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Potential role for aspirin in the prevention of pre-eclampsia-like syndrome in bevacuzimab-treated patients with colorectal carcinoma

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SUBMITTED
Chapter 6

ABSTRACT

Anti-vascular endothelial growth factor (VEGF) therapy may induce a pre-eclampsia-like syndrome with hypertension and proteinuria. Aspirin reduces pre-eclampsia risk, but its effect has not been studied during anti-VEGF therapy. In this study, we aimed to assess whether aspirin limits the hypertensive and proteinuric effects of VEGF-inhibition by bevacizumab. For this purpose, we performed a post-hoc analysis of the multicenter randomized CAIRO2 trial conducted between 2005-2006 in the Netherlands, in which metastatic colorectal carcinoma (mCRC) patients were randomized to receive capecitabine, oxaliplatin and the VEGF inhibitor bevacizumab (CB regimen). We compared blood pressure (BP) and proteinuria among patients with and without concomitant aspirin use.

Of 365 patients randomized to receive the CB regimen, 35 (10%) patients were concomitantly treated with aspirin. During the trial, BP elevation (≥30/20 mmHg systolic or diastolic respectively) or intensification of antihypertensive medication occurred less often in aspirin users vs. non-aspirin users (23% vs. 48%, odds ratio 0.33 (95% CI 0.14-0.79, p<0.01). This effect of aspirin remained present after adjustment for baseline differences in BP and antihypertensive medication. Macroalbuminuria developed in similar proportions of aspirin users (2 (6%)) and non-aspirin users (20 (6%); p=0.93). Bleeding episodes of any kind were reported in 8 (23%) patients with and 80 (24%) patients without concomitant aspirin treatment (p=0.86). In conclusion, CAIRO2 trial data suggest that aspirin limits the hypertensive effect of bevacizumab without increasing bleeding risk in patients with mCRC. Aspirin had no effect on macroalbuminuria, but this analysis was hampered by the small number of patients developing macroalbuminuria.
INTRODUCTION

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) that is currently part of the standard first line systemic treatment in patients with metastatic colorectal carcinoma (mCRC). Hypertension and proteinuria are well-known complications of anti-angiogenic therapy, frequently necessitating blood pressure (BP) lowering medication. In addition, a subset of patients develops severe hypertension requiring cessation of anti-angiogenic treatment.

The mechanism and clinical sequelae of hypertension and proteinuria induced by anti-VEGF therapy bears resemblance with pre-eclampsia and has also been described as ‘pre-eclampsia-like syndrome.’ In pre-eclampsia, scavenging of circulating VEGF results from excessive placental production of the soluble VEGF receptor fms-like tyrosine kinase-1 (sFLT-1), subsequently leading to activation of the endothelin-signaling pathway and a decrease in nitric oxide bioavailability. Blockade of the endothelin receptors has been shown to prevent BP elevation induced either by sFLT-1 in pregnant animals and by the tyrosine-kinase inhibitor sunitinib in non-pregnant animals. Downstream of endothelin-1, production of vasocontractile prostanoids contributes to anti-VEGF induced BP elevation and pre-eclampsia. This is supported by the observation that the prostacyclin/thromboxane A₂ (TXA₂) ratio is decreased in pre-eclampsia and by the observation that aspirin, which inhibits production of vasocontractile TXA₂, reduces the risk of pre-eclampsia.

In patients receiving anti-VEGF therapy with bevacizumab, aspirin use might limit the excess risk of cardiovascular events, potentially due to effects on BP and proteinuria. However, the role of aspirin in preventing hypertension and proteinuria induced by anti-VEGF therapy has not been addressed previously. In the present post-hoc analysis of the multicenter randomized CAIRO2 trial in mCRC patients, we compared BP, antihypertensive medication and proteinuria among patients with and without aspirin use who were randomized to receive capecitabine, oxaliplatin and the VEGF inhibitor bevacizumab.

PATIENTS AND METHODS

Participants and trial details

The CAIRO2 study was a multicenter randomized open-label phase III study, which evaluated the addition of the epidermal growth factor (EGFR) inhibitor cetuximab to a standard regimen of capecitabine, oxaliplatin and bevacizumab as first-line treatment of patients with mCRC between June 2005 and December 2006 in 79 centers in The Netherlands. All eligible participants who were randomized to receive the standard regimen of capecitabine, oxaliplatin and bevacizumab were included in the current study. Eligibility criteria were
previously described in detail. Briefly, adult patients (>18 years of age) with histologically proven metastatic colon or rectal carcinoma were included if the tumor was not amenable for curative surgery and no previous systemic chemotherapy for metastatic disease was initiated. Patients with symptomatic central nervous system metastases, bleeding diathesis, coagulation disorders, clinically significant cardiovascular disease or other malignancy within 5 years preceding the trial were excluded. The study was approved by an ethics committee and local institutional review boards. An independent data and safety monitoring committee evaluated all serious adverse events and all patients provided written informed consent for participation in the trial. Patients were randomized at a 1:1 ratio to receive capecitabine, 1000 mg/m² of body-surface area given orally twice daily on days 1 to 14; oxaliplatin 130 mg/m², given intravenously on day 1; and bevacizumab 7.5 mg/kg, given intravenously on day 1 (CB regimen) or the same regimen plus cetuximab 400 mg/m², given intravenously on day 1 of the first treatment cycle, followed by 250 mg/m² given weekly thereafter (CBC regimen). The duration of each treatment cycle was 3 weeks. The primary end point of CAIRO2 was progression-free survival, which was defined as the interval from the date of randomization to the date of disease progression, death, or last to follow-up whichever occurred first. The trial showed that progression-free survival was significantly lower in the CBC group (9.4 months) compared to the CB group (10.7 months, \( p=0.01 \)). The median overall survival was 20.3 months in the CB group and 19.4 months in the CBC group (\( p=0.16 \)).

**Post-hoc comparison of patients with and without aspirin treatment**

The primary aim of the current study was to compare BP elevation and intensification of antihypertensive medication among patients in the CB arm of the CAIRO2 trial with and without concomitant aspirin treatment. Cetuximab-treated patients (CBC arm) developed significantly less often hypertension and were excluded from the primary analysis. First we compared baseline characteristics of patients with and without concomitant treatment with any dose of aspirin. Post-hoc analysis of BP was limited to the first 12 treatment cycles because BP elevation is expected to develop rapidly during anti-VEGF treatment,\(^{13}\) and only a small proportion of study patients received more than 12 treatment cycles. Secondary aims were comparison of proteinuria, incidence of cardiovascular events, venous thromboembolism (VTE) and bleeding episodes among patients with and without aspirin. BP was measured prior to each treatment cycle using locally available BP measurement devices and according to local BP measurement protocols. Presence of a rise in BP was assessed for three predefined cut-off values of BP, including a rise of ≥10/5 mmHg, ≥20/10 mmHg and ≥30/20 mmHg systolic or diastolic BP, respectively. BP elevation compared to baseline or increase in the number of antihypertensive drugs at any one of 12 treatment cycles was compared among aspirin and non-aspirin users. Proteinuria was assessed by dipstick and if present quantified by 24-hour urine samples. We compared the proportion
of patients who developed macroalbuminuria (>300mg/24 hours) among aspirin and non-aspirin users in both treatment arms.

Cardiovascular events were defined as a documented episode of any of the following conditions: 1) coronary artery disease (including myocardial infarction, acute coronary syndrome requiring percutaneous coronary intervention or angina pectoris), 2) cerebrovascular accidents including ischemic and/or hemorrhagic stroke, transient ischemic attack or subarachnoid bleeding, 3) heart failure or 4) peripheral artery disease. VTE was defined as pulmonary embolism or deep venous thrombosis. Finally, as aspirin use may increase bleeding risk, we compared the total number of reported bleeding episodes including mild and severe bleedings of any kind.

**Statistical analysis**

Continuous data are expressed as mean and standard deviation (SD). Categorical data are expressed as number and percentages. Between group differences were assessed by t-test for parametric and Mann–Whitney U test for non-parametric distributions. Chi-square statistics were used for categorical variables. Odds ratio with 95% confidence interval (CI) was calculated to compare the risk of BP elevation or intensification of antihypertensive treatment among aspirin and non-aspirin users. A multiple logistic regression analysis was carried out to assess to adjust for baseline differences in age, gender, BP and antihypertensive medication among aspirin and non-aspirin users. For statistical analyses, SPSS software was used (Statistical Package for the Social Sciences, version 19.0, Inc. Chicago, Illinois, USA). P-values were considered to indicate a significant difference if \( p < 0.05 \).

**RESULTS**

**Baseline characteristics**

In total 365 were randomized to receive capecitabine, oxaliplatin and bevacizumab (CB regimen), of which 35 (10%) were concomitantly treated with aspirin. Baseline characteristics of patients with and without aspirin are presented in Table 1. Aspirin users were older, had a lower BP and more frequently received antihypertensive medication at baseline compared to non-aspirin users. There were no differences with regard to severity of the underlying malignancy as indicated by similar WHO performance scores and the number of affected organs.
Table 1: Baseline characteristics with comparison of patients with and without aspirin

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Aspirin</th>
<th>No Aspirin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>35</td>
<td>330</td>
<td>-</td>
</tr>
<tr>
<td>Age, years</td>
<td>68±6</td>
<td>60±10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male</td>
<td>25 (71%)</td>
<td>182 (55%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>131±20</td>
<td>138±19</td>
<td>0.05</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>75±10</td>
<td>80±11</td>
<td>0.01</td>
</tr>
<tr>
<td>Use of antihypertensives</td>
<td>29 (83%)</td>
<td>72 (22%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26±4</td>
<td>25±4</td>
<td>0.57</td>
</tr>
<tr>
<td>WHO performance 0</td>
<td>24 (69%)</td>
<td>189 (58%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Primary colon tumor</td>
<td>21 (60%)</td>
<td>142 (43%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Primary rectum</td>
<td>6 (17%)</td>
<td>101 (31%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Primary rectosigmoid</td>
<td>8 (23%)</td>
<td>85 (26%)</td>
<td>0.71</td>
</tr>
<tr>
<td>No. of affected organs ≥1</td>
<td>21 (60%)</td>
<td>220 (67%)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Table presents the number of patients in each group with percentages or the mean with standard deviation.

**Effect of aspirin use on blood pressure and antihypertensive medication**

BP elevation or escalation in the number of antihypertensive medication at any treatment cycle, occurred less often in aspirin users compared to non-aspirin users for the BP cut-off value of ≥30/20 mmHg (23% vs. 48%, p<0.01). A trend towards less BP elevation or intensification of antihypertensive therapy was also observed for the other predefined BP cut-off values (50% vs. 67%, p=0.06 for ≥20/10 mmHg) and (50% vs. 67%, p=0.06 for ≥10/5 mmHg). The odds ratio for developing ≥30/20 mmHg BP elevation or increase in antihypertensive medication was 0.33 (95% CI: 0.14-0.79) for aspirin users compared to non-aspirin users. The proportion of patients developing ≥30/20 mmHg BP elevation or intensification of antihypertensive medication at each separate treatment cycle is shown in Figure 1. In patients who were additionally treated with cetuximab (CBC arm), there was no difference in the proportion of aspirin and non-aspirin users that developed ≥30/20 mmHg BP elevation or increase in antihypertensive treatment (22% vs. 27%, p=0.61; data not shown). Irrespective of aspirin use, patients in the CB arm developed more often BP elevation (≥30/20 mmHg) or increase in BP lowering medication compared to the CBC arm (46% vs. 26%, respectively, p<0.001), but less often macroalbuminuria (6% vs. 10%, respectively, p=0.03).

**Multiple logistic regression analysis**

To assess whether baseline differences in age, gender, BP and antihypertensive medication have influenced the apparent effect of aspirin, we carried out a multiple logistic regression analysis (Table 2). Aspirin users remained to have a lower risk of developing ≥30/20 mmHg BP elevation or escalation in the number of antihypertensive drugs compared to non-aspirin users after correction for possible confounders.
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Figure 1: BP elevation (30/20 mmHg) or intensification of antihypertensive treatment among patients with and without aspirin

Comparison of the proportion of aspirin and non-aspirin using patients developing systolic or diastolic BP elevation (30/20mmHg) or intensification of BP lowering medication at each treatment cycle. Figures above bars represent the total number of patients remaining at each treatment cycle. *indicates $p<0.05$

**Proteinuria**

Macroalbuminuria developed in 2 (6%) aspirin using patients and in 20 (6%) non-aspirin using patients ($p=0.93$).

**Bleeding events**

In total 88 (24%) patients developed at least one bleeding episode during the first 12 treatment cycles. Bleeding episodes were reported in 8 (23%) patients with and 80 (24%) patients without concomitant aspirin treatment ($p=0.86$). The vast majority of bleeding episodes consisted of lower gastrointestinal tract bleedings (44%) or epistaxis (36%). Other bleeding episodes included hemorrhoid bleeding (7%), gingival bleeding (4%), hematuria (4%), vaginal bleeding (2%) and hemoptysis (2%).
Table 2: Multiple logistic regression analysis of risk factors associated with BP elevation (≥30/20 mmHg) or intensification of BP lowering treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>P-value</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.88</td>
<td>1.0</td>
<td>0.98-1.03</td>
</tr>
<tr>
<td>Male</td>
<td>0.52</td>
<td>0.86</td>
<td>0.53-1.38</td>
</tr>
<tr>
<td>BMI</td>
<td>0.50</td>
<td>1.02</td>
<td>0.96-1.09</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>&lt;0.01</td>
<td>0.21</td>
<td>0.08-0.59</td>
</tr>
<tr>
<td>Baseline systolic BP</td>
<td>0.06</td>
<td>0.99</td>
<td>0.97-1.00</td>
</tr>
<tr>
<td>Baseline diastolic BP</td>
<td>0.67</td>
<td>1.01</td>
<td>0.98-1.03</td>
</tr>
<tr>
<td>Use of BP lowering treatment at baseline</td>
<td>0.63</td>
<td>1.16</td>
<td>0.63-2.13</td>
</tr>
<tr>
<td>WHO performance 0</td>
<td>0.14</td>
<td>0.70</td>
<td>0.43-1.13</td>
</tr>
<tr>
<td>No. of affected organs ≥1</td>
<td>0.22</td>
<td>0.73</td>
<td>0.45-1.20</td>
</tr>
</tbody>
</table>

Adjustment for possible confounders in the risk of developing BP elevation (≥30/20 mmHg) or intensification of antihypertensive medication using a multiple logistic regression model. CI indicates confidence interval.

**Cardiovascular disease and VTE**

One patient (0.3%) developed a cardiovascular event during the trial, whereas VTE occurred in 2 (0.5%) patients. None of these three patients were treated with aspirin.

**DISCUSSION**

This post-hoc analysis shows that severe BP elevation or escalation of antihypertensive treatment occurred less often in aspirin users compared to non-aspirin users on a combination of chemotherapy and the VEGF inhibitor bevacizumab for mCRC.

The beneficial effect of aspirin in preventing hypertensive complications in pregnancy, pre-eclampsia in particular, has been extensively studied, but has - to our knowledge - not been addressed in anti-angiogenic hypertension associated with VEGF inhibition. Clinical and pre-clinical studies suggest that in both conditions VEGF inhibition leads to a disturbance in the balance between endothelin-1 and nitric oxide, thereby contributing to BP elevation. Endothelin-1-mediated vasoconstriction was previously shown to be increased in non-pregnant mice treated with the VEGF scavenger sFLT-1. Interestingly, this increased endothelin-1-mediated vasoconstriction of isolated arteries could be abrogated by COX-inhibition. Moreover, the BP elevation observed with VEGF inhibition could be prevented in vivo by concomitant high-dose aspirin treatment. These data, together with the data from the present post-hoc analysis, indicate that the prostanoid system is pivotal in VEGF inhibitor-induced BP elevation.

Differences in baseline characteristics may have influenced our observations that aspirin protects to BP elevations in the CB arm, as aspirin users were older, had more antihypertensive medication and tended to be more often male compared to non-aspirin users. However,
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the risk of developing hypertension increases with age, while men have a higher risk of hypertension compared to women, suggesting that baseline these differences would lead to underestimation rather than overestimation of the effect of aspirin in this post-hoc analysis. Moreover, adjustment for these possible confounders in a multiple logistic regression model showed that baseline differences did not explain the observed effect of aspirin in the current study.

Besides hypertension, proteinuria is a frequent adverse effect of bevacizumab. The number of patients with macroalbuminuria among aspirin and non-aspirin users in the current study was, however, too small to draw any conclusions on the effect of aspirin on proteinuria. Nevertheless, macroalbuminuria occurred more often in patients who were additionally treated with cetuximab, while BP elevation occurred less frequently in these patients. This suggests that cetuximab-induced proteinuria is independent of BP elevation. Two previously published case-reports have demonstrated that cetuximab might lead to direct kidney injury due to deposition of immune-complexes in the mesangium and capillaries of the glomerulus as well as peritubular capillaries, eventually leading to nephrotic syndrome and diffuse proliferative and crescentic glomerulonephritis. In regard of direct bevacuzimab-induced injury to podocytes and glomerular endothelium, combined cetuximab and bevacuzimab treatment may pose subjects to an increased risk of kidney injury.

Treatment of cancer patients with bevacizumab is associated with an increased risk of all grade bleeding. Antiplatelet therapy with aspirin has been shown to further increase the risk of major bleeding in these patients, contrasted by findings showing that mCRC patients receiving bevacizumab have a similar bleeding risk regardless of anticoagulant treatment. In line with previous observations, we did not observe any difference in bleeding risk in the CAIRO2 trial between patients with and without concomitant aspirin treatment. The number of aspirin using patients in the current study is however limited.

The risk of cardiovascular events and VTE is higher in cancer patients treated with bevacizumab and chemotherapy compared to patients receiving chemotherapy alone. Among aspirin using patients, this excess risk of cardiovascular disease was previously shown to be absent. In the CAIRO2 trial, one cardiovascular event and two episodes of VTE occurred in the CB arm during the first 12 treatment cycles. None of these patients used aspirin, but the number of events was too low for assessment of the potential preventive effect of aspirin.

In conclusion, aspirin seems to limit BP elevation in patients receiving bevacizumab and chemotherapy for mCRC. Although the amount of aspirin using patients in this study was limited, aspirin use did not increase bleeding risk. Aspirin had no effect on macroalbuminuria, but the number of patients developing macroalbuminuria was too small to allow for any definitive conclusions. Combined bevacizumab and cetuximab therapy resulted in less BP elevation, but more frequently induced proteinuria, suggesting a kidney-specific pathophysiology for proteinuria caused by these agents rather than a BP-mediated effect.
REFERENCES


