Symptomatic Venous Thromboembolism in Cancer Patients Treated With Chemotherapy

An Underestimated Phenomenon

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Background: The exact incidence of venous thromboembolism (VTE) in cancer patients is unknown, partly because of confounding factors. Prophylactic treatment is warranted in surgical patients with cancer because of a high incidence of VTE. We performed a retrospective study to evaluate if the same applies for cancer patients treated with chemotherapy.

Methods: The medical records of 206 consecutive patients with malignancy, treated with chemotherapy, were identified. The kind of malignancy and chemotherapeutic treatment were recorded, as was the date of treatment. The records were reviewed for other risk factors for VTE, and were searched for proved deep venous thrombosis or pulmonary embolism.

Results: Of those 206 patients, 15 (7.3%) had proved VTE during or within 3 months after chemotherapeutic treatment. The annual incidence was 10.9%. The incidence of VTE was specifically high in the 39 patients treated with a combination of fluorouracil and leucovorin calcium because of colorectal cancer (6 [15%] of the patients were affected). The occurrence of VTE in the latter group of patients was not influenced by factors such as surgery, central venous catheters, or tumor load.

Conclusions: The annual incidence of VTE in patients treated with chemotherapy was high, specifically in patients with colorectal cancer treated with fluorouracil-leucovorin. If these observations are confirmed, trials to evaluate the use of prophylactic anticoagulant treatment should be conducted.

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The relation between cancer and venous thromboembolism (VTE) has been known since at least 1865, and it is generally accepted that the incidence of VTE in cancer patients is high. Nevertheless, the true incidence of VTE in cancer patients is unknown. One of the reasons for this lack of clarity is the presence of confounding factors. Most cancer patients need surgery for their malignancy, will be exposed to chemotherapy and/or intravenous catheters, and may become immobilized during their disease. The relation between VTE and different kinds of chemotherapy has been most extensively investigated in patients with breast cancer. In patients with breast cancer stage I or II, the incidence of VTE seemed to increase from 0.2% to 2.0% in those receiving chemotherapy. In most of those studies, patients were also treated with tamoxifen citrate, which itself is thrombogenic. In patients with high-grade glioma treated with chemotherapy, the incidence of VTE was 12% in a prospective study and 16% in a retrospective study. Finally, Grem et al reported an incidence of 17% in 36 patients with unresectable or metastatic colon carcinoma treated with a combination of fluorouracil and leucovorin calcium and granulocyte-macrophage colony-stimulating factor. These data suggest a significantly increased risk for VTE in patients with different kinds of malignancies who are receiving chemotherapy.

In general, prevention for VTE is not given to patients with cancer being treated with chemotherapy. However, in analogy with surgical patients, such a prophylaxis might be warranted if the incidence of VTE was demonstrated to be high enough. Therefore, we performed a retrospective study to evaluate the incidence of VTE among consecutive patients treated with chemotherapy for malignant disease in a teaching hospital in Amsterdam.
STUDY DESIGN AND POPULATION

We performed a retrospective, single-institution, cohort study. In the Slotervaart Hospital, all patients are registered according to the Systematic Information center for Health Care system, the Dutch medical registration system. This registration system enabled us to identify all patients, aged at least 18 years, treated with chemotherapy because of malignant disease between January 1, 1995, and January 1, 2000. A search of the registration systems of the internal medicine department and the oncology nurses revealed no additional cases. After identification, the computerized and the medical records of each patient were retrieved and evaluated. The data were retrieved according to the local rules of the medical ethical board.

DATA RETRIEVAL

Besides the age and sex of the patients, the kind of malignant disease and the various chemotherapeutic agents administered to each patient were recorded. We retrieved the exact date the chemotherapy was started and stopped. Furthermore, we reviewed the records of all patients for the exact date and kind of surgery (if any) and the introduction of central venous catheters. In addition, we registered the use of coumarin or heparin calcium derivatives. The radiological history of all patients was checked for the performance of ultrasonography of the extremities, a ventilation-perfusion lung scan, and/or pulmonary angiography. In all patients with proved VTE, we actively searched the records and radiological reports for indicators of tumor load at the time of VTE.

STUDY DEFINITIONS

The malignant disease had to be proved by histological and/or cytological reports according to current standards. The stages of the various cancers are according to the definitions used by the American Joint Committee on Cancer/Union Internationale Contre le Cancer.20 The stage of disease was considered a marker for the tumor load. The criterion for deep venous thrombosis by compression ultrasonography was noncompressibility of a proximal vein.21 A perfusion-ventilation scan was diagnostic for a pulmonary embolism if the perfusion scan showed one or more segmental defects and the ventilation scan showed no abnormalities in the same segment(s) (mismatch).22,23 In case of a subsegmental mismatch or a matched defect (perfusion and ventilation defect), pulmonary angiography had to demonstrate pulmonary emboli.24

ANALYSIS

The incidence of VTE, for the entire group of patients, was expressed as a proportion and as an annual incidence. For this latter purpose, we considered the patients at risk for VTE during the treatment with chemotherapy and the first 13 weeks after the last treatment in analogy to postsurgical patients.26 We counted the periods at risk for VTE for all patients, and calculated the years at risk for VTE and the subsequent incidence of VTE per year. In addition, the proportion of patients with VTE was calculated for subgroups of patients defined by type of cancer and chemotherapeutic regimen. If fewer than 6 patients had a specific hematological or solid malignancy, we rubricated them as “other hematological” and “other solid,” respectively. If fewer than 6 patients were treated with a specific (combination of) chemotherapeutic agent(s), we classified them as “other for hematological malignancy” and “other for solid malignancy,” depending on the underlying malignancy.

If applicable, the 93% confidence interval was calculated using statistical software (StatXact, version 3.0; Cytel Software Corp, Cambridge, Mass).

RESULTS

PATIENT POPULATION

In total, 209 patients with cancer who were treated with chemotherapy because of malignant disease were identified. For 206 (98.6%) of these patients, the hospital medical records were available for review. The mean age at the start of chemotherapy was 58 years (range, 20-88 years), and 116 patients (55.5%) were women. The most common malignancies were colorectal carcinoma, non-Hodgkin disease, breast carcinoma, ovarian carcinoma, multiple myeloma, and Kaposi sarcoma (Table 1). In 8 (3.8%) of the 209 patients, central venous catheter (7 Port-A-Cath systems [Deltec, Inc, St Paul, Minn] and 1 percutaneously inserted central venous catheter) access was present, because of medication or feeding (n=5) or inaccessible peripheral veins (n=3). In 94 (45.6%) of the 206 patients, surgical treatment had preceded the chemotherapeutic treatment. The mean interval between surgery and chemotherapy was 7.9 weeks (range, 2-34 weeks). The average period of chemotherapeutic treatment was 22.6 weeks (range, 1-145 weeks). One patient received anticoagulant treatment because of a heart valve prosthesis. Two patients were immobile during the chemotherapeutic treatment. None of the patients was treated with epoetin alfa.

INCIDENCE OF VTE

Overall, 15 (7.3%) of the 206 patients had a proved VTE during, or within 3 months after, chemotherapy. The characteristics of these patients are shown in Table 2. One patient had a retinal vein thrombosis. Two patients had an upper limb thrombosis, 4 had a pulmonary embolism (fatal in 2 of them), and 8 had a deep venous thrombosis of the lower limb. Of these latter 8 patients, 2 had bilateral deep venous thrombosis.
In the entire group of patients, the annual incidence of VTE was 10.9% (95% confidence interval, 6.1%-18.0%).

**RISK FACTORS FOR VTE**

**Surgery**

None of the patients with VTE underwent surgery in the 12 weeks preceding chemotherapeutic treatment. In 5 patients, surgery had been performed 13 to 39 weeks (mean, 21.5 weeks) before the initiation of chemotherapeutic treatment.

**Central Venous Catheters**

One of the patients with a central venous catheter had a symptomatic deep venous thrombosis a year before the implantation of a central venous access device (Port-A-Cath); none of the others experienced signs of VTE.

**Timing of VTE With Regard to Chemotherapy**

Nine patients had a VTE during their chemotherapeutic treatment. In 2 patients, the VTE became symptomatic within a week after their last treatment. Two patients experienced the first symptoms within a month and 2 within 2 months after their last treatment.

**Chemotherapeutic Treatment**

The incidence of VTE in relation to chemotherapeutic regimen is given in **Table 3**. Venous thromboembolism was most frequent in the 41 patients treated with 5 daily bolus injections of fluorouracil-leucovorin every month (6 [15%] of these 41 patients had a VTE; 95% confidence interval, 6%-29%). Of these patients, 18 had a limited colorectal carcinoma (Dukes classification C) and in 3 (17%) of these 18 patients, a VTE occurred.

**Tumor Load**

Tumor load was limited in 4 patients with a VTE, of whom 3 had a colorectal carcinoma. The disease of the other patients was extensive, with multiple metastases, stage III multiple myeloma, or stage IV non-Hodgkin disease.

**COMMENT**

Our retrospective analysis indicates that among patients with malignant disease treated with chemotherapy, the risk of symptomatic VTE is high, with an annual incidence of 10.9%. In general, VTE occurred in...
all subgroups, defined by kind of malignancy, extent of malignancy, and chemotherapeutic regimen. The observed incidence of VTE is in concordance with the incidence reported by others,2,7,13,14 as mentioned before. This also applies to the remarkably high incidence (6 [15%] of 39 patients) in those with colorectal carcinoma treated with fluorouracil-leucovorin.15

Our study had several limitations. Because of its retrospective nature, the data could be underestimated. We could only detect patients with symptomatic and objectively proved VTE, and could have missed patients with subtle clinical manifestations of VTE or patients who were treated for probable VTE without performing adequate diagnostic tests. On the other hand, the high incidence could be solely because of chance and could represent a high variation of the normal spectrum.

Because of the relatively few patients, it was impossible to demonstrate a statistically significant difference between the subgroups.

We were not able to find a matched control group because of highly standardized treatment policies for cancer patients in our hospital. In earlier treatment studies of cancer patients comparing a chemotherapeutic regimen with placebo, the occurrence of VTE was seldom mentioned in the toxicity score.

It is unlikely that the high incidence of VTE in patients with colorectal carcinoma treated with fluorouracil-leucovorin can be attributed to the colorectal carcinoma alone: in large epidemiological studies,27-29 the reported incidence of VTE in patients with colorectal malignancies did not differ from incidences in patients with other adenocarcinomas. Most patients with breast carcinoma were treated with a fluorouracil-containing chemotherapeutic regimen as well, so it is unlikely that fluorouracil alone is responsible for the excess of VTE in the patients treated with fluorouracil-leucovorin.

Several mechanisms have been proposed to be responsible for the hypercoagulable state of cancer patients treated with chemotherapy. Alterations in coagulation factors,30-33 anticoagulant proteins34-36 and endothelial cells33,37-42 have been shown to occur following the administration of various cytotoxic agents. In an experimental model, the endothelium of fluorouracil-treated rabbits was badly damaged, leading to intima disruption and denudation of underlying structures, with accompanying platelet accumulation and fibrin formation.43 Two groups31,32 demonstrated a significant increase in fibrinopeptide A levels in patients treated with fluorouracil.

Others44-36 discovered a reduction of protein C levels of different degrees during treatment with cyclophosphamide, methotrexate, and fluorouracil, but a link to clinically apparent VTE could not be made. Therefore, the exact pathophysiological mechanism for the observed excess of VTE in our group of patients remains to be determined.

In conclusion, the annual incidence of VTE in patients treated with chemotherapy in this study is high (10.9%). A remarkably high incidence of VTE was shown in patients with a colorectal malignancy treated with fluorouracil-leucovorin (15%). Before recommending prophylactic anticoagulant treatment to this category of patients, the observation should be confirmed and the efficacy and safety of the anticoagulants in this setting should be tested; the effect on mortality and the impact on the quality of life of these patients should be tested as well.

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