Randomized Controlled Trial on Malignant Brain Tumors

—Activities of the Japan Clinical Oncology Group-Brain Tumor Study Group—

Soichiro SHIBUI, M.D.

Neurosurgery Division, National Cancer Center Hospital, Tokyo

Abstract

The Japan Clinical Oncology Group (JCOG)-Brain Tumor Study Group was organized with the support of the Health and Labour Sciences Research Grants of the Ministry of Health, Labour and Welfare. The group is now preparing a multi-institutional randomized controlled phase II/III study of chemoradiotherapy using ACNU versus procarbazine and ACNU for astrocytoma grades 3 and 4. The overall survival and response rates will be compared between the patients treated with ACNU and those treated with ACNU plus procarbazine. This study, under the surveillance of the JCOG, aims to set a standard protocol for treating patients with malignant glioma. Moreover, the study will establish a proper methodology for performing randomized studies in the field of neuro-oncology.

Key words: Japan Clinical Oncology Group, randomized controlled trial, malignant glioma, ACNU, procarbazine, O⁶-methylguanine deoxyribonucleic acid-methyltransferase

Introduction

The Japan Clinical Oncology Group (JCOG) is a multi-institutional cooperative oncology group conducting clinical research for cancer and related problems.²⁾ JCOG consists of 13 oncology groups as of 2003. The Brain Tumor Study Group (JCOG-BTSG) was organized in April 2002 with support from the Health and Labour Research Grants of the Ministry of Health, Labour and Welfare in order to establish a standard therapy for malignant brain tumors.

This study describes a randomized controlled phase II/III study of chemoradiotherapy using ACNU versus procarbazine and ACNU for astrocytoma grades 3 and 4.

Materials and Methods

Patients with newly diagnosed supratentorial astrocytoma grade 3 or 4 will be enrolled and randomly divided into two groups. Patients in Group A will be treated with ACNU (80 mg/m² iv) during the postoperative radiotherapy (60 Gy local), whereas patients in Group B with procarbazine (80 mg/m² for 10 days per os) preceding and in addition to the administration of ACNU. Each regimen will be repeated every 8 weeks for 2 years if tolerated by the patients. The primary endpoint is the overall survival rate and the secondary endpoints are the response rate on magnetic resonance imaging and the frequency of adverse events. This study starts as a randomized phase II trial and proceeds to the phase III study if the efficacy of the Group B regimen in phase II warrants a study continuation.

The study protocol was developed under guidance of the JCOG and approved by the institutional review board of the institution to which each JCOG-BTSG member belongs. The study will be performed under surveillance by the JCOG.

Results

This study starts at the beginning of 2004. The expected number of patient enrollments is 310 in 5 years. The collected data will be monitored and statistical analyses carried out by the JCOG Data Center. The results will be evaluated by the Steering Committee.

Discussion

A standard therapy for malignant gliomas has not been established and various trials have been carried out. In most neurosurgical institutes in Japan, nimustine hydrochloride (ACNU) is administered in conjunction with conventional radiotherapy after surgical removal of the tumor. However, this common treatment regimen has never been scientifically justified by a randomized controlled study, and so should be considered "community standard."

The efficacy of ACNU in malignant glioma patients was evaluated in a group who received postoperative administration of ACNU in conjunction with radiation therapy and another group was received only radiation therapy.⁴⁾ This controlled study revealed an improved response rate for the patients treated with ACNU, however, no significant difference in overall survival was observed between the two groups.

ACNU is one of the most effective chemotherapeutic agents to date for malignant gliomas. ACNU passes through the intact blood-brain barrier and alkylates deoxyribonucleic acid (DNA) causing the anti-tumor effect. Most malignant gliomas nevertheless recur after ACNU chemotherapy and radiotherapy. Malignant gliomas frequently express high activities of O⁶-methylguanine DNA-methyltransferase (MGMT), a DNA repair enzyme, which is considered to be one of the causes of the chemoresistance to ACNU. Procarbazine is another alkylating agent that yields O⁶-alkylguanine.³⁾ If procarbazine is administered prior to ACNU as in our current

Correspondence to: Soichiro Shibui, M.D., Neurosurgery Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81-3-3542-2511, Fax: +81-3-3542-3815, e-mail: sshibui@ncc.go.jp

protocol, we expect the abundant O⁶-alkylguanine to deprive MGMT, leading to increased efficacy of ANCU.⁵⁾ A similar treatment protocol was applied using BCNU, procarbazine, and vincristine to 58 patients with recurrent glioblastoma and reported a high response rate of 29% (complete response 10.3%, partial response 19%).¹⁾

In order to establish a standard therapy for a certain clinical entity, strict randomized controlled studies are essential. Few such studies in the neuro-oncological field have been carried out in Japan. Brain tumor is one of the so-called orphan diseases. Hence, multi-institutional cooperation is essential to accomplish randomized trials that require a large number of patient enrollment. JCOG is a group of oncologists that conduct cooperative studies on various cancers in Japan. The BTSG was newly organized in JCOG and is now preparing this randomized trial in an unprecedented organized manner. Upon completion, this study should provide a scientific basis for the standard therapy for malignant gliomas. Moreover, we hope to establish a proper methodology for performing randomized studies in the field of neuro-oncology.

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Appendix: Members of the Japan Clinical Oncology Group-Brain Tumor Study Group

Akio Asai (Saitama Medical School, Saitama), Takamitsu Fujimaki (Teikyo University, Tokyo), Takamasa Kayama (Yamagata University, Yamagata), Masato Kochi (Kumamoto University, Kumamoto), Toshihiro Kumabe (Tohoku University, Sendai, Miyagi), Yoshihiro Muragaki (Tokyo Women's Medical University, Tokyo), Motoo Nagane (Kyorin University, Mitaka, Tokyo), Hirohiko Nakamura (Nakamura Memorial Hospital, Sapporo, Hokkaido), Ryo Nishikawa (Saitama Medical School, Saitama), Kazuhiro Nomura (National Cancer Center Hospital, Tokyo), Yutaka Sawamura (Hokkaido University, Sapporo, Hokkaido), Soichiro Shibui (National Cancer Center Hospital, Tokyo), Hideaki Takahashi (Niigata University, Niigata), Katsuyuki Tanaka (St. Marianna University School of Medicine, Kawasaki, Kanagawa), Tomoki Todo (University of Tokyo, Tokyo), Toshiaki Yamaki (Sapporo Medical University, Sapporo, Hokkaido), Takahito Yazaki (Keio University, Tokyo), Minako Sumi (National Cancer Center Hospital, Tokyo)