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research article

Evaluation of toxic effects of chemotherapy in lung malignancies on cerebral white matter using diffusion tensor imaging

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Radiol Oncol 2022; 56(2): 150-155.

Received 2 December 2021
Accepted 18 March 2022

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Disclosure: No potential conflicts of interest were disclosed.

Background. Non-small cell lung cancer (NSCLC) is a leading cause of morbidity and mortality. Carboplatin and cisplatin based regimens are used in the treatment of NSCLC. The aim of the study was to find out whether there is a difference in white matter (WM) changes between two platinum-based chemotherapy agents using diffusion tensor imaging (DTI).

Patients and methods. 25 patients who received chemotherapy for NSCLC and 27 age-matched healthy controls were enrolled in the study. Fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD) and radial diffusivity (RD) values of the study population were measured from 11 regions of interest in pre-chemotherapy and post-chemotherapy MRI data.

Results. Cisplatin group showed a significant decrease in the FA of the inferior longitudinal fasciculus (P = 0.028). Carboplatin group showed a significant FA decrease and RD increase in the forceps minor (P = 0.022 and P = 0.011, respectively), and a significant reduction in AD and increase in MD in frontal white matter (WM) (P = 0.008 and P = 0.029, respectively). In comparison of post chemotherapy DTI values of the two groups, carboplatin group showed lower FA, and higher MD and RD values than cisplatin group in parieto-occipital WM (P = 0.034, P = 0.034, P = 0.029, respectively).

Conclusions. The findings of the study suggest that subtle effects of chemotherapy detectable with DTI may emerge after the treatment. In addition, carboplatin regimen may have more impact on WM than cisplatin regimen.

Key words: diffusion tensor imaging; chemotherapy; carboplatin; cisplatin; carcinoma; non-small-cell lung cancer

Introduction

Chemotherapy has a substantial role in cancer treatment. Chemotherapeutic agents have increased the survival in most types of cancers and provided symptomatic relief. However, these agents have potential to harm normal tissue cells while removing the tumor. Damage to normal neuronal structure or function is a well-known side effect of chemotherapeutic agents.[1-3] Progressive structural damage to the cerebral white matter (WM) is called leukoencephalopathy and caused by various chemotherapeutic agents. Methotrexate, vincristine, ifosfamide, fludarabine, cytarabine, 5-fluorouracil (5-FU) and cisplatin are known to be main contributors to chemotherapy induced toxic leukoencephalopathy.[4,5]

With the widespread use of MRI and advancing technology, the effects of chemotherapy on cerebral WM are better demonstrated. The appearance

of chemotherapy-induced WM abnormality is bilateral hyperintensity on T2-weighted and FLAIR images, which may be focal or, in later stages, confluent and symmetrical. In addition to these visible effects, chemotherapy is also said to have subtle effects on WM revealed by diffusion tensor imaging (DTI).[6] DTI is a quantitative MRI technique enabling the visualization and characterization of the WM fasciculi via the self-diffusion of water molecules.[7] It is a sensitive method to determine microstructural injury to WM tracts. Fractional anisotropy (FA) is the most widely used DTI index and represents the fraction of the tensor that can be assigned to anisotropic (directional) diffusion.[8] Axial diffusivity (AD), mean diffusivity (MD) and radial diffusivity (RD) are other parameters that enhances exploring tissue microstructure.

Non-small cell lung cancer (NSCLC) is a leading cause of morbidity and mortality. Carboplatin and cisplatin based regimens are used in the treatment of NSCLC. Our study aimed to find out whether there is a difference between two platin based chemotherapy agents in cerebral white matter changes using DTI.

Patients and methods

Patients

This study was approved by our institutional ethical board. 25 patients (20 men, 5 women, mean age 60.9 ± 9.5 years) who received chemotherapy for NSCLC and 27 age-matched healthy controls (20 men, 7 women, mean age 58.4 ± 8.8 years) were enrolled in the study.

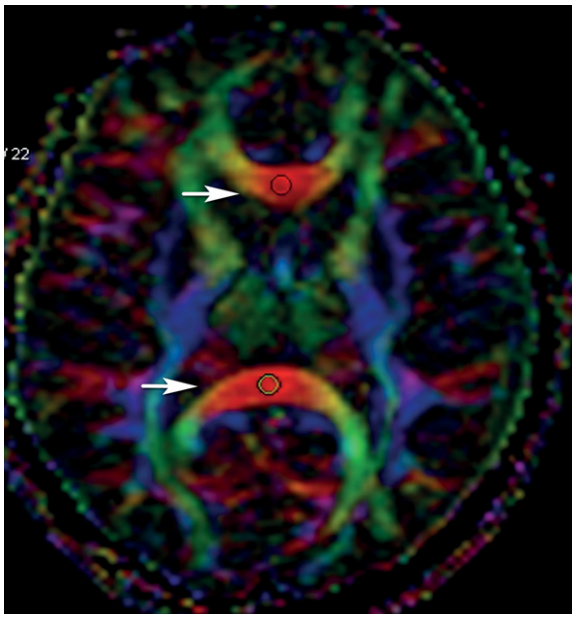

FIGURE 1. Fractional anisotropy value measurement at the genu and splenium of corpus callosum (circles).

The normal MRI examinations of the age and sex-matched control group were selected from the PACS of our institution. The information about the control group was checked from the hospital information system. Patients with diabetes mellitus or hypertension, previous history of cancer, history of traumatic brain injury, neurologic or cerebrovascular disease were excluded from the study. Any contraindications, such as pacemakers, metallic implants, claustrophobia and MRI contrast allergy were ruled out before the MRI examination.

Of NSCLC group, 7 received cisplatin regimen (group 1, cisplatin with gemcitabine or etoposide or pemetrexed), 18 received carboplatin regimen (group 2, carboplatin with paclitaxel). None of the patients received cranial irradiation. A pre-chemotherapy MRI examination had been performed in all 25 patients to exclude brain metastases. Patients were examined in 6 months after completion of chemotherapy.

Image acquisition

All patients were scanned on a 1.5 T MR scanner (Siemens, Avanto, Erlangen, Germany) with a maximum gradient strength of 43 mT/m and an 18-channel head coil. The conventional MRI protocols included T2-weighted turbo spin echo (repetition time [TR] = 2500 ms, echo time [TE] = 80 ms), FLAIR images (TR = 8000 ms, TE = 90 ms), T1-weighted spin echo (TR = 460 ms, TE = 14 ms), T1-weighted with fat suppression (TR = 715 ms, TE = 7.5 ms). NSCLC patients were added post-contrast T1-weighted images. DTI data were acquired by using a single-shot spin-echo, echo-planar imaging sequence with the following parameters: TR = 2700 ms, TE = 89 ms; a matrix size of 128×128; field of view of 230 mm, slice thickness 5 mm and 30 diffusion-encoding directions were used at b = 0 s/mm^2 and b = 1000 s/mm^2. The DTI data were transferred to a Leonardo console (software version 2.0; Siemens) and the color-coded FA maps were reconstructed. Regions of interest along the following locations were drawn bilaterally for evaluation of FA: inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), forceps minor, anterior thalamic radiation (ATR), anterior corona radiata (ACR), external capsule, inferior fronto-occipital fasciculus (IFOF), genu and splenium of corpus callosum (CC), cerebral white matter in frontal

TABLE 1. Fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD) and radial diffusivity (RD) values of the defined regions of interest in the patients with non-small cell lung cancer (NSCLC) and the control group

Regions of interest	NSCLC patients (n = 25)				Control (n = 27)			
	FA	AD	MD	RD	FA	AD	MD	RD
R ILF	591.86±74.62	1500.75±122.17	863.76±65.15	545.27±96.29	575.66±79.55	1458.45±131.20	843.76±76.46	536.41±93.74
L ILF	600.06±59.94	1529.15±173.76	868.6±97.02	538.32±103.53	613.26±80.83	1543.02±136.96	856.6±105.47	513.38±125.10
R SLF	558.53±114.37	1299.28±201.73	754.18±67.60	481.63±88.42	595.02±87.69	1411.18±141.51	792.77±46.74	483.57±74.45
L SLF	532.01±118.55	1299.01±173.29	778.50±71.55	518.24±110.51	591.15±96.81	1416±149.16	795.97±59.44	485.95±82.96
R FM	554.53±100.65	1338.19±156.48	769.57±105.53	512.13±99.98	629.28±151.29	1508.51±288.33	813.40±80.35	465.84±139.28
L FM	507.28±109.36	1307.52±188.16	807.18±63.09	557.02±109.36	653.10±173.43	1605.51±322.02	836.1±86.54	451.52±168.22
R ATR	340.74±88.42	1103.33±81.11	808.82±52.68	661.56±75.32	356.29±93.06	1079.83±101.61	785.80±60.54	638.79±74.98
L ATR	346.5±80.36	1106.73±129.93	787.19±107.16	654.76±99.75	370.34±99.10	1106.84±127.16	795.80±78.49	640.28±91.63
R ACR	462.64±165.21	1257.80±260.67	796.58±212.71	593.33±239.64	474.52±112.45	1189.22±123.22	766.57±64.26	555.24±93.58
L ACR	426.54±118.96	1132.28±137.42	771.2±75.36	590.67±106.29	493.42±113.02	1204.54±150.69	762.29±68.51	541.17±86
R EC	421.5±103.19	1186.76±131.98	801.44±49.57	608.78±75.25	467.90±76.67	1206.38±142.25	785.90±67.27	575.67±66.99
L EC	473.82±92.65	1207.59±112.50	775.09±67.91	558.84±93.05	496.03±82.19	1220.38±150.32	766.20±69.01	539.11±75.26
R IFOF	492.68±71.61	1265.71±107.18	790.68±68.32	553.16±80.63	518.93±69.64	1319.51±149.14	803.93±64.48	546.14±61.75
L IFOF	475.18±85.00	1235.06±108.44	786.80±56.69	562.67±77.186	492.90±88.55	1305.21±143.83	817.78±68.26	574.07±80.16
G CC	805.78±79.27	1773.6±231.49	799.20±135.38	312±138.14	792.98±56.11	1810.47±167.43	822.28±72.58	328.19±75.54
S CC	806.87±83.00	1862.29±206.96	832.26±115.01	317.24±143.53	845.36±49.03	1823.75±243.74	775.42±113.42	251.25±81.05
R FWM	383.34±89.30	1171.85±148.03	822.22±66.41	647.41±81.58	388.92±109.23	1137.18±106.56	798.74±61.26	629.51±98.77
L FWM	377.06±89.53	1143.71±126.45	810.22±55.30	643.47±69.93	399.48±116.43	1147.24±114.15	798.29±78.91	623.81±114.37
R POWM	353.36±76.49	1155.84±130.45	837.16±70.62	677.82±70.49	394.78±91.19	1182.94±193.23	818.38±108.45	636.1±103.87
L POWM	344.49±75.64	1142.25±122.83	834.81±74.07	681.09±75.55	388.00±89.02	1254.38±148.62	871.37±93.75	679.86±102.15

ACR = anterior corona radiata; ATR = anterior thalamic radiation; CC = splenium of corpus callosum; EC = external capsule; FM = forceps minor; G CC = genu of corpus callosum; IFOF = inferior fronto occipital fasciculus; ILF = inferior longitudinal fasciculus; L = left; POWM = parieto-occipital white matter; R = right; S CC = superior corpus callosum; S FWM = superior frontal white matter; SLF = superior longitudinal fasciculus

(FWM) and parieto-occipital regions (PWM). AD, MD and RD indices were calculated from the tensor using eigenvalues (λ_1, λ_2, and λ_3): AD is λ_1, MD is $(\lambda_1+\lambda_2+\lambda_3)/3$, and RD is $(\lambda_2+\lambda_3)/2$. The regions of interest (ROIs) were drawn manually on the axial FA map by the same radiologist (Figure 1). Sizes of all ROIs were kept constant.

Statistical analysis

Statistical analyzes were performed by using IBM SPSS Version 22.0. Descriptive statistics were presented as mean and standard deviation. Nonparametric tests were used for non-normally distributed data. The DTI measurements obtained from the control group and the patients' pre-chemotherapy MRI were compared with Mann-Whitney test. The DTI data obtained from the patients' pre-chemotherapy and post-chemotherapy MRI were compared by Wilcoxon rank sum test. *P* values less than 0.05 were accepted as significant.

Results

The mean FA, AD, MD and RD values of patients before receiving chemotherapy and of the control group are summarized in Table 1.

There was no statistical difference in the DTI data of the defined anatomical locations between the control group and the pre-chemotherapy measurements of the NSCLC patients.

In comparison of the DTI data of group 1 before and after chemotherapy, there was a significant decrease in the FA value of the right inferior longitudinal fasciculus ($P = 0.028$).

In group 2, there was a significant FA decrease and RD increase in the right forceps minor ($P = 0.022$ and $P = 0.011$, respectively). We found significant reduction in AD and increase in MD values in the right FWM ($P = 0.008$ and $P = 0.029$, respectively) (Table 2).

In comparison of post-chemotherapy DTI values of the two groups, group 2 showed lower FA

TABLE 2. Comparison of diffusion tensor imaging (DTI) values of the defined anatomic locations before and after chemotherapy (the significant results are in italics)

Group 1 (n:7)				Group 2 (n:18)			
Region of interest	Pre-chemotherapy values (Median (min-max))	Post-chemotherapy values (Median (min-max))	*P* value	Regions of interest	Pre-chemotherapy values (Median (min-max)	Post-chemotherapy values (Median (min-max)	*P* value
R ILF FA	623 (514–703.3)	522 (418.7–679.8)	*0.028*	R ILF FA	600 (395.3–694.5)	593 (336–707)	0.89
R FM FA	539 (448–591)	471 (379.7–615.8)	0.31	R FM FA	525 (454.5–864)	487 (322.3–712)	*0.022*
R FM RD	487.4 (465.5–605.65)	619.4 (439.5–667.85)	0.062	R FM RD	533.275 (201–689)	580.35 (367.8–819.15)	*0.011*
R FWM AD	1123.5 (912.8–1244)	1135.5 (988.3–1265.5)	0.39	R FWM AD	1157.65 (1011.3–1556.5)	1104.15 (854.8–1256.3)	*0.008*
R FWM MD	786.1 (699.1–871.26)	823.26 (658.93–855.1)	0.31	R FWM MD	793.01 (658.2–955.36)	812.33(704.53–1006.9)	*0.029*

AD = axial diffusivity; FA = Fractional anisotropy; FM = forceps minor; FWM = frontal white matter; ILF = inferior longitudinal fasciculus; MD = mean diffusivity; R = right; RD = radial diffusivity

($P = 0.034$), and higher MD ($P = 0.034$) and RD ($P = 0.029$) values than group 1 in the parieto-occipital WM (Table 3).

TABLE 3. Comparison of the diffusion tensor imaging (DTI) results of the two chemotherapy regimens on the defined anatomic locations (only the significant results are shown)

Region of interest	Cisplatin	Carboplatin	*P*
Left POWM FA	389 (273.3–531)	319 (167.3–423)	0.034
Left POWM MD	767.6 (727.53–925.27)	837.13 (737.2–1071.77)	0.034
Left POWM RD	606.1 (507.9–726.65)	705.92 (592.80–905.15)	0.029

FA = Fractional anisotropy; MD = mean diffusivity; POWM = parieto-occipital white matter; RD = radial diffusivity

Discussion

Neurotoxic side effects such as peripheral neuropathy and cerebral WM changes may frequently be encountered during chemotherapy and cause the clinician to reduce agent dose. Recent neuroimaging studies reported the association between chemotherapy and structural brain changes.[9-11] Methotrexate (MTX) is the most frequent cause of neurotoxicity. High-dose MTX chemotherapy shows side effects range from asymptomatic WM changes to severe demyelination. 5-FU is another important leukoencephalopathy causative agent. High dose cisplatin therapy may also cause WM myelin destruction. It may cause posterior reversible leukoencephalopathy syndrome manifested by bilateral reversible abnormalities in the occipital, parietal, and frontal WM.

In addition to neurons, WM contains oligodendrocytes, which produce and maintain myelin, and microglia which function as the macrophages and maintain active immune defense. Chemotherapy is thought to injure microglia, oligodendrocytes, and neuronal axons with direct neurotoxic effect.[12] It is also supposed to impair normal oligodendrocyte regulation.[13] In an autopsy series with leukoencephalopathy due to chemotherapy, postmortem brains demonstrated swollen axons, focal demyelination with edema, myelin pallor, macrophage infiltrate, and gliosis.[14]

DTI both enables anatomically delineation of WM tracts and detection of subtle changes in their microstructure associated with brain development, degeneration, and injury.[15] FA represents the fraction of the tensor that can be assigned to directional diffusion[8] and is highly sensitive to microstructural changes.[16,17] Decreased FA is attributed to WM damage.[18] RD increase is said to be a response to demyelination and dysmyelination and may accompany FA decrease.[19] AD is another metric that refers to identify axonal damage or degeneration. MD is inverse measure of the membrane density and fluid viscosity. It is sensitive to cellularity, edema, and necrosis. Simó *et al.*[9] compared small cell lung cancer patients with NSCLC and healthy controls in terms of FA, RD and AD changes and cognitive functions. Lung cancer patients both receiving and not receiving chemotherapy showed higher AD and lower FA values in left inferior longitudinal fasciculus when compared with healthy controls. Additionally, patients who were taking platinum-based chemotherapy were compared with healthy control, and higher AD values were obtained in left cingulum. The authors concluded that deterioration of WM integrity began with the disease and proceeded with chemotherapy. In contrast with their study, our findings suggest no difference between the patients and healthy control

at baseline. This may be due to genetic variability among patients, variations in the immune response of the patients to the cancer disease, and differences in oxidative and inflammatory processes. However, we detected carboplatin was associated with FA decrease and RD increase in forceps minor, and cisplatin was associated with FA decrease in inferior longitudinal fasciculus. In our study, decreased FA values in forceps minor and inferior longitudinal fasciculus may indicate white matter disintegration, axonal degeneration and axonal structural irregularity, demyelination, edema, inflammation, and gliosis of these fibers.[20,21] Madden *et al*.[22] proposed that associative WM pathways are vulnerable to the accumulation of metabolic damage. Inferior longitudinal fasciculus is an important associative fiber that connects the occipital lobe with the anterior part of the temporal lobe. As a late myelinating part of the brain, it may be more susceptible to degenerating effects of toxic agents like chemotherapy.

While Simó *et al*.[9] did not report such an association, our study demonstrated that carboplatin was associated with reduction in AD and increase in MD in frontal white matter. Axonal injury decreases AD, and axonal degeneration and demyelination increase MD values. As mentioned before, carboplatin was associated with similar changes in forceps minor which is a white matter fiber bundle connecting the lateral and medial surfaces of the frontal lobes and receives fibers from the genu of the corpus callosum. Forceps minor is also related with cognitive dysfunction. This result may strengthen the hypothesis that neurocognitive disfunction developing in lung cancer patients after chemotherapy is associated with WM damage.

Of note, in the comparison of the post chemotherapy DTI data of the two regimens, the subtle destructive effects of carboplatin on parieto-occipital WM was more prominent than cisplatin. Carboplatin was associated with significant decrease in FA, and increase in MD and RD values that may be attributed to axonal degeneration and demyelination. Although carboplatin is said to be associated with a lower incidence of serious side effects than cisplatin, it seemed to be associated with more neurotoxicity in the posterior WM regions.[23]

There are three major limitations of our study. Firstly, the study had a retrospective design. Secondly, the study population was small. Future attempts for prospective studies with larger cohorts may be encouraged. Thirdly, the study design did not comprise neurocognitive testing.

Conclusions

Some disadvantages of chemotherapy which occur with system toxicities are extensively known. Our findings suggest that subtle effects of chemotherapy detectable with DTI may emerge in early periods of treatment. In addition, carboplatin regimen may have more toxic impact on WM than cisplatin regimen. These findings may be important in the planning and monitoring of future chemotherapy regimens. DTI guides to conceive subtle microstructural alterations and may be useful for understanding neurocognitive disfunctions that may be caused by chemotherapy. To investigate functional neurocognitive outcomes may be a future perspective.

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