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REVIEW ARTICLE

Chemotherapy and cerebrovascular disease

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Summary

Cerebrovascular disease is common in cancer patients. Some tumors are at high risk for cerebrovascular complications. The development of cerebrovascular disease may be provoked by cancer treatment. No well-planned prospective studies about other causes of thrombosis are available, although various case reports about thrombosis related to chemotherapy have been published. L-asparaginase, cisplatin, 5-fluorouracil (5-FU) and methotrexate are anticancer agents which are reported to relate to stroke. The mechanisms by which antineoplastic agents may lead to stroke include endothelium toxicity and abnormalities of coagulation factors. Also, brain hemorrhages that could result from chemotherapy effects on the hemostatic system were reported. Besides, it is difficult to determine whether stroke is caused by chemotherapy or cancer itself. Clinicians deal not only with problems originating from cancer itself, but also with the complications resulting from its treatment. Treatment-induced cerebrovascular disorders affect quality of life and survival in cancer patients. For this reason, cancer treatment should be planned by taking into consideration the possibility of cerebrovascular complications.

Key words: chemotherapy, coagulopathy, disseminated intravascular coagulation, embolism, intracranial hemorrhage, stroke

Introduction

Cerebrovascular disease is the second most common central nervous system (CNS) pathology in cancer patients, next to metastasis. Cerebrovascular disease manifests in approximately 15% of cancer patients [1]. The most classic and severe clinical form of the disease is hemiplegia accompanied by coma. The least severe clinical form of the disease includes neurological deficiencies too inconspicuous and ambiguous to be dealt medically. Cerebrovascular disease can be considered under two main titles: ischemic and hemorrhagic.

Cancer patients are at risk of stroke due to direct or indirect effects of malignancies. Pressure and blockage by tumor of brain vessels, coagulopathy triggering hemorrhage or thrombosis, and atherosclerosis resulting from treatment, are stroke mechanisms related to cancer [2]. Some tumors have a high risk of cerebrovascular complications. Rarely, cerebrovascular disease may be the first sign of cancer [3]. Table 1 summarises the causes of stroke in cancer patients.

The development of cerebrovascular disease is also provoked by cancer treatment. Radiotherapy and chemotherapy are the two main treatment methods used in cancer therapy. Application of radiotherapy on

Table 1. Etiology and mechanisms of stroke in cancer patients

Etiology	*Mechanisms*
Thrombosis	Coagulopathy
	Vessel compression/infiltration
	Treatment-related
Embolism	Tumor-related
	Septic embolization
	Non-bacterial thrombotic endocarditis
Intracranial hemorrhage	Tumor-related
	Coagulopathy
	Treatment-related

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epithelial tumors of the head and neck or lymphoma can cause late atherosclerosis of the carotid artery. Radiotherapy-induced carotid injury is serious and life-threatening, and has adverse impact on the patients' quality of life [4].

Chemotherapy has an important role in cancer treatment. No well-planned prospective studies about other causes of thrombosis are available, although various case reports about thrombosis related to chemotherapy have been published [5]. Geiger et al. reported that chemotherapy for breast cancer increased the risk of stroke up to approximately 2.5-fold [6]. Opportunistic infections, especially fungal infections, can complicate cancer or its treatment. Chemotherapy-related neutropenia can induce fungal hyphae dissemination from the lung to the brain, resulting in fungal emboli [7]. Cancer treatment is considered to be able to activate a low level of coagulation and cause thrombosis of the cerebral arteries and vessels as well as systemic arteries and vessels. L-asparaginase, cisplatin, 5-FU and methotrexate are anticancer agents which are reported to be related to stroke (Table 2).

L-Asparaginase

L-asparaginase, having a well-known relation with thrombosis, is an anticancer agent used in the induction treatment of acute lymphoblastic leukemia. This enzyme is obtained from *E. coli* or *Erwinia*. Among its most common side effects are sensitivity reactions and decrease in protein synthesis [8]. The inhibition of protein synthesis by L-asparaginase causes deficiencies of numerous plasma proteins including albumin, insulin, thyroxine-binding globulin, and various coagulation proteins. Related studies concluded that thrombosis developed in 1-15% of children with acute lymphoblastic leukemia (ALL) receiving L-asparaginase-containing therapy [9,10]. Qualitative abnormalities of von Willebrand factor have been described as well in leukemic children with thrombosis after therapy with L-asparaginase, prednisone, and vincristine. Pui et al. reported that L-asparaginase treatment increased large plasma von Willebrand factor multimers temporarily [11,12]. Vascular events occur at a median of 19 days following the initiation of therapy. Cerebral hemorrhage may be cortical (lobar) or subcortical, and thromboses may affect cerebral arteries or dural venous sinuses.

Cisplatin

Ischemic stroke cases related to cisplatin-based chemotherapy have often been reported in the literature [13].

Hypomagnesemia-based vasospasm, hyperreninemia or hyperaldosteronemia, platelet hyperaggregation, monocyte procoagulant hyperactivity, fibrinopeptide A increase or decrease in tissue activators, endothelial dysfunction, and increase of serum cholesterol levels may play a role in the pathogenesis of chemotherapy-based stroke (Table 3).

Cisplatin coagulation changes accelerate atherosclerosis as a result of vasospasm or endothelial changes, which can cause ischemic stroke. Cisplatin treatment can cause hypomagnesemia related to renal tubular dysfunction. The incidence of hypomagnesemia is likely to increase up to 87% after cisplatin treatment. Low levels of magnesium increase the transition of calcium ions into the cell, which was reported to start contractile function, escalate the contractile effects of other vasoactive materials and cause vasospasm [14,15].

Ruiz et al. investigated plasma coagulation and fibrinolysis changes after cytotoxic treatment in 40 patients with inoperable lung cancer, 30 of whom were treated with cisplatin-based chemotherapy, and they found significant increase in fibrinopeptide A levels and decrease in fibrinolytic activity. The authors concluded that cytotoxic treatment may create a tendency to thromboembolic episodes by decreasing the fibrinolytic activity [16].

Table 2. Treatment-related stroke mechanisms in cancer patients

Treatment	*Stroke mechanisms*
Radiation therapy	Atherosclerosis Cardiac valve disorders
Systemic therapy	Thrombosis Vasospasm Thrombocytopenia Decreased renewal capacity of the endothelial cells

Table 3. Ischemic stroke mechanisms related to cisplatin-based chemotherapy

Hypomagnesemia-based vasospasm
Hyperreninemia or hyperaldosteronemia
Platelet hyperaggregation
Monocyte procoagulant hyperactivity
Increased fibrinopeptid A
Decreased tissue activators
Endothelial dysfunction
Increased serum cholesterol levels

There exists a well-known relationship between plasma renin-angiotensin-aldosterone system and renal tubular dysfunction. Lack of magnesium may cause increase in plasma renin activity. In humans, lack of magnesium is related to hypokalemia, hypophosphatemia, and hypocalcemia. Decrease in magnesium content of the myocardium may cause sudden death due to ischemic heart syndrome [17-19].

Literature shows that ischemic stroke occurs within 10 days following the last chemotherapy administration. It is thought that this relation points to a direct effect of chemotherapy. This also partially overlaps with the pharmacokinetic features of cisplatin. After intravenous administration of cisplatin, biphasic decay curves with a half life of 0.46 and 42.2 h are seen. Renal excretion of cisplatin mainly occurs within the first 10 days following administration. Ischemic stroke mostly occurs following the first chemotherapy course contrary to nephrotoxicity and neurotoxicity which generally occur later. In a small group of patients, ischemic stroke occurs within 21-30 days following the last cycle of chemotherapy. This may result from the effect of the metabolites of the drugs used [20].

Li et al. studied retrospectively 10963 patients with cancer and reported an ischemic stroke incidence of 0.035% following chemotherapy. Eventually 16 ischemic palsies were registered in 15 patients. Twelve (75%) of these palsies occurred within 10 days after the last chemotherapy cycle. Stroke after the first course of chemotherapy occurred in 10 (62.5%) patients. Median survival time after ischemic stroke was 4 weeks. The most frequent histological type was adenocarcinoma in the stroke group (40%) as well as in the whole group (36.7%). Moreover, cisplatin-based chemotherapy, not histological type, dictated ischemic stroke risk following chemotherapy. Ischemia occurred more often in the middle cerebral arterial territory and non-lacunar type ischemia was seen more often, which was similar to the general population [21].

Yen et al. evaluated the effects of cytotoxic drugs on platelet functions in tissue culture. No direct effect of cisplatin on platelets was detected. Prothrombinase activity was significantly high in cultures containing cisplatin. Prothrombinase activity was also related to the platelet availability and thrombin generation ratio was determined to be increased by factor X-a which was generated by tissue factor-factor VII-a complex. The authors concluded that vascular and thrombotic complications were, at least partly, related to platelet activation and aggregation, and monocyte procoagulant activity [22].

Raghavan et al. conducted a prospective study to see for any relation between cisplatin-based chemotherapy applied in the treatment of germ cell tumors and serum lipid abnormalities. Eventually, an increase in the serum cholesterol level was detected in 14 out of 17 patients who were given cisplatin-based treatment. However, as for other serum lipids, there was no similar relation [23]. No study exists about the evaluation of vascular effects and the increase in the cholesterol level in cancer patients. Additionally, hypercholesterolemia is known to be a risk factor for stroke in normal population [24].

Methotrexate

Dihydrofolate reductase is the main target of methotrexate. Methotrexate, a structural analog of folic acid, inhibits this enzyme, causing decreased folate levels and decreased synthesis of both purines and pyrimidines. Methotrexate-induced neurotoxicity is considered to happen owing to disturbances of the vascular function. High-dose intravenous methotrexate (1-15 g/m^2) and intrathecal methotrexate administration could cause sudden, transient, focal, neurological deficit with mental state changes, somnolence, aphasia, headache or stroke. The direct effect of methotrexate on neurons and the resulting change in biochemical paths form the mechanisms of neurotoxicity [25]. Methotrexate increases homocysteine and its metabolites in the blood and cerebrospinal fluid (CSF). Homocysteine is an amino acid neurotransmitter that contains sulfur; it may cause ischemic microvascular illness through direct toxic effect on the vascular endothelium [26,27].

Methotrexate-induced acute neurotoxicity usually occurs between the 3rd and 7th course of high-dose methotrexate treatment. Symptoms generally appear within 1-13 days post-treatment and disappear without intervention within 15 min to 72 h. Quinn et al. determined that in the CSF of children treated with methotrexate there was an increase in homocysteic acid and cysteine sulfonic acid concentrations compared to the control group in the first 7 days of the treatment [28].

5-Fluorouracil

5-FU, although mostly may cause neurotoxicity due to lack of dihydropyrimidine dehydrogenase, it can also cause cerebrovascular disorders. 5-FU-induced vascular toxicity is thought to relate to vasospasm. Palsy cases were reported after administration of 5-FU, especially in combination with cisplatin. El Amrani et al. stated that in 5 patients with oropharyn-

geal cancer who were treated with 5-FU and cisplatin, ischemic stroke occurred within 2 to 5 days after infusion of both chemotherapeutic agents [13]. In another report, ischemic stroke following 5-FU therapy in 2 patients with prostate adenocarcinoma was registered [29]. Therefore, 5-FU should be used carefully in patients who are known to have ischemic heart and vascular diseases.

Other chemotherapeutic drugs

Other chemotherapeutic drugs are less commonly associated with stroke. Microangiopathic hemolytic anemia, which can cause both thrombotic and hemorrhagic strokes, may be triggered by numerous agents including bleomycin, mitomycin C, cytarabine and lomustine [30]. Necrotizing encephalopathy related to intraarterially injected carmustine has been reported [31]. Doxorubicin-induced cardiomyopathy can cause embolic stroke from cardiac thrombus [32].

Bevacizumab

Vascular endothelial growth factor (VEGF) is the most potent and specific of the endothelial cell mitogens, acting both as an endothelial cell survival factor and as a key factor in mobilizing circulating endothelial cell precursors to nascent blood vessels. Bevacizumab binds to all biologically active isoforms of VEGF and neutralizes their biologic properties, including endothelial cell mitogenic activity, vascular permeability-enhancing activity, and those that promote angiogenesis [33]. Inhibition of VEGF results in inhibition of vascular development and significant alteration in epithelial development. That's why it seems possible that antagonizing VEGF might decrease the renewal capacity of the endothelial cell, which in turn causes endothelial dysfunction in the supporting layers of blood vessels. Consequently, the final event of anti-VEGF therapy might be a tendency for bleeding from normal tissues, leading to CNS hemorrhage, epistaxis or gastrointestinal bleeding [34]. However, anti-VEGF therapy might cause not only a tendency to bleed resulting from a decreased renewal capacity of endothelial cells, but also an augmented frequency of thrombotic events that could also be encountered as a result of tissue factor activation secondary to exposure to subendothelial collagen. Owing to all these actions bevacizumab therapy may lead to arterial thromboembolic events, including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina.

Tamoxifen

Antiestrogen treatment can also create negative effects on the coagulation system. Tamoxifen is a selective estrogen receptor modulator and with its estrogen antagonistic effects is used in the treatment of breast cancer. Even though it is reported to have positive effects on cardiovascular risk factors, increase in venous thrombosis and stroke risk was reported in several studies. The use of tamoxifen on its own may decrease anti-thrombin III, protein S, and fibrinogen levels, and may slightly increase ischemic stroke risk [35]. In the NSABP P-1 trial (National Surgical Adjuvant Breast and Bowel Project), tamoxifen use was associated with a nonsignificant increase in stroke. However, strokes were almost twice as common among women >50 years of age receiving tamoxifen compared with younger women taking the drug (relative risk 1.75) [36]. Treatment with tamoxifen in the ATAC trial was associated with statistically significant higher incidence of ischemic cerebrovascular and thromboembolic events compared with anastrozole [37]. However a meta-analysis of randomized trials of tamoxifen used for breast cancer prevention found no elevated stroke risk [6]. Further exploration of possible increased stroke risk following tamoxifen treatment for breast cancer is needed.

Diagnosis and treatment

Computed tomography and magnetic resonance imaging could show infarct or hemorrhage in the brain. D-dimers is a direct measure of activated coagulation and fibrinolysis and is used in many studies as a measure of hypercoagulability. It can be difficult to attribute a stroke definitely to hypercoagulability based on D-dimers alone. In general, a screening prothrombin time, activated partial thromboplastin time, D-dimers, or fibrin degradation products are sensitive enough to discern most diffuse intravascular coagulation (DIC) cases [38].

DIC treatment is controversial. Replacement of coagulation factors, fresh frozen plasma, cryoprecipitate and platelet suspension application may be beneficial. Also, heparin may be used to stop the thrombotic process. If stroke is due to hemorrhage, hematoma may need to be evacuated by surgical operation [1,31].

Septic cerebral infarction is usually secondary to *Aspergillus*, *Candida*, or *Mucor*. These opportunistic organisms produce secondary vasculitis. The infarctions are often multiple and hemorrhagic. *Aspergillus* is the most common causative agent and is always associated with pulmonary infection; discovery of the lat-

ter may be a clue for correct diagnosis. Antifungal therapy is rarely successful and the outcome is usually fatal.

L-asparaginase causes thrombosis by depleting plasma coagulation inhibitors, primarily antithrombin III [39]. The administration of antithrombin III constantly increased the plasma antithrombin III activity in acute lymphoblastic leukemia children treated with L-asparaginase, which may minimize the acquired prothrombotic state [40]. Administration of fresh frozen plasma to patients experiencing vascular complications has been suggested. Retreatment with L-asparaginase may result in repeated or worsening neurologic symptoms and signs, but pretreatment with fresh frozen plasma may prevent or lessen their severity [31].

Methotrexate-induced neurotoxicity still remains controversial. Winick et al. reported that in 22 out of 211 children diagnosed with acute lymphoblastic leukemia, stroke or transient ischemic attack occurred during the consolidation phase including intrathecal methotrexate and low-dose oral methotrexate. The authors concluded that folate replacement could affect methotrexate-induced or other chemotherapy medication-based neurotoxicity inasmuch as neurotoxicity developed in none of the 24 patients having undergone a folate replacement within 24-36 h after methotrexate treatment [41].

Intrathecal leucovorin administration still remains controversial as it has an epileptic potential [42, 43].

Bernini et al. stated that in patients whose CSF adenosine concentrations increase during methotrexate treatment, aminophylline - which is an adenosine receptor antagonist - may reverse symptoms in methotrexate-related acute neurotoxicity which is based on ischemic microvascular disease. In 4 of the 6 symptomatic patients, symptoms including confusion, seizures and focal deficits completely disappeared within 30 min following aminophylline administration [44]. Dextromethorphan, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has been used successfully in cases with methotrexate neurotoxicity [45,46]. Drachtman et al. reported that all 5 patients with severe methotrexate toxicity who were treated with 1-2 mg/kg oral dextromethorphan had resolution of their neurovascular symptoms [46].

Conclusion

Cerebrovascular complications are the most common cause of CNS lesions in cancer patients after CNS metastasis. Multiple mechanisms can cause ischemic and hemorrhagic stroke in cancer patients. Chemotherapy is an important treatment method that has a significant place in cancer treatment. The relation between chemotherapy and cerebrovascular disease is usually controversial as it is based mainly on case reports. Besides, it is difficult to determine whether stroke is caused by chemotherapy or cancer itself. The lack of other causes despite detailed examinations, the occurrence of symptoms soon after treatment, the occurrence of similar symptoms in the subsequent cycles of chemotherapy may serve as relative proofs of the relation between treatment and stroke.

Chemotherapy has been shown to cause cerebral thrombotic events without evidence of active, demonstrable cancer. Even though patients without cardiovascular risk factors treated with chemotherapy are at risk for ischemic stroke. Clinicians deal not only with problems originating from cancer itself, but also with the complications resulting from its treatment. Treatment-induced cerebrovascular disorders affect quality of life and survival in cancer patients. For this reason, cancer treatment should be planned by taking into consideration the possibility of cerebrovascular complications.

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