A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score

Melina Verso · Giancarlo Agnelli · Sandro Barni · Giampietro Gasparini · Roberto LaBianca

The association between cancer and venous thromboembolism (VTE) is well established [1]. Indeed, up to 20 % of cancer patients have a symptomatic VTE, which is recognized to be one of the leading causes of death in these patients [2].

Patients with cancer are heterogeneous concerning the risk for VTE. Some solid malignancies including pancreatic, lung, colon-rectum, ovarian, and brain cancer are associated with a particularly high risk for VTE. A risk assessment score for VTE, known as Khorana score, was validated for cancer patients treated with chemotherapy in order to identify high risk patients [2]. Among cancer patients receiving chemotherapy, rates of VTE seem to be particularly high in those receiving cisplatin or carboplatin-based chemotherapy as well as gemcitabine [3]. We designed a modified Khorana risk assessment score (the Protecht score) by adding platinum or gemcitabine-based chemotherapy to the predictive variables already taken into account in the Khorana score.

The role of antithrombotic prophylaxis in cancer patients receiving chemotherapy is currently an area of active investigation. Recently, in the Protecht (PROphylaxis of ThromboEmbolism during CHemoTherapy) study, a 50 % risk reduction in the incidence of thromboembolic complications is associated with nadroparin in these patients (NCT 00951574) [4]. The need for VTE risk assessment in cancer patients receiving chemotherapy has been emphasized in the most recent oncology guidelines [5] to optimize the benefit of antithrombotic prophylaxis in this setting.

The aims of this analysis were: (1) to evaluate the Protecht score, in comparison with the Khorana score, for identifying high risk cancer patients in a post hoc analysis of the placebo group of the Protecht study, and (2) to assess the effect of nadroparin for VTE prophylaxis according to the Khorana and Protecht scores.

The Khorana predictive score assigns 2 points to very high risk cancer sites (pancreatic or gastric) or 1 point to high risk cancer sites (lung, ovarian or bladder). In addition, 1 point is assigned for each of the following: platelet count ≥350 × 10^9/L, hemoglobin ≤10 g/dL, or use of erythropoietin-stimulating agents, leukocyte count ≥11 × 10^9/L and body mass index ≥35 kg/m^2. The assigned point for each variable included in the risk model was calculated on bases of the regression coefficients obtained from the derivation model. In the Protecht predictive score, treatment with cisplatin or carboplatin-based chemotherapy or gemcitabine adds 1 point and the association 2 points to the score based on the five predictive variables of the Khorana score. The assigned point for each variable was based on the estimation of risk as extrapolated from the literature. For the purpose of this analysis, the group of high-risk patients was identified by a score ≥3, whereas patients with a score between 0 and 2 were considered at low-intermediate risk for VTE.

For the Protecht investigators.

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Among the 1,150 evaluable Protecht patients, 381 were allocated to the placebo arm; in 378 of these patients an evaluation of Khorana and Protecht scores was performed. Of evaluated patients, 138 patients (36.5 %) received a cisplatin or carboplatin-based chemotherapy, 37 patients (9.8 %) gemcitabine and 49 patients (12.9 %) a combination of platinum compound and gemcitabine. The mean number of chemotherapy cycles was 3.39 (SD ± 1.54). Of the patients included in the analysis, 11.9 % (45/378) and 32.8 % (124/378) were in the high risk groups according to the Khorana and Protecht score, respectively. A total of 15 VTE was reported: 33.3 % (5/15) and 66.7 % (10/15) of VTE events occurred in the high risk patients according to the Khorana and Protecht score, respectively.

The second aim of this analysis was to assess the effect of nadroparin for VTE prophylaxis according to the Khorana and Protecht score. We included all patients randomized in the Protecht study: 769 patients of the nadroparin group and 381 patient of the placebo group. We found that the rate of VTE in patients identified as at high VTE risk according to the Khorana score was 4.5 % (3/70) in the nadroparin group and 11.1 % (5/45) in the placebo group with a RR = 0.38 (95 % CI 0.09–1.53). The number needed to treat (NNT) was 15. The rate of VTE in the 349 patients identified as at high VTE risk according to the Protecht score was 2.2 % (5/225) in the nadroparin group and 8.1 % (10/124) in the placebo group with a RR = 0.27 (0.09–0.78). The NNT was 17 (Table 1). Any difference in distribution of major bleeding event was documented in patients with high risk according to the Protecht score and receiving thromboprophylaxis with nadroparin.

In conclusion, regardless of the score used, the stratification of cancer patients seems to reduce the NNT from 50, in the whole study population, to <20. This post hoc analysis, limited by both retrospective nature and low rate of thromboembolic events, may have only an exploratory value. However, the Protecht score showed an improved ability to identify patients at high risk for VTE in comparison to the Khorana score. The efficacy analysis in high-risk patients receiving nadroparin compared to those receiving placebo showed a statistical significant RRR of 62 % of VTE complications according to the Khorana score, and a further 73 % RRR according to the Protecht score. Furthermore, an additional advantage of this new Protecht score is to potentially rule out an indication for prophylaxis in one out of three patients. Further investigations are needed to validate this modified risk assessment score, and to evaluate the risk/benefit ratio of this new approach for the focusing antithrombotic prophylaxis in high risk cancer patients.

**Conflict of interest** None.

**References**


**Table 1** Efficacy of nadroparin by VTE risk according to Khorana and Protecht scores

<table>
<thead>
<tr>
<th>VTE</th>
<th>Nadroparin n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>RR (95 % CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>15/769 (2.0)</td>
<td>15/381 (3.9)</td>
<td>0.49 (0.24–1.00)</td>
<td>50</td>
</tr>
<tr>
<td>Khorana score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE risk score 0–2</td>
<td>12/699 (1.7)</td>
<td>10/336 (3.0)</td>
<td>0.57 (0.25–1.32)</td>
<td>77</td>
</tr>
<tr>
<td>VTE risk score ≥3</td>
<td>3/70 (4.3)</td>
<td>5/45 (11.1)</td>
<td>0.38 (0.09–1.53)</td>
<td>15</td>
</tr>
<tr>
<td>Protecht score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE risk score 0–2</td>
<td>10/540 (1.9)</td>
<td>5/254 (2.0)</td>
<td>0.94 (0.32–2.72)</td>
<td>–</td>
</tr>
<tr>
<td>VTE risk score ≥3</td>
<td>5/225 (2.2)</td>
<td>10/124 (8.1)</td>
<td>0.27 (0.09–0.78)</td>
<td>17</td>
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</tbody>
</table>
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