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Secondary hematological malignancies associated with temozolomide in patients with glioma

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Background. The alkylating agent temozolomide (TMZ) is widely used for the treatment of gliomas. Although reports of treatment-related myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL) associated with TMZ are accumulating, it remains unclear whether TMZ has the same leukemogenic potential as other alkylating agents.

Methods. We performed a single-institution retrospective analysis using a database of 359 glioma patients given nimustine (ACNU)-based therapy, TMZ-based therapy, or combination therapy, who were followed up for a minimum of 2 months, between January 1990 and December 2009, at the National Cancer Center Hospital in Japan.

Results. Of the 359 patients, 225 received ACNU alone or ACNU plus other chemotherapeutic drugs (ACNU-based group; median follow-up period, 31.4 mo), 63 patients received ACNU-based therapy followed by TMZ therapy (ACNU-TMZ group; median follow-up period, 19.1 mo), and 71 patients received TMZ alone or TMZ plus other chemotherapeutic drugs (TMZ-based group; median follow-up period, 16.9 mo). Three patients in the ACNU-based group developed MDS/AML (incidence rate: 2.9 cases per 1000 person-years), 2 patients in the ACNU-TMZ group developed MDS/AML (13.0 cases per 1000 person-years), and 1 patient in the TMZ-based group developed ALL (9.9 cases per 1000 person-years).

Conclusions. Despite the limitations of this study, published reports and our results suggest that TMZ induces secondary hematological malignancies, particularly ALL, and might shorten the latency period when used in combination with other chemotherapeutic agents.

Keywords: alkylating agent, glioma, secondary hematological malignancy, temozolomide.

Gliomas are the most common malignant primary brain tumors, consisting mainly of astrocytic, oligodendroglial, and oligoastrocytic tumors. Malignant gliomas that represent World Health Organization (WHO) grades III and IV tumors form one of the most malignant and devastating groups of human cancers.[1] Malignant gliomas are intractable to combination therapy with surgical resection, radiation, and chemo, and their prognosis remains dismal, with a poor median survival.[2] Although a number of chemotherapies had been tested and several chemotherapeutic agents, such as nitrosoureas, demonstrated significant effect for the treatment of gliomas,[3–6] there was no standard chemotherapy regimen until temozolomide (TMZ) was introduced into clinical practice.[7]

TMZ is an oral alkylating agent, and its efficacy was initially tested and demonstrated in the treatment of glioblastoma. The antitumor effect of TMZ was observed when combined with radiotherapy in patients with glioblastoma.[7] Following the demonstration of prolonged survival in glioblastoma patients treated with TMZ compared with patients receiving radiotherapy alone (14.6 mo vs 12.1 mo),[7] TMZ became the most widely used chemotherapeutic agent for various types of gliomas.[2] Although the mechanism of action of TMZ is similar to that of other alkylators, TMZ causes side effects such as lymphocytopenia.[8] Although the long-term side effects of TMZ are still uncertain, reports of treatment-related myelodysplastic syndrome (MDS) and leukemia associated with TMZ are accumulating.[9–16]

Cancer survivors are at a substantially higher risk for developing additional cancers than the general

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population, and this risk for secondary malignancy should be noted by health care professionals.[17] Alkylating agents are generally known as leukemogenic drugs, and their potential for causing cancers is higher than that of other chemotherapeutic agents.[17–19] Before the TMZ era, the alkylator nimustine (ACNU) was predominantly used for the treatment of malignant gliomas in Japan, and we encountered several cases of secondary MDS and acute myeloid leukemia (AML) after ACNU-based chemotherapy. Since TMZ became available in Japan in September 2006, we switched the first-line chemotherapeutic agent from ACNU to TMZ for newly diagnosed malignant gliomas and recurrent gliomas. After sequential use of TMZ following ACNU, we encountered additional cases of secondary MDS/AML. However, it remains unclear whether TMZ has the same leukemogenic potential as other alkylating agents. To characterize secondary hematological malignancies and to estimate the rate of MDS and leukemias associated with TMZ-based therapy compared with ACNU-based therapy, we reviewed 359 glioma patients receiving ACNU and/or TMZ-containing chemotherapy.

Patients and Methods

Study Population and Therapeutic Management

The study population consisted of 359 consecutive glioma patients of Japanese origin who had received chemotherapy at the National Cancer Center Hospital, Tokyo, Japan from 1990 to 2009. All patients were diagnosed with glioma of WHO grades I to IV either pathologically (in most cases) or radiographically (in cases of brainstem tumors) and were treated with one of the following: (i) ACNU-based therapy: ACNU alone or ACNU plus other chemotherapeutic drugs; (ii) TMZ-based therapy: TMZ alone or TMZ plus other chemotherapeutic drugs; or (iii) ACNU-TMZ therapy: ACNU-based therapy followed by TMZ-based therapy. In the TMZ-based group, TMZ was continued for 24 cycles or until the tumor disappeared. The patients in all 3 groups were followed up for a minimum of 2 months. Secondary hematological malignancies were diagnosed by bone marrow aspiration either by a pediatric oncologist or by a hematologist. Local brain radiotherapy was performed in most patients within 2 weeks after the operation, using a dose of 54 Gy in patients with WHO grade II gliomas or 60 Gy with a local boost in patients with WHO grades III and IV gliomas. To estimate the actual time at risk, person-years (the total sum of the number of years that each patient of a population had been under observation) and the incidence rate per 1000 person-years were calculated.

Statistical Analysis

Comparison between 2 groups was performed using Student's *t*-test. Correlations between 2 groups were assessed using a chi-square test. The analyses were performed using JMP7 version 7.0.1 software (SAS Institute). $P < .05$ was considered statistically significant.

Results

Patient Characteristics and Clinical Outcome

The patient demographics and follow-up periods in the 3 treatment groups are shown in Table 1. Of the 359 patients included in the study, 210 were men and 149 were women. The median age was 47 years (range, 0–80 y), and the median follow-up time was 22.0 months (range, 2.2–232.6 mo). Because TMZ was introduced in Japan when ACNU was the first-line therapy for glioma patients, the numbers of patients were smaller and the follow-up periods were shorter in the ACNU-TMZ and TMZ-based groups than in the ACNU-based group. Pathological or radiographical diagnosis and WHO grade of the tumors at the start of treatment are shown in Table 2. The most frequent tumor type was glioblastoma (37.3%), followed by anaplastic astrocytoma (18.1%) and diffuse astrocytoma (18.1%). High-grade gliomas of WHO grades III and IV accounted for 66.5% of the tumors.

Treatment, Follow-up Period, and Hematological Malignancy

The chemotherapeutic drugs used in the patients and the related hematological malignancies are summarized in Table 3. In the ACNU-based group, 72 of 225 patients were treated with ACNU alone, and the other patients received a combination chemotherapy such as ACNU + etoposide (VP-16), ACNU + vincristine (VCR), or procarbazine (PCZ) + ACNU + VP-16. Because the patients with recurrence received second-line or third-line therapy, the number of chemotherapeutic drugs used was higher in cases with recurrence. In the ACNU-TMZ group, all 63 patients received ACNU-based therapy as first line, and TMZ was administered at recurrence. In the TMZ-based group, all 71 patients were treated with TMZ according to the regimen previously reported,[3] and in patients with recurrent tumors, either TMZ + PCZ or carboplatin + VP-16 therapy was sequentially administered. The median follow-up time was longer ($P < .001$) and the percentage of 2-year survivors was higher ($P < .001$) in the ACNU-based group than in the other groups treated with TMZ for the abovementioned reason. The median duration of TMZ therapy was 19.9 months (range, 1.0–51.5 mo) in the ACNU-TMZ group and 17.0 months (range, 2.5–24.5 mo) in the TMZ-based group.

Hematological malignancies were observed during or after chemotherapy in 6 patients. In the ACNU-based group, all 3 MDS/AML patients were treated with ACNU + VP-16. In the ACNU-TMZ group, 2 patients developed MDS/AML after ACNU followed by TMZ

Table 1. Patient characteristics and treatment

	ACNU-based	ACNU-TMZ	TMZ-based	Total
n (%)	225 (62.7)	63 (17)	71 (19.8)	359 (100)
Sex ratio (M/F)	1.45 (133/92)	1.42 (37/26)	1.29 (40/31)	1.41 (210/149)
Median age, y (range)	45.0 (0–77)	48.0 (19–66)	58.0 (12–80)	47.0 (0–80)
Median follow-up, mo (range)	31.4 (2.2–232.6)	19.1 (2.3–227.4)	16.9 (2.5–37.4)	22.0 (2.2–232.6)

Table 2. Pathological diagnosis and treatment

n (%)	ACNU-based	ACNU-TMZ	TMZ-based	Total
Patients	225 (62.7)	63 (17.5)	71 (19.8)	359 (100)
Glioblastoma	75 (33.3)	19 (30.2)	40 (56.3)	134 (37.3)
Anaplastic astrocytoma	38 (16.9)	15 (23.8)	12 (16.9)	65 (18.1)
Anaplastic oligoastrocytoma	12 (5.3)	6 (9.5)	5 (7.0)	23 (6.4)
Anaplastic oligodendroglioma	9 (4.0)	2 (3.2)	2 (2.8)	13 (3.6)
Anaplastic ependymoma	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)
Anaplastic ganglioglioma	0 (0.0)	0 (0.0)	2 (2.8)	2 (0.6)
Anaplastic glioneuronal tumor	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.3)
Diffuse astrocytoma	42 (18.7)	18 (28.6)	5 (7.0)	65 (18.1)
Oligoastrocytoma	21 (9.3)	2 (3.2)	0 (0.0)	23 (6.4)
Oligodendroglioma	4 (1.8)	0 (0.0)	1 (1.4)	5 (1.4)
Pleomorphic xanthoastrocytoma	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)
Ependymoma	8 (3.6)	0 (0.0)	1 (1.4)	9 (2.5)
Ganglioglioma	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.6)
Pilocytic astrocytoma	3 (1.3)	0 (0.0)	1 (1.4)	4 (1.1)
Myxopapillary ependymoma	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)
Brainstem glioma	9 (4.0)	0 (0.0)	0 (0.0)	9 (2.5)
Unknown glioma	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)
WHO grade IV	75 (33.3)	19 (30.2)	40 (56.3)	134 (37.3)
WHO grade III	59 (26.2)	24 (38.1)	22 (31.0)	105 (29.2)
WHO grade II	76 (33.8)	20 (31.7)	7 (9.9)	103 (28.7)
WHO grade I	5 (2.2)	0 (0.0)	2 (2.8)	7 (1.9)
Unknown grade	10 (4.4)	0 (0.0)	0 (0.0)	10 (2.8)

or PCZ + ACNU + VP-16 followed by TMZ. In the TMZ-based group, 1 patient treated with TMZ alone developed acute lymphoblastic leukemia (ALL) as reported previously.[10] The incidences and mean person-years of hematological malignancies were 1.33% and 6.4 years, respectively, in the ACNU-based group, 3.17% and 2.4 years in the ACNU-TMZ group, and 1.41% and 1.1 years in the TMZ-based group, with no significant differences in the incidence between the groups. The incidence rates of hematological malignancies per 1000 person-years were 2.9 cases in the ACNU-based group, 13.0 cases in the ACNU-TMZ group, and 9.9 cases in the TMZ-based group, with no significant differences between the groups as well (Table 4). All of the 3 MDS/AML patients in the ACNU-based group were treated in combination with VP-16, and the incidence rate of this ACNU + VP-16 group was 6.1 cases per 1000 person-years. The 3 cases of secondary hematological malignancies after TMZ treatment are summarized in Table 5.

Discussion

In this report, we describe 6 cases of treatment-related hematological malignancies. Before the TMZ era, several other alkylating agents were used for glioma treatment. Among these alkylators, nitrosoureas such as carmustine (BCNU), lomustine (CCNU), and ACNU are known to be strong leukemogenic agents, and reports of treatment-related MDS (t-MDS) or acute leukemia (AL) in glioma patients treated with these nitrosoureas have accumulated.[9,20,21] In contrast, the alkylator TMZ has been approved for use only in the last decade, and its leukemogenic activity has not yet been fully evaluated. Although there are several reports of t-MDS/AL in association with TMZ, most of these patients were treated with TMZ after treatment with other alkylating agents.[9–11] To our knowledge, only 6 cases of t-MDS/AL have been reported to have occurred after chemotherapy with TMZ alone in glioma patients, including ours.[12–15,22] Interestingly, 4 out of 6 cases

Table 3. Treatment and hematological malignancy

Chemotherapy	Incidence of MDS/AL (%)	Hematological Malignancy	Median Follow-up, mo (range)	Two-Year Survivors (%)
ACNU-based	3/225 (1.33)		31.4 (2.2–232.6)	126/225 (56.0)
ACNU	0/72		38.6 (2.7–205.4)	46/72 (63.9)
ACNU, VP-16	3/35	MDS/AML	82.0 (2.2–228.5)	21/35 (60.0)
ACNU, VCR	0/24		68.6 (9.6–151.5)	20/24 (83.3)
ACNU, PCZ, VCR	0/18		55.2 (5.1–196.1)	17/18 (94.4)
ACNU, CBDCA, VP-16	0/29		18.2 (3.9–126.3)	11/29 (37.9)
ACNU, CDDP, VP-16	0/10		13.3 (6.5–109.5)	2/10 (20.0)
ACNU, PCZ, VCR, CBDCA, VP-16	0/3		31.4 (16.0–139.8)	2/3 (66.7)
ACNU, IFN, VP-16	0/4		13.3 (6.5–109.5)	3/4 (75.0)
ACNU, IFN, CDDP, VP-16	0/3		19.6 (9.1–53.9)	1/3 (33.3)
ACNU, CBDCA, VP-16, VCR	0/3		21.0 (17.7–36.3)	1/3 (33.3)
ACNU, VP-16, 5-FU	0/2		122.7 (14.5–230.9)	1/2 (50.0)
ACNU, IFO, VCR, CDDP, VP-16	0/2		16.4 (4.2–28.6)	1/2 (50.0)
ACNU, PCZ, VCR, CDDP, VP-16	0/2		36.1 (17.6–54.6)	1/2 (50.0)
ACNU, PCZ	0/2		14.2 (11.5–16.8)	0/2 (0.0)
ACNU, other drugs	0/16		19.25 (3.3–232.6)	4/16 (25.0)
ACNU-TMZ	2/63 (3.17)		19.1 (2.3–227.4)	27/63 (42.9)
ACNU, TMZ	1/21	MDS/AML	9.1 (2.3–76.6)	8/21 (38.1)
ACNU, CBDCA, VP-16, TMZ	0/9		8.2 (3.3–16.2)	0/9 (0.0)
ACNU, PCZ, TMZ	0/9		38.8 (5.5–76.0)	6/9 (66.7)
ACNU, VCR, TMZ	0/7		24.4 (3.9–48.9)	4/7 (57.1)
ACNU, PCZ, VCR, TMZ	1/6	MDS/AML	23.4 (4.8–227.4)	3/6 (50.0)
ACNU, PCZ, CBDCA, VP-16, TMZ	0/4		21.0 (19.1–35.3)	1/4 (25.0)
ACNU, other drugs, TMZ	0/7		51.8 (10.1–72.3)	5/7 (71.3)
TMZ-based	1/71 (1.41)		16.9 (2.5–37.4)	16/71 (22.5)
TMZ	1/59	ALL	16.6 (2.5–37.4)	12/59 (20.3)
TMZ, PCZ	0/10		19.1 (6.9–36.6)	3/10 (30.0)
TMZ, PCZ, CBDCA, VP-16	0/2		21.8 (19.1–24.5)	1/2 (50.0)

Abbreviations: CBDCA, carboplatin; CDDP, cisplatin; IFN, interferon-beta; 5-FU, 5-fluorouracil; IFO, ifosfamide.

Table 4. Incidence and person-years of hematological malignancies

Chemotherapy	Number of Patients	Mean Follow-up (y)	Number of MDS/AL	Incidence per Protocol (%)	Total P-Ys	Incidence per 1000 P-Ys (95% CI)
ACNU-based	225	4.53	3	1.3	1020	2.9 (1.0–8.6)
(ACNU, VP-16)	105	4.67	3	2.9	493	6.1 (2.1–17.7)
ACNU-TMZ	63	2.43	2	3.2	153	13.0 (3.6–46.4)
TMZ-based	71	1.41	1	1.4	101	9.9 (1.8–54.0)

Abbreviations: P-Ys, person-years; CI, confidence interval.

were ALL, suggesting that secondary hematological malignancy after single-agent chemotherapy with TMZ may manifest as ALL.[14,15]

Secondary leukemia in cancer survivors accounts for 5%–10% of all ALs.[23] Although secondary MDS/AML is the most frequent entity among patients with secondary leukemia, secondary ALL accounts for ~10% of all secondary leukemia cases.[23,24] The incidence of t-AL has been reported in a large prospective study of 1628 brain tumor patients treated with CCNU.[20] In that study, only 2 cases (0.12%) of t-AL were observed, but only 10.9% of the study participants

Table 5. Cases with secondary hematological malignancies after TMZ treatment

Age, y/sex	Primary Tumor	ACNU-based Therapy	RT Dose (Gy)	TMZ Dose (mg/m^2)	Latency After TMZ (mo)	Secondary Leukemia
58/M	DA	ACNU × 2	50.0	23 750	41	MDS/AML
64/M	DA	PAV × 4	50.0	8750	16	MDS/AML
12/F	AA	None	60.0	12 900	13	ALL

Abbreviations: DA, diffuse astrocytoma; RT, radiation therapy; PAV, procarbazine; ACNU, and etoposide (VP-16); AA, anaplastic astrocytoma.

were followed up for more than 2 years. Because the median latency between the initiation of therapy and the diagnosis of t-MDS/AML and ALL has been reported to be 31 months in brain tumor patients and 50–70 months in patients with other malignancies,[21,25,26] the incidence of t-AL may be much higher than reported. Chamberlain and Raizer[12] reported 7 cases of t-MDS/AML during the treatment of gliomas. Of the 7 patients, 5 were treated with nitrosoureas + TMZ and 2 were treated with TMZ alone. These data suggest that the combination of nitrosoureas and TMZ may increase the incidence of alkylator-induced MDS/AML and ALL. However, there are no data to indicate that TMZ is more likely to induce secondary hematological malignancies than nitrosoureas or to enhance the leukemogenic activity of other alkylators.

ACNU-based chemotherapy was predominant in Japan for the treatment of malignant gliomas until TMZ was introduced into clinical practice. The ACNU-based group represents the era of 1990–2004, and 3 patients with glioma in our facility presented with MDS/AML. Of note, all 3 patients with MDS/AML received combination therapy including ACNU and VP-16 with a relatively high incidence rate per 1000 person-years (6.1 cases), although the mean follow-up period in this group was longer than the others. Because VP-16 is also known to increase the risk for treatment-related hematological malignancies,[27,28] the combination of ACNU and VP-16 would have a higher leukemogenic risk. During the era when TMZ was used following ACNU-based therapy, we encountered 2 more patients with MDS/AML. Although the mean follow-up period was shorter in the ACNU-TMZ group than in the ACNU-based group (2.43 y vs 4.53 y), the incidence rate of MDS/AML per 1000 person-years was higher in the ACNU-TMZ group (13.0 cases vs 2.9 cases). Although data based on time of exposure are required to achieve a more accurate analysis, these results suggest that additional TMZ after ACNU-based therapy increases the risk and shortens the latency period of t-MDS/AML. In the TMZ-based group, the median follow-up period was too short to determine the leukemogenic potential of TMZ alone. However, as described previously, t-ALL is a potential secondary malignancy in patients who undergo TMZ treatment.[14,15]

In conclusion, our data and reported evidence indicate that TMZ may exhibit leukemogenic potential similar to other alkylating agents. The leukemogenic activity of TMZ may be manifested particularly when it is used sequentially after other alkylators. Because TMZ is a relatively new drug in clinical practice and can prolong survival in glioma patients, TMZ-related MDS/AML and ALL will become more frequent. Close follow-up of hematopoietic function is needed for patients treated with TMZ.

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