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Chemotherapeutic drugs that penetrate the blood–brain barrier affect the development of hyperactive delirium in cancer patients

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ABSTRACT

Objective: Delirium is a frequently encountered psychiatric disease in terminal cancer patients. However, the mechanism of delirium is unclear. The aim of our study was to investigate the relationship between administration of chemotherapy drugs that penetrate the blood–brain barrier (BBB) and the development of delirium in cancer patients.

Method: We retrospectively analyzed 166 cancer patients (97 males, 69 females) continuously who died between September of 2007 and January of 2010 using a review of medical charts. Multiple logistic regression analysis was employed to investigate the effects of antineoplastic drugs penetrating the BBB on development of delirium in cancer patients with control for other risk factors.

Results: In multivariate analysis, antineoplastic drugs that penetrated the BBB were significantly associated with development of delirium ($OR = 18.92$, $CI_{95} = 1.08–333.04$, $p < 0.001$).

Significance of results: The use of chemotherapy drugs that penetrate the BBB may be a risk factor for delirium. This information may allow palliative care doctors and medical oncologists to predict which patients are at increased risk for delirium.

KEYWORDS: Cancer patients, Chemotherapeutic drugs, Delirium, Blood–brain barrier, P glycoprotein

INTRODUCTION

Delirium is a frequent neurological complication in hospitalized cancer patients (Clouston et al., 1992) and occurs in up to 85% of cancer patients during their last weeks of life (Massie et al., 1983). The probability of developing delirium is determined by the combined effects of predisposing or vulnerability factors such as age and previous cognitive dysfunction or dementia; incident factors such as drug toxicity and metabolic abnormalities; and other conditions that are often associated with the severity of the underlying illness (Inouye et al., 1993; American Psychiatric Association., 2000). However, the mechanism of delirium remains unclear.

Metaanalyses have shown that women who undergo adjuvant chemotherapy for breast cancer may experience a subtle yet consequential cognitive

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decline (Falleti et al., 2005; Stewart et al., 2006). Thus, cancer patients who receive chemotherapy are at high risk of a treatment-induced decrease in cognitive function. However, few studies have investigated development of delirium following chemotherapy. Furthermore, most such studies are case reports or have no control group and are limited to specific antineoplastic drugs.

Chemotherapeutic agents including methotrexate, fluorouracil, vincristine, vinblastine, bleomycin, bischloronitrosourea, cisplatin, ifosfamide, interferon, asparaginase, and procarbazine have been reported to cause delirium in single case reports or studies with small populations (Brunner & Young, 1965; Holland et al., 1974; Stolinsky et al., 1974; Greenwald, 1976; Yamada et al., 1979; Berman & Mann, 1980; Priestman, 1980; Heim et al., 1981; Silberfarb, 1983). Some larger studies showed the possibility of developing delirium due to the use of vincristine and vinblastine, as well as combinations of vincristine and high-dose methotrexate plus citrovorum factor rescue (Frei et al., 1961; Holland et al., 1973; Allen & Rosen, 1978).

In an evaluation of the records of 100 consecutive hospitalized cancer patients referred for psychiatric consultation, another study found that delirium was frequently misdiagnosed as depression, was not recognized, or was recognized but undertreated (Levine et al., 1978). To avoid missing an organic brain syndrome, the importance of examining the mental status of all patients as a routine procedure was emphasized. However, this study did not take into account a possible relationship between chemotherapy and delirium.

Aging, systemic diseases, and ischemic brain injury can disrupt the blood–brain barrier (BBB) and result in a decline in overall BBB function and integrity, as shown by Zeevi and coworkers (2010). Their evidence linked deficits in the cerebral microvasculature and BBB integrity with dementia, medication-related cognitive decline, white matter disease, and related geriatric syndromes (including delirium and gait disorders). Temozolomide, lapatinib, topotecan, nitroso derivatives, tamoxifen, idarubicin and methotrexate can penetrate the BBB (Lin et al., 2004; Wong & Berkenblit, 2004), and capecitabine has been shown to cause changes in the brain by penetrating the BBB (Ekenel et al., 2007). However, the relationship between delirium and the use of chemotherapy drugs that penetrate the BBB has not been examined sufficiently. Therefore, the objective of our study was to investigate the effects of chemotherapy, in particular with agents that penetrate the blood–brain barrier, and other risk factors on the development of delirium in cancer patients.

DESIGN

We retrospectively analyzed continuous data for 166 cancer patients (97 males, 69 females) who were hospitalized and died at the palliative care unit at Kinki University Sakai Hospital between September of 2007 and January of 2010. Patients were ineligible if they had cognitive dysfunction (e.g., dementia). Two psycho-oncologists reviewed medical charts and diagnosed delirium according to DSM–IV–TR criteria. The effects of anticipated risk factors on development of delirium in cancer patients were investigated. Utilization of hormone therapy, a molecular-targeted drug, and an antineoplastic agent were considered to be chemotherapy. Patients treated with an antineoplastic drug as neoadjuvant or adjuvant therapy were also included in the chemotherapy group, and those treated at least once with a drug that penetrates the BBB were placed in the BBB group (Lin et al., 2004; Wong & Berkenblit, 2004; Ekenel et al., 2007).

Patients exposed to corticosteroids at daily doses greater than 15 mg had a 2.7-fold increase in the risk of developing delirium, compared with patients exposed to smaller doses (Gaudreau et al., 2005). Therefore, daily use of betamethasone in doses larger than 2 mg (almost equal effect to 15 mg corticosteroids) to treat an illness was considered "steroid use," but steroid treatment employed in combination with chemotherapy was defined as "non-steroid use," because daily steroid doses were not larger than 15 mg.

Many potentially important delirium risk factors within one week of onset of delirium were included in our analysis, including infections, anemia, and metabolic abnormalities (hepatic function, renal function, electrolyte imbalance, and dehydration), hypooxgenation, and intracranial disease. Patients with a specific cause of delirium and those with delirium induced by medication, such as that occurring immediately after opioid treatment (within one week before), were excluded to investigate the effects of chemotherapy alone.

Clinically, it is difficult for medical staff such as nurses and oncologists without expertise in delirium to discern hypoactive delirium. Therefore, we limited our study to hyperactive and mixed-type delirium. We also excluded cases of delirium occurring within two weeks before death, because it is difficult to identify a single cause of delirium in an end-term cancer patient (Lawlor et al., 2000).

Our study was approved by the institutional review board of the Kinki University Faculty of Medicine. Because this was a retrospective study using variables obtained during routine clinical practice, written informed consent was not required according

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to the ethics guidelines for epidemiological studies developed by the Japanese Ministry of Labor, Health, and Welfare. Instead, the study was disclosed on the website of Kinki University Hospital built to receive requests for withdrawal from the study by a patient's family.

Measurements

Logistic regression analysis was performed using univariate and multivariate models with development of delirium as the dependent variable. Age, sex, use of steroids, use of opioids, use of antineoplastic drugs penetrating the BBB, use of antineoplastic drugs not penetrating the BBB, and ECOG performance status were included as independent variables. A two-sided significance level of 0.05 was utilized. All statistical analyses were conducted using SPSS software (v. 19.0; SPSS Japan Inc., Tokyo).

Table 1. *Demographic and clinical characteristics of patients* (n = *166)*

Variable	Data	
Age (years)[a]	68.4 ± 11.6	
Gender		
Male	97	58%
Female	69	42%
Use of steroid drugs		
Yes	116	70%
No	50	30%
Use of opioid drugs		
Yes	107	64%
No	59	36%
Use of psychotropic drugs		
Yes	56	34%
No	110	66%
Use of antiepileptic drugs		
Yes	49	30%
No	117	70%
Undergoing chemotherapy		
Yes	114	69%
No	52	31%
Development of delirium		
Yes	58	35%
No	108	65%
ECOG performance status		
1 to 2	132	80%
3 to 4	34	20%
Days from initiation of chemotherapy to development of delirium[b]	570	244–1262
Primary tumor site		
Lung	41	24.7%
Stomach	29	17.5%
Colon	29	17.5%
Breast	21	12.7%
Pancreas	9	5.4%
Urological	8	4.8%
Gynecological	7	4.2%
Liver	6	3.6%
Neck	4	2.4%
Gall bladder duct	3	1.8%
Esophagus	2	1.2%
Unknown	3	1.8%
Other	4	2.4%

Data are shown as a number and percentage, unless indicated as [a] mean ± *SD*, [b] median and interquartile range.

RESULTS

Patient Characteristics

The demographic, disease, and treatment information for the 166 cancer patients are shown in Table 1. Characteristics were assessed at time of death. Performance status was documented at the first medical examination. Some 114 patients received chemotherapy. The drugs employed for chemotherapy are shown in Table 2.

Risk Factors for Delirium (see Table 3)

In the multiple logistic regression model, antineoplastic drugs that penetrate the BBB were significantly associated with development of delirium (odds ratio, 18.92; CI_{95} = 1.08–333.04; $p < 0.001$). Patients suffering from metabolic abnormalities and dehydration were also significantly more likely to develop delirium in the multivariate model.

DISCUSSION

The present study demonstrated that chemotherapy with agents that penetrate the BBB may be a risk factor for development of delirium in cancer patients. There is growing evidence in the medical literature for increased incidence of cognitive decline—so-called "chemobrain" or "chemofog"—in cancer

Table 2. *Agents used in the 114 treatment groups*[a]

Variable	BBB	Number
Carboplatin/cisplatin	Nonpenetrating	63
Taxane	Nonpenetrating	60
Irinotecan	Nonpenetrating	34
Oxaliplatin	Nonpenetrating	27
Fluorouracil/S-1	Nonpenetrating	26
Capecitabine	Penetrating	26
Gemcitabine	Nonpenetrating	23
Anthracycline	Nonpenetrating	20
Vinorelbine	Nonpenetrating	12
Topotecan	Penetrating	5
Others	Penetrating	3
	Nonpenetrating	7

[a] Some patients received multiple drugs. BBB = blood–brain barrier.

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Table 3. *Results of multiple logistic regression analysis*

Variable	Univariate Model			Multivariate Model		
	Odds Ratio	95% Confidence Interval	*p* Value	Odds Ratio	95% Confidence Interval	*p Value*
Age (years)						
<70	1.0			1.0		
≥70	1.07	0.56–2.02	0.884	1.46	0.49–4.39	0.496
Gender						
Female	1.0			1.0		
Male	1.29	0.67–2.47	1.288	1.21	0.39–3.75	0.740
Use of steroid drugs						
No	1.0			1.0		
Yes	1.21	0.60–2.44	0.602	1.08	0.31–3.82	0.90
Use of opioid drugs						
No	1.0			1.0		
Yes	4.69	2.10–10.50	<0.001	2.85	0.82–9.90	0.100
Use of psychotropic drugs						
No	1.0			1.0		
Yes	5.54	2.75–11.17	<0.001	1.71	0.58–5.03	0.328
Use of antiepileptic drugs						
No	1.0			1.0		
Yes	10.22	4.73–22.06	<0.001	3.42	0.58–20.01	0.173
Use of antihistamine drugs						
No	1.0			1.0		
Yes	7.47	2.96–18.86	<0.001	1.28	0.14–11.37	0.827
Hypooxgenation						
No	1.0			1.0		
Yes	3.46	1.68–7.14	<0.001	0.93	0.28–3.13	0.933
Metabolic abnormalities (electrolyte imbalance, hepatic dysfunction, renal dysfunction etc)						
No	1.0			1.0		
Yes	3.12	1.61–6.06	0.001	4.30	1.43–12.96	0.009
Infections						
No	1.0			1.0		
Yes	9.58	4.07–22.54	<0.001	2.83	0.79–10.12	0.112
Dehydration (BUN/Cr ratio > 20)						
No	1.0			1.0		
Yes	8.76	4.17–18.38	<0.001	5.16	1.83–14.59	0.002
Anemia						
No	1.0			1.0		
Yes	6.71	3.14–14.38	<0.001	2.83	0.11–3.69	0.612
Intracranial disease (brain metastases etc)						
No	1.0			1.0		
Yes	13.68	4.39–42.62	<0.001	3.16	0.56–17.82	0.193
ECOG performance status						
PS1-2 ($n = 132$)	1.0			1.0		
PS3-4 ($n = 34$)	1.16	0.52–2.58	0.72	1.05	0.24–4.56	0.947
No chemotherapy						
($n = 52$)	1.0			1.0		
Chemotherapy with drugs that do not penetrate the blood–brain barrier						
($n = 83$)	3.70	1.41–9.72	0.008	2.58	0.24–27.19	0.432
Chemotherapy with drugs that penetrate the blood–brain barrier						
($n = 31$)	31.94	9.32–109.50	<0.001	18.92	1.08–333.04	<0.001

survivors that results from chemotherapy (Argyriou et al., 2010). A study by Wefel and colleagues (2004) showed that at 3 weeks postchemotherapy, 61% of participants experienced a decline in certain cognitive skills, including verbal and visual memory, executive function, visuospatial ability, and information-processing speed. A prospective, multicenter, longitudinal study using 12 neuropsychological tests showed that chemotherapy-induced cognitive impairment affected 27% of 101 patients with breast cancer after neoadjuvant chemotherapy (Hermelink et al., 2007). Another review showed that impairment induced by chemotherapy significantly affected visual memory only (Jansen et al., 2005). These studies investigated the association between chemotherapy and slight cognitive dysfunction detected

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by specialized tests. However, prior to our current study, descriptions of delirium after chemotherapy have been limited to case reports. Few macromolecules are transferred into the brain because vesicular transcytosis in the endothelial cells is considerably limited, and the tight junction is located between the endothelial cells. In addition, there are several types of influx or efflux transporters at the BBB, such as P-glycoprotein (P-gp), multidrug resistance-associated protein, and breast cancer-resistant protein (Cordon-Cardo et al., 1989; Ueno, 2009). The reason for the developing delirium might be a disruption of the BBB that leads chemotherapy drugs into brain tissue and results in accumulation of high levels of these drugs within the brain.

There are several limitations of our study. First, this study was not prospective but retrospective in design and employed chart review. The diagnosis of delirium could thus be unreliable, a factor that could not be overcome. Second, we did not investigate differences among duration of illness, presence of comorbidities, duration of the use of drugs, and the patient's psychosocial background (e.g., educational level and employment status). Third, several potentially important delirium risk factors were not taken into account in the analysis, including opioid dose and pain. Fourth, exposure to chemotherapy was not sufficiently examined, with no information included on dose, duration, and route, all of which may have had an impact on delirium onset. Fifth, the temporal link between chemotherapy and delirium that occurs 570 days later may be uncertain. Finally, we limited the study to cases of hyperactive and mixed-type delirium because of the difficulty involved in diagnosing hypoactive delirium by general medical staff. Further studies are needed to clarify the effects of these factors.

In conclusion, our findings suggest that chemotherapy agents that penetrate the BBB can be a risk factor for development of delirium. This information may allow palliative care doctors and medical oncologists to predict which patients are at increased risk of developing delirium.

DISCLOSURE STATEMENT

The authors have no competing financial interests to declare.

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