

## Stopping the Bleeding in Intracerebral Hemorrhage

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Beyond aggressive supportive care, clinicians have not had specific treatments to offer patients with intracerebral hemorrhage. The article by Mayer et al.<sup>1</sup> in this issue of the *Journal* offers new hope for targeted therapy for this frequent cause of neurologic disability and death. Intracerebral hemorrhage is estimated to account for 10 to 15 percent of all strokes and to have a one-year mortality greater than 60 percent.<sup>2</sup> In the Far East, intracerebral hemorrhage is even more common, accounting for almost 30 percent of strokes in China.<sup>3</sup> Approximately 37,000 to 52,000 cases of intracerebral hemorrhage occur in the United States each year, and an estimated 413,000 cases occur annually in China.<sup>2,3</sup> Moreover, the incidence of intracerebral hemorrhage is expected to grow, given the aging of the population. Despite the enormous international public health importance of intracerebral hemorrhage, little research has been dedicated to finding effective treatments.

Neuronal injury in patients with intracerebral hemorrhage is due to primary factors, including direct tissue damage, as well as to secondary factors that probably include inflammation, edema formation, intraventricular extension of hemorrhage, and hydrocephalus. After the initial ictus, natural-history imaging studies have shown that continued expansion of the hematoma is common, occurring in approximately one third of cases, probably as a result of continued bleeding or rebleeding.<sup>4,5</sup> Most rebleeding appears to occur within the first few hours after the onset of symptoms and is associated with deterioration in neurologic status.<sup>4</sup> Treatments that target rebleeding are therefore likely to have a large clinical effect.

Mayer et al. report the results of a phase 2B, dose-ranging, proof-of-concept study, the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial, evaluating the ability of recombinant activated factor VIIa (rFVIIa) to reduce hematoma expansion.<sup>1</sup> The study was a multicenter, double-blind, placebo-controlled trial involving patients who had primary intracerebral hemorrhage but did not have coagulopathy. A total of 399 patients were assigned to receive one of three doses of rFVIIa (40, 80, or 160  $\mu$ g per kilogram of body weight) or pla-

cebo, administered within four hours after the onset of symptoms. In terms of the primary outcome — the mean percent increase in the volume of intracerebral hemorrhage at 24 hours — the group that received the highest dose of rFVIIa had a significantly smaller increase than did the placebo group; the same was not true for the other two rFVIIa groups, although a test for trend was significant. In all three rFVIIa groups combined, there was a smaller expansion of hematoma volume from baseline (4.2 ml) than in the placebo group (8.7 ml). Furthermore, the scores on many of the measures assessing functional outcome at three months were superior in each of the rFVIIa groups.

The combined rFVIIa groups had lower mortality at three months than did the placebo group, without an increase in severe disability. The reduction in mortality, always difficult to demonstrate in studies of stroke, testifies to the robustness of the benefit. The main safety outcome was severe thromboembolism at 90 days. Severe arterial and venous thromboembolic adverse events were more than three times as common in the rFVIIa groups as in the placebo group (7 percent vs. 2 percent). The events in the rFVIIa groups included seven myocardial infarctions and nine cerebral infarctions (for a combined rate of 5 percent); there were no arterial thromboembolic events in the placebo group.

The results of this trial are important but not clinically directive. The four-hour treatment window used in the trial, although narrow, would not insurmountably limit the application of rFVIIa in routine clinical practice. Community and professional interventions to increase the use of therapy for acute stroke have had demonstrated success.<sup>6</sup> However, at this point the results of the trial by Mayer et al. should be viewed as preliminary. Tempering the enthusiasm for rFVIIa as a treatment for intracerebral hemorrhage is the risk of arterial thromboembolic complications. In fact, the exclusion criteria of the study were changed midway through the trial, because of concerns about safety, to exclude patients with any history of thrombotic or vaso-occlusive disease. The highest dose of rFVIIa, 160  $\mu$ g per kilogram, is almost twice the amount given per dose to treat patients with hemophilia. Overall, the

total experience with this highest dose in patients with intracerebral hemorrhage in studies from this group is limited.<sup>1,7</sup> Further data on complications will need to be gleaned from more clinical trial experience with rFVIIa in patients with intracerebral hemorrhage.

There are limitations to this study. The treatment groups in the trial by Mayer et al. may not have been comparable in terms of important factors known to be associated with outcomes. Observational studies have shown that blood pressure is a prognostic factor with respect to the outcome of intracerebral hemorrhage,<sup>8,9</sup> with extremely high or low pressure predicting a poor outcome. Yet there was no adjustment for blood pressure in the analysis of clinical outcomes in the trial by Mayer et al. Blood-pressure management during the trial was also not stipulated. A possible interaction of blood pressure and the effect of rFVIIa is not discussed in the article. To date, there have been no large trials addressing the effects of blood-pressure management in patients with acute intracerebral hemorrhage. As is the case with ischemic stroke, there has been concern that lowering blood pressure may precipitate neurologic deterioration as a result of hypoperfusion of a perihematomal region of ischemia. However, studies with positron-emission tomography in human subjects have failed to support the existence of an ischemic penumbra surrounding the area of hemorrhage.<sup>10</sup> Further study of the clinical effect of blood-pressure control in acute intracerebral hemorrhage — and of a possible treatment interaction with rFVIIa — appears to be warranted.

The lack of adjustment for the withdrawal of care represents a limitation of the rFVIIa trial by Mayer et al. Recent work has demonstrated the important interplay between the withdrawal of medical support and the clinical outcome.<sup>11,12</sup> In patients with intracerebral hemorrhage, withdrawal of support tends to occur within the first two days and uniformly leads to death.<sup>11</sup> Unfortunately, predictive models of outcomes of intracerebral hemorrhage, biased by the early withdrawal of care, lead physicians to be less aggressive in the management of intracerebral hemorrhage. When entered into multivariable statistical models to predict in-hospital mortality, the withdrawal or nonwithdrawal of support was the only variable significantly associated with the outcome, despite the

inclusion of radiographic and clinical variables thought to be associated with mortality.<sup>11</sup> It appears that institutions that have high rates of use of do-not-resuscitate (DNR) orders for patients with intracerebral hemorrhage have higher mortality associated with intracerebral hemorrhage, regardless of patients' clinical status, than do institutions with low rates of DNR use.<sup>12</sup> This association suggests that there may be differences in outcome according to the overall aggressiveness of care. We may give up on patients with intracerebral hemorrhage too early, often because we rely on data that are imperfect, at best.

A potential approach to the treatment of intracerebral hemorrhage is the surgical evacuation of hematoma. The International Surgical Trial in Intracerebral Hemorrhage compared the use of "early" surgery for intracerebral hemorrhage with initial conservative management.<sup>13</sup> Investigators selected patients and excluded those thought likely to benefit from surgery. No significant differences were detected between the two groups in terms of the rates of a favorable neurologic outcome or death. These results have been viewed with some skepticism, given the method of enrolling subjects and the delays before surgery in the early-treatment group, since patients were randomly assigned within 72 hours after the onset of hemorrhage and then treated within 24 hours after randomization. The role of surgical treatment for intracerebral hemorrhage, including the optimal surgical technique, therefore remains controversial and deserves further study. The use of an agent such as rFVIIa may prove to enhance the safety of early surgical hematoma evacuation.<sup>14</sup>

This is a very exciting time in the study of intracerebral hemorrhage. It is possible that we are on the brink of having a successful targeted treatment in rFVIIa; only time and more investigation will tell. Fortunately, the enthusiasm for collaborative investigation in the treatment of intracerebral hemorrhage is building. The National Institute of Neurological Disorders and Stroke workshop on intracerebral hemorrhage recently outlined future directions for research, including basic-science and imaging endeavors and trials of medical and surgical treatments.<sup>15</sup> Although further study of rFVIIa is warranted, other trials of methods to prevent rebleeding and investigations of blood-pressure lowering, the optimal management of intracranial pressure, and

surgical and medical treatments directed at removal or dissolution of clots are also likely to be of great benefit in the treatment of this common and devastating disease.

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## Chasing Mutations in the Epidermal Growth Factor in Lung Cancer

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Non-small-cell lung cancer is the leading cause of death from cancer in men and women in the United States, and worldwide it kills more than 1 million people annually. Approximately two thirds of patients with non-small-cell lung cancer present with locally advanced or metastatic disease that requires systemic therapy in addition to surgery or radiation therapy. The good news is that the results of systemic therapy are improving: chemotherapy prolongs survival and improves the quality of life for patients with non-small-cell lung cancer. The bad news is that systemic therapy is still woefully inadequate: only 30 to 40 percent of patients with metastatic non-small-cell lung cancer survive for even one year.

For this reason, the finding that therapy targeted against the epidermal growth factor receptor (EGFR) had substantial clinical benefits in 10 to 20 percent of patients with non-small-cell lung cancer was of great interest. An important example of targeted therapy that is revolutionizing cancer treat-

ment is imatinib, which inhibits the ABL tyrosine kinase that is activated by the *BCR-ABL* translocation in chronic myeloid leukemia, and *c-kit*, which is activated by a somatic mutation in gastrointestinal stromal tumors.

EGFR, a receptor tyrosine kinase, is frequently overexpressed and activated to a phosphorylated state in non-small-cell lung cancer. The tyrosine kinase activity of phosphorylated EGFR in cancer cells results in the phosphorylation of downstream proteins that incite cell proliferation, invasion, metastasis, and inhibition of apoptosis. Because several cancers overexpress EGFR, this tyrosine kinase has been a favorite target for treatment. Two oral anilinoquinazoline EGFR tyrosine kinase inhibitors, gefitinib (Iressa) and erlotinib (Tarceva), have been approved in the United States for use as second-line or third-line therapy in advanced non-small-cell lung cancer. In comparison with placebo, treatment with erlotinib improved one-year survival rates, from 22 to 31 percent, in patients with non-