Research Article

Intravenous Thrombolysis in Acute Ischemic Stroke with Active Cancer

Ki-Woong Nam,1 Chi Kyung Kim,2 Tae Jung Kim,1 Sang Joon An,1 Kyungmi Oh,2 Sang-Bae Ko,1 and Byung-Woo Yoon1

1Department of Neurology, Seoul National University Hospital, Seoul, Republic of Korea
2Department of Neurology, Korea University Guro Hospital and Korea University College of Medicine, Seoul, Republic of Korea

Correspondence should be addressed to Byung-Woo Yoon; bwyoon@snu.ac.kr

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Ischemic stroke patients with active cancer are known to have poor clinical outcomes. However, the efficacy and safety of intravenous alteplase (IV t-PA) in this group are still unclear. In this study, we aimed to evaluate whether stroke patients with cancer had poor clinical outcomes after use of IV t-PA. We reviewed ischemic stroke patients with active cancer treated with isolated IV t-PA between April 2010 and March 2015 at three national university hospitals from the registry for ischemic stroke in Korea. The clinical outcomes of early neurological deterioration (END), hemorrhagic transformation, in-hospital mortality, 3-month modified Rankin scale (mRS), the National Institutes of Health Stroke Scale (NIHSS) discharge score, and duration of hospitalization were compared.

We enrolled a total of 12 patients, and the cohort showed poor outcomes including 4 (33%) END events, 7 (58%) hemorrhagic transformations, 3 (25%) in-hospital mortality cases, and 7 (58%) poor mRS (3–6) scores. Additionally, the cryptogenic stroke group (n = 6) more frequently had high mRS scores (P = 0.043) as well as tendencies for frequent END events, hemorrhagic transformations, in-hospital mortality cases, and higher discharge NIHSS scores without statistical significance. In conclusion, ischemic stroke patients with active cancer, especially those with a cryptogenic mechanism, showed poor clinical outcomes after use of IV t-PA.

1. Introduction

Ischemic stroke in cancer patients, with a frequent occurrence of up to 15%, has been recently studied [1]. These patients have complicated stroke mechanism by conventional stroke mechanisms (e.g., large-artery atherosclerosis, small-vessel disease, and cardioembolism) and cancer-specific mechanisms (e.g., hypercoagulability, tumor embolism, and nonbacterial thrombotic endocarditis) [2]. Previously, patients who experienced stroke with cryptogenic mechanism, who had no evidence of conventional mechanisms, were proven to be more closely related to those with stroke with cancer-specific mechanisms (especially hypercoagulability) and had poorer clinical outcomes [1, 3–9].

Intravenous alteplase (IV t-PA) is a well-known treatment option to recover from poststroke disability during the acute period. However, its efficacy and safety in patients with active cancer have not been well addressed due to its complex stroke mechanisms [6]. With longer life-expectancy due to improved cancer treatments, we needed to assess the exact prognosis and identify the high-risk subset after use of IV t-PA in ischemic stroke patients with active cancer.

In this study, we evaluated whether ischemic stroke patients with active cancer had poor clinical outcomes after use of IV t-PA. In addition, we also aimed to evaluate the impact of stroke mechanisms (e.g., conventional versus cryptogenic mechanisms) on the clinical outcomes after use of IV t-PA.

2. Methods

2.1. Study Population. We retrospectively reviewed medical records from the consecutively enrolled stroke registry for ischemic stroke patients with active cancer who visited three national university hospitals (Seoul National University Hospital, Korea University Guro Hospital, and Seoul National University Bundang Hospital). The inclusion criteria were as follows: ischemic stroke according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [10] and active cancer confirmed by imaging evidence and the results of clinical examination.

The study was approved by the institutional review board of each participating hospital (Seoul National University Hospital, IRB No. 1012-009-429; Korea University Guro Hospital, IRB No. 2011-05-006-H; Seoul National University Bundang Hospital, IRB No. 2011-22-003-H). All patients or their legal guardians provided written informed consent before enrollment. The registry data were used for research purposes without identifying any individual patient's information.

The clinical outcomes of early neurological deterioration (END), hemorrhagic transformation, in-hospital mortality, 3-month modified Rankin scale (mRS), the National Institutes of Health Stroke Scale (NIHSS) discharge score, and duration of hospitalization were compared. The clinical outcomes were defined as follows: END events were identified when neurological deterioration occurred within 24 hours of stroke onset, according to the TOAST classification [10]. Hemorrhagic transformation was identified when new hemorrhage was demonstrated on magnetic resonance imaging (MRI) or computed tomography (CT) scans after IV t-PA therapy. In-hospital mortality was defined as death occurring during hospitalization. The 3-month modified Rankin scale (mRS) scores were recorded as defined by the mRS classification [11]. The National Institutes of Health Stroke Scale (NIHSS) discharge score was recorded as the NIHSS score on discharge. The duration of hospitalization was recorded as the number of days from the onset of stroke to hospital discharge.

The clinical outcomes were compared between patients with conventional stroke mechanisms and those with cryptogenic stroke mechanisms. Conventional stroke mechanisms were defined as large-artery atherosclerosis, small-vessel disease, and cardioembolism. Cryptogenic stroke mechanisms were defined as hypercoagulability, tumor embolism, and nonbacterial thrombotic endocarditis.

The statistical analyses were performed using the SPSS software (version 21.0; IBM Corp, Armonk, NY, USA). The categorical variables were analyzed using the chi-square test or Fisher’s exact test. The continuous variables were analyzed using the unpaired t-test or Mann-Whitney U test, as appropriate. A P-value of less than 0.05 was considered statistically significant.
Ischemic stroke patients using thrombolytic therapy (n = 480)

Without active cancer

(i) No cancer or nonactive cancer (n = 432)

Ischemic stroke patient with active cancer using thrombolytic therapy (n = 48)

Exclude IA or both IV and IA thrombolysis

(i) IA only: n = 18
(ii) Both IA and IV thrombolysis: n = 14

Ischemic stroke patients with active cancer using IV thrombolysis only (n = 16)

(i) age < 18 years: n = 1
(ii) Hematologic malignancy: n = 2
(iii) Primary intracranial tumor: n = 1

Final analysis (n = 12)

Figure 1: Patient selection for the study.

Hospital, Seoul National University Bundang Hospital, and Seoul Metropolitan Government-Seoul National University Boramae Medical Center) in Korea between April 2010 and March 2015. Active cancer was defined as any diagnosis, recurrence, metastasis, and progression of cancer within 6 months of enrollment [6]. Among the cases, we extracted the subpopulation that was treated with IV t-PA. Patients using both IV t-PA and intra-arterial thrombectomy were excluded as to evaluate the sole effects of IV t-PA for the study. In addition, we also excluded patients under the age of 18 years and those who had a hematologic malignancy or a primary intracranial tumor which are known to have different stroke mechanisms [6]. Finally, a total of 12 patients remained for the analysis (Figure 1). This study was approved by the institutional review board (IRB) of Seoul National University Hospital (H-1610-036-797) and designed according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

2.2. Clinical Assessment. We collected demographic, clinical, and cardiovascular risk factors, including the presence of hypertension, diabetes, hyperlipidemia, current smoking, use of alcohol, history of stroke, initial stroke severity, mechanisms of stroke, blood pressure (BP), initial antithrombotics taken, and dose of t-PA [3]. The initial stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) by well-trained neurologists. The mechanisms of stroke were classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. We, then, dichotomized the stroke mechanisms into conventional (large-artery atherosclerosis, small-vessel occlusion, and cardioembolism) and cryptogenic mechanisms [6]. BP was assessed for initial systolic BP and diastolic BP. Initial antithrombotics were divided into low-molecular weight heparin, warfarin, antiplatelet agent, and no treatment. Data regarding the patient’s cancer were also assessed including cancer type, systemic or brain metastasis, and venous thromboembolism (e.g., deep-vein thrombosis, pulmonary embolism).

We assessed the clinical outcomes in variable aspects. We evaluated early neurological deterioration (END), hemorrhagic transformation, hospitalization duration, discharge NIHSS scores, in-hospital mortality events, and the 3-month modified Rankin scale (mRS) scores. END was defined as an increase of ≥1 in the motor NIHSS score or ≥2 in the total NIHSS score [3].

2.3. Radiological Assessment. All patients underwent brain magnetic resonance imaging (MRI) within 4 hours of admission using a 3.0-Tesla MR scanner (Achieva 3.0T; Philips, Eindhoven, Netherlands). We dichotomized the initial diffusion-weighted image lesion into single territory lesions and multiple territory lesions [7]. Laboratory results, including C-reactive protein, D-dimer, prothrombin time, and activated partial thromboplastin time were assessed within 24 hours of admission.

2.4. Statistical Analysis. All statistical analyses were conducted using SPSS version 22 (IBM SPSS, Chicago, IL, USA). We presented continuous variables as the mean ± SD when data were normally distributed, while the others were presented as the median + interquartile range. Student's t-test or Mann–Whitney U test were used for continuous variables, and the chi-squared test or Fisher's exact test were
Table 1: Brief profile of participants in the study.

| Number/sex/age, y | Cancer type | t-PA dose | Initial D-dimer | Mechanism | Initial NIHSS | END | 3m mRS | Hemorrhagic transformation | Initial treatment |
|------------------|-------------|-----------|-----------------|-----------|--------------|-----|-------|--------------------------|------------------|
| 1/F/64           | Lung        | 0.9       | 26.8            | Cryptogenic | 20           | N   | 5     | Y                        | Enoxaparin       |
| 2/M/61           | Pancreas    | 0.9       | 5.11            | Cryptogenic | 7            | Y   | 6     | Y                        | Enoxaparin       |
| 3/F/74           | Pancreas    | 0.9       | 3.7             | Cryptogenic | 13           | Y   | 6     | N                        | No treatment     |
| 4/M/61           | Lung        | 0.6       | 2.01            | Cryptogenic | 7            | N   | 0     | N                        | Enoxaparin       |
| 5/M/76           | Lung        | 0.6       | 3.91            | Cryptogenic | 15           | Y   | 6     | Y                        | No treatment     |
| 6/M/82           | Gastric     | 0.6       | 20              | Cryptogenic | 7            | N   | 6     | Y                        | Enoxaparin       |
| 7/M/70           | Gastric     | 0.9       | 11.1            | CE         | 7            | N   | 1     | Y                        | Warfarin         |
| 8/M/81           | Colon       | 0.6       | 0.82            | LAD        | 19           | Y   | 3     | Y                        | Antiplatelet     |
| 9/M/64           | Colon       | 0.6       | 0.73            | LAD        | 3            | N   | 0     | N                        | Antiplatelet     |
| 10/M/67          | Lung        | 0.6       | 1.77            | LAD        | 19           | N   | 1     | N                        | Antiplatelet     |
| 11/F/56          | Cervical    | 0.6       | 0.16            | LAD        | 5            | N   | 1     | N                        | Antiplatelet     |
| 12/F/76          | Lung        | 0.9       | 8.28            | CE         | 24           | N   | 5     | Y                        | Enoxaparin       |

used for categorical variables. All variables with $P < 0.05$ were considered significant in the statistical analyses.

3. Results

We enrolled a total of 12 ischemic stroke patients with active cancer who were treated with IV t-PA (mean age of 69 years, visit time $[0.5–1.75]$ hours, median NIHSS scores $[7–19]$, Table 1). Among them, 6 patients were classified as having a conventional stroke mechanism, and the remaining with a cryptogenic mechanism. In clinical outcomes, the cohort had $4 (33\%)$ END events, $7 (58\%)$ hemorrhagic transformations, $3 (25\%)$ in-hospital mortalities, and $7 (58\%)$ poor mRS (3–6) scores. The duration of hospitalization was $12 [9–25]$ days.

None of the demographic, clinical, cardiovascular, laboratory, or radiological variables were significantly different between the conventional and the cryptogenic groups (Table 2). However, in clinical outcomes, the cryptogenic group had higher 3-month mRS scores ($P = 0.043$, Figure 2). The cryptogenic group also had a tendency of more frequent END events, hemorrhagic transformations, in-hospital mortality cases, and higher discharge NIHSS scores without statistical significance. Three in-hospital mortality cases occurred only in the cryptogenic group, and the causes of death were pneumonia aggravation, myocardial infarction, and stroke recurrence.

4. Discussion

In this study, ischemic stroke patients with active cancer showed poor outcomes after use of IV-tPA. Furthermore, cryptogenic stroke mechanisms seemed to be related to poor outcomes.

According to a previous study, ischemic stroke patients with cancer were proven to be as safe as noncancer patients in a large population study, showing 12% in-hospital mortality and 6% intracerebral hemorrhage cases [10]. However, this study included cancer-associated stroke with relatively heterogeneous traits (e.g., including hematologic malignancy, nonactive cancer with stably controlled states, treated by both IV-tPA and intra-arterial thrombectomy). Thus, the pure outcomes of cancer-associated stroke may be hard to interpret. Additionally, there have also been two case-series studies that reported on safety and hazardous events after use of t-PA in ischemic stroke with cancer [11, 12]. The cases that resulted in hazardous events occurred in patients with newly diagnosed cancer and high elevated D-dimer levels with nonbacterial thrombotic endocarditis, similar to our participants [11, 12]. In contrast, patients with fair outcomes were those with nonactive cancer status, defined as being stable after operation or in complete remission with regular treatment [12]. In this study, we attempted to collect data from patients with relatively homogenous cancer-related stroke, and these patients showed poorer outcomes than previous studies in variable clinical aspects (e.g., in-hospital mortality,
|                          | Conventional (n = 6) | Cryptogenic (n = 6) | P value |
|--------------------------|----------------------|---------------------|---------|
| **Time delay to visit, h [IQR]** | 1 [1–2]             | 1 [0–1]             | 0.624   |
| **Age, y [SD]**           | 69 ± 9               | 70 ± 9              | 0.899   |
| **Sex, male %**           | 4 (67)               | 4 (67)              | 1.000   |
| **Hypertension, %**       | 3 (50)               | 1 (17)              | 0.545   |
| **Diabetes, %**           | 2 (33)               | 0 (0)               | 0.455   |
| **Hyperlipidemia, %**     | 1 (17)               | 2 (33)              | 1.000   |
| **Current smoking, %**    | 2 (33)               | 1 (17)              | 1.000   |
| **Alcohol, %**            | 4 (67)               | 1 (17)              | 0.242   |
| **History of stroke, %**  | 1 (17)               | 0 (0)               | 1.000   |
| **Venous thrombosis, %**  | 0 (0)                | 2 (33)              | 0.455   |
| **Cancer type, %**        |                      |                     | 0.688   |
| Lung                      | 2 (33)               | 3 (50)              |         |
| Gastric                   | 1 (17)               | 1 (17)              |         |
| Colorectal                | 2 (33)               | 0 (0)               |         |
| Hepatobiliary             | 0 (0)                | 2 (33)              |         |
| Genitourinary             | 1 (17)               | 0 (0)               |         |
| **Systemic metastasis, %**| 1 (17)               | 5 (83)              | 0.080   |
| **Brain metastasis, %**   | 0 (0)                | 3 (50)              | 0.182   |
| **Initial NIHSS [IQR]**   | 13 [5–19]            | 10 [7–15]           | 0.935   |
| **SBP, mmHg [SD]**        | 130 ± 27             | 151 ± 28            | 0.213   |
| **DBP, mmHg [SD]**        | 77 ± 23              | 84 ± 12             | 0.479   |
| **Initial antithrombotics, %** |                    |                     | 0.476   |
| Low-molecular weight heparin | 1 (17)               | 4 (67)              |         |
| Warfarin                  | 1 (17)               | 0 (0)               |         |
| Antiplatelet agent        | 4 (67)               | 0 (0)               |         |
| No treatment              | 0 (0)                | 2 (33)              |         |
| **Intravenous alteplase dose, %** |                    |                     | 1.000   |
| 0.6 mg/kg                 | 4 (67)               | 3 (50)              |         |
| 0.9 mg/kg                 | 2 (33)               | 3 (50)              |         |
| **Initial DWI lesion**    |                      |                     | 0.061   |
| Single territory          | 6 (100)              | 2 (33)              |         |
| Multiple territory        | 0 (0)                | 4 (67)              |         |
| **D-dimer, µg/mL [IQR]**  | 1.30 [0.73–8.28]     | 4.51 [3.70–20.0]    | 0.109   |
| **CRP, mg/dL [IQR]**      | 0.03 [0.03–0.11]     | 2.79 [0.38–12.20]   | 0.085   |
| **PT, INR [SD]**          | 1.09 ± 0.05          | 1.15 ± 0.20         | 0.497   |
| **aPTT, sec [SD]**        | 34.1 ± 4.6           | 31.5 ± 9.8          | 0.578   |
| **Hospital stay, day [IQR]** | 16 [9–28]           | 12 [6–17]           | 0.420   |
| **Discharge NIHSS [IQR]** | 4 [2–7]              | 28 [8–42]           | 0.063   |
| **Early neurological deterioration, %** | 1 (17)               | 3 (50)              | 0.545   |
| **Hemorrhagic transformation, %** | 2 (33)               | 5 (83)              | 0.242   |
| **In-hospital mortality, %** | 0 (0)                | 3 (50)              | 0.182   |
| **3m mRS, %**             |                      |                     | 0.043   |
| 0                        | 1 (17)               | 1 (17)              |         |
| 1                        | 3 (50)               | 0 (0)               |         |
| 2                        | 0 (0)                | 0 (0)               |         |
hemorrhagic transformation, and END), although the 3-month mRS scores were not significantly different [13].

Additionally, the mechanisms of stroke in this group seemed to play a role in the clinical outcomes. Those with cryptogenic stroke showed more frequent END events, hemorrhagic transformation, and mortality and the risk of recurrent systemic thromboembolism in cancer patients suffering acute ischemic stroke, "Early neurologic deterioration in cancer patients with active cancer," European Journal of Neurology, vol. 24, no. 1, pp. 205–211, 2017.

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