Thrombolytic therapy for stroke in patients with preexisting cognitive impairment

ABSTRACT

Objective: We aimed to evaluate the influence of prestroke cognitive impairment (PSCI) on outcomes in stroke patients treated with IV recombinant tissue plasminogen activator (rtPA).

Methods: OPHELIE-COG was a prospective observational multicenter study conducted in French and Japanese patients treated with IV rtPA for cerebral ischemia. The preexisting cognitive status was evaluated by the short version of the Informant Questionnaire on Cognitive Decline in the Elderly. PSCI was defined as a mean score >3. The primary endpoint was a favorable outcome (modified Rankin Scale [mRS] score 0–1) after 3 months. Secondary endpoints were symptomatic intracerebral hemorrhage (sICH), mRS scores 0–2, and mortality at 3 months. We performed a pooled analysis with Biostroke and Strokedom.

Results: Of 205 patients, 62 (30.2%) met criteria for PSCI. They were 11 years older (p < 0.001). Although they had more sICH and were less frequently independent after 3 months, they did not differ for any endpoint after adjustment for age, baseline NIH Stroke Scale score, and onset-to-needle time: sICH (odds ratio [OR] 2.78; 95% confidence interval [CI] 0.65–11.86), mRS 0–1 (OR 0.82; 95% CI 0.41–1.65), mRS 0–2 (OR 0.62; 95% CI 0.28–1.37), death (OR 0.40; 95% CI 0.08–2.03). The pooled analysis found no association of PSCI with any endpoint.

Conclusions: Ischemic stroke patients with PSCI should receive rtPA if they are eligible. This conclusion cannot be extended to severe cognitive impairment or severe strokes.

Classification of evidence: This study provides Class IV evidence that in patients with PSCI presenting with acute ischemic stroke, IV rtPA improves outcomes. Neurology® 2014;82:2048–2054

GLOSSARY

CI = confidence interval; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; IQR = interquartile range; MMSE = Mini-Mental State Examination; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio; PSCI = prestroke cognitive impairment; rtPA = recombinant tissue plasminogen activator; sICH = symptomatic intracerebral hemorrhage.

At the acute stage of cerebral ischemia, treatment with IV recombinant tissue plasminogen activator (rtPA) is recommended worldwide2–3; it increases survival without dependency in patients treated within 4.5 hours of the onset of symptoms4,7 even in elderly participants.8,9 At least 10% of stroke patients have preexisting dementia,10 and even more in elderly patients and in patients with recurrent strokes.10,11 Patients with prestroke cognitive impairment (PSCI) frequently have vascular lesions, such as cerebral amyloid angiopathy and hypertensive deep perforating vasculopathy, and brain lesions, such as white matter changes and microbleeds.10–14 All these pathologic changes are associated with an increased risk of cerebral hemorrhage.15,16

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Patients with PSCI might also be more sensitive to the neurotoxic effects of rtPA on the ischemic brain tissue. However, none of the previously reported observational studies has shown a clear association between PSCI and the risk of symptomatic intracerebral hemorrhage (sICH) after treatment with rtPA. However, these studies were limited by their small sample size, the lack of systematic search for PSCI, the absence of important predictors of outcome in the analysis, and the lack of evaluation at 3 months. In our previous retrospective study, in which most of these limitations were solved, we found no difference in outcome after IV rtPA treatment between patients with and without PSCI, but patients were highly selected and accounted for less than 20% of all patients treated with IV rtPA. To determine whether rtPA is safe and effective in ischemic stroke patients with PSCI would need a randomized placebo-controlled trial. Such a trial would not be ethical in the absence of evidence that rtPA is unsafe in patients with PSCI. The aim of this multicenter study was to evaluate the influence of PSCI on the clinical outcome of consecutive stroke patients treated with IV rtPA.

METHODS Setting. We prospectively included all patients who were treated with IV rtPA for an acute cerebral ischemia in participating centers. The French part of OPHELIE-COG was conducted in the framework of the Strokeavenir network, supported by the French Ministry of Health. The Japanese part of OPHELIE-COG was conducted in the 7 hospitals participating in the Fukuoka Stroke Registry and in the Kawasaki Medical School Hospital. Centers became active between January 2012 and March 2013, and the last follow-up visit was on July 30, 2013.

Standard protocol approvals, registrations, and patient consents. OPHELIE-COG was an observational multicenter study conducted in French and Japanese centers. It recruited adults of both sexes who were treated with IV rtPA for cerebral ischemia and gave informed consent themselves or via a close relative. The study was approved by health authorities in both countries and by relevant ethical committees: Comité de Protection des Personnes (CPP) Nord Ouest IV Lille, France, by March 9, 2010, under registration number 10.677, and ethical committee of Kyushu Medical Center, Japan, by November 16, 2011, under registration number 11–75. We were not allowed to record in the database the ethnicity by French health authorities. OPHELIE-COG is registered under ClinicalTrials.gov identifier no. NCT01713491.

General management. French patients were treated according to the revised recommendations of the European Stroke Organisation, in which the time window for IV rtPA was extended up to 4.5 hours after onset. Japanese patients were treated according to the Japanese guidelines for IV rtPA therapy, which mainly differ from European ones by the dose of rtPA (Japan: 0.6 mg/kg body weight, maximum 60 mg; Europe: 0.9 mg/kg body weight, maximum 90 mg). The time window was extended to 4.5 hours on September 1, 2012, in Japan.

Inclusion and exclusion criteria. All consecutive patients who were treated with IV rtPA in participating centers during the study period and consented for participation were eligible. Age over 80 years was not regarded as an exclusion criterion. Exclusion criteria were (1) an acute ischemic stroke sparing the middle cerebral artery territory; (2) thrombolytic therapy administered intra-arterially or combined with thrombectomy; (3) impaired daily living before stroke onset with a prestroke modified Rankin Scale score of 2 or 3; and (4) impossibility to perform the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) within 48 hours after admission, except when the patient had been diagnosed as cognitively impaired by a specialist (e.g., neurologist, psychiatrist, or geriatrician) before stroke onset, or classified as cognitively normal because of a score of 30 at discharge on the Mini-Mental State Examination (MMSE).

Clinical assessment. The severity of the neurologic deficit at admission was evaluated by the NIH Stroke Scale (NIHSS). The preexisting level of independence and functional outcome at 3 months after stroke onset were evaluated by the mRS. When a face-to-face visit was not possible 3 months after stroke, the functional outcome was evaluated by a telephone survey with the patient, the family, or the treating physician. Stroke subtypes were classified according to the criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study. The evaluation of the preexisting cognitive status was assessed within 48 hours after stroke onset by French or Japanese translations of the short version of the IQCODE. This questionnaire consists of 16 questions regarding the changes observed in patients over the last 10 years in aspects of daily behavior requiring memory and other intellectual abilities. A close relative needs to be interviewed. Each item is given a score of 0–3 (0 = much improved; 2 = a bit improved; 3 = not changed; 4 = a bit worse; 5 = much worse). The overall score is the sum of the scores of each item, ranging from 16 to 80. The informant should have known the patient for at least 10 years and meet him or her at least once a week. The questionnaire has good reproducibility. In the community, there is a good correlation between MMSE and IQCODE scores.

We classified patients as (1) having PSCI when the mean IQCODE score was greater than 3 (i.e., total score >48); and (2) cognitively normal when the mean IQCODE score was 3 or less. The threshold of 3 was chosen to consider in the PSCI group all patients who had a change over the last 10 years in one question of the questionnaire, and to increase the sensitivity of the test for a diagnosis of very mild cognitive impairment.

Study outcomes. The primary endpoint was favorable functional outcome (mRS score 0–1) at the 3-month visit. Secondary endpoints were (1) sICH defined according to the European Cooperative Acute Stroke Study II criteria, (2) mRS score 0–2 (absence of dependence) at 3 months, or (3) death at 3 months.

Sample size calculation. As available data on rtPA in patients with cognitive impairment were scarce when the study was initiated, an intermediate analysis was planned after inclusion of 500 patients who reached the 3-month follow-up, to reevaluate the sample size.
While the OPHELIE-COG study was running, we retrospectively analyzed the data that became available in patients who had been treated with IV rtPA before inclusion in either Biostroke (NCT00763217) or Strokdem (NCT01330160), 2 studies of biomarkers conducted in the stroke unit of the Lille University Hospital. Although patients included in these studies were highly selected and the sample size was limited, this analysis showed that the chance to detect a significant difference between patients with and without PSCI would be small, and it was therefore decided to anticipate the intermediate analysis of OPHELIE-COG and to analyze available data. After this intermediate analysis, it was decided to stop OPHELIE-COG for futility.

Statistical analyses. We performed the statistical analysis with the SPSS 22.0 package for windows. We used median values, interquartile ranges (IQRs), and percentages. We used the Mann-Whitney U test to compare continuous variables. Probability values <0.05 were considered statistically significant. We compared groups for categorical variables with unadjusted odds ratio (ORs) with 95% confidence intervals (CIs). Adjusted ORs and 95% CIs for the study outcome were estimated by logistic regression analyses with the variables PSCI (classified 1 when present, 0 when absent), age (years), baseline NIHSS score (points), and onset-to-needle time (minutes) forced into the model. Finally, we performed a pooled analysis of the results of OPHELIE-COG and of the previously published joined analysis of Biostroke and Strokdem to test consistency of the results in different settings.

The primary research question was whether the outcome of patients treated by IV rtPA was influenced by the presence of PSCI to such an extent that the benefit of rtPA could be lost.

Table 1  Baseline characteristics according to prestroke cognitive status

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>With PSCI (n = 62)</th>
<th>Without PSCI (n = 143)</th>
<th>Unadjusted OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>26 (41.9)</td>
<td>80 (55.9)</td>
<td>0.57 (0.31-1.04)</td>
<td></td>
</tr>
<tr>
<td>Recruited in France</td>
<td>46 (74.2)</td>
<td>123 (86.0)</td>
<td>0.47 (0.22-0.98)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Age, y, median IQRa</td>
<td>77 (67-82)</td>
<td>66 (54-77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, kg, median (IQR)</td>
<td>71 (59-83)</td>
<td>74.4 (67.3-82.8)</td>
<td>0.087</td>
<td></td>
</tr>
<tr>
<td>Prestroke mRS = 0</td>
<td>50 (80.6)</td>
<td>135 (94.4)</td>
<td>0.25 (0.10-0.64)</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>7 (11.3)</td>
<td>8 (5.6)</td>
<td>2.15 (0.74-6.21)</td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>6 (9.7)</td>
<td>24 (16.8)</td>
<td>0.53 (0.21-1.37)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>15 (24.2)</td>
<td>26 (18.2)</td>
<td>1.44 (0.70-2.95)</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>43 (69.4)</td>
<td>86 (60.1)</td>
<td>1.50 (0.79-2.83)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (16.1)</td>
<td>24 (16.8)</td>
<td>0.95 (0.43-2.14)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>11 (17.7)</td>
<td>46 (32.2)</td>
<td>0.45 (0.22-0.95)</td>
<td></td>
</tr>
<tr>
<td>Excessive alcohol consumption</td>
<td>4 (6.5)</td>
<td>15 (10.5)</td>
<td>0.59 (0.19-1.85)</td>
<td></td>
</tr>
<tr>
<td>Ongoing anticoagulant therapy</td>
<td>5 (8.1)</td>
<td>9 (6.3)</td>
<td>1.31 (0.42-4.07)</td>
<td></td>
</tr>
<tr>
<td>Ongoing antiplatelet therapy</td>
<td>20 (32.3)</td>
<td>29 (20.3)</td>
<td>1.87 (0.96-3.66)</td>
<td></td>
</tr>
<tr>
<td>IQCODE score, median (IQR)</td>
<td>3.25 (3.22-3.38)</td>
<td>3.00 (2.88-3.00)</td>
<td>&lt;0.0001b</td>
<td></td>
</tr>
<tr>
<td>Presumed cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>7 (11.3)</td>
<td>30 (21)</td>
<td>0.48 (0.20-1.16)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>25 (40.3)</td>
<td>52 (36.4)</td>
<td>1.18 (0.64-2.18)</td>
<td></td>
</tr>
<tr>
<td>Small-vessel occlusion</td>
<td>3 (4.8)</td>
<td>5 (3.5)</td>
<td>1.40 (0.32-6.06)</td>
<td></td>
</tr>
<tr>
<td>Other definite causes</td>
<td>1 (1.6)</td>
<td>6 (4.2)</td>
<td>0.37 (0.04-3.18)</td>
<td></td>
</tr>
<tr>
<td>Unknown causes</td>
<td>26 (41.9)</td>
<td>50 (35.0)</td>
<td>1.34 (0.73-2.47)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BP = blood pressure; CI = confidence interval; INR = international normalized ratio; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; IQR = interquartile range; MI = myocardial infarction; mRS = modified Rankin Scale; NA = not assessable; NIHSS = NIH Stroke Scale; OR = odds ratio; PSCI = prestroke cognitive impairment; rtPA = recombinant tissue plasminogen activator.

Values are number of patients (%) unless specified, with unadjusted OR and 95% CI.
aMedian values (IQR) with Mann-Whitney U test. ORs >1 mean that the variable is more frequent in patients with PSCI.
bSignificant difference.
RESULTS We recruited 205 patients, including 106 men (51.7%), with a median age of 70 years (IQR 56–80) and a median NIHSS score of 8 (IQR 5–16). The 169 patients (82.4%) recruited in France were younger than those recruited in Japan: median age 69 years (IQR 56–78) vs 77 years (IQR 61–85) ($p = 0.03$). Sixty-two patients (30.2%) met criteria for PSCI.

The baseline characteristics of patients with and without PSCI are compared in table 1: patients with PSCI were significantly older and more likely to have mRS 1 prior to stroke than those without.

The whole range of mRS scores 3 months after stroke is detailed in figure 1. Although patients with PSCI had more sICH and were less frequently independent 3 months after stroke than those without, they did not differ for any of the 4 outcome measures after adjustment for age, baseline NIHSS score, and onset-to-needle time (table 2).

The pooled analysis of patients included in OPHELIE-COG and in the Biostroke/Strokdem study found no significant association of PSCI with any of the 4 endpoints, despite a small tendency toward a lower frequency of mRS 0–1/0–2 after 3 months and a slightly lower mortality in patients with PSCI (figure 2). The risk of being dependent (mRS 3–5) after 3 months was not significantly increased in patients with PSCI after adjustment for age, baseline NIHSS, and onset-to-needle time.

DISCUSSION Our study has shown that, although patients with PSCI had more sICH and were less frequently independent 3 months after stroke than those without, they did not differ for any of the 4 outcome measures after adjustment for age, baseline NIHSS score, and onset-to-needle time. Therefore, the small differences in outcomes are the consequence of differences in case mix. This study provides Class IV evidence that in patients with PSCI presenting with acute ischemic stroke, IV rtPA improves outcomes.

The strengths of OPHELIE-COG are the prospective design, the standardized evaluation of the preexisting cognitive status, and the multicenter,
binational, and multietnic recruitment. To our knowledge, there was until now no study that prospectively and systematically evaluated the safety of IV rtPA in cognitively impaired patients consecutively admitted for cerebral ischemia. The use of a standardized and validated questionnaire was of major importance, because the preexisting cognitive status could not be directly evaluated by usual neuropsychological tests, because of the influence of the stroke lesion. Up to now, the IQCODE is the most appropriate test to evaluate the preexisting cognitive status.10 Besides, the results of OPHELIE-COG are in line with those of our retrospective analysis of highly selected patients recruited in the Strokdem and Biostroke studies.23

The main limitation of OPHELIE-COG is that this study mainly provides safety information and no direct evidence of the efficacy of rtPA in patients with PSCI in the absence of a control group and randomization. Heterogeneity in the dose of rtPA between Europe and Japan has no reason to have influenced the results, as suggested by a Japanese postmarketing survey showing a proportion of favorable outcomes at 3 months of 39%,34 i.e., very close to that found in the European registry.35,36 The absence of patients with major PSCI, because of the exclusion of patients with a prestroke mRS of 2 or more, does not allow any conclusion for patients with severe cognitive impairment. As the baseline severity of the study population was slightly lower than those in trials and in most observational cohorts, with a median NIHSS score of 8,37 OPHELIE-COG does not allow any conclusion for severe strokes. Therefore, OPHELIE-COG provides interesting conclusions that are valid only for patients with mild cognitive impairment and ischemic stroke of moderate severity. We could not adjust for ethnicity because the French regulation does not allow inclusion of ethnicity in a database in the absence of a strong rationale.

As PSCI was evaluated retrospectively at admission, we could not differentiate vascular, degenerative, and mixed causes, and therefore we included both pathologies in the same group, although efficacy and safety of rtPA may differ between vascular and degenerative PSCI.

OPHELIE-COG provides another piece of evidence that patients with mild cognitive impairment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>With PSCI</th>
<th>Without PSCI</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sICH</td>
<td>Biostroke/Strokdem</td>
<td>0/31</td>
<td>3/68</td>
<td>N.A.</td>
</tr>
<tr>
<td></td>
<td>OPHELIE-COG</td>
<td>7/62</td>
<td>5/143</td>
<td>2.78 (0.65-11.86)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>7/93</td>
<td>8/211</td>
<td>1.55 (0.48-5.04)</td>
</tr>
<tr>
<td>mRS 0-1</td>
<td>Biostroke/Strokdem</td>
<td>15/31</td>
<td>34/68</td>
<td>0.74 (0.27-2.04)</td>
</tr>
<tr>
<td></td>
<td>OPHELIE-COG</td>
<td>26/62</td>
<td>75/143</td>
<td>0.82 (0.41-1.65)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>41/93</td>
<td>109/211</td>
<td>0.82 (0.46-1.45)</td>
</tr>
<tr>
<td>mRS 0-2</td>
<td>Biostroke/Strokdem</td>
<td>19/31</td>
<td>44/68</td>
<td>0.84 (0.30-2.21)</td>
</tr>
<tr>
<td></td>
<td>OPHELIE-COG</td>
<td>35/62</td>
<td>102/143</td>
<td>0.62 (0.28-1.37)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>54/93</td>
<td>146/211</td>
<td>0.69 (0.37-1.28)</td>
</tr>
<tr>
<td>Death</td>
<td>Biostroke/Strokdem</td>
<td>2/31</td>
<td>6/68</td>
<td>0.46 (0.08-2.63)</td>
</tr>
<tr>
<td></td>
<td>OPHELIE-COG</td>
<td>3/62</td>
<td>7/143</td>
<td>0.40 (0.08-2.03)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>5/93</td>
<td>13/211</td>
<td>0.44 (0.14-1.42)</td>
</tr>
</tbody>
</table>

Adjusted odds ratios (\( \text{adj} \text{OR} \)) and 95% confidence intervals (CI) for the outcomes at 3 months in patients with and without prestroke cognitive impairment (PSCI). The ORs are adjusted for age, baseline NIH Stroke Scale score, and onset-to-needle time. mRS = modified Rankin Scale; NA = not assessable; sICH = symptomatic intracerebral hemorrhage.
before stroke should receive rtPA if they are otherwise eligible. This conclusion cannot be extended to patients with severe cognitive impairment or to patients with severe strokes.

AUTHOR CONTRIBUTIONS
Kei Murao analyzed and interpreted all data, performed the literature search, and drafted the manuscript. Didier Leys conceptualized the study, analyzed, interpreted, and collected data, and drafted the manuscript. Agnès Jacquin interpreted study data and revised the manuscript. Takanari Kitazono conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Olivier Godofrey conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Yasushi Okada conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Hilde Hénon interpreted study data and revised the manuscript. Charlotte Cordonnier interpreted study data and revised the manuscript. Maurice Giroud conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Kazumi Kimura conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Agnès Jacquin interpreted study data and revised the manuscript. Yosihide Wakisaka conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Olivier Godofrey conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Tetsuro Ago collected and interpreted study data and revised the manuscript. Igor Sibon conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Stéphanie Bombois interpreted study data and revised the manuscript. Jean-Louis Mas conceptualized and designed the study, interpreted study data, and revised the manuscript. Hilde Hénon conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Florence Pasquier interpreted study data and revised the manuscript. Maurice Giroud conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Charlotte Cordonnier interpreted study data and revised the manuscript. Yasushi Okada conceptualized and designed the study, interpreted and collected study data, and revised the manuscript.

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DISCLOSURE
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