Safety and Efficacy of Reperfusion Therapies for Acute Ischemic Stroke Patients with Active Malignancy

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Background and Purpose: Epidemiological correlations between active malignancy (AM) and acute ischemic stroke (AIS) are well-established. However, the effect of reperfusion strategies, particularly mechanical thrombectomy (MT), has been barely investigated in patients with AIS and AM. We aim to evaluate safety and efficacy of reperfusion strategies in such patients. *Materials and Methods:* We performed a case-control analysis comparing patients with AM and AIS (AM group) to a group of cancer-free patients with AIS (control group). All enrolled patients underwent reperfusion therapies (i.e. intravenous thrombolysis, MT, intravenous thrombolysis plus MT). Main outcomes were 3-month functional independence, successful reperfusion, 3-month mortality, symptomatic intracranial hemorrhage. *Results:* Total 24 patients with AM and AIS (mean age: 69 ± 10.1) were individually matched to 24 control patients (mean age: 70.7 ± 9.3). In both groups 50% were treated with MT, 46% with intravenous thrombolysis and 4% with intravenous thrombolysis plus MT. No difference were found in successful reperfusion, 3-month functional independence, symptomatic intracranial hemorrhage, and mortality. However an overall mortality of 33% in the AM group was reported. *Conclusions:* Reperfusion strategies for AIS patients with AM seem to be safe and effective. However an individualized approach to understand cancer stage and life-expectation is warranted.
Key Words: Acute ischemic stroke—active malignancy—safety—efficacy—reperfusion strategies

Introduction

Active malignancy (AM: i.e. malignant cancer, metastasis, current chemo, or radiotherapy) is a well-known risk factor for ischemic stroke.[1] Cancer-related hypercoagulability has been shown to be the most likely factor leading to this cascade.[2] AM and ischemic stroke are associated to an increased risk of short-term mortality compared to stroke without AM.[3] For this reason, stroke physicians often face with the ethical matter of managing such patients in the acute phase of ischemic stroke when intravenous thrombolysis (IVT) and/or, mechanical thrombectomy (MT), or combined IVT and MT (IVMT) must be considered and information about details regarding AM should be obtained. Safety concerns could increase uncertainty, making clinical decision even more challenging. Small series investigating the effects of IVT in patients with acute ischemic stroke (AIS) and AM have shown poor efficacy and safety outcomes with high rate of

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Received March 8, 2019; revision received May 5, 2019; accepted May 17, 2019.
Financial Disclosure: This work was supported by a grant of the Italian Ministry of Health (RF-2013-02358679) to F.S. and G.K.
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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.05.018

hemorrhagic transformation.[4] Despite benefit exceeds costs deriving from the worldwide spread of MT, previous studies have not included patients with chronic diseases affecting life-expectancy.[5,6]

Our aim was to test the efficacy and safety of reperfusion strategies (IVT, MT, and IVMT) among AIS patients with AM.

Material and Methods

We performed a retrospective matched cohort study using our prospective local stroke treatment registry between January 2011 and March 2018. Each AM patient with AIS was individually matched to a cancer-free control patient with AIS by the following variables: age, sex, cardiovascular risk factors (hypertension, diabetes, atrial fibrillation, smoking), glycemia, and blood pressure (systolic and diastolic), prestroke modified Rankin Scale (mRS), clinical severity measured by National Institute of Health Stroke Scale (NIHSS), ischemic lesion size on computed tomography quantified by Alberta Stroke Program Early CT score (ASPECTS)[7] on admission, type of reperfusion treatments (IVT, MT, or IVMT) and year of stroke onset. All analyzed patients were affected by AIS of the anterior circulation. Patients were also matched for leptomeningeal collaterals on computed tomography-angiography and site of arterial occlusion. For assessment of collaterals on computed tomography-angiography we adopted a scale from 0 to 3 derived from the Prolyse in Acute Cerebral Thromboembolism II trial (0: no collaterals; 1: collaterals to the periphery of ischemia; 2: collaterals filling 50%-100% of ischemic area; 3: collaterals filling 100% of ischemic area).[8] Collateral score was then dichotomized in poor (0-1) and good (2-3). The validity of dichotomization has been already established.[9]

Primary outcomes were:

i. Successful reperfusion evaluated by Thrombolysis in Cerebral Infarction score and defined as a score ≥2b.[10]
ii. 3-month functional independence defined as a mRS ≤ 2.
iii. Symptomatic intracranial hemorrhage (sICH) defined as an hemorrhage associated with an increase of at least 4 points in the NIHSS.[11]
iv. 3-month mortality.

Secondary outcomes were 24-hour ASPECTS, in-hospital mortality, cause of death, any (intracranial hemorrhage) ICH, 24-hour clinical improvement. The study was approved by local ethical committee. Informed consent was obtained from all patients or their relatives.

Statistical Analysis

Continuous variables are summarized as mean ± standard deviation or median with interquartile range. Categorical variables are expressed as percentages (%). To determine differences between groups Student's t test or Mann-Whitney U test or Kolmogorov-Smirnov test was used for continuous variables. Comparison of frequencies among groups was performed with Fisher's exact test. A P value of $< .05$ was considered statistically significant.

Results

Out of 1243 patients undergoing one of the above mentioned reperfusion strategies, 24 AM patients with AIS in the anterior circulation were found and matched with a control group of 24 AIS patients without history of cancer treated with one of the above mentioned reperfusion therapies. Clinical characteristics of AM group are shown in Table 1. In this group, 41.6% of patients had advanced malignancy (stage IV) and the most frequent type of cancer was lung, followed by colorectal, breast and ovarian types. More than 90% of AM patients were successfully matched to controls. Most of patients were older than 65 years of age, affected by hypertension and had good collaterals. In both groups 50% of patients were treated by MT alone, nearly 46% by IVT alone, and 4% with IVMT. While the most frequent site of occlusion was isolated middle cerebral artery, half of which in the M1 segment, a minority of patients had tandem internal carotid-middle cerebral artery occlusion. Most of them had an admission ASPECTS higher than 8, indicating a relatively small brain tissue ischemic damage before treatment. Mean admission NIHSS was 14 for both groups indicating moderate to severe stroke (Table 2).

AM patients were more frequently treated with general anesthesia (41.6% versus 16.6%; P = .11) and showed a shorter groin puncture to reperfusion time (52.9 ± 37 minutes versus 75.7 ± 41.1 minutes; P = .14). When primary outcomes were analyzed no statistically significant differences were found in successful reperfusion after MT, sICH, and 3-month mortality; regarding 3-month functional independence, despite a trend toward a higher rate in the control group, this difference was not statistically significant (41.6% versus 66.6%; P = .14). The rate of patients with a mRS ≤3 at 3 months (independence in walking) was also similar in the 2 groups (62.5% versus

Table 1. *Clinical characteristics of active malignancy group*

Cancer type	No (%)	Metastatic, No (%)	Current chemo/ radiotherapy, No (%)
Lung	8 (33.3)	5/8 (62.5)	3/8 (37.5)
Colorectal	5 (20.8)	2/5 (40)	2/5 (40)
Non-Hodgkin lymphoma	1 (4.1)	0	1(100)
Pancreas	1 (4.1)	0	1(100)
Breast	4 (16.6)	1/4 (25)	4/4 (100)
Ovarian	4 (16.6)	2/4 (50)	1/4 (25)
Chronic myeloid leukemia	1	0	0

Table 2. *Demographics and baseline characteristics*

	Active malignancy (n = 24)	Controls (n = 24)	*P*
Age, years (mean ± SD)	69 ± 10.1	70.7 ± 9.3	.54
Gender (male) (%)	8 (33.3)	8 (33.3)	1.00
Hypertension (%)	15 (62.5)	17 (70.8)	.76
Diabetes (%)	8 (33.3)	5 (20.8)	.51
Atrial fibrillation (%)	7 (29.1)	9 (37.5)	.76
Smoking (%)	8 (33.3)	6 (25)	.75
Baseline glycemia (mean ± SD)	142.9 ± 58.1	131.3 ± 57.8	.5
Baseline NIHSS (mean ± SD)	14.2 ± 5.2	14.1 ± 4.9	.97
Baseline SBP (mean ± SD)	135.1 ± 22.2	145 ± 19.4	.14
Baseline DBP (mean ± SD)	78.2 ± 13	81.1 ± 13.6	.5
Baseline ASPECTS (mean ± SD)	9.1 ± 0.9	8.8 ± 1	.38
Prestroke mRS ≤ 2	23 (95.8)	24 (100)	1.00
Tandem occlusion (%)	4 (16.6)	5 (20.8)	1.00
MCA (%)	14 (58.3)	15 (62,5)	1.00
M1 (%)	7 (29.2)	8 (33.3)	1.00
Good collaterals (%)	18 (75)	20 (83.3)	.72
I.V. thrombolysis	11 (45.8)	11 (45.8)	1.00
Bridging therapy	1 (4.1)	1 (4.1)	1.00
Mechanical thrombectomy	12 (50)	12 (50)	1.00

79.1%; P = .14). No difference was found for any other variable such as any ICH, in-hospital mortality, 24-hour neurological improvement. However mortality (mRS = 6) at 3-month follow-up was more than double among AM group compared to controls (29.1% versus 12.5%; P = .28), but this difference was not statistically significant; the rate of cancer-related mortality was 25% and the overall mortality in the AM group was 33%. The only statistically significant difference in secondary outcomes was found for 24-hour ASPECTS which was higher in the AM group (6.7 ± 2.1 versus 5.3 ± 2.3; P = .03) (Table 3). In a subgroup analysis of patients treated with IVT alone we found no statistical difference in main outcomes with a trend toward higher rate of 3-month functional independence and higher onset-discharge NIHSS difference in the control group compared to the AM group (81.8% versus 45.4% P= .18; −7.6 ± 5.4 versus −4.6 ± 3.9 P= .15).

Discussion

AM may affect short-term survival and represents a challenging ethical matter for stroke physicians. In these patients AIS treatment could result in therapeutic obstinacy if neurological improvement cannot overwhelm quickly worsening of cancer disease. On the other side decision for no AIS treatment could result in a shortening of life-expectancy.

Few studies have investigated outcomes of cancer-related stroke patients after reperfusion strategies. In one of these recanalization after endovascular treatment was lower and the rate of good clinical outcomes was similar compared to controls.[12] A recent large-cohort study compared outcomes after acute reperfusion strategies between cancer-related and noncancer-related stroke patients. Main evaluated outcomes were the rate of home discharge and in-hospital mortality which were not different after adjusting for confounders.[13] However in both mentioned studies no data regarding 3-month functional independence and 3-month mortality were available even though these should be, in our opinion, the most critical outcomes affecting decision-making for AIS treatment. Furthermore the latter study lacks details concerning stroke severity at onset (i.e. NIHSS) preventing any conclusions regarding this fundamental variable as a clinical predictor of stroke outcome in the hyperacute setting.

Our match-paired analysis found no difference at all in main safety and efficacy outcomes such as successful reperfusion, 3-month functional independence, 3-month mortality, and sICH. These results seem to suggest that reperfusion treatments should be taken into consideration for AM patients with AIS.

However some data of our analysis need to be focused on. Cancer-related mortality was 25% (with an overall mortality of 33% in the AM group). Twenty four-hour ASPECTS was higher in the AM group suggesting a more successful rescue of brain tissue in this group. Despite this AM patients did not reach better clinical outcomes, likely because of cancer-related morbidity. These points should be considered, together with other variables, in the triage setting when AM patients present with AIS. Further, as suggested by previous studies, aggressiveness of the underlying cancer type relates to the risk of ischemic stroke.[1] Notwithstanding our results suggest not to withhold treatment in such patients we recommend an individualized approach to screen as accurately as possible AM patients presenting with AIS for recent history of neoplastic disease, its stage and life expectancy. We think this strategy could assume a clear relevance as immunotherapy actually allows longer survivals in cancer patients and further progress in this field is expected in the near future.[14]

Conclusions

Our study suggest that reperfusion strategies such as IVT, MT, and IVMT are safe and effective for AIS patients with AM but an individualized screening for life-expectancy seems warranted (Table 4).

Table 3. *Procedural characteristics and outcomes*

	Active malignancy (n = 24)	Controls (n = 24)	*P*
General anesthesia (%)	10 (41.6)	4 (16.6)	.11
**Onset-groin puncture time, min (mean ± SD)*	258.3 ± 95	252.1 ± 99.6	.87
**Onset-reperfusion time, min (mean ± SD)*	311.2 ± 110.6	328.6 ± 99.9	.67
**Groin-reperfusion time, min (mean ± SD)*	52.9 ± 37	75.7 ± 41.1	.14
**Device attempts (mean ± SD)*	2 ± 1.2	2.2 ± 1.4	.66
Successful reperfusion after thrombectomy	10/13 (76.9)	8/13 (61.5)	.67
24-hour ASPECTS (mean ± SD)	6.7 ± 2.1	5.3 ± 2.3	.03
Any intracranial hemorrhage (%)	6 (25)	7 (29.1)	1.00
Subarachnoid hemorrhage (%)	0	1 (4.1)	1.00
Hemorrhagic infarction-1 (%)	0	1 (4.1)	1.00
Hemorrhagic infarction-2 (%)	2 (8.3)	3 (12.5)	1.00
Parenchymal hemorrhage-1 (%)	1 (4.1)	2 (8.3)	1.00
Parenchymal hemorrhage-2 (%)	3 (12.5)	0	.23
Symptomatic intracranial hemorrhage (%)	0	0	1.00
3-month mRS ≤ 2 (%)	10 (41.6)	16 (66.6)	.14
3-month mRS ≤ 3 (%)	15 (62.5)	19 (79.1)	.34
3-month mRS 5-6 (%)	8 (33.3)	5 (20.8)	.5
3-month mortality (%)	7 (29.1)	3 (12.5)	.28
Cancer-related mortality (%)	6 (25)	-	
In-hospital mortality (%)	2 (8.3)	1 (4.1)	1.00
24-hour neurological improvement (%)	13 (54.1)	16 (66.6)	.55
Onset-discharge NIHSS difference (mean ± SD)	−7 ± 5.2	−7.3 ± 4.9	.82

*Analysed in 13 thrombectomy treated patients.

Table 4. *Outcomes in IVT alone treated patients*

	Active malignancy (n = 11)	Controls (n = 11)	*P*
Any intracranial hemorrhage (%)	3 (27.2)	3 (27.2)	1.00
Symptomatic intracranial hemorrhage (%)	0	0	1.00
3-month mRS ≤ 2 (%)	5 (45.4)	9 (81.8)	.18
3-month mRS ≤ 3 (%)	7 (63.6)	10 (90.9)	.31
3-month mortality (%)	2 (18.1)	1 (9)	1.00
Cancer-related mortality (%)	1	-	
In-hospital mortality (%)	1	1	1.00
24-hour neurological improvement (%)	6 (54.5)	8 (72.7)	1.00
Onset-discharge NIHSS difference (mean ± SD)	−4.6 ± 3.9	−7.6 ± 5.4	.15

Acknowledgments: We thank all stroke neurologists at the comprehensive stroke center of university of Tor Vergata (Angela Giordano MD, Vittoria Carla D'Agostino PhD, Marta Panella MD, Barbara Rizzato PhD, Simone Napolitano MD, Domenico Samà PhD, Francesco Mori, MD) for collection of data.

Authorship Conformation

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.

Conflict of Interest

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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