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Extended follow-up of recurrent glioblastoma patients treated with boron neutron capture therapy (BNCT): Long-term survival from a Phase II trial (JG002) using Cyclotron Neutron Source and Boronophenylalanine

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Highlights

- BNCT yielded a 2-year survival rate of 33.3% in patients with recurrent glioblastoma.
- Median survival of 19.2 months observed in recurrent glioblastoma post-BNCT.
- Long-term BNCT effects suggest a sustained survival benefit for malignant gliomas.
- Recurrent glioma patients demonstrated extended overall survival beyond 2 years.
- BNCT's long-term efficacy supports its use in treating recurrent malignant gliomas.

Abstract

Purpose

The Phase II clinical trial (JG002) investigating accelerator-based boron neutron capture therapy (AB-BNCT) using a cyclotron-based epithermal neutron source for recurrent malignant gliomas has since concluded. The trial demonstrated favorable survival outcomes during the 1-year evaluation period defined in the protocol for patients with recurrent glioblastoma, a population with notoriously poor prognosis. Follow-up was originally limited to up to two years. This study extends the follow-up period to explore the long-term outcomes of AB-BNCT in the same patient population.

Materials and methods

This extended observational study collected survival data from patients who participated in the JG002 trial, focusing on long-term clinical outcomes. Patients with recurrent glioblastoma, previously treated with standard radiotherapy and chemotherapy but without prior bevacizumab exposure, were included. Bevacizumab was administered only after imaging-confirmed progression. Kaplan-Meier survival analysis was performed, and exponential and Weibull models were used to estimate long-term survival trends.

Results

Kaplan-Meier analysis showed a 1-year survival rate of 79.2% (95% CI: 63.3–88.7) for glioblastoma patients, with a median overall survival of 19.2 months (95% CI: 13.1–24.8). The 2-year and 3-year survival rates were 33.3% and 20.8%, respectively. The fitted survival models provided additional context, with the exponential model estimating a slightly lower median survival. However, the Weibull model, which better reflects the progressive nature of glioblastoma, produced estimates more closely aligned with the observed Kaplan-Meier survival outcomes.

Conclusion

AB-BNCT showed long-term survival benefits and acceptable safety in recurrent glioblastoma patients. Extended follow-up confirms the durability of BNCT's efficacy, particularly in extending survival. Future research should investigate bevacizumab's role post-BNCT and refine imaging assessment methods to better evaluate treatment response.

Introduction

Boron Neutron Capture Therapy (BNCT) is a tumor-selective particle therapy that involves administering a ^{10}B compound, which selectively accumulates in tumor cells, followed by neutron irradiation (Barth et al., 2012; Kawabata et al., 2003). The ^{10}B (n, α) ^{7}Li reaction generates high linear energy transfer particles (alpha particles and lithium-7 nuclei) that selectively damage tumor cells while sparing surrounding healthy tissues. In Japan, BNCT has traditionally

been performed using nuclear reactors and has been applied to more than 500 cases, targeting brain tumors, malignant melanomas, and head and neck cancers. Since 2008, efforts to develop a cyclotron-based epithermal neutron source (C-BENS) for accelerator-based BNCT (AB-BNCT) system have been led by Kyoto University and Sumitomo Heavy Industries. In 2012, a Phase I/II clinical trial for malignant gliomas commenced, with the authors' involvement. Later, this AB-BNCT system was installed at Kansai BNCT Medical Center of Osaka Medical and Pharmaceutical University, where a Phase II investigator-initiated clinical trial targeting recurrent high-grade meningiomas began in August 2019. In June 2020, BNCT for head and neck cancer was included under insurance coverage in Japan (Hirose et al., 2021; Takeno et al., 2024), and to date, more than 300 patients have been treated at this single institution.

The Phase II clinical trial (JG002) investigating AB-BNCT for recurrent malignant gliomas, especially for glioblastoma, has since concluded (Kawabata et al., 2021). This trial demonstrated a promising 1-year survival rate of 79.2% (95% CI: 57.0–90.8) for the patients with recurrent glioblastoma, a population with notoriously poor prognosis. However, the data have not yet led to regulatory approval for BNCT in brain tumors based on the JG002 results. In the JG002 trial, the primary endpoint was the 1-year survival rate following BNCT, with follow-up limited to two years after treatment.

Numerous clinical trials have identified critical factors influencing the use of bevacizumab in recurrent glioblastoma. Its efficacy is influenced by factors such as patient condition, prior therapies, and tumor characteristics, making its role in treatment still a matter of debate. Bevacizumab is commonly administered as monotherapy or in combination with other treatments, and the optimal therapeutic approach requires careful consideration of both benefits and risks by clinicians and patients alike. In the JG002 trial, bevacizumab was used in many patients during the follow-up period after BNCT, which has been suggested to complicate the interpretation of the trial results.

The goal of this study is to provide a comprehensive analysis of the treatment outcomes with extended follow-up period of accelerator-based BNCT for recurrent glioblastoma, focusing not only on standard survival metrics such as median overall survival (OS) and specific survival rates but also on model-based survival trends. By integrating these approaches, this study aims to establish a more comprehensive benchmark for the BNCT clinical trials in brain tumor research, enhancing our understanding of therapeutic effectiveness across the entire observation period.

Section snippets

Study design

This study aims to collect survival data beyond the trial period for patients who participated in the JG002 trial, in order to explore the long-term clinical outcomes of AB-BNCT for recurrent glioblastoma. Despite the tumor selectivity of BNCT, its use as a treatment for recurrent malignant gliomas, following prior X-ray radiation therapy, has been associated with challenges

such as pseudo-progression and radiation necrosis. These conditions often complicate imaging evaluations post-BNCT. …

Results

Table 1 summarizes the BNCT dose and the associated treatment parameters, such as blood boron concentration and neutron irradiation time, which were used to calculate the prescribed dose. Specifically, the average BNCT dose in GTV was 55.5 Gy-Eq (range: 37.6–71.8 Gy-Eq), and the minimum dose in GTV was 38.2 Gy-Eq. The maximum BNCT dose in the brain was 11.0 Gy-Eq. Blood boron concentrations measured just before neutron irradiation ranged from 26.3 to 42.1 ppm, and the irradiation time varied …

Survival trends and model fitting in recurrent glioblastoma in BNCT

This study aimed to analyze long-term follow-up data from the JG002 trial, focusing on the survival outcomes of recurrent glioblastoma patients treated with AB-BNCT. By extending the follow-up period beyond the initial study's endpoints, this analysis provides a more comprehensive understanding of survival patterns. The Kaplan-Meier analysis showed 1-, 2-, and 3-year survival rates of 79.2%, 33.3%, and 20.8%, respectively, with a median OS of 19.2 months. The Weibull model, better suited for …

Conclusions

Despite certain limitations, this study provides compelling evidence of long-term efficacy, particularly in improving survival outcomes for patients with recurrent glioma. AB-BNCT appears to hold significant potential as a durable treatment option for this challenging condition.

The findings of this study underscore the acceptable safety profile and survival benefit of AB-BNCT, particularly in relapsed malignant gliomas, predominantly glioblastoma. Tumor contrast enhancement within the …

CRediT authorship contribution statement

Shinji Kawabata: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hiromi Goto:** Resources, Investigation. **Yoshitaka Narita:** Resources, Investigation, Data curation. **Motomasa Furuse:** Writing – review & editing, Validation, Methodology. **Naosuke Nonoguchi:** Writing – review & editing, Visualization, Formal analysis. **Rina Shidoh-Kazuki:** Writing – review & editing, Validation. **Kenichiro Eza:** Writing – review & editing. **Katsumi** …

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author used ChatGPT for the purpose of improving the

clarity and expression of the English language. After using this tool, the authors reviewed and edited the content as necessary and take full responsibility for the content of the published article. …

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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In this study, which involved post-trial observations following the completion of the JG002 trial, the sponsor companies that led and funded the JG002 trial not been involved in any aspect of data collection or analysis.

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