Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials

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Purpose: Anti-epidermal growth factor receptor (EGFR) agents [monoclonal antibodies (MoAbs), tyrosine kinase inhibitors (TKIs)] are targeted therapies used in advanced cancers. Arterial and venous thromboembolic events (ATEs and VTEs excluding catheter-related events) were not investigated with these agents, and the risk of these events is still unknown.

Patients and methods: We have carried out a meta-analysis in order to determine the incidence and the relative risk (RR) of VTEs and ATEs associated with these agents. Statistical analyses were conducted to calculate the summary incidence, RRs and 95% confidence intervals (CIs) by using either random effects or fixed effect models according to the heterogeneity of the included studies.

Results: A total of 13 studies (7611 patients) was selected for this meta-analysis. The associated RRs of VTEs (11 studies comprising 7073 patients) and ATEs (5 studies consisting of 3030 patients) were 1.32 (95% CI 1.07–1.63; P equals 0.01) and 1.34 (95% CI 0.94–1.9; P equals 0.11) compared with control patients. The analysis of VTEs was also stratified by class of agents: MoAbs (RR 1.34; P equals 0.01) and oral TKIs (RR 1.16; P equals 0.65).

Conclusion: Anti-EGFR agents are associated with a significant increase in the risk of VTEs. In particular, the risk is significant with cetuximab and panitumumab in settings where these drugs are currently approved.

Key words: cetuximab, erlotinib, gefitinib, panitumumab, thromboembolic events

introduction

Venous and arterial thromboembolism events (VTEs and ATEs) are a major cause of death in cancer patients. The importance of cancer-associated thrombosis comes from the fact that it is exceedingly common in patients with cancer. One-fifth of all VTE events occur in cancer patients and the ones who develop VTE may experience serious consequences [1]. The most important consequence is the risk of mortality; pulmonary embolism (PE) and arterial events such as myocardial infarction and stroke can lead to death in cancer patients [2]. In particular, modern targeted therapies as antiangiogenic agents (sunitinib, sorafenib and bevacizumab) targeting vascular endothelial growth factor receptor (VEGFR) are associated with an increased risk of developing VTE and ATEs [3–7]. The epidermal growth factor receptor (EGFR) signaling pathway comprises a major target against which several new drugs are being currently developed. Cetuximab (C) is a chimeric monoclonal antibody (MoAb) that binds to the EGFR and blocks the EGFR signaling cascade, thus inhibiting the growth of the tumor [8]. Panitumumab (P) is an anti-EGFR MoAb which, like C, binds to the EGFR to prevent ligand binding and inhibits the subsequent activation of key downstream signaling molecules involved in tumorigenesis [9]. Both C and P are parentheral drugs administered as i.v. infusion. Erlotinib and gefitinib are oral small molecules designed to selectively inhibit the phosphorylation of EGFR intracellular kinase domain [10–13].

The main toxic effects of these drugs are cutaneous (skin rash), gastrointestinal (diarrhea) and metabolic (hypomagnesemia). Little is known about the risk of vascular events associated with these agents. To our knowledge, no published article explored cardiovascular toxicity associated to these drugs. Since the indications for anti-EGFR agents are increasing, it is important to carefully recognize and document the vascular toxicity patterns of these drugs to perform an early and adequate intervention. In order to determine the risk of VTEs and ATEs associated with the clinical use of anti-EGFR drugs, we have investigated the incidence and the relative risk (RR) of these events in patients treated with C, P, erlotinib or gefitinib. We have then carried out a systematic review and a meta-analysis of the published articles and abstracts presented at the major oncology meetings.
patients and methods

selection of studies

We have conducted an independent review of Medline and EMBASE citations with no date restriction. The keywords included in the search were ‘cetuximab’, ‘panitumumab’, ‘gefitinib’ and ‘erlotinib’. The search was limited to randomized controlled trials in humans published in English. In case duplicate publications were identified, only the most recent or complete report of clinical trials was included. The updated manufacturer’s package inserts of approved agents (C, P, gefitinib or erlotinib) were also reviewed to identify relevant information [10–13].

The trials that met the following criteria were chosen for the analysis: prospective randomized (phase II and III) clinical trials in patients with cancer, patients assigned to treatment with C, P, gefitinib or erlotinib (alone or in combination), and safety data available for VTEs and ATEs.

Phase I studies were excluded because of the different drug dosage and the relatively small number of patients enrolled in the trials, in line with several other meta-analyses carried out in this context [6, 7].

data extraction and clinical end points

Data abstraction was conducted independently by two investigators (FP and KB), and any discrepancy between the reviewers was resolved by consensus. For each study, the following information was extracted: author’s name, year of publication, trial phase, number of enrolled subjects, treatment arms, number of patients in treatment and placebo groups when available, underlying malignancy, median age, median treatment duration, median progression-free survival, adverse outcomes of interest (venous and arterial thrombotic events), name and dosage of the anti-EGFR agent and the dosing schedules used. The following adverse outcomes were considered as VTE/ATEs and included in the main analysis: thrombosis/thrombus/embolism (excluded vascular access related-thrombosis if reported separately), arterial thrombosis, cerebral infarct, cerebral ischemia, cerebrovascular accident, myocardial infarction and myocardial ischemia.

Phlebitis (including superficial thrombosis) was initially included and subsequently extracted from analysis to observe if they led to different results of the main comparisons. All studies except four (that used version 2) reported adverse events according to Common Toxicity Criteria (CTC) version 3. Severe events (grade 3 and 4) are defined as deep vein thrombosis or cardiac thrombosis that requires interventions and embolic event including pulmonary embolism or life-threatening thrombus, respectively. In the previous version (version 2), grades 3 and 4 included deep vein thrombosis, requiring anticoagulant therapy and embolic event including pulmonary embolism.

statistical analysis

All statistical analyses were carried out with Review Manager 5.1 (RevMan (Computer program), Version 5.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). The number of VTEs/ATEs and patients receiving anti-EGFR agents was extracted from the safety profile to calculate the incidence. The proportion of patients with such adverse outcomes and 95% confidence intervals (CIs) was calculated for each study. The studies that included a comparative arm were used to calculate the RRs of VTEs and ATEs in patients assigned to anti-EGFR agents versus controls in the same trial. Both fixed effect (weighted with inverse variance) and random effects models were considered in the meta-analyses. The latter was calculated by using DerSimonian and Laird’s method [14], which considers both within- and between-study variation. The statistical heterogeneity among the studies included in the meta-analysis was assessed by using Cochrane’s Q statistic, and the inconsistency was quantified with the I2 statistic, which is used to describe the percentage of total variation among the studies due to heterogeneity rather than chance; a value of 0% indicates no heterogeneity, while values between 0% and 100% show an increasing heterogeneity [15]. The assumption of homogeneity was considered invalid for P values < 0.1; in this case, we have reported summary estimates from random effects models, otherwise, we have reported summary estimates from fixed effect models. In order to investigate the possible reasons for heterogeneity, we have carried out subgroup analyses based on either the underlying malignancy or the agent used. Additionally, to test whether effect sizes were moderated by differences in length of treatment, we have carried out meta-regressions with difference in median length of experimental and control treatments (expressed in months) as predictor and risk ratio as dependent variable. A test for subgroup difference (MoAbs versus oral agents) was also carried out. Finally, potential publication biases were evaluated with Begg’s funnel plots to examine the relative symmetry of individual study estimates around the overall estimate and then with both Begg and Egger’s tests [16, 17]. A two-tailed P value of < 0.05 was considered statistically significant. Trim and fill method was also used to explore potential biases.

results

Our search yielded a total of 192 potentially relevant studies with C, P, erlotinib or gefitinib. Initially, 179 trials were excluded for at least one of the following reasons: absence of data on VTEs and ATEs, duplicate trials, phase I trials, nonrandomized trials, review articles, observational studies, case reports, editorials, letters and commentaries. Finally, 13 trials were considered highly relevant for the meta-analysis (phase II and III trials reporting VTEs and ATEs in the toxicity section of the publication) [18–30]. See supplemental Figure S1 (available at Annals of Oncology online) for flow diagram of trial’s selection progress according to PRISMA guidelines.

The baseline characteristics of each trial are presented in Table 1. The most frequently reported adverse events were pulmonary embolism and venous thrombotic events, while only four trials reported cardiac events. Drug dosage and schedule were those currently approved (P 6 mg/kg every 14 days, C 400 mg/m2 loading dose followed by 250 mg/m2 weekly, erlotinib 150 mg/day, and gefitinib 250 mg/day) except for those of P in Vermorken and Okines trials, where a dose of 9 mg/kg was administered every 21 days.

A total of 7611 patients was available for the meta-analysis; 3778 of these patients were assigned to treatment arms and 3833 to placebo or control arms for the analysis of the RR.

incidence of VTEs and ATEs

A total of 7073 patients (11 trials) was considered for the incidence analysis of VTEs. VTEs occurred in 186 of 3508 patients, showing an incidence of 5% (compared with 3.7% in control arms). The incidence of VTEs was calculated separately for MoAbs and oral tyrosine kinase inhibitors (TKIs) (Table 2). The incidence was 5.9% for MoAbs and 2.6% for TKIs. The difference in the incidence of VTEs between MoAbs and TKIs trials was statistically significant (difference 3.3%; P < 0.001). The trials were also stratified by underlying malignancy (gastrointestinal versus lung). The incidence was then calculated and was 6.5% in gastrointestinal cancer patients
Table 1. Baseline characteristics of patients of the 14 trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Treatment arm</th>
<th>Phase</th>
<th>Patients enrolled</th>
<th>Histology</th>
<th>Median age (years)</th>
<th>Median anti-EGFR duration (weeks)</th>
<th>Median CT duration experimental versus control arm (weeks)</th>
<th>Median PFS (months)</th>
<th>No. of patients for analysis</th>
<th>No. of events G3/G4 experimental/ control arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vermorken et al. 2010 [30]</td>
<td>P + CDDP + FU versus CDDP + FU</td>
<td>III</td>
<td>657</td>
<td>SCCHN</td>
<td>58/59</td>
<td>5 cycles</td>
<td>5 cycles (CDDP)</td>
<td>5.8 versus 4.6</td>
<td>650</td>
<td>6 versus 3</td>
</tr>
<tr>
<td>Bukowski et al. 2007 [27]</td>
<td>Bev + E/placebo</td>
<td>II</td>
<td>104</td>
<td>RCC</td>
<td>66/61</td>
<td>NR</td>
<td>17 versus 16 cycles (Bev)</td>
<td>8.5 versus 9.9</td>
<td>104</td>
<td>0 versus 1</td>
</tr>
<tr>
<td>Crinò et al./2008</td>
<td>Gefitinib VNB</td>
<td>II</td>
<td>196</td>
<td>NSCLC</td>
<td>74</td>
<td>NR</td>
<td>NR</td>
<td>2.7 versus 2.9</td>
<td>190</td>
<td>NR</td>
</tr>
<tr>
<td>Douillard et al. 2010 [18]</td>
<td>P + FOLFOX-4 versus FOLFOX-4</td>
<td>III</td>
<td>1183</td>
<td>mCRC</td>
<td>62.5/61</td>
<td>11 cycles (wild type)</td>
<td>11 cycles (OHP in wild type)</td>
<td>9.6 versus 8a</td>
<td>904</td>
<td>16 versus 13</td>
</tr>
<tr>
<td>Gatzeemeier et al. 2007 [28]</td>
<td>CDDP/GEM + erlotinib/placebo</td>
<td>III</td>
<td>1172</td>
<td>NSCLC</td>
<td>61/60</td>
<td>5–6 cycles</td>
<td>5–6 cycles</td>
<td>6.5 versus 5.9</td>
<td>1159</td>
<td>19 versus 11</td>
</tr>
<tr>
<td>Herbst et al. 2007 [26]</td>
<td>D or P + placebo versus Bev + D or P or E</td>
<td>II</td>
<td>120</td>
<td>Non-squamous NSCLC</td>
<td>65/63.5/68</td>
<td>NR</td>
<td>NR</td>
<td>3.0 versus 4.8</td>
<td>120</td>
<td>5b versus 1</td>
</tr>
<tr>
<td>Okines et al. 2010</td>
<td>EOX ± P</td>
<td>II/III</td>
<td>29</td>
<td>Esophageogastic</td>
<td>60/64</td>
<td>8 cycles</td>
<td>8 cycles</td>
<td>NR</td>
<td>18</td>
<td>0 versus 1</td>
</tr>
<tr>
<td>Hecht et al. 2009 [21]</td>
<td>Bev/Ox-CT ± P or Bev/Iri-CT ± P</td>
<td>IIIB</td>
<td>1053</td>
<td>mCRC</td>
<td>62/61/59/60</td>
<td>NR</td>
<td>NR</td>
<td>11.5 versus 9.8/12.5 versus 10b</td>
<td>804</td>
<td>12 versus 13/11</td>
</tr>
<tr>
<td>Peeters et al. 2010 [19]</td>
<td>P + FOLFIRI versus FOLFIRI</td>
<td>III</td>
<td>1186</td>
<td>mCRC</td>
<td>61/62.5</td>
<td>9</td>
<td>10 versus 8 cycles (irinotecan)</td>
<td>3.9 versus 5.9</td>
<td>1079</td>
<td>22 versus 12</td>
</tr>
<tr>
<td>Pirker et al. 2010 [22]</td>
<td>C + CDDP-VNB versus CDDP-VNB</td>
<td>III</td>
<td>1125</td>
<td>NSCLC</td>
<td>59/60</td>
<td>18</td>
<td>14 (all patients)</td>
<td>NR</td>
<td>1110</td>
<td>23 versus 16</td>
</tr>
<tr>
<td>Tol et al. 2009 [23]</td>
<td>X + OHP + Bev + C versus X + OHP + Bev</td>
<td>III</td>
<td>755</td>
<td>mCRC</td>
<td>62</td>
<td>6 months</td>
<td>7 months</td>
<td>10.7 versus 9.4</td>
<td>732</td>
<td>37 versus 38</td>
</tr>
<tr>
<td>Burtner et al. 2005 [25]</td>
<td>CDDP + C versus CDDP + placebo</td>
<td>III</td>
<td>116</td>
<td>SCCHN</td>
<td>60.6/58.3</td>
<td>4.5 versus 3 cycles of treatment</td>
<td>4.2 versus 3.1</td>
<td>NR</td>
<td>116</td>
<td>6 versus 2</td>
</tr>
</tbody>
</table>

Bev, bevacizumab; CBDCA, carboplatin; C, cetuximab; CT, chemotherapy; CDDP, cisplatin; D, docetaxel; EOC, epirubicin, oxaliplatin and capecitabine; E, erlotinib; FOLFIRI, infusional fluorouracil, leucovorin and irinotecan; FOLFOX-4, infusional fluorouracil, leucovorin and oxaliplatin; FU, fluorouracil; GEM, gemcitabine; Iri-CT, irinotecan-based chemotherapy; mCRC, metastatic colorectal cancer; NR, not report; NSCLC, non-small-cell lung cancer; OHP, oxaliplatin; Ox-CT, oxaliplatin-based chemotherapy; P, panitumumab; P, permetrexed; RCC, renal cell cancer; SCCHN, squamous cell carcinoma of the head and neck; VNB, vinorelbine; X, capecitabine.

aKRAS wild type.
bOne event G5 for chemotherapy.
and 3.3% in lung cancer patients. The difference between the two groups was statistically significant ($P < 0.001$).

A total of 3030 patients (five trials) was considered for the incidence analysis of ATEs. ATEs occurred in 69 of 1509 patients, showing an incidence of 4.5% (3.4% in control arms; $P$ equals 0.11) (Table 3). The incidence was 4.6% for MoAbs and 1.9% for TKIs in one trial only. The difference in the incidence of ATEs between MoAbs and TKIs trials was not statistically significant (2.7% for MoAbs; $P$ equals 0.37).

### relative risk of VTEs and ATEs

Eleven randomized studies were available to calculate the RR of VTEs in patients assigned to anti-EGFR agents versus controls in the same trial. The results are presented in supplemental Figure S2 (available at *Annals of Oncology* online). The meta-analysis showed that the summary RR of VTEs in experimental versus control arms was 1.32 (95% CI 1.07–1.63; $P$ equals 0.01), suggesting a 32% higher risk of developing VTEs with anti-EGFR agents compared with controls. The test for heterogeneity was not significant [$\chi^2$ equals 7.64; $df$ equals 10, ($P$ equals 0.66); $I^2$ equals 0%]. The risk difference was 1% [($P$ equals 0.01; heterogeneity: $\chi^2$ equals 11.03, $df$ equals 10, ($P$ equals 0.36); $I^2$ equals 9%]. All events except nine are of high grade (RR equals 1.36 for grades 3–4).

After stratifying patients by their underlying malignancy (supplemental Table S1, available at *Annals of Oncology* online), an RR of VTE of 1.31 (95% CI 0.84–2.04) was reported in lung cancer patients and an RR of 1.25 (95% CI 0.97–1.61) was reported in gastrointestinal cancer patients ($P$ not significant for both). The correspondent RR reported in head and neck trials ($n$ equals 2) was 2 ($P$ equals 0.06). After stratifying patients by the class of drug used, an RR of VTE of 1.34 (95% CI 1.07–1.68) was reported in MoAbs-treated

### Table 2. Incidence of venous thromboembolic events in cancer patients stratified by drug type

<table>
<thead>
<tr>
<th>Drug/study</th>
<th>Underlying malignancy</th>
<th>No. of events/sample size (experimental versus control arms)</th>
<th>Incidence experimental versus control arms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirker et al. 2009 [22]</td>
<td>Lung cancer</td>
<td>23/548 versus 16/562</td>
<td>4.1 versus 2.8</td>
</tr>
<tr>
<td>Vermorken et al. 2010 [30]</td>
<td>Head and neck</td>
<td>19/325 versus 10/325</td>
<td>5.8 versus 3</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>75/1297 versus 52/1311</td>
<td>5.7 versus 3.9*</td>
</tr>
<tr>
<td>Panitumumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peeters et al. 2010 [19]</td>
<td>Colorectal</td>
<td>22/539 versus 12/540</td>
<td>4 versus 2.2</td>
</tr>
<tr>
<td>Douillard et al. 2010 [18]</td>
<td>Colorectal</td>
<td>16/539 versus 13/545</td>
<td>2.9 versus 2.3</td>
</tr>
<tr>
<td>Okines et al. 2010 [20]</td>
<td>Gastroesophageal</td>
<td>0/13 versus 1/16</td>
<td>0</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>92/1498 versus 72/1498</td>
<td>6.1 versus 4.8</td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herbst et al. 2007 [26]</td>
<td>Lung cancer</td>
<td>0/39 versus 1/81</td>
<td>0 versus 1.2</td>
</tr>
<tr>
<td>Gatzeumer et al. 2007 [28]</td>
<td>Lung cancer</td>
<td>19/580 versus 11/579</td>
<td>3.2 versus 1.9</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>3 versus 1.8</td>
</tr>
<tr>
<td>Gefitinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crino' et al. 2008 [29]</td>
<td>Lung cancer</td>
<td>0/94 versus 5/96 (phlebitis only)</td>
<td>0 versus 5.2</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>176/3508 versus 135/3565</td>
<td>5 versus 3.7 ($P$ equals 0.0136)</td>
</tr>
</tbody>
</table>

\*Statistically significant.

### Table 3. Incidence of arterial thromboembolic events in cancer patients stratified by drug type

<table>
<thead>
<tr>
<th>Drug/study</th>
<th>Underlying malignancy</th>
<th>No. of events/sample size (experimental versus control arms)</th>
<th>Incidence experimental versus control arms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vermorken et al. 2010 [30]</td>
<td>Head and neck</td>
<td>13/325 versus 3/325</td>
<td>4 versus 0.9*</td>
</tr>
<tr>
<td>Pirker et al. 2009 [22]</td>
<td>Lung cancer</td>
<td>31/548 versus 28/562</td>
<td>5.6 versus 4.9</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bukowski et al. 2007 [27]</td>
<td>Renal cell carcinoma</td>
<td>1/51 versus 0/53</td>
<td>1.96 versus 0</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>69/1509 versus 52/1521</td>
<td>4.5 versus 3.4</td>
</tr>
</tbody>
</table>

\*Statistically significant.
patients (P equals 0.01; heterogeneity: $\chi^2$ equals 3.70, df equals 7, (P equals .81); $I^2$ equals 0%) and an RR of VTE of 1.16 (95% CI 0.61–2.18) was reported in oral TKIs-treated patients (P equals 0.65) (supplemental Figure S2 and Table S1, available at Annals of Oncology online). The risk difference for VTEs in MoAbs meta-analysis was 2% (P equals 0.01; heterogeneity: $\chi^2$ equals 2.81, df equals 7, (P equals 0.9); $I^2$ equals 0%). After analysis of Crino’ trial [29] that reported only five cases of superficial phlebitis, we decided to perform the analysis after excluding this study. After exclusion of this trial, the overall result did not change (RR 1.37; 95% CI 1.37; P equals 0.04). The test for subgroup differences between MoAbs and TKIs studies ($\chi^2$ equals 0.28, df equals 1 (P equals 0.60), $I^2$ equals 0%) remained positive (RR 1.34 for MoAbs, P equals 0.01; RR 1.64 for TKIs, P equals 0.17).

An exploratory analysis of RR of VTE calculated including trials with improved outcome associated with experimental arms (only C and P trials) showed a RR of 1.61 (95% CI 1.15–2.27; P equals 0.006). A similar result is obtained after inclusion of trials that included a cisplatin-based combination, known for its vasculotoxic properties (RR 1.69; 95% CI 1.06–2.07; P equals 0.03).

Additionally, a meta-regression was carried out to test whether the RR of VTEs varied as function of difference in length of the experimental and control treatments. Since in 3 studies data about length of treatment were not reported, 8 of 11 studies were included in the analysis (see Table 1). Results indicated that the RR tended to be higher in studies in which the experimental treatment was longer than the control treatment. However, this effect was not statistically significant (β equals 0.18; P equals 0.31).

Five randomized trials were available to calculate the RR of ATEs. The meta-analysis showed that the summary RR of ATEs in experimental versus control arms was a nonsignificant 1.34 (95% CI 0.94–1.9; P equals 0.11). The test for heterogeneity was not significant ($\chi^2$ equals 6.93; df equals 4, (P equals 0.14); $I^2$ equals 42%). After stratifying patients by the class of drug used, an RR of ATEs of 1.38 (95% CI 0.76–2.51) was reported in C- and P-treated patients (P equals 0.29), while an RR of 3.12 (95% CI 0.13–74.76) was reported in one trial with oral TKIs-treated patients (P equals 0.48). The risk of ATEs in head and neck cancer trials (n equals 2/5 trials) was 2.39 (95% CI 1.24–4.62; P equals 0.01) [heterogeneity: $\chi^2$ equals 1.48, df equals 1, (P equals 0.22); $I^2$ equals 32%].

**publication bias**

No evidence of publication bias was detected for the incidence or the RR of VTEs in this study by either Begg or Egger’s tests (RR of VTEs: Begg’s test P equals 0.5; Egger’s test P equals 0.35). The absence of a ‘dominant’ study driving the results was demonstrated by the ‘one-study removed’ procedure that generated an overall similar RR estimate. Analogously, the trim and fill analysis did not show a publication bias for VTEs events.

**discussion**

Our meta-analysis is the first, to our knowledge, to explore the risk of thromboembolic events with anti-EGFR drugs (either MoAbs or TKIs), and shows that, overall, they increase by 32% the risk of VTEs, but not of ATEs, in patients with advanced solid tumors. The result remains unchanged (37% of increase) after exclusion of superficial phlebitis reported only by Crinò et al. [29] study. Unfortunately, no author says how many events are catheter-related thromboses but these occurrences are likely reported separately as for CTC version 3 and according to international guidelines, central venous catheters do not need thromboprophylaxis. Also, no trial regarded as mandatory a central venous catheter for parenteral infusions.

In particular, thrombotic risk is increased with C and P but not with gefitinib and erlotinib. It has to be noted that all the trials implemented a treatment with an anti-EGFR agent (C or P) associated with chemotherapy, in particular, platinum-based chemotherapy, a well-known thromboembolic treatment. These results remained unaltered even after pooling the trials that enrolled only colorectal and head and neck cancer patients, where C and P are currently approved (RR equals 1.33; P equals 0.02).

The differences in the results between MoAbs and oral TKIs are still unknown. The association with other citotoxic agents probably matters; in fact, gefitinib and erlotinib are usually prescribed as single agents in lung cancer. The length of treatment and so the prolonged exposure in experimental arms to a thrombogenic agent could be an explanation of increased RR with MoAbs. Findings of meta-regression pointed out, for both VTEs and ATEs, that the RR tended to be higher in studies in which the experimental treatment was longer than the control treatment. However, this effect was not statistically significant ($\beta$ equals 0.18; $P$ equals 0.31). If the way of administration (parenteral versus oral) or the site of EGFR blockade works is also uncertain from the present data. However, the longer half-life of MoAbs (some days versus some hours) rises the possibility that the different pharmacokinetic of the two classes of agents somehow matters.

To note that 67% of VTEs in Mandalà clinical trial comparing continuous versus intermittent chemotherapy [31] occurred within few months of the onset of chemotherapy. This is in agreement with the data reported for a recent large population-based study [32]. This time-dependent hypothesis of VTE development was refused by Hurwitz et al. [33] too, which calculated the (time adjusted) RR of thromboembolic events of patients treated with bevacizumab. In that meta-analysis, there were no statistically significant increases in the exposure-adjusted incidences of all-grade VTEs for bevacizumab versus controls.

Another possible explanation of MoAbs/TKIs different results is the underreporting of VTEs; in fact, the number of trials with oral TKIs in lung cancer reporting these vascular events is very low. In our search, 80% of randomized trials were excluded because did not report thromboembolic events. VTEs are usually underdiagnosed because they are asymptomatic at presentation and therefore, often diagnosed incidentally. In Mandalà trial [31], only 2/27 VTEs were recorded and diagnosed spontaneously by the medical oncologist, while the other 25 (92%) were identified during radiological examination scheduled for tumor reevaluation.

The possible mechanism that links anti-EGFR drugs and the risk of thrombosis is probably the antiangiogenic effect of C.
and P [34–41]. The blockade of EGFR activation by C and oral TKIs results, in fact, in a significant decrease in tumor cell production of angiogenic growth factors such as basic fibroblast growth factor, VEGF and interleukin-8. The decrease in angiogenic growth factors, in turn, is correlated with a significant decrease in microvessel density and an increase in apoptotic endothelial cells (ECs) in human tumor xenografts. An essential mechanism through which VEGF promotes the formation of new blood vessels and maintains their integrity is the activation of EC survival and the upregulation of the antiapoptotic cellular cascade. VEGF is also known to increase nitric oxide (NO) production by ECs. NO has several vascular protective effects, including antiplatelet actions and the inhibition of leukocyte adhesion. As a result, indirect VEGF signaling inhibitors such as anti-EGFR drugs can disrupt the regenerative capacity of ECs and cause vascular wall defects, exposing prothrombotic phospholipids on the luminal plasma membrane and the underlying matrix, thus leading to thrombosis. In addition, a NO reduction by a VEGF inhibitor can also predispose to thrombosis. Up to today, only anti-VEGFR(R) agents (as sorafenib and sunitinib) are known as thromboembolic molecules, other than immunomodulatory agents such as thalidomide and lenalidomide. Our results are not surprising at all. In fact, as explained above, these drugs ultimately retain antiangiogenic properties.

However, inhibition of angiogenesis is probably not the only mechanism that works even in light of the uncertain role of bevacizumab in VTE development [33]. Their mode of action however could at least partially explain their added value on the risk of VTEs compared with chemotherapy alone. Chemotherapy infact is an endothelium damaging agent and this could warrant the increased risk found in this meta-analysis [42]. This means that association with chemotherapy really matters. A confirmation of this in the prescribing information insert [10], it is reported an increased incidence of cardiac events, including deaths, when C is combined with chemotherapy (in particular fluoropyrimidines). Recently, a mono-institutional retrospective analysis of 932 patients who represented all patients treated with cisplatin-based chemotherapy for any type of malignancy in 2008 was published. The authors found that, overall, 169 patients (18.1%) developed a thromboembolic event either during treatment or within 4 weeks of their last cisplatin dose [43].

In our analysis, the RR of ATEs is not different, but the number of reported events and analyzed trials are limited. Currently [44–46], the international guidelines do not recommend routine VTE prophylaxis during chemotherapy in outpatient settings. Some recent data suggest that low-molecular-weight heparin prophylaxis can reduce the risk of VTE [47, 48] in patients with certain types of cancer. Our data and those (already published) of an increased risk of VTEs with antiangiogenic agents used in solid tumors could be used as the basis for testing thromboprophylaxis in an appropriate clinical trial setting.

This meta-analysis has some limitations. First, these studies were conducted at various international institutions by different investigators and may have potential bias in reporting the types of adverse events; in particular, the frequency of VTEs is underreported in clinical trials. Second, these studies were conducted at major academic institutions among patients with adequate major organ function and may not reflect the general patient population in the community or patients with organ dysfunction. It could be that, thrombosis is even more frequent in a ‘real-life’ setting, as a retrospective cohort analysis showed [49]. Finally, this is a meta-analysis at the study level; therefore, confounding variables at the patient level could not be assessed properly and incorporated into the analysis. All trials included, nevertheless, are well-conducted, multicentre randomized phase III trials and in this research setting (many are registrative studies), all efforts have been made to record the more threatening toxic effects (in this case cardiovascular events). Our meta-analysis so pooled a limited but robust ‘core’ of clinical data with a final unequivocal result.

Our results show that VTEs are increased in studies where anti-EGFR (parenteral) MoAbs are associated to citotoxic agents. No data exist regarding vascular effect of C and P when administered as monotherapy up today but this is likely due to possible underreporting of data. In addition, it seems that the thrombotic risk is likely not correlated to the longer duration of therapy in experimental arms. Infact, the meta-regression indicated that the RR tended to be higher in studies in which the experimental treatment was longer (because more effective) than the control treatment but the result is not significant.

Excluding two studies where the addition of an anti-EGFR agents to chemotherapy and bevacizumab decreased patient outcome due to an excess of toxicity, the meta-analysis of all ‘positive’ trials with C and P showed a stronger VTE risk compared with the overall meta-analysis. However, if VTEs can actually represent a predictive factor as cutaneous rash is presently unknown. This hypothesis-generating data could stimulate a retrospective analysis of outcome in patients who developed VTEs events. Prolonged monitoring of patients exposed to these treatments become however crucial.

conclusion

In conclusion, we have observed that anti-EGFR MoAbs C and P are associated with a significant increase in the risk of venous but not of arterial thromboembolism in advanced solid tumors. In particular, they increase the risk of VTEs in patients treated with both anti-EGFR MoAb and platinum-based chemotherapy. Clinicians should be aware of the increase in VTEs, especially in patients with colorectal and head and neck cancer settings, where these drugs are currently labeled. Careful surveillance and prompt reporting of these serious vascular events are crucial and, at the same time, thromboprophylaxis could be a challenge for the future.

disclosure

The authors declare no conflict of interest.
refereces


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