Prophylaxis of catheter-related deep vein thrombosis in cancer patients with low-dose warfarin, low molecular weight heparin, or control: a randomized, controlled, phase III study.

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DISCLOSURE SLIDE

The authors declare no Conflict of Interest that may be inherent in their work
BACKGROUND

• Catheter-related deep vein thrombosis (CRDVT) are known to be an important risk factor of morbidity and mortality in cancer patients.

• The incidence ranges from 0.3% to 28.3% in symptomatic patients and from 27% to 66% when asymptomatic CRDVT are included.

• Current guidelines of American and European Societies do not recommend prophylactic anticoagulant treatment for cancer outpatients BUT major studies focused on symptomatic CRDVT.
ENDPOINTS

• Phase III, open-label, randomized prospective trial (1999-2009, started before guidelines)

• **Main objective**: rate of symptomatic and asymptomatic CRDVT of the ipsilateral upper limbs and cervical veins
  – with or without prophylaxis,
  – excluded intra-luminal thrombosis

• **Secondary objectives**:
  – Rate of symptomatic venous thromboembolic events in other venous territories (catheter-unrelated)
  – Feasibility of prophylaxis
  – Comparison between the 2 different anticoagulants in case of positive main objective
STUDY DESIGN

Randomization

A

Control (N=140)

B or C

Warfarin (1mg/day) (N=138)

LMWH (recommended dose in medical prevention) (N=142)

Participation of each patient: 3 months

Evaluations:

– D1 and D90 (or sooner in case of symptoms):
  • Systematic Doppler ultrasound (US) of the upper limbs and cervical veins
  • Venography by CVAD

– Clinical and Biological exams: each chemotherapy course (every 3 or 4 weeks)

– Weekly platelets control under LMWH, no other blood coagulation tests
INCLUSION CRITERIA

- Aged 18 years or older
- Life expectancy > 3 months
- Performance status < 3, ambulatory patients
- Solid tumour: locally advanced or metastatic status (excepted cerebral metastasis)
- Subcutaneous central venous catheter inserted for less than 7 days
- Starting a first line of chemotherapy
- No contra-indication to anticoagulation
- No formal indication for anticoagulation or anti-platelets agents in preventive or curative treatments
- No recent history of DVT in the past 6 months
STATISTICAL CONSIDERATIONS

Sample size
– Based an incidence of DVT of 40%* in absence of prophylaxis versus 20% in presence of prophylaxis during the 3-month period
– Allowing also a comparison between the 2 regimens of prophylaxis

→ 420 patients (α=5%, β=10%)

Analysis
- Intention to treat
- Using consort guidelines
- Chi square tests

Randomized patients
\((N = 420)\)

- **Control**
  \((N = 140)\)
  - Withdrawn or no data
  \((N = 3)\)
  - Initial baseline assessment
  \((N = 137)\)
  - Analysed population
  \((N = 135)\)
  - Lost to follow up
  \((N = 2)\)

- **Warfarin**
  \((N = 138)\)
  - Withdrawn or no data
  \((N = 3)\)
  - Initial baseline assessment
  \((N = 135)\)
  - Analysed population
  \((N = 134)\)
  - Lost to follow up
  \((N = 1)\)

- **LMWH**
  \((N = 142)\)
  - Withdrawn or no data
  \((N = 1)\)
  - Initial baseline assessment
  \((N = 141)\)
  - Analysed population
  \((N = 138)\)
  - Lost to follow up
  \((N = 3)\)

**407 patients were evaluable**
# PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (N=135)</th>
<th>Warfarin (N=134)</th>
<th>LMWH (N=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, years (range) (SD)</td>
<td>60 (21-85) (+/-11.8)</td>
<td>59 (24-81) (+/-10.9)</td>
<td>61 (21-84) (+/-10.6)</td>
</tr>
<tr>
<td>Male</td>
<td>84 (62 %)</td>
<td>81 (60 %)</td>
<td>78 (56 %)</td>
</tr>
<tr>
<td>Metastatic setting</td>
<td>42%</td>
<td>45%</td>
<td>51%</td>
</tr>
<tr>
<td>Locally advanced setting</td>
<td>28%</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>Resected metastatic or locally advanced disease</td>
<td>30%</td>
<td>27%</td>
<td>21%</td>
</tr>
<tr>
<td>Lower extremity of catheter higher than T5</td>
<td>7 (5.5%)</td>
<td>7 (5.5%)</td>
<td>8 (5.8%)</td>
</tr>
<tr>
<td>Hb &lt; 10 g/dl</td>
<td>4 (3.0%)</td>
<td>8 (6.0%)</td>
<td>14 (10%)</td>
</tr>
<tr>
<td>Very high or high risk thrombogenic tumour</td>
<td>50 (37%)</td>
<td>40 (30%)</td>
<td>48 (35%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Stomach</td>
<td>14</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Lung</td>
<td>16</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Pelvic gynaecological</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Testicle</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bladder</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>85</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>Platelets ≥ 350x10⁹/L</td>
<td>42 (31%)</td>
<td>53 (40%)</td>
<td>49 (35%)</td>
</tr>
<tr>
<td>BMI ≥ 35 (kg/m²)</td>
<td>4 (3.0%)</td>
<td>2 (1.5%)</td>
<td>3 (2.0%)</td>
</tr>
</tbody>
</table>
# RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Control (N=135)</th>
<th>Anticoagulation (N=272)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRDVT thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic (N=12)</td>
<td>20 (14.8%)</td>
<td>22 (8.1%)</td>
<td>0.0357</td>
</tr>
<tr>
<td>Asymptomatic (N=30)</td>
<td>9 (6.7%)</td>
<td>3 (1.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 (8.1%)</td>
<td>19 (7.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean delay, days (range)</strong></td>
<td>45 (1-90)</td>
<td>54 (1-90)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Unrelated DVT thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic (N=8)</td>
<td>7 (5.1%)</td>
<td>2 (0.7%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Asymptomatic (N=1)</td>
<td>6 (4.4%)</td>
<td>2 (0.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (0.7%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Symptomatic thrombosis / Both DVT thrombosis</strong></td>
<td>15/27 (55.6%)</td>
<td>5/24 (20.8%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

→ 2 arterial thrombosis (myocardial infarction) in control arm

→ No difference between Warfarin and LMWH (p=0.2 for CRDVT, p=1 for unrelated DVT)
## ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Adverse event (under chemotherapy)</th>
<th>Control (N=135)</th>
<th>Warfarin (N=134)</th>
<th>LMWH * (N=138)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>1 (0.7%)</td>
<td>6 (4.5%)</td>
<td>3 (2.2%)</td>
<td>0.1361</td>
</tr>
<tr>
<td>Thrombocytopenia Grade 3-4 (NCI CTC v3.0)</td>
<td>12 (8.8%)</td>
<td>4 (3%)</td>
<td>7 (5.0%)</td>
<td>0.1039</td>
</tr>
<tr>
<td>Allergy</td>
<td>0</td>
<td>2 (1.5%)</td>
<td>0</td>
<td>0.1290</td>
</tr>
</tbody>
</table>

* No treatment-related death

* *3 patients developed renal failure under chemotherapy*
## DISCONTINUATION

<table>
<thead>
<tr>
<th></th>
<th>Control N=135</th>
<th>Warfarin N=134</th>
<th>LMWH N=138</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of discontinuation</td>
<td>34 (25%)</td>
<td>36 (27%)</td>
<td>45 (33%)</td>
</tr>
<tr>
<td>Mean delay of discontinuation (days)</td>
<td>37 (1-82)</td>
<td>36 (1-81)</td>
<td>38 (1-82)</td>
</tr>
<tr>
<td><strong>Reasons :</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant event</td>
<td>15 (11.1%)</td>
<td>20 (15%)</td>
<td>20 (14.5%)</td>
</tr>
<tr>
<td>Thrombosis event</td>
<td>17 (12.5%)</td>
<td>3 (2.2%)</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Non compliance</td>
<td>2 (1.5%)</td>
<td>3 (2.2%)</td>
<td>9 (6.5%)</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>0</td>
<td>4 (3.0%)</td>
<td>8 (5.8%)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>0</td>
<td>6 (4.5%)</td>
<td>5 (3.6%)</td>
</tr>
</tbody>
</table>

→ No difference between allocated arms
LIMITS

- Monocentric study
- Long-term inclusion
- Multiple chemotherapy protocols, no antiangiogenic drug
- Univariate analysis
- CRDVT rate less than scheduled initially
CONCLUSION

- Efficacy on symptomatic and asymptomatic CRVT of anticoagulation prophylaxis in ambulatory cancer patients with locally advanced or metastatic tumours
  - No difference between Warfarin and LMWH
  - No bleeding increase

- Burden of subcutaneous prophylaxis for patients
FUTURE

✧ Optimization of identification of high-risk hyper-clotting patients

✧ Testing of short-term prophylaxis

✧ Assessment of new oral anticoagulants