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CHAPTER 8

Extensive screening for occult malignant disease in idiopathic venous thromboembolism: a prospective randomized clinical trial.

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Summary

Patients with symptomatic idiopathic venous thromboembolism and apparently cancer-free have an approximate 10% incidence of subsequent cancer. Apparently cancer free patients with acute idiopathic venous thromboembolism were randomized to either the strategy of extensive screening for occult cancer or to no further testing. Patients had a 2-year follow-up period. Of the 201 patients, 99 were allocated to the extensive screening group and 102 to the control group. In 13 (13.1%) patients, the extensive screening identified occult cancer. In the extensive screening group, a single (1.0%) malignancy became apparent during follow-up, whereas in the control group a total of 10 (9.8%) malignancies became symptomatic relative risk, 9.7 (95% CI, 1.3–36.8; P < 0.01). Overall, malignancies identified in the extensive screening group were at an earlier stage and the mean delay to diagnosis was reduced from 11.6 to 1.0 months (P < 0.001). Cancer-related mortality during the 2 years follow-up period occurred in two (2.0%) of the 99 patients of the extensive screening group vs. four (3.9%) of the 102 control patients (absolute difference, 1.9% (95% CI), 5.5–10.9)). Although early detection of occult cancers may be associated with improved treatment possibilities, it is uncertain whether this improves the prognosis.

Introduction

There is convincing evidence that the risk of subsequent clinically overt malignancy is increased among patients with idiopathic deep-vein thrombosis or pulmonary embolism (1–10). Part of these malignancies can be identified by routine assessments at the time of the thrombotic event (3–6,8,11). However, in patients who are apparently cancer-free at baseline, there remains an approximate 10% incidence of subsequent overt malignant disease in the early period after the thrombotic event (1,7,9,10). These malignancies are not limited to certain subtypes but involve virtually all body systems (1–11). The high incidence does not automatically imply that screening for malignancy is indicated in these patients since it is unknown whether a substantial proportion of the malignancies can be diagnosed, whether the diagnosed malignancies are treatable, and most importantly, whether the early discovery of these malignancies ultimately prolongs life rather than merely advance the date of diagnosis. Moreover, screening could be harmful due to additional invasive procedures to follow-up abnormalities. Therefore, we embarked on a randomized trial that assessed the clinical outcome in patients with idiopathic venous thromboembolism in whom routine clinical examinations did not reveal malignancies. These patients were allocated to either extensive diagnostic screening or no further diagnostic studies and were followed up for 2 years.

Methods

Patients

This was a randomized multicenter clinical study in apparently cancer-free patients with acute idiopathic venous thromboembolism to compare the strategy of extensive screening for occult malignant disease with no further testing. Consecutive patients were eligible for inclusion if they had a documented first episode of symptomatic deep-vein thrombosis of the lower extremity or pulmonary embolism as described elsewhere (12). The thrombotic episode had to be idiopathic, i.e. occurring in the absence of known malignant disease, trauma of the leg, surgical procedures or immobilization within 6 months, confirmed spontaneous venous thromboembolism in a first degree relative, thrombocytosis (platelet count >600 · 109/L), deficiency of antithrombin, protein C or S or presence of circulating lupus anticoagulant, estrogen use, pregnancy or childbirth. In
addition, the attending physicians performed a routine screening for malignant disease, including a clinical history, thorough physical examination focusing on telltale signs and symptoms of malignant disease, laboratory tests (i.e. CBC, AST, ALT, ALP, calcium and urinalysis) and chest X-ray. Patients were excluded if they had previously documented venous thromboembolism, were below 25 years of age, or were unable to attend follow-up because of geographic inaccessibility. Patients passing this screen of criteria were included in the study and were randomized. The protocol was approved by the Institutional Review Board of the participating centers and was endorsed by the International Society of Thrombosis and Haemostasis and the Italian Society for Cancer Research (13).

Randomization procedures

Randomization was performed centrally. According to the Zelen design (14), patients randomized to extensive screening were informed about the study, the screening procedures and their potential risks, and were asked for written informed consent. Patients randomized to the control group were not informed about the study and consequently not asked to give informed consent.

Intervention

Patients randomized to the extensive screening group were offered ultrasound of the abdomen, including the pelvis, followed by CT-scan of these areas, gastroscopy or double contrast barium swallowing, colonoscopy or sigmoidoscopy followed by barium enema, hem occult, sputum cytology and tumormarkers including carcinoembryonic antigen (CEA), a-fetoprotein (a-FP) and CA125. These tests were extended with mammography and Pap smear for women and transabdominal ultrasound of the prostate (performed before the CT-scan) and total specific prostatic antigen (PSA) for men. These investigations had to be completed within a four-week period from the diagnosis of venous thromboembolism. If the screening suggested the presence of a malignant process, further investigations were performed according to current standards. As patients allocated to the control group were not informed about the study, patients and their physicians were not discouraged to search for malignant disease.

Follow-up

All patients had their routine follow-up visits for the index thrombotic event at 3, 12 and 24 months, respectively. Follow-up was continued for a period of up to 24 months. At these visits, special attention was paid to the recent medical history. To avoid diagnostic suspicion bias, the medical history concerning general health, hospital admission and occurrence of signs and symptoms of cancer were obtained on a standardized form by a physician unaware of allocation of the patient. If malignant disease had become apparent during follow-up, information from the attending specialist was sought after consent of the patient.

Outcome events

The primary outcome event consisted of cancer related mortality, defined as death due to a malignant disease itself, or death due to complications of diagnostic or surgical procedures performed to diagnose or treat cancer. The secondary outcome event consisted of the cluster of cancer-related mortality and documented residual malignancy or recurrent malignancy at 24 months. An additional outcome of interest was the sensitivity of the diagnostic work-up for occult malignancy. All potential outcome events were reassessed centrally by experts unaware of strategy assignment.
Biometrics

The prevalence of occult cancer at the time of the thrombotic episode was estimated to be 10% in patients with idiopathic venous thromboembolism (1). It was expected that approximately half of these patients would die during the 2 years of follow-up, resulting in a cancer-related mortality of 4–6%. In order to detect a 75% reduction of cancer-related mortality, as ample size of 500 patients per group was required (type 1 error 0.05, two-sided; type 2 error 0.2). Due to a lower than anticipated number of participating centers, and an increasing tendency among physicians in study centers to perform screening tests for occult cancer in control patients, it was decided to stop the study prematurely.

All analyses were performed based on the intention to treat principle. The difference in incidence of the primary and secondary outcomes was compared between the two groups and an exact 95% confidence interval was calculated (StatXact, version 3.1). The sensitivity of screening was calculated as the number of malignancies identified at screening divided by the total number of malignancies found during screening and the 2 years of follow-up in the extensive screening group. The proportion of early stage malignancies defined as T1 or T2 without loco-regional or distant metastases (N0 M0) was compared between the two groups using the Fisher’s exact test’s the factor V and prothrombin gene mutations were discovered during conduct of the study and it was the intention of the protocol to exclude patients with thrombophilic conditions, it was decided to analyze the occurrence of cancer in relation to these mutations.

Results

Study population

Between January 1993 and December 1997, a total of 1020 patients were referred to the participating hospitals with acute deep-vein thrombosis or pulmonary embolism. Of these patients, 681 had a recognized risk factor for venous thrombosis. Of the 339 remaining patients with idiopathic venous thromboembolism, 138 were not included because of previous venous thromboembolism (n = 65), malignant disease identified at routine physical examination, history taking, laboratory assessment, or chest X-ray at referral (n = 32), geographic inaccessibility (n = 25), or age below 25 years (n = 16). Therefore, a total of 201 patients were included into the study. Of these patients, 99 were allocated to the extensive screening group and 102 to the control group. Only patients allocated to the extensive screening group were informed about the study, the type of screening procedures, and were asked to participate. All these 99 patients signed informed consent forms. The demographic and clinical characteristics of the patients of both groups are provided in Table 1.

Performance of screening procedures

All patients allocated to the extensive screening group underwent screening procedures and the complete battery of tests was done in 79 (80%) of the patients. The number of patients who underwent each test is specified in Table 2. In a total of 13 (13.1%) patients, this work-up resulted in a histologically confirmed diagnosis of malignancy. In Table 3, the timing of diagnosis, type and stage of cancer are given. All patients who had cancer identified were treated according to current standards. CT scan of the abdomen and pelvis was able to detect 10 of the 13 malignancies of which five were also found by ultrasound assessment. The additional three malignancies were identified by sputum cytology, colonoscopy, or mammography. Gynecologic examination and gastroscopy each found one malignancy that was
also identified on CT scan. In four other patients, the extensive diagnostic work-up revealed neoplastic growths that were benign on biopsy. Three of these were tubular adenomas of the colon, and one a myoma of the uterus. Prostate-specific antigens were elevated in seven of the 54 males. In one of these seven patients indeed a prostatic carcinoma was present, which had also been seen on ultrasound and CT scan. In the other six patients, transrectal ultrasound procedures, including guided biopsies if needed, revealed no malignant disease. CEA, a-FP, or CA-125 were positive in 27 patients, of whom seven had malignant disease. A test for occult fecal blood was positive in 15 patients of whom one had intestinal malignancy. In total, 49 patients had at least one of the markers with a positive result of whom eight (16.3%) had cancer. The addition of ultrasound to the markers would have resulted in the identification of 10 of the 13 cancers. In four patients, the procedures for screening or confirmation of diagnosis of malignancy were associated with minor transient complications. Of the 102 patients in the control group, 23 had one or more screening tests done. The number of patients who had each test done is specified in Table 2. This crossover occurred mainly in the second half of the inclusion period. These screening procedures did not identify any malignancies in the control group.

**Cancer during follow-up**

All patients completed the two-year follow-up period. In the extensive screening group, a single (1.0%) malignancy became apparent during follow-up, whereas in the control group a total of 10 (9.8%) malignancies became symptomatic for a risk difference of 8.8% (95% CI, 0.8–19.1; P < 0.01; Table 3). All patients with cancer were treated according to current standards. Therefore, 13 of the 14 malignancies that became apparent in the extensive screening group were identified at the time of screening, for a sensitivity of initial screening of 93% (95 CI, 66–100%). Overall, malignancies were less advanced in patients belonging to the extensive screening group than those of the control group (Table 3). Stage T3 was found in one patient of the extensive screening group as compared with four patients of the control group. In total, nine of the 14 patients with cancer in the extensive screening group vs. two of the 10 patients in the control group had a T1 or T2 stage malignancy without loco-regional or distant metastases (P = 0.047). Overall, malignancies were identified in the extensive screening group with a mean delay of 1.0 month vs. 11.6 months in the control group (P < 0.001).

**Outcome events**

The primary outcome, cancer related mortality, occurred in two (2.0%) of the 99 patients of the extensive screening group vs. four (3.9%) of the 102 control patients, for an absolute difference of 1.9% (95% CI, 5.5–10.9%). The secondary outcome, the cluster of cancer related mortality, presence of objectively documented residual or recurrent malignancy occurred in five (5.1%) of the 99 patients of the extensive screening group as compared with eight (7.9%) of the 102 control patients, for an absolute difference of 2.8% (95% CI, 6.3–13.4%). Additional observations the factor V and prothrombin gene mutations were present in 33 (16.5%) of the participating patients. A diagnosis of cancer was made in one (3.0%) of the 33 patients with these thrombophilic mutations vs. 23 (13.7%) in the 168 patients without such defects. Most cancers were identified in elderly patients, i.e. three (4.9%) in the 61 patients who were 60 years of age or younger vs. 21 (15.0%) in the 140 patients above this age (Table 4).

**Discussion**

This randomized study was designed to resolve the longstanding debate on the need for an extensive screening for occult malignancy in patients with idiopathic venous thromboembolism (4,8,11,15–19). The results show that extensive screening is able to detect hidden malignancies with a high degree of sensitivity. The extensive screening led not only to an early detection of malignancies, but also to the identification of malignancies at an earlier stage. Due to the limited sample size, the effects on the prognosis remain uncertain. Several unforeseen circumstances contributed to the failure to include the projected 1000 patients in the study. Only five of the
more than 40 potential participating centres could contribute patients to the study. The first major obstacle was created by the proposed use of the Zelen randomization procedure (14). This procedure was chosen since many potential investigators found it unethical to inform patients about a substantial risk (i.e. 10%) for malignant disease without taking further measures if they were randomized to the control arm. Thus, this design allowed for the usual clinical practice in the control patients without exposing them to the emotional upset created by the information about the possibility of hidden cancer without performing any further screening. While many investigators would not participate in the study using a conventional randomization procedure, the Zelen randomization procedure caused rejection of the protocol by several medical ethics committees (including that of the coordinating center). The key argument for these rejections was that patients would participate in a study without being asked. The second major obstacle was the existence of strong opinions on the need for screening for malignancy in patients with idiopathic venous thromboembolism, despite the lack of conclusive clinical evidence. Thus, while some medical ethics committees rejected the protocol because of the absence of screening for occult cancer in the control group, other centers could not start because the proposed extensive screening was judged to be unethical. Finally, the identification of cancer at an apparent early stage in the extensive screening group led to an increasing tendency among physicians in the participating hospitals to initiate screening for cancer in the control patients. These problems prompted a premature termination of the study after inclusion of only 201 patients over a period of 5 years. Does the failure to complete the study as projected render its results useless? Although the study did not reach a conclusive result for the primary clinical outcome, lessons learnt from the study might be of benefit for future management of patients with idiopathic venous thromboembolism. First, the results of the study confirm the earlier findings of an association between idiopathic venous thromboembolism and the approximately 10% risk of clinically manifest malignancy during the period thereafter (1,7,9,10). Second, the extensive screening was able to identify the majority of occult malignancies as shown by the low number that became apparent afterwards in comparison to the control group. Third, malignancies detected by screening were found on average 10.6 months earlier than malignancies that were found in the control group. Also the stage of malignancies was on average less advanced in the extensive screening group than those in the control group. Despite the conduct of the total battery of tests in 80% of patients in the extensive screening group, no major complications were observed. Based on our difficulties in conducting the study, it is unlikely that a definitive large randomized trial addressing the effect of screening on cancer related mortality would ever be completed. Therefore, physicians are confronted with the challenge to define their approach to patients with idiopathic venous thromboembolism based on the current evidence. We believe that the results of our study support screening for malignancy in patients with idiopathic venous thromboembolism. A substantial proportion of occult cancers could indeed be identified and many were in a relative early phase allowing for curative treatment. This could be achieved without procedure-related complications. However, the psychological effects and economical consequences are not established yet. Although the data do not demonstrate conclusively that early diagnosis resulted from screening ultimately prolongs life, the collective observations make such a beneficial effect likely. Which screening test should then be used? Clearly, the first step should consist of specific investigations guided by signs and symptoms elicited by clinical history or the results of thorough physical examination or routine laboratory tests (4,8,11). In the current cohort, such an initial work-up identified 32 (9.4%) malignancies among 339 patients. If this initial work-up is negative, our data suggest that a systematic CT-scan of the pelvis, abdomen and chest would have the highest yield. This is based on the observation that CT-scan of pelvis and abdomen identified 10 cancers, while after positive sputum cytology at screening in one patient and after the occurrence of clinical symptoms an other patient the CT-scan of the chest showed the malignant mass. Therefore, CT-scan of pelvis, abdomen and chest alone could have detected 12 of the 14 cancers at baseline, for the price of a single false-positive result. Alternatively, markers (CEA, CA125, a-FP, PSA), and Haem occult combined with abdominal and pelvic ultrasound would have identified 10 of the 14 cancers at baseline. However, falsely positive markers would have led to a variety of additional diagnostic procedures in 39 additional patients, rendering this approach more
laborious. Whether all patients with idiopathic venous thromboembolism should be selected to undergo screening or that such screening could be limited to certain subgroups of patients cannot be derived from our study. Subgroup analysis showed that the risk for occult cancer was higher among elderly patients and in those without thrombophilic conditions. Obviously, the yield of extensive screening is highly dependent on the actual prevalence of undetected cancers (Table 4). In summary, the risk for occult cancer in patients with idiopathic venous thromboembolism approximates 10%. A selected diagnostic work-ups capable of identifying the majority of these cancers. The earlier detection is likely to be associated with improved treatment possibilities and thus prognosis.
References


