Chemotherapy Increases Stroke: Fact or Fiction?

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Cancer is associated with an increased risk of thromboembolic events (TEEs).[1–6] The underlying mechanisms of cancer-associated thrombosis are complex because many factors can contribute to TEE, including site and stage of the cancer, type of treatment, such as chemotherapy, and patient characteristics, such as age (►**Fig. 1**).[7] Cancer type-specific mechanisms include tissue factor-positive extracellular vesicles for pancreatic cancer and podoplanin expression for brain cancer.[8–10] Therefore, it is difficult to determine the relative contribution of these different factors to thrombosis. In this issue of *Thrombosis and Haemostasis*, Kitano et al analyzed the effect of chemotherapy on stroke in cancer patients.[11]

The rate of venous thromboembolism (VTE) (1–19%) in cancer is much higher than the rate of arterial thromboembolism (ATE) (0–5%).[1–5] One study found that the 6-month cumulative incidence of ATE (composite of myocardial infarction and ischemic stroke) and ischemic stroke was significantly increased in cancer patients compared with controls patients (ATE 4.7% vs. 2.2%; ischemic stroke 3.0% vs. 1.6%).[12] The risk of ATE in cancer patients was affected by cancer stage and to a lesser extent by cancer type (with the highest rate for lung cancer). Another study also found an increase in the 3-month cumulative incidence of ischemic stroke was higher in patients with cancer compared to controls and affected by cancer type (lung 5.1%, pancreatic 3.4%, colorectal 3.3%, breast 1.5%, and prostate 1.2%).[13] Cerebral infarction was also observed in nonsmall cell lung cancer patients (2.9%) with those with brain metastasis having the highest rate (6.3%).[14] Gastric cancer patients are also prone to ischemic stroke after surgery.[15] Stroke patients with cancer have a worse prognosis compared with stroke patients without cancer.[14,16,17]

Numerous chemotherapeutic agents are used to treat various forms of cancer that include untargeted "conventional" agents, such as cisplatin, and targeted "unconventional" agents, such as tyrosine kinase inhibitors. Cisplatin-based chemotherapy was shown to be associated with a high rate of TEE (18.1%) in 932 patients with a variety of cancers, but most of these events were VTEs with only 1.5% of the events being ATEs.[18] Another study with bladder cancer patients found that patients treated with platinum-based chemotherapy had a significantly higher rate of TEE compared with patients who did not receive chemotherapy (19.5% vs. 11.6%).[19] Several studies have investigated the effect of both conventional and nonconventional chemotherapy on stroke in cancer patients (►**Table 1**). One study investigated the effect of chemotherapy and/or radiotherapy on stroke in head and neck cancer patients and concluded that patients < 55 years of age but not patients ≥ 55 years of age had an increased risk of stroke with chemotherapy, radiotherapy, or both compared with patients with surgery alone.[20] Another study concluded that chemotherapy, especially platinum-based regimes, was an independent risk factor for stroke in ovarian cancer patients.[21] In contrast, chemotherapy (cisplatin or carboplatin) did not increase the risk of stroke in patients with stage II to III bladder cancer.[19] Other studies have investigated the effect of nonconventional chemotherapeutic agents on stroke. For instance, the vascular endothelial growth factor inhibitor bevacizumab increased the overall relative risk of cerebrovascular events in patients with a variety of cancers by 3.28.[22] In addition, use of the vascular endothelial growth factor receptor tyrosine kinase inhibitors sunitinib and sorafenib was associated with an increase in stroke in patients with renal cell carcinoma.[23]

Kitano et al[11] analyzed the effect of chemotherapy on stroke by comparing the rates in patients with ($n = 5{,}887$) or without ($n = 13{,}119$) chemotherapy. The study included a variety of cancer types and both conventional (9–60% of patients) and nonconventional (6–14% of patients) chemotherapeutic agents. Cancer patients who received chemotherapy had a higher rate of stroke (0.75%) compared with patients who did not receive chemotherapy (0.39%). Kaplan–Meier curve analysis of the data indicated a significant difference between the two groups (hazard ratio 1.84; 95% confidence interval 1.23–2.75). Importantly, however, there was no significant difference after adjustment for cancer

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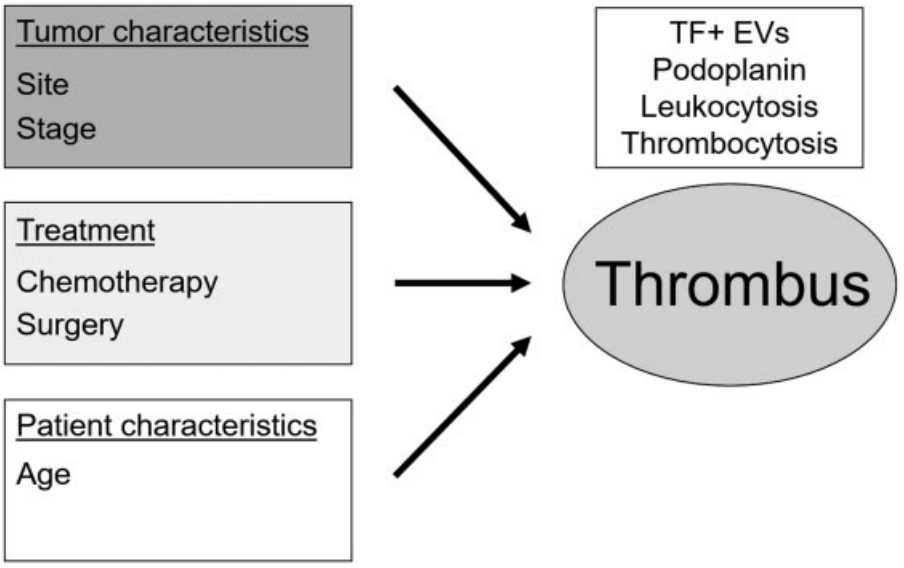

Fig. 1 Risk factors for cancer-associated thrombosis. Risk factors for thrombosis in cancer patients include tumor characteristics, treatment, and patient characteristics. Tissue factor (TF)-positive extracellular vesicles (EV), podoplanin, leukocytosis, and thrombocytosis may enhance thrombosis in cancer patients.

Table 1 Studies investigating the association between chemotherapy and stroke in cancer patients

Study	Cancer type	Chemotherapy type	Total no. of patients	No. of patients received chemotherapy (%)	No. of stroke in patients without chemotherapy (%)	No. of stroke in patients received chemotherapy (%)	Association between chemotherapy and stroke	Ref
Kuan et al	Ovarian	Various types	8,810	6,590 (74.8)	N/A	N/A	Yes	21
Huang et al	Head and neck	Platinum	10,172	663 (under the age of 55) (6.5)	42 (surgery only) (2.5)	24 (3.6)	Yes	20
Gupta et al	Bladder	Platinum	5,057	1,079 (21.3)	216 (5.4)	54 (5.0)	No	19
Zuo et al	Various types	Bevacizumab	12,705	6,421 (50.5)	14 (0.2)	59 (0.9)	Yes	22
Jang et al	Kidney	Tyrosine kinase inhibitors	1,458	670 (46.0)	N/A	24 (3.6)	Yes	23
Kitano et al	Various types	Various types	19,007	5,887 (31)	51 (0.39)	44 (0.75)	Yes/No[a]	11

[a]The association was not significant after adjusting for cancer status.

status (cancer stage and site). In addition, chemotherapy was also not associated with increased stroke after adjustment for cancer status in either a stratified Cox regression model or a time-dependent covariate Cox regression model. Similarly, subanalysis indicated platinum-based chemotherapy did not increase stroke.

The strengths of the study by Kitano et al[11] are its size and the adjustment for cancer status and age. However, there are some limitations. For instance, the study includes a variety of cancer types, which are known to have a different incidence of stroke, and various types of conventional and nonconventional chemotherapies, which have a different impact on the risk of stroke. The authors did not perform subanalysis of chemotherapy other than platinum-based regimes and did not perform subanalysis of cancer type because the number of events in each cancer type was too small.

In conclusion, Kitano et al concluded that chemotherapy is not associated with increased risk of stroke in a general cancer patient population after adjustment for cancer status. However, future studies are needed to investigate the effect of specific classes of agents in specific cancer types.

Conflict of Interest
None declared.

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