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NEUROLOGY OF SYSTEMIC DISEASES (J. BILLER, SECTION EDITOR)

Cancer and Cerebrovascular Disease

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Abstract

Purpose of Review To review the latest information about the interactions between cancer and cerebrovascular disease.

Recent Findings Additional data support the finding that both ischemic and hemorrhagic stroke are important complications of cancer or its treatment. Reperfusion therapy is being given successfully to patients with stroke complicating cancer.

Summary Hemorrhagic stroke may occur with metastatic disease to the brain, coagulopathies from cancer, in particular leukemia, or as complications of chemotherapy. Ischemic stroke also may be a complication of metastatic disease with local invasion of vessels, a pro-thrombotic disorder such as non-bacterial thrombotic endocarditis (NBTE) or disseminated intravascular coagulation (DIC), or secondary to chemotherapy. Stroke also is a potential consequence of radiation therapy to the head and neck. Venous sinus thrombosis may develop with hematologic malignancies or chemotherapy. Although many patients will have a history of cancer at the time of stroke, a cerebrovascular event may be the initial manifestation of a malignancy.

Keywords Ischemic stroke · Venous sinus thrombosis · Non-bacterial thrombotic endocarditis · Intracerebral hemorrhage · Disseminated intravascular coagulation

Introduction

The diagnosis of both cancer and stroke in the same patient is not surprising; both are common diseases and leading causes of death. Both share important risk factors including heavy drinking and smoking [1]. The traditional stroke risk factors of heart disease, hypertension, and hyperlipidemia also are present among persons with cancer. While stroke is not a likely cause of cancer, the reverse is true. Approximately 15% of patients with cancer have a cerebrovascular event with equal rates of hemorrhages and infarctions [2••]. Patients whose cancer has been cured have a lifetime increased risk of stroke (Table 1). The vascular events may be an initial feature of the malignancy, a complication of active malignancy or acute therapies, or a delayed consequence of cancer and its management [2••, 3]

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Stroke Complicating Active Cancer

In a large study of 2209 patients with acute stroke, 4.4% also had active cancer [2••]. Most cases of stroke complicating cancer follow the diagnosis of the malignancy in the previous few months or years [1, 3, 4]. Stroke complicates a wide range of malignancies including cancer of the lung, breast, pancreas, colon, stomach, and ovary [5, 6••, 7–10] (Table 2).

Ischemic Stroke

Ischemic events complicating cancer often are severe and affect multiple areas of the brain. The most common findings are altered mental status, hemiparesis, and seizures. In comparison to the clinical findings of metastatic disease, focal motor weakness, aphasia, and altered mental status are prominent [7]. The finding of ischemic lesions in multiple vascular territories on brain imaging raises consideration of a cardiac or proximal arterial source and an underlying tumor is a possibility if no other cause for embolization is found [6••, 11]. The presence of venous thrombosis occurring at the same time as ischemic stroke should raise consideration of a pro-thrombotic disorder possibly due to an occult malignancy. The usual causes of stroke, such as heart disease or atherosclerosis, are

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Table 1 Cerebrovascular complications in patients with cancer

Ischemic stroke
Large artery atherosclerosis
Cardioembolism
Cryptogenic
Transient ischemic attack
Intracerebral hemorrhage
Subarachnoid hemorrhage
Subdural hematoma
Venous sinus thrombosis
Intravascular lymphoma
Posterior reversible encephalopathy syndrome/reversible cerebral vasoconstrictive syndrome
Radiation necrosis

less frequently discovered among persons with cancer [2••, 8]. However, if a cause of stroke is established, there is no reason to screen for occult cancer [5].

Cryptogenic Ischemic Stroke

On the other hand, the diagnosis of cryptogenic stroke should lead to consideration of an active but occult malignancy [12]. The patient and family should be queried about weight loss, unexplained fevers, or exposure to risk factors for cancer. A physical examination can be done to look for a malignancy. In particular, the skin, lymph nodes, testes, and breasts should be assessed. Consultation from other specialties such as dermatology or gynecology may be necessary. Imaging should be ordered to screen for a solid tumor. Hypercoagulability is the most common mechanism for ischemic stroke linked to active cancer [13]. Multiple venous thromboses (Trousseau syndrome) increase the likelihood of an underlying prothrombotic disorder secondary to cancer. Among patients with stroke, the presence of cancer is correlated with an increased risk of venous thromboembolism [14]. The presumed mechanism for ischemic events is related to the production of mucin and release of tissue factors and procoagulants [5, 15]. Among the procoagulant cytokines elevated with cancer are tumor necrosis factor (TNF) alpha, interleukin (IL)-1, and IL-6 [5, 15]. The tumor cells may interact with the vascular endothelium causing the release of thrombin and proteases [15].

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC), which appears among patients with advanced malignancies, may lead to an intracranial hemorrhage. In addition, DIC may be discovered among patients with ischemic stroke, often in association with non-bacterial thrombotic endocarditis (NBTE). Besides low levels of fibrinogen and thrombocytopenia, patients with DIC also have a prolonged prothrombin time and an activated partial thromboplastin time. In addition, levels of D-dimer and fibrin split products are increased. The prognosis among patients with DIC secondary to cancer is very poor. Treatment centers on heparin or the low molecular weight (LMW) heparins.

Table 2 Potential causes of stroke in patients with cancer

Direct tumor invasion of blood vessels
Primary or metastatic tumor
Cardiac tumors
Intravascular lymphoma
Compression by tumor or associated edema
Skull and meninges
Coagulation disorder
Thrombocytopenia
Leukemia
Elevated inflammatory markers
Elevated procoagulant cytokines
Disseminated intravascular coagulation
Non-bacterial thrombotic endocarditis
Infection-related stroke
Immune compromised
Leukopenia
Opportunistic infections
Infective endocarditis
Surgical interventions
Radical neck dissection
Carotid sacrifice
Radiation therapy
Radionecrosis
Leukoencephalopathy
Accelerated atherosclerosis
Moyamoya
Cavernous malformations
Rupture of common carotid artery
Chemotherapy
Thrombocytopenia
Thrombotic microangiopathy
Cardiac toxicity
Infections
Posterior reversible encephalopathy syndrome

Non-Bacterial Thrombotic Endocarditis

NBTE entails sterile vegetations consisting of fibrin and platelets developing on the aortic and mitral valves, which may be normal [5, 15]. The valvular vegetations are the source of emboli. NBTE is most commonly found among patients with adenocarcinoma of the breast, pancreas, or lung [16–18]. A

high index of suspicion should lead to consideration of NBTE in a patient with a cryptogenic stroke particularly if there is evidence of DIC. Because the vegetations are small, they may not be detected by cardiac imaging. As a result, many cases of NBTE are not diagnosed until post-mortem examination. Treatment is similar to those patients who have DIC.

Secondary Infections

Because many patients with cancer are immune-compromised, which may be worsened by treatment, infection-related stroke is a possible complication [6••]. A wide variety of infections, many of which are opportunistic, cause hemorrhagic or ischemic stroke. Among the infections, herpes zoster may be reactivated leading to shingles and when the ophthalmic division of the trigeminal nerve is involved, the infection may lead to an arteritis affecting the internal carotid artery. Aspergillosis is an opportunistic fungal infection that has a stroke-like presentation with both ischemia and bleeding.

Direct Tumor Invasion

Direct invasion of blood vessels (arteries or veins) may complicate tumors of the brain, meninges, and head or neck. Both venous and arterial thrombosis may occur. Involvement of the superior sagittal sinus may cause signs of increased intracranial pressure [5, 16]. In addition, the tumor may lead to necrosis of the wall of the blood vessel with resultant hemorrhage. This scenario may occur with primary or metastatic tumors including carcinomatous meningitis. Growth of a tumor of the head or neck may compress major vessels including the internal carotid artery.

Intravascular Lymphoma

Intravascular lymphoma is a rare cause of neurologic symptoms that mimic vasculitis and include dementia, paralysis, and seizures [19, 20]. Diagnosis is difficult and requires a brain and meningeal biopsy. While the prognosis generally is poor, intravascular lymphoma has been treated successfully with rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone [21].

Hemorrhagic Stroke

Bleeding may be the result of direct tumor invasion of the blood vessels, secondary invasion of blood vessels by infections, bleeding disorders, and neoplastic aneurysms from tumor emboli among patients with myxoma or choriocarcinoma [22, 23•]. Hemorrhage secondary to a hypertensive crisis may occur in patients with pheochromocytoma. Intracranial bleeding also is a potential consequence of chemotherapy. Besides intracerebral hemorrhage, subarachnoid hemorrhage and subdural bleeding may happen. Subdural hematomas are most commonly found among patients with leukemia, gliomas, and metastatic carcinoma of the prostate [24]. Although most hemorrhages occur late in the course of the disease, brain hemorrhage may be the initial finding of cancer [25]. In a Japanese registry, cancer was found in 15% of 399 patients with intracranial hemorrhage [26]. No differences from hemorrhages of other causes as far as location, volume of the hematoma, or Glasgow Coma Scale scores were found. In 70% of cases, the patients had metastatic disease and the cancer was a predictor of poor outcome. Sprugel [27] et al. evaluated 973 patients with intracerebral hemorrhage; cancer was diagnosed in 83. While hemorrhage is a potential complication of any brain neoplasm, bleeding is most likely to occur among highly vascular tumors such as glioblastoma, melanoma, renal cell carcinoma, thyroid cancer, and choriocarcinoma [5]. Bleeding disorders include thrombocytopenia, hyperviscosity, and DIC. [28] Bleeding also may complicate surgery on the brain or head or neck. [29] This complication usually happens within the first 24 h of surgery. Intracranial hemorrhage also may be a complication of anticoagulants being given for prophylaxis for deep vein thrombosis or pulmonary embolism. Other than the scenario of carotid blowout, bleeding generally is not a major complication among patients receiving radiation therapy.

Cerebral Venous Sinus Thrombosis

Cancer is an important cause of cerebral venous sinus thrombosis (CVT). It may be the result of direct tumor invasion of the vessels, secondary to a pro-thrombotic disorder, secondary to an opportunistic infection, or a complication of general poor health. CVT is most common among patients with leukemia and other hematologic malignancies [28, 30]. In addition, CVT has been associated with chemotherapy, particularly with the use of L-asparaginase; this complication may occur immediately after induction of treatment [30]. The usual presentation involves headache, seizures, and a slow evolution of focal neurologic impairments. On examination, focal neurologic impairments are found in conjunction with signs of increased intracranial pressure. The diagnosis is often missed because of the atypical presentation.

Evaluation

The evaluation of patients with cancer-associated hemorrhage includes brain imaging for detection of the bleeding and the presence of neoplastic disease. Brain imaging often demonstrates lesions in multiple vascular territories among patients

with ischemic stroke [11]. Vascular imaging is done to check for the presence of occlusive arterial or venous disease.

Examination for a bleeding diathesis includes assessment of coagulation studies. Blood work also screens for a prothrombotic state with abnormal coagulation tests and elevated markers of inflammation. Echocardiography is done to look for vegetations on the valves; the yield of transthoracic studies is low [31•]. The transesophageal approach is more successful in detecting the lesions of NBTE. Other cardiac imaging studies are diagnostic alternatives. Because the lesions of NBTE are small, detection is difficult. Myxomas and other primary cardiac tumors are relatively easily detected by cardiac imaging studies. [32, 33]

Prognosis

The prognosis among persons with stroke complicating cancer generally is poor. [13] In one study, the median survival was 4.5 months and 25% of patients were dead within 30 days [34]. Another group reported that the median survival was 28 days among patients with stroke complicating pancreatic cancer [35]. Similarly, high rates of early mortality also happen among patients with carcinoma of the lung or melanoma. In most cases, the cancer, not the stroke, is the primary reason for the early deaths. In addition, most survivors have poor outcomes and the risk of recurrent stroke is high [13] [36].

Acute Treatment

In many cases, the cancer is not known at the time of the ictus and as a result, these patients are treated like any other acute ischemic stroke, which centers on restoring perfusion. These interventions have been modestly successful [13]. A Korean study found that patients with active cancer and stroke had poor clinical outcomes despite treatment with alteplase [36]. In a nationwide survey of 416 patients with brain tumors and stroke treated with alteplase, Murthy et al. [37] reported that the risk of intracerebral hemorrhage was high among patients with malignant tumors. Conversely, thrombolytic therapy was relatively safe among patients with benign brain tumors [37]. Among patients with malignant tumors elsewhere in the body and who have stroke, cancer should not be an absolute contraindication to thrombolytic treatment [6••, 38]. Experience with endovascular therapy is limited. Besides removing clots, an endovascular intervention could remove tumor emboli, such as a fragment of a myxoma. Jung et al. [39] treated 19 patients with endovascular interventions; the success in recanalization was less than patients who did not have cancer. Although the long-term prognosis of patients having ischemic stroke complicating cancer is poor, aggressive management of the stroke may allow them to preserve their quality of life. Thus, many patients with known cancer complicated by acute ischemic stroke should be treated.

The acute treatment of CVT complicating cancer primarily is anticoagulation to prevent propagation of the thrombus. Thrombolytic agents or endovascular treatment are potential options.

Reports about treatment of brain hemorrhage complicating cancer are few. Management consists of controlling the bleeding and preventing the life-threatening effects of the hemorrhage.

Prevention of Recurrent Stroke

Long-term secondary prevention of recurrent stroke focuses on antithrombotic agents. Choices include antiplatelet agents, LMW heparins, warfarin, and the direct oral anticoagulants (DOAC). Because the ischemic events are often related to coagulation abnormalities, anticoagulants are presumed to be the best treatment option [5]. Subcutaneous administration of heparin has been used but in one study, half the cases discontinued the agent because of bleeding or worsening of the cancer [40]. Long-term use of the LMW heparins may be helpful and may be superior to warfarin [41•, 42] [43]. Warfarin must be used with caution [6••]. Besides the risk of bleeding, the malignancy and cancer therapies may cause difficulty in maintaining a therapeutic INR [43]. The new oral anticoagulants hold promise [6••]. A subanalysis of the ARISTOTLE trial suggested that apixaban was superior to warfarin among patients with active cancer and atrial fibrillation [44]. However, Naito et al. [45] concluded that information about the DOAC was insufficient and that heparin remains the best choice for treatment of patients with cancer-associated stroke. The choices for prophylactic therapy to prevent recurrent stroke must be weighed carefully given the patient's overall poor prognosis and shortened life expectancy. The risk of bleeding and issues in regard to stabilizing the treatment regimen are important factors when deciding about institution of long-term anticoagulation. Still, lowering the risk of another stroke or thromboembolic event that may lead to further disability and reduced quality of life remains an important component of management.

The role of surgical procedures in the setting of cancer-associated stroke is limited. The long-term benefit of traditional surgical procedures (carotid endarterectomy or angioplasty/stenting) might not overcome the perioperative risks among patients with a short life expectancy. One exception would be removal of a cardiac myxoma, which may be curative [46] [47]. The success in treatment of primary malignant cardiac tumors or metastatic lesions is less [48]. Surgery or endovascular procedures are recommended for the treatment of patients who have tumor compression of an intracranial or extracranial artery or vein. Surgery or endovascular therapy is

advised for patients who have severe stenotic large artery disease following radiation therapy.

Patients with CVT secondary to an obstructed vessel may be treated with surgical correction. In most cases, management of CVT to prevent recurrent thrombosis is similar to that prescribed to patients who do not have cancer.

Prevention of recurrent hemorrhage focuses on the treatment of the malignancy and the avoidance of bleeding diatheses secondary to chemotherapy.

Stroke as a Delayed Complication of Cancer or its Treatment

The risk factor profile for patients who have a past history of cancer is similar to patients without a past history of malignancy [12]. Still, vascular events often are related to treatments for the cancer and may take years to appear. The risk of stroke soon after diagnosis and treatment of cancer in childhood is relatively low. Noje et al. [49] reported 15 cases among 1411 children with the median interval of 5 months. All the children had either brain tumors or hematologic malignancies. Additional long-term studies of childhood cancer survivors demonstrate an increased risk of stroke that persists for more than 20 years [50] [51] [52] [53]. The association is most strongly correlated with malignancies of the head and neck, radiation therapy to the head or neck, and chemotherapy, primarily with platinum and alkylating agents. Addison et al. [54] reported that testing positive for the human papillomavirus also is correlated with an increased risk of stroke among people who have survived cancer. The traditional risk factors for stroke in young adulthood also increase the likelihood of an ischemic stroke; thus, it is important to address hypertension, hyperlipidemia, diabetes, tobacco or drug use, and use of oral contraceptives in long-term care. There are no studies to provide guidance about the use of antithrombotic agents among asymptomatic young adults who have a remote history of cancer.

Stroke Complicating Treatment for Cancer

Surgery

Cerebrovascular complications are uncommon among patients having neurosurgical procedures including treatment of brain tumors. Larsen et al. [55] reported that the rate in the USA was 0.5%. Similar low rates have been reported following radical neck dissections. A large Canadian study found the incidence of stroke within 30 days of surgery to be 0.7% [56]. Those patients older than 75, those with a prior stroke, and those with either diabetes or hypertension had the highest risk. CVT is a potential complication of surgery. Even among patients who had sacrifice of the carotid artery for treatment of head and neck cancer, the risk of stroke was relatively low. Mourad et al. [57] reported that only 2/51 patients had stroke complicating major neck dissections with implementation of strategies such as bypass procedures as part of the operation.

Radiation Therapy

Neurologic complications follow all types of radiation therapy of the head and neck [53]. Vascular events may occur during treatment or months to years later. Radiation injures the vascular endothelium and the vasa vasorum leading to fibrosis; it also accelerates the process of atherosclerosis.

Acute complications include radionecrosis and leukoencephalopathy, which are most commonly found with treatment to the brain or sellar region [58] [59]. Aizer et al. [60] described that radiation therapy for brain tumors is accompanied by an increased risk of death from stroke, particularly if the tumor is near the central vasculature of the brain. Exposure to the circle of Willis has also been associated with increased risk of stroke [53].

One group reported that one out of eight survivors of childhood cancer who are treated with radiation therapy subsequently had a stroke by the age of 45 [61••]. In another series of 100 survivors of primary brain tumors treated with radiation therapy in childhood, vascular complications were diagnosed in 36 [62]. The average interval was approximately 15 years and more extensive vascular disease was found among those treated with whole-brain radiation. Another survey of 4394 patients with pituitary adenoma reported the incidence of delayed stroke was 6.7% [63]. The dosage of radiation impacts the risk. Bowers et al. [64] found that the risk of stroke increased when cranial radiation exceeded 30 GY. Another study noted that the risk of stroke increased ten times higher among patients who received radiation therapy with more than 10 GY [53]. Overall, the interval between cranial radiation and the development of smaller intracranial arterial disease is several years [58]. Partap et al. [65] described cavernous malformations as a potential complication of cranial radiation.

Moyamoya is another potential complication of a cranial radiation therapy. This vasculopathy is most likely among children who receive radiation therapy for optic nerve glioma or craniopharyngioma [65, 66].

Stroke-like migraine attacks after cerebral radiation therapy (SMART syndrome), particularly following treatment to the posterior fossa, have been described [28, 67] [68]). Patients have prolonged unilateral migraine symptoms that take weeks to resolve. In addition, these patients may have seizures. The syndrome appears to be secondary to a mineralizing microangiopathy [68]. Focal slowing is found on EEG and the MRI may show enhancement of the cortical ribbon. Treatment is similar to that used for

management of complex migraine. Superficial siderosis is an uncommon complication detected among cancer survivors [65]. Affected patients have deafness, cerebellar signs, and myelopathy.

Patients with head and neck cancer treated with local radiation therapy have an increased risk of atherosclerotic carotid artery disease. In the past, persons with lymphoma or Hodgkin's disease often were treated with large doses of radiation to the neck and chest. They subsequently had accelerated vascular disease leading to both stroke and heart disease. Fortunately, advances in treatment have improved the situation. A small increase in risk has followed modern radiation therapy for lymphoma of the neck [69]. Patients younger than 40 who receive radiation treatments for oral cancer are at an increased risk of stroke. The frequency of carotid artery complications is estimated to be from 12–60% [70]. In one study of 50 patients with neck radiation, 38 had carotid stenosis or plaques [71]. Most of the patients with this vascular complication were treated for carcinoma of the throat or larynx. In a Canadian registry of more than 14,000 patients with head and neck cancer, 8% had stroke after radiation therapy [72]. Addison et al. [54] followed 326 patients who received radiation therapy for head and neck cancers for a median of 3.4 years. The annual rate of cerebral ischemic events was 1.8%. Patients older than 59 years, men, and those with hypertension or smoking had the highest risk. Because of the aggressive nature of radiation-induced atherosclerosis of the carotid artery, regular surveillance of the vessel is recommended. Non-invasive choices include carotid duplex, CTA, or MRA. Digital subtraction angiography is the diagnostic procedure of choice but its invasive nature and potential for complications usually limit the test to an adjunct to endovascular treatment. Surgical management involves endarterectomy with reconstruction of the artery, but for the risk of poor wound healing in the field of the radiation, endovascular treatment is more commonly done.

Blowout of the common carotid artery may complicate radical neck dissection and radiation treatment of neck cancers [28, 73] [74]. The surgery and radiation appear to damage the arterial wall so that it can no longer sustain an elevated blood pressure [75]. It also may be associated with local metastatic disease, wound breakdown, infection, or a development of a fistula [74] [75]. In some cases, minor bleeding may precede the major hemorrhage. However, in most instances, the hemorrhage is a dramatic, life-threatening event. The artery can be treated with emergency endovascular occlusion of the artery or with coil embolization and stent grafts [73, 74]. Bond et al. [73] reported a perioperative mortality of 11% and a 3% rate of stroke when endovascular treatment was used in this setting.

Chemotherapy

Although both hemorrhagic and ischemic stroke complicate chemotherapy for cancer, the risks are relatively low. In a review of 45,294 chemotherapy sessions, 16 strokes were diagnosed within 1 month of treatment [76]. The most commonly implicated agents are L-asparaginase, cisplatin, 5-flourouracil, and methotrexate [77] [78]. Stroke from chemotherapy may be due to direct neuro- and vascular toxicity or indirectly through effects on the heart, a secondary coagulopathy, or immune compromise [77]. For example, Fitzpatrick et al. [79] report that chemotherapy increases the risk of atrial fibrillation. A thrombotic microangiopathy may follow chemotherapy [28, 58]. Most of the complications of chemotherapy occur during the acute treatment period; a French study showed that there were no long-term effects on stroke risk [53].

Cisplatin-based chemotherapy causes cardiotoxicity and may promote a pro-thrombotic state [80]. In a series of 179 patients with germ cell tumors treated with cisplatin, 15 patients had thromboembolic complications including stroke in two [81]. L-asparaginase, which is used to treat acute lymphoblastic leukemia (ALL), reduces levels of plasminogen, fibrinogen, antithrombin, and protein C [16]. Among 240 treated patients with ALL, 9 developed CVT [82]. Eight patients had the complication shortly after treatment with L-asparaginase. Intrathecal administration of methotrexate may cause stroke. Although information is mixed, there may be an increased risk of stroke among women with breast cancer who are receiving adjuvant tamoxifen therapy. Posterior reversible encephalopathy syndrome (PRES) is associated with chemotherapy for treatment of a wide variety of diseases, particularly in childhood and with intrathecal administration of agents. Intra-arterial treatment with chemotherapy also may cause stroke.

Biological Therapy

While information about the potential risk of cerebrovascular complications is limited, there is some information about both hemorrhage and infarction happening in patients receiving biological agents. Trastuzumab, a monoclonal antibody used to treat women with metastatic carcinoma of the breast, does have cardiac toxicity. Indirectly, stroke is a potential complication. Bevacizumab (BVZ) is an angiogenesis inhibitor that is prescribed to patients with a wide range of tumors including glioblastoma. It is associated with life-threatening bleeding. Letarte and colleagues [83] reported that the brain was an uncommon site for bleeding but that the events usually were lethal. Ischemic stroke also is a complication [84]. The likelihood of cerebrovascular events

may be dose-related. Auer et al. [85] studied 82 patients with glioblastoma; 40 were treated with BVZ while 42 did not receive the therapy; no increased risk of either ischemic or hemorrhagic stroke was found. A study of vascular thromboembolic complications among men with advanced urologic cancers noted a high rate of events among those patients who received the combination of cisplatin and BVZ [86]. PRES has been reported among patients with cancer who received treatment with BVZ and or allogeneic stem cell transplantation [87].

Cancer After Stroke

Stroke is not a direct cause of cancer but the incidence of cancer among people with a history of stroke is increased [88]. In some instances, stroke may have been the initial manifestation of an undiagnosed malignancy. Quintas et al. [89] reported that the mean time from stroke until the diagnosis of cancer was 6 months. In the NORSTROKE study, among 1282 patients with stroke and no history of cancer, 23 had a malignancy diagnosed within 1 year [90]. Carcinoma of the lung was the most common tumor. A German study that followed stroke survivors for 10 years demonstrated increased risks of respiratory cancers in men and women and an increased risk of gastrointestinal malignancies in men [91•]. More research on the potential relationships of stroke followed by cancer is needed.

Conclusion

Both ischemic and hemorrhagic stroke are well-recognized complications of cancer and its therapies. These events may be the initial manifestation of cancer or may occur months or years after the malignancy has been treated. Physicians should consider an underlying cancer as a potential explanation for a cryptogenic ischemic stroke particularly if the stroke is multifocal and associated with abnormal blood studies. Acute treatment of patients with stroke complicating cancer should be similar to other patients. Long-term management emphasizes use of anticoagulants. Cancer is the primary predictor of survival.

Compliance with Ethical Standards

Conflict of Interest Harold P. Adams Jr. declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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