Safety and outcome of rtPA in acute ischemic stroke in patients with active cancer: case-control study

Tiago Geraldes, Liliana Pereira, Claudia Guarda, Miguel Grunho, Ana Cláudia Ribeiro, João Coimbra, Irene Mendes, Miguel Rodrigues

Introduction. Cancer patients have increased stroke risk from direct and indirect malignancy effects. Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) is standard medical treatment for acute ischemic stroke (AIS).

Aim. To review rtPA use in AIS patients with active cancer.

Subjects and methods. Retrospective observational case-control study evaluating patients with AIS and cancer admitted to our stroke unit between January/2010 and June/2015.

Results. Seven cases were identified (86% male; median age: 76), and 20 controls were included matched for age and Oxfordshire Community Stroke Project classification. 29% experienced direct procedure complications vs 30% within the control group, 14% suffered haemorrhagic transformation (vs 20%), one patient experienced serious systemic haemorrhage (case) and one patient experienced serious intracerebral haemorrhage (control). After three months' follow-up, 43% were independent compared with 25% controls, and 29% had died (vs 30%). Undetermined aetiology subtype (TOAST classification) was more frequent in cancer patients when compared to controls (71% vs 20%).

Conclusion. Severe haemorrhagic complications, potentiated by rtPA, carry increased risk of morbidity and mortality. Nevertheless, selected cancer patients with AIS may benefit from rtPA treatment. Active cancer should not be considered an absolute contraindication to rtPA use. Risk of complications and life expectancy should be assessed when making this decision.

Key words. Cancer. Outcome. rtPA. Safety. Stroke. Thrombolysis.

Neurology Department. Hospital Garcia de Orta. Almada, Portugal.

Corresponding author:
Tiago Geraldes, MD. Neurology Department. Hospital Garcia de Orta EPE. Av. Torrado da Silva. 2805-267 Almada, Portugal.

E-mail:
tgeraldes@yahoo.com

Accepted:
04.01.17.

How to cite this paper:
Geraldes T, Pereira L, Guarda C, Grunho M, Ribeiro AC, Coimbra J, et al. Safety and outcome of rtPA in acute ischemic stroke in patients with active cancer: case-control study. Rev Neurol 2017; 65: 13-8.

Versión española disponible en www.neurologia.com

Introduction

Stroke remains a major health care problem and one of the leading causes of morbidity and mortality worldwide [1]. Patients with cancer are at increased risk for stroke, which may worsen the prognosis of the neoplastic disease and be the cause of increased morbidity and mortality [2,3]. Estimated prevalence of stroke in cancer patients is about 15% and can occur as an early or late complication in the clinical course of the neoplastic disease [4]. Besides traditional vascular risk factors, multiple mechanisms have been proposed for the occurrence of stroke in cancer patients: directly related to the tumour such as coagulation disorders, direct compression or meningeal extension of the tumour, medical complication of cancer or treatment related [2,5-10]. Current clinical guidelines recommend thrombolytic therapy with intravenous recombinant tissue plasminogen activator (rtPA) as a well-established specific treatment for patients presenting with AIS up to 4.5 hours from symptom onset. Effective management and treatment of AIS requires fast clinical assessment, imaging and correct selection of patients according to eligibility criteria established in clinical trials in order to minimise the risk of major bleeding complications increasing the odds of a favourable outcome [11]. The evolution of endovascular therapies was stimulated by the limitations of IV therapy, to complement this treatment in selected patients, or to help patients who are ineligible to IV rtPA therapy. However, this approach still requires highly specialized stroke centres that currently are not widely available as desired [12]. There is limited data on the use and safety of rtPA in patients with active cancer [13-17]. Cancer patients have a unique bleeding risk profile and factors such as direct tumor effect, coagulopathy and infection were the more significant causes of intracerebral haemorrhage [18]. Thrombolytic therapy in cancer patients with acute ischemic stroke who meet other standard criteria for rtPA use might be particularly beneficial, but prospective studies validating its' safety profile are still lacking [15].

Table I. Stroke risk factors by cancer status.

	Cancer (n = 7)	Without cancer (n = 20)	Total	p
Arterial hypertension	5	15	20 (74.1%)	1.00
Diabetes mellitus	2	6	8 (29.6%)	1.00
Dyslipidemia	3	9	12 (44.4%)	1.00
Smoking	2	5	7 (25.9%)	1.00
Alcohol consumption	2	5	7 /25.9%)	1.00
Prior stroke	3	3	6 (22.2%)	0.29
Prior myocardial infarction	0	5	5 (18.5%)	0.28
Atrial fibrillation	2	13	15 (55.6%)	0.19
Prior stroke prevention therapy	2	10	12 (44.4%)	0.41

We reviewed the use of rtPA to treat acute stroke in patients with active cancer at our institution. Using a clinical registry we also evaluated efficacy and safety outcomes of intravenous rtPA in patients with acute ischemic stroke and current active malignancy.

Subjects and methods

We conducted a retrospective observational case-control study, evaluating patients with acute ischemic stroke (AIS) and concomitant neoplastic disease, admitted to our stroke unit. Patients who received rtPA were identified through the Hospital's and Stroke Unit's databases between January 2010 and June 2015. All patients were examined at the time of admission by a neurologist, and the severity of stroke symptoms was assessed using the National Institutes of Health Stroke Scale (NIHSS) [19]. Patients with AIS with clinical or imaging evidence of brain infarct were eligible for the study. Routine evaluation in all stroke patients preceding rtPA treatment included neurological and physical examination, brain computed tomography (CT) scan, electrocardiogram and laboratory tests. Intravenous rtPA was administered according to the recommendations for thrombolytic treatment. To evaluate the aetiology of stroke, brain magnetic resonance imaging (MRI), transcranial Doppler, carotid ultrasonography, Holter electrocardiography, transthoracic echocardiography and in some cases transesophageal echocardiography were performed. Medical records were reviewed for all clinical information. Acute ischemic stroke etiology was classified at patient discharge, according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Study [20]. Stroke outcomes were measured using the modified Rankin scale (mRS) [21]. A favourable outcome was defined as a mRS score ≤ 2 points, while an unfavourable outcome was defined as a mRS score of 3-6 points.

All included patients were specifically interviewed searching for past or current neoplastic disease. Cancer diagnosis was based on clinical, laboratory, imaging and histological examinations. Malignancy was classified as either current or past. Patients with active cancer were selected as cases. Cancer treatment included surgery, chemotherapy, radiotherapy, hormonal therapy, combined therapy and no treatment.

Patients with acute ischemic stroke and without history of cancer were randomly selected as controls, matched for admission to the stroke unit during the same time period, age and Oxfordshire Community Stroke Project (OCSP) classification. A control group was constructed in a 3:1 ratio. If there wasn't enough adequate age-matching controls a 2:1 ratio was used.

Statistical analysis

Analysis was performed using IBM SPSS Statistics v. 23. Categorical data were compared using chi-squared tests and p values < 0.05 were considered statistically significant.

Results

There were a total of 387 patients treated with rtPA for AIS admitted to our Stroke Unit between January 2010 and June 2015. Of these, seven patients, 6 males and 1 female, treated with rtPA for AIS aged between 51 and 82 years (median age of 76 years) were identified with a diagnosis of active cancer. Vascular risk factors and previous thrombotic events were not significantly different between groups. Hypertension was the most common classical vascular risk factor for both groups (Table I).

The most common primary tumor locations were gastrointestinal system (n = 3) and prostate (n = 2). One patient had two simultaneously independent primary tumors (Table II). Three had a prior history of stroke (patients 2, 5 and 6) and two were taking stroke preventive therapy (patients 2 and 6).

Table II. Clinical characteristics of the stroke patients with malignancy treated with intravenous thrombolysis.

	Gender	Age (years)	Diagnosis	Previously known cancer diagnosis	Cancer treatment	Haemorrhagic complications	NIHSS on admission	NIHSS on discharge	Rankin at 3 months
Patient 1	Male	51	Oropharyngeal cancer	No	Chemotherapy	–	19	12	4
Patient 2	Male	76	Rectal cancer	Yes	Surgery	–	12	1	2
Patient 3	Female	72	Uterine cancer	No	Chemotherapy	–	6	1	1
Patient 4	Male	69	Bladder and prostatic cancer	Yes	Chemotherapy + hormonal therapy	–	6	1	1
Patient 5	Male	78	Hepatic cancer	No	–	Retroperitoneal hematoma	11	–	6
Patient 6	Male	82	Non-Hodgkin lymphoma	No	–	–	22	–	6
Patient 7	Male	80	Prostatic cancer	Yes	Hormonal therapy	Asymptomatic haemorrhagic transformation	16	15	4

In the active cancer group, patients had a National Institutes of Health Stroke Scale median of 12 (range 6-22), and all received rtPA within 3 h of symptom onset. Cancer had been diagnosed before rtPA administration in three (43%) patients. Two patients (29%) experienced direct procedure complications, compared with six in the control group (30%; p = 1.00), 14% suffered haemorrhagic transformation (vs 20%; p = 1.00), one patient experienced serious systemic haemorrhage (case group) and one patient experienced serious intracerebral haemorrhage (control). After 3 months' follow-up, 43% were independent (modified Rankin scale 0-2) compared with 25% of the control group (p = 0.63), and 29% had died (vs 30%; p = 1.00) (Table III).

Using the TOAST classification, in the cancer group, two strokes were cardioembolic and the other five were of unknown cause, suggesting that undetermined aetiology subtype was more frequent in cancer patients when compared to controls (71% vs 20%; $p < 0.05$).

Table III. Stroke characteristics by cancer status.

	Cancer (n = 7)	Without cancer (n = 20)	Total	p
NIHSS < 7 on admission	2	1	3 (11.1%)	0.16
NIHSS < 7 on discharge	3	11	14 (51.9%)	0.68
TOAST: undetermined etiology (5b)	5	4	9 (33.3%)	0.02
Direct procedure complications	2	6	8 (29.6%)	1.00
mRS 0-2 at three months	3	5	8 (29.6%)	0.63
Death at three months	2	6	8 (29.6%)	1.00

Discussion

In our study, using TOAST classification, and matching case and controls for age and OCSP type of stroke, undetermined aetiology subtype was more frequent in cancer patients. These results seem to agree with current literature, which states that undetermined etiology subtype is more prevalent in cancer related stroke and an independent risk factor for stroke recurrence [9,10,22]. Systemic cancer may have several neurological complications, AIS being relatively common in these patients [2,23]. Many pathophysiological mechanisms have been proposed to explain this association, including atherosclerosis, embolism, hypercoagulability, cancer treatment effects, with no consensus in multiple studies [2,5-8].

The difference in prevalence of classical vascular risk factors between cancer patients and controls with AIS was not statistically significant in our analyses, also in agreement with recent studies [2,23].

In our study there were only two direct procedure complications, one serious systemic haemor-

rhage (hepatic carcinoma patient) and one haemorrhagic transformation (prostatic carcinoma patient). The low incidence of serious complications in the cohort of active cancer patients treated with rtPA concurs with current literature [14].

There were no statistically significant differences between groups regarding 3-month stroke outcome and mortality. In our study active malignancy in patients with AIS, showed no significant impact on rtPA treatment's efficacy and safety.

Gastrointestinal and prostate cancer were the most prevalent primary cancer localizations. This may be influenced by our study's small cohort and different geographical localization cancer prevalence. In Portugal, the most common cancer sites are prostate, breast, colorectal, lung, corpus uteri and stomach [24]. In our patients, deaths and direct procedure complications were not cancer-type specific.

Active cancer is often an exclusion criteria in several rtPA studies, ranging from clinical trials to observational studies [25-27]. Only few studies were performed reporting data on the safety and outcome of rtPA treatment in patients with malignancy [14-17]. Since AIS in active cancer setting may be associated with worse outcome, increased morbidity and mortality, rtPA treatment may be more valuable to these patients. However, as it was recently published in a Scientific Statement, its efficacy and safety profiles have yet to be clearly established (class IIb; level of evidence C). Notwithstanding, the same authors recommend that thrombolytic therapy in cancer patients with AIS without other contraindications to rtPA use and reasonable (> 6 months) life expectancy might be particularly beneficial [28]. Our results meet this expert opinion and are intended to add knowledge to an area with little research. We emphasize the difficulty experienced to identify patients that fulfilled the cases' inclusion criteria, as after evaluating a high number of patients we achieved 7 cases of active cancer with AIS that were treated with rtPA.

The main limitations of our study include its small sample size, retrospective nature and the single center design. Nevertheless, based in our findings we suggest that active malignancy, in patients with AIS treated with rtPA, may not imply an increased risk of serious haemorrhagic transformation, worse outcome or increased mortality. We suggest that selected cancer patients with AIS, even discounting the risk of complications and life expectancy, may benefit from rtPA treatment.

Patients with known cancer are frequently excluded from rtPA treatment in AIS due to history of bleeding, know dissemination of the neoplasm, including to the central nervous system or because they are in palliative care only. Our cases are a particular subset of cancer patients, who physicians not knowing about this condition or despite of knowing it, considered the patients fit enough to receive rtPA. Therefore, our conclusions are not generalizable to all cancer patients with acute stroke.

In addition, we still have to consider that patients with possible contraindications to rtPA use, such has advanced metastatic disease, thrombocytopenia, coagulopathy or recent surgery, may benefit from Endovascular therapy [29,30]. Given the increasing incidence and survival rates in patients with neoplastic disease cancer related-stroke could become more prevalent in the future [31]. So we suggest not only to develop efforts in studying the safety and efficacy of intravenous thrombolysis but also of endovascular therapy.

In conclusion, severe hemorrhagic complications, potentiated by rtPA, carry an increased risk of morbidity and mortality, especially if underlying cancer related coagulopathy. Nevertheless, selected cancer patients with AIS may benefit from rtPA treatment. Active cancer should not be considered an absolute contraindication to rtPA use. Risk of complications and life expectancy should be accounted for when accessing these patients for acute stroke revascularization procedures, although that reasoning should never delay significantly the decision.

References

1. Jacquin GJ, Van Adel BA. Treatment of acute ischemic stroke: from fibrinolysis to neurointervention. J Thromb Haemost 2015; 13 (Suppl 1): S290-6.
2. Cestari DM, Weine DM, Panageas KS, Segal AZ, De Angelis LM. Stroke in patients with cancer: incidence and etiology. Neurology 2004; 62: 2025-30.
3. Oberndorfer S, Nussgruber V, Berger O, Lahrmann H, Grisold W. Stroke in cancer patients: a risk factor analysis. J Neurooncol 2009; 94: 221-6.
4. Arboix A. Enfermedad cerebrovascular en el paciente con cáncer. Rev Neurol 2000; 31: 1250-2.
5. Zhang YY, Cordato D, Shen Q, Sheng AZ, Hung WT, Chan DKY. Risk factor, pattern, aetiology and outcome in ischaemic stroke patients with cancer: a nested case-control study. Cerebrovasc Dis 2007; 23: 181-7.
6. Seok JM, Kim SG, Kim JW, Chung CS, Kim GM, Lee KH, et al. Coagulopathy and embolic signal in cancer patients with ischaemic stroke. Ann Neurol 2010; 68: 213-9.
7. Li SH, Chen WH, Tang Y Rau KM, Chen YY, Huang TL, et al. Incidence of ischemic stroke post-chemotherapy: a retrospective review of 10,963 patients. Clin Neurol Neurosurg 2006; 108: 150-6.
8. Grisold W, Oberndorfer S, Struhal W. Stroke and cancer: a review. Acta Neurol Scand 2009; 119: 1-16.
9. Schwarzbach CJ, Schaefer A, Ebert A, Held V, Bolognese M, Kablau M, et al. Stroke and cancer: the importance of cancer-

associated hypercoagulation as a possible stroke aetiology. Stroke 2012; 43: 3029-34.
10. Lee EJ, Nah HW, Kwon JY, Kang DW, Kwon SU, Kim JS. Ischaemic stroke in patients with cancer: is it different from usual strokes? Int J Stroke 2014; 9: 406-12.
11. Jauch EC, Saver JL, Adams HP, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2013; 44: 870-947.
12. Goyal M, Yu AY, Menon BK, Dippel DW, Hacke W, Davis SM, et al. Endovascular therapy in acute ischemic stroke: challenges and transition from trials to bedside. Stroke 2016; 47: 548-53.
13. Casado-Naranjo I, Calle ML, Falcón A, Serrano A, Portilla JC, Ramírez-Moreno JM. Intravenous thrombolysis for acute stroke in patients with cancer. J Neurol Neurosurg Psychiatry 2000; 82: 1404-5.
14. Masrur S, Abdullah AR, Smith EE, Hidalgo R, El-Ghandour A, Rordorf G, et al. Risk of thrombolytic therapy for acute ischemic stroke in patients with current malignancy. J Stroke Cerebrovasc Dis 2011; 20: 124-30.
15. Murthy SB, Karanth S, Shah S, Shastri A, Rao CP, Bershad EM, et al. Thrombolysis for acute ischemic stroke in patients with cancer: a population study. Stroke 2013; 44: 3573-6.
16. Cappellari M, Carletti M, Micheletti N, Tomelleri G, Ajena D, Moretto G, et al. Intravenous alteplase for acute ischemic stroke in patients with current malignant neoplasm. J Neurol Sci 2013; 325: 100-2.
17. Sobolewski P, Brola W, Szczuchniak W, Fudala M, Sobota A. Safety of intravenous thrombolysis for acute ischaemic stroke including concomitant neoplastic disease sufferers –experience from Poland. Int J Clin Pract 2015; 69: 666-73.
18. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. Medicine (Baltimore) 1985; 64: 16-35.
19. Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989; 20: 864-70.
20. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24: 35-41.
21. UK-TIA Study Group. The UK-TIA aspirin trial: interim results. Br Med J 1988; 296: 316-20.
22. Kim JM, Jung KH, Park KH, Lee ST, Chu K, Roh JK. Clinical manifestation of cancer related stroke: retrospective case-control study. J Neurooncol 2013; 111: 295-301.
23. Lindvig K, Møller H, Mosbech J, Jensen OM. The pattern of cancer in a large cohort of stroke patients. Int J Epidemiol 1990; 19: 498-504.
24. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013; 49: 1374-403.
25. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischaemic stroke. N Engl J Med 2008; 359: 1317-29.
26. IST-3 Collaborative Group, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet 2012; 379: 2352-63.
27. Hacke W, Kaste M, Fieschi C, Von Kummer R, Dávalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998; 352: 1245-51.
28. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke. Stroke 2015; 47: 581-641.
29. Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, et al. Endovascular treatment for acute ischemic stroke. N Engl J Med 2013; 368: 904-13.
30. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013; 368: 893-903.
31. Bang OY, Seok JM, Kim SG, Hong JM, Kim HY, Lee J, et al. Ischemic stroke and cancer: stroke severely impacts cancer patients, while cancer increases the number of strokes. J Clin Neurol 2011; 7: 53.

Seguridad y efectividad del rtPA en el ictus isquémico agudo en pacientes con cáncer activo: estudio de casos y controles

Introducción. Los pacientes con cáncer tiene un mayor riesgo de ictus debido a los efectos malignos directos e indirectos. La trombólisis intravenosa con activador tisular del plasminógeno recombinante (rtPA) constituye un tratamiento médico estándar para el ictus isquémico agudo.

Objetivo. Revisar el uso de rtPA en el ictus isquémico agudo en pacientes con cáncer activo.

Sujetos y métodos. Estudio retrospectivo observacional de casos y controles para evaluar pacientes con ictus isquémico agudo y cáncer admitidos en la unidad de ictus entre enero de 2010 y junio de 2015.

Resultados. Se identificaron siete casos (86% varones; mediana de edad: 76 años) y también se incluyeron 20 controles pareados por edad y clasificación del *Oxfordshire Community Stroke Project.* Un 29% de casos experimentó complicaciones directas del procedimiento frente a un 30% en el grupo control. Un 14% sufrió transformación hemorrágica (frente a un 20%). Un paciente (caso) sufrió una hemorragia sistémica grave, y otro (control), una hemorragia intracerebral grave. A los tres meses, un 43% era independiente (frente a un 25% de los controles) y un 29% había fallecido (frente a un 30%). Un subtipo etiológico indeterminado (clasificación TOAST) era más frecuente en pacientes con cáncer (71% frente a 20%).

Conclusión. Complicaciones hemorrágicas graves, potenciadas por el rtPA, pueden incrementar el riesgo de morbilidad y mortalidad. Sin embargo, pacientes seleccionados con cáncer que padecen un ictus isquémico agudo pueden beneficiarse del tratamiento con rtPA. Un cáncer activo no debería considerarse una contraindicación de uso de rtPA, aunque debe evaluarse el riesgo de complicaciones y la esperanza de vida para tomar la decisión.

Palabras clave. Cáncer. Efectividad. Ictus. Seguridad. rtPA. Trombólisis.