Treatment of Deep Vein Thrombosis with Oral Anticoagulants in Patients with Malignancy: Prospective Cohort Study

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Aim. To assess the outcome of deep vein thrombosis in patients with malignancy after 6 months of oral anticoagulant therapy, and to compare it with international normalized ratio (INR).

Methods. Thirty-one patients with malignancy (13 with hematological and 18 with solid tumors) and deep vein thrombosis (29 leg thrombosis and 2 upper extremity thrombosis) were included into a prospective cohort study that lasted from March 2000 until May 2001. The presence of malignant tumors was histologically proved and documented, and deep vein thrombosis was proved by ultrasound or venography. Patients were treated with heparin during the acute phase, and with oral anticoagulant therapy during further 6 months. INRs and ultrasound examination performed during the acute event were repeated one month and 6 months afterwards for the needs of analysis.

Results. Twenty-four patients concluded the study. Clot resolution was achieved in 13 patients after 6 months of therapy. The patients with INR>2 (n=10) had better clot resolution than those with INR<2 (n=3); p=0.012. There was no statistically significant difference in the outcome of thrombosis with regard to the INR level after a month of therapy (p=0.555). Three patients experienced bleeding, one patient had recurrent thrombosis, and two patients suffered pulmonary embolism.

Conclusion. Appropriate anticoagulation during 6 months after the acute deep vein thrombosis enhances the rate of the complete clot resolution. The INR values can be used as predictive of complete recovery from the thrombosis. Complications are comparable with those reported for patients without malignancy.

Key words: anticoagulants; international normalized ratio; neoplasms; treatment outcome; venous thrombosis; thromboembolism; warfarin

The association between solid tumors or hematologic malignancies and deep vein thrombosis is well known and documented (1-4). Neoplastic cells activate the clotting system directly by generating thrombin, or indirectly by stimulating mononuclear cells to synthesize and express various procoagulants. Cancer cells and chemotherapeutic agents can injure endothelial cells and thereby intensify hypercoagulability. Other triggers of deep vein thrombosis development are vein compression and surgery (5). Moreover, idiopathic deep vein thrombosis, development of deep vein thrombosis at unusual places, and warfarin resistance can often indicate underlying occult malignancy (1-3). The prevailing treatment in the acute phase of vein thrombosis includes short heparin therapy according to several protocols or low molecular weight heparin therapy (6-10). Further treatment of the disease consists of oral anticoagulation therapy during 6 months to lifetime (11), the purpose of which is to prevent the recurrence of thrombosis, acute pulmonary embolism, and postthrombotic syndrome sequelae.

The duration of oral anticoagulation therapy, its intensity, and success rate with regard to patency of affected vein remain unresolved. Complication rates of recurrence of thrombosis, pulmonary embolism, and bleeding seem to be slightly higher in patients with malignancy (12).

Caprini et al (14) reported the 68% rate of complete vein resolution after one-year study period in patients who mostly did not have malignant disease. Median INR values were significantly higher in patients with complete deep vein thrombosis than in those with residual thrombosis (14). Our aim was to assess the development of deep vein thrombosis in patients with malignancies during 6-month period of treatment and see how much the clot resolution rate correlated with INRs. We also wanted to evaluate the rate of complications during the therapy.

Patients and Methods

Eligibility Criteria

Eligibility criteria for patients to be included in the study were the following: 1) the presence of malignancy either before or after the episode of venous thromboembolism, 2) venous thromboembolism itself, 3) applicability of oral anticoagulant therapy after heparin treatment, and 4) life expectancy of more than 6 months. Patients had to meet all 4 criteria to be eligible for...
the study. Introduction of oral anticoagulant therapy marked the moment of inclusion into the study.

Deep vein thrombosis was proven by compression ultrasonography or ascending venography. The latter was performed in cases of upper-extremity deep vein thrombosis (n = 2) or when necessary in cases of lower-extremity deep vein thrombosis (n = 3).

Exclusion criteria were the following: 1) baseline INR > 1.6, because it carried higher risk of bleeding, 2) anticipated poor compliance to prescribed drug regimen, and 3) geographical inaccessibility that would make the follow-up impossible.

**Patient Population**

Thirty-one patients (18 women and 13 men) were included in the study. Their mean age was 65 years (range, 4-81)

There were 13 patients with hematomatologic malignancies and 18 with solid tumors (Table 1). The acute episode of venous thromboembolism often led to detection of occult malignancy (11 patients) or happened during chemotherapy (10 patients). The onset of thromboembolic incident occurred after surgery in 9 patients, of whom one after irradiation treatment and in four after or during chemotherapy.

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal:</td>
<td>8</td>
</tr>
<tr>
<td>colon</td>
<td>4</td>
</tr>
<tr>
<td>stomach</td>
<td>3</td>
</tr>
<tr>
<td>pancreas</td>
<td>1</td>
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<td>Genitourinary:</td>
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<td>prostate</td>
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</tr>
<tr>
<td>urinary bladder</td>
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</tr>
<tr>
<td>endometrial</td>
<td>1</td>
</tr>
<tr>
<td>kidney</td>
<td>1</td>
</tr>
<tr>
<td>Other solid malignancies:</td>
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</tr>
<tr>
<td>brain</td>
<td>2</td>
</tr>
<tr>
<td>breast</td>
<td>1</td>
</tr>
<tr>
<td>maxilla</td>
<td>1</td>
</tr>
<tr>
<td>lung</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoproliferative disorders:</td>
<td>9</td>
</tr>
<tr>
<td>non-Hodgkin lymphoma</td>
<td>5</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
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</tr>
<tr>
<td>chronic lymphatic leukemia</td>
<td>1</td>
</tr>
<tr>
<td>plasmocytoma</td>
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<td>Myeloproliferative disorders:</td>
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<td>polycytemia rubra verna</td>
<td>1</td>
</tr>
<tr>
<td>chronic myelogenous leukemia</td>
<td>2</td>
</tr>
<tr>
<td>acute myelogenous leukemia</td>
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</tr>
</tbody>
</table>

**Study Protocol**

The patients with deep vein thrombosis were treated with heparin administered intravenously or subcutaneously, according to accepted regimens (8,9). The dose was adjusted to achieve the activated partial thrombin time 2-2.5 times higher than the baseline value. Oral sodium warfarin was introduced between 5th and 10th day. Heparin was discontinued after a few days of overlapping therapy with warfarin as soon as the INR reached 2.0. The warfarin therapy was continued for at least 6 months to maintain INR between 2 and 3.

Compression ultrasonography or venography was performed at the time of the diagnosis and 6 months later, as described elsewhere (8). The location of thrombosis was determined as either proximal (thrombi found within deep ileo-femoral-popliteal segment), distal (thrombi found in the calf veins: posterior tibial, gastrocnemius, soleal, peroneal, and anterior tibial vein), or combined. Thrombosis load was measured 6 months later; complete compressibility of previously clotted venous segment was regarded as the resolution of the clot, whereas either complete or partial compressibility was regarded as non-resolution of the clot.

During the acute event, INR had been measured frequently before its stabilization, and afterward once a month. The baseline INRs determined in the first and sixth month were taken for statistical analysis.

Eleven patients with malignant diseases and venous thromboembolism were not included in the study because of the following reasons: 1) their initial INR suggested high risk of bleeding during the oral anticoagulant therapy (INR > 1.6), 2) the lethal outcome was expected within 3 months, or 3) were inaccessible for follow-up.

**Outcome**

We wanted to determine the proportion of patients with the complete resolution of the clot and the number of complications (recurrent thrombosis, acute pulmonary embolism or bleeding).

We had two cases of major and one case of minor bleeding. Major bleeding was defined as an overt bleeding associated with hemoglobin decrement of at least 20 g/L or transfusion of at least 2 units of blood products, or any intracranial, retroperitoneal, intracutaneous, or mediastinal bleeding that occurred during the oral anticoagulant therapy. Minor bleeding was defined as an overt bleeding that did not meet the above criteria for major bleeding. Minor hemorrhagic events, such as small bruising or ecchymoses, self-limiting epistaxis (not requiring emergency visit or tamponade), occasional hemorrhoidal bleeding, and microscopic hematuria, were not classified as bleeding episodes. Patients with suspected pulmonary embolism underwent ventilation-perfusion lung scanning (n = 4) or pulmonary angiography (n = 1). Pulmonary embolism was diagnosed in two patients. Recurrent thrombosis was diagnosed according to the algorithm proposed by Prandoni et al (7).

**Statistical Analysis**

Descriptive data that did not pass the test for normal distribution were expressed as medians and ranges. Mann-Whitney rank-sum test was used to compare INR results, whereas chi-square test or the Fisher exact test were applied in comparison of proportions as appropriate. Statistical significance was defined at p < 0.05; actual probabilities are presented in the text.

**Results**

Out of 31 patients, five died during the 6 months of the study; one died from pulmonary embolism and four from the progression of the underlying disease. Thus, 26 patients completed the study. Three patients had major bleeding. In two of them the therapy was replaced with the low molecular weight heparin. In a patient with chronic myelogenous leukemia bleeding from the gastrointestinal tract was successfully stopped with 2 units of fresh frozen plasma and vitamin K, as well as in a patient with lung malignancy who had gross hematuria. These bleedings occurred during the second (at INR of 2.3) and the fifth month (at INR of 2.7) of the therapy. These patients’ data were included in the analysis of the data from the first month of therapy. The third patient had epistaxis (at INR of 3.3), which was stopped by tamponade and fresh frozen plasma. Warfarin treatment was reintroduced later. That left 24 patients with complete data for analysis. Two patients had pulmonary embolism: one died, whereas the other was treated with heparin and recovered. Recurrence of thrombosis (extension of the existing clot from the ileo-femoral to popliteal segment) was documented in a patient at INR of 1.6 during the second month of treatment and was managed with heparin.

After a month of warfarin therapy, clot resolution was achieved in only 4 patients (15%, Table 2). There was no statistical significance in outcome of thrombosis regarding the INR at this time point (p = 0.555). After 6 months of therapy, resolution was achieved in 13 out of 24 patients (54%). Complete resolution of the clot was found in 10 of 12 patients (83%) with INR between 2 and 3 (Fig. 1) and in 3 of 12 patients
not influence the outcome of thrombosis (p=0.32). Disease (hematological or solid malignancy) also did not play any role in resolution of thrombosis (p=0.52 and p=0.46, respectively). The type of malignancy (15,16), but the genesis of the hypercoagulable state is still poorly understood.

Eleven patients out of 31 in our study had occult malignancy. Such a high proportion could be explained by patient sampling. Patients came to us with signs suggestive of deep vein thrombosis and the malignancy would be detected later. One of the patients was diagnosed with brain tumor one month after the warfarin therapy was stopped. Four patients had resistance to warfarin (one of them with occult brain tumor) but did not experience recurrence of thrombosis. One case of thrombosis recurrence in our study could be attributed to the low level of anticoagulation, but there were 2 cases of pulmonary embolism with INR values within the therapeutic limits. It is possible that we underestimated the true recurrence rate, as only two of five nonsurvivors were autopsied. The high proportion of unrecognized fatal pulmonary embolism in a series of autopsies of cancer patients supports this hypothesis (15,16).

Current evidence suggests that the tissue factor/factor VIIa pathway mediates the most abundant procoagulant stimulus in malignancy via the increase in thrombin generation. The tissue factor has been suggested to mediate pro-metastatic properties via both coagulation-dependent and coagulation-independent pathways and also implicated in tumor neoangiogenesis (1-4). Antineoplastic therapy, including single and multiagent chemotherapy, hormonal therapy, and hematopoietic growth factors, is a significant precipitant of venous thrombosis. Other risk factors contributing to the development of thrombosis are advanced age, surgery, immobilization, and the use of central venous catheters.

The incidence of cancer in patients with venous thromboembolism varies with their age, approaching 10% in those over 50. The extent of evaluation of an underlying occult malignancy should be dictated by clinical judgment. Unexplained recurrent deep vein thrombosis, resistance to warfarin, and thrombosis at unusual sites should arouse suspicion of an occult malignancy (15).

In our study, five patients suffered venous thromboembolism after surgery, four after surgery and during chemotherapy, and one after surgery and during irradiation. According to available medical data, they all received anticoagulant prophylaxis. Such patients require intense prophylactic measures comparable to those usually recommended in major orthopedic surgery (17). It should be noted that 17 patients in our study had INRs within therapeutic limits after a month of therapy, but only 12 had INR > 2 after 6 months. Since INR sometimes behaves in unpredictable manner, physicians aim to avoid potentially lethal bleeding by decreasing the intensity of anticoagulation therapy after 6 months.

Palareti et al (12) found that patients with malignancy had higher bleeding rate than patients without malignancy (major bleeding 5.4% vs 0.9%) and probably higher recurrence rate (6.8% vs 2.5%). In our small sample the bleeding rate of 3/31 and recurrence rate of 1/31 were comparable to their results.
In a recent study, the achieved activated partial thromboplastin time has been shown to be predictive of the recurrence of thrombosis and recanalization rate (13). Caprini et al (14) found the INR to be predictive of deep vein thrombosis resolution rate; 3/4 of clots resolved within one year of acute event when INR levels were within targeted values. In another study the same group found 20-30% resolution rate after 4 months of therapy and 45-56% improvement (clot retraction) (18). After 12 months, resolution rate was around 55%, depending on the affected venous segment. There was no difference in resolution rate regarding the site or load of the clot (18). The latter finding is in line with our results. Other investigators also emphasize the role of enhanced endogenous fibrinolytic system mediated by increased tissue activator of plasminogen activity (19,20). van Ramshorst et al (21) reported that thrombus recanalization occurred mainly in the first 6 weeks after diagnosis, whereas thrombus resolution occurred eventually in 75% of the occluded vein segments within 6 months. Our study found 56% thrombus resolution rate but in a different setting. The maintenance of therapeutic INRs is more difficult in malignant patients because of activated coagulation system and resistance to warfarin. At times, these patients bleed easily, even when having appropriate INRs, as a result of local tumor finding or low platelets count (22). Low incidence of bleeding in our study is in contrast to these findings, but it may be a result of our sampling of patients. None of our patients were at the terminal stage of disease, when there is an incipient multi-organ failure and an overall damage of bone marrow and other organs as a consequence of therapy.

In conclusion, maintenance of INRs in cancer patients with venous thromboembolism seems to be very important for accomplishment of the clot resolution. In our study, patients with cancer did not have serious bleeding and recurrence of thrombosis more frequently than patients who did not have malignant disease, but this might be a consequence of a small sample of patients. The patients with cancer and baseline INRs>1.6 were not eligible for our study because they were at higher risk of bleeding when on oral anticoagulant therapy, and proper therapy for them, in our opinion, were low molecular weight heparins. This may also be an explanation for bleeding rate in our patients. The main limitation of our study was a small sample of patients. Further research with large number of patients is necessary to define the most appropriate therapeutic approach to patients with thrombosis and malignancy.

References
21 van Ramshorst B, van Bemmelen PS, Hoeneveld H, Faber JA, Eikelboom BC. Thrombus regression in deep vein...


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