Arterial Thromboembolism in Cancer Patients Treated With Cisplatin: A Systematic Review and Meta-analysis


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Cisplatin has been associated with an increased risk of arterial thromboembolic events (ATEs). However, because this association is mostly based on case reports and retrospective studies, we conducted a systemic review and meta-analysis of randomized controlled trials evaluating the incidence and risk of ATEs associated with cisplatin. Eligible studies included prospective randomized phase II and III trials evaluating cisplatin-based vs non-cisplatin-based chemotherapy in patients with solid tumors, which were identified from PubMed articles published between 1990 and 2010. Incidence rates, relative risks (RRs), and 95% confidence intervals (CIs) were calculated using a random effects model. A total of 8216 patients from 38 trials were included. Among patients treated with cisplatin-based chemotherapy, the summary incidence of ATEs was 0.67% (95% CI = 0.40% to 0.95%), and the RR of ATEs was 1.36 (95% CI = 0.86 to 2.17; P = .19). No increase in ATEs was detected in any prespecified subgroup.

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Thromboembolic events are a significant cause of morbidity and mortality in patients with cancer (1). Although cancer itself is an established risk factor for thromboembolism, cancer treatments have also been implicated. Cisplatin, a widely used DNA crosslinking agent, is perhaps the most commonly implicated agent. In a meta-analysis of randomized trials comparing cisplatin-based and non-cisplatin-based chemotherapy, we demonstrated that cisplatin-based therapy is associated with a 1.67-fold increased risk for venous thromboembolic events (2). Case reports and retrospective studies suggest that arterial thromboembolic events (ATEs) also occur more frequently with cisplatin therapy (3,4). Thus, we performed a systemic review and meta-analysis to evaluate the incidence and relative risk (RR) of ATEs in patients receiving cisplatin-based versus non-cisplatin-based chemotherapy.

Trials were selected from those published in PubMed between January 1, 1990, and December 31, 2010, with “cisplatin,” “cancer,” and “randomized clinical trial” as keywords. Inclusion criteria included 1) prospective randomized phase II or III trial of cancer patients, 2) random assignment of participants to treatment with cisplatin or non-cisplatin-containing chemotherapy, and 3) available data on ATEs. Methodological quality was assessed using the Jadad scale, an instrument based on trial design elements such as blinding and randomization to rank trials on a 0–5 scale (5).

Data extraction was independently performed by two investigators (S.K. Chiu and T. Proverbs-Singh), and discrepancies were resolved by consensus (S. Seng, M.D. Galsky, S.K. Chiu, and T. Proverbs-Singh). For each study, we extracted publication year, trial phase, treatment arms, underlying malignancy, number of subjects enrolled, number evaluable for toxicity, gender, median age, cisplatin dose (mg/m²), median follow-up time, and toxicity data of interest, including the number of all-grade arterial events. Dose intensity was calculated by dividing the cisplatin dose by frequency or schedule to standardize cisplatin dosing. All reported ATEs were captured, regardless of attribution assigned in the original publication, and classified as myocardial infarction (MI), cerebrovascular accident (CVA), or ATE other/unspecified.

Analyses were performed using R statistical software with the metafor package (6). Random effects models were used regardless of the actual inter-study heterogeneities, which were quantified using the I² statistic. The I² statistic measures the percentage of overall variability due to between-study heterogeneity. Zero suggests that all variability arises from within-study sampling errors. Individual trials were pooled and weighted by the DerSimonian–Laird method (7). Continuity corrections with 0.5 were adopted for trials with zero events in either or both arms. The incidence and relative risk of ATE were calculated for each study along with appropriate 95% confidence intervals (CIs) and P values. A two-sided P less than .05 was considered to indicate statistical significance. Prespecified subgroup analyses were performed with heterogeneity tests by meta-regression using dummy variables according to Deeks et al (8).

Of the 2359 publications identified during the initial search, 38 trials (phase 2 = 19; phase 3 = 19) met criteria for inclusion (Supplementary Figure 1, available online). The median Jadad score was 3 (range = 2–3). No evidence of publication bias was detected by the Begg test (P = .82). A total of 8216 patients (cisplatin, n = 4154; non-cisplatin, n = 4062) were included in the analysis (Supplementary Table 1, available online).

In the cisplatin group, 34 patients experienced arterial events (12 MI, 17 CVA, 5 other arterial events) compared with 21 patients (10 MI, 11 CVA) in the non-cisplatin group. The summary incidence of ATEs in patients receiving cisplatin-based chemotherapy was 0.67% (95%
CI = 0.40% to 0.95%; $P = 11.91\%$). The relative risk of ATE for cisplatin-based versus non-cisplatin-based chemotherapy was 1.36 (95% CI = 0.86 to 2.17; $P = .19$) (Figure 1).

To better delineate possible relationships between cisplatin and ATEs, we performed several exploratory subgroup analyses (Table 1). No statistically significant increase in the relative risk of ATE with cisplatin-based chemotherapy was observed according to cisplatin dose intensity, platinum vs non-platinum comparator, primary tumor site, or publication year.

Given the statistically nonsignificant results, we performed a posteriori power analyses (9). With the ATE incidence fixed at 1.5% (based on historical data (10)), the powers for relative risk of 1.5 and 2.0 are 0.70 and 0.96, respectively. Although a statistically significant increase in the relative risk of ATE with cisplatin may have been missed, based on the observed incidence and relative risk, such an increase is very unlikely to be of clinical significance.

Our analysis revealed a very low event rate of ATE (0.67%) with cisplatin. Prior studies, reporting higher event rates, have been either small and/or retrospective in nature (10,11). Discrepancies in rates of thromboembolism between retrospective and prospective analyses have previously been highlighted (12,13). Strict eligibility criteria in randomized trials may have contributed, at least in part, to the lower incidence of ATE observed. Notably, this should have impacted both cisplatin and non-cisplatin arms equally.

Several included trials reported zero ATE events in one or both arms. In this setting, using random effects models and continuity corrections would bias the results towards null (14), but we felt that including trials reporting zero ATE events would provide the most conservative estimate. A bias towards null implies that some true differences might have been missed, but again, given the low overall event rate, such a difference is unlikely to be of clinical significance.

Another limitation involves differences in the treatment regimens aside from cisplatin for some trials, and we cannot rule out their possible influence on the results. We found that the diagnosis, reporting, and definition of thromboembolic events varied widely across trials. Severity grading was often missing, precluding an analysis of the risk of high-grade events.

The present study reveals that ATEs in patients treated with cisplatin are uncommon. We did not detect an increase in the relative risk of ATE with cisplatin-based chemotherapy compared with non-cisplatin-based chemotherapy. Although we cannot exclude that a statistically significant

**Figure 1.** Relative risk of arterial thromboembolism associated with cisplatin-based vs non-cisplatin-based chemotherapy.
Table 1. Incidence and relative risk of arterial thromboembolism based on prespecified subgroups*

<table>
<thead>
<tr>
<th>Group</th>
<th>Subgroup</th>
<th>No. of trials</th>
<th>Cisplatin</th>
<th>Non-cisplatin</th>
<th>$P$, %</th>
<th>Relative risk (95% CI)</th>
<th>$P$ for relative risk</th>
<th>$P$ for group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>38</td>
<td>34/154</td>
<td>2/4062</td>
<td>0.00</td>
<td>13.6 (0.88 to 2.17)</td>
<td>.19</td>
<td>NA</td>
</tr>
<tr>
<td>Tumor type</td>
<td>NSCLC</td>
<td>15</td>
<td>12/216</td>
<td>9/686</td>
<td>0.00</td>
<td>1.00 (0.47 to 2.13)</td>
<td>.99</td>
<td>.97</td>
</tr>
<tr>
<td></td>
<td>Gastric/esophageal</td>
<td>8</td>
<td>15/909</td>
<td>5/1023</td>
<td>0.00</td>
<td>2.25 (0.99 to 5.14)</td>
<td>.054</td>
<td>.97</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>3</td>
<td>0/134</td>
<td>2/264</td>
<td>0.00</td>
<td>1.47 (0.15 to 13.94)</td>
<td>.74</td>
<td>.64</td>
</tr>
<tr>
<td></td>
<td>Head and neck</td>
<td>3</td>
<td>2/191</td>
<td>2/84</td>
<td>0.00</td>
<td>0.93 (0.16 to 5.32)</td>
<td>.94</td>
<td>.64</td>
</tr>
<tr>
<td></td>
<td>Small cell lung</td>
<td>3</td>
<td>2/14</td>
<td>2/34</td>
<td>0.00</td>
<td>1.45 (0.96 to 2.44)</td>
<td>.16</td>
<td>.64</td>
</tr>
<tr>
<td></td>
<td>Weekly equivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cisplatin dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10–20 mg/m²</td>
<td>13</td>
<td>17/1232</td>
<td>9/1487</td>
<td>0.00</td>
<td>1.74 (0.86 to 3.54)</td>
<td>.12</td>
<td>.64</td>
</tr>
<tr>
<td></td>
<td>&gt;20–30 mg/m²</td>
<td>17</td>
<td>12/2378</td>
<td>9/1970</td>
<td>0.00</td>
<td>1.06 (0.51 to 2.22)</td>
<td>.16</td>
<td>.64</td>
</tr>
<tr>
<td></td>
<td>&gt;30 mg/m²</td>
<td>8</td>
<td>5/543</td>
<td>3/605</td>
<td>0.00</td>
<td>1.31 (0.42 to 4.11)</td>
<td>.64</td>
<td>.64</td>
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<tr>
<td>Non-cisplatin</td>
<td>Non-platinum</td>
<td>24</td>
<td>10/1856</td>
<td>10/2296</td>
<td>0.00</td>
<td>1.20 (0.62 to 2.32)</td>
<td>.59</td>
<td>.59</td>
</tr>
<tr>
<td></td>
<td>&quot;Other&quot; platinum</td>
<td>14</td>
<td>24/2298</td>
<td>11/1766</td>
<td>0.00</td>
<td>1.55 (0.80 to 2.99)</td>
<td>.19</td>
<td>.19</td>
</tr>
<tr>
<td>Publication year</td>
<td>1990–1999</td>
<td>10</td>
<td>4/893</td>
<td>4/1130</td>
<td>0.00</td>
<td>1.26 (0.45 to 3.59)</td>
<td>.66</td>
<td>.67</td>
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<tr>
<td></td>
<td>2000–2010</td>
<td>28</td>
<td>30/3261</td>
<td>17/2932</td>
<td>0.00</td>
<td>1.39 (0.83 to 2.34)</td>
<td>.22</td>
<td>.22</td>
</tr>
</tbody>
</table>

* CI = confidence interval; NA = not applicable; NSCLC = non–small cell lung cancer.
increase in relative risk was missed, the observed incidence and relative risk suggest that such a finding would be very unlikely to be of clinical significance. Studies in patients with advanced cancer receiving chemotherapy that integrate analyses of potential genetic susceptibility loci could be considered in an effort to identify patients at the highest risk for this uncommon, yet potentially serious, complication.

References

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Notes
S. K. Chiu, Z. Liu, and S. Seng contributed equally to this work.

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