CLINICAL STUDY - PAIENT STUDY

Stroke in cancer patients: a risk factor analysis

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Abstract *Background and Purpose* In patients already suffering from cancer, the additional occurrence of stroke can aggravate the burden of the disease. The purpose of this study was to compare risk factors for haemorrhagic and ischemic strokes in cancer and non-cancer patients. *Methods* A retrospective analysis, including 1,274 stroke patients admitted to a stroke unit, was conducted from 2004 to 2007. Classical risk factors for stroke and clinical outcome measures were compared between cancer and non-cancer patients. *Results* Twelve percent of stroke patients had an additional diagnosis of cancer. In the non-cancer population, 84% had ischemic and 16% had haemorrhagic strokes. In cancer patients, 86% had ischemic and 14% had haemorrhagic strokes. Vascular risk factors in cancer patients, including hypertension, atrial fibrillation, coronary vessel disease, smoking, hypercholesterolemia and diabetes mellitus, showed no difference compared to the non-cancer population. Only thrombotic events occurred more often in the cancer cohort. The most frequent cancer types were urogenital, breast and gastrointestinal. Regarding clinical outcome, cancer patients had an inferior neurological condition at discharge and a trend towards a longer stay in the stroke unit. *Conclusions* The frequency of ischemic and haemorrhagic stroke in tumour patients is similar to that in the non-cancer population. Cerebrovascular risk factors do not significantly vary between cancer and non-cancer patients. The higher frequency of thrombotic events in cancer patients may reflect a coagulation disorder, commonly found in patients with malignancy. Clinical outcome in cancer patients may be worsened by the pre-existent co-morbidity.

Keywords   Cerebrovascular risk factors ·
Neurooncology · Stroke and cancer

Introduction

Cerebrovascular disorders are the most frequent neurological disease and cancer is the second most frequent cause of death in the industrial world. From the neurologist's point of view, however, stroke is a less frequent neurological complication in cancer patients, as compared to metastases or neurotoxicity of anticancer treatment [1].

However, according to an autopsy study [2], cerebrovascular ischemic infarcts occur in a large number of cancer patients. The clinical significance of these findings is not clear, as the range includes silent infarcts and diffuse vascular encephalopathies. In the literature, the incidence of stroke in cancer patients is quoted as being a common neurological complication [2–4].

Cerebral haemorrhages have been reported more frequently, especially in haematological malignancies. In patients with leukaemia and lymphoma, 72% and 36% of strokes, respectively, were haemorrhagic [5].

Evaluations based on stroke criteria [6] and common risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, coronary vessel disease and smoking, suggest a more even distribution between cancer- and non-cancer-related strokes [7–10].

Beside the classical risk factors for stroke, several cancer-specific types and causes of stroke, such as direct tumour effects, coagulation disorders, intravascular coagulation, infection, septic thrombi and therapeutic and

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diagnostic procedures, have to be considered. These additional factors have not been analysed in the present study.

The purpose of this study was to investigate the occurrence of ischemic and haemorrhagic stroke, and to compare classical risk factors and clinical outcome measures in patients with cancer and stroke versus non-cancer patients with stroke.

Methods

Patients admitted between 2004 and 2007 to the stroke unit of the KFJ-Hospital in Vienna, a teaching hospital of the Medical University of Vienna, were included in the study, using data from the facility's computerised database. Analysis was performed according to an anonymous protocol. Patients had to sign a general informed consent on admission, which includes medical data processing.

Our stroke unit takes the form of an intermediate care setting. After acute admission and acute diagnosis and treatment, patients are transferred to normal care and rehabilitation units. Patients were identified according to the ICD 10 classification for stroke and cancer. The study followed stringent criteria for stroke diagnosis, including only patients with computer tomography of the brain (CCT) or magnetic resonance imaging (MRI) of the brain showing a new vascular lesion according to neurological signs and symptoms. Patients with possible stroke, negative CCT or MRI of the brain or TIA-like (transient ischemic attack) syndromes were excluded. Each patient record was reviewed separately in order to obtain detailed information. The analysis protocol included age, gender, history of cancer and risk factors for stroke, such as hypertension, atrial fibrillation, diabetes mellitus, coronary vessel disease, smoking, hypercholesterolemia and history of thrombosis (deep vein thrombosis, pulmonary embolism). Etiological evaluations for stroke were based on the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria [6].

Routine examinations in all stroke patients included electrocardiogram, CCT, MRI—in most cases including T_1-, T_2-weighted images, echo planar imaging, and the apparent diffusion coefficient, laboratory tests (routine haematology and biochemistry including cardial enzymes, and coagulation parameters), neurological and physical examination, and patients' medical history and medication.

We also considered length of stay in the stroke unit, and NIHSS (National Institute of Health Stroke Scale) score at admission and discharge from the stroke unit. The cancer cohort included patients with known cancer and with newly diagnosed cancer at the time of stroke. Cancer-related data, such as prior anti-cancer treatment and time of cancer diagnosis, were taken from patient files. Patients with

cerebral metastases initially considered as stroke were excluded from the study, as were strokes in cancer patients where the cause of stroke was directly related to a primary brain tumour or associated treatment (neurosurgical procedure, radionecrosis, gamma knife treatment, etc.). Patients admitted to the stroke unit with diagnoses other than stroke were excluded.

Data analysis

The standard version of the SPSS statistical package for Windows 12.0G was used for data evaluation. Analysis of differences in the frequency of categorical variables was performed using the chi-square test. The Mann–Whitney U test was used to compare ordinal data between cancer and non-cancer patients. The reported P values are the results of two-sided tests. A P value <0.05 was considered statistically significant.

Results

In total, 1,274 consecutive patients with stroke, admitted to our stroke unit, were assessed for type of stroke, common risk factors for stroke, and clinical outcome measures. During the investigation period, 191 patients were admitted with diseases other than stroke, and were excluded from the analysis.

The median age in cancer patients with stroke was 68.1 years (range: 28–96 years) and 66.9 years (range: 31–93 years) in non-cancer patients. Fifty-eight percent of cancer patients with stroke were males compared to 53% males in the non-cancer group.

Of all the stroke patients, 153 (12%) had an additional diagnosis of cancer. In cancer patients, 86% had ischemic and 14% had haemorrhagic strokes. In the non-cancer population, 84% had ischemic and 16% had haemorrhagic strokes. According to the TOAST criteria, there was no statistically significant difference between cancer and non-cancer patients with respect to the subtypes of ischemic strokes (Table 1).

Vascular risk factors in cancer patients, including hypertension, atrial fibrillation, coronary vessel disease, smoking, diabetes mellitus and hypercholesterolemia, showed no statistically significant difference compared to the non-cancer population. Only thrombotic events [deep vein thrombosis (DVT) and pulmonary embolism (PE)] yielded a statistically significant difference (Table 2).

Echocardiography was performed in 57% of patients with stroke and cancer and in 61% of non-cancer stroke patients. Valvular vegetations without clinical and laboratory signs of infection were detected in only ten patients (three cancer and seven non-cancer patients), and retrospectively

Table 1 Frequency of ischemic and haemorrhagic stroke in cancer and non-cancer patients

	Cancer patients n (%)	Non-cancer patients n (%)	P value
Ischemic (TOAST subtype)	131 (86%)	942 (84%)	n.s.
Large vessel disease	54 (41%)	347 (37%)	n.s.
Cardioembolism	23 (18%)	172 (18%)	n.s
Small vessel disease	26 (20%)	209 (22%)	n.s
Not determined (unknown/other)	28 (21%)	214 (23%)	n.s
Haemorrhagic	22 (14%)	179 (16%)	n.s.
Total	153 (100%)	1,121 (100%)	–

Data obtained from 1,274 consecutive patients with stroke admitted to the *Stroke Unit* at KFJ-Hospital, Vienna

n.s. Not significant

Table 2 Risk factor profile for stroke in cancer patients versus non-cancer patients

	Cancer patients n (%)	Non-cancer patients n (%)	P value
Hypertension	117 (79%)	889 (78%)	n.s.
Atrial fibrillation	42 (27%)	358 (32%)	n.s.
Coronary vessel disease	21 (14%)	142 (13%)	n.s.
Smoking	41 (27%)	274 (24%)	n.s.
Diabetes mellitus	36 (24%)	312 (28%)	n.s.
Hypercholesterolemia	31 (21%)	270 (24%)	n.s.
Thrombosis	16 (10%)	42 (4%)	<0.05

n.s. Not significant

Table 3 Ischemic versus haemorrhagic stroke in patients with different types of cancer

Cancer patients with stroke	Total n (% from total)	Ischemic n (%)	haemorrhagic n (%)
Breast cancer	34 (22%)	29 (85%)	5 (15%)
Lung cancer	11 (7%)	9 (73%)	3 (27%)
Melanoma	6 (4%)	5 (83%)	1 (17%)
Ear-nose-throat cancer	8 (5%)	7 (87%)	1 (13%)
Urogenital cancer	42 (27%)	36 (86%)	6 (14%)
Gastrointestinal cancer	28 (18%)	27 (96%)	1 (4%)
Haematological malignancies	16 (10%)	12 (75%)	4 (25%)
Others	5 (3%)	4 (80%)	1 (20%)
CUP	2 (2%)	2	0
Total	153 (100%)	131 (84%)	22 (14%)

classified as non-thrombotic endocarditis (NBTE). Only four non-cancer patients had transoesophageal echocardiography; all other patients received transthoracic echocardiography.

The most frequent cancer types associated with stroke were urogenital, breast, gastrointestinal, haematological and lung. Haematological malignancies, lung cancer and melanoma had the highest proportion of haemorrhagic strokes (Table 3). In four patients (two lung cancer, one ovarian cancer and one patient with CLL) the cancer was diagnosed at the time of the stroke. In cancer patients with haemorrhagic strokes, thrombocytopenia was present in nine patients (41%). According to the NCI-CTC criteria, six patients had grade I thrombocytopenia and three grade II thrombocytopenia. Whereas in non-cancer patients with haemorrhagic strokes, only seven patients (4%) with thrombocytopenia (NCI-CTC grade I) could be detected. One patient (NHL) had a multilocular occipital and mid

brain bleeding, and eight patients had basal ganglia and thalamus haemorrhages in a rather classic distribution normally seen in hypertensive haemorrhagic strokes. In 18 patients (77%), the haemorrhage occurred during progressive cancer disease or during anticancer treatment.

The median NIHSS on admission in stroke patients with cancer was seven, compared to six in the non-cancer cohort, but the difference did not reach statistical significance. Conversely, at discharge, patients with cancer and stroke had a significantly worse NIHSS than the non-cancer patients (eight vs five) (Table 4). Analysing the NIHSS according to different cancer entities, lung cancer, urogenital cancers and breast cancer patients exhibited the most pronounced neurological deterioration at discharge (Table 5).

Out of 942 patients with ischemic stroke, 89 underwent thrombolysis (9%). From 131 cancer patients, 7 received thrombolysis (5%).

Table 4 Clinical outcome measures from a stroke unit of cancer patients ($n = 153$) versus non-cancer patients ($n = 1,121$)

	Cancer patients	Non-cancer patients	P value
Length of stay at the stroke unit (median in days)	3.4 (range 1–23)	3.1 (range 1–18)	0.0601
NIH at admission (median)	7 (range 1–24)	6 (range 2–30)	n.s.
NIH at discharge (median)	8 (range 1–33)	5 (range 1–27)	<0.05

n.s. Not significant

Table 5 Age, relation to incidence of various cancers, and clinical outcome measures (NIHSS) from stroke patients with different cancers on admission and at discharge

	Age (median)	n (%)	Incidence in population (21)		NIH at admission (median)	NIH at discharge (median)
			Male	Female		
Breast cancer	50	34 (22%)	–	26%	6	8
Lung cancer	68	11 (7%)	15%	15%	7	10
Melanoma	52	6 (4%)	4%	4%	5	5
Ear-nose-throat cancer	57	8 (5%)	3%	–	5	6
Gastrointestinal cancer	63	28 (18%)	10%[b]	11%[b]	7	8
Haematological malignancies	38	16 (10%)	7%	7%	5	6
Urogenital cancer	70	42 (27%)[a]	40%[a]	12%	7	9
Others	–	5 (3%)	–	–	4	5
CUP	–	2 (2%)	–	–	4	4
Total	–	153 (100%)	–	–	7	8

[a] Including prostate cancer [study population: 20% and 29% (21)]

[b] Excluding gastric and oesophageal cancer

The median length of stay at the stroke unit was 3.6 days for the non-cancer patients and 3.9 days for the cancer patients. The difference did not reach statistical significance. Four cancer patients (3%) and 19 (2%) non-cancer patients died during their stay at the stroke unit.

Discussion

This study highlights the relationship between two common diseases of stroke and cancer. Analysis of classical risk factors concerning cerebrovascular disease showed a similar distribution in cancer patients with stroke as compared to non-cancer patients with stroke. Only thrombotic events occurred more often in cancer patients with stroke than in non-cancer patients with stroke.

Some papers have stated that classical risk factors are not as important as factors attributed to the cancer, such as direct tumour effects, coagulation disorders, infection, and therapeutic and diagnostic procedures [2]. Two large clinical studies by Cestari [10], and Zhang [11] found no significant differences in classical vascular risk profile between cancer patients and a series of stroke patients. In our study, only thrombotic events occurred statistically more often in cancer patients than in the non-cancer cohort. There were also fewer patients with atrial fibrillation in the cancer population, although statistical significance was not reached. Similar results were found by Cestari et al. [10].

Some contradictory results are reported in the literature regarding epidemiological data on stroke in cancer patients. Some authors quote stroke as a common neurological complication in cancer patients [2–4], while others, including review articles, tend to describe a lack of significant difference regarding the frequency of stroke for both groups [10–12]. As compared to most of the previous studies, the present investigation is strengthened by inclusion of modern imaging techniques, clinical and neurological stroke criteria adopted by a specialised stroke unit, and by the distinction between ischemic and haemorrhagic strokes.

In our study, the overall frequency of ischemic and haemorrhagic stroke was similar in both groups. However, there was a high proportion of ischemic strokes (96% ischemic vs 4% haemorrhagic strokes) in patients with gastrointestinal cancers (Table 3). At least for gastric cancer and colorectal cancer, no increased risk for strokes was reported by Lindvig et al. [4] and Kune et al. [13]. These studies did not, however, differentiate between ischemic and haemorrhagic.

Besides chemotherapy-related increased risks for ischemic stroke, such as cisplatin-based chemotherapy, cyclophosphamide, 5 FU, taxol, paclitaxel l-asparaginase and tamoxifen, no specific malignancies have been reported to cause ischemic strokes more often than others [14–19]. Generally, the risk of chemotherapy-induced stroke seems low and not highly influenced by the histological type of cancer [20]. Therefore, the high proportion

of ischemic stroke in gastrointestinal tumours in our series remains unclear and may be due to the small sample size. In addition, the distribution of primary malignancies, most commonly urogenital, gastrointestinal and breast, does not reflect the incidence of these tumours and may be attributed to a referral bias [21].

It is postulated that distinct mechanisms initiated by the cancer cause coagulopathy, by activation of the coagulation system through inflammation and/or procoagulants. The acquired prothrombotic state is argued to be associated with an increased risk for ischemic stroke [22, 23]. This assumption is in line with our findings of significantly more thrombotic events in cancer patients with ischemic strokes, which may be interpreted as a clinical sign for a coagulation disorder. Nonetheless, this was not reflected by a higher frequency of strokes in our cancer population.

It is assumed that the most common single cause of ischemic stroke in cancer patients is NBTE [2, 24] yet only 59% of patients with NBTE in a large autopsy series of 171 cases suffered from malignancy [25]. It can be associated with any type of cancer, but seems to be more frequent in adenocarcinoma, particularly pancreatic carcinoma, mucin-producing carcinomas of the lung or gastrointestinal tract, and lymphoma [26–29]. The low proportion of patients with NBTE (1%) in our study seems under-represented, but similar infrequent findings of NBTE were also reported in the paper by Cesatri, with 3% [10]. In our survey, this finding might be due to the relatively low proportion of echocardiography performed in the study population, or to the strict criteria regarding additional signs of infection, or to imaging results showing multiple infarcts [29–33].

In our series, no major differences were detected between cancer and non-cancer patients with respect to subtypes of stroke, based on the TOAST classification. Cestari [10] and Zhang [11], who also analysed stroke etiologies by means of TOAST criteria, reported fewer patients with large vessel atherosclerosis (21% in Zhang's series vs 10% in Cestari's) than the 41% observed in our study. Results were more similar to our findings for cardioembolism and small vessel disease (see also Table 1). The reason for the discrepancy in the frequency of large vessel disease may be the ambiguous classification of stroke types according to clinical and radiological parameters. The standardised workup performed in our specialised cerebrovascular unit may explain the more comparable frequencies of different stroke etiologies in our patient groups, as seen in a large series of stroke patients [34].

Cerebral haemorrhages seem to occur more often in patients with haematological malignancies and in lung cancer [3, 35, 36]. These reports may be confirmed in our study, as the highest frequencies for haemorrhagic strokes were found for haematological malignancies and lung cancer. In the paper by Zhang [11], there was an increased risk for haemorrhagic strokes in the cancer population, which was attributed to several factors, such as chemotherapy-induced thrombocytopenia, disseminated intravascular coagulopathy (DIC) and other coagulation disorders. In our study, thrombocytopenia occurred more often in the cancer population. However, the pathophysiological mechanism of intracerebral haemorrhages in cancer patients, which is generally attributed to a coagulopathy, is a matter of discussion and cannot be attributed to thrombocytopenia alone [2, 37]. At least for leukaemia and lymphoma, the coagulopathy is typically acute DIC or thrombocytopenia or hyperviscosity that can lead to systemic and brain haemorrhage [3, 12, 36, 37].

Outcome measures exhibited significant higher neurological impairment in cancer patients with stroke at time of discharge. Lung and urogenital cancers showed the most pronounced neurological deterioration at discharge, but these two groups also showed the highest median age. A clear clustering for any cancer entity with a worse outcome could not be detected. However, the sample size concerning each tumour was small.

Further, patients with stroke and cancer had a tendency to stay longer at the stroke unit than non-cancer patients. These results may be explained by the generally impaired general health of cancer patients and by the concurrence of two severe diseases, although there is currently a lack of evidence to support this point [10, 11, 18, 24, 28].

The lower proportion of thrombolysis in the cancer cohort may be attributed to the physicians' concerns regarding possible haemorrhagic complications in cancer patients. However, related data are missing. Further investigations are warranted to evaluate the impact of thrombolysis in stroke patients with cancer.

The results of this study demonstrate that the overall frequency of ischemic and haemorrhagic stroke in cancer patients is similar to that of non-cancer patients. In addition, classical risk factors, except for thrombotic events, do not differ significantly between the two groups.

Based on these results, management of stroke in cancer patients should probably be based on general recommendations for stroke treatment and prevention. However, comorbidity in cancer patients, such as thrombocytopenia, recent surgery and treatment with drugs that may increase the risk for intracerebral heemorrhage (heparin, anticancer drugs), have to be considered, especially in the case of thrombolysis. To date, no specific approach to patients with both stroke and cancer is known. This demands future research.

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