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Cardio-Oncology

The Incident Ocular Diseases Related to Chemotherapy in Cancer Patients are Associated with Increasing Risk of Incident Stroke

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Background: In addition to cardiotoxicity, ocular toxicity induced by chemotherapeutic agents is not uncommon.
Objective: This study aimed to explore the association between ocular adverse events and major adverse cardiovascular events (composite endpoint) caused by chemotherapy, and whether specific ocular events could be potential predictors of some specific components of the composite endpoint.
Methods: A total of 5378 newly diagnosed patients (age > 18 y/o) with any malignancy or metastatic solid tumors who received chemotherapy from January 1997 to December 2010 were enrolled from the Taiwan National Health Insurance Research Database. Patients who developed new incident ocular diseases were classified as the study group, and those who did not develop incident ocular diseases as the control group.
Results: After propensity score matching, there was a significant increase in the incidence of stroke in the ocular diseases group compared to the no ocular diseases group (13.4% vs. 4.5%, $p < 0.0001$). Tear film insufficiency, keratopathy, glaucoma, and lens disorders were associated with a significantly higher risk of stroke. A longer duration of methotrexate and a longer duration with higher total amount of tamoxifen were associated with both incident ocular diseases and incident stroke. Cox proportional hazards regression showed that the only independent risk factor for stroke was incident ocular diseases [Adjusted relative risk (95% confidence interval): 2.96 (1.66-5.26), $p = 0.0002$]. In addition, incident ocular disease was the most significant risk factor compared with other traditional cardiovascular risk factors.
Conclusion: Incident ocular diseases related to chemotherapy were associated with a significantly higher risk of stroke.

Key Words: Chemotherapy • Methotrexate • Stroke • Tamoxifen • Tear film insufficiency

Abbreviations

ARR	Adjusted relative risk
cDDD	Cumulative defined daily dose
CI	Confidence intervals
CV	Cardiovascular
DDD	Defined daily dose
Gb-3	Globotriaosylceramide
HR	Hazard ratio
IQR	Interquartile range
MDR	Multidrug resistance
MTX	Methotrexate
NHI	National Health Insurance
NHIRD	National Health Insurance Research Database
RR	Relative risk
95% CI	95% confidence interval

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INTRODUCTION

Despite great progress in the systemic treatment of solid tumors in past years, these treatments offer only limited benefits in the majority of patients while exposing them to the very real possibility of toxicity from such management.[1] In addition to cardiotoxicity,[2,3] other systemic organ damage driven by the administration of chemotherapeutic agents while treating cancer is well known.[4-6] Among them, ocular toxicity induced by chemotherapeutic agents is not uncommon, a common complaint of patients, easily detected by ophthalmologists, and generally not preventable.[7,8] Chemotherapy regimens may produce a broad spectrum of ocular disorders such as dry eye, keratitis, lens disorders, retinopathy, and optic neuropathy.[7,9-12] Some ocular symptoms can be warning signs of specific cardiovascular diseases.[13,14] An interesting feature of cardiovascular disease, taking atherosclerosis as an example, is that disease progress is not only present in the body, but can also occur in the eyes.[15] Individuals with changes in ocular blood vessels have been reported to be at a higher risk of heart attack, heart failure or stroke.[16] In addition, examining the eyes is an easy and non-invasive method for doctors to check the condition of the vascular system. However, to date, little research has investigated whether ocular changes may be a potential predictor of specific treatment-related composite endpoints including major adverse cardiovascular events. To the best of our knowledge, few studies have explored the time sequence and the associations of incident ocular diseases with incident cardiovascular (CV) events caused by chemotherapy. Furthermore, if certain ocular diseases occur earlier than the CV events and their associations are significant, it is unclear whether these incident ocular diseases could potentially predict certain CV events in the future. In addition, it is also important to investigate which chemotherapy drugs (including cumulative dose and treatment duration) are associated with these eye and CV associations. Hence, this study aimed to explore these issues.

METHODS

Data resource

The National Health Insurance (NHI) program in Taiwan was initiated in March 1995, and it currently covers more than 95% of the population, making it one of the biggest resources for health research in the world. Information available from the National Health Insurance Research Database (NHIRD) includes patient demographics, disease diagnoses, contracted medical care institutions, medical expenditure, and prescription claims data. To ensure anonymity, the patients' identification is encrypted and investigators are only permitted to perform data linkage, processing and statistical analyses on an assigned computer in a strictly monitored room. Using an encrypted personal identifier for each patient, researchers can connect files to acquire socio-demographic data, longitudinal medical history and other information. Researchers are only allowed to carry out statistical analysis. This study was approved by the Institutional Review Board (Approval No. KMUHIRB-E(1)-20220212) at Kaohsiung Medical University Hospital.

Study design

A sample of 5378 patients who had any malignancy or metastatic solid tumor and who received chemotherapy (cisplatin, carboplatin, methotrexate, etoposide, tamoxifen, carmustine, pentostatin, leuprolide, vemurafenib, gefitinib) were selected from the NHIRD. The exclusion criteria were: 1) age at cohort entry < 18 years, 2) first chemotherapy drug use after Jan. 1, 2009, 3) undergoing radiotherapy prior to chemotherapy, 4) diagnosis of an ocular disease before chemotherapy, 5) fewer than three clinical visits, and 6) < 2 years of follow-up. Patients with new incident ocular diseases identified according to the following ICD-9-CM codes were defined as the study group: retinopathy: 362.x, 363.x, 379.23 and 379.24; uveitis 364.00, 364.01, 364.10, and 364.24; glaucoma 365.x; tear film insufficiency 375.15; keratopathy 370.x and 371.x; lens disorders 366.x and 379.x; optic neuropathy 377.x. The patients without incident ocular diseases were defined as the control group. The composite endpoint was defined as including myocardial infarction (ICD-9-CM 410.x, 412.x), congestive heart failure (ICD-9-CM 428.x), stroke or cerebrovascular disease (ICD-9-CM 430.x-438.x), dementia (ICD-9-CM 290.x), hemiplegia or paraplegia (ICD-9-CM 342.x, 344.1), renal disease (ICD-9-CM 582.x, 583.0-583.7, 585, 586, 588.x), end-stage renal disease (ICD-9-CM 585 plus ICD-9-CM procedure codes 58001C, 58002C, and 580011A), peri-

pheral vascular disease (ICD-9-CM 443.9, 441.x, 785.4, V43.4, plus ICD-9-CM procedure code 38.48).

Statistical analysis

Data of continuous and categorical variables were analyzed using the t-test or Wilcoxon rank sum test and chi-square test to compare the data of chemotherapy patients with and without ocular diseases. Continuous data were presented as mean (standard deviation) or median [interquartile range (IQR)], and categorical data were presented as percentages. Adjusted relative risk (ARR) with 95% confidence interval (95% CI) for ocular diseases with the risk of incident composite endpoint and its individual components (see Table 2) were calculated after adjusting for age on chemotherapy, sex, hypertension, diabetes mellitus and radiotherapy using a Cox proportional hazards model. A propensity analysis for stroke or dementia was performed through logistic regression to obtain a 2-digit match of the propensity score for each patient with the covariates, such as chemotherapy age group, sex, hypertension, diabetes mellitus, and radiotherapy region (1:1 matching for chemotherapy patients with ocular diseases and without ocular diseases). We estimated the cumulative incidence of stroke in the patients with and without ocular diseases separately by fitting Kaplan-Meier curves and comparing them using the log-rank test. A Cox proportional hazards regression model was used to calculate hazard ratio (HR). The matched data set of age group, sex, hypertension, diabetes mellitus and radiotherapy were used in the STRATA statement such that each unique value for age group, sex, hypertension, diabetes mellitus and radiotherapy was defined as a stratum. A Cox proportional hazards regression model, including chemotherapy by sex interaction term, was used. Average chemotherapy drug dose (DDD, defined daily dose per day) was calculated as cumulative defined daily dose (cDDD) divided by total drug prescription days. The average chemotherapy drug dose was classified using two approaches: stratifying the chemotherapy exposure by DDD category ($0 < DDD \leq 52.0$, $52.0 < DDD \leq 363.5$, $363.5 < DDD \leq 920.0$, $DDD > 920.0$ per day) according to a quartile method. In addition, the quartile method was used to classify the L02BA01 tamoxifen of average chemotherapy drug dose ($0 < DDD \leq 312.0$, $312.0 < DDD \leq 660.0$, $660.0 < DDD \leq 1274.0$, $DDD > 1274.0$ per day). A Cox proportional hazards regression model, including DDD or tamoxifen DDD by chemotherapy (without/with ocular diseases) interaction term was used. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). All statistical tests were two-sided, and a two-tailed p value of < 0.05 was considered significant.

RESULTS

Patients

From January 1997 to December 2010, 5378 patients with any newly diagnosed malignancy or metastatic solid tumor who received chemotherapy (ICD-9 codes 140.x-172.x, 174.x-195.8, 200.x-208.x, 196.x-199.1) were identified from the NHIRD as the study population. After excluding patients with the first chemotherapy drug use after Jan. 1, 2009 or with < 2 years of follow-up (n = 1520), who received radiotherapy before chemotherapy (n = 476), diagnosed with incident ocular diseases before chemotherapy (n = 719), and with < 3 clinic visits during follow-up (n = 431), 483 cancer patients who had received chemotherapy and developed incident ocular diseases and 1651 cancer patients who had received chemotherapy but without developing incident ocular diseases were identified (Figure 1). No subjects were lost to follow-up in this cohort during the 14-year study period.

Baseline characteristics

The patients with ocular diseases were significantly older than those without ocular diseases, and they had a significantly higher prevalence of hypertension and diabetes mellitus, but significantly fewer received radiotherapy. Significantly less cisplatin and epirubicin but more etoposide and leuprorelin were found in the chemotherapy regimens in the patients with ocular diseases (Table 1).

Endpoint during the 14-year follow-up period

The mean follow-up periods were 4.19 ± 3.11 and 7.00 ± 3.59 years in the patients with and without ocular diseases, respectively. During the follow-up period, there was no significant difference in the composite endpoint between the two groups, with 483 in the ocular diseases group and 1651 in the no ocular diseases

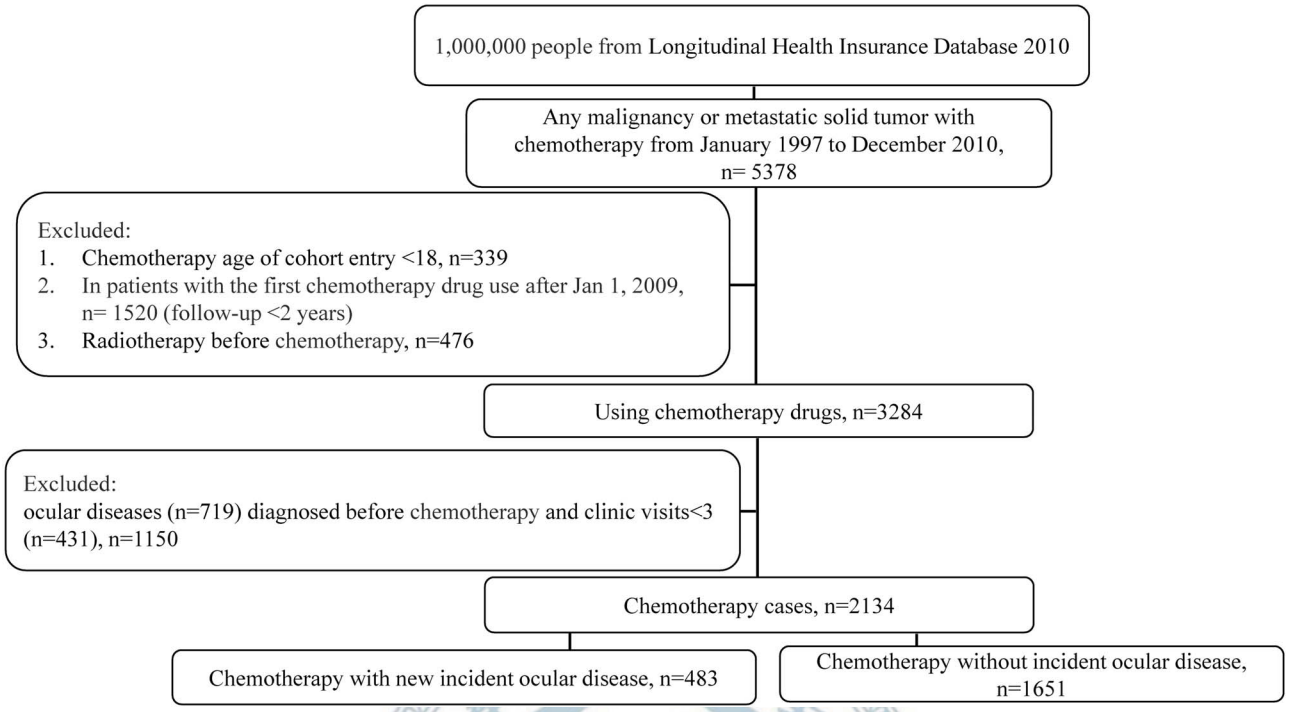

Figure 1. *Study flow.*

Table 1. Characteristics of chemotherapy patients with ocular diseases and without ocular diseases

	Chemotherapy with ocular diseases (n = 483)	Chemotherapy without ocular diseases (n = 1651)	p value
Age, mean (SD) years	58.05 (10.9)	48.22 (11.7)	< 0.0001*
Sex (males), n (%)	97 (20.1)	329 (19.9)	0.9401
Hypertension, n (%)	300 (62.1)	505 (30.6)	< 0.0001*
Diabetes mellitus, n (%)	180 (37.3)	232 (14.1)	< 0.0001*
Radiotherapy, n (%)	95 (19.7)	458 (27.7)	0.0004*
Chemotherapy drug			
Cisplatin, n (%)	25 (5.2)	171 (10.4)	0.0005*
Carboplatin, n (%)	5 (1.0)	18 (1.1)	0.9179
Methotrexate, n (%)*	117 (24.2)	355 (21.5)	0.2050
Etoposide, n (%)	1 (0.2)	33 (2.0)	0.0057*
Tamoxifen, n (%)	301 (62.3)	983 (59.5)	0.2725
Carmustine, n (%)	1 (0.2)	1 (0.1)	0.3548
Leuprorelin, n (%)	16 (3.3)	27 (1.6)	0.0210*
Gefitinib, n (%)	4 (0.8)	14 (0.9)	0.9666
Doxorubicin, n (%)	62 (12.8)	247 (15.0)	0.2433
Epirubicin, n (%)	111 (23.0)	504 (30.5)	0.0013*
Any malignancy, n (%)	483 (100.0)	1651 (100.0)	1.0000
ICD-9 codes: 140.x-173.x	141 (29.2)	442 (26.8)	0.2936
ICD-9 codes: 174.x-195.x	412 (85.3)	1352 (81.9)	0.0816
ICD-9 codes: 200.x-208.x	29 (6.0)	128 (7.8)	0.1954
Metastatic solid tumor, n (%)			
ICD-9 codes: 196.x-199.x	145 (30.0)	575 (34.8)	0.0494*

* $p < 0.05$. Hypertension and diabetes mellitus were defined as ≥ 3 clinic visits. Data of continuous and categorical variables were analyzed using t-test and chi-square test to compare the data of chemotherapy patients with ocular diseases and without ocular diseases.

SD, standard deviation.

group and the adjusted relative risk (RR) with 95% CI after adjusting for age on chemotherapy, sex, hypertension, diabetes mellitus and radiotherapy was 1.18 (0.88-1.58) (p = 0.2682) (Table 2). However, there were signifi-

Table 2. The association of the chemotherapy related incident ocular diseases with the risk of incident composite endpoint (major adverse cardiovascular events, including all individuals), and its individual components

	Ocular diseases (n = 483)	No ocular diseases (n = 1651)	p value
Composite endpoints			
No. of events (%)/total patients	72 (36.36)/198	224 (20.70)/1082	
Crude RR (95% CI)	1.76 (1.35-2.29)	1.00	< 0.0001*
Adjusted RR (95% CI)	1.18 (0.88-1.58)	1.00	0.2682
Prior event or clinic visits < 3	285	569	
Myocardial infarction			
No. of events (%)/total patients	2 (0.42)/474	4 (0.24)/1639	
Crude RR (95% CI)	1.73 (0.32-9.44)	1.00	0.5273
Adjusted RR (95% CI)	0.62 (0.11-3.53)	1.00	0.5854
Prior event or clinic visits < 3	9	12	
Congestive heart failure			
No. of events (%)/total patients	16 (3.78)/423	26 (1.63)/1592	
Crude RR (95% CI)	2.32 (1.24-4.32)	1.00	0.0082*
Adjusted RR (95% CI)	0.92 (0.48-1.76)	1.00	0.8013
Prior event or clinic visits < 3	60	59	
Stroke (cerebrovascular disease)			
No. of events (%)/total patients	50 (13.44)/372	61 (3.99)/1528	
Crude RR (95% CI)	3.37 (2.32-4.89)	1.00	< 0.0001*
Adjusted RR (95% CI)	1.81 (1.21-2.71)	1.00	0.0036*
Prior event or clinic visits < 3	111	123	
Dementia			
No. of events (%)/total patients	18 (3.89)/463	13 (0.80)/1632	
Crude RR (95% CI)	4.88 (2.39-9.96)	1.00	< 0.0001*
Adjusted RR (95% CI)	2.20 (1.07-4.54)	1.00	0.0329*
Prior event or clinic visits < 3	20	19	
Hemiplegia or paraplegia			
No. of events (%)/total patients	3 (0.63)/479	3 (0.18)/1642	
Crude RR (95% CI)	3.43 (0.69-16.98)	1.00	0.1313
Adjusted RR (95% CI)	1.64 (0.3-9.12)	1.00	0.5717
Prior event or clinic visits < 3	4	9	
Renal Disease			
No. of events (%)/total patients	24 (5.87)/409	46 (2.96)/1552	
Crude RR (95% CI)	1.98 (1.21-3.24)	1.00	0.0067*
Adjusted RR (95% CI)	1.11 (0.66-1.88)	1.00	0.6851
Prior event or clinic visits < 3	74	99	
End-stage renal disease			
No. of events (%)/total patients	4 (0.83)/481	7 (0.43)/1644	
Crude RR (95% CI)	1.95 (0.57-6.67)	1.00	0.2855
Adjusted RR (95% CI)	1.14 (0.31-4.23)	1.00	0.8464
Prior event or clinic visits < 3	2	7	
Peripheral vascular disease			
No. of events (%)/total patients	5 (1.10)/456	12 (0.75)/1604	
Crude RR (95% CI)	1.47 (0.52-4.16)	1.00	0.4722
Adjusted RR (95% CI)	0.69 (0.23-2.05)	1.00	0.4995
Prior event or clinic visits < 3	27	47	

* p < 0.05. Adjusted relative risk (RR) with 95% confidence intervals (CI) and their p values were calculated after adjustment for age on chemotherapy, sex, hypertension, diabetes mellitus and radiotherapy by using Cox proportional hazards regression model.
Note: In order not to sacrifice some temporal related specific event regarding to chemotherapy with ocular diseases (e.g., stroke), the exclusions for each endpoint of prior events or clinic visits < 3 were performed in this step.

cant increases in the incidence rates of stroke and dementia (two individual components of the composite endpoint) in the ocular diseases group compared to the no ocular diseases group, with ARRs (95% CIs) of 1.81 (1.21-2.71) (p = 0.0036) and 2.20 (1.07-4.54) (p = 0.0329), respectively (Table 2). In order to clarify the relationships of incident ocular diseases with stroke and dementia, each propensity analysis of the two was performed through logistic regression to obtain a 2-digit match of the propensity score for each patient with the covariates, including chemotherapy age group, sex, hypertension, diabetes mellitus, and radiotherapy region (Table 3 and Supplemental Table 1). After propensity score matching, the incident stroke rate was still significantly increased in the ocular diseases group compared to the no ocular diseases group (13.4% vs. 4.5%, p < 0.0001) (Table 3), but dementia was not (2.8% vs. 1.8%, p = 0.3655) (Supplemental Table 1). The median (IQR) stroke event was 4.6 years (IQR 2.7-7.5) in the ocular diseases group and 5.8 years (IQR 3.3-9.5) in the no ocular diseases group (p < 0.0001). Since incident ocular diseases occurred significantly ahead of incident stroke, we further investigated whether the incident ocular diseases could assess the risk of incident stroke. To clarify the relationship between incident ocular diseases with incident stroke, we used time-to-event analysis with a Cox proportional hazards regression model (Figure 2). The results showed that the ocular diseases group had a significantly higher risk of developing stroke [adjusted HR: 4.23 (95% CI: 2.29-7.81), p < 0.0001]. Since there was a trend of more males in the no ocular diseases group for stroke, another Cox proportional hazards regression model regarding sex was analyzed, which showed significantly higher risks of developing incident stroke in both male and female groups [adjusted HR: 4.54 (95% CI: 1.69-12.16), p = 0.0026 in males and 4.04 (1.85-8.82), p = 0.0005 in females] (Table 4).

The sub-phenotypes of incident ocular diseases associated with an increased risk of stroke

Adjusted RR and p values were calculated according to the ocular disease phenotypes compared to those without ocular diseases and adjusted for chemotherapy, age, sex, hypertension, diabetes mellitus and radiother-

Table 3. Characteristics of chemotherapy patients with ocular diseases and matched without ocular diseases

	Ocular diseases	No ocular diseases	p value
N	358	358	
Stroke events, n (%)	48 (13.4)	16 (4.5)	< 0.0001*
Chemotherapy age, mean (SD) years	56.52 (10.9)	55.19 (13.3)	0.1425
Chemotherapy age ≥ 55 years, n (%)	202 (56.4)	178 (49.7)	0.0723
Sex, males, n (%)	63 (17.6)	84 (23.5)	0.0520
Hypertension, n (%)	197 (55.0)	184 (51.4)	0.3302
Diabetes mellitus, n (%)	116 (32.4)	103 (28.8)	0.2917
Radiotherapy, n (%)	73 (20.4)	82 (22.9)	0.4141
Metastatic solid tumor, n (%)	109 (30.4)	120 (33.5)	0.3781
Comorbidities, n (%)			
Myocardial Infarction	2 (0.6)	1 (0.3)	0.5629
Congestive heart failure	9 (2.5)	16 (4.5)	0.1541
Dementia	11 (3.1)	5 (1.4)	0.1293
Hemiplegia or paraplegia	1 (0.3)	1 (0.3)	1.0000
Renal disease	16 (4.5)	13 (3.6)	0.5695
End-stage renal disease	3 (0.8)	2 (0.6)	0.6536
Peripheral vascular disease	3 (0.8)	4 (1.1)	0.7041
Peptic ulcer disease	40 (11.2)	37 (10.3)	0.7174

* p < 0.05. Comorbidities were defined as ≥ 3 clinic visits. Data of continuous and categorical variables were analyzed using t-test and chi-square test to compare the data of chemotherapy patients with ocular diseases and without ocular diseases. A propensity analysis was performed through logistic regression to obtain a 2-digit match of the propensity score for each patient with the covariates, such as chemotherapy age group, sex, hypertension, diabetes mellitus, and radiotherapy region (1:1 for chemotherapy patients with ocular diseases and without ocular diseases). SD, standard deviation.

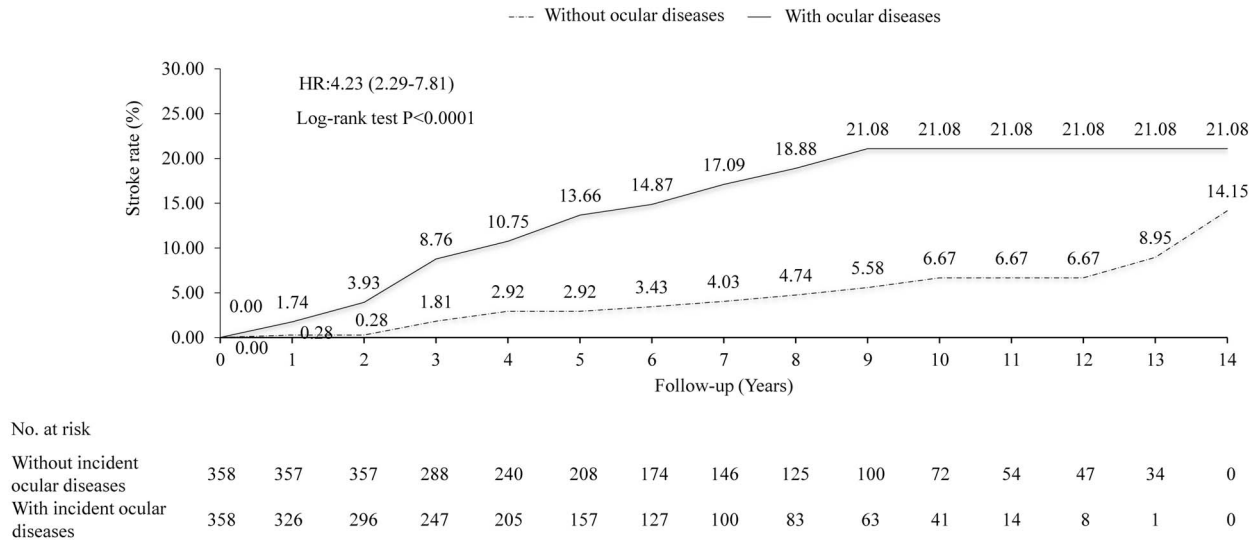

Figure 2. *Cumulative incidences of stroke between chemotherapy patients with and without incident ocular diseases.*

Table 4. Association of chemotherapy with ocular diseases with risk of incident stroke in terms of gender

Chemotherapy	Stroke events/ total subjects, %	Person-years	Events per 1000 person-years (95% CI)	HR (95% CI)	p value	p for interaction*
Men						
Without ocular diseases	7/84, 8.33	551.64	12.69 (11.67-13.79)	1.00		
With ocular diseases	14/63, 22.22	299.58	46.73 (41.73-52.34)	4.54 (1.69-12.16)	0.0026*	
Women						
Without ocular diseases	9/274, 3.28	1828.86	4.92 (4.70-5.15)	1.00		
With ocular diseases	34/295, 11.53	1546.82	21.98 (20.91-23.10)	4.04 (1.85-8.82)	0.0005*	
Combined group						
Without ocular diseases	16/358, 4.47	2380.5	6.72 (6.46-7.00)	1.00		
With ocular diseases	48/358, 13.41	1846.4	26.00 (24.84-27.21)	4.23 (2.29-7.81)	< 0.0001*	0.9396

* p < 0.05. Hazard ratios (HRs) with 95% confidence intervals (CI) and their p values were calculated by using Cox proportional hazards regression model. Age group, sex, hypertension, diabetes mellitus and radiotherapy were used in the STRATA statement such that each unique value for age group, sex, hypertension, diabetes mellitus and radiotherapy defines a stratum. Cox proportional hazards regression model, including chemotherapy × sex interaction term, was applied.

apy using a Cox proportional hazards regression model. Tear film insufficiency, followed by keratopathy, glaucoma, and lens disorders were associated with significantly higher risks of stroke, with RRs and 95% CIs of 5.08 (2.47-10.44), 4.27 (1.53-11.93), 3.72 (1.23-11.19) and 2.98 (1.66-5.35), respectively (all p < 0.05) (Supplemental Table 2).

Comparison of chemotherapy drug administration patterns and stroke rate in the patients with and without incident ocular diseases

Supplemental Table 3 shows the chemotherapy drug administration patterns in the patients with and without incident ocular diseases. The total dosage of methotrexate was the same between the two groups. However, the duration of usage was significantly longer in the ocular diseases group than in the no ocular diseases group [median (IQR), 90.0 (42.0-284.0) days vs. 63.0 (28.0-140.0) days, p = 0.0446]. As to tamoxifen, the average daily dosage (total dosage/total dosage use days) was the same in both groups. However, the duration and, therefore, the total dosage were significantly longer and higher in the ocular diseases group than in the no ocular diseases group [median (IQR), 779.0 (448.0-1370.0) days vs. 532.0 (252.0-904.0) days, and 17000.0 (8960.0-28120.0) mg vs. 10700.0 (5380.0-18880.0), both p <

0.0001]. Furthermore, analysis of the average dosage effect of tamoxifen to stroke by DDD showed no significant dose effect (Supplemental Table 4). Therefore, tamoxifen toxicity was found to be duration dependent but not dosage dependent.

Incident ocular diseases but not chemotherapy were associated with the occurrence of stroke

To investigate whether incident ocular diseases, chemotherapy with methotrexate and/or tamoxifen or both were independent risk factors associated with stroke, further Cox proportional hazards regression analysis was performed adjusting for chemotherapy, age, sex, hypertension, diabetes mellitus and radiotherapy (Supplemental Table 5-1). In Supplemental Table 5-2, neither methotrexate nor tamoxifen was a risk for stroke. Only incident ocular diseases were associated with the risk of stroke, with an ARR and 95% CI of 2.96 (1.66-5.26) (p = 0.0002). In addition, incident ocular diseases with or without methotrexate/tamoxifen both significantly increased the risk of stroke [adjusted HR (95% CI) 5.91 (2.08-16.77), p = 0.0009 in those without methotrexate/tamoxifen and 4.03 (1.43-11.38), p = 0.0084 in those with methotrexate/tamoxifen] (Table 5) [ARR (95% CI) 4.19 (1.49-11.80, p = 0.0067 in those without methotrexate/tamoxifen and 3.75 (1.37-10.26), p = 0.0099 in with those methotrexate/tamoxifen] (Supplemental Table 5-1). After adjusting for the baseline risk factors, chemotherapy and radiotherapy, incident ocular diseases for stroke, age (chemotherapy at an age of ≥ 55 y/o), hypertension and diabetes mellitus were still risk factors for stroke with ARRs and 95% CIs of 2.96 (1.66-5.26, p = 0.0002), 2.47 (1.29-4.72, p = 0.0061), 2.45 (1.27-4.72, p = 0.0073), and 1.73 (1.04-2.87, p = 0.0339), respectively. Among them, incident ocular diseases were the highest risk (Supplemental Table 5-2).

DISCUSSION

To the best of our knowledge, this is the first and biggest observational study to explore the associations between incident ocular diseases caused by chemotherapy and the risk of CV events. Among those CV events, the ocular diseases group was significantly associated with a higher risk of developing stroke. As to the phenotypes of ocular diseases, tear film insufficiency, followed by keratopathy, glaucoma, and lens disorders were associated with significantly higher risks of stroke. Comparing the chemotherapy drugs and their patterns of us-

Table 5. Ocular diseases predicted risk of incident stroke

	Stroke events (%)	Total subjects	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Methotrexate						
No	48 (8.6)	559	1.00		1.00	
Yes	16 (10.2)	157	1.15 (0.65-2.02)	0.6377	1.13 (0.64-2.00)	0.6784
Tamoxifen						
No	30 (10.3)	290	1.00		1.00	
Yes	34 (8.0)	426	0.71 (0.43-1.15)	0.1654	0.93 (0.47-1.82)	0.8247
Methotrexate/Tamoxifen						
No	18 (9.4)	191	1.00		1.00	
Yes	46 (8.8)	525	0.79 (0.46-1.36)	0.3945	1.03 (0.52-2.03)	0.9297
Ocular diseases						
No	16 (4.5)	358	1.00		1.00	
Yes	48 (13.4)	358	4.30 (2.37-7.78)	< 0.0001	3.99 (2.20-7.23)	< 0.0001
Methotrexate/Tamoxifen and Ocular diseases						
No and No	5 (4.3)	115	1.00		1.00	
Yes and No	11 (4.5)	243	0.84 (0.29-2.45)	0.7549	1.20 (0.39-3.72)	0.7559
No and Yes	13 (17.1)	76	6.46 (2.29-18.27)	0.0004	5.91 (2.08-16.77)	0.0009
Yes and Yes	35 (12.4)	282	3.35 (1.30-8.58)	0.0120	4.03 (1.43-11.38)	0.0084

Adjusted hazard ratio (HR) and p value were calculated after adjustment for chemotherapy age, sex, hypertension, diabetes mellitus and radiotherapy by using Cox proportional hazards regression model. CI, confidence interval.

age, only a longer duration of methotrexate was associated with both incident ocular diseases and incident stroke after propensity score matching for baseline characteristics. However, tamoxifen was significantly associated with both incident ocular diseases and incident stroke in terms of both duration and total amount of usage. We further analyzed chemotherapy with methotrexate and tamoxifen and incident ocular diseases with regards to the risk of stroke, and the results showed that the phenotype of incident ocular diseases was the only risk for stroke but not methotrexate and tamoxifen. In addition, the phenotype of incident ocular diseases had the highest risk compared to traditional risks including age, hypertension and diabetes mellitus.

Chemotherapy-related incident ocular diseases

Among the phenotypes of ocular diseases, tear film insufficiency, keratopathy, glaucoma, and lens disorders were most strongly associated with the risk of stroke. These phenotypes have also been reported after chemotherapy.[9,17] In addition, a longer duration of methotrexate and both a longer duration and subsequent increased total amount of tamoxifen were associated with both incident ocular diseases and incident stroke. Methotrexate has been reported to have the side effect of decreased tears.[9] Tamoxifen has been associated with an increased rate of keratopathy[18,19] and lens disorders.[17,20,21] Mitomycin has been associated with an increased rate of glaucoma,[22] but few studies have reported on glaucoma with methotrexate and tamoxifen. In addition, steroids are included in many chemotherapy regimens, and steroid-induced glaucoma should also be taken into consideration.[23]

Chemotherapy-related incident stroke

Stroke can occur in a variety of tumor-related conditions, including direct invasion, coagulopathy, chemotherapy side effects and nonbacterial thrombotic endocarditis.[24] Among the chemotherapy drugs, tamoxifen is well known to increase the risk of both stroke and venous thrombosis, especially in women.[25,26] In addition, tamoxifen has been associated with an increased risk of atrial fibrillation.[27] Methotrexate has also been associated with an increased risk of stroke.[28] In addition, methotrexate has also been reported to provoke new-onset atrial fibrillation.[29] In patients with solid tumors, coagulation is mildly activated, and cancer treatment can further enhance the formation of systemic and cerebral arterial or venous thrombosis.[30] In addition, cancer and atrial fibrillation are both independent risk factors for ischemic stroke, and systemic inflammation and autonomic dysregulation are thought to play critical roles.[31]

The association between phenotypes of ocular diseases and stroke

The cancer patients receiving chemotherapy with incident ocular diseases had a significantly higher risk of developing stroke with an adjusted HR and 95% CI of 4.23 (2.29-7.81) ($p < 0.0001$), and the curves separated very early within 1 year. In addition to the cumulative incidence rate of 8.76% within 3 years, the individual cumulative incidence rates were 1.74% in first year, 3.93% in second year, and 8.76% in third year, which showed the novel findings in the study – that the phenotype of ocular diseases is a strong potential predictor of stroke (Figure 2), possibly through inflammation-related atherothrombotic effects due to the stroke endpoint. For the possible mechanisms or connections of specific subphenotypes of ocular diseases with stroke, tear film insufficiency, or dry eye disease, has been more frequently associated with comorbidities of not only stroke, per se, but also of stroke-related risk factors including ischemic heart disease, diabetes mellitus, hyperlipidemia, cardiac arrhythmias, and peripheral vascular disorders.[32] In addition, tear film insufficiency has also been significantly associated with solid tumors without metastasis.[32] As to the relationship of keratopathy and lens disorders with stroke, Anderson-Fabry disease, a disease of vascular endothelial accumulation of globotriaosylceramide (Gb-3), may suggest a possible link.[33] Gb3 is overexpressed in many human tumors and tumor cell lines with inherent or acquired multidrug resistance (MDR). Gb3 is co-expressed and interplays with the membrane efflux transporter P-gp encoded by the MDR1 gene. P-gp can act as a lipid flippase and stimulate Gb3 induction when tumor cells are exposed to cancer chemotherapy.[34,35] In addition, patients with stroke have been reported to have a high prevalence of lens disorders.[36] Glaucoma has been reported to be a significant risk factor for subsequent stroke.[37-39] Abnormal ocular blood flow has also been implicated as a risk factor for both glaucoma and stroke.[40]

Limitations

The present study had some limitations. First, personal variables, such as smoking habits, alcohol intake, body mass index, and physical activity were not available in the NHIRD. Second, the presence of comorbidities relied on the claims data based on ICD-9-CM diagnosis codes, which could have potentially led to disease misclassification. Therefore, we used hospital admission follow-up records of cardiovascular events with the main ICD-9-CM diagnosis codes as incident events to minimize possible misclassification. Third, blood pressure profiles were not available in the NHIRD, and details of blood pressure control were unknown. Finally, the project has closed, the deadline to access the NHIRD has passed, and no further analysis is allowed. Owing to these limitations, a large-scale, prospective trial is necessary to confirm our findings. Fourth, two issues should be considered when evaluating an observational cohort study. First, loss of follow-up. However, the NHIRD represents > 99% of Taiwan's population and no one was lost during follow-up in our study. Second, it is often difficult to blind the investigators who are assessing the study outcomes. However, both the exposure status and outcomes of the study participants were assessed by their own doctors who did not participate in or knew about this study, which may have attenuated the influence of bias on the assessment of the outcomes. Finally, there was a female predominance, and therefore it was possible to have skewed cancer types in our study. The advantage of an observational cohort study design is the possibility of assessing incidence rates, relative risks, and causality.

CONCLUSION

Chemotherapy-related incident ocular diseases were associated with a significantly increased risk of stroke in this 14-year follow-up study. Tear film insufficiency, keratopathy, glaucoma, and lens disorders were the leading phenotypes for stroke. A longer duration of methotrexate and a longer duration and higher total amount of tamoxifen were associated with incident ocular diseases. Finally, incident ocular diseases occurring after chemotherapy were associated with the risk of future stroke.

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Author contributions

The first author, Dr. Kai-Chun Cheng, and corresponding author, Dr. Kai-Hung Cheng, participated on the generation of the original ideas, in the study design and on the analysis of data, in drafting of the manuscript, in revising it critically for important intellectual content and in final approval of the manuscript submitted. Other authors participated in 1) conception and design or analysis and interpretation of data, or both: Hung-Pin Tu, 2) drafting of the manuscript or revising it critically for important intellectual content: Hung-Pin Tu and Tsung-Hsien Lin.

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There is no sponsorship/funding.

DECLARATION OF FINANCIAL/OTHER RELATIONSHIPS

There are no relationships to be declared.

DECLARATION OF CONFLICT OF INTEREST

All authors declare no conflict of interest.

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SUPPLEMENTARY MATERIALS

Supplemental Table 1. Chemotherapy with ocular diseases revealed no significant association with incident dementia

	Ocular diseases	No ocular diseases	p value
N	433	433	
Dementia events, n (%)	12 (2.8)	8 (1.8)	0.3655
Chemotherapy age, mean (SD) years	57.0 (10.7)	55.6 (13.8)	0.0997
Chemotherapy age ≥ 55 years, n (%)	251 (58.0)	233 (53.8)	0.2180
Sex, males, n (%)	82 (18.9)	95 (21.9)	0.2733
Hypertension, n (%)	255 (58.9)	231 (53.3)	0.1003
Diabetes mellitus, n (%)	146 (33.7)	129 (29.8)	0.2146
Radiotherapy, n (%)	92 (21.2)	93 (21.5)	0.9339
Metastatic solid tumor, n (%)	129 (29.8)	154 (35.6)	0.0701
Comorbidities, n (%)			
Myocardial infarction	2 (0.5)	1 (0.2)	0.5630
Congestive heart failure	12 (2.8)	13 (3.0)	0.8392
Stroke	36 (8.3)	26 (6.0)	0.1875
Hemiplegia or paraplegia	2 (0.5)	2 (0.5)	1.0000
Renal disease	19 (4.4)	20 (4.6)	0.8698
End-stage renal disease	3 (0.7)	3 (0.7)	1.0000
Peripheral vascular disease	4 (0.9)	6 (1.4)	0.5247
Peptic ulcer disease	52 (12.0)	46 (10.6)	0.5198

Comorbidities were defined as ≥ 3 clinic visits. Data of continuous and categorical variables were analyzed using t-test and chi-square test to compare the data of chemotherapy patients with ocular diseases and without ocular diseases. A propensity analysis was performed through logistic regression to obtain a 2-digit match of the propensity score for each patient with the covariates, such as chemotherapy age group, sex, hypertension, diabetes mellitus, and radiotherapy region (1:1 for chemotherapy patients with ocular diseases and without ocular diseases). SD, standard deviation.

Supplemental Table 2. Phenotypes of chemotherapy related incident ocular diseases with their risk of following incident stroke

	Stroke events/ total subjects, %	Crude RR (95% CI)	p	Adjusted RR (95% CI)	p
Chemotherapy without ocular diseases	16/358, 4.47	1.00		1.00	
Chemotherapy with ocular diseases	48/358, 13.41	3.00 (1.70-5.28)	0.0001	3.11 (1.76-5.49)	< 0.0001
Retinopathy					
No	41/271, 15.13	3.39 (1.90-6.03)	< 0.0001	3.20 (1.79-5.72)	< 0.0001
Yes	3/41, 7.32	1.64 (0.48-5.62)	0.4333	2.28 (0.65-7.97)	0.1966
Other phenotypes	4/46, 8.70	1.95 (0.65-5.82)	0.2337	2.89 (0.95-8.85)	0.0627
Uveitis					
No	48/342, 14.04	3.14 (1.78-5.53)	< 0.0001	3.19 (1.80-5.64)	< 0.0001
Yes	0/8, 0.00	-	-	-	-
Other phenotypes	0/8, 0.00	-	-	-	-
Glaucoma					
No	40/306, 13.07	2.92 (1.64-5.22)	0.0003	2.98 (1.66-5.35)	0.0002
Yes	4/30, 13.33	2.98 (1.00-8.92)	0.0505	3.72 (1.23-11.19)	0.0196
Other phenotypes	4/22, 18.18	4.07 (1.36-12.17)	0.0121	4.22 (1.39-12.8)	0.0111
Tear film insufficiency					
No	20/209, 9.57	2.14 (1.11-4.13)	0.0232	2.07 (1.07-4.00)	0.0307
Yes	15/89, 16.85	3.77 (1.86-7.63)	0.0002	5.08 (2.47-10.44)	< 0.0001
Other phenotypes	13/60, 21.67	4.85 (2.33-10.08)	< 0.0001	4.97 (2.38-10.41)	< 0.0001
Keratopathy					
No	39/284, 13.73	3.07 (1.72-5.50)	0.0002	2.98 (1.66-5.35)	0.0003
Yes	5/37, 13.51	3.02 (1.11-8.25)	0.0308	4.27 (1.53-11.93)	0.0056
Other phenotypes	4/37, 10.81	2.42 (0.81-7.24)	0.1141	3.48 (1.15-10.57)	0.0276
Lens disorders					
No	4/79, 5.06	1.13 (0.38-3.39)	0.8234	2.79 (0.89-8.79)	0.0796
Yes	39/250, 15.60	3.49 (1.95-6.25)	< 0.0001	2.98 (1.66-5.35)	0.0003
Other phenotypes	5/29, 17.24	3.86 (1.41-10.53)	0.0084	5.72 (2.05-15.94)	0.0009
Optic nerve disorders					
No	47/345, 13.62	3.05 (1.73-5.38)	0.0001	3.15 (1.78-5.57)	< 0.0001
Yes	0/8, 0.00	-	-	-	-
Other*	1/5, 20.00	4.48 (0.59-33.74)	0.1460	3.49 (0.45-26.85)	0.2292

* Stroke events before retinopathy, uveitis, glaucoma, tear film insufficiency, corneal opacity, cataract, or optic nerve and clinic visits < 3.

Adjusted relative risk (RR) and p value were calculated by ocular diseases phenotypes, when compared with no ocular diseases, after adjustment for chemotherapy age, sex, hypertension, diabetes mellitus and radiotherapy by using Cox proportional hazards regression model. CI, confidence interval.

Supplemental Table 3. Comparison of chemotherapy drug administration patterns and stroke rate in patients with and without incident ocular diseases

	Ocular diseases	No ocular diseases	p value
N	358	358	
Stroke events, n (%)	48 (13.4)	16 (4.5)	< 0.0001*
L01XA01 cisplatin, n	22	39	
Total clinic visits (frequencies), median (IQR)	5.0 (3.0-6.0)	3.0 (2.0-4.0)	0.0620
Total drug use (days), median (IQR)	31.0 (15.0-56.0)	18.0 (11.0-35.0)	0.0580
Total dosage, median (IQR), mg	6.0 (4.0-13.0)	4.5 (3.0-9.0)	0.6373
Total dosage/total dosage use days	0.2 (0.1-0.5)	0.3 (0.1-0.8)	0.2576
L01XA02 carboplatin, n	5	5	
Total clinic visits (frequencies), median (IQR)	4.0 (4.0-6.0)	5.0 (4.0-6.0)	0.8362
Total drug use (days), median (IQR)	20.0 (7.0-23.0)	42.0 (19.0-43.0)	0.2788
Total dosage, median (IQR), mg	230.0 (140.0-400.0)	2700.0 (1800.0-4050.0)	0.1753
Total dosage/total dosage use days	11.5 (9.5-20.0)	64.3 (30.3-180.0)	0.3235
L01BA01 methotrexate, n	92	65	
Total clinic visits (frequencies), median (IQR)	9.0 (6.0-12.5)	9.0 (3.0-12.0)	0.1638
Total drug use (days), median (IQR)	90.0 (42.0-284.0)	63.0 (28.0-140.0)	0.0446*
Total dosage, median (IQR), mg	300.0 (145.0-610.0)	300.0 (85.0-450.0)	0.2909
Total dosage/total dosage use days	2.3 (1.3-4.3)	3.6 (1.7-7.1)	0.0426*
L01CB01 etoposide, n	0	6	
Total clinic visits (frequencies), median (IQR)	-	3.0 (2.0-6.0)	-
Total drug use (days), median (IQR)	-	41.5 (14.0-58.0)	-
Total dosage, median (IQR), mg	-	635.0 (320.0-1500.0)	-
Total dosage/total dosage use days	-	23.9 (15.9-30.0)	-
L02BA01 tamoxifen, n	229	197	
Total clinic visits (frequencies), median (IQR)	27.0 (17.0-50.0)	20.0 (9.0-33.0)	< 0.0001*
Total drug use (days), median (IQR)	779.0 (448.0-1370.0)	532.0 (252.0-904.0)	< 0.0001*
Total dosage, median (IQR), mg	17000.0 (8960.0-28120.0)	10700.0 (5380.0-18880.0)	< 0.0001*
Total dosage/total dosage use days	20.0 (20.0-20.0)	20.0 (20.0-20.0)	0.9862
L01AD01 carmustine, n	1	0	
Total clinic visits (frequencies), median (IQR)	2.0 (2.0-2.0)	-	-
Total drug use (days), median (IQR)	28.0 (28.0-28.0)	-	-
Total dosage, median (IQR), mg	600.0 (600.0-600.0)	-	-
Total dosage/total dosage use days	21.4 (21.4-21.4)	-	-
L02AE02 leuprorelin, n	7	9	
Total clinic visits (frequencies), median (IQR)	31.0 (12.0-66.0)	12.0 (11.0-34.0)	0.1859
Total drug use (days), median (IQR)	790.0 (342.0-1841.0)	336.0 (84.0-950.0)	0.1887
Total dosage, median (IQR), mg	116.3 (45.0-247.5)	45.0 (41.3-127.5)	0.1859
Total dosage/total dosage use days	0.1 (0.1-0.1)	0.1 (0.1-0.1)	0.3489
L01XE02 gefitinib, n	1	3	
Total clinic visits (frequencies), median (IQR)	39.0 (39.0-39.0)	3.0 (1.0-18.0)	0.4370
Total drug use (days), median (IQR)	510.0 (510.0-510.0)	79.0 (14.0-250.0)	0.4370
Total dosage, median (IQR), mg	127250.0 (127250.0-127250.0)	19750.0 (3500.0-62500.0)	0.4370
Total dosage/total dosage use days	249.5 (249.5-249.5)	250.0 (250.0-250.0)	0.3318
L01DB01 doxorubicin, n	50	48	
Total clinic visits (frequencies), median (IQR)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	0.6504
Total drug use (days), median (IQR)	35.0 (12.0-87.0)	23.0 (8.5-58.0)	0.1377
Total dosage, median (IQR), mg	290.0 (180.0-400.0)	270.0 (145.0-400.0)	0.3937
Total dosage/total dosage use days	6.9 (4.0-13.3)	9.7 (4.3-17.0)	0.3578
L01DB03 epirubicin, n	79	99	
Total clinic visits (frequencies), median (IQR)	6.0 (4.0-7.0)	6.0 (3.0-7.0)	0.9134
Total drug use (days), median (IQR)	42.0 (16.0-72.0)	42.0 (21.0-80.0)	0.5269
Total dosage, median (IQR), mg	360.0 (200.0-520.0)	400.0 (200.0-600.0)	0.3450
Total dosage/total dosage use days	7.5 (4.8-14.3)	7.1 (4.3-15.0)	0.5288

* $p < 0.05$. p values were calculated by using Wilcoxon rank sum test to compare the data of with ocular diseases and without ocular diseases. IQR, interquartile range.

Supplemental Table 4. Average chemotherapy dosage effect in ocular diseases group on the risk of incident stroke

	Stroke events	Total subjects	Crude RR (95% CI)	p value	p for interaction
Chemotherapy use					
0 < DDD ≤ 52.0	19 (10.5)	181	1.00		
52.0 < DDD ≤ 363.5	14 (7.91)	177	0.75 (0.38-1.50)	0.4216	
363.5 < DDD ≤ 920.0	15 (8.38)	179	0.80 (0.41-1.57)	0.5142	
DDD > 920.0	16 (8.94)	179	0.85 (0.44-1.66)	0.6357	0.2927
L02BA01 tamoxifen					
0 < DDD ≤ 312.0	11 (10.28)	107	1.00		
312.0 < DDD ≤ 660.0	5 (4.67)	107	0.45 (0.16-1.31)	0.1438	
660.0 < DDD ≤ 1274.0	9 (8.49)	106	0.83 (0.34-1.99)	0.6704	
DDD > 1274.0	9 (8.49)	106	0.83 (0.34-1.99)	0.6704	
Other chemotherapy drugs	30 (10.34)	290	1.01 (0.5-2.01)	0.9859	0.2691

Average chemotherapy drug dose [defined daily dose (DDD) per day] was calculated as cDDD divided by total drug prescription days. The average chemotherapy drug dose was classified by using two approaches: stratifying the chemotherapy exposure into categorizing the DDD (0 < DDD ≤ 52.0, 52.0 < DDD ≤ 363.5, 363.5 < DDD ≤ 920.0, DDD > 920.0 per day) according to a quartile method. In addition, the quartile method was adopted to classify the L02BA01 tamoxifen of average chemotherapy drug dose (0 < DDD ≤ 312.0, 312.0 < DDD ≤ 660.0, 660.0 < DDD ≤ 1274.0, DDD > 1274.0 per day).
Crude relative risk (RR) and p value were calculated by using Cox proportional hazards regression model. p for interaction: Cox proportional hazards regression model, including DDD or tamoxifen DDD × chemotherapy (without/with ocular diseases) interaction term, was applied. CI, confidence interval.

Supplemental Table 5-1. Ocular diseases predicted risk of incident stroke

	Stroke events (%)	Total subjects	Crude RR (95% CI)	p value	Adjusted RR (95% CI)	p value
Methotrexate						
No	48 (8.6)	559	1.00		1.00	
Yes	16 (10.2)	157	1.19 (0.67-2.09)	0.5529	1.08 (0.61-1.92)	0.7849
Tamoxifen						
No	30 (10.3)	290	1.00		1.00	
Yes	34 (8.0)	426	0.77 (0.47-1.26)	0.3004	1.10 (0.56-2.14)	0.7857
Methotrexate/tamoxifen						
No	18 (9.4)	191	1.00		1.00	
Yes	46 (8.8)	525	0.93 (0.54-1.60)	0.7933	1.24 (0.65-2.36)	0.5189
Ocular diseases						
No	16 (4.5)	358	1.00		1.00	
Yes	48 (13.4)	358	3.00 (1.70-5.28)	0.0001	2.93 (1.66-5.18)	0.0002
Methotrexate/tamoxifen and ocular diseases						
No and No	5 (4.3)	115	1.00		1.00	
Yes and No	11 (4.5)	243	1.04 (0.36-3.00)	0.9404	1.54 (0.51-4.66)	0.4450
No and Yes	13 (17.1)	76	3.93 (1.4-11.04)	0.0092	4.19 (1.49-11.80)	0.0067
Yes and Yes	35 (12.4)	282	2.85 (1.12-7.29)	0.0282	3.75 (1.37-10.26)	0.0099

Adjusted relative risk (RR) and p value were calculated after adjustment for chemotherapy age, sex, hypertension, diabetes mellitus and radiotherapy by using Cox proportional hazards regression model. CI, confidence interval.

Supplemental Table 5-2. Ocular diseases predicted risk of incident stroke

	Crude RR (95% CI)	p	Adjusted RR (95% CI)	p
L01BA01 methotrexate	1.19 (0.67-2.09)	0.5529	0.92 (0.50-1.69)	0.7916
L02BA01 tamoxifen	0.77 (0.47-1.26)	0.3004	1.01 (0.50-2.07)	0.9712
Ocular diseases	3.00 (1.70-5.28)	0.0001	2.96 (1.66-5.26)	0.0002
Chemotherapy at age ≥ 55 years old, n (%)	3.83 (2.05-7.18)	< 0.0001	2.47 (1.29-4.72)	0.0061
Sex, males, n (%)	1.89 (1.12-3.19)	0.0168	1.86 (0.90-3.87)	0.0962
Hypertension, n (%)	3.81 (2.03-7.14)	< 0.0001	2.45 (1.27-4.72)	0.0073
Diabetes mellitus, n (%)	2.27 (1.39-3.70)	0.0010	1.73 (1.04-2.87)	0.0339
Radiotherapy, n (%)	0.37 (0.16-0.87)	0.0220	0.54 (0.23-1.26)	0.1548

Adjusted relative risk (RR) and p value were calculated by using Cox proportional hazards regression model. CI, confidence interval.