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Risk factors for nausea and vomiting requiring the daily administration of 5-HT_3 receptor antagonists in radiotherapy combined with temozolomide for high-grade glioma

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ABSTRACT

Radiotherapy combined with temozolomide (TMZ+RT) is the primary treatment for high-grade glioma. TMZ is classified as a moderate emetic risk agent and, thus, supportive care for nausea and vomiting is important. In Nagoya University Hospital, all patients are treated with a 5-hydroxy-tryptamine 3 receptor antagonist (5-HT_3RA) for the first 3 days. The daily administration of 5-HT_3RA is resumed after the 4th day based on the condition of patients during TMZ+RT. Therefore, the present study investigated risk factors for nausea and vomiting in patients requiring the daily administration of 5-HT_3RA. Patients with high-grade glioma who received TMZ+RT between January 2014 and December 2019 at our hospital were included. Patients were divided into two groups: a control group (patients who did not resume 5-HT_3RA) and resuming 5-HT_3RA group (patients who resumed 5-HT_3RA after the 4th day), and both groups were compared to identify risk factors for nausea and vomiting during TMZ+RT. There were 78 patients in the control group (68%) and 36 in the resuming 5-HT_3RA group (32%). A multivariate analysis of patient backgrounds in the two groups identified age <18 years, PS 2 or more, and occipital lobe tumors as risk factors for nausea and vomiting. Nausea and vomiting were attenuated in 30 patients (83%) in the resuming 5-HT_3RA group following the resumption of 5-HT_3RA. The results obtained highlight the importance of extracting patients with these risk factors before the initiation of therapy and the early resumption or daily administration of 5-HT_3RA according to the condition of each patient.

Keywords: temozolomide, glioma, 5-hydroxy-tryptamine 3 receptor antagonist, nausea and vomiting, antiemetic

Abbreviations:
D_2RA: dopamine D_2 receptor antagonist
5-HT_3RA: 5-hydroxy-tryptamine 3 receptor antagonist
MARTA: multi-acting receptor-targeted antipsychotics
PS: performance status
TMZ+RT: temozolomide combination chemoradiotherapy

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INTRODUCTION

Temozolomide is an anticancer drug classified as an alkylating agent, that is primarily used to treat malignant gliomas. High-grade glioma is treated with initial and maintenance therapy. Initial therapy is radiotherapy combined with temozolomide (TMZ+RT; TMZ 75 mg/m^2 + RT 54–60 Gy/30 fr) for 42–49 days, followed by a rest period of 4 weeks. After initial therapy, temozolomide 150–200 mg/m^2 is administered as maintenance therapy for 5 days, followed by a rest period of 23 days as 1 cycle, for a total of 6 cycles. Among the dosage forms of temozolomide, including capsules, tablets, and injections, oral agents that are easy to administer are often selected.

In the 2016 Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) Antiemetic Guidelines,[1] oral and injectable preparations of temozolomide are classified as moderate emetic risk (30–90%), while cranial irradiation is associated with a low emetic risk (30–60%). Therefore, antiemetic measures are required for TMZ+RT. In addition, the brain tumor itself is regarded as a risk factor for nausea and vomiting, and, thus, appropriate management is needed. The 2016 MASCC/ESMO Antiemetic Guidelines[1] recommend the combined use of a 5-hydroxy-tryptamine 3 receptor antagonist (5-HT$_3$RA) and dexamethasone as antiemetic therapy for moderate-risk anticancer drugs in adult patients. The National Comprehensive Cancer Network Guidelines version 2.2022 Antiemesis[2] recommend daily 5-HT$_3$RA as antiemetic therapy for moderate-risk oral anticancer drugs.

Patients receive TMZ+RT for 42–49 days, which requires the long-term concomitant administration of 5-HT$_3$RA; however, limited information is currently available on the safety of the long-term use of 5-HT$_3$RA. Therefore, the upper limit of the number of days for the administration of oral 5-HT$_3$RA is specified in the Japanese package insert: 6 days in principle for granisetron tablets (excluding administration before irradiation), and 5 days in principle for ramosetron oral disintegration tablets. Furthermore, the long-term administration of oral 5-HT$_3$RA is not covered by the national health insurance system in Japan. On the other hand, dexamethasone is often administered for therapeutic purposes, such as cerebral edema, in glioma patients and is rarely used for antiemetic purposes.

In our hospital, all patients receive 5-HT$_3$RA treatment for the first 3 days. 5-HT$_3$RA is only resumed after the 4th day and administered daily based on decisions by the attending physician or recommendation by pharmacist according to the condition of patients during TMZ+RT. While many patients in our hospital complete TMZ+RT without developing nausea or vomiting, the daily administration of 5-HT$_3$RA is resumed for some patients who develop nausea and vomiting after the 4th day. However, the actual status of specific patient backgrounds is unknown. Therefore, the present study investigated risk factors for nausea and vomiting in patients who required the daily administration of 5-HT$_3$RA. The need and effective for the daily administration of 5-HT$_3$RA after the 4th day in patients who developed nausea and vomiting was also examined.

METHODS

Patients

Patients who started TMZ+RT during hospitalization at Nagoya University Hospital from January 1st, 2014 to December 31st, 2019 were included. Patients with glioma outside the skull

were excluded. The dose of TMZ was 75 mg/m^2/day, and a dose closer to the actual calculated dose was selected for oral administration using the 100- and 20-mg standards (eg, 1.8 m^2 × 75 mg/m^2/day = 135 mg/body/day ≈ 140 mg/day). TMZ was administered until the end of RT, with a maximum of 49 days. All patients received 5-HT$_3$RA for the first 3 days, and 5-HT$_3$RA was only resumed after the 4th day based on decisions by the attending physician or recommendation by pharmacist according to the condition of patients during TMZ+RT. Granisetron or ramosetron tablets were used as 5-HT$_3$RA when TMZ was orally administered, and granisetron injections when TMZ was intravenously administered. Oral TMZ and 5-HT$_3$RA were administered by the nurse each time in all patients.

In the present study, patients were divided into the following groups based on the status of 5-HT$_3$RA resumption as follows: a control group consisting of patients with no or mild nausea and vomiting after day 4 who did not resume 5-HT$_3$RA, and a resuming 5-HT$_3$RA group comprising patients with severe nausea and vomiting after day 4 who resumed 5-HT$_3$RA.

Study design

The present study was a single-center observational study that was retrospectively performed using medical records. The following information on patient backgrounds was investigated and compared between the control group and resuming 5-HT$_3$RA group: age, sex, Eastern Cooperative Oncology Group performance status (PS), body mass index, tumor site, pathological diagnosis WHO grade, surgery type, days until the start of chemotherapy after surgery, the TMZ dose and its route of administration, the RT dose, cerebral edema treatment, the use of bevacizumab, IFNβ, steroids, 5-HT$_3$RA, dopamine D$_2$ receptor antagonists (D$_2$RA), and multi-acting receptor-targeted antipsychotics (MARTA), clinical laboratory data before the initiation of TMZ+RT (estimated glomerular filtration rate [eGFR], aspartate aminotransferase [AST], alanine aminotransferase [ALT], γ-glutamyl transpeptidase [γ-GTP], total bilirubin [T-B], albumin [ALB], sodium [Na], calcium corrected for ALB [correct Ca]), and clinical laboratory data during TMZ+RT (lowest value of Na, highest value of correct Ca). Adverse events, namely, nausea, and vomiting, were evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 (CTCAE v4.0).

As supplementary data, the grade of nausea before and after resumption of 5-HT$_3$RA was investigated in the resuming 5-HT$_3$RA group to determine the efficacy of resumption of it. The amelioration of nausea and vomiting after the resumption of 5-HT$_3$RA was considered to be effective when its grade judged by CTCAE v4.0 after the resumption of 5-HT$_3$RA was at least 1 level lower than before its resumption.

Statistical analyses

Fisher's exact tests and Mann–Whitney U tests were used to analyze nominal and continuous variables, respectively. A multivariate logistic regression analysis was performed to examine risk factors for nausea and vomiting in TMZ+RT. All significance levels were set at 0.05. All statistical analyses were performed using Easy R (EZR).[3]

Ethical approval and consent to participate

The present study was conducted in accordance with the principles of the Declaration of Helsinki, in compliance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects," and with the approval of the ethics committee of Nagoya University Hospital (Approval number: 2019-0167). Informed consent was not obtained because this was a retrospective observational study. We posted information (opt-out enrolment method) about this study on the website of our hospital.

RESULTS

Patient characteristics are summarized in Table 1. We identified 114 patients, and 2 with glioma outside the skull were excluded. The route of administration of TMZ was oral administration in 107 patients (94%) and intravenous administration in 7 (6%). There were 78 patients in the control group (68%) and 36 in the resuming 5-HT_3RA group (32%). Therefore, approximately 1 out of 3 patients required the resumption of 5-HT_3RA after day 4. The timing of resumption of 5-HT_3RA differed from patient to patient, but 8 patients had already had nausea on days 1–3 and continued daily administration after day 4 without discontinuation. Twenty-eight patients resumed 5-HT_3RA when nausea appeared on or after day 4, and the timing of resumption varied.

The resuming 5-HT_3RA group was significantly younger than the control group, especially minors age <18 years who significantly resumed 5-HT_3RA (P = 0.01; Table 1). In addition, the proportion of females, PS 2 or more, and bevacizumab combination was slightly higher in the resuming 5-HT_3RA group than in the control group (female, P = 0.10, PS 2 or more, P = 0.13, bevacizumab combination, P = 0.07; Table 1).

Table 1 Patient characteristics

	All	Control	Resuming 5-HT_3RA	P
Number of patients	114	78	36	
Age (years)	53[a] (3–81)	54[a] (6–81)	41.5[a] (3–76)	0.01[b]
<18/≥18	14/100	5/73	9/27	0.01[c]
Sex (male/female)	67/47	50/28	17/19	0.10[c]
PS (0–1/2–4)	92/22	66/12	26/10	0.13[c]
Body mass index	21.0[a] (13.3–35.9)	21.0[a] (13.3–35.9)	20.8[a] (13.6–25.9)	0.56[b]
WHO grade IV/II+III/unknown[#]	61/49/4	42/35/1	19/14/3	0.84[c#]
Pathological diagnosis				
Glioblastoma	58	40	18	0.84[c]
Anaplastic astrocytoma	18	14	4	0.58[c]
Diffuse astrocytoma	6	4	2	1.00[c]
Anaplastic oligodendroglioma	10	9	3	1.00[c]
Oligodendroglioma	7	5	2	1.00[c]
Diffuse midline glioma	5	3	2	0.64[c]
Other	6	2	2	0.58[c]
No diagnosis (No surgery)	4	1	3	–
Tumor site				
Cerebrum	85	58	27	1.00[c]
Frontal lobe	39	29	10	0.40[c]
Parietal lobe	24	17	7	1.00[c]
Temporal lobe	5	3	2	0.65[c]
Occipital lobe	6	2	4	0.08[c]

2 lobe or more	11	7	4	0.74[c]
Supratentorial brain ventricles	4	4	0	0.31[c]
Corpus callosum	5	4	1	1.00[c]
Infratentorial	20	12	8	0.43[c]
Brain stem	13	7	6	0.34[c]
Thalamus	5	4	1	1.00[c]
Infratentorial brain ventricle	1	0	1	0.32[c]
Cerebellum	1	1	0	1.00[c]
Surgery type				
Endoscopic biopsy/tumor removal by craniotomy/no surgery[#]	15/94/5	11/65/2	4/29/3	1.00[c#]
Days from surgery to the start of chemotherapy	24[a] (11–59)	22[a] (11–59)	24[a] (12–53)	0.79[b]
TMZ % dose (mg/m^2)	98.6[a] (70.0–112.5)	99.0[a] (73.4–107.9)	97.7[a] (70.0–112.5)	0.66[b]
Route of administration (oral/intravenous)	107/7	73/5	34/2	1.00[c]
RT dose (≥2 Gy/fr/1.8 Gy)	94/20	66/12	28/8	0.43[c]
Cerebral edema treatment				
Osmotic diuretic (with/without)	8/106	5/73	3/33	0.71[c]
Steroid (with/without)	25/89	18/60	7/29	0.81[c]
Bevacizumab (with/without)	31/83	17/61	14/22	0.07[c]
IFNβ (with/without)	2/112	1/77	1/35	0.53[c]

5-HT$_3$RA: 5-hydroxy-tryptamine 3 receptor antagonist
PS: Eastern Cooperative Oncology Group performance status
TMZ: temozolomide
RT: radiotherapy
[a] Median (range), [b] Mann-Whitney U test, [c] Fisher's exact test.
[#] Comparison between two groups excluding [unknown] and [No surgery].

Table 2 shows the results of blood examinations before the initiation of TMZ+RT. No significant differences were observed in hepatic function before the initiation of TMZ+RT between the groups. On the other hand, regarding renal function, eGFR was slightly higher in the resuming 5-HT$_3$RA group than in the control group (P = 0.10); however, the median in both groups was within the reference value. Hyponatremia (<136 mmol/L), which is a risk factor for nausea and vomiting,[2,4] was detected in 7 patients (9%) in the control group and 4 (11%) in the resuming 5-HT$_3$RA group, and no significant differences were noted in the median between the groups (P = 0.29; Table 2). Furthermore, hypercalcemia (>10.4 mg/dL), another risk factor for nausea and vomiting, was not detected in any patients and no significant differences were observed in the median between the groups (P = 0.53; Table 2).

Table 2 Results of blood examinations before the initiation of TMZ+RT

	Control	Resuming 5-HT_3RA	*P*
eGFR (mL/min/1.73 m^2)	88.7 (49.3-170.0)[a]	101.0 (64.1–227.8)[a]	0.10[c]
AST (U/L)	19.2 (9–74)[a]	19.3 (10–44)[a]	0.63[c]
ALT (U/L)	25.5 (4–216)[a]	22.0 (10–121)[a]	0.93[c]
γ-GTP (U/L)	36.0 (9–447)[a]	33.5 (10–255)[a]	0.44[c]
T-B (mg/dL)	0.6 (0.2–1.2)[a]	0.6 (0.3–1.0)[a]	0.92[c]
ALB (g/dL)	3.8 (2.8–4.6)[a]	3.9 (3.1–4.7)[a]	0.27[c]
Na (mmol/L)	140 (130–147)[a]	141 (133–145)[a]	0.29[c]
Hyponatremia (<136 mmol/L)	7 (9%)[b]	4 (11%)[b]	1.00[d]
Correct Ca (mg/dL)	9.3 (7.6–10.0)[a]	9.4 (8.6–10.2)[a]	0.53[c]
Hypercalcemia (>10.4 mg/dL)	0 (0%)[b]	0 (0%)[b]	–

TMZ+RT: temozolomide combination chemoradiotherapy
5-HT_3RA: 5-hydroxy-tryptamine 3 receptor antagonist
eGFR: estimated glomerular filtration rate
AST: aspartate aminotransferase
ALT: alanine aminotransferase
γ-GTP: γ-glutamyl transpeptidase
T-B: total bilirubin
ALB: albumin
Na: sodium
Correct Ca: calcium corrected for ALB
[a] Median (range), [b] number of patients (percent), [c] Mann-Whitney U test, [d] Fisher's exact test.

Tumor sites were divided into four sites: the cerebrum, supratentorial brain ventricles, corpus callosum, and infratentorial region, compared between the control and resuming 5-HT_3RA groups, and no significant differences were observed. The cerebrum was then subdivided into five sites: the frontal lobe, parietal lobe, temporal lobe, occipital lobe, and 2 lobes or more, and the infratentorial region into four sites: the brain stem, thalamus, infratentorial brain ventricle, and cerebellum. Comparisons at each subdivided site between the control and resuming 5-HT_3RA groups revealed no significant differences. In the brain stem where the vomiting center is located, there were 6 patients in the resuming group and 7 in the control group, with no significant differences. This result may have been influenced by patient background, because 1 patient in the resuming group and 3 in the control group were able to undergo tumor resection, and 4 pediatric patients in the resuming group and 2 in the control group. On the other hand, the incidence of occipital lobe tumors tended to be higher in the resuming 5-HT_3RA group than in the control group (P = 0.08: Table 1). To examine risk factors for nausea and vomiting that result in the resumption of 5-HT_3RA, a multivariate logistic regression analysis was performed on the four factors identified in the univariate analysis: <18 years, PS 2 or more, occipital lobe tumors, and bevacizumab combination. Among the factors identified in the univariate analysis, we excluded female sex,[2,5] which is a well-known risk factor for nausea and vomiting, and eGFR, the median value of which was within the reference value in both groups. In the multivariate analysis, <18 years, PS 2 or more, and occipital lobe tumors remained as significant factors for nausea and vomiting (<18 years old, P = 0.01, odds ratio = 0.19; PS 2 or more, P = 0.04, odds ratio = 2.99; occipital lobe, P = 0.04, odds ratio = 6.63: Table 3).

Table 3 Multivariate analysis of risk factors for nausea and vomiting

	Control	Resuming 5-HT$_3$RA	Odds ratio[a]	95% confidence interval[a]	P^a
Number of patients	78	36			
Age (years) <18/≥18	5/73	9/27	0.19	0.05–0.65	0.01
PS (0–1/2–4)	66/12	10/26	2.99	1.08–8.28	0.04
Tumor site					
Occipital lobe/other	2/76	4/32	6.63	1.04–42.10	0.04
Bevacizumab (with/without)	17/61	14/22	0.18	0.72–4.65	0.20

5-HT$_3$RA: 5-hydroxy-tryptamine 3 receptor antagonist
PS: Eastern Cooperative Oncology Group performance status
[a] Logistic regression analysis.

Regarding the use of antiemetics other than 5-HT$_3$RA during TMZ+RT, D$_2$RA was administered to 19 patients (24%) in the control group and 26 (72%) in the resuming 5-HT$_3$RA group, while MARTA was administered to 3 (4%) in the control group and 1 (3%) in the resuming 5-HT$_3$RA group (Table 4). MARTA was introduced as antiemesis for only 1 patient in the resuming 5-HT$_3$RA group, while it was already being administered to 3 in the control group to treat mental illness before the initiation of TMZ+RT. Steroid drugs were administered to 18 patients (23%) in the control group and 7 (19%) in the resuming 5-HT$_3$RA group (Table 1). The type of steroid administered was dexamethasone for cerebral edema in 21 patients, hydrocortisone for corticosteroid replacement in 2 patients, and prednisolone, one for cerebral edema and the other for treatment of another disease.

Table 4 Use of antiemetics other than 5-HT$_3$RA

	Control	Resuming 5-HT$_3$RA	P^a
D$_2$RA	19 (24%)	26 (72%)	< 0.01
At a fixed time every day	2 (3%)	5 (14%)	0.03
Used as needed	17 (22%)	21 (58%)	< 0.01
MARTA	3 (4%)	1 (3%)	1.00
No rescue drug	57 (73%)	10 (28%)	< 0.01

5-HT$_3$RA: 5-hydroxy-tryptamine 3 receptor antagonist
D$_2$RA: dopamine D2 receptor antagonist
MARTA: multi-acting receptor-targeted antipsychotics
[a] Fisher's exact test.

A supplementary data in the resuming 5-HT$_3$RA group, the grade of nausea and vomiting was judged to have ameliorated in 30 patients (83%) according to CTCAE v4.0 after the resumption of 5-HT$_3$RA was at least 1 level lower than before its resumption but was not in 6 (17%). The following is a breakdown of the status of 5-HT$_3$RA administration in those 6 patients; 1 patient was continued daily administration after day 4 without discontinuation, and 5 were resumed

5-HT_3RA when nausea appeared on or after day 4.

DISCUSSION

The present study identified three risk factors for nausea and vomiting during TMZ+RT: <18 years, PS 2 or more, and occipital lobe tumors. Those who are <18 years old have higher incidence of diffuse midline glioma which occurs in the brainstem, and surgery is a severe risk. Therefore, many patients undergo endoscopic biopsy only or no surgery, and they are more likely to experience nausea and vomiting due to residual tumor. However, when examined by tumor site in this study, there was no significant difference between the control and resuming 5-HT_3RA groups in brain stem tumor (Table 1). Possible reasons are brain stem tumors may be removed in some adult patients and cerebral edema is less likely to occur in brain stem tumors; therefore, the risk of increased intracranial pressure is lower than in other areas. In addition, the incidence of nausea and vomiting in children and adults currently remains unknown; however, the present study for the first time identified age <18 years as a risk factor. Since the majority of clinical trials on antiemetic therapy in chemotherapy have been conducted on adults, there is limited information on the use and efficacy of antiemetic agents in pediatric patients.[6,7]

In patients with poor PS (≥2), gastrointestinal dysfunction as a result of lower activities of daily living and prolonged bedrest because of lower-body paralysis due to tumors may cause nausea and vomiting. However, since patients with poor PS often cannot participate in clinical studies, there is a paucity of supportive evidence. In the study by Stupp et al,[8] patients with PS >2 were also excluded. However, a previous study[9] suggested that among patients receiving chemotherapy, the incidence of vomiting was significantly higher in those with PS = 1-2 than in those with PS = 0, which is consistent with the present results.

We could not find any previous reports similar to the present study that reported occipital lobe tumors as a risk factor for nausea and vomiting. Nausea and vomiting may be attributed to a dysfunction in vision, which is controlled by the occipital lobe. However, patients with occipital lobe tumors are very rare, accounting for only 5% of all patients, and should be considered after increasing the number of cases.

The present study identified age <18 years and PS 2 or more as important risk factors for nausea and vomiting, and suggested that occipital lobe tumors may be a risk factor; however, further evidence is needed because of the lack of similar results in previous reports.

A supplementary data in the present study, the resumption of 5-HT_3RA attenuated nausea and vomiting in approximately 80% of patients, which was similar to the complete response rates reported in two prospective studies (67-79 and 76.2%) using intravenous palonosetron.[10,11] However, 26 patients (72%) in the resuming 5-HT_3RA group were treated with a combination of D_2RA or MARTA, and, thus, the complete response rate with only 5-HT_3RA remains unknown due to the retrospective design of the present study. The number of patients treated with D_2RA was 19 (24%) in the control group and 26 (72%) in the resuming 5-HT_3RA group, in which the usage rate was high. However, in contrast to previous studies, 5-HT_3RA was administered to patients who developed nausea and vomiting in the present study, and many patients also received 5-HT_3RA because D_2RA alone was not sufficiently effective. Therefore, the present results are consistent with the findings of these two studies. The amelioration of nausea and vomiting in approximately 80% of patients in the present study suggests the need for and efficacy of the daily administration of first-generation 5-HT_3RA in addition to D_2RA for nausea and vomiting during TMZ+RT. Furthermore, intravenous palonosetron used in previous reports is invasive, whereas first-generation 5-HT_3RA used in the present study can select orally administered, which is not

invasive and easier to administer. Palonosetron capsules are distributed in the United States and other countries outside Japan, and although there is no evidence for their efficacy for nausea and vomiting associated with TMZ+RT, they have the potential as oral 5-HT_3RA during TMZ+RT.

In the present study, approximately 50% of all patients (55 patients; 19 who received D_2RA in the control group and 36 in the resuming 5-HT_3RA group) required antiemetics (5-HT_3RA, D_2RA, and MARTA) due to nausea and vomiting during TMZ+RT. However, nineteen patients (24%) in the control group treated with D_2RA developed nausea and vomiting, but did not require additional 5-HT_3RA. This result suggests that D_2RA alone may be sufficient for mild nausea and vomiting. In contrast, the resumption of 5-HT_3RA was ineffective for nausea and vomiting in 6 patients (17%) according to CTCAE v4.0. Three of these patients underwent endoscopic biopsies, but not tumor removal by craniotomy, and, thus, 5-HT_3RA may have been ineffective because nausea and vomiting were caused by the residual tumor. To mitigate nausea and vomiting, intracranial pressure needs to be reduced by removing as much of the tumor as possible, unless surgery poses a severe risk, such as brainstem tumors. Furthermore, patients with cerebral edema may require anti-edema treatment such as dexamethasone too.

Chemotherapy-induced nausea and vomiting occur when the area postrema (vomiting center) in the medulla oblongata is activated by the stimulation of 5-HT_3 receptors, and neurokinin receptors and D_2 receptors.[12] On the other hand, nausea and vomiting caused by brain tumors are attributed to increased intracranial pressure because of cerebral edema or intracranial compression by the tumor, and the direct stimulation of the area postrema by the tumor near the medulla oblongata.[13] Therefore, it is important to establish whether the cause of nausea and vomiting during chemotherapy for patients with brain tumors is due to chemotherapy-induced nausea and vomiting or the brain tumor itself. If it is then considered nausea and vomiting due to TMZ+RT, that is necessary to consider the daily administration of 5-HT_3RA to patients whose nausea and vomiting are not controlled by other antiemetic agents, such as D_2RA, rather than unconditionally to all patients.

The first limitation of the present study is that it was a single-center study and the sample size was small. Since the incidence of brain and central nervous system tumors in Japan is low (4.7 per 100,000 population),[14] and only approximately 16% of patients with grade III or IV malignant glioma require TMZ+RT,[15] the results obtained are of value. The second limitation is that this is a retrospective study, and some bias, such as psychological factors of patients and medical staff due to the lack of clear criteria for the resumption of 5-HT_3RA, may have affected grouping. However, no studies have investigated risk factors for nausea and vomiting caused by TMZ+RT, the present results are novel. Further prospective studies are needed to identify more accurate risk factors for nausea and vomiting caused by TMZ+RT.

CONCLUSION

The present study identified three factors for nausea and vomiting during TMZ+RT: age <18 years, PS 2 or more, and occipital lobe tumors. In patients with these risk factors, confirm in advance that the cause of nausea and vomiting is not other than TMZ+RT, and it was suggested that it is necessary to consider the daily administration of 5-HT_3RA to patients whose nausea and vomiting are not controlled by other antiemetic agents, such as D_2RA.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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