TO THE EDITOR: Moyamoya disease presents most often as a transient ischemic attack or stroke. Apart from surgical revascularization procedures, medical therapeutic measures such as antiplatelet agents and even anticoagulation have been used for stroke prevention. In completed stroke, as confirmed by means of diffusion-weighted magnetic resonance imaging, antiplatelet agents should be administered to reduce the formation of microthrombi at the site of the stenosis.

We would like to raise a question about thrombolytic therapy with the use of tissue plasminogen activator (t-PA), which is today an accepted treatment for ischemic strokes. The threat of hemorrhage from the fragile collateral vessels that develop as compensation for carotid artery stenosis might prevent application of this effective therapy. Have there been any reports about stroke in patients with moyamoya disease who were treated with t-PA, perhaps in patients in whom the diagnosis of the underlying vasculopathy was revealed subsequently? Should moyamoya disease be considered to be a contraindication for t-PA administration?

Lea Pollak, M.D.
Assaf Harofeh Medical Center
70315 Zerifin, Israel
lea.pollak@gmail.com

THE AUTHORS REPLY: We appreciate the comments of both Derdeyn and Pollak regarding our review of moyamoya syndrome and moyamoya disease. Derdeyn points out that the natural history of North American adults with the “angiographic disorder” of moyamoya is unknown and that the typical North American adult with moyamoya is a woman in the fourth or fifth decade of life presenting with ischemic symptoms. In our small series of adult patients with moyamoya, ages ranged from 21 to 50 years at the time of their revascularization surgery and 19 of 20 patients were female. Twelve of these women presented with strokes (four of which were bilateral), and one presented with intracranial hemorrhage. We do not believe that our patients’ history of ischemic symptoms or strokes can be considered benign. In the article by Hallemeyer et al. referenced in Derdeyn’s letter, the 5-year risk of recurrent stroke in the patients treated only medically was 65%. These two series show that adult patients with moyamoya do not have a “benign clinical course,” and we believe that at the completion of Derdeyn’s NIH-funded natural-history study, his conclusions will probably be similar to ours.

In answer to Pollak’s query regarding the use of thrombolytic therapy for stroke in moyamoya disease and moyamoya syndrome: we did not encounter any reports of such treatment in preparing our review. Moreover, many strokes in moyamoya appear to be caused by hemodynamic factors rather than by thrombus formation and embolization. Since patients with moyamoya have a risk of hemorrhage in areas of extensive formation of moyamoya collateral vessels, we would be reluctant to recommend thrombolytic therapy in a patient with moyamoya who has just had a stroke.

R. Michael Scott, M.D.
Edward R. Smith, M.D.
Children’s Hospital Boston
Boston, MA 02115
edward.smith@childrens.harvard.edu

BRAF Mutation in Metastatic Colorectal Cancer

TO THE EDITOR: We recently found that progression-free survival was shorter among patients with metastatic colorectal cancer treated with chemotherapy, bevacizumab, and cetuximab (CBC regimen) than among patients who received chemotherapy and bevacizumab alone (CB regimen) (Feb. 5 issue). Other investigators have found that the efficacy of cetuximab is limited to patients with wild-type-KRAS tumors. In a subgroup of 520 patients with available tumor samples, we observed a shorter median progression-free survival among patients with a mutated-KRAS oncogene in the CBC group than among patients with mutated-KRAS tumors who received the CB regimen and among patients with wild-type-KRAS tumors who received the CBC regimen. An activating mutation in the B-type Raf kinase (BRAF) oncogene encoding the BRAF protein, localized direct-
ly downstream of RAS, leads to stimulation of the mitogen-activated protein kinase pathway. In a recent study, the efficacy of antibody therapy against the epidermal growth factor receptor for wild-type–KRAS tumors appeared to be restricted to wild-type–BRAF tumors. We performed a retrospective analysis of the BRAF V600E mutation status in 519 tumors that were tested in our study to determine KRAS status. A BRAF mutation was detected in 45 tumors (8.7%) (Table 1). BRAF and KRAS mutations were mutually exclusive. Patients with BRAF-mutated tumors had a significantly shorter median progression-free and median overall survival than patients with wild-type–BRAF tumors, both in the CB group and in the CBC group (Table 1). No difference in response rate was observed. We conclude that a BRAF mutation is a negative prognostic marker in patients with metastatic colorectal cancer and that this effect, in contrast to KRAS mutations, is not restricted to the outcome of cetuximab treatment.

Jolien Tol, M.D.
Iris D. Nagtegaal, M.D., Ph.D.
Cornelis J.A. Punt, M.D., Ph.D.
Radboud University Nijmegen Medical Center
6500HB Nijmegen, the Netherlands
c.punt@onco.umcn.nl

The DCCG received unrestricted scientific grants from Roche, Merck Serono, and Sanofi-Aventis. Dr. Punt reports receiving grant support from Roche and consulting fees from Roche and Merck Serono, and Sanofi-Aventis. Dr. Punt reports receiving c.punt@onco.umcn.nl
6500HB Nijmegen, the Netherlands
Radboud University Nijmegen Medical Center

Table 1. Association of the Mutation Status of the BRAF Oncogene with Progression-free Survival, Overall Survival, and Response Rate.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wild-Type BRAF</th>
<th>Mutated BRAF</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB group</td>
<td>243</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>CBC group</td>
<td>231</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Median progression-free survival (mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB group</td>
<td>12.2</td>
<td>5.9</td>
<td>0.003</td>
</tr>
<tr>
<td>CBC group</td>
<td>10.4</td>
<td>6.6</td>
<td>0.010</td>
</tr>
<tr>
<td>Median overall survival (mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB group</td>
<td>24.6</td>
<td>15.0</td>
<td>0.002</td>
</tr>
<tr>
<td>CBC group</td>
<td>21.5</td>
<td>15.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB group</td>
<td>50</td>
<td>35</td>
<td>0.32</td>
</tr>
<tr>
<td>CBC group</td>
<td>48</td>
<td>39</td>
<td>0.43</td>
</tr>
</tbody>
</table>

* BRAF denotes B-type Raf kinase, CB capecitabine, oxaliplatin, and bevacizumab, and CBC capecitabine, oxaliplatin, and bevacizumab plus cetuximab.

This letter (10.1056/NEJMc0904160) was updated on August 31, 2011, at NEJM.org.


Correspondence Copyright © 2009 Massachusetts Medical Society.

**CORRESPONDENCE**

**INSTRUCTIONS FOR LETTERS TO THE EDITOR**

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following:

- Letters in reference to a Journal article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article. Letters not related to a Journal article must not exceed 400 words. All letters must be submitted over the Internet at authors.NEJM.org.
- A letter can have no more than five references and one figure or table. A letter can be signed by no more than three authors.
- Financial associations or other possible conflicts of interest must be disclosed. (Such disclosures will be published with the letters. For authors of Journal articles who are responding to letters, this information appears in the published articles.)
- Include your full mailing address, telephone number, fax number, and e-mail address with your letter.

Our Web site: authors.NEJM.org

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. Letters that do not adhere to these instructions will not be considered. Rejected letters and figures will not be returned. We are unable to provide prepublication proofs. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the Journal’s various print and electronic publications and in collections, revisions, and any other form or medium.