Cancer-associated cerebral infarction during direct oral anticoagulant treatment in cancer patients: a case series

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Abstract

The effect of direct oral anticoagulants (DOACs) on cancer-associated cerebral infarction (CI) is unclear. We present the clinical course of 20 consecutive patients with cancer-associated CI that developed during treatment with DOACs. The incidence rate of cancer-associated CI during the treatment with DOACs was 3.4%. The median modified Rankin scale (mRS) and Karnofsky performance status (KPS) after CI were 5 and 30, respectively. The median survival time after CI was 1 month. In the group in which the thrombus due to venous thromboembolism (VTE) was reduced before CI, the median mRS, KPS, and prognosis after CI were significantly better than in those of the group with unchanged thrombus. Cancer-associated CI also developed in patients taking DOACs and those who did not show VTE recurrence. When the VTE thrombus decreased or disappeared with DOAC treatment, the clinical course after cancer-associated CI was improved.

Keywords Cancer-associated thrombosis · Cerebral infarction · Direct oral anti-coagulant · Venous thromboembolism · Cardio-oncology

Introduction

Most arterial and venous thromboembolism (VTE) events in cancer patients are considered to be cancer-associated thromboses [1]. Among the types of cancer-associated thrombosis, arterial thrombosis, including cerebral infarction (CI) and peripheral arterial embolism, has an incidence of 4.7% [2, 3]. The incidence of cancer-associated CI is approximately 3% [2], and non-bacterial thrombotic endocarditis, intravascular coagulation, atrial fibrillation, and paradoxical cerebral embolism have also been reported in cancer patients [1, 4, 5]. Coagulation is enhanced in cancer patients, and various anticancer drugs can also cause arterial thrombosis [6]. However, medications for cancer-associated CI have yet to be developed, although unfractionated heparin has been proposed [7]. In recent years, direct oral

anticoagulants (DOACs) have been used to prevent thrombosis caused by non-valvular atrial fibrillation and to treat VTE. DOACs reportedly have a similar therapeutic effect to low molecular weight heparin in the treatment of VTE in patients with cancer [8, 9]. However, the effect of DOACs on cancer-associated CI is unclear. Herein, we report on patients with cancer-associated CI that developed during treatment with a DOAC.

Case series

Patients and methods

Patients with active cancer who had cancer-associated CI that developed during treatment with a DOAC for VTE from April 2015 to September 2018 in our hospital were included. VTE was defined as pulmonary thromboembolism and/or deep vein thrombosis. The thrombus was assessed via contrast-enhanced computed tomography or ultrasonography.

CI was classified according to the Trial of Org 10,172 in Acute Stroke Treatment guidelines [10]. Patients with large-artery atherosclerosis, cardioembolism, small-vessel occlusion, and stroke of other determined etiology were excluded. Therefore, we defined cancer-associated CI as stroke of

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undetermined etiology [10–12]. Cancer-associated CI was diagnosed by a neurologist or a neurosurgeon. Patients with atrial fibrillation were excluded to exclude cardioembolism. Thus, the included patients were those being treated for VTE with DOACs. The DOACs used included apixaban, edoxaban, and rivaroxaban, and patients were treated in accordance with manufacturer guidelines. The clinical course was confirmed from the start date of DOAC treatment to post-CI. Factors related to the course of cancer-associated CI were investigated.

Data were collected on age; sex; performance status; Karnofsky performance status (KPS); modified Rankin Scale (mRS); cancer stage; body weight; history of smoking, hypertension, diabetes mellitus, and hyperlipidemia; creatinine; platelet count; hemoglobin; types of cancer; types of DOACs; types of VTE; D-dimer at VTE onset and stroke onset; effect of DOAC on VTE before CI; treatment for cancer; magnetic resonance imaging (MRI) findings; treatment for stroke; stroke recurrence; outcome; and time from stroke to outcome. These factors related to the clinical course were statistically analyzed.

Wilcoxon's signed rank sum test was used to examine two corresponding variables. The Kaplan–Meier method was used for the survival curve, and the log-rank test was used to compare the two groups. Two-group comparisons were performed using Wilcoxon's rank sum test or Fisher's exact test. Data were analyzed using JMP 9 (SAS, Institute Inc., Cary, NC, USA), and $P < 0.05$ was considered to indicate statistical significance.

Our institutional review board approved the design of this study.

Results

During the observation period, 715 patients developed new VTE. Among these, 611 patients were treated for VTE with DOACs, and 16 patients who had atrial fibrillation were excluded. The DOACs used for the treatment of VTE were edoxaban ($n = 368$), apixaban ($n = 187$), and rivaroxaban ($n = 40$). No patients were treated with dabigatran. Cerebral infarction developed in 22 of the patients taking DOAC; 2 were diagnosed with large-artery atherosclerosis, and 20 were diagnosed with cancer-associated CI. Ultimately, 20 out of 595 patients were enrolled. The incidence rate of cancer-associated CI during treatment with DOACs was 3.4%.

The patients' characteristics and clinical course are shown in Tables 1 and 2. The median KPS before the onset of CI was 75, which significantly decreased to 30 after the onset ($p < 0.01$). The median mRS after CI was 5. All patients had advanced cancer. The most common cancer type was lung ($n = 12$), followed by pancreatic ($n = 5$) and others ($n = 3$). The mean D-dimer at the time of diagnosis of VTE

Table 1 Patient characteristics before cancer-associated cerebral infarction ($n = 20$)

Age, years	
Median (range)	66 (51–80)
Sex	
Male	9
Female	11
Performance status	
0	1
1	8
2	9
3	2
4	0
Cancer stage	
IV	20
Body weight	
Mean (standard deviation) kg	54.4 (13.4)
Smoking history	
Yes	9
No	11
Hypertension	
Yes	7
No	13
Diabetes mellitus	
Yes	4
No	16
Hyperlipidemia	
Yes	2
No	18
Creatinine	
Mean (standard deviation) mg/dL	0.72 (0.28)
Platelet count	
Mean (standard deviation) $10^4/\mu\text{L}$	19.9 (9.9)
Hemoglobin	
Mean (standard deviation) g/dL	11.0 (2.2)

DOAC direct oral anticoagulant

was $19 (\pm 15.3) \mu\text{g/mL}$ in 17 patients that were examined, while the mean level at the onset of CI was $19.7 (\pm 16.5) \mu\text{g/mL}$ in 18 patients. VTE treatment led to a decrease or disappearance of thrombus ($n = 11$) or no change ($n = 9$). No patients developed recurrence of VTE. The treatments for cancer comprised chemotherapy, palliative care, and others in 15, 3, and 2 patients, respectively. The treatment regimens changed after CI, where chemotherapy, palliative care, and chemotherapy combined with surgery were administered to 5, 14, and 1 patient, respectively. In the 18 patients in which MRI diffusion-emphasized images were taken on the day of CI onset, the median widest diameter of the infarct lesion in the coronary section was 22 mm, and the median number of infarct lesions was 48. CI treatment comprised unfractionated heparin ($n = 10$), symptomatic treatment ($n = 9$), and

Table 2 Clinical course of the 20 patients

Patient	KPS before stroke	KPS after stroke	Type of cancer	Treatment (VTE)	Types of VTE	Effect of DOAC on VTE	D-dimer at VTE onset	D-dimer at stroke onset	Cancer treatment before stroke	Cancer treatment after stroke	Treatment for stroke	Stroke recurrence	Outcome	Time from stroke to outcome (months)
1	90	20	Lung	Edoxaban	Distal DVT	No change	39.9	21.1	Chemo-therapy	BSC	Heparin	No	Dead	0.3
2	70	30	Pancreas	Rivaroxaban	Proximal DVT	No change	9	9	Chemo-therapy	BSC	Supportive measure	No	Dead	1.8
3	70	60	Lung	Rivaroxaban	Proximal DVT	Decrease	22.1	46.4	Chemo-therapy	Chemo-therapy	Heparin	No	Alive	13.6
4	70	20	Pancreas	Edoxaban	PE, Proximal DVT	No change	25.2	42.5	Chemo-therapy	BSC	Supportive measure	No	Dead	0.8
5	90	30	Lung	Apixaban	PE, Proximal DVT	No change	44.5	46.3	Chemo-therapy	BSC	Heparin	No	Dead	1.0
6	60	30	Lung	Rivaroxaban	PE, Proximal DVT	Decrease	14.9	11.5	Chemo-therapy	BSC	Heparin	No	Dead	0.6
7	90	90	Lung	Edoxaban	Distal DVT	Decrease	15.1	2.9	Chemo-therapy	Chemo-therapy	Supportive measure	yes	Dead	5.0
8	50	10	Pancreas	Edoxaban	PE, Proximal DVT	No change	7.8	–	None	BSC	Supportive measure	No	Dead	0.3
9	80	60	Lung	Rivaroxaban	Proximal DVT	Decrease	1.9	2.5	None	BSC	Antiplatelet drug	Yes	Dead	1.6
10	50	10	Lung	Edoxaban	Distal DVT	No change	31	18.6	Palliative irradiation	BSC	Supportive measure	No	Dead	0.2
11	90	40	Lung	Edoxaban	Distal DVT	Decrease	20.3	3.8	Chemo-therapy	Chemo-therapy	Heparin	No	Alive	6.2
12	60	40	Primary unknown	Edoxaban	Proximal DVT	Decrease	4.1	2.4	None	BSC	Supportive measure	No	Dead	2.2
13	90	80	Uterus	Edoxaban	Proximal DVT	Decrease	–	16.6	None	Chemo-therapy, surgery	Heparin	No	Dead	16.2
14	70	10	Pancreas	Edoxaban	PE, Proximal DVT	No change	–	–	Chemo-therapy	BSC	Heparin	No	Dead	0.4
15	90	10	Lung	Edoxaban	Distal DVT	No change	8	8.1	Chemo-therapy	BSC	Heparin	No	Dead	0.2
16	90	30	Biliary	Edoxaban	PE, Proximal DVT	Decrease	52.4	16.8	None	BSC	Supportive measure	No	Dead	0.7
17	70	30	Pancreas	Edoxaban	Distal DVT	No change	–	16.7	None	BSC	Heparin	No	Dead	0.8
18	60	20	Lung	Edoxaban	Proximal DVT	Decrease	2.7	53.5	Chemo-therapy	BSC	Supportive measure	No	Dead	1.1

Table 2 (continued)

Patient	KPS before stroke	KPS after stroke	Type of cancer	Treatment (VTE)	Types of VTE	Effect of DOAC on VTE	D-dimer at VTE onset	D-dimer at stroke onset	Cancer treatment before stroke	Cancer treatment after stroke	Treatment for stroke	Stroke recurrence	Outcome	Time from stroke to outcome (months)
19	90	40	Lung	Apixaban	Distal DVT	Decrease	5.4	12.4	Chemo-therapy	Chemo-therapy	Supportive measure	No	Dead	5.2
20	100	70	Lung	Apixaban	Distal DVT	Decrease	18.3	24.2	Chemo-therapy	Chemo-therapy	Heparin	Yes	Alive	5.8

BSC best supportive care, DVT deep vein thrombosis, KPS Karnofsky performance status, PE pulmonary thromboembolism, VTE venous thromboembolism

Fig. 1 Prognosis after cancer-associated cerebral infarction VTE thrombus decrease or disappearance vs. no change in thrombus. VTE venous thromboembolism

antiplatelet agents ($n = 1$). The median survival after CI was 1.0 months.

The median KPS after CI was better in patients with decreased or resolved thrombus after VTE treatment compared to those with no change in thrombus (40 vs. 20, $p < 0.01$). Similarly, the median mRS after CI was also better in this group of patients (4 vs. 5, $p < 0.01$). Analysis of the relationship between the effect of VTE and the MRI findings showed that the widest diameter of the CI lesion tended to be smaller in the group in which the VTE thrombus was decreased or disappeared (mean: 25.7 mm vs. 45.6 mm, $p = 0.18$). The number of CI lesions also tended to be lower in the group in which the VTE thrombus was decreased or disappeared (mean: 42.2 vs. 57.6, $p = 0.33$). Finally, the prognosis after CI was also better in this group of patients (5.0 vs. 0.4 months, $p < 0.01$) (Fig. 1).

Discussion

In our study, the incidence rate of cancer-associated CI during treatment with DOACs was 3.4%, and the median survival after cancer-associated CI was 1.0 months. When the VTE thrombus decreased or disappeared with DOAC treatment, the clinical course after cancer-associated CI improved.

In this case series, patients who did not develop recurrent VTE following treatment with DOACs still developed CI. Previous reports have also shown occurrence of CI without VTE recurrence during DOAC therapy in cancer patients [11, 13, 14]. It is still unknown whether DOACs have a preventive effect against cancer-associated CI, but cases of cancer-associated CI in patients using DOACs have been reported. The incidence rate of cancer-associated CI during DOAC treatment was 3.4% in this study,

similar to a previously reported rate of approximately 3% [2]. In the NAVIGATE ESUS study, although cancer patients comprised only 9% of their subjects, the authors reported that the incidence rate of embolic stroke of undetermined source in patients receiving rivaroxaban was 4.7% and concluded that rivaroxaban had no effect on the recurrence of CI [15, 16].

Unfractionated heparin is considered to be effective for the treatment of cancer-associated CI [7]. It binds with antithrombin and inhibits thrombin and factor Xa. Furthermore, unfractionated heparin inhibits selectin binding, which is involved in the aggregation of platelets and other pathways related to thrombus formation. Therefore, unfractionated heparin is considered to be effective for cancer-related thrombosis [17]. DOACs inhibit factor Xa or thrombin, but do not act on selectin and other pathways, which may be among the reasons why cancer-associated CI can occur during DOAC therapy.

In our study, analysis of the factors affecting the clinical course after CI showed that decrease or resolution of VTE thrombus was associated with a better clinical course after CI. When the cause of CI is unknown, it is typically necessary to perform transesophageal echocardiography to determine the presence of thrombus in the heart or a patent foramen ovale. However, considering the clinical condition of the patients in our study, none underwent transesophageal echocardiography. Therefore, the presence, or size, of intracardiac thrombus or a patent foramen ovale was unknown. Patent foramen ovale can cause paradoxical CI, but the CI may be mild if the VTE thrombus is reduced by DOAC therapy. Even if the VTE thrombus is reduced, cancer-associated CI cannot be prevented; however, patients with reduced VTE thrombus may have smaller thrombus sizes or fewer cardiac emboli. In this study, both the size of the largest CI lesion and the number of lesions tended to be smaller in patients with decreased or disappeared VTE thrombus. This may be the cause of the improved KPS, mRS, and prognosis after CI observed in these patients.

In conclusion, it is still unclear whether DOACs are useful for the prevention or treatment of cancer-associated CI. However, cancer-associated CI also developed in patients taking DOACs who did not develop recurrent VTE. When the VTE thrombus decreased or disappeared with DOAC treatment, the clinical course after cancer-associated CI was improved. The above findings may indicate that VTE in cancer patients should be treated with the goal of thrombus reduction. In the future, prospective studies to confirm the therapeutic and preventive effects of DOACs against cancer-associated CI are needed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from the patients included in the study by written notification.

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