Thrombosis-related complications and mortality in cancer patients with central venous devices: an observational study on the effect of antithrombotic prophylaxis

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Background: Recent guidelines do not recommend antithrombotic prophylaxis (AP) to prevent catheter-related thrombosis in cancer patients with a central line.

Patients and methods: This study assessed the management of central lines in cancer patients, current attitude towards AP, catheter-related and systemic venous thromboses, and survival.

Results: Of 1410 patients enrolled, 1390 were seen at least once in the 6-month median follow-up. Continuous AP, mainly low-dose warfarin, was given to 451 (32.4%); they were older, with a more frequent history of venous thromboembolism (VTE), and more advanced cancer. There was no difference in catheter-related thrombosis in patients given AP or not (2.8% and 2.2%, odds ratio 1.29, 95% confidence interval 0.64–2.6). The median time to first catheter-related complication was 120 days. Systemic VTE including deep and superficial thromboses and pulmonary embolism, were less frequent with AP (4% versus 8.2%, P = 0.005). Mortality was also lower (25% versus 44%, P = 0.0001). Multiple logistic regression analysis found only advanced cancer and no AP significantly associated with mortality. No major bleeding was recorded with AP.

Conclusions: Current AP schedules do not appear to prevent catheter-related thrombosis. Systemic VTE and mortality, however, appeared lower after prophylaxis.

Key words: cancer, catheter-related thrombosis, central venous catheters, deep vein thrombosis, low-dose warfarin, pulmonary embolism

introduction

Recent guidelines do not recommend antithrombotic prophylaxis (AP) for the prevention of central venous catheter (CVC)-related thrombosis in cancer patients [1]. These recommendations are based on the results of recent prospective randomized trials that found no advantage of low-molecular-weight heparin (LMWH) [2, 3] or warfarin [4] in preventing catheter-related thrombotic complications. These findings run counter to earlier evidence of a significant protective effect of mini-warfarin or LMWH [5, 6].

Today’s lower rate of events probably helps explain these differences, but also important is the inconsistent nature of diagnosis of catheter-related complications, which range from occlusive forms or those involving the whole vessel wall to much more limited ones such as catheter tip thrombosis or sleeve thrombosis. Then, two different methods are used to detect and classify them [7].

The observational prospective study described here was designed to assess the management of central venous devices (CVDs) in cancer patients in current practice. Information was collected on the clinical course, particularly catheter-related thromboses and systemic complications. The results cover a broad series of strictly consecutive patients, and therefore give a fairly reliable picture of Italian oncologists’ attitudes. It is clear that observation needs to be extended beyond the effects on a single end point such as catheter-related
The following events were recorded during follow-up.

**outcomes**

Catheter-related complications: pneumothorax, catheter malposition, infection (of the pocket and the catheter), catheter breakage, disconnection or occlusion (one-way flow only, or unusable for blood sampling or infusion), symptomatic venous thrombosis at the catheter site, and symptomatic DVT of the subclavian/axillary axis where the catheter was placed or the superior vena cava, and decubitus sores. Systemic thromboembolic events: symptomatic PE and DVT other than on the venous axis of the CVD, symptomatic SVT. In case of clinical suspicion of VTE, each center undertook to do all the necessary instrumental examinations such as venography to check for occlusion or thrombosis in the catheter or the surrounding area; compression ultrasonography was done if DVT was suspected in other sites, pulmonary scintigraphy or computed tomography scan for clinically suspected PE.

**removal of the CVD:** recording the date of removal and reason.

**bleeding:** classified as major in case of intracranial, retroperitoneal, or intraocular hemorrhage or bleeding causing hemoglobin to drop by ≥3 g/dl. Bleeding causing death or requiring more than two units of transfused blood was considered major.

**course of the neoplastic disease progression or death with date and cause.**

**patients and methods**

**study design**

This observational prospective study was conducted in 18 hospital oncology units in Lombardy (northern Italy), all members of the ‘Polonord’ group. Patients were enrolled during the 30 months from January 2003 to June 2005. The study protocol was approved by the institutional review boards of each hospital, and all patients provided written informed consent. The accrual was stopped after the studies by Verso et al. [2] and Couban et al. [4] were published, since their results raised ethical questions about the utility of AP in centers that routinely employed it.

**patients**

Consecutive patients attending each hospital were eligible if they had solid or hematological tumors, were aged over 18, and had a CVD: a totally implantable CVD (PORT), indwelling CVC, or a peripherally inserted catheter (PICC). Each hospital was free to decide which device was most suitable for each individual patient. Catheters could be silicone or polyurethane, with double or single lumen. Similarly, each center applied its own routine policy for managing these patients, including whether or not to prescribe AP when or after the catheter was placed.

Data were collected in a computer database, using the Web server method. Each center had exclusive, univocal access, with ID and password, to the e-CRF (electronic clinical record form) and could enter patients’ data online. Each center was asked to provide the following information in a specific enrolment form: patients’ main demographic details, type of CVD, position of the catheter tip, type of tumor and stage, clinical history as regards previous venous thromboses, past and current treatments (chemotherapy, radiotherapy, hormone therapy, and growth factors), whether they flushed the CVD, and if so at what intervals, and whether or not the patient received AP. Follow-ups for each patient were scheduled every 4 months during the first year, every 6 months during the second and third years or until removal of the CVD. During follow-up, a record was kept of any catheter-related complications (defined below), systemic venous thromboembolism (VTE), meaning deep venous thrombosis (DVT) of the upper or lower limbs, excluding DVT at the catheter site, superficial venous thrombosis (SVT) of the upper or lower limbs, pulmonary embolism (PE), bleeds, and removal of the CVD giving details of the reasons and the progression of the cancer.

**statistical analysis**

Demographic data and clinical features were analyzed using descriptive methods. Quantitative variables were summarized using mean and standard deviation. Categorical variables were summarized as counts and percentages. Baseline analysis included all enrolled patients. Categorical variables were compared using the chi-square test. Common odds ratio (OR) and its 95% confidence intervals (CI) were also calculated. Continuous variables were compared using unpaired t-tests. P values were calculated for the two-tailed test with α = 0.05. For analysis, patients who had received periprocedural prophylaxis were considered part of the group not given prophylaxis. The proportion of patients receiving continuous AP was calculated overall, and according to the specific treatment used.

Survival was analyzed by the Kaplan–Meier method. The log-rank test was used to compare survival curves for AP and no AP. The Cox proportional hazards regression model was employed to assess the relationship between deaths and the following covariates: age, sex, history of VTE, type of cancer (breast, colon/rectum, gastric, lung, advanced disease or not), type of CVD, chemotherapy or not, and AP or not. All these covariates, except age (continuous), were included in the model as dichotomous variables. A backward procedure was used. SPSS version 12.0 (Chicago, IL) was used for statistical analysis.

**results**

In 30 months, 1494 CVD were placed in the 1410 patients enrolled. A total of 1390 were seen at least at one 4-month follow-up. The median follow-up was 6 months. Of the 20 cases enrolled but who had no follow-up data, one had been assigned continuous AP (low-dose warfarin) and the other 19 received no prophylaxis. Their baseline characteristics were analyzed, although the clinical course was not in fact known. Table 1 summarizes the patients’ main characteristics at baseline.

All centers stated they flushed the CVD, at intervals ranging between 1 and 4 weeks during chemotherapy and 3 and 4 weeks in the intervals between cycles.

Table 2 sets out the types and frequencies of continuous AP. Periprocedural AP was only given to 20 patients (1.4%), 13 LMWH, and seven unfractioned heparin. So most patients
received the AP on a continuous basis: 76% of cases received minidose warfarin (40% according to Levine et al. [8]); 24% received LMWH. The median treatment time for patients given continuous AP was 6 months.

Table 3 divides the patients according to whether or not they received continuous AP. Those assigned continuous AP were significantly older, more frequently already had a history of VTE, and at baseline had more advanced cancer.

CVD-related complications in the groups receiving continuous AP or not are shown in Table 4. The CVD had to be removed because of complications in 26 of those receiving AP (5.8%) and in 93 not given continuous AP (9.9%). This difference was significant (OR = 0.55, 95% CI 0.35–0.87).

The median time of CVD removal was 140 days in patients receiving continuous AP and 110 days in those without AP. The catheter had to be repositioned in 76 cases. Median time to the first catheter-related thrombotic complications in the 1390 patients was 120 days, and the mean was 177 ± 138 days (range 30–540, interquartile 120–240 days).

Table 5 lists the systemic VTE in patients with or without AP. The cumulative rate was significantly higher among patients not given AP and this finding was mainly driven by the reduction of SVTs. There were no differences in the rate of systemic VTE or CVD-related thrombosis according to different types of CVD (PORT, CVC, or PICC).

mortality

During the study 535 patients died, giving 38% overall mortality. Of these, 419 were in the no-AP group (44%) and 116 were receiving AP (25%); the difference was highly significant (OR = 0.42, 95% CI 0.33–0.55, P = 0.0001). Figure 1 reports the Kaplan–Meier survival curves of patients receiving continuous AP or not. Mean general survival was 8.6 ± 6 months, with a median of 8 months. Overall, 150 patients were lost to follow-up (10.7%), 137 with no AP (14%) and 13 with (2.8%) AP. The difference was highly significant (OR = 0.17, 95% CI 0.009–0.25, P = 0.0001). Multiple regression analysis showed that only advanced disease (OR: 2.74, 95% CI 1.9–3.8, P = 0.00001) and no continuous AP (OR: 1.69, 95% CI 1.3–2.1, P = 0.00001) were significantly associated with mortality.

safety

Four percent of patients given mini-warfarin had INR values of more than two; there were no major bleeds.

discussion

This study on thrombotic complications in cancer patients with a CVD covers the biggest series reported so far on an observational, prospective basis. The follow-up was also long. Only 30% of patients with a CVD received continuous AP, although guidelines in use when this study was conducted recommended this strategy to prevent axillary-subclavian thrombosis, despite the questionable solidity of the evidence [9].
Table 4: CVD-related complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prophylaxis (n = 451) (%)</th>
<th>No prophylaxis (n = 939) (%)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decubitus</td>
<td>5 (1.1)</td>
<td>14 (1.5)</td>
<td>NA</td>
<td>0.7</td>
</tr>
<tr>
<td>Disconnection</td>
<td>2 (0.4)</td>
<td>8 (0.8)</td>
<td>NA</td>
<td>0.6</td>
</tr>
<tr>
<td>Infection</td>
<td>11 (2.4)</td>
<td>50 (5.3)</td>
<td>0.44</td>
<td>0.020</td>
</tr>
<tr>
<td>Malposition</td>
<td>11 (2.4%)</td>
<td>19 (2.0)</td>
<td>NA</td>
<td>0.7</td>
</tr>
<tr>
<td>Occlusion</td>
<td>5 (1.1%)</td>
<td>9 (0.9)</td>
<td>NA</td>
<td>0.8</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1 (0.2)</td>
<td>4 (0.4)</td>
<td>NA</td>
<td>0.5</td>
</tr>
<tr>
<td>Breakage</td>
<td>2 (0.4)</td>
<td>22 (2.3)</td>
<td>0.18</td>
<td>0.020</td>
</tr>
<tr>
<td>Catheter-related</td>
<td>13 (2.8%)</td>
<td>21 (2.2%)</td>
<td>NA</td>
<td>0.5</td>
</tr>
<tr>
<td>venous thrombosis</td>
<td>Total complications</td>
<td>50 (11.1)</td>
<td>147 (15.6)</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.047–0.94)</td>
<td></td>
</tr>
</tbody>
</table>

CVD, central venous devices; OR, odds ratio; CI, confidence interval; NA, not applicable.

Table 5: Systemic venous thromboembolism

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prophylaxis (n = 451) (%)</th>
<th>No prophylaxis (n = 939) (%)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis</td>
<td>10 (2.2)</td>
<td>40 (4.2)</td>
<td>0.50 (0.25–1.05)</td>
<td>0.07</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>4 (0.9)</td>
<td>10 (1)</td>
<td>0.93 (0.2–2.9)</td>
<td>0.98</td>
</tr>
<tr>
<td>Superficial vein thrombosis</td>
<td>4 (0.9)</td>
<td>27 (2.9)</td>
<td>0.3 (0.1–0.86)</td>
<td>0.031</td>
</tr>
<tr>
<td>Total systemic thrombotic events</td>
<td>18 (4.0)</td>
<td>77 (8.2)</td>
<td>0.46 (0.27–0.78)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.

Previous observational studies found that in clinical routine AP was not in fact widely employed in this type of population [10]. As Table 3 shows, the frequency of continuous AP was not higher for patients with breast cancer, although minidoses of warfarin are reportedly effective in metastatic disease regardless of whether the patient has a CVD [8].

In the present study, patients appeared to be assigned continuous AP or not depending on their baseline characteristics. Older patients with previous VTE or with advanced disease (see Table 3)—basically those at the highest risk of VTE or death—were most frequently assigned prophylaxis. The frequency of symptomatic CVD-related VTE in studies coming close to this in size ranges between 3.1% and 4.3% [4, 11], and we found 2.4%, which is in line with and confirms the findings of recently published randomized trials. This low rate, contrasting with the first figures from early studies, probably reflects better techniques for inserting these devices, correct positioning of the catheter tip, and the use of less thrombogenic materials. The lack of venographic assessment of catheter-related complications in the present study, however, is certainly a limit and precludes any further conclusions on the real frequency of this complication. The median time to the first CVD-related thrombosis in our series was 120 days, compared with 30–40 days from recent and earlier studies [11, 12]. The timing for recording the end points in interventional studies was largely on the basis of the earlier figures, and in most cases was no longer than 90 days, except in the study by Karthaus et al. [3] where venography was done at 20 weeks. Assessing catheter-related thrombosis too soon might imply failure to obtain a full picture of how the therapy affects the risk of CVC-related complications when a catheter with a longer life span is used; the catheter employed in this series, mainly Port-A-Cath, is usually left in place much longer than other types, for instance, PICC, which have been mentioned more in recent studies [11]. For the same reasons, depending on the type of catheter employed, we did not try to draw any statistical inference on the median time of removal of the CVD in our patients; besides complications, some basic features of the device itself—for instance, whether it is peripherally or centrally inserted—can influence the need for removal.

The effect of continuous AP on catheter-related thrombosis (mainly minidose warfarin according to Levine et al. [8]) in our series was comparable to other recent reports: protection was inadequate against CVD-related thrombosis, defined as catheter tip thrombosis or sleeve thrombosis or subclavian-axillary DVT taken together. AP, however, did appear to offer significant protection against the burden of systemic VTE, although the favorable cumulative effect was mainly driven by the reduction of SVTs which was the only factor that reached statistical significance.

In contrast with these findings, recently published observational studies, such as CATHEM, in patients with CVD, mainly with hematological cancers, also assessed all the end points linked to VTE, systemic and catheter related, together, and found AP gave no protection [13]. Couban et al. [4] too reported that minidose warfarin failed to protect against non-catheter-related VTE. The difference between our study findings and the others may lie partly in the different types of patient recruited and the sizes of the populations. Our findings do agree with those reported by Levine et al. [8] in patients with advanced breast cancer. Those patients were all given minidose warfarin, with a detailed schedule in which INR was checked after 6 weeks of therapy; this significantly reduced symptomatic VTE, but had no effect on mortality.

The large population and long follow-up have the advantage that in this study we could assess how prophylaxis affected the end points likely to be influenced by continuous AP, i.e. not only catheter-related thrombosis but also the systemic VTE burden and overall mortality. The mortality rate in the group given AP was significantly lower, and the difference persisted even after multivariate analysis taking age, previous VTE, tumor type, and therapy received as covariates. It is not easy to suggest an explanation for this, and the literature offers contradictory results on the action of warfarin in cancer patients [14, 15].

Our findings indicate that AP, mainly with minidoses of vitamin K antagonist had a positive effect on survival, at least in the short term, in a selected population of cancer patients with a CVD. It would be, however, wrong to draw any firm conclusions from an observational, nonrandomized study like this, in which, in addition, a fairly high proportion of patients was lost to follow-up. The only reasonable conclusion that can
be drawn from our findings is that in clinical practice AP tends to be used in patients with central lines if they have selected clinical features, meaning a high risk of VTE and death. In such cases, AP with minidose warfarin does not ensure protection against catheter-related thrombosis, but might well reduce the risk of systemic VTE, at least the symptomatic forms, with no negative effect on survival.

The proposal to reserve continuous AP for selected patients [16] such as those with advanced disease or previous VTE seems practicable using the therapeutic regimens employed today—i.e. minidose warfarin—but further randomized, interventional studies are undoubtedly needed to clarify these points.

**contributors**

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**references**


