Heparins, cancer and thrombosis: clinical and experimental studies
Smorenburg, S.M.

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THE EFFECTS OF VITAMIN K-ANTAGONISTS ON SURVIVAL OF PATIENTS WITH MALIGNANCY. A SYSTEMATIC REVIEW

Susanne M. Smorenburg, Roel Vink, Hans-Martin Otten, Francis Swaneveld, Harry R. Büller
SUMMARY

Various experimental studies have shown that tumor development and metastasis can be inhibited by anticoagulants, including vitamin K-antagonists. However, it is still a matter of debate whether anticoagulant treatment also affects cancer progression in man. We systematically reviewed all published clinical reports concerning effects of vitamin K-antagonists, as compared to no or placebo treatment on survival of cancer patients. Before analysis, studies were classified on methodological strength, to avoid the potential for bias. One-year mortality rates were extracted or calculated. Five randomized studies and one prospective, non-randomized study that reported effects of vitamin K-antagonists on survival of patients with various types of cancer were included in the analysis. A subgroup analysis was performed to evaluate whether vitamin K antagonists have differential effects in diverse types of cancer. Although a non-statistically significant trend towards mortality reduction was observed in the subgroup of patients with small cell lung carcinoma (SCLC), the results do not provide sufficient evidence to warrant treatment with vitamin K-antagonists in patients with cancer with the aim of improving survival.

INTRODUCTION

Venous thromboembolism is a recognized complication of malignancy (1). Even in the absence of clinically evident thrombotic disease, cancer patients commonly have laboratory signs of coagulation activation (2;3). The biologic significance of this activation in cancer patients is not clear, but experimental and pathological studies have indicated that the hemostatic system may play a crucial role in cancer spread (4-9). Hence, it has been postulated that anticoagulant agents, such as vitamin K-antagonists and heparins, platelet aggregation inhibitors and agents that affect fibrinolysis may inhibit progression of malignancy. Indeed, various experimental studies have shown that tumor growth and metastasis can be inhibited by anticoagulants (10-14). However, it is still a matter of debate whether anticoagulant treatment also affect cancer progression in man. Thus far, various clinical studies have evaluated effects of anticoagulant treatment on survival of cancer patients, but most of these studies are methodologically imperfect and, therefore, do not allow for definitive conclusions. To estimate the effects of anticoagulant treatment on survival, the analysis should be limited to investigations with a minimal of bias. In a recent systematic review of effects of unfractionated heparin on survival of cancer patients, we first categorized studies according to their methodological strength (15). When limited to the strongest studies, the results did not reveal convincing evidence that unfractionated heparin affects survival of patients with malignancy. To address the issue whether and to what extent vitamin K-antagonists affect survival of cancer patients, we performed a similar analysis of all available clinical studies that reported effects of vitamin K-antagonists, in comparison with placebo or no treatment on mortality of cancer patients.
METHODS

SELECTION OF STUDIES

To identify eligible reports in which effects on survival of patients with cancer of vitamin K-antagonists versus placebo or no treatment were evaluated, a computer-assisted search in Medline, Embase and Current Contents databases was performed over the period 1966-1999. Terms that were used for the search were both MESH terms and text words ‘coumarins’, ‘warfarin’, ‘vitamin K-antagonists’, or ‘oral anticoagulants’, in combination with ‘neoplasms’, ‘cancer’ and ‘survival’. All titles and abstracts of the selected studies were screened for controlled clinical trials investigating effects of vitamin K-antagonists, as compared to placebo or no (additional) treatment on survival of patients with malignancy. The references of all articles were cross-checked to identify additional papers. When studies reported incomplete data, the authors were contacted to retrieve additional information, if available.

QUALITY ASSESSMENT OF STUDIES

Potentially eligible studies were evaluated independently by two authors for methodological strength. Studies were classified as level 1 when: (1) the study was properly randomized; (2) the study groups were treated equally besides intervention; (3) dosage and duration of anticoagulant treatment was specified and (4) the follow-up was complete. Studies which were non-randomized but fulfilled criteria 2, 3 and 4 were classified as level 2 studies. Other studies, i.e. cohort studies or not appropriately controlled studies were excluded from the analysis.

DATA EXTRACTION AND STATISTICAL ANALYSIS

From all level 1 and level 2 studies, the one-year total-mortality rates were extracted or calculated. The follow up was limited to this one-year mortality to allow for a uniform assessment of the effects of vitamin K-antagonists across all studies. Odds ratios for patients treated with vitamin K-antagonists or placebo/no (additional) treatment were calculated separately for each study and then pooled over the studies using the Mantel-Haenszel method when appropriate (16). A statistical test of homogeneity was used to decide whether trials could be combined. The test analyzes whether differences in effects of treatment over individual trials are consistent with natural variations around a constant effect. One-year survival rates of patients with either small cell lung cancer (SCLC) or colorectal cancer were also analyzed separately in level 1 studies.

RESULTS

The initial literature search identified 19 articles that reported effects of vitamin K-antagonists on survival of cancer patients. Five studies fulfilled the criteria for level 1 (17-21) whereas one study was classified as level 2 (22). All other investigations were excluded from further analysis because they were cohort studies (23-27), lacked appropriate control groups, i.e. the study groups were not
equally treated besides intervention with vitamin K-antagonists (28-32), used a mixture of anticoagulant agents, which precluded the analysis of effects of vitamin K-antagonists alone (33), or were published in part elsewhere (20;34). The details of level 1 and 2 studies are presented in Table 1.

**Level 1 Studies**

Five randomized studies were found that evaluated effects of vitamin K-antagonists versus placebo or no treatment on survival of cancer patients. A total of 1443 patients were included in these studies, 725 patients received vitamin K-antagonists, and 718 patients belonged to the control group. In the study of Zacharski et al., patients with various types of cancer were included and divided in categories, including (1) limited or disseminated SCLC, (2) limited or disseminated non-small cell lung cancer (NSCLC), (3) NSCLC without evidence of disseminated disease, following 'curative' surgery or radiation therapy, (4) disseminated or local recurrence of colorectal cancer, (5) disseminated prostate cancer, and (6) head and neck cancer with recurrent or progressive disease following adequate primary treatment (20). Patients in the active treatment arm received therapeutic dosages of warfarin in addition to conventional therapy for the respective malignancies. In this study, warfarin treatment was maintained lifelong.

In the study of Daly et al. (17), patients with resectable colon cancer (Dukes B or C) were randomized after resection to therapeutic dosages of warfarin for a period of 2 years or no anticoagulant therapy. Neither group received chemotherapy.

In the other 3 studies, patients received lower dosages of warfarin with a target prolongation of the international normalized ratio (INR) of 1.3-1.9 (19), or a prolongation of the prothrombin time of 1.4-1.6 or 1.5-2 x, respectively (18;21). Warfarin was given throughout courses of chemotherapy to patients in the active treatment arm, whereas control patients received placebo or no additional treatment to chemotherapy (Table 1). In the studies of Maurer et al. (21) and Chahinian et al. (18), effects of warfarin in addition to chemotherapy were studied on survival of patients with limited SCLC or extensive SCLC, respectively. In the study of Levine et al. (19), the initial study question pertained to the efficacy of low dose-warfarin in terms of reduction in venous thromboembolic complications during chemotherapy for metastatic breast cancer. As a consequence of variability in the frequency and duration of chemotherapy for the respective malignancies in the studies, the duration of warfarin treatment varied.

The overall one-year mortality of cancer patients in level 1 studies was not significantly affected by vitamin K-antagonists. The calculated common odds ratio was 0.89 (95% CI: 0.70-1.13, Table 2). As discussed, the duration and intensity of warfarin treatment varied among the level 1 studies, but a correlation between the outcome of the studies and these factors could not be observed. Therapeutic dosages of warfarin or continuous treatment did not have any effect on survival.
The effects of treatment with vitamin K-antagonists on one-year mortality were also analyzed separately for patients with either SCLC or colon cancer. In the subgroup of patients with SCLC, the common odds ratio for one-year mortality of warfarin as compared to no additional treatment to chemotherapy was 0.72 (95% CI: 0.44-1.16) in favor of warfarin (Table 3). The calculated odds ratio for one-year mortality was 1.40 (95% CI: 0.65-3.00) for patients with colorectal cancer, in favor of no additive treatment (Table 4).

**Level 2 studies**

One prospective, non-randomized study evaluated effects of oral anticoagulant treatment on survival of patients with various types of cancer. Each alternate patient with the same type of malignancy received warfarin in therapeutic dosages in addition to conventional anticancer therapy, with a target prothrombin time that was double the normal control prothrombin time. Warfarin treatment was continued lifelong. A total of 128 patients were included, distribution of patient-characteristics among the 2 study groups was not reported. The odds ratio for one year mortality was 0.23 (95% CI: 0.09-0.54) (Table 5).

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**Table 1. Characteristics of level 1 and level 2 studies on effects of vitamin K-antagonists on one-year mortality of patients with various types of cancer**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of cancer</th>
<th>Number of patients</th>
<th>Intervention</th>
<th>Control</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maurer et al. (21)</td>
<td>SCLC</td>
<td>347</td>
<td>CT(^1) and RT(^1) warfarin during CT and RT, PTT 1.4-1.6</td>
<td>CT and RT</td>
<td>At least 100 months</td>
</tr>
<tr>
<td>Zacharski et al. (20)</td>
<td>SCLC</td>
<td>50</td>
<td>CT and RT(^1) warfarin continued indefinite, 2-3 x start PTT</td>
<td>CT and RT</td>
<td>At least 135 weeks</td>
</tr>
<tr>
<td>NSCLC</td>
<td></td>
<td>194</td>
<td>CT(^1) warfarin continued indefinite, 2-3 x start PTT</td>
<td>CT</td>
<td>At least 135 weeks</td>
</tr>
<tr>
<td>NSCLC, ‘curative’</td>
<td></td>
<td>41</td>
<td>RT warfarin continued indefinite, 2-3 x start PTT</td>
<td>RT</td>
<td>At least 135 weeks</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td></td>
<td>68</td>
<td>CT(^1) warfarin continued indefinite, 2-3 x start PTT</td>
<td>CT</td>
<td>At least 135 weeks</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td></td>
<td>24</td>
<td>HT(^1) warfarin continued indefinite, 2-3 x start PTT</td>
<td>HT</td>
<td>At least 135 weeks</td>
</tr>
<tr>
<td>Head and Neck cancer</td>
<td>SCLC</td>
<td>41</td>
<td>CT warfarin continued indefinite, 2-3 x start PTT</td>
<td>CT</td>
<td>At least 135 weeks</td>
</tr>
<tr>
<td>Chahinian et al. (18)</td>
<td>SCLC</td>
<td>189</td>
<td>CT warfarin during CT, 1.5-2x start PTT</td>
<td>CT</td>
<td>At least 30 months</td>
</tr>
<tr>
<td>Levine et al. (19)</td>
<td>Breast cancer</td>
<td>311</td>
<td>CT warfarin during CT, 6 weeks lmg daily, then INR 1.3-1.9</td>
<td>CT placebo</td>
<td>At least 15 months</td>
</tr>
<tr>
<td>Daly (17)</td>
<td>Colorectal cancer</td>
<td>178</td>
<td>CT warfarin for 2 years, 2 x start PTT</td>
<td>no treatment</td>
<td>At least 72 months</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td>Various types of cancer</td>
<td>128</td>
<td>warfarin continued indefinite, 2x start PTT</td>
<td>no treatment</td>
<td>At least 24 months</td>
</tr>
</tbody>
</table>

\(^1\) CT, chemotheraphy  
\(^1\) RT, radiotherapy  
\(^1\) HT, hormone therapy
<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of malignancy</th>
<th>OAC</th>
<th>no OAC</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maurer et al. (21)</td>
<td>SCLC</td>
<td>43/178</td>
<td>47/169</td>
<td>0.83 (0.50-1.38)</td>
</tr>
<tr>
<td>Zacharski et al. (20)</td>
<td>SCLC</td>
<td>15/25</td>
<td>21/25</td>
<td>0.29 (0.06-1.26)</td>
</tr>
<tr>
<td></td>
<td>NSCLC</td>
<td>77/96</td>
<td>78/98</td>
<td>1.04 (0.48-2.24)</td>
</tr>
<tr>
<td></td>
<td>NSCLC, ‘curative’</td>
<td>3/21</td>
<td>6/20</td>
<td>0.39 (0.06-2.27)</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer</td>
<td>20/34</td>
<td>18/34</td>
<td>1.27 (0.44-3.69)</td>
</tr>
<tr>
<td></td>
<td>Prostate cancer</td>
<td>5/14</td>
<td>3/10</td>
<td>1.30 (0.17-11.2)</td>
</tr>
<tr>
<td></td>
<td>Head and Neck cancer</td>
<td>17/20</td>
<td>14/21</td>
<td>2.83 (0.51-19.7)</td>
</tr>
<tr>
<td>Levine et al. (19)</td>
<td>Breast cancer</td>
<td>58/152</td>
<td>64/159</td>
<td>0.92 (0.57-1.48)</td>
</tr>
<tr>
<td>Daly (17)</td>
<td>Colorectal cancer</td>
<td>9/82</td>
<td>7/86</td>
<td>1.57 (0.49-5.20)</td>
</tr>
<tr>
<td>Chahinian et al. (18)</td>
<td>SCLC</td>
<td>75/103</td>
<td>69/86</td>
<td>0.66 (0.31-1.38)</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>322/725</td>
<td>327/718</td>
<td>0.89 (0.70-1.13)</td>
</tr>
</tbody>
</table>

(Table 2. One-year mortality rates of patients with various types of cancer, who received either vitamin K-antagonists or no (additional) therapy or placebo treatment in level 1 studies)

<table>
<thead>
<tr>
<th>Reference</th>
<th>OAC</th>
<th>no OAC</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maurer et al. (21)</td>
<td>43/178</td>
<td>47/169</td>
<td>0.83 (0.50-1.38)</td>
</tr>
<tr>
<td>Zacharski et al. (20)</td>
<td>15/25</td>
<td>21/25</td>
<td>0.29 (0.06-1.26)</td>
</tr>
<tr>
<td>Chahinian et al. (18)</td>
<td>75/103</td>
<td>69/86</td>
<td>0.66 (0.31-1.38)</td>
</tr>
<tr>
<td>All</td>
<td>133/306</td>
<td>137/280</td>
<td>0.72 (0.44-1.16)</td>
</tr>
</tbody>
</table>

(Table 3. One-year mortality rates of patients with SCLC who received either vitamin K-antagonists in addition to conventional therapy or no additional therapy in level 1 studies)

<table>
<thead>
<tr>
<th>Reference</th>
<th>OAC</th>
<th>no OAC</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zacharski et al. (20)</td>
<td>20/34</td>
<td>18/34</td>
<td>1.27 (0.44-3.69)</td>
</tr>
<tr>
<td>Daly (17)</td>
<td>9/82</td>
<td>7/96</td>
<td>1.57 (0.49-5.20)</td>
</tr>
<tr>
<td>All</td>
<td>29/116</td>
<td>25/130</td>
<td>1.4 (0.65-3.00)</td>
</tr>
</tbody>
</table>

(Table 4. One-year mortality rates of patients with colorectal cancer who received either vitamin K-antagonists or no (additional) therapy in level 1 studies)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of malignancy</th>
<th>OAC</th>
<th>no OAC</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thornes (22)</td>
<td>Various types</td>
<td>32/64</td>
<td>52/64</td>
<td>0.23 (0.09-0.54)</td>
</tr>
</tbody>
</table>

(Table 5. One-year mortality rates of patients with various types of cancer, who received either vitamin K-antagonists or no additional therapy to conventional therapy in level 2 studies)

**DISCUSSION**

Despite an abundance of experimental studies which have indicated inhibitory effects of vitamin K-antagonists on cancer progression (10-13;35-42), the present analysis of clinical trials, including 1443 patients, does not reveal a clear effect of vitamin K-antagonists on one year survival of patients with malignancy (OR 0.89; 95% CI 0.70-1.13). We purposely limited our analysis to one year survival and methodologically more rigorous studies, in order to limit the potential for bias. Interestingly, the only level 2 study that was included in this review revealed a clear positive effect.
in a modestly sized study of 128 patients (OR 0.23; 95% CI 0.09-0.54). This observation is in agreement with our earlier analysis of the effects of unfractionated heparin on survival of cancer patients (15). It illustrates the importance of a priori assessment of methodological quality, because studies using less rigorously validated methods usually overestimate possible effects (43;44). A potential confounder in our analysis is the intensity and duration of warfarin treatment. We limited our analysis to one year, although the duration of warfarin treatment varied from several months to indefinite. In three studies, the intensity of warfarin treatment was sub-therapeutic, whereas therapeutic doses were given to patients in the other two level 1 trials. Although we were unable to formally analyze the influence of duration and intensity of treatment on survival, there was no obvious difference in the outcome of these two groups of studies. In addition, in those studies in which anticoagulant treatment was continued for at least 2 years, no clear benefit of prolonged warfarin exposure was reported, except in the subgroup of patients with SCLC (17;20). These findings support the conclusion that vitamin K-antagonists are unlikely to affect overall survival of cancer patients.

To evaluate whether vitamin K-antagonists have differential effects in various types of cancer, we performed a subgroup analysis of the level 1 studies and separated SCLC from colorectal cancer. In the subgroup of SCLC, a trend to mortality reduction of approx. 30% was found in warfarin-treated patients after one year of follow up, although the results were not statistically significant. Interestingly, these findings are comparable to effects of unfractionated heparin on SCLC. In a randomized study, including 277 patients with SCLC who received either therapeutic dosages of unfractionated heparin or no additive treatment to chemotherapy, a similar trend to mortality reduction was observed in heparin-treated patients (15;45). Despite the limited number of patients included in the studies, our subgroup analysis also indicates that there is no convincing evidence of any beneficial effect of vitamin K-antagonists on other types of malignancy, in particular colorectal cancer (Table 4). It has previously been suggested that coagulation activation and fibrin formation play a major role in SCLC, whereas this may be less apparent for other types of malignancy such as colorectal cancer (46). Nevertheless, before anticoagulants such as vitamin K-antagonists or heparin can be recommended in SCLC, a more definitive study is mandatory in this subgroup.

In conclusion, this systematic review does not provide sufficient evidence to warrant treatment with vitamin K-antagonists in patients with cancer with the aim of improving survival.

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REFERENCES


