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Original

Assessment of Effect and Toxicity of Temozolomide Combined with Radiation Therapy for Newly-Diagnosed Glioblastoma in Japan

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Objective: Temozolomide has been used since 1999 in North America and Europe. However, it has been used in Japan for 3 years, resulting in a lack of sufficient efficacy and toxicity data for Japanese. We summarized the result of temozolomide treatment in our institute, focusing on toxicity. **Methods:** The 26 newly-diagnosed glioblastoma patients with concomitant and adjuvant radiation and temozolomide were included. Adverse events, overall survival and prograssion-free survival were assessed. **Results:** The median age was 57 years old and 66% were men. The overall and the progression-free survival were 19.8 months and 10.3 months, respectively. Adverse events of grade 3 and higher were observed in 23% of the patients, if hematologic toxicity was evaluated by leukopenia. Lymphopenia was seen in 35%, resulting in all adverse events seen being 46%. Three had severe gastrointestinal toxicity and four showed mental toxicity. Almost all patients suffered mild constipation (grade 2). There was no incidence of *Pneumocystis* pneumonia. **Conclusion:** Our incidence of adverse events of grade 3 and higher seemed comparable to other reports. Severe gastrointestinal toxicity or mental toxicity was not reported before. Considering racial/ethnic difference of reaction to the drugs, collecting and sharing data from Japanese patients will be necessary.

Key words: brain tumor, toxicities, Japanese, GI bleeding, depression

Introduction

Malignant gliomas in general are considered to have poor prognoses. In particular, the most malignant type, glioblastoma, shows only 12 months of median survival time even with surgical resection, radiation therapy and chemotherapy.

Since the 1970s, a number of chemotherapeutic agents have been introduced to treat malignant gliomas, such as nitrosoureas (lomustine: CCNU, nimustine: ACNU, carmustine wafers: BCNU), carboplatin, cisplatin, etoposide, procarbazine, vincristine and so on. However, therapeutic effects of those agents had been insignificant. After the introduction of those agents, no agent for gliomas was clinically approved for 20 years and finally, an oral alkylating agent, temozolomide (TMZ), was approved in North America and Europe. Then in 2005, it was first proven effective to malignant gliomas in the multi-centered phase III studies by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC)[1].

Subsequently, TMZ was approved for clinical application in Japan in September 2006 for malignant gliomas after clinical trial for recurrent grade III gliomas in Japan and also based on the results of clinical evidences in North America and Europe. At that time, the clinical trials were performed for re-

current patients based on the adjuvant therapeutic protocol by Stupp et al (5 days TMZ on, 23 days off), and patients suffered little toxicity. However, Stupp's concomitant therapeutic protocol for newly diagnosed cases assigned a different dosage; 42 days consecutive administration of TMZ along with concomitant radiation therapy, followed by an adjuvant protocol of 6 courses of 5 days with TMZ on, 23 days without. The whole initial therapy seemed to show stronger toxicity.

We have treated 26 newly-diagnosed Japanese glioblastoma patients with TMZ based on Stupp's protocol and observed adverse events of grade 3 and higher for 23% of the patients. A not insignificant number of patients suffered from severe gastrointestinal (GI) toxicity and/or mood alteration that featured a depressive state. There has been no report on racial/ethnic variation of the toxicity of TMZ and we felt it important to report on toxicities that might to be distinctive to Japanese patients.

Patients and Methods

1. Patients

All the patients, who were newly diagnosed with glioblastoma〔World Health Organization (WHO) grade IV astrocytoma〕by their surgical specimens or clinical/radiological manifestations in the Tokyo Women's Medical University from September 2006 through March 2008, and who were treated with the standard radiotherapy plus concomitant daily TMZ followed by the adjuvant regimen according to the EORTC/NCIC protocol, were included in this study.

2. Treatment

The patients received temozolomide according to the EORTC/NCIC protocol of concomitant and adjuvant temozolomide; the concomitant chemotherapy consisted of temozolomide at a dose of 75 mg per square meter per day, given 7 days per week from the first day of radiotherapy until the last day of radiotherapy, but for no longer than 49 days. After a 4 weeks break, the patients were then to receive adjuvant temozolomide according to the standard 5 days schedule every 28 days. The dose was 150 mg per square meter for the first cycle and was increased to 200 mg per square meter beginning with the second cycle, so long as there were no severe toxic effects.

Radiotherapy consisted of fractionated focal irradiation at a dose of 2 Gy per fraction given once daily 5 days per week (Monday through Friday) over a period of 6 weeks, for a total dose of 60 Gy.

Antiemetic prophylaxis with a 5-hydroxytryptamine3 antagonist was administered 1 hour before taking TMZ. The patients presented lymphopenia (800/μl and fewer, or 1,000/μl or fewer if corticosteroids were given) was administered prophylaxis against *Pneumocystis* pneumonia with oral trimethoprim-sulfamethoxazole (160 mg trimethoprim per day every other day).

3. Evaluation of toxicity and efficacy

Adverse events during concomitant and adjuvant therapy were retrospectively investigated and evaluated according to the CTCAE Ver.3[2]. The overall survival (OS) and the progression-free survival (PFS) times were calculated by using the Kaplan-Meier methods.

Results

1. Patient Characteristics

There were 26 patients entered in this study. The median age was 57 years old (range 22-71) and 66% were men. Of these 26 patients, 25 were surgically operated on (5 received surgery in other institutes) and one was diagnosed according to clinical and radiological manifestations. Of those who received surgical resection, 16 patients (61%) had total (more than 98% contrast-enhanced area by MRI) resection and 9 (35%) had partial resection (Table 1).

2. Treatment

Of all 26 patients, 25 patients (96%) completed the concomitant therapy without discontinuation. One had to discontinue the therapy because of fever of unknown origin. The median number of the adjuvant courses was 5 (range 0-18). Eight patients (31%) had to discontinue the adjuvant therapy. Of these, 6 showed progression of the disease, one had GI toxicity because of the therapy and one patient voluntarily discontinued (Table 2).

3. Survival and Progression

The median observation time was 11 months.

Table 1 Patient characteristics (n=26)

Age (median, range=57 years, 22-71)		
< 50	9	34%
> 50	17	66%
Sex		
Men	17	66%
Women	9	34%
Karnofsky performance status		
> 80	21	81%
< 80	5	19%
Extent of surgery*		
Total	16	61%
Partial	9	35%
(one patient had no surgery, diagnosed by MRI)		
Use of corticosteroids		
Yes	3	12%
No	23	88%

*Total resection; > 98% contrast-enhanced area by MRI.

Table 2 Adjuvant therapy (n=26)*

Radiation therapy	Median dose given (Gy)=60 (50-60)
Temozolomide (TMZ)**	
Concomitant TMZ (75 mg/m^2, given daily)	
Median days given=42 (27-48)	
Discontinuation=1 patient	
Adjuvant TMZ (150-200 mg/m^2×5 days/28 days in 1 course)	
Median courses given=5 (0-18)	
Discontinuation=8 patients***	

*Numbers in parentheses after median numbers represent ranges.

**15 patients (58%) received prophytaxis for *Pneumocystis carinii* pneumonia.

***6 patients due to progression of the disease, 1 due to toxicity, 1 voluntarily.

Table 3 Adverse events (n=26)

	Number of patients (percent)	
	All	grade > 3
Total (by leukopenia)*	26 (100)	6 (23)
Total (by lymphopenia)**	26 (100)	12 (46)
Hematologic		
Leukopenia	9 (35)	0
Neutropenia	2 (8)	0
Lymphopenia	18 (69)	9 (35)
Anemia	3 (12)	1 (4)
Thrombopenia	1 (4)	0
Gastrointestinal		
Abdominal pain	1 (4)	1 (4)
Constipation	21 (81)	0
Diarrhea	2 (8)	2 (8)
Nausea/vomiting***	3 (12)	0
Mental		
Mood changes	4 (15)	0
General		
Anorexia	9 (35)	0
Fatigue	3 (12)	0
Fever	1 (4)	0
Musculoskeletal		
Myalgia	1 (4)	0
Hepatic		
AST/ALT	6 (23)	1 (4)
γ-GTP	6 (23)	4 (15)
Hypoalbumin	1 (4)	0
Respiratory		
Coughing	3 (12)	0

*Hematologic toxicity was evaluated by total leukocyte loss.

**Lymphopenia was counted as independent ematologic toxicity.

***All patients were on antiemetic prophylaxis with 5-HT antagonist.

The OS was 19.8 months and the PFS was 10.3 months.

4. Safety and Tolerability (Table 3)

Adverse events of grade 3 and higher were observed in 6 (patients (23%), if hematologic toxicity was evaluated by leukopenia.

The number of lymphocytes decreased in all the patients at various levels and grade 3 and higher toxicity was detected in 9 patients (35%). The average decrease of individual patient from the pretreatment level to the nadir was 49%. We administered sulfamethozazole/trimethoprim to 15 patients (58%) in order to prevent *Pneumocystis* pneumonia.

Severe GI adverse events of grade 3 and higher were detected in 2 patients, including one with abdominal pain and hemorrhagic diarrhea and the other with severe non-hemorrhagic diarrhea. For those with diarrhea, stool culture was performed and all negative for clostridium difficile, norovirus and rotavirus. Continuous nausea and loss of appetite was seen in 9 patients (23%). Almost all patients suffered mild constipation (grade 2) and elevated hepatic transaminase (grade 2).

We detected mood changes in 4 patients. All these presented a depressive state. They were diagnosed by psychiatrists and given medication. There was no incidence of *Pneumocystis* pneumonia.

5. A Notable Case

There was one patient who presented severe GI toxicity. The patient was a 37 years old woman who presented no history of GI diseases. She started to present coughing and abdominal pain several days before completion of concomitant therapy (60 Gy radiation and 42 days TMZ). Two days after comple-

tion, she presented severe abdominal pain and repetitive hemorrhagic diarrhea for more than 20 times. She was treated by fasting and hydration for a month and it took 48 days for her to be discharged. At discharge, she was still having soft stool and was on a soft-meal diet and it took 4 months for her to be completely recovered.

Discussion

The comparison of our study vs. Stupp's study (insert reference) is as follows: median age 57 (range 22-71) vs. 56 (19-70); proportion of older patients (> 50 years) 66 vs. 69%; sex (proportion of men) 66 vs. 64%; proportion of patients with good PS 81 (KPS > 80) vs. 86% (PS > 1); proportion with total resection 61 vs. 39%; administration of corticosteroids 12 vs. 67%. The backgrounds were similar except for the extent of surgery and use of corticosteroids[1].

In this study, the OS was 19.8 months and the PFS was 10.3 months. Before TMZ was introduced, we performed ACNU-based chemotherapy and the OS was 16 months and the PFS was 8.5 months[3]. There was no significant difference compared to TMZ-treated cases.

Both were longer than the results of the clinical study by Stupp et al, which reported an OS of 14.6 months and a PFS of 6.9 months[1]. The final report by the EORTC/NCIC in 2009 showed OS of 14.6 months, which was not that longer than the ad interim report[4]. Compared to their report, out result showed much longer OS. The EORTC/NCIC report concluded that the higher the resection rate was, the longer the OS was and our result shows the similar tendency (total resection, which was defined to be the resection of 98% or higher of the Gd-contrast area, was 61% of patients in our institute and 39% for the report of the EORTC/NCIC). One of the reasons that dedicated to the higher resection rate might have been use of 5-ALA in our institute[5].

The incidence of adverse events was 23% in our study, if hematologic toxicity was evaluated by leukopenia, lower than the previous report (28% of the concomitant phase and 37% of the adjuvant phase) (data of the Food and Drug Administration (FDA))[6].

However, if lymphopenia (seen in 35%), was independently evaluated, 46% of the patients showed adverse events of grade 3 and higher. The FDA summarized the ECOTC/NCIC study and reported that 37% of the patients experienced adverse events of grade 3 and higher, though this result did not include lymphopenia[6].

There is a report (Stupp, Journal of Clinical Oncology, 2002) in which grade 3 and higher lymphopenia was observed in 79 and 64% of the glioblastoma patients during the concomitant and adjuvant phase, respectively. Of those, 3 patients suffered from infectious disease and two developed *Pneumocystis* pneumonia. Both of these patients were receiving corticosteroids and presented simultaneous grade 3 or 4 neutropenia and lymphopenia at the time of infection[7]. We did not experience any infectious complication. Besides having fewer patients presenting lymphopenia (35%), we administered prophylaxis as soon as we detected lymphocytopenia. It should be fairly critical to monitor changes of lymphocytes, as well as to take efforts to prevent loss of lymphocytes.

One measurement that could be recommended to prevent loss of lymphocytes is to avoid use of corticosteroids as much as possible. At the beginning of this discussion, we mentioned that we used corticosteroids on fewer patients compared to Stupp's report (12 vs. 67%). Another thing that was outstanding in that comparison was that we achieved total resection for more patients than in Stupp's report (61 vs. 39%). We assume that the extensive surgical resection we usually perform contributed to bulk reduction of intracranial volume, then resulted in little necessity of administering corticosteroids. Extensive surgical resection may be one approach to suppress complications of TMZ.

As for GI toxicities, nausea/vomiting was observed in 3 patients (12%), which is a much lower incidence than in Stupp's report (nausea 36–49%, vomiting 20–29%)[6]. We administered antiemetic prophylaxis with a 5-hydroxytryptamine3 antagonist to all the patients and instructed them to take TMZ before bedtime to reduce nausea during day-

time. Constipation was observed in 21 (81%) patients, which seemed to be a higher incidence compared to previous reports (around 22%), but we could manage all of these with mild laxative agents.

We reported a case of a patient who suffered from GI toxicity who presented GI hemorrhage and severe diarrhea and was hospitalized for 48 days. We also experienced another case in which the patient had to receive intravenous fluid infusion because of severe diarrhea. The post-marketing surveillance study of TMZ in Japan (April 2007, data not published) showed a case from Japan in which the patient died of severe hemorrhagic GI toxicity. Stupp reported 2 patients (1%) who had diarrhea of grade 3 and higher during adjuvant therapy[6]. There was no report of any case from other countries that required hospitalization.

We observed mood changes for 4 patients (15%). All of these presented a depressive state. Stupp et al. have reported no such complications. There has been no such complication resulting from ACNU applied to glioblastomas reported in this country. Psychological complications such as depressive state or anxious state (2 patients out of 143 patients or 1.4%) were detected in the post-marketing surveillance study of TMZ in Japan (April 2007, data not published). It might be speculated that no such complications were detected in the previous reports and our results may be the first to suggest that TMZ has the potential to cause a depressive state.

On the other hand, it has been reported that the incidence of depression in patients during cancer therapy is 13%, and that 15% of high-grade glioma patients will show depressive mental status in the post-operative period[8)9)]. These incidences resemble our reports on TMZ treatment and therefore, the depressive state shown in the middle of TMZ treatment might be merely the result of cancer-bearing patients' general psychological reaction.

However, we may have to pay attention to the patients' psychological status to elucidate a cause-and-effect relationship of TMZ and depressive status. Also, we should carefully observe the patients being treated with TMZ for the possibility that this treatment may initiate depression.

Conclusion

Adverse events of grade 3 and higher were observed in 23% of the patients. Lymphopenia was almost inevitable, but prevention of *Pneumocystis* pneumonia can be achieved by prophylactic use of antibiotics (or anti-microorganisms) and avoidance of corticosteroids. We experienced more patients with GI toxicity and mental toxicity compared to the reports from North America and Europe. Accumulating toxicity data from Japanese patients and sharing those with other investigators, especially discussing racial/ethnic variation of toxicities, will be necessary.

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日本人における初発膠芽腫に対するテモゾロミドを用いた初期放射線化学療法の治療成績と有害事象

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〔背景〕膠芽腫標準治療薬である temozolomide（テモダール™：TZM）は，1999年より使用開始されている欧米では効果・副作用に関する充分なデータの蓄積がなされつつあるが，国内では市販後調査が行われ始めてわずか3年が経過したに過ぎず，数年後と予測されるその解析が待たれているところである．我々の施設での初発膠芽腫患者における temozolomide を用いた初期放射線化学療法の使用成績を，特に有害作用に重点をおいて報告する．また TZM との因果関係が否定できない重篤な消化管障害を誘発した1例を報告する．〔方法〕2006年9月～2008年3月までに temozolomide 併用初期放射線化学療法を受けた膠芽腫全患者を対象とし，初期治療中の有害事象，Kaplan-Meier 法を用いて平均生存期間を算出した．〔結果〕対象となった患者26例，年齢中央値57歳，男女比2対1，全生存期間19.8ヵ月，無増悪生存期間10.3ヵ月であった．初期治療終了までに，TZM との因果関係が否定できない有害事象が46%（12/26例）の患者に生じ，そのうちリンパ球減少症を取り上げると35%（9/26例），また grade 3（CTCAE Ver.3）以上の重篤な有害事象を生じたものは23%（6/26例）に見られた．また重篤な例として48日間の入院加療を要した消化管出血を伴う消化管壊死（grade3），輸液を必要とする下痢（grade2）それぞれ1例があった．持続する悪心・食欲不振35%（9/26例），ほぼ全例にみられた便秘，肝機能値の上昇はいずれも軽度（grade2）であり，また *Pneumocystis* 肺炎の発症はなかった．今回これまでになかった有害事象として抑うつ状態15%（4/26例）も報告した．〔結語〕我々の調査では TMZ による grade3 以上の有害事象は，これまでに報告されてきた以上の頻度で発生していたことがわかった．また今回報告する TMZ による重篤な消化管障害や抑うつ状態はこれまでに報告されていない．人種差の検討も含めて今後日本人データの蓄積と共有が必要である．