Does cancer diagnosis in elderly patients with deep venous thrombosis modify the middle-term outcome?

Summary. Objectives: To assess whether cancer screening in elderly patients with deep venous thrombosis (DVT) could modify their outcome. Design: Prospective, case-control study. Setting: Department of internal medicine and gerontology at Angers University Hospital, from February 1999 to January 2000. The 5.8-year-follow-up was realized by means of postal questionnaires sent to patients’ family doctors. Participants: One hundred and eighteen DVT patients hospitalized for DVT were recruited and stratified into two groups (A and B) according to the age of 75 years and matched for 118 controls (groups C and D). Measurements: DVT was confirmed by a venous ultrasonography and cancer was screened by routine investigations. Outcome measures over 5.8 years: mortality rate and cancer diagnosis. Results: Cancer diagnosis during hospitalization was comparable between groups (A: 10.2% vs C: 5.1%, p = 0.488; B: 8% vs D: 0%, p = 0.06). After discharge, it was similar (A and C: 5.1%; B and D: 3.4%). Cancer-related deaths were not statistically different (A: 6/21 vs C: 5/23, p = 0.85; B: 6/8 vs D: 1/5, p = 0.103). Mortality ratios were comparable (A: 35.6% vs C: 39%, p = 0.849; B: 13.5% vs D: 8.5%, p = 0.555), but a high mortality was noted in the group B as compared with group C (57% vs 8%; p = 0.0006) in the first year following DVT. Conclusion: Cancer diagnosis at the time of DVT does not modify outcomes of patients aged 75 years and older. Hence, a systematic screening for cancer among older patients could be unjustified. Other case-control studies are necessary to validate these results.

Key words: cancer, deep venous thrombosis, elderly, vital outcome

The strong association between venous thromboembolism (VTE) and cancer was first described by Armand Trousseau in 1865 [1]. Since then, multiple studies have reported a higher incidence of cancer during the first year after VTE diagnosis in relation to the general population [2-4]. The relationship between the age of occurrence of VTE and the diagnosis of subsequent cancer is still controversial. In several studies [5-7], the risk of subsequent cancer appeared to be lower in the sub-group of elderly patients, while in other studies the risk was higher in older subjects [8, 9].

In spite of a high cancer-related mortality rate, particularly in the first two years after diagnosis of VTE [2, 5, 10], a disagreement subsists about screening for occult cancers at time of VTE diagnosis. Some [3, 7, 11] recommend a limited work-up including thorough history taking coupled with an attentive physical examination while others [12-17] propose a routine screening by adding a basic laboratory tests: complete blood count, measurement of ESR, liver and renal functions, urinalysis and chest X-ray. On the other hand, an extensive screening for occult cancers is supported by a number of researchers [18-22] including serum protein electrophoresis, tumor markers, abdominal ultrasonography and/or CT scan, upper gastrointestinal endoscopy and eventually a mammography. However, there is little evidence to date that such extensive screening would be worthwhile or cost-effective in term of vital outcome [15, 23] and cancer-related mortality [17, 24, 25]. At our knowledge, data regarding this issue in elderly population is absent.

Therefore, the aim of our study was to assess if the detection of cancer at time or after VTE diagnosis in elderly would have an impact on middle-term outcome and cancer-related mortality.

Methods

Study design

Cases

In order to assess the outcomes of elderly and young adult patients hospitalized for deep venous
thrombosis (DVT), we have recruited prospectively and consecutively all patients hospitalized for DVT over a one-year period. After they gave their informed consent for participation in the study, cases were stratified into two groups according to the age of 75 years which corresponds to the median age of patients hospitalized for DVT in the department. Group A included patients with DVT aged 75 years and older and group B included those less than 75 years.

**Controls**

Controls were identified by using a computerized database of the department’s activity and selected among patients who had not been hospitalized for DVT in the same study period and in the same department from which the cases were recruited. Controls were matched for age (± 2 years) and sex, randomly selected and then classified into two groups: C and D.

**Follow-up**

After discharge, outcomes of all patients included in the study have been assessed by means of postal questionnaires sent to patients’ family doctors.

**Participants**

All patients admitted at the department of internal medicine and gerontology of the university hospital of Angers, from February 1999 to January 2000 with a diagnosis of DVT, were recruited prospectively and consecutively. The DVT was confirmed by a venous ultrasonographic examination according to usual criteria [26]. At admission, screening for occult cancer was carried out for all cases and controls by a routine investigation proposed by many authors [12-17], including:

- a thorough history taking;
- an attentive physical examination;
- a simple laboratory tests (complete blood count, measurement of ESR, liver and renal functions and urinalysis);
- a chest X-ray.

For each patient with or without DVT, two main criteria were searched for throughout the follow-up period:

- diagnosis of new malignancies;
- death from any causes mainly cancer-related.

**Statistical analysis**

Data were collected by means of Microsoft Excel 7.0 (Microsoft®, USA) software. Statitical analysis was done with the Statview 4.5© (Abacus concept®, USA) software. Probability threshold of 0.05 was considered significant. For the qualitative variables, the comparison between two groups was done by Chi-2 test with a Yates’ correction if necessary. The Mann-Whitney test was used to compare between quantitative variables of two groups. Survival curves were established according to Kaplan-Meier method and the comparison between them was made by the log-rank test.

**Results**

During the one-year study period, 118 patients hospitalized for DVT have been recruited. The age distribution was similar with 59 patients aged 75 years and older (group A) and 59 patients under 75 years (group B). Two matched control groups, each of 59 patients free from DVT, have been constituted (group C and D respectively). So, the study included 236 patients. The mean age and sex distributions of

<table>
<thead>
<tr>
<th>Patients ≥ 75 years</th>
<th>Control</th>
<th>Patients &lt; 75 years</th>
<th>Control</th>
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<tbody>
<tr>
<td>DVT*</td>
<td>C</td>
<td>DVT*</td>
<td>D</td>
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<tr>
<td>Patients’ groups</td>
<td>A</td>
<td>59</td>
<td>59</td>
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<tr>
<td>Patients’ number</td>
<td>39</td>
<td>59</td>
<td>59</td>
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<tr>
<td>Mean age (years)</td>
<td>82.5 ± 4.9</td>
<td>82.6 ± 4.6</td>
<td>55.9 ± 15</td>
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<tr>
<td>Sex (F/M)</td>
<td>40/19</td>
<td>40/19</td>
<td>36/23</td>
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<tr>
<td>Patients lost to follow-up</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Patients with a known cancer at admission</td>
<td>10</td>
<td>7</td>
<td>10</td>
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<tr>
<td>Cancer diagnosis during hospitalization</td>
<td>6</td>
<td>3</td>
<td>5</td>
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<tr>
<td>Cancer diagnosis during follow-up period</td>
<td>3</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Total number of cancers</td>
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<td>13</td>
<td>17</td>
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<td>Total number of deaths</td>
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<td>23</td>
<td>8</td>
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<td>Number of cancer-related deaths</td>
<td>6</td>
<td>5</td>
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</tbody>
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* DVT = deep venous thrombosis

Table 1. Comparison between patients with deep venous thrombosis and their group control according to age.
the study population are shown in the table 1. Six patients aged 75 years and older were lost to follow-up: 2 patients with DVT and 4 in the control group while 8 patients under 75 years were lost to follow-up: 4 in each group.

Prevalence of cancer

The prevalence of a known cancer at admission was not statistically different between patients aged 75 years and older and those under 75 years (17/59 [28.8%] vs 14/59 [23.7%]; p = 0.676).

The comparison between patients hospitalized for DVT and their group control according to age shows that the number of cancer diagnosis during hospitalization for DVT among patients under 75 years was high, but not significant, as compared with their controls (5/59 [8.5%] vs 0/59 [0%]; p = 0.061) and it was statistically indifferent between the 2 groups of patients aged 75 years and older (6/59 [10.2%] vs 3/59 [5.1%]; p = 0.488). Throughout the period of 5.8-year-follow-up, the number of cancer diagnosis was comparable between groups:

– 6 patients aged 75 years and older, 3 in each group;
– 4 patients under 75 years, 2 in each group.

No significant difference was found in the total number of cancers among both groups of patients aged 75 years and older (19/59 [32.2%] vs 13/59 [22%]; p = 0.301) while the total number of cancer was significantly higher in patients with DVT under 75 years as compared with their controls (17/59 [28.8%] vs 6/59 [10.2%]; p = 0.005).

Mortality

The mortality ratio in the group of patients with DVT aged 75 years and older was comparable to that of the control group (21/59 [35.6%] vs 23/59 [39%]; p = 0.849) even when patients lost to follow-up have been excluded (21/57 [36.8%] vs 23/55 [41.8%]; p = 0.730). The number of cancer-related deaths was not significantly different in these 2 groups (6/21 vs 5/23; p = 0.85).

The mortality ratio in the cohort of patients under 75 years was not statistically different in the groups B and D (8/59 [13.5%] vs 5/59 [8.5%]; p = 0.557), even after exclusion of patients lost to follow-up (8/55 [14.5%] vs 5/55 [9.1%]; p = 0.555), and cancer related deaths were comparable between both groups (6/8 vs 1/5; p = 0.103).

Survival curves of the study cohort compared with that of the general population for the entire follow-up period are shown in figure 1. There is no statistical difference between the rate of survival of patients with DVT and their matched controls (Chi2 = 0.137), however, both group of patients have a lower rate of survival as compared with the general population (Chi2 = 32.57, degrees of freedom = 2; p < 0.01).

Survival curves of patients aged 75 years and older, with or without DVT, were not statistically different (log-rank = 0.163). In patients under 75 years in whom cancer was diagnosed at the time of a DVT, the first part of their survival curve reflects their precocious deaths within the first year after the DVT event, as compared with their matched controls (57% vs 8%; p = 0.0006). This difference decreased progressively to disappear by the end of the third year. At 5 years, the rate of survival of both group of patients younger than 75 years were not statistically different (log-rank = 0.61).

Discussion

Cancer and risk factor for VTE events

The cancer is an established risk factor for VTE events, although the accurate mechanism is not well known. The prevalence of patients with known cancer at the time of DVT reported in literature varies from 10 to 20% [22] and corresponds well with that in our study (18.5%). After exclusion of patients lost to follow-up, 4.9% of those with DVT developed a subsequent cancer, which is comparable to that found in other studies [22] (3.2-13.3%). The prevalence of concomitant diagnosis of cancer at time of DVT is high in our study (10.2%) as compared with that reported in literature (1.6 to 7.1%) [22]. This could be explained by differences between characteristics of studied populations: the number of included patients and their mean age. Also, it could be in relation to the type of DVT, whether idiopathic or secondary, since the prevalence of concomitant cancer in patients with idiopathic VTE, reported in same studies, was higher (3.3 to 12.9%) [22].

Relation between the age of appearance of VTE and cancer

The relation between the age of appearance of VTE and a subsequent diagnosis of cancer remains contradictory. Our study did not show significant difference in cancer incidence after an episode of DVT between patients aged 75 years and older and those under 75 years. This is not in agreement with other studies findings [5-10].

In the study of Baron et al. [7], the incidence of subsequent cancer within the year following the diagnosis of DVT was statistically lower in patients older than 65 years as compared with those younger than 65 years. However, this difference disappeared within the second year of follow-up.

Sorensen et al. [8] observed a lower subsequent cancer risk in patients older than 60 years as compared with younger ones, mainly within the first 6 months after an episode of DVT. This risk decreased to be similar to that of the general population at 12 months.

Goldberg et al. [5] found a high cancer incidence within the first 2 years following the diagnosis of DVT, mainly in patients under 50 years.

Mortality

Data concerning the outcome of patients with a cancer revealed by an episode of TVE, in term of mortality are limited [11, 18]. In the large analysis of Sorensen et al. [11] comporting more than 34000 patients with cancer, the work-team concluded that the prognosis of patients in whom cancer was diagnosed at the same time of or within one year after an episode of VTE tend to be relatively poor with a higher mortality rate. In this analysis the patients mean age varied between 69 and 72 years.

At our knowledge, no study has assessed the outcome of elderly patients in whom the cancer was revealed by a VTE. In our study, a cancer diagnosis at
the time of or after an episode of DVT had no impact neither on the mortality ratio nor the number of deaths and it did not modify the vital prognosis of elderly patients aged 75 years and older at mean-term. On the other hand, we observed precocious deaths related to cancer in the first year following the diagnosis of DVT among patients under 75 years as compared with their controls, which is in concordance with results of other studies [5-7].

Systematic screening

These findings raise the question of the usefulness of an exhaustive screening for occult cancer in older patients with VTE. Many studies [16, 18, 24, 25, 27] showed that a systematic screening for cancer in case of VTE diagnosis did not improve overall survival nor prognosis, even with an exhaustive investigations [28], so most authors [29, 30] agree that in the absence of definitive data to demonstrate an advantage in terms of survival using invasive diagnostic tests and intensive follow-up, patients should undergo only routine tests.

Limitations of study

Our study has both strengths and limitations. All patients and controls have been included consecutively and recruited from a department of geriatric internal medicine that receives patients with a profile closer to that of the general population. A routine cancer screening, recommended by many authors [13-18, 29, 30], has been carried out for all of them. This limited work-up represents in practice, a significant time gaining and a considerable economy in term of health care expenditure. Another two strong points, the weak number of patients lost to follow-up and the duration of the follow-up period. On the other hand, a limitation of our study is that we considered neither TVP characters: idiopathic or secondary, recurrent or no, unilateral or bilateral, nor cancers identification: type, grade, localisation, extent of spread...

Conclusion

Our data show that in elderly aged 75 years and older the association of cancer to DVT did not modify their middle-term vital outcome and the diagnosis of cancer at time of an episode of DVT did not affect the overall survival and hat no impact on the number of cancer-related deaths in these patients. Hence, a systematic screening for cancer among older patients, mainly by exhaustive investigations and in the absence of clinical orientations seems to be unjustified. However in younger patients, a careful screening for cancer could be useful in term of vital outcome and survival. Other case-control studies concerning the elderly population and compering a large number of patients are necessary to confirm results of this study.


