Heparins, cancer and thrombosis: clinical and experimental studies
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Citation for published version (APA):
SHOULD THE TREATMENT OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER BE DIFFERENT?
Susanne M. Smorenburg, Barbara A. Hutten, Martin H. Prins
Patients with malignant disease constitute a significant subgroup of patients with venous thromboembolism (VTE). Patients with cancer have an increased risk to develop VTE, particularly after surgery or during chemotherapy. Except for breast cancer, exact incidences of VTE complications are not well determined for the various types of cancer. The risk of VTE in relation to cancer type and anticancer treatment, as well as potential beneficial effects of VTE prophylaxis in cancer patients require assessment. At present, patients with VTE are usually treated with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for at least 5 days. Treatment with vitamin K-antagonists is started concomitantly and is continued for at least 3 months. This strategy is similar for patients with and without malignancy. However, patients with cancer have an increased risk to suffer from recurrent VTE and major bleeding during anticoagulant treatment for VTE. Moreover, long-term treatment with vitamin K-antagonists is often difficult to manage in patients with malignancy. Therefore, treatment of VTE in cancer patients should be reconsidered and alternatives in treatment should be investigated. In randomized trials, LMWH was found to be at least equivalent to UFH in terms of efficacy, but safer than UFH during initial treatment of VTE. Moreover, a mortality reduction was observed in cancer patients who were treated with LMWH, as compared with UFH recipients. Therefore, LMWH is recommended for the initial treatment of VTE in cancer patients. A possible alternative for vitamin K-antagonists is prolonged treatment with LMWH. However, the efficacy and safety of long-term use of LMWH in therapeutic dosages for treatment of VTE in cancer patients should first be assessed in randomized clinical trials.

Patients with cancer represent an important subgroup of patients with venous thromboembolism (VTE) (1). Several, sometimes conflicting, reports have been published on the relation between malignancy and the risk of both recurrent VTE and bleeding complications (2-4). When rates of these complications are indeed higher in patients with malignancy as compared with patients without cancer, both the therapeutic approach to cancer patients with VTE and the design of trials that are intended to optimise treatment of VTE may be affected. In this review, we have assessed the numerical importance of patients with malignancy among patients with VTE. Furthermore, differences in rates of complications and their potential consequences for both initial and long-term phases of treatment are reviewed and discussed.
PREVALENCE OF MALIGNANCY AMONG PATIENTS WITH VTE

It is generally assumed that the risk of VTE is increased in patients with malignancy. Clinically overt VTE complications have been observed in up to 26% of cancer patients, whereas considerable higher incidences of VTE, up to 50%, have been observed in post mortem studies, especially in patients with mucinous carcinomas of the lung, pancreas, and the gastrointestinal tract (5-7). The enhanced risk of VTE in patients with cancer can be partly explained by disturbances in the haemostatic and fibrinolytic systems (8). Intravascular coagulation and/or fibrinolytic activation can be found in almost all cancer patients (9), but there is no clear association between changes in clotting or fibrinolytic indicators and the occurrence of clinically manifest VTE (5;10). In addition to the enhanced risk of VTE caused by the tumor itself, comorbid predisposing factors such as prolonged immobility, surgery, the use of central venous catheters and chemotherapy enhance the risk to develop VTE (11-14). However, it is unknown to what extent these comorbid factors contribute to the risk of VTE in cancer patients. For most types of cancer, there is a lack of prospective studies documenting the precise incidence of VTE (15). Moreover, most of the studies that reported on the incidence of VTE in cancer patients studied the incidence after surgery or during chemotherapeutic treatment (13;16-19). Therefore, these studies do not enable distinction between the risk of thrombosis due to the presence of cancer itself and these factors.

Reliable information on the incidence of thromboembolism with and without anticancer treatment is available of patients with breast cancer. In the absence of anticancer treatment, the incidence of VTE in patients with stage I and II breast cancer was comparable with that in the general population (approx. 0.2% in 4 years; Table 1) (20;21). Higher incidences were observed in patients who received chemotherapy, especially in women who were postmenopausal (Table 1) (22-25). The combination of chemotherapy and hormonal treatment further enhanced the risk of thromboembolic complications (incidences were in the range of 2-8% during 6-12 months of treatment; Table 1). These trials thus suggest that anticancer treatment, and especially combined chemotherapy and hormonal treatment, contributes significantly to VTE in patients with early stages of breast cancer. Similar incidences of VTE complications were observed during chemotherapeutic treatment of patients with metastatic breast cancer (4-8%; Table 1) (26). However, the reported incidences are dependent on the periods of time of observation, which varied greatly among the studies (from 6 weeks up to 63 months; Table 1).

The incidence of thrombotic complications during chemotherapeutic treatment has also been investigated in patients with high-grade gliomas. In a prospective study, the incidence of clinically overt deep vein thrombosis among 77 patients receiving adjuvant chemotherapy following surgery for high-grade gliomas was 26% (n=20), during a follow-up period of 74.4 weeks (27). Four of these 20 patients had massive pulmonary embolisms. The highest incidence was found in the first 7 months after surgery, when chemotherapy was still applied. In a retrospective analysis of 77 patients with high-grade gliomas, 15 patients (19%) developed clinically manifest VTE during the
course of their disease (28). Twelve of these patients received chemotherapy when thrombosis occurred. On the other hand, the incidence of clinically manifest venous thrombosis or embolism among 1703 patients who underwent initial craniotomy for gliomas, meningiomas, or cerebral metastasis was 1.6% within 4 weeks of surgery (29). None of these patients received chemotherapy. Although the results of the latter study may seem distinctly dissimilar from the results of the two former studies, the differences can be entirely explained by differences in follow-up periods.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Menopausal status</th>
<th>Therapy</th>
<th>VTE incidence</th>
<th>Duration of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiss et al. (46)</td>
<td>pre + post</td>
<td>CT</td>
<td>22/433 (5.1%)</td>
<td>2 years</td>
</tr>
<tr>
<td>Fisher et al. (20)</td>
<td>pre + post</td>
<td>HT</td>
<td>12/1318 (0.9%)</td>
<td>4 years</td>
</tr>
<tr>
<td>Clahsen et al. (21)</td>
<td>pre + post</td>
<td>placebo</td>
<td>2/1326 (0.2%)</td>
<td>4 years</td>
</tr>
<tr>
<td>Levine et al. (47)</td>
<td>pre + post</td>
<td>CT</td>
<td>7/1292 (0.5%)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>no CT</td>
<td>4/1332 (0.3%)</td>
<td>6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Von Tempel-hoff et al. (22)</td>
<td>pre</td>
<td>CT</td>
<td>9/102 (8.8%)</td>
<td>36 weeks</td>
</tr>
<tr>
<td>post</td>
<td>CT + HT</td>
<td>5/103 (4.9%)</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>Saphner et al. (48)</td>
<td>pre</td>
<td>no CT, no HT</td>
<td>0/89 (0.0%)</td>
<td>18 weeks</td>
</tr>
<tr>
<td>post</td>
<td>no HT, no CT</td>
<td>0/89 (0.0%)</td>
<td>18 weeks</td>
<td></td>
</tr>
<tr>
<td>Rivkin et al. (23)</td>
<td>post</td>
<td>CT</td>
<td>4/471 (0.8%)</td>
<td>6-12 months</td>
</tr>
<tr>
<td>post</td>
<td>CT + HT</td>
<td>21/740 (2.8%)</td>
<td>6-12 months</td>
<td></td>
</tr>
<tr>
<td>no HT, no CT</td>
<td>1/232 (0.4%)</td>
<td>6-12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>2/86 (2.3%)</td>
<td>6-12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>5/132 (3.8%)</td>
<td>6-12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT + HT</td>
<td>74/923 (8.0%)</td>
<td>6-12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher et al. (24)</td>
<td>post</td>
<td>HT</td>
<td>0/295 (0.0%)</td>
<td>1 year</td>
</tr>
<tr>
<td>post</td>
<td>CT</td>
<td>3/300 (1.0%)</td>
<td>1 year</td>
<td></td>
</tr>
<tr>
<td>post</td>
<td>CT + HT</td>
<td>6/303 (2.0%)</td>
<td>1 year</td>
<td></td>
</tr>
<tr>
<td>Pritchard et al. (25)</td>
<td>post</td>
<td>HT</td>
<td>7/367 (1.9%)</td>
<td>4-10 months</td>
</tr>
<tr>
<td>post</td>
<td>CT + HT</td>
<td>30/757 (4.0%)</td>
<td>4-10 months</td>
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<tr>
<td>CT + HT</td>
<td>1/352 (0.3%)</td>
<td>62 months(^1)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Menopausal status</th>
<th>Therapy</th>
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<th>Duration of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IV</td>
<td>pre + post</td>
<td>CT</td>
<td>13/159 (8.2%)</td>
<td>63 months(^1)</td>
</tr>
<tr>
<td>Levine et al. (26)</td>
<td>pre + post</td>
<td>CT</td>
<td>7/159 (4.4%)</td>
<td>188 days</td>
</tr>
</tbody>
</table>

\(^1\) Definition of VTE unclear; might include superficial phlebitis
\(^2\) approx. 70% of all events occurred during chemotherapeutic treatment
\(^3\) approx. 85% of all events occurred during chemotherapeutic treatment

\(^1\) pre, premenopausal; post, postmenopausal
\(^2\) CT, chemotherapy; HT, hormonal therapy

Table 1. Incidences of clinically overt and objectively documented venous thromboembolic complications among patients with breast cancer, with and without chemotherapy and/or hormonal therapy
Higher incidences of thrombosis following surgery have been reported for various types of malignancies, even when heparin was given prophylactically (12;16;18;30;31). However, in most of these studies, the presence of deep vein thrombosis was detected by fibrinogen leg scan and, thus, many of these thrombi were asymptomatic (12;16;30;31).

Patients with cancer represent a significant subgroup of patients with VTE. In randomized trials which compared low-molecular weight heparin (LMWH) with unfractionated heparin (UFH) in the initial treatment of symptomatic VTE, the proportion of cancer patients included varied between 6% and 23%, with a mean prevalence of 16% (1). The prevalence of specific types of malignancies was available from 3 recent trials (32-34), including 405 patients with cancer (Table 2). The distribution of the various malignancies in these trials followed the frequency of cancer in the general population.

<table>
<thead>
<tr>
<th>Primary site of malignancy</th>
<th>Number of patients* (%)</th>
<th>Number of deaths in a 3 month period after treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genito-urinary tract</td>
<td>118 (29%)</td>
<td>13 (11%)</td>
</tr>
<tr>
<td>Gastro-intestinal tract</td>
<td>80 (20%)</td>
<td>24 (30%)</td>
</tr>
<tr>
<td>Breast</td>
<td>57 (14%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>42 (10%)</td>
<td>20 (48%)</td>
</tr>
<tr>
<td>Hematological</td>
<td>40 (10%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>37 (9%)</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Other</td>
<td>31 (8%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Total</td>
<td>405</td>
<td>77 (19%)</td>
</tr>
</tbody>
</table>

* Percentage of total population of 405 cancer patients included in the trials

**Table 2: Distribution of types of malignancy in 3 recent clinical trials [32-34], in which LMWH was compared to UFH for the initial treatment of venous thromboembolism (50).**

**COMPLICATIONS DURING TREATMENT**

Patients with confirmed VTE are usually treated initially with UFH or LMWH for at least 5 days. Treatment with vitamin K antagonists is started concomitantly and is continued for at least 3 months. This strategy is similar for patients with and without malignancies.

A recent meta-analysis of all published randomized clinical trials comparing UFH with LMWH for the initial treatment of VTE showed no significant differences in recurrent VTE (3.8% in the LMWH group versus 4.8% in the UFH group; common odds ratio (OR) 0.77; 95% confidence interval (CI): 0.56-1.04), a significant decrease in the risk of major bleeds in favor of LMWH (1.3% versus 2.2%; OR 0.60, 95% CI: 0.38-0.95) and a significant decrease in 3-month mortality rate, also in favor of LMWH (4.8% versus 6.5%; OR 0.72, 95% CI: 0.55-0.96) (1). Therefore, it can be concluded that LMWH was at least equivalent in terms of efficacy, but safer than UFH for the initial treatment of VTE. Interestingly, patients with malignancy included in the individual trials had a statistically significant effect on both incidence of recurrent VTE and mortality. A 10% increase in
the proportion of patients with malignancy increased the incidence of recurrent VTE by 1.7% (95% CI: 0.1-3.2%) and that of mortality by 2.6% (95% CI: 1.1-4.1%) (1). In addition, it has been demonstrated that the decreased mortality of patients treated with LMWH can be explained entirely by the decreased mortality among patients with cancer (35). Consequently, the initial use of LMWH can be strongly recommended for patients with VTE and underlying malignancy. It can also be concluded that the subgroup of cancer patients significantly affects the total outcome of clinical trials, in which antithrombotic agents are evaluated for their efficacy and safety. Therefore, the proportion of patients with cancer in a particular study should be taken into account when comparing results from individual studies of the efficacy of treatment of VTE.

The situation with respect to preferred long-term treatment in patients with cancer is less clear. In a recent cohort study it was shown that patients with malignancy are not only at higher risk for VTE than patients without malignancy (28% versus 8% , annually), but also have an increased risk for haemorrhagic complications while receiving treatment with vitamin K antagonists (13% versus 2%, annually) (4). Similar trends were observed by Bona et al. (3), that were not statistically significant due to the low number of patients included in their study. Prandoni et al. (2) found an increased risk for recurrent VTE, but a similar risk for major bleeding in patients with cancer, as compared with patients without cancer. Moreover, Bona et al. reported that patients with cancer are more frequently outside the therapeutic range of the international normalized ratio (INR), despite more frequent monitoring (3). These findings suggest that treatment with vitamin K antagonists could be improved, or alternative treatments should be considered. A possible alternative for oral anticoagulants to prevent recurrence of VTE is LMWH. Three recent randomized studies have evaluated the long-term use of LMWH as compared to vitamin K antagonists as secondary prophylaxis of VTE (36-38). The dosages of LMWH that were used, and the incidences of recurrent VTE and bleeding during the 3 months of treatment in these trials are summarized in Table 3. The incidence of recurrent VTE and major bleeding was similar in patients treated with LMWH and vitamin K antagonists, whereas the incidence of minor bleeding complications was significantly lower in LMWH recipients. In a large cohort study, a similar reduction of major bleeding was observed during long-term treatment with LMWH (39). Trials with prolonged LMWH therapy, focussing specifically on patients with VTE and cancer are not currently available. Since dosages of LMWH were used that were lower than recommended for initial treatment in the above mentioned trials, it is conceivable that long-term therapeutic dosages provide a better protection against recurrences of VTE, although that will be at a price of increased bleeding rates, similar to treatment with vitamin K antagonists.

The duration of oral anticoagulant treatment is usually 3 to 6 months for most patients. However, recent evidence suggests that prolongation of treatment with vitamin K antagonists beyond this period may be beneficial for patients at high risk of recurrence of VTE. Since patients with
malignancy are reported to be at high risk of recurrent VTE, it is likely, although not documented, that prolongation of treatment is also beneficial for this group of patients (2;40;41).

The use of vena cava filters instead of anticoagulant treatment in patients with cancer has been evaluated in various trials (42-45). Although cohort analyses reported apparent beneficial effects of vena cava filters, a large randomized study failed to demonstrate any long term advantage (45).

![Table 3. Incidence of thromboembolic and bleeding complications during 3 months of secondary prophylaxis with LMWH or vitamin K antagonists.](image)

**CONCLUSION**

Patients with cancer are at higher risk to develop VTE, especially in relation with chemotherapy or surgery. However, the exact incidence of thrombosis in these patients is not well-established, and the risk of VTE depending on cancer type and anticancer treatment, as well as the potential beneficial effects of prophylaxis for VTE have to be evaluated in prospective trials. As a result of the enhanced risk to develop VTE, patients with cancer represent a large subgroup of patients with VTE. Moreover, these patients have an increased risk of bleeding complications when treated with anticoagulants. Consequently, the optimal management of VTE in cancer patients is controversial. Recently, subcutaneous LMWH has been shown to be at least as safe and efficacious as intravenous UFH in the initial treatment of VTE. The facts that monitoring is not required and subcutaneous injections are necessary only once daily are major therapeutic advantages of LMWH. Moreover, there is preliminary evidence from meta-analyses of large randomized studies of cancer and non-cancer patients with VTE, that LMWH may reduce total mortality in cancer patients as compared to UFH. Therefore, it is recommended to start initial treatment of VTE with LMWH in these patients. The usual long-term vitamin K antagonist therapy is more difficult to manage in patients with cancer and therefore frequent laboratory monitoring is necessary to maintain blood levels within the therapeutic range. Long-term use of LMWH in therapeutic dosages has not been investigated thus far in patients with cancer. Most studies reported on prophylactic or subtherapeutic
dosages of LMWH, and showed comparable incidences of VTE recurrence and major bleeding. Since patients with cancer are already at increased risk of recurrent VTE, a randomized trial in which the efficacy and safety of long-term use of LMWH in therapeutic dosages is compared to conventional warfarin therapy (with a target INR of 2-3) is warranted. Currently, it seems practical to prescribe LMWH in therapeutic dosages to patients with cancer who are difficult to treat with oral anticoagulants.

REFERENCES


CHAPTER 10 TREATMENT OF VTE IN PATIENTS WITH CANCER


