$), vomiting ($P = 0.7559$) and infection ($P = 0.6438$) did not reach statistical significance. The following factors were statistically significant: cytotoxic chemotherapy ($P = 0.0080$), fever ($P = 0.0093$) and inpatient treatment ($P = 0.0004$).

Antineoplastic agents grouped according to ATC
This logistic regression model included inpatient treatment and six groups of antineoplastic medication applied within the 30-day time frame described above (anthracyclines, platinum compounds, podophyllotoxins, pyrimidine analogues, nitrogen mustard analogues and vinca alkaloids) as well as inpatient treatment (Figure 5). The factors podophyllotoxins ($P = 0.6127$), pyrimidine analogues ($P = 0.6009$) and vinca alkaloids ($P = 0.2107$) did not reach statistical significance.

Figure 2. Disposition of patients.

Figure 3. Logistic regression model including variables present at enrollment.

Figure 4. Logistic regression model including variables documented within a 30-day period before the new venous thromboembolic events (VTE) were proved.

Figure 5. Logistic regression model including variables present at enrollment.
laboratory parameters

The only laboratory parameter reaching statistical significance was C-reactive protein (CRP) (data documented within the 30-day time frame described above, \( P < 0.0001 \)).

Neither the analysis for correlation between all factors included in the regression models nor the analysis for correlation between these factors and the dependent variable showed correlations necessitating further exploration.

A stepwise analysis with the regression models listed above showed nearly the same findings except for the model including the six groups of antineoplastic agents. Here, only the platinum-based drugs show significance (\( P = 0.0259 \)).

A re-analysis without patients on therapeutic heparin (using a 5-day time-frame before new VTE) shows similar findings. Of those risk factors present at enrollment the following factors were statistically significant: inpatient treatment (\( P = 0.0001 \)) and prior DVT in medical history (\( P = 0.0283 \)). Of the other risk factors cytotoxic chemotherapy (\( P = 0.0366 \)), fever (\( P = 0.0193 \)) and inpatient treatment (\( P = 0.0002 \)) were significant. In the model including the grouped antineoplastic agents none of the six groups was significant, only the factor inpatient treatment (\( P < 0.0001 \)). The only laboratory parameter reaching statistical significance still remained C-reactive protein (CRP).

risk assessment

Based on the backward variable elimination regression models including all patients, the factors inpatient treatment, prior DVT in medical history, DVT in family history, chemotherapy, fever and CRP showed up as significant with respect to the development of VTE in cancer patients. After combining factors in one variable (number of risk factors), the predicted VTE risk increased with the number of factors in both outpatients (OR 1.85, 95% CI 1.18–2.88, \( P = 0.0071 \)) and inpatients (OR 2.34, 95% CI 1.63–3.36, \( P = 0.0001 \)). If none of these factors were present, the predicted VTE risk was 2.3%, increasing to 72% if all were simultaneously present (Figure 6). Only 18% of the included patients had none of these risk factors, and about 30% had three and more risk factors.

discussion

This register tries to specify the risk of VTE in cancer patients considering a variety of classical risk factors, which are already included in risk assessment tools used in surgical and medical patients. The register mirrors the range of patients and the routine work in departments of medical oncology and hematology. We did not specify any inclusion or exclusion criterion that could have changed the awareness of the medical oncologists for specific aspects. Neither did the project and its performance affect routine workflows in the Tumor Clinics or induce additional visits (e.g. by actively screening patients for VTE or PE). The number of deaths documented during follow-up indicates that there was no focus on surviving cancer patients. Thus, the results drawn from this register could be generalized for cancer patients. The disadvantage in proceeding like this is that more specific questions which are also important, e.g. regarding the type of underlying malignancies or specific treatment regimes, could not be answered and cases of VTE and/or PE may have been overlooked. Missing values for some variables, which reduce the explanatory power of results, are due to the register design which was set up to include existing and available data only. The time consuming interview technique, the restriction to the morning hours and the need for as much follow-up contact as possible had limited the number of enrolled patients and may consequently limit the generalizability of the results.

We used the date of proven diagnosis as the relevant date for any new VTE although it is known that thromboembolic events begin a few days before. We chose a 5-day time-frame before diagnosis confirmation in order to account appropriately for this, especially in regard to the re-analysis without those patients who were on therapeutic heparin. This re-analysis mostly confirmed the logistic regression results as seen for all patients. The differences seen especially in the model with grouped antineoplastic agents might be explained by the lower \( N \) (492 instead of 507).

The following risk factors have been shown to increase the individual risk for VTE in our analysis: prior DVT in medical history, DVT in family history, chemotherapy, fever, CRP and inpatient treatment. All of these risk factors have already been discussed in the literature but they have not been analyzed in a comparable population of cancer patients.

Figure 5. Logistic regression model including groups of antineoplastic medication applied within the 30-day time frame before the new venous thromboembolic events (VTE) was proved.

Figure 6. Predicted probability for any venous thromboembolic events (VTE) based on the factors inpatient treatment, prior thrombosis in medical history, thrombosis in family history, chemotherapy, fever and C-reactive protein (CRP), showing the rate of patients with a given number of risk factors as calculated from the total of 507 patients included.
Oncological patients who have established thrombosis exhibit a remarkably high risk of recurrent thromboembolism, particularly in the first months after the interruption of anticoagulant treatment [2]. In the CLOT study, 11% of all patients recruited had prior thrombotic events [17], in the Oncenox study the rate was even higher with 24% [18]. Thus, our rate of 23% with prior DVT is plausible. In the Medenox study a previous DVT was associated with the highest risk of developing VTE with an odds ratio of 2.06 (95% CI 1.10–3.69), which is comparable to our findings as well [4]. Because the information regarding the prior thrombotic events is anamnestic, neither a complete recall nor a strict differentiation between DVT involving the lower or upper limb, between primary or secondary DVT or deep or superficial DVT was possible.

Data about the rate of DVT in first-grade family members of cancer patients are not available. With 21%, the rate we found appears rather high. As patients cannot be expected to differentiate between forms or localizations of VTE (especially when reporting events in the family) the rates given probably summate all forms of deep and superficial thrombosis. Independent from this lack of specificity, prior DVT and DVT in the family increased the risk for new VTEs in cancer patients.

Antineoplastic chemotherapy increased the rate of VTE with an odds ratio of 2.15. In a population-based, nested case–control study of 625 patients with a first lifetime VTE diagnosed during a 15-year period, the increased DVT risk associated with cancer with ongoing chemotherapy was reported with an odds ratio of 6.5 (95% CI 2.1–20.2) and without chemotherapy with 4.1 (95% CI 1.9–8.5) [19]. We think it is remarkable that the difference in these odds ratios is rather similar to the magnitude of effect seen for antineoplastic chemotherapy in our register. Of a total of 1041 patients with solid tumors admitted to three major medical centers, patients were more likely to develop DVT during chemotherapy (P = 0.0001) [20]. There have been fewer efforts to investigate specific antineoplastic agents or combinations associated with high VTE risk. Older studies regarding the therapy of breast cancer have shown that combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF) might be associated with a lower VTE risk than the combination of CMF with vincristine [21]. Among the causal mechanisms associated with antineoplastic agents, which might increase VTE risk, an increase in soluble ICAM-1 and vascular endothelial growth factor are discussed. Such changes have been described for a standard anthracycline-based chemotherapy in women with stage I–IIIA breast cancer [22]. A study on 1023 patients with stage IIB, IV, or recurrent non-small-cell lung cancer (NSCLC) showed that combined treatment with 15 mg prinomastat (matrix metalloproteinase inhibitor) approximately doubles VTE hazard [23].

Fever can be regarded as a systemic symptom of an infection. Different mechanisms might explain the association of infections with an increased risk of VTE. Patients could have been more immobilized, they could have suffered from fluid loss and showed an increase in acute-phase proteins (e.g. fibrinogen). We were surprised to see that fever reached significance level, whereas infection did not. In a case–control study on inpatients aged 65 years and older, infections increased the rate of VTE with an odds ratio of 2.10 (95% CI 1.40–3.13) [24]. One reason might be that in reporting toxicities a broad concept of infection was used including infections without fever as a systemic inflammation component. Skeptics might argue that VTE cause fever, but this has not been generally proven. In a study on 1847 patients with suspected VTE the incidence of fever, defined as a temperature $\geq 38\,^\circ\mathrm{C}$, was not different between those with and those without acute DVT [25]. Fever can also be drug-induced but we could not show an explicit attribution.

A similar causal relationship can be discussed for CRP. CRP and D-dimer correlate ($\rho = 0.64$, $P < 0.01$) and increase significantly in patients suffering from DVT ($P < 0.001$). In a multivariate analysis of 233 consecutive patients with suspected DVT the presence of DVT ($P < 0.001$), the presence of malignancy ($P < 0.001$) and the presence of inflammatory diseases ($P = 0.009$) significantly influenced plasma CRP levels. The sensitivity (75% versus 93%) to specificity (69% versus 55%) relationship showed inferior results for CRP compared with D-dimer. The authors concluded that CRP cannot provide additional information either for the diagnostic process in patients with suspected DVT or for a differential diagnosis of DVT and inflammatory diseases [26]. We chose a high cut-off level (>400 mg/dl) to rule out smaller fluctuations. In contrast to CRP, frequently clinically used prothrombotic parameter such as antithrombin III or fibrinogen did not achieve a significant level.

Inpatient treatment generally increases VTE risk. In the population-based Olmsted County Study, hospitalization without surgery went along with an attributable risk of 21.5% (95% CI 17.3% to 25.6%) for VTE [19]. It is difficult to pinpoint any single reason but higher degrees of morbidity and immobility as well as more intensive therapy has to be discussed. Other risk factors such as age, gender, obesity, chronic venous insufficiency, time elapsed since first diagnosis of cancer, fibrinogen >400 mg/dl or diarrhea seem to play a minor role for VTE in cancer patients. This might be due to the specific population treated in cancer centers today. Very old patients or patients with severe heart insufficiency are not usually treated there. This may change with the over aging of the population in industrial countries and the increasing need for mild or moderate treatment strategies for geriatric cancer patients.

**Conclusion**

The risk of DVT is low in cancer patients without additional risk factors. This fact is in accordance with the ACCP Guidelines, which do not recommend routine prophylaxis for VTE prevention in cancer patients per se [12]. The risk steadily increases with the number of risk factors. Thus, risk assessment tools seem to be feasible to stratify prophylaxis regimes in these patients. Therefore, risk assessment is mandatory to identify patients at high risk with respect to the application of prophylactic therapeutic regimens, which have to be carefully investigated in randomized clinical studies.

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references