

Clinical Trial Note

## A Multicenter Phase I Trial of Interferon- $\beta$ and Temozolomide Combination Therapy for High-grade Gliomas (INTEGRA Study)

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A multicenter phase I clinical trial, namely, Integrated Japanese Multicenter Clinical Trial: A Phase I Study of Interferon- $\beta$  and Temozolomide for Glioma in Combination with Radiotherapy (INTEGRA Study), is being conducted for patients with high-grade glioma in order to evaluate the safety, feasibility and preliminary clinical effectiveness of the combination of interferon- $\beta$  and temozolomide. The primary endpoint is incidence of adverse events. The secondary endpoints are progression-free survival time and overall survival time. In addition, objective tumor response will be evaluated in a subpopulation of patients with the measurable disease. The reduction rate of tumor will be calculated according to Response Evaluation Criteria In Solid Tumors for measurable tumors as determined by magnetic resonance imaging. Subsequently, the overall response will be evaluated based on the results of measurable and non-measurable tumors. Ten newly diagnosed and 10 recurrent patients will be enrolled in this study.

*Key words:* chemo-phase I-II-III – clinical trials – CNS

### INTRODUCTION

Gliomas account for ~40% of all brain tumors and are thus the most common primary tumors of the central nervous system. Primary brain tumors are classified according to their cell type and histological grade into categories defined by the World Health Organization (WHO) (1). High-grade (WHO grades III and IV) gliomas, which include anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), anaplastic oligoastrocytoma (AOA) and glioblastoma multiforme (GBM), are often resistant to treatment; GBM, the most common glioma in adults, kills patients within a median time span of a year after diagnosis despite treatment

with aggressive surgical resection, nitrosourea-based chemotherapy and radiotherapy (2–4). A number of studies by large cooperative groups have shown the benefits of radiation therapy in doses up to 60 Gy after surgery for improving overall survival and time to progression (5). In Japan, nitrosourea agents such as 1-(4-amino-2-methyl-5-pyridiminy)l-methyl-3-(2-chloroethyl)-3-nitrosourea and methyl-6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-alpha-D-glucopyranoside have been used to treat malignant gliomas for a long time; however, this treatment offered few clinical benefits. Temozolomide (TMZ), an oral alkylating agent, has been demonstrated to possess antitumor activity against malignant gliomas, with minimal additional toxicity; furthermore, in a previous study of concomitant radiation therapy and chemotherapy with TMZ followed by adjuvant TMZ, survival duration substantially improved (6). In 2006, TMZ

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was certified as the treatment agent for malignant gliomas by the National Ministry of Health and Welfare of Japan, and a combination of radiotherapy and chemotherapy with TMZ is now used as the first-line therapy. However, its clinical outcomes depend on the *O*-(6)-methylguanine-DNA methyltransferase (MGMT) status, and MGMT modification is one of the key factors to obtain greater clinical benefits in the future.

Interferon- $\beta$  (IFN- $\beta$ ) exhibits pleiotropic biological effects and has been widely used either alone or in combination with other antitumor agents in the treatment of malignant gliomas and melanomas (7). In the treatment of malignant gliomas, IFN- $\beta$  can act as a drug sensitizer, enhancing toxicity against various neoplasms when administered in combination with nitrosourea. IFN- $\beta$  and nitrosourea combination therapy has been particularly used for the treatment of gliomas in Japan (8). Previously, we demonstrated that IFN- $\beta$  markedly enhanced chemosensitivity to TMZ in an *in vitro* study of human glioma cells (9); this finding suggested that one of the major mechanisms by which IFN- $\beta$  enhances chemosensitivity is the downregulation of MGMT transcription via *p53* induction. This effect was also observed in an experimental animal model (10). These two studies suggested that chemotherapy with IFN- $\beta$  and TMZ plus radiation might further improve the clinical outcome in malignant gliomas when compared with TMZ plus radiation therapy. Here, in order to evaluate the safety, feasibility and preliminary clinical effectiveness of the combination of IFN- $\beta$  and TMZ, we are conducting a clinical study, namely, Integrated Japanese Multicenter Clinical Trial: A Phase I Study of Interferon- $\beta$  and Temozolomide for Glioma in Combination with Radiotherapy (INTEGRA study). This study involves eight medical institutions, covering the entire regional population of Japan.

## PROTOCOL DIGEST OF THE STUDY

### PURPOSE

The main aim of this study is to evaluate the safety, feasibility and preliminary clinical effectiveness of IFN- $\beta$  and TMZ for the treatment of malignant gliomas.

### STUDY SETTING AND PROTOCOL REVIEW

This is a multicenter clinical trial involving eight neurosurgical institutions: Yamagata, Saitama Medical, Nippon Medical, Nagoya, Osaka, Kyoto, and Hiroshima Universities and Kitano Hospital. The protocol has been reviewed and approved by institutional review boards of each of these institutions.

### REGISTRATION AND MONITORING

Participating investigators are instructed to send an eligibility criteria report to the Data Center at Nagoya University,

which is a third party different from the study director. Ten newly diagnosed and 10 recurrent patients are registered for a period of 6 months from December 2007. Data, including those of magnetic resonance imaging (MRI), blood tests, and pathology, will be collected at the data center. The quality of data will be checked and verified at the data center. If required, the data center would provide feedback to the institutions. The data center will send high-quality data to the study director. Committees of safety and efficacy (Dr Kazuo Tabuchi, Koyanagi Memorial Hospital, Saga), radiotherapy (Dr Shinji Naganawa, Department of Radiology, Nagoya University School of Medicine), pathological review (Dr Youichi Nagasato, Department of Pathology, Gunma University School of Medicine) and statistics (Dr Kunihiko Hayashi, Gunma University School of Health Science) will send their reports to the head office.

### ENDPOINTS

The primary endpoint is incidence of adverse events. The secondary endpoints are progression-free survival time and overall survival time. In addition, objective tumor response will be evaluated in a subpopulation of patients with measurable disease. The reduction rate of tumor will be calculated according to Response Evaluation Criteria In Solid Tumors for measurable tumors as determined by MRI. Non-measurable tumors are classified into four grades: complete remission, partial response, progression and not evaluable. Subsequently, the overall response will be evaluated based on the results of measurable and non-measurable tumors.

### ELIGIBILITY CRITERIA

The eligibility criteria are as follows:

- (i) Histologically confirmed diagnosis of newly diagnosed or recurrent high-grade glioma (AA, AO, AOA or GBM). More than 50% volume of tumor is located in the supratentorial region.
- (ii) No tumor recognized in the optic nerve, olfactory nerve and pituitary gland on pretreatment MRI.
- (iii) No dissemination detected by MRI. Age between 18 and 75 years at the time of registration.
- (iv) Performance status is 0–2, 3 only due to neurological deficits.
- (v) Sufficient organ function before chemotherapy according to the following laboratory data: WBC  $\geq 3000/\text{mm}^3$  or neutrophils  $\geq 1500/\text{mm}^3$ , platelets  $\geq 100\,000/\text{mm}^3$ , hemoglobin  $\geq 8.0$  g/dl, bilirubin  $\leq 1.5$  mg/dl, serum glutamic oxaloacetic transaminase  $\leq 100$  IU, serum glutamic pyruvic transaminase  $\leq 100$  IU, creatinine  $\leq 1.5$  mg/dl, creatinine clearance  $\geq 50$  ml/min and electrocardiogram showing no serious arrhythmia and no serious ischemic heart disease.
- (vi) No prior chemoradiotherapy for newly diagnosed patients.

- (vii) The interval from the end of prior anti-tumor therapy (e.g. chemotherapy, radiotherapy, immunotherapy) must be at least 4 weeks for recurrent patients, regardless of the regimen.
- (viii) Written informed consent.

#### EXCLUSION CRITERIA

The exclusion criteria are as follows:

- (i) synchronous double cancer or metachronous double cancer in last 5 years; carcinoma *in situ* accepted;
- (ii) meningitis or pneumonia;
- (iii) pregnant, possibly pregnant, or nursing women;
- (iv) mental disorder;
- (v) uncontrolled diabetes mellitus (DM) or under treatment with insulin for DM;
- (vi) myocardial infarction in last 3 months;
- (vii) history of pulmonary fibrosis or interstitial pneumonia.

#### TREATMENT METHODS

For newly diagnosed patients:

Radiotherapy 60 Gy/30 fr, 2 Gy  $\times$  5 days/week;  
 IFN- $\beta$  3 MIU/body, administered intravenously on alternate days during radiotherapy;  
 TMZ 75 mg/(m<sup>2</sup> day), daily from the first day to the last day of radiotherapy.

After completing this induction period, all patients will have 4 weeks of washout period, and they will be then shifted to adjuvant period.

IFN- $\beta$  3 MIU/body, administered on the first day morning every 4 weeks;  
 TMZ 150 mg/(m<sup>2</sup> day) (days 1–5: first cycle);  
 200 mg/(m<sup>2</sup> day) (days 1–5: second to sixth cycle).

In the absence of hematologic toxicity, the dose is increased to 200 mg/(m<sup>2</sup> day), beginning with the second cycle to the sixth cycle.

This cycle is repeated six times every 28 days in the absence of tumor progression, serious adverse events such as grade 4 hematological toxicity, refusal of therapy and deviation from the protocol.

For recurrent patients:

IFN- $\beta$  3 MIU/body, administered the first day morning every 4 weeks (day 1);  
 TMZ 150 mg/(m<sup>2</sup> day) (days 1–5: first cycle);  
 200 mg/(m<sup>2</sup> day) (days 1–5: second to sixth cycle).

In the absence of hematologic toxicity, the dose is increased to 200 mg/(m<sup>2</sup> day), beginning with the second cycle to the sixth cycle.

This cycle is repeated six times every 28 days.

This regimen has been considered to be the most promising based on previous clinical studies (8,11–14). Thus, dose-limiting toxicity was not evaluated in this study.

#### FOLLOW-UP AND STATISTICAL METHODS

Disease progression and occurrence of new disease will be examined by MRI performed at baseline and at least after every 4–5 weeks during treatment. Blood tests and symptom checks will be carried out before treatment and at least after every 2 weeks during treatment. Follow-up will continue for 3 months from the end of treatment. In cases wherein therapy is discontinued due to toxicity, clinicians would follow-up patients until they recover from toxicity. In addition, overall survival, progression-free survival and treatment success curves are constructed as time-to-event plots by the Kaplan–Meier method.

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#### Conflict of interest statement

None declared.

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