Table 3 Comparison of cancer-specific HRQOL in children with brain tumors and those with other cancers

	This study[a]		Tsuji et al. [25][b]			P[c]	Effect size d[d]
	Mean	SD	n	Mean	SD		
N = 143							
Child report (n = 124)							
Pain and Hurt	89.8	19.3	202	84.7	19.7	0.024	0.26
Nausea	88.0	20.0	199	83.0	24.0	0.044	0.23
Procedural Anxiety	72.5	32.8	203	72.9	31.0	0.910	−0.01
Treatment Anxiety	90.7	22.8	203	93.1	17.0	0.302	−0.12
Worry	81.0	25.8	202	76.6	25.9	0.140	0.17
Cognitive Problems	72.3	23.8	200	71.5	22.1	0.775	0.03
Perceived Physical Appearance	71.9	28.7	204	70.3	28.6	0.639	0.05
Communication	65.5	32.6	204	67.0	27.0	0.656	−0.05
Parent report (n = 143)							
Pain and Hurt	84.9	20.9	242	82.9	22.0	0.367	0.09
Nausea	87.0	20.8	233	80.5	25.7	0.008	0.28
Procedural Anxiety	55.7	36.6	242	63.2	31.8	0.043	−0.22
Treatment Anxiety	77.9	24.4	241	84.9	19.0	0.004	−0.32
Worry	79.0	23.6	242	81.4	21.9	0.334	−0.10
Cognitive Problems	65.8	24.9	243	69.4	21.6	0.151	−0.15
Perceived Physical Appearance	71.7	25.3	243	73.8	24.9	0.437	−0.08
Communication	60.1	31.1	241	62.2	25.4	0.496	−0.07

HRQOL health-related quality of life, *SD* standard deviation

[a] Means and SDs of the PedsQL Cancer Module score in children with brain tumors adjusted for age and treatment status to subjects reported by Tsuji et al. [25]

[b] Previously reported data in children with the other cancers

[c] P value from the Welch t test

[d] Effect size d defined by Cohen [28] is the difference between two means divided by a pooled SD with two samples. A positive value indicates that children with brain tumors have higher HRQOL scores compared with children with other cancers

Agreement between the PedsQL cancer and the PedsQL Brain Tumor Modules of the PedsQL

Children and parents reported higher Pain and Hurt scores ($d = 0.29$, $P = 0.001$ and $d = 0.22$, $P = 0.010$, respectively) on the Cancer than on the Brain Tumor Module (Table 4). Children reported higher Procedural Anxiety ($d = 0.31$, $P = 0.001$) and Cognitive Problems scores ($d = 0.28$, $P = 0.003$) on the Cancer Module. The agreement between the PedsQL Cancer and the PedsQL Brain Tumor Modules was very high (ICC > 0.80) except for the Pain and Hurt scale for the child report where the agreement was moderate (ICC = 0.43). The agreement according to treatment status is shown in Supplementary Table 2.

Discussion

We report here that children with brain tumors perceive their HRQOL differently from children with other cancers.

Several aspects of HRQOL were more difficult (for example, procedural and treatment anxiety) for patients with brain tumors, while other aspects (nausea, pain and hurt) were less difficult, and a number of factors may be responsible for these differences. In particular, the brain is the center of multiple functions. The brain integrates the information received from, and coordinates the physical and mental activity of, the whole body. Thus, the unique HRQOL of children with brain tumors likely reflects the vast complexity of brain function. Knowledge of these differences should help medical practitioners design-specific support and care strategies for these children.

A total of 29 % of children in this study suffered from embryonal tumors (mainly medulloblastomas), and treatment for these tumors requires surgery, radiation, and chemotherapy [32, 33]. The main treatments for children with germ cell tumors (mainly germinomas) include surgery, radiation, and chemotherapy [34], with chemotherapy representing the main treatment for children with leukemia (controls). Each treatment method will affect a child's HRQOL differently.

Table 4 Comparison of cancer-specific HRQOL using the PedsQL cancer and PedsQL Brain Tumor Modules

	n	Dif.[a]	95 % CI of the Dif.		P[b]	Effect size d[c]	ICC (5–18 years)[d]	ICC (2–18 years)[e]
			Lower	Upper				
$N = 143$								
Child report ($n = 124$)								
Pain and Hurt	124	5.41	2.12	8.70	0.001	0.29	0.43	–
Nausea	124	0.91	−0.91	2.72	0.325	0.09	0.88	–
Procedural Anxiety	123[f]	4.34	1.80	6.87	0.001	0.31	0.89	–
Worry	124	1.95	−0.39	4.30	0.102	0.15	0.84	–
Cognitive Problems	124	3.64	1.29	5.99	0.003	0.28	0.81	–
Parent report ($n = 143$)								
Pain and Hurt	143	2.50	0.60	4.40	0.010	0.22	0.82	0.91
Nausea	143	0.59	−1.20	2.39	0.515	0.05	0.91	0.89
Procedural Anxiety	142[f]	2.14	−0.77	5.05	0.148	0.12	0.88	0.87
Worry	143	1.46	−0.20	3.11	0.084	0.15	0.90	0.90
Cognitive Problems	124[g]	−0.99	−2.89	0.91	0.304	−0.09	0.89	–

CI confidence interval, *Dif.* difference, *HRQOL* health-related quality of life, *ICC* intraclass correlation coefficients, *PedsQL* pediatric quality of life inventory, *SD* standard deviation

[a] Mean score differences (PedsQL Cancer Module—PedsQL Brain Tumor Module). A positive value indicates that participants (children with brain tumors or parents of children with brain tumors) have higher scores in the PedsQL Cancer Module (fewer problems) than in the PedsQL Brain Tumor Module

[b] P value from the paired t test

[c] Effect size d defined by Cohen [28] is the mean score difference divided by SD of the mean score difference. A positive value indicates that participants (children with brain tumors or parents of children with brain tumors) scored higher in the PedsQL Cancer Module (fewer problems) than the PedsQL Brain Tumor Module

[d] ICC values for the PedsQL Cancer Module and the PedsQL Brain Tumor Module in the one-way random effects model among children aged 5–18 years

[e] ICC values for the PedsQL Cancer Module and the PedsQL Brain Tumor Module in the one-way random effects model among children aged 2–18 years

[f] Missing data for the Brain Tumor Module ($n = 1$) were excluded

[g] The PedsQL Brain Tumor Module parent report for toddlers (ages 2–4) does not include the Cognitive Problems scale

Children with brain tumors reported less difficulty with pain and hurt than children with other cancers; however, we believe it unlikely that these children actually experienced less pain, as here and in a previous study [17], parents reported similar difficulty with pain and hurt irrespective of cancer type. Children with brain tumors reported pain and hurt more frequently than children with lymphoma at a similar frequency to children with leukemia and less frequently than children with solid tumors [4]. These inconsistencies may arise due to scale characteristics. The agreement between Pain and Hurt scores in the Cancer and Brain Tumor Modules was moderate, while the agreement on other scales was high. These findings suggest that the Pain and Hurt scale of the PedsQL Cancer Module may not consider problems for children with brain tumors compared with the Brain Tumor Module.

The Pain and Hurt scale of the Cancer Module asks about generalized body pain but does not localize the pain. For example, "I ache or hurt in my joints and/or muscles," versus "I hurt a lot." Further, the Brain Tumor Module measures two items present in the Cancer Module and, uniquely, "I get headaches." Thus, the Brain Tumor Module includes a question about headaches, which are frequent in patients and survivors of brain tumors [35]. Headache is the most frequently reported initial symptom of pediatric brain tumors in children aged ≥ 2 years and may be interpreted with particular meaning for these children [36]. Headache would remind the children and parents of the first brain tumor and induce worry about a relapse. Such headaches cause physical distress and psychosocial concern. Therefore, we prefer to use the Brain Tumor to the Cancer Module to measure disease-specific HRQOL for these children.

Children with brain tumors and their parents reported less difficulty with nausea than children with other cancers. Causes of nausea may include side effects of chemotherapy, radiation sickness, postoperative reactions, tumors close to the area postrema, intracranial hypertension, gastrointestinal pathology, and anxiety [37, 38]. Here, at least 1 month had passed since diagnosis, and factors such as

postoperative reaction, brain-tumor activity, and intracranial hypertension would have been controlled, resulting in less difficulty with nausea [39, 40].

Patients may experience strong nausea and vomiting at the onset of brain tumors as well as in the perioperative period; therefore, pediatric patients may evaluate their experience with treatment-induced nausea and vomiting as less trying than that experienced perioperatively. In contrast, children with ALL (control group majority) are treated at the first remission-induction phase using moderately emetogenic chemotherapy (i.e., vincristine, daunorubicin, L-asparaginase) [41], and severe emetogenic chemotherapy (i.e., cyclophosphamide, ifosfamide) is added during the intensification phase. Treatment type and course will affect a child's experience, so a longitudinal study will be required to assess how the experience of children with brain tumors changes after diagnosis and treatment.

Parents of children with brain tumors reported more procedural and treatment anxiety for their children than did the parents of children with other cancers. The PedsQL Cancer Module evaluates children's and parents' perception of a child's anxiety about needle sticks, blood tests, seeing a doctor, and hospitalization, which relate to trauma and stressor-related symptoms that are classified as anxiety disorders. Perceived life threat and treatment intensity are directly associated with posttraumatic stress disorder [42]. We assume that intensive symptoms and the treatment of pediatric brain tumors increase anxiety.

Our findings here of increased anxiety in children with brain tumors differ from those of a previous study conducted in the United States [17]. Although we cannot explain the reason for this discrepancy, pediatric oncology practice differs between the United States and Japan [43], and patients in Japan may not be fully informed of the diagnosis, which affects posttraumatic stress disorder [44]. Cognitive problems of children with brain tumors might also limit their understanding of disease and treatment course. Each child's psychological readiness for each stage of the diagnosis and treatment may be affected by the information provided and by the child's cognitive ability.

Several limitations of the present study warrant mention. First, the study and controls were heterogeneous and included various pathologies. All children in this study suffered central nervous system damage from invasion, compression, or hydrocephalus as well as from therapy. Further investigations of tumor types and treatment should reveal how HRQOL differs between children with brain tumors and those with other cancers.

Second, data obtained from children and parents were not completely equivalent; the ages of self-reporting children ranged between 5 and 18 years, whereas parental-reporting included children 2–18 years of age. Further, the

varying degrees of patients' impairments prevented optimum accuracy of reporting [17]. However, the number of children participating in the present study (133) was similar to that of participating parents of children aged 5–18 years (140) because of assisted administration. Further, HRQOL reporting by children is not significantly influenced by the administration technique [24, 45].

Third, the PedsQL Cancer and Brain Tumor Modules employ different recall periods, as described above [15, 25]. This difference must be taken into account when interpreting data. Although the items on the Procedural Anxiety subscale are identical in both modules, children with brain tumors studied here reported less difficulty with procedural anxiety using the Cancer than with the Brain Tumor Module. The recall period may alter a child's perception of procedural anxiety. Further research is required to determine why children reported less anxiety over the past month than over the previous 7 days.

Fourth, our ability to generalize the data is limited. For example, at the CCAJ, several hundred families, including those not eligible to participate, were notified of this study; therefore, the true response rate is unknown. Families were excluded if doctors or social workers determined that the family found the child's condition too uncomfortable to discuss. Although the number of such excluded families was not recorded, this exclusion may have limited data collection.

Fifth, when comparing children with brain tumors to those with other cancers, certain parental characteristics could not be taken into account, as Tsuji et al. [25] did not report them. Parental reports might have been influenced by factors such as parental mental health, which may limit comparability. However, all child and parent characteristics reported here, except for age and tumor pathology, were similar.

Conclusion

Here, we found that children with brain tumors reported less difficulty with the categories of pain and hurt and nausea than children with other cancers that included mostly leukemia. Parents of the children with brain tumors reported more procedural and treatment anxiety. The information will help medical professionals and researchers to understand the influence of the disease and treatment on the HRQOL of children with brain tumors regardless of age and treatment status.

This study is the only comparison, to our knowledge, of the PedsQL Cancer and Brain Tumor Modules. The PedsQL Cancer Module compares cancer-specific HRQOL of children with brain tumors and those with other cancers. However, the PedsQL Brain Tumor Module is more

sensitive for brain-tumor-specific aspects of the HRQOL and should be used to assess HRQOL in children with brain tumors.

References

1. Gatta, G., Corazziari, I., Magnani, C., Peris-Bonet, R., Roazzi, P., Stiller, C., et al. (2003). Childhood cancer survival in Europe. *Annals of Oncology, 14*(Suppl. 5), v119–v127.
2. Baba, S., Ioka, A., Tsukuma, H., Noda, H., Ajiki, W., & Iso, H. (2010). Incidence and survival trends for childhood cancer in Osaka, Japan, 1973–2001. *Cancer Science, 101*(3), 787–792.
3. Siegel, R., Naishadham, D., & Jemal, A. (2012). Cancer statistics, 2012. *CA: A Cancer Journal for Clinicians, 62*(1), 10–29.
4. Collins, J. J., Byrnes, M. E., Dunkel, I. J., Lapin, J., Nadel, T., Thaler, H. T., et al. (2000). The measurement of symptoms in children with cancer. *Journal of Pain and Symptom Management, 19*(5), 363–377.
5. Hedstrom, M., Haglund, K., Skolin, I., & von Essen, L. (2003). Distressing events for children and adolescents with cancer: Child, parent, and nurse perceptions. *Journal of Pediatric Oncology Nursing, 20*(3), 120–132.
6. Oeffinger, K. C., Mertens, A. C., Sklar, C. A., Kawashima, T., Hudson, M. M., Meadows, A. T., et al. (2006). Chronic health conditions in adult survivors of childhood cancer. *New England Journal of Medicine, 355*(15), 1572–1582.
7. Geenen, M., Cardous-Ubbink, M., Kremer, L., van den Bos, C., van der Pal, H., Heinen, R., et al. (2007). Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA, 297*(24), 2705–2715.
8. Kamibeppu, K., Sato, I., Honda, M., Ozono, S., Sakamoto, N., Iwai, T., et al. (2010). Mental health among young adult survivors of childhood cancer and their siblings including posttraumatic growth. *Journal of Cancer Survivorship, 4*(4), 303–312.
9. Werba, B. E., Hobbie, W., Kazak, A. E., Ittenbach, R. F., Reilly, A. F., & Meadows, A. T. (2007). Classifying the intensity of pediatric cancer treatment protocols: The intensity of treatment rating scale 2.0 (ITR-2). *Pediatric Blood & Cancer, 48*(7), 673–677.
10. Kazak, A. E., Hocking, M. C., Ittenbach, R. F., Meadows, A. T., Hobbie, W., DeRosa, B. W., et al. (2012). A revision of the intensity of treatment rating scale: Classifying the intensity of pediatric cancer treatment. *Pediatric Blood & Cancer, 59*(1), 96–99.
11. Armstrong, G. T., Liu, Q., Yasui, Y., Neglia, J. P., Leisenring, W., Robison, L. L., et al. (2009). Late mortality among 5-year survivors of childhood cancer: A summary from the childhood cancer survivor study. *Journal of Clinical Oncology, 27*(14), 2328–2338.
12. Zebrack, B. J., Gurney, J. G., Oeffinger, K., Whitton, J., Packer, R. J., Mertens, A., et al. (2004). Psychological outcomes in long-term survivors of childhood brain cancer: A report from the childhood cancer survivor study. *Journal of Clinical Oncology, 22*(6), 999–1006.
13. Zeltzer, L. K., Recklitis, C., Buchbinder, D., Zebrack, B., Casillas, J., Tsao, J. C. I., et al. (2009). Psychological status in childhood cancer survivors: A report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology, 27*(14), 2396–2404.
14. Gurney, J. G., Krull, K. R., Kadan-Lottick, N., Nicholson, H. S., Nathan, P. C., Zebrack, B., et al. (2009). Social outcomes in the Childhood Cancer Survivor Study cohort. *Journal of Clinical Oncology, 27*(14), 2390–2395.
15. Palmer, S. N., Meeske, K. A., Katz, E. R., Burwinkle, T. M., & Varni, J. W. (2007). The PedsQL Brain Tumor Module: Initial reliability and validity. *Pediatric Blood & Cancer, 49*(3), 287–293.
16. Bhat, S. R., Goodwin, T. L., Burwinkle, T. M., Lansdale, M. F., Dahl, G. V., Huhn, S. L., et al. (2005). Profile of daily life in children with brain tumors: An assessment of health-related quality of life. *Journal of Clinical Oncology, 23*(24), 5493–5500.
17. Meeske, K., Katz, E. R., Palmer, S. N., Burwinkle, T., & Varni, J. W. (2004). Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer, 101*(9), 2116–2125.
18. Pogorzala, M., Styczynski, J., Kurylak, A., Debski, R., Wojtkiewicz, M., & Wysocki, M. (2010). Health-related quality of life among paediatric survivors of primary brain tumours and acute leukaemia. *Quality of Life Research, 19*(2), 191–198.
19. Cella, D. F., Tulsky, D. S., Gray, G., Sarafian, B., Linn, E., Bonomi, A., et al. (1993). The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. *Journal of Clinical Oncology, 11*(3), 570–579.
20. Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., et al. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute, 85*(5), 365–376.
21. Varni, J. W., Burwinkle, T. M., Katz, E. R., Meeske, K., & Dickinson, P. (2002). The PedsQL in pediatric cancer: Reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer, 94*(7), 2090–2106.
22. Weitzner, M. A., Meyers, C. A., Gelke, C. K., Byrne, K. S., Cella, D. F., & Levin, V. A. (1995). The Functional Assessment of Cancer Therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. *Cancer, 75*(5), 1151–1161.
23. Osoba, D., Aaronson, N. K., Muller, M., Sneeuw, K., Hsu, M. A., Yung, W. K., et al. (1996). The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Quality of Life Research, 5*(1), 139–150.
24. Sato, I., Higuchi, A., Yanagisawa, T., Mukasa, A., Ida, K., Sawamura, Y., et al. (2010). Development of the Japanese version of the Pediatric Quality of Life Inventory Brain Tumor Module. *Health and Quality of Life Outcomes, 8*(1), 38.
25. Tsuji, N., Kakee, N., Ishida, Y., Asami, K., Tabuchi, K., Nakadate, H., et al. (2011). Validation of the Japanese version of the Pediatric Quality of Life Inventory (PedsQL) Cancer Module. *Health and Quality of Life Outcomes, 9*(1), 22.
26. Cronbach, L. J. (1951). Coefficient alpha and the internal structure of tests. *Psychometrika, 16*(3), 297–334.
27. Bartko, J. J. (1966). The intraclass correlation coefficient as a measure of reliability. *Psychological Reports, 19*(1), 3–11.
28. Cohen, J. (1988). The t test for means. In J. Cohen (Ed.), *Statistical power analysis for the behavioral sciences* (pp. 19–74). New York: Lawrence Erlbaum Associates.
29. Gurney, J. G., Davis, S., Severson, R. K., Fang, J.-Y., Ross, J. A., & Robison, L. L. (1996). Trends in cancer incidence among children in the U.S. *Cancer, 78*(3), 532–541.
30. Bernard, J. L., Bernard-Couteret, E., Coste, D., Thyss, A., Scheiner, C., Perrimond, H., et al. (1993). Childhood cancer incidence in the south-east of France: A report of the Provence-Alpes-Cote d'Azur and Corsica Regions Pediatric Cancer Registry, 1984–1991. *European Journal of Cancer, 29*(16), 2284–2291.

31. Armitage, P., Berry, G., & Matthews, J. N. S. (2002). The method of weighting. In P. Armitage, G. Berry, & J. N. S. Matthews (Eds.), *Statistical methods in medical research* (pp. 215–218). Oxford: Blackwell Scientific Publications.

32. Packer, R. J., Gajjar, A., Vezina, G., Rorke-Adams, L., Burger, P. C., Robertson, P. L., et al. (2006). Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *Journal of Clinical Oncology, 24*(25), 4202–4208.

33. Gajjar, A., Chintagumpala, M., Ashley, D., Kellie, S., Kun, L. E., Merchant, T. E., et al. (2006). Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): Long-term results from a prospective, multicentre trial. *Lancet Oncology, 7*(10), 813–820.

34. Matsutani, M., & Japanese Pediatric Brain Tumor Study, G. (2001). Combined chemotherapy and radiation therapy for CNS germ cell tumors—The Japanese experience. *Journal of Neuro-Oncology, 54*(3), 311–316.

35. Ullrich, N. J. (2009). Neurologic sequelae of brain tumors in children. *Journal of Child Neurology, 24*(11), 1446–1454.

36. Dobrovoljac, M., Hengartner, H., Boltshauser, E., & Grotzer, M. (2002). Delay in the diagnosis of paediatric brain tumours. *European Journal of Pediatrics, 161*(12), 663–667.

37. Hamada, Y. (2009). Nausea and vomiting. In: M. Maru, & Y. Ishida (Eds.), *Pediatric oncology nursing* (pp. 237–240). Tokyo: Herusu Shuppan. [In Japanese].

38. American Society of Health-System Pharmacists. (1999). ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. *American Journal of Health-System Pharmacy, 56*(8), 729–764.

39. Schwartz, C. E., & Sprangers, M. A. G. (1999). Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. *Social Science and Medicine, 48*(11), 1531–1548.

40. Sprangers, M. A. G., & Schwartz, C. E. (1999). Integrating response shift into health-related quality of life research: a theoretical model. *Social Science and Medicine, 48*(11), 1507–1515.

41. Holdsworth, M. T., Raisch, D. W., & Frost, J. (2006). Acute and delayed nausea and emesis control in pediatric oncology patients. *Cancer, 106*(4), 931–940.

42. Stuber, M. L., Kazak, A. E., Meeske, K., Barakat, L., Guthrie, D., Garnier, H., et al. (1997). Predictors of posttraumatic stress symptoms in childhood cancer survivors. *Pediatrics, 100*(6), 958–964.

43. Ishibashi, A. (1996). Four concepts that distinguish pediatric oncology care in Japan from that in the United States: Telling the diagnosis, length of hospitalization, home care, and support systems. *Journal of Pediatric Oncology Nursing, 13*(4), 226–231.

44. Izumi, M., Ozawa, M., & Hosoya, R. (2002). Focusing on posttraumatic stress of survivors of childhood cancer. *Journal of Japan Pediatric Society, 106*(4), 464–471. [Abstract in English].

45. Sato, I., Higuchi, A., Yanagisawa, T., Mukasa, A., Ida, K., Sawamura, Y., et al. (2013). Factors influencing self- and parent-reporting health-related quality of life in children with brain tumors. *Quality of Life Research, 22*(1), 185–201.

ORIGINAL ARTICLE

A Multicenter Phase I/II Study of the BCNU Implant (Gliadel® Wafer) for Japanese Patients with Malignant Gliomas

Tomokazu AOKI,[1] Ryo NISHIKAWA,[2] Kazuhiko SUGIYAMA,[3] Naosuke NONOGUCHI,[4] Noriyuki KAWABATA,[4] Kazuhiko MISHIMA,[2] Jun-ichi ADACHI,[2] Kaoru KURISU,[3] Fumiyuki YAMASAKI,[3] Teiji TOMINAGA,[5] Toshihiro KUMABE,[5,†] Keisuke UEKI,[6] Fumi HIGUCHI,[6] Tetsuya YAMAMOTO,[7] Eiichi ISHIKAWA,[7] Hideo TAKESHIMA,[8] Shinji YAMASHITA,[8] Kazunori ARITA,[9] Hirofumi HIRANO,[9] Shinobu YAMADA,[10] and Masao MATSUTANI[2] for the NPC-08 study group

[1]Department of Neurosurgery, National Hospital Organization Kyoto Medical Center, Kyoto, Kyoto;
[2]Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, Hidaka, Saitama;
[3]Department of Neurosurgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Hiroshima;
[4]Department of Neurosurgery, Kitano Hospital, Osaka, Osaka;
[5]Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi;
[6]Department of Neurosurgery, Dokkyo Medical University Hospital, Shimotsuga, Tochigi;
[7]Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki;
[8]Department of Neurosurgery, Faculty of Medicine, University of Miyazaki Hospital, Miyazaki, Miyazaki;
[9]Department of Neurosurgery, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Kagoshima;
[10]Nobelpharma Co., Ltd., Tokyo;
[†]Department of Neurosurgery, Kitasato University School of Medicine, Sagamihara, Kanagawa (current affiliation)

Abstract

Carmustine (BCNU) implants (Gliadel® Wafer, Eisai Inc., New Jersey, USA) for the treatment of malignant gliomas (MGs) were shown to enhance overall survival in comparison to placebo in controlled clinical trials in the United States and Europe. A prospective, multicenter phase I/II study involving Japanese patients with MGs was performed to evaluate the efficacy, safety, and pharmacokinetics of BCNU implants. The study enrolled 16 patients with newly diagnosed MGs and 8 patients with recurrent MGs. After the insertion of BCNU implants (8 sheets maximum, 61.6 mg BCNU) into the removal cavity, various chemotherapies (including temozolomide) and radiotherapies were applied. After placement, overall and progression-free survival rates and whole blood BCNU levels were evaluated. In patients with newly diagnosed MGs, the overall survival rates at 12 months and 24 months were 100.0% and 68.8%, and the progression-free survival rate at 12 months was 62.5%. In patients with recurrent MGs, the progression-free survival rate at 6 months was 37.5%. There were no grade 4 or higher adverse events noted due to BCNU implants, and grade 3 events were observed in 5 of 24 patients (20.8%). Whole blood BCNU levels reached a peak of 19.4 ng/mL approximately 3 hours after insertion, which was lower than 1/600 of the peak BCNU level recorded after intravenous injections. These levels decreased to less than the detection limit (2.00 ng/mL) after 24 hours. The results of this study involving Japanese patients are comparable to those of previous studies in the United States and Europe.

Key words: BCNU implant, Gliadel® Wafer, malignant gliomas, phase I/II study, pharmacokinetic

1

Introduction

Malignant gliomas (MGs) are highly malignant cancers with 5-year survival rates of 25% or less.[1] The outcomes of MG treatments have been unsatisfactory, and drugs available in Japan for the treatment of MGs are limited to certain chemotherapeutic agents such as temozolomide (TMZ, Temodar®; Merck, Whitehouse Station, New Jersey, USA). There is no standard method for the treatment of recurrent MGs.

A BCNU implant is a controlled-release preparation of carmustine (BCNU; an alkylation agent of the nitrosourea family) that is inserted into the brain. BCNU was first approved in 1979 in the United States (USA) for the treatment of multiple myeloma and other conditions. Because this drug is highly lipid-soluble and can cross the blood-brain barrier effectively, it has been used primarily by injection for the treatment of brain tumors in USA and Europe.

Conventional BCNU preparations were effective against brain tumors; however, increasing the dose level to achieve a higher efficacy caused severe adverse systemic reactions (bone marrow suppression, lung toxicity, etc.). A BCNU implant is a sterile disc-like formulation (approximately 14.0 mm in diameter and approximately 1.3 mm in thickness) containing BCNU. Under moisture-rich conditions, the biodegradable component of the preparation is gradually hydrolyzed leading to release of the active ingredient BCNU, which exerts an anti-tumor effect (Fig. 1). If this preparation is inserted in the vicinity of residual tumor tissue during surgical resection of MGs, the tumor cells can be directly and efficiently exposed to high levels of BCNU for a certain period of time starting immediately after surgery while avoiding bone marrow suppression, lung toxicity, and other negative effects. This preparation is thus expected to be beneficial for diminishing residual tumors and
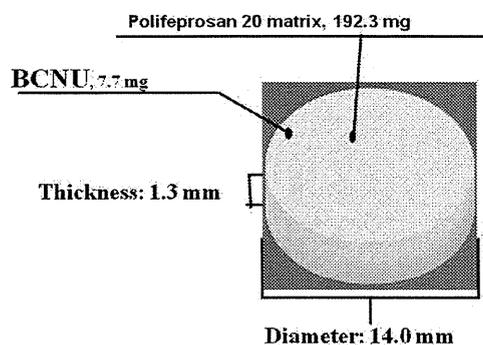

Fig. 1   BCNU implant configuration.

suppressing tumor growth. In a placebo-controlled, double-blind comparative study of patients with recurrent MGs, Brem et al.[2] reported that the cumulative death rate of glioblastoma (GBM) patients during the 6-month post-BCNU implant period was significantly lower than that in the placebo group (P = 0.013). In a placebo-controlled, double-blind comparative study of patients with newly diagnosed MGs, Valtonen et al.[3] reported that the survival rates of patients receiving BCNU implants were significantly higher than those of patients in the placebo group during the 12-month implant insertion period (P = 0.029). Westphal et al.[4] reported that the survival period was extended significantly by this preparation (P = 0.027). In these studies, the safety profile of BCNU implants was comparable to that of placebo, and no severe adverse events (bone marrow suppression, pulmonary fibrosis, etc.) due to BCNU implants were noted. On the basis of these clinical results, the BCNU implant is now recommended as an additional postoperative therapy for MGs in the treatment guidelines prepared by the National Comprehensive Cancer Network[5] and The National Cancer Institute (USA)[6] as well as the treatment guidelines prepared by the National Institute for Health and Clinical Excellence (UK).[7] However, in these clinical studies, radiotherapy was primarily utilized as concomitant therapy after BCNU implantation. These clinical studies were conducted between 1990 and 2002, and during that period, TMZ was approved only for the treatment of recurrent anaplastic astrocytoma. Therefore, combined therapy involving TMZ plus radiotherapy for newly diagnosed cases was not approved. In recent years, TMZ is often used as the standard therapy for MGs in combination with radiotherapy, and bevacizumab (BEV, Avastin®; Genentech, San Francisco, California, USA), an antivascular endothelial growth factor antibody. Therefore, it has recently been attracting attention as a new potential treatment for recurrent MGs. Retrospective reports on the safety and efficacy of BCNU implants in combination with these new treatments is available, but no prospective study has been carried out in compliance with Good Clinical Practice. Furthermore, the BCNU exposure level *in vivo* and the timing of its disappearance following insertion into the brain remain unknown. To evaluate the efficacy, safety, and pharmacokinetics of the BCNU implant combined with chemotherapy and radiation therapy after its insertion into the removal cavity in Japanese patients with MGs (newly diagnosed MGs and recurrent GBM), a prospective, uncontrolled, open-label, multicenter phase I/II study (NPC-08 study) was carried out from 2009

to 2012 after acquisition of the approval from the institutional review board of each participating facility. This paper will present the results of the survival survey conducted over 24 months after insertion of the BCNU implant, evaluations during the first 12 months after insertion, and the results of simultaneous BCNU blood level measurements.

Materials and Methods

This study (NPC-08 study) was carried out in compliance with ethical principles based on the Declaration of Helsinki, the study protocol, and Good Clinical Practice. Informed consent for treatment and postoperative follow-up was obtained from all patients. NPC-08 study was registered with ClinicalTrials.gov (number NCT00919737).

I. Patients

The study enrolled patients satisfying all of the following requirements: (1) presence of tumorous lesions in the cerebral parenchyma confirmed by magnetic resonance imaging (MRI), (2) age over 18 and less than 65, (3) Karnofsky performance status (KPS) 60 or over, and (4) histological suspicion of newly diagnosed MGs or recurrent GBM by intraoperative pathological diagnosis. Patients with recurrent GBM were enrolled in the study only when they had received prior conventional radiotherapy. The histopathological diagnosis was reviewed by a central pathological assessment committee separate from the participating facilities to ensure diagnosis by a third party. The required number of cases (24 cases) was defined under the consideration for previously reported adverse events in overseas (CSF leakage etc.). Concerning the required number (24 cases), each recurrent and newly diagnosed

MGs should include at least 8 cases to detect the expected side effect.

II. Procedures

A maximum of 8 sheets of BCNU implants were inserted into the removal cavity during surgery (maximum of 61.6 mg BCNU). Re-insertion during the study period was prohibited. On the 14th day following BCNU implant insertion, patients with newly diagnosed MGs received concomitant therapy, i.e., the standard therapy proposed by Stupp et al.[8] involving TMZ (75 mg·m-2day-1) plus radiation (60 Gy) for a maximum period of 6–7 weeks and adjuvant TMZ therapy with 1 cycle consisting of 5-day consecutive TMZ administration (150–200 mg·m^{-2}day^{-1}) and a subsequent 23-day cessation. For patients with recurrent GBM, appropriate adjuvant chemotherapy [e.g., chemotherapy with TMZ alone or TMZ plus Interferon- (INF-β)] was permitted (Fig. 2).

In this study, first we evaluated the status of the occurrence of adverse events carefully in a small number of patients (6 patients) at the efficacy and safety evaluation committee, and then, based on the judgment of the committee, we moved to a multicenter study with larger sample size.

Methods and Statistical Analyses

For efficacy evaluation, the overall survival (OS) rate at 24 months after insertion, median overall survival (mOS) period, and progression-free survival (PFS) rate at 12 months after insertion of BCNU implants were calculated by the Kaplan-Meier method. The following two population groups were an effective analysis set and are defined as a full analysis set (FAS) unless otherwise specifically noted:
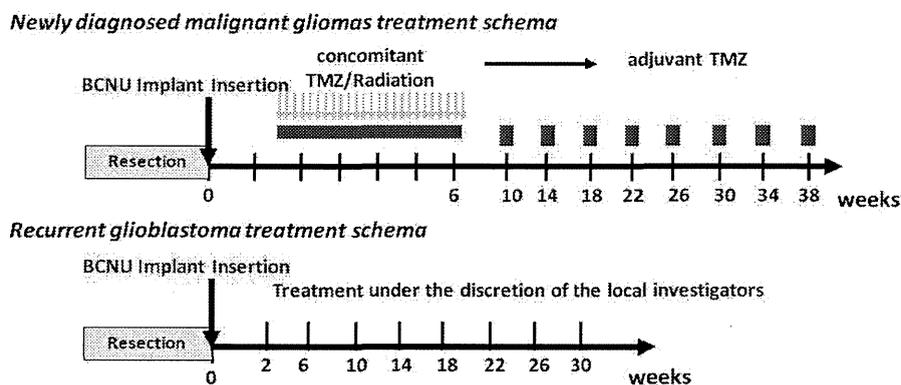

Fig. 2 Treatment schema. TMZ: temozolomide.

(a) An FAS group consisting of all subjects enrolled in the clinical study excluding those who never underwent implantation with the present formulation and (b) A group verified to have GBM/other GBM (non-GBM) based on the central pathological diagnosis.

To evaluate PFS, tumor progression was rated based on the following criteria: the tumor was classified as progressive if its major diameter multiplied by its vertical dimension (short minor diameter) showed a > 25% increase in comparison with the preceding image showing the minimum value for each parameter or if any new lesion(s) appeared (McDonald criteria). Evaluation of MRIs was carried out by the efficacy and safety evaluation committee in accordance with the McDonald criteria, and the evaluators were blinded to the background variables of the subjects. For efficacy analysis, the OS rate, mOS period, PFS rate, and median PFS period were determined by the Kaplan-Meier method, and 95% confidence intervals (95% CIs) were calculated for each parameter. The OS time and PFS time were not analyzed in this study.

However, when OS and PFS were lower than 50% up to the cutoff time in a given patient population, a median survival period was calculated. One month was defined as 30 days, and 1 year was defined as 360 days. To determine safety profiles, adverse events and abnormal changes in laboratory parameters were evaluated until the 12th month in all patients who received BCNU implants in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Adverse events were classified in accordance with the Medical Dictionary for Regulatory Activities Japanese translation (MedDRA/J) version 14.0. The number of patients who experienced each event and the incidence of each event were analyzed in relation to severity. All evaluations performed by attending physicians were reviewed by the efficacy and safety evaluation committee.

For pharmacokinetic analysis, BCNU levels in the blood were measured periodically (before insertion and 3–6 hours, 24 hours, 72 hours, or 168 hours after insertion). Validation and BCNU measurement in blood samples were carried out by liquid chromatography-tandem mass spectrometry (LC/MS/MS) at Celerion Inc (Lincoln, Nebraska, USA).

Validation of the quantification method employed in this study confirmed good linearity of BCNU and the internal standard (d8-BCNU) within the range of quantification (2.00–100 ng/mL) (≥ 0.9952). The lower limit of quantitation was set at 2.00 ng/mL.

Table 1 Patient characteristics

		Newly diagnosed malignant gliomas (n = 16)	Recurrrent malignant gliomas (n = 8)
Age (years)	Mean	46.6	42.9
	SD	14.09	14.57
	Min	21	25
	Median	49.5	41
	Max	63	63
Male/Female		8/8	4/4
Preoperative tumor sizes	Mean	23.0	16.9
	SD	15.0	10.5
	Min	2.0	3.5
(cm^2)	Median	22.5	22.6
	Max	62.4	26.3
Rate of tumor resection	Mean	91.9	87.3
	SD	8.5	17.0
	Min	80.0	55.0
(%)	Median	92.5	95.0
	Max	100	100
Number of BCNU implants	Mean	7.7	7.9
	SD	0.87	0.35
	Min	5.0	7.0
(sheets)	Median	8.0	8.0
	Max	8	8
Pre-insertion KPS score	60	1 (6.3)	0 (0.0)
	70	1 (6.3)	2 (25.0)
	80	4 (25.0)	1 (12.5)
(%)	90	7 (43.8)	3 (37.5)
	100	3 (18.8)	2 (25.0)
	≤70	2 (12.5)	2 (25.0)
	80≤	14 (87.5)	6 (75.0)
1st/2nd recurrence	1st	–	6 (75.0)
	2nd	–	2 (25.0)
History of medical treatment for tumor	Yes	–	7 (87.5)
	No	–	1 (12.5)

KPS: Karnofsky performance status.

Results

Table 1 outlines the patient characteristics. During this study, BCNU implants were inserted in a total

of 24 patients. At intraoperative pathological consultations, these 16 newly and 8 recurrent patients were diagnosed as MGs or GBM. However, after the central pathological diagnoses of the 16 newly diagnosed MGs during the central review were GBM in 9 cases and other tumors in 7 cases (3 cases of anaplastic oligodendroglioma, 2 cases of oligodendroglioma, and 1 case each of anaplastic ganglioglioma and oligoastrocytoma). Of the 8 recurrent GBMs, the diagnoses were GBM in 4cases and other tumors in 4 cases (1 case each of anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic astrocytoma, and high-grade glioma).

In 6 of 24 patients, whole blood BCNU levels were measured. The ages (mean ± SD) were 45.4 ± 14.05 years, 46.6 ± 14.09 years, and 42.9 ± 14.57 years in the entire population, patients with newly diagnosed MGs, and patients with recurrent MGs, respectively. There were 12 male (50.0%) and 12 female (50.0%) patients, indicating no gender bias. The duration of illness were 16.7 ± 28.88 months, 5.7 ± 15.07 months, and 38.8 ± 37.71 months in the entire population, patients with newly diagnosed MGs, and patients with recurrent MGs, respectively. The preoperative tumor sizes were 21.0 ± 13.8 cm², 23.0 ± 15.0 cm², and 16.9 ± 10.5 cm² in the entire population, patients with newly diagnosed MGs, and patients with recurrent MGs, respectively. The median tumor sizes were 22.6 cm², 22.5 cm² and 22.6 cm² in the entire population, patients with newly diagnosed MGs, and patients with recurrent MGs, respectively. The rates of tumor resection were 90.3 ± 11.8%, 91.9 ± 8.5%, and 87.3 ± 17.0% in the entire population, patients with newly diagnosed MGs, and recurrent MGs, respectively. The rates of median tumor resection were 92.5%, 92.5%, and 95.0% in the entire population, patients with newly diagnosed MGs, and patients with recurrent MGs, respectively. The number of patients with a pre-insertion KPS score over 80 was 20 (83.3%) in the entire population, 14 (87.5%) in patients with newly diagnosed MGs, and 6 (75.0%) in patients with recurrent MGs. Of the recurrent MGs patients, recurrence occurred once in 6 cases (75.0%) and twice in 2 cases (25.0%). All recurrent MG patients received conventional radiotherapy (local), and 7 of these patients (87.5%) had a history of medical treatment for the tumor. Tumor resection in the newly diagnosed MG patients was partial removal: 9 cases (56.3%) and total removal: 7 cases (43.7%). Tumor resection in the previous treatment of recurrent MG patients was biopsy: 2 cases (25.0%), partial removal: 4 cases (50.0%), and total removal: 2 cases (25.0%). In this study, the period from the first operation to

the second was less than 1 year in 4 recurrent MG patients (50.0%). Eight sheets of BCNU implants were inserted in 21 of 24 patients. One patient each received 7, 6, and 5 sheets.

After surgery, standard TMZ plus conventional radiotherapy was utilized for all newly diagnosed MG patients (n = 16). For recurrent MG patients, TMZ alone (n = 7) or TMZ plus INF-β therapy (n = 1), BEV therapy (n = 2), or IMRT therapy (n = 1) was utilized.

I. Efficacy

Using the Kaplan-Meier method, OS rates at 12 and 24 months for patients with newly diagnosed MGs were 100% and 68.8%, respectively (95% CI: 40.5–85.6%). The mOS in this group could not be calculated (Fig. 3). For patients with recurrent MGs, the OS rate at 6 months was 87.5% (95% CI: 38.7–98.1%), the OS rate at 12 months was 62.5% (95% CI: 22.9–86.1%), the OS rate at 24 months was 25.0% (95% CI: 3.7–55.8%), and the mOS was 12.0 months (361 days) (Fig. 3). In subgroup analysis of patients according to histological type, the 16 patients with newly diagnosed MGs were divided into the GBM group and the non-GBM group. In the GBM group (n = 9), the OS rate at 24 months and the mOS were 44.4% (95% CI: 13.6–71.9%) and 20.2 months, respectively. In the non-GBM group (n = 7), the OS rate was 100%. For patients with recurrent MGs, the OS rate at 12 months and the mOS were 50.0% (95% CI: 5.8–84.5%) and 8.6 months, respectively, in the GBM group (n = 4). In the non-GBM group (n = 4), the OS rate was 75.0% (95% CI: 12.8–96.1%) and the mOS was 12 months. According to the Kaplan–Meier method, the PFS rate at 6 months was 75.0% (95% CI: 46.3–89.8%) and
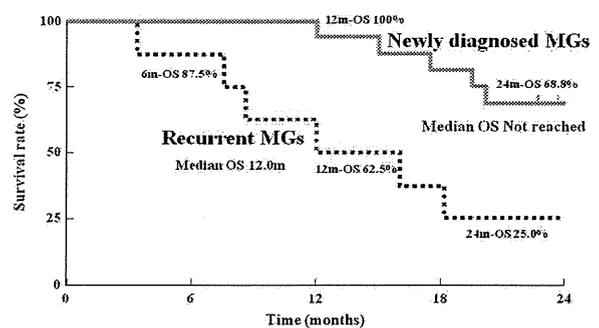

Fig. 3 Kaplan-Meier curve of survival period/rate. MGs: malignant gliomas, OS: overall survival rate, m: months, 6m-OS: the overall survival rates at 6 months, 12m-OS: the overall survival rates at 12 months, 24m-OS: the overall survival rates at 24 months.

T. Aoki et al.

that at 12 months was 62.5% (95%CI: 34.9–81.1%) in patients with newly diagnosed MGs (Fig. 4). When this group was subdivided, the PFS rate at 12 months was 55.6% (95% CI: 20.4–80.5%) in the GBM group and 71.4% (95% CI: 25.8–92.0%) in the non-GBM group. For patients with recurrent MGs, the PFS rate at 6 months was 37.5% (95% CI: 8.7–67.4%), the PFS rate at 12 months was 25.0% (95% CI: 3.7–55.8%), and the median PFS was 170

days (Fig. 4). When this group was subdivided, the PFS rates at 6 monthsand 12 months were both 25.0% (95% CI: 0.9–66.5%) in the GBM group and 50.0% (95% CI: 5.8–84.5%) in the non-GBM group. Figure 5 shows gadolinium contrast-enhanced T_1 MRIs before insertion, within 3 days of insertion, and 6 months and 12 months after insertion of BCNU implants in a patient with recurrent GBM (first relapse). A tumor, 5 cm in size, was noted in the left frontal lobe, and 8 sheets of the BCNU implant were inserted. Subsequently, TMZ alone (220–260 mg/day) was applied for 9 cycles. Even at 12 months after insertion, there was no tumor growth or any other changes observable on MRI images.

During this study, non-responders to TMZ received either BEV therapy (1 newly diagnosed GBM patient and 1 recurrent GBM patient) or IMRT therapy (1 recurrent anaplastic astrocytoma patient). BEV therapy for the newly diagnosed GBM patient involved 5 cycles of treatment (330 mg/day) after recurrence at 8.4 months after insertion of BCNU implants. The patient died 12 months (362 days) after insertion of the BCNU implants. BEV therapy for the second recurrence GBM patient involved 10 cycles of treatment (500 mg/day) at 5.7 months after insertion of the BCNU implants. The patient died at 18.2 months (546 days) after insertion of the BCNU implants. IMRT therapy was applied at a dose of 60 Gy to the enhanced area and 50 Gy to the area around the lesion after the
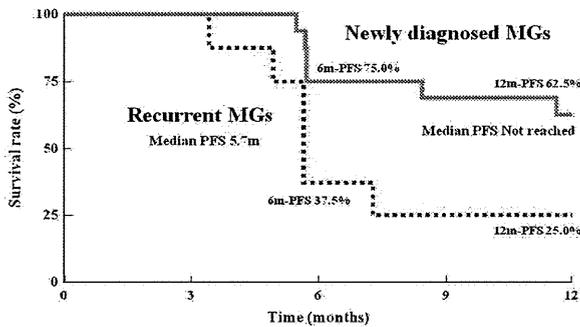

Fig. 4 Kaplan-Meier curve of progression-free survival period/rate (judged by the efficacy and safety evaluation committee). MGs: malignant gliomas, PFS: progression-free survival rate, m: months, 6m-PFS: progression-free survival rate at 6 months, 12m-PFS: progression-free survival rate at 12 months.
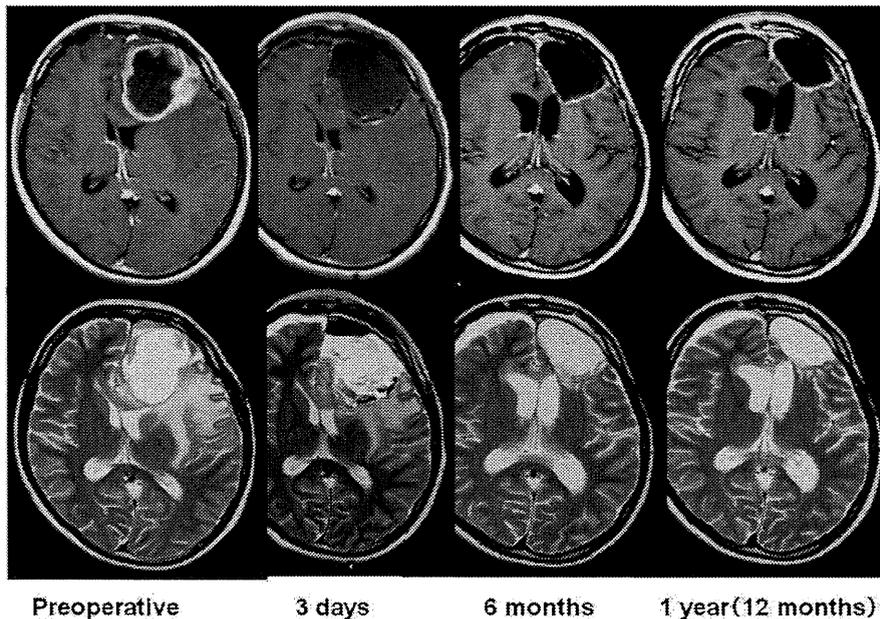

Preoperative   3 days   6 months   1 year(12 months)

Fig. 5 Time course of magnetic resonance (MR) imaging findings (1st relapse of recurrent glioblastoma), axial gadolinium contrast-enhanced T_1-weighted MR images (upper row), and T_2-weighted MR images (lower row).

second recurrence at 7.3 months after insertion of the BCNU implants. The patient died at 16.1 months (483 days) after insertion of the BCNU implants.

II. Safety

Adverse events were noted in 24 of 24 (100%) patients who received BCNU implants and adverse events attributable to BCNU implants were 13 of 24 patients (54.2%). Major adverse events (over 20%, Table 2) listed in descending order of incidence were fever (18 cases, 75.0%); alopecia (16 cases, 66.7%); constipation (14 cases, 58.3%); headache (13 cases, 54.2%); nausea (12 cases, 50.0%), wound complication and leukocytopenia (11 cases each, 45.8%); brain neoplasm (10 cases, 41.7%); vomiting, malaise, brain edema, and lymphopenia (9 cases each, 37.5%); anorexia and hemiparesis (8 cases each, 33.3%); insomnia (7 cases, 29.2%); aphasia, seizure, and increase in blood creatine phosphokinase (CPK; 6 cases each, 25.0%); and pruritus, facial swelling, radiation-induced skin injury, and weight loss (5 cases each, 20.8%). Of these adverse events, severe events (grade 3) included brain neoplasm (7 cases, 29.2%), hemiplegia (6 cases, 25.0%), brain edema (4 cases, 16.7%), and aphasia (3 cases, 12.5%). Adverse, life-threatening events or those causing disabilities (grade 4) included tumor progression (3 cases, 4.2%).

Within 12 months (360 days) of BCNU implant insertion, 3 patients died from tumor progression. None of the deaths had causal relationships with the investigational drug. Within 24 months of BCNU implant insertion, 6 patients died in addition to the above-mentioned 3 patients (9 deaths in total). The cause of death was progressive disease (PD) in 5 cases (2 newly diagnosed MGs and 3 recurrent MGs) and respiratory failure in 1 case (newly diagnosed MG). None of these deaths had causal relationships with the investigational drug.

Frequently noted adverse events attributable to BCNU implants (adverse reactions, Table 3) were brain edema (6 cases, 25.0%); fever and lymphocytopenia (3 cases each, 12.5%); and nausea, vomiting, headache, hemiparesis, anorexia, and increase in alanine aminotransferase (ALT; 2 cases each, 8.3%). None of these adverse reactions were rated as grade 4 or worse. There were 6 cases of grade 3 events in 5 of 24 patients (20.8%) including brain edema (2 cases), hemiparesis (2 cases), increase in ALT (1 case), and increase in CPK (1 case). None of the patients experienced convulsion, poor wound healing, infection, meningitis, or hydrocephalus as an adverse reaction. The adverse reactions listed above appeared within 3 months of BCNU implant insertion.

Among the patients who did not respond to TMZ

Table 2　Number of patients (%) who experienced adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) grade (events with an incidence over 20%)

System organ class/event name	Cases (%) (n = 24)			
	All grades		Grade 3 or higher	
All adverse events	24	(100.0)	19	(79.2)
Gastrointestinal disorders				
Nausea	12	(50.0)		–
Constipation	14	(58.3)		–
Vomiting	9	(37.5)		–
General disorders and administration site conditions				
Malaise	9	(37.5)		–
Fever	18	(75.0)	1	(4.2)
Injury, poisoning, and procedural complications				
Wound complication	11	(45.8)		–
Nervous system disorders				
Aphasia	6	(25.0)	3	(12.5)
Headache	13	(54.2)		–
Brain edema	9	(37.5)	4	(16.7)
Hemiparesis	8	(33.3)	6	(25.0)
Seizure	6	(25.0)	1	(4.2)
Psychiatric disorders				
Insomnia	7	(29.2)		–
Metabolism and nutrition disorders				
Anorexia	8	(33.3)		–
Skin and subcutaneous disorders				
Pruritus	5	(20.8)		–
Facial swelling	5	(20.8)		–
Alopecia	16	(66.7)		–
Radiation-induced skin injury	5	(20.8)		–
Neoplasms (benign, malignant, and unspecified)				
Brain neoplasm	10	(41.7)	7	(29.2)
Investigations				
Lymphopenia	9	(37.5)	2	(8.3)
Blood creatine phosphokinase increased	6	(25.0)	2	(8.3)
Weight loss	5	(20.8)		–
Leukocytopenia	11	(45.8)	2	(8.3)

MedDRA/J Version 14.0. Event name: The same event name seen in the same patient was counted as one case. If severity differed between multiple episodes of the same event, then the most severe episode was selected. System organ class: If there were multiple event names within the same system organ class in the same patient in one line, the patient was counted as one. Incidence (%) = No. of patients developing the event/All patients studied × 100.

T. Aoki et al.

Table 3 Number of patients (%) who attributable to BCNU implants according to Common Terminology Criteria for Adverse Events (CTCAE) grade

System organ class/event name	Cases (%) (n = 24)			
	All grades		Grade 3 or higher	
All adverse reactions	13	(54.2)	5	(20.8)
Gastrointestinal disorders				
Nausea	2	(8.3)	–	
Abdominal discomfort	1	(4.2)	–	
Vomiting	2	(8.3)	–	
General disorders and administration site conditions				
Hypothermia	1	(4.2)	–	
Fever	3	(12.5)	–	
Edema	1	(4.2)	–	
Nervous system disorders				
Hyperesthesia	1	(4.2)	–	
Memory disorder	1	(4.2)	–	
Aphasia	1	(4.2)	–	
Heterotropia	1	(4.2)	–	
Headache	2	(8.3)	–	
Homonymous hemianopsia	1	(4.2)	–	
Urinary incontinence	1	(4.2)	–	
Brain edema	6	(25.0)	2	(8.3)
Monoparesis	1	(4.2)	–	
Hemiparesis	2	(8.3)	2	(8.3)
Hemiplegia	1	(4.2)	–	
Reproductive system and breast disorders				
Irregular menstruation	1	(4.2)	–	
Metabolism and nutrition disorders				
Anorexia	2	(8.3)	–	
Investigations				
C-reactive protein increased	1	(4.2)	–	
Alanine aminotransferase increasd	2	(8.3)	1	(4.2)
Lymphocyte decreased	3	(12.5)	–	
Platelet decreased	1	(4.2)	–	
Blood creatine phosphokinase increased	1	(4.2)	1	(4.2)
Leukocyte increased	1	(4.2)	–	

※ MedDRA/J Version 14.0. Event name: the same event name seen in the same patient was counted as one case.

and who received BEV therapy (1 newly diagnosed GBM patient and 1 recurrent GBM patient) or IMRT therapy (1 recurrent anaplastic astrocytoma patient), leukocytopenia (grade 2) was noted in a patient who underwent BEV therapy and alopecia (grade 2) and malaise (grade 2) were noted in a patient who underwent IMRT therapy.

III. Pharmacokinetics

BCNU levels in whole blood were measured in 6 of the patients who received BCNU implants. The age of these 6 patients (mean ± SD) was 45.5 ± 15.7 years (21–61 years), body weight was 59.2 ± 14.2 kg (42.9–77.1 kg), median number of BCNU implant sheets inserted was 8 sheets (5–8 sheets: 8 in 4 cases, 7 and 5 in 1 case each), and the administration of BCNU at a median dose level were 61.6 mg (38.5–61.6 mg). As shown in Fig. 6, BCNU levels reached a peak approximately 3 hours after insertion and ranged from 6.49 ng/mL to 19.4 ng/mL (10.19 ± 4.77 ng/mL). After 24 hours, levels were in the vicinity of or below the lower limit of quantification (2.00 ng/mL).

Discussion

This study (NPC-08 study) was designed to evaluate the efficacy, safety, and pharmacokinetics of BCNU implants with chemotherapy (including TMZ) and radiotherapy for Japanese patients with newly diagnosed MGs or recurrent GBM (under conditions indicated for BCNU in USA and Europe). Of the 24 patients who received BCNU implants (newly diagnosed MG, 16 cases; recurrent MG, 8 cases), the survival rate for patients with newly diagnosed
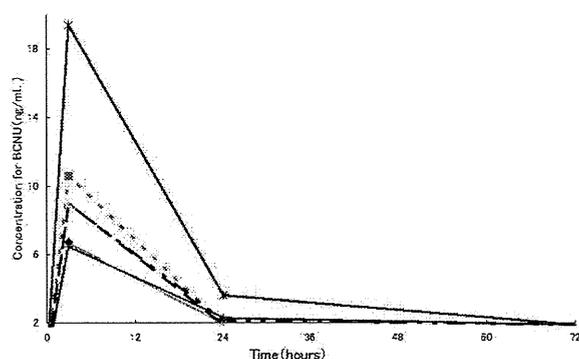

Fig. 6 Time course of BCNU levels in whole blood. Six Japanese patients with malignant gliomas received the maximum blood concentration of BCNU at about 3 hours after implant placement was 19.4 ng/mL. The lower limit of quantitation (2.00 ng/mL).

MGs was 100.0% at 12 months and 68.8% at 24 months, making it impossible to calculate the median survival time in this group. These results were superior those of placebo-controlled double-blind comparative studies[3,4] conducted in USA and Europe in which the OS rate at 12 months was 59.2% (95% CI: 50.4–68.0%) and the mOS was 13.8 months (95% CI: 12.1–15.1 months). However, these studies from USA and Europe were not combined therapy involving TMZ plus radiotherapy for newly diagnosed MGs cases. In NPC-08 study, combined TMZ plus radiotherapy was applied to all patients with newly diagnosed MGs after insertion of BCNU implants. According to previous reports[9–13] examining combined TMZ plus radiotherapy after insertion of BCNU implants, the OS rate at 12 months and 24 months was 56.8–81.0% and 13.0–47.0%. Furthermore, the OS rate at 6 months with recurrent MG was 87.5% in NPC-08 study. According to a clinical study by Brem et al.,[2] the OS rate at 6 months in patients with recurrent MG was 60%. Thus, although the number of patients studied was small, the results of the NPC-08 study were comparable to the results of USA and European studies.

Potential adverse effects of BCNU implants were noted in 13 of 24 patients (54.2%). Severe adverse reactions were noted in 5 of 24 patients (20.8%), although none were live threatening. Important adverse events requiring close attention include brain edema, seizure, poor wound healing, infection, headache, hemiparesis, meningitis, and hydrocephalus according to clinical reports from USA and Europe. We compared the adverse event data in NPC-08 study with the data from three placebo-controlled double-blind comparative studies conducted in USA and Europe (Table 4).

The incidence of Brain edema was higher in the NPC-08 study (25.0%, 6/24 patients) than that in the double-blind studies (4.9%, 12/246 patients). However, there was no significant difference between the BCNU implant group and the placebo group regarding brain edema on grade 3 or worse in the double-blind studies. Brain edema can also be caused by tumor resection, MGs themselves, dose of steroid and so on, therefore, the expression of the brain edema is necessary to be careful, it is necessary to consider the administration of steroid drug. In this study, brain edema of any CTCAE grade occurred in 6 of 24 patients. There were no patients with brain edema of CTCAE grade 4. Two patients developed brain edema of CTCAE grade 3. These two patients were not from a specific facility. We examined the occurrence rate of brain edema by each patient's background in the Japanese studies, but were unable to find any tendency due to the

small sample size. Nearly 700 patients were enrolled in foreign studies. Among those patients, 3.8% (26/676) developed brain edema of any CTCAE grade, and 1.9% (12/676) developed brain edema of CTCAE grade 3 or 4. On the other hand, the total number of patients enrolled in the Japanese study was small (24 patients). We consider that this small number of patients (denominator) may have contributed to a large difference; i.e., in the present case, higher rate of brain edema occurrence than in foreign studies. In addition, we infer that one of the reasons that brain edema were more often observed in Japan than in foreign countries is as follows: the protocol for the Japanese study has described "brain edema, convulsion, cerebrospinal fluid (CSF) leakage, and limited hypofunction" as notable adverse events that were reported in foreign studies, and requested investigators and clinical research coordinators to carefully watch for these adverse events. This may have encouraged physicians to conduct CT/MRI testing more frequently than is required in the protocol, leading to observation of higher occurrence rate of brain edema. In summary, although the occurrence rate of brain edema was higher in the Japanese study than in the foreign studies, it is difficult to determine whether the Japanese patients are more likely to develop brain edema than the foreign patients because of the small number of the Japanese patients enrolled in this study. This question should be addressed in future studies. Seizure is one of the complications of brain tumors and neurosurgical interventions, and its incidence differed little between NPC-08 study and the combined double-blind studies. There was no difference between the BCNU implant group and the placebo group in terms of overall incidence or incidence of seizure grade 3 or worse. One of the 3 double-blind studies, Brem et al.[2] reported that the median day of onset of seizures was faster in the BCNU implant group (3.5 days) than in the placebo group (55.5 days) (Wilcoxon test: P = 0.01). In the NPC-08 study, the median day of onset of seizures was 91.5 days.

Since the number of patients studied was small, these results were not clear that the day of onset of seizures was tended to be faster by BCNU implant. However, it is necessary to consider the administration of anticonvulsant drugs. None of the patients was experienced poor wound healing after craniotomy as adverse reactions in the NPC-08 study. In the combined double-blind studies, the incidence of poor healing was slightly higher in the BCNU implant group (7.3%, 18/246 patients) than in the placebo group (3.2%, 8/248 patients). Therefore, the expression of poor wound healing is necessary to

T. Aoki et al.

Table 4   Comparison of the number of patients (incidence) who experienced major adverse reactions in the NPC-08 study and in the combined double-blind comparative studies

System organ class/Event name	The NPC-08 study All grades			Double-blind studies[2,10,13] All grades						Placebo					
	All grades	Grade 3	Grade 4	All grades		Grade 3		Grade 4		All grades		Grade 3		Grade 4	
Total patients	24			246						248					
Brain edema	6 (25.0)	2 (8.3)	—	12	(4.9)	2	(0.8)	3	(1.2)	12	(4.8)	4	(1.6)	2	(0.8)
Seizure	—	—	—	31	(12.6)	7	(2.8)	2	(0.8)	39	(15.7)	11	(4.4)	2	(0.8)
Major seizure	—	—	—	1	(0.4)		—		—	2	(0.8)		—	1	(0.4)
Poor healing	—	—	—	18	(7.3)	4	(1.6)		—	8	(3.2)	1	(0.4)		—
Infection	—	—	—	13	(5.3)	2	(0.8)	3	(1.2)	16	(6.5)	2	(0.8)		—
Headache	2 (8.3)	—	—	28	(11.4)	8	(3.3)		—	22	(8.9)	8	(3.2)	1	(0.4)
Hemiplegia	1 (4.2)	—	—	24	(9.8)	5	(2.0)		—	34	(13.7)	15	(6.0)		—
Monoparesis	1 (4.2)	—	—		—		—		—		—		—		—
Hemiparesis	2 (8.3)	2 (8.3)	—		—		—		—		—		—		—
Meningitis	—	—	—	5	(2.0)	2	(0.8)		—	1	(0.4)		—		—
Hydrocephalus	—	—	—	2	(0.8)	1	(0.4)	1	(0.4)	1	(0.4)		—		—

MedDRA/J Version 14.0. Event name: The same event name seen in the same patient was counted as one case. If severity differed between multiple episodes of the same event, then the most severe episode was selected. Incidence (%) = No. of patients who experienced adverse reaction / all patients studied × 100.

be careful. Infection and meningitis were not observed in the NPC-08 study. In the combined double-blind studies, the overall incidence of this event and the incidence of grade 3 or worse differed little between the BCNU implant group and the placebo group, and the incidence was also high in the placebo group.

The incidence of headache was not high in the NPC-08 study (8.3%) and differed little between the BCNU implant group and the placebo group. The incidence of hemiparesis was slightly higher in the combined double-blind studies. Hydrocephalus did not develop in any patient in the NPC-08 study. In the combined double-blind studies, the incidence of hydrocephalus was approximately 0.8% in the BCNU implant group, which was comparable to its incidence in the placebo group. All of the important adverse events discussed above were symptoms accompanying a brain tumor or surgical resection of the tumor.

For pharmacokinetic analysis, BCNU levels in the blood were measured at multiple time points after surgery. The administration of BCNU at a median dose level of 61.6 mg (38.5–61.6 mg) to 6 patients caused a mean peak BCNU level of 10.19 ng/mL. BCNU has been administered intravenously and inserted into the removal cavity for the treatment of brain tumors in USA and Europe. According to a report[14] describing the pharmacokinetics of intravenous BCNU injection, the peak BCNU level in the blood averaged 6.2 µg/mL, whereas the peak level following insertion in the brain averaged 0.01 µg/mL.

Thus, the BCNU level in the blood after insertion into the brain was much lower (1/600) than that after intravenous injection, and BCNU disappears from the blood almost completely within 24 hours of insertion into the brain.

Systemic administration of BCNU often induces severe adverse events such as leucopenia and thrombocytopenia. Insertion of BCNU implants into the brain is expected to markedly reduce systemic adverse events as compared with intravenous BCNU.

Taken together, these results indicate that when insertion of BCNU implants into the brain (maximum of 8 sheets containing a maximum of 61.6 mg BCNU) was followed by chemotherapy or radiotherapy in patients with newly diagnosed or recurrent MGs, there are no major safety concerns associated with the use of BCNU implants. The BCNU implant is now recommended as a treatment option along with the surgical resection of MGs on the basis of established treatment guidelines. The data from this clinical study was comparable to previous data from USA and Europe with

respect to efficacy and safety. Therefore, from a risk/benefit viewpoint, the use of BCNU implants is recommended.

Acknowledgments

support for planning the protocol, monitoring, data management, statistical analysis, and many other activities in the NPC-08 study.

Conflicts of Interest Disclosure

Dr. Tomokazu Aoki is a member of the medical advisory committee of NPC-08 study and received consulting fees from Nobelpharma Co. Ltd. and an honoraria for speaking from Eisai Co. Ltd. Dr. Ryo Nishikawa is a member of the medical advisory committee of NPC-08 study and received consulting fees from Nobelpharma Co. Ltd. Dr. Nishikawa is also a member of the Avaglio study steering committee (funded by F. Hoffmann-La Roche, Ltd) and has received research funding and speaking fees from MSD KK as well as honoraria for speaking from Eisai Co. Ltd. Dr. Kazuhiko Sugiyama is a member of the medical advisory committee of NPC-08 study and received consulting fees from Nobelpharma Co. Ltd. and honoraria for speaking from Eisai Co. Ltd. Dr Masao Matsutani is a coordinating investigator of NPC-08 study, a member of the advisory committee of MSD KK, and a coordinating investigator for Chugai Pharmaceutical Co. Ltd. Dr. Matsutani also received consulting fees from Nobelpharma Co. Ltd.

The authors declare no other conflicts of interest.

References

1) Committee of Brain Tumor Registry of Japan: Report of brain tumor registry of Japan (1984–2000), 12th ed. *Neurol Med Chir (Tokyo)* 49(Suppl): S1–96, 2009

2) Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G: Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. *Lancet* 345: 1008–1012, 1995

3) Valtonen S, Timonen U, Toivanen P, Kalimo H, Kivipelto L, Heiskanen O, Unsgaard G, Kuurne T: Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. *Neurosurgery* 41: 44–48; discussion 48–49, 1997

4) Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, Whittle IR, Jääskeläinen J, Ram Z: A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol* 5: 79–88, 2003

5) National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology-v.1, 2013

6) National Cancer Institute Cancer Information Physician Data Query (May, 2012)

7) National Institute for Health and Clinical Excellence. (June, 2007)

8) Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352: 987–996, 2005

9) Affronti ML, Heery CR, Herndon JE, Rich JN, Reardon DA, Desjardins A, Vredenburgh JJ, Friedman AH, Bigner DD, Friedman HS: Overall survival of newly diagnosed glioblastoma patients receiving carmustine wafers followed by radiation and concurrent temozolomide plus rotational multiagent chemotherapy. *Cancer* 115: 3501–3511, 2009

10) Bock HC, Puchner MJ, Lohmann F, Schütze M, Koll S, Ketter R, Buchalla R, Rainov N, Kantelhardt SR, Rohde V, Giese A: First-line treatment of malignant glioma with carmustine implants followed by concomitant radiochemotherapy: a multicenter experience. *Neurosurg Rev* 33: 441–449, 2010

11) Larocca RV, Vitaz TW, Morassutti DJ, Doyle MJ, Glisson SD, Hargis JB, Goldsmith GH, Cervera A, Stribinskiene L, New P: A phase II study of radiation with concomitant and then sequential temozolomide (TMZ) in patients with newly diagnosed supratentorial high-grade malignant glioma who have undergone surgery with carmustine (BCNU) wafer insertion. *Neuro-oncology* 8: 391–500, 2006

12) McGirt MJ, Than KD, Weingart JD, Chaichana KL, Attenello FJ, Olivi A, Laterra J, Kleinberg LR, Grossman SA, Brem H, Quiñones-Hinojosa A: Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. *J Neurosurg* 110: 583–588, 2009

13) Pan E, Mitchell SB, Tsai JS: A retrospective study of the safety of BCNU wafers with concurrent temozolomide and radiotherapy and adjuvant temozolomide for newly diagnosed glioblastoma patients. *J Neurooncol* 88: 353–357, 2008

14) Jones RB, Matthes S, Shpall EJ, Fisher JH, Stemmer SM, Dufton C, Stephens JK, Bearman SI: Acute lung injury following treatment with high-dose cyclophosphamide, cisplatin, and carmustine: pharmacodynamic evaluation of carmustine. *J Natl Cancer Inst* 85: 640–647, 1993

Address reprint requests to: Tomokazu Aoki MD, PhD, Department of Neurosurgery, National Hospital Organization Kyoto Medical Center, 1-1, Fukakusa Mukaibatacho, Fushimi-ku, Kyoto, Kyoto 612-8555, Japan.
e-mail: totorolangdom@yahoo.co.jp

Repeated cyst formation in a patient with leukoencephalopathy, cerebral calcifications, and cysts: effectiveness of stereotactic aspiration with Ommaya reservoir placement

Case report

Hiroshi Ooba, M.D., Ph.D., Tatsuya Abe, M.D., Ph.D., Yoshinori Hisamitsu, M.D., and Minoru Fujiki, M.D., Ph.D.

Department of Neurosurgery, Oita University Faculty of Medicine, Oita, Japan

The combination of leukoencephalopathy, cerebral calcifications, and cysts (LCC) constitutes a rare cerebral disorder characterized by distinctive neuroradiological and clinical findings. Twenty-eight cases of LCC have been reported. Surgery is usually required to treat progressively expanding cysts, but surgical strategies have been varied.

The authors present the case of a patient who underwent 4 surgical procedures for repeated cyst formation. The first operation was performed for the removal of a cyst and to make a histopathological diagnosis. The second and third operations were performed to treat de novo cysts. The fourth operation was performed to treat a recurrence.

This is the first reported case of LCC in which it was necessary to perform surgery 4 times, in large part due to de novo cyst formation. It provides evidence that multiple cysts may develop in these patients and that several surgical operations may be needed to treat LCC. Stereotactic aspiration with Ommaya reservoir placement is an appropriate procedure for this condition because it is less invasive and more repeatable than open surgery.
(http://thejns.org/doi/abs/10.3171/2013.5.PEDS1328)

Key Words • LCC • leukoencephalopathy • Ommaya reservoir • cerebral calcifications and cysts • stereotactic aspiration

L EUKOENCEPHALOPATHY, cerebral calcifications, and cysts (LCC) is a rare disorder characterized by distinctive neuroradiological and clinical findings. The first case was reported by Labrune et al. in 1996,[11] and a total of 28 cases have been reported to date.

The neuroradiological findings include leukoencephalopathy, which exhibits high signal intensity in white matter on T2-weighted and FLAIR images. Cerebral calcifications in the white matter, basal ganglia, and cerebellum are also prominent findings in patients with LCC. Cyst formation, the third primary neuroradiological finding, occurs in various sites, including the white matter,[1,3–5,8–10,12,13,15–17] cerebellum,[4,5,7,11–14,16] brainstem,[2,12,15] lateral ventricles,[1,4] basal ganglia, and thalmus.[4,7,12,13,15]

The clinical symptoms of this entity include seizures, cognitive decline, and a combination of pyramidal, extrapyramidal, and cerebellar signs, with symptoms primarily related to the progression of leukoencephalopathy, cerebral calcifications, and cyst formation.[1–17] Although there are no effective preventive or medical treatments

for LCC, surgery has therapeutic value in patients with clinical symptoms due to cyst expansion.[1,2,4,7,9,11,13,15,16]

In the present report, we describe the case of a patient with LCC who underwent surgery for repeated cyst formation. The procedures included open surgical removal, stereotactic aspiration, and stereotactic aspiration with Ommaya reservoir placement. In this case, stereotactic aspiration with Ommaya reservoir placement was an appropriate method to treat repeated cyst formation. In addition to describing our patient and discussing the surgical strategy, we also review the previous literature.

Case Report

This 25-year-old man had a normal gestation and birth, but began to have epileptic seizures at 1.5 months of age. Computed tomography scans revealed cerebral calcification. Similar lesions were observed in the patient's father and sister. His father developed normally; however, his sister exhibited developmental delay and died at 17

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
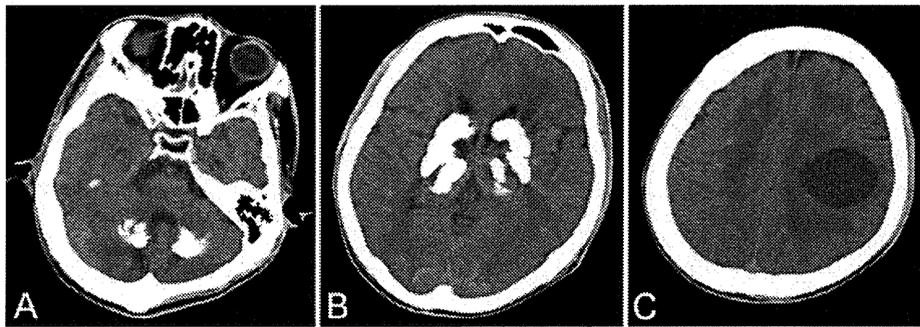
Fig. 1. Axial CT scans obtained on the first admission demonstrating obvious cerebral calcifications in the basal ganglia, thalamus, and cerebellum (A), numerous areas of calcification in the white matter (B), and leukoencephalopathy and an large expanding cyst (C).

years of age. The patient also exhibited developmental delay and was barely able to walk at 20 months of age. He slowly developed progressive pyramidal, extrapyramidal, and cerebellar symptoms. Thereafter, he was unable to walk and instead used an electrically powered wheelchair starting at 18 years of age. The patient's arm function was relatively preserved, and he was able to eat by himself and handle his wheelchair. At 24 years of age, he developed right hemiparesis and dysphagia. Magnetic resonance imaging revealed cyst formation in the left frontal lobe. His symptoms progressively worsened, and MRI showed that the cyst was expanding. He was admitted to our hospital for further examination and treatment.

A neurological examination revealed cognitive decline, an inability to talk, mild dysphagia, and right hemiparesis equivalent to a manual muscle test score of 2/5. Mild rigidity, dystonia, and ataxia were also observed in

the limbs and trunk. In addition, the patient had severe joint contractures due to long-term disuse syndrome. Laboratory studies demonstrated normal results of a complete blood cell count and biochemical analysis, including normal levels of serum calcium and alkaline phosphatase.

Computed tomography scans obtained on admission demonstrated obvious cerebral calcifications in the basal ganglia, thalamus, and cerebellum in addition to extensive spotty calcification in the white matter (Fig. 1). Leukoencephalopathy and a large cyst were also evident. Magnetic resonance imaging showed clear leukoencephalopathy on T2-weighted and FLAIR images and spotted calcifications on T2*-weighted images (Fig. 2). The cyst wall was partially enhanced after administration of gadolinium, suggesting the presence of a vascular-rich component (Fig. 2).

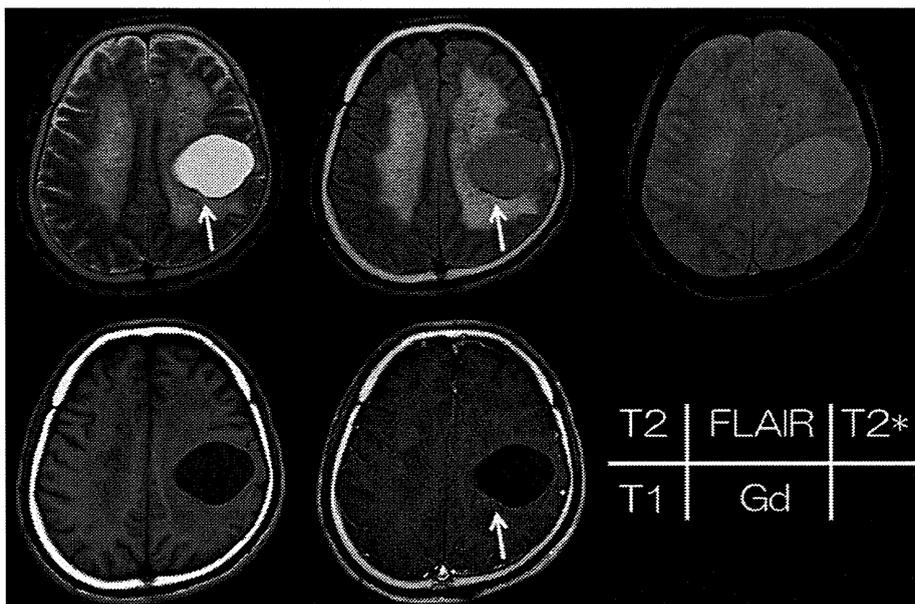*First Operation.* LCC was suspected as a preopera-

Fig. 2. Axial T2-weighted and FLAIR MR images showing obvious leukoencephalopathy. The spotty calcifications became more distinctive on T2*-weighted images. On T2-weighted and FLAIR images, the cyst wall appeared partially thickened. The thickened area of the wall (arrows) showed enhancement on T1-weighted images obtained after gadolinium (Gd) administration. The presence of a vascular-rich component was suggested. In addition, a high concentration of proteins was suggested in the large cyst by slightly high intensity on FLAIR images.
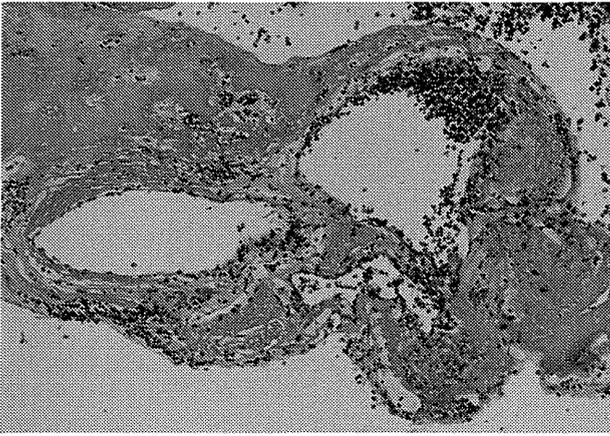
FIG. 3. Photomicrograph of cyst wall specimen. Histopathological examination showed prominent angiomatous changes, including numerous dilated, thickened, and hyalinized blood vessels. No Rosenthal fibers or calcification were found in the cyst wall. No parenchymal tissue was obtained during surgery. H & E, original magnification ×200.

tive diagnosis, and open surgical removal of the cyst was performed to determine the definitive diagnosis and treatment. The cyst contained a high concentration of proteins (1600 mg/dl), as previously indicated by the MRI findings. We placed an Ommaya reservoir in the cavity of the cyst because we took the possibility of recurrence into consideration. We planned to remove viscous fluid by puncturing the Ommaya reservoir when the cyst recurred in the future. A histopathological examination showed that the cyst wall exhibited prominent angiomatous changes (Fig. 3) and confirmed the diagnosis of LCC. The patient's right hemiparesis improved immediately after surgery.

Second Operation. Seventeen months after the first operation, the patient again presented with right hemiparesis. No recurrence was evident on CT or MRI, but 2 de novo cysts were observed in the bilateral frontal lobes (Fig. 4). The patient underwent stereotactic aspiration of both cysts, and an additional Ommaya reservoir was placed in the right frontal lobe cyst. The patient's symptoms improved after this surgery.

Third Operation. Nine months after the second op-

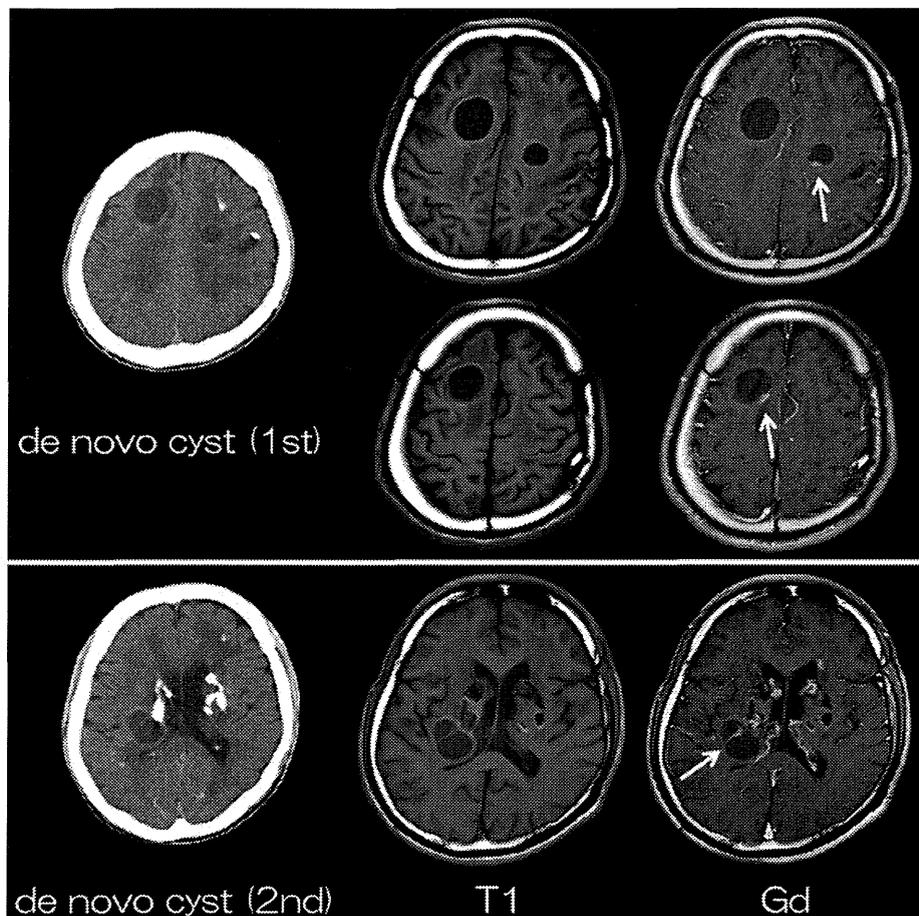FIG. 4. **Upper:** Axial CT and MR images obtained 17 months after the first operation revealing 2 de novo cysts in the bilateral frontal lobes. A part of the cyst wall showed obvious enhancement on T1-weighted images obtained after Gd administration, suggesting the presence of a mural nodule *(arrow).* **Lower:** Axial CT and MR images obtained 9 months after the second operation revealing another de novo cyst in the right thalamus. A mural nodule was also noted *(arrow).*