Correlation between alterations in blood flow of malignant lymphomas after induction chemotherapies and clinical outcomes: a pilot study utilising contrast-enhanced ultrasonography for early interim evaluation of lymphoma treatment


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AIM: To clarify the utility of contrast-enhanced ultrasonography (CEUS) for interim evaluation of response to chemotherapy in lymphoma treatment.

MATERIALS AND METHODS: CEUS was performed both before (day 0) and after the treatment (7 and/or 14 days), and a time-intensity curve was obtained. The patients were divided into two groups (complete remission [CR] group and non-CR group) according to the results of conventional response evaluation, and peak enhancement (PE), time to peak enhancement, perfusion index (PI), the total area under the curve during wash-in (AUC-in), and the total AUC were compared between the groups.

RESULTS: Among 27 patients with various types of lymphoma, the median change ratio of PE and PI at day 7 evaluation were significantly different between the CR group and the non-CR group (0.81 versus 1.39, \( p = 0.017 \) for PE and 0.92 versus 2.09, \( p = 0.010 \) for PI). The change ratio of PE < 1.09 (specificity: 86%; sensitivity: 88%) and PI < 1.65 (specificity: 86%; sensitivity: 94%) distinguished CR from non-CR. Patients who achieved a PE change ratio < 1.09 or a PI change ratio < 1.65 had significantly better estimated progression-free survival (\( p < 0.001 \)).

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Introduction

Lymphomas are the seventh most common cancer worldwide, but they are also among the most chemotherapy-responsive malignancies, which has contributed to the decrease in lymphoma-associated mortality in the last decade. Lymphomas arise from different stages of differentiation of the immune system, so their histological classification is diverse. Many clinical symptoms and imaging findings are common to various lymphomas, and one of the main symptoms is lymphadenopathy and tumour formation that progresses without spontaneous pain. In lymphomas, the time to achieve complete remission (CR) is a prognostic factor, and the longer the period, the higher the rate of recurrence; however, the degree of tumour reduction is influenced by the size and location of the tumour before treatment, histological type, and treatment method, and thus the time to achieving CR may be an insufficient prognostic factor. Moreover, it is difficult to evaluate fibrosis and the viable site in the remaining tumour shadow by measuring the size at computed tomography (CT) alone. Because 2-[18F]-fluoro-deoxy-p-glucose positron-emission tomography (FDG-PET) has the ability to distinguish between viable tumour and non-metabolic mass, and evaluate systemically without being affected by tumour localisation, combined PET and CT (PET/CT) is usually used for pre-treatment staging and evaluation of response to treatment in lymphoma patients. The goal of treatment for aggressive lymphomas, such as Hodgkin's lymphoma (HL) or aggressive non-Hodgkin's lymphoma (NHL), is increasing the cure rate and reducing mortality. Although evaluating response to treatment via PET/CT and achieving complete remission are essential, the change in tumour size obtained radiologically is late as the timing for determining the therapeutic effect. Recently, interim PET has been introduced in the management of lymphomas as a method for evaluating treatment response. Several studies have proven that PET shadow findings during the treatment predicted clinical outcomes in HL and diffuse large B-cell lymphoma (DLBCL); however, there remains concern for radiation exposure and high cost in repeated evaluation using PET/CT.

Contrast-enhanced ultrasonography (CEUS), which has been mainly used for the diagnosis of hepatic nodules, has the advantage of high spatial and time resolution, low frequency of adverse effects, absence of radiation exposure, and wide availability. CEUS can be performed even in patients with renal dysfunction or allergy to iodine-based contrast agents. It can be used to measure tumour size and contrast agent uptake accurately, and so CEUS has been also used to evaluate treatment response in various malignancies, however, few studies have investigated the performance of CEUS for assessing early treatment response in lymphomas. Thus, the aim of the present study was to clarify the feasibility of CEUS for early, interim evaluation of response to chemotherapy in various lymphoma subtypes independent of the chemotherapy regimen.

Materials and methods

Patients

This was a prospective observational study conducted between February 2013 and June 2017 for the purpose of evaluating the value of CEUS evaluation of the treatment response in patients with various lymphomas. The inclusion criteria were age >20 years, the pathological diagnosis of lymphoma, at least one detectable lesion via ultrasonography, hospitalisation during the study period, and written informed consent. Meanwhile, the exclusion criteria were allergy to the ultrasonography contrast agent or egg and assumed unsuitable for enrolment at the physician's discretion. The International Prognostic Index was used for clinical prognostic scoring, and pathological diagnosis was according to the World Health Organization classification.

Ultrasonography scanning technique

B-mode ultrasonography and CEUS were scheduled as follows: before the treatment (day 0), 7 days after the treatment (day 7), and 14 days after the treatment (day 14). In principle, undergoing the full three sets of CEUS was encouraged, but choosing only either day 7 or 14 as a follow-up was permitted according to the patient preference. Ultrasonography was performed using Aplio MX (Canon Medical Systems Corporation, Tochigi, Japan), and a 3.5-MHz convex transducer (PV-375BT). A single target lesion, which could be depicted on one screen and showed the least mobility from breathing, was selected for the response evaluation. For each examination, a morphological study was performed in B-mode with a measurement of the two largest diameters of the lesion. CEUS was used for functional evaluation. Briefly, a 0.5-ml bolus of perfluorobutane microbubbles (Daichi-Sankyo, Tokyo, Japan) was injected into the antecubital vein via a 22-G peripheral intravenous cannula, followed by a 10-ml saline flush. The recording was started at the time of contrast agent injection. Raw data were acquired in 1 minute, and the mechanical index was set at 0.2. CEUS was performed at a rate of 15 frames/second and with a dynamic range of 45 dB. Receiver gain and image depth were optimised for each patient at baseline examination. Transit focus was set at the
bottom of the target lesion. These settings were kept identical in each patient in the follow-up examinations. All CEUS evaluations were performed by three investigators who had 8–16 years of experience.

**Perfusion parameter analysis**

Raw data were retrieved from the workstation and then quantified on the computer using the original time-intensity curve (TIC) analysis software developed by R.K. Because the targets were tumours, the target areas were assumed to be elliptical. Specifically, the area of the ellipse centre was selected. Next, the lengths of the longitudinal and transverse axes of the ellipse on the ultrasound image were set such that the elliptical region contained the tumour. Finally, TIC analysis was performed by calculating the average luminance in the selected elliptical region for each frame. The regions of interest (ROIs) surrounding the lesion, including the lymph nodes, were defined. Changes in perfusion imaging of ROIs on CEUS were expressed as TICs, which were calculated as the sum of TICs of all pixels using linear raw data obtained via the original software and the proportion to the real perfusion of the target lesion. The arithmetic operation was conducted on 900 images acquired during each examination at 15 images/s for 1 min (Electronic Supplementary Material Fig. S1). Five quantitative perfusion parameters were determined based on TICs, namely, peak enhancement (PE), time to peak enhancement (TTP), perfusion index (PI), the total area under the TIC during wash-in (AUC-in), and the total AUC. PE, AUC-in, and total AUC corresponded to blood volume, whereas TTP and PI corresponded to blood flow (Fig 1). ROI selection and TIC analysis were performed by two operators. The perfusion parameters calculated by the two operators were very strongly correlated ($r = 0.930, p=2.24 \times 10^{-6}$ for PE and $r = 0.897, p=2.70 \times 10^{-6}$ for PI).

**Measurement of clinical outcomes**

The clinical prognostic scoring systems used for each patient to evaluate progression and count risk factors were based on the International Prognostic Score (IPS) for HL, the International Prognostic Index (IPI) for non-Hodgkin’s lymphoma, and Follicular Lymphoma Prognostic Index (FLPI) for follicular lymphoma (FL). PET/CT imaging was performed before the start of chemotherapy and after the completion of the planned chemotherapy. Treatment response was categorised into CR, partial remission (PR), stable disease (SD), or progressive disease (PD) according to the standard criteria.\(^1\) Progression-free survival (PFS) was defined as the time from treatment initiation to disease progression. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Clinical data, including serological and follow-up data, were obtained from the hospital records in all cases. The study was approved by the institutional review board (RK-130208-1). Informed consent was obtained from all individual participants included in the study.

**Statistical analysis**

The patients were divided into the CR group or the non-CR group according to the results of PET/CT for response evaluation. Variations for each CEUS perfusion parameter was calculated as the ratio of the value on each day of treatment (days 7 and 14) to the baseline value (day 0). Variations between the CR and non-CR groups were compared using the Wilcoxon rank-sum test. The receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic power of the parameters. PFS between the two groups was compared using the log-rank test. A $p$-value of $<0.05$ was considered statistically significant. All statistical analyses were performed using the JMP software version 8.0.1 (SAS Institute, Cary, NC, USA).

**Results**

**Patient characteristics**

A total of 41 patients were enrolled in the study. Of these, nine patients did not undergo CEUS after the initiation of the treatment because of withdrawal of consent.
(n=1), incomplete execution of CEUS schedule (n=2), severe illness (n=3), no ROIs detected (n=2), and no treatment initiated (n=1). Furthermore, TICs could not be depicted in five patients because the target lesion moved during their breathing. All 14 patients were excluded, and thus 27 patients (18 men and nine women) with a median age of 66 years were evaluable for the final analysis. The histological types of lymphoma consisted of DLBCL (n=17), FL (n=3), anaplastic large cell lymphoma (n=2), HL (n=1), nodal marginal zone lymphoma (NMZL; n=1), mantle cell lymphoma (MCL; n=1), angio-immunoblastic T-cell lymphoma (n=1), and enteropathy-associated T-cell lymphoma (n=1). Patients with newly diagnosed DLBCL (n=14), T-cell lymphomas (n=4), FL (n=2), and NMZL (n=1) were treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP)-based chemotherapies with or without rituximab. Patients with relapsed/refractory DLBCL (n=2) and FL (n=1) were administered rituximab, ifosfamide, etoposide, cytarabine, and dexamethasone treatment. One patient with relapsed/refractory DLBCL was administered gemcitabine, carboplatin, dexamethasone, and rituximab treatment. One patient with MCL received rituximab and bendamustine. One patient with HL received doxorubicin, bleomycin, vinblastine, and dacarbazine treatment. At the end of the chemotherapies, all 27 patients were evaluated using the standardised response criteria for HL and non-HL. According to the treatment response. Accordingly, 18 and nine patients were classified into the CR and non-CR groups, respectively (Fig 2). The distributions of the patient characteristics in the CR and the non-CR groups were not significantly different (Table 1).

Perfusion parameters

In total, 11 patients underwent the complete set of CEUS on days 0, 7, 14, while 13 patients were examined on days 0 and 7, and the remaining three patients were examined on days 0 and 14. The selected ROIs were intra-abdominal lymph nodes (n=13), cervical lymph nodes (n=9), axillary lymph nodes (n=1), inguinal lymph node (n=1), ileum (n=1), liver (n=1), and mammary gland (n=1). All patients in the study experienced a decrease in lesion size at a median ratio of 48% (range, 0–77%) as determined via B-mode ultrasonography on days 7 or 14. The median ratio of size reduction was higher in the CR group than that in the non-CR group, but the difference was not significant (49% versus 33%, p=0.491). The median scores of PE, PI, AUC-in, and AUC tended to decrease in the CR group after the treatment, whereas these scores increased in the non-CR group (Table 2). Meanwhile, the median score of TTP in the non-CR group became shorter after the treatment. Thus, the median PI in the CR group decreased, whereas that in the non-CR group increased after the treatment. Particularly, the median change ratio of PE and PI at day 7 evaluation was significantly different between the CR group and the non-CR group (0.81 versus 1.39, p=0.017 for PE and 0.92 versus 2.09, p=0.010 for PI; Fig 3).

Clinical outcomes

To predict CR, cut-off values of changes in the ratio of PE and PI between days 0 and 7 that showed high specificity and sensitivity in correlation with CR were calculated. Accordingly, changes in the ratio of PI < 1.09 (specificity: 86%; sensitivity, 88%; area under ROC, 0.82) and changes in the ratio of PI < 1.65 (specificity: 86%; sensitivity, 94%; area under ROC, 0.84) distinguished CR from non-CR accurately. When these cut-off values were applied to the 24 patients who underwent CEUS on day 7, the estimated PFS for patients who obtained changes in the ratio of PE < 1.09 or of PI < 1.65 was significantly better than that for the other patients (Fig 4). Patient characteristics and images of typical CR group case with favourable changes in CEUS on day 7.

Table 1 General characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CR group (n=18)</th>
<th>Non-CR group (n=9)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, men/women</td>
<td>11/7</td>
<td>7/2</td>
<td>0.667</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>67.5 (47–80)</td>
<td>65 (49–79)</td>
<td>0.439</td>
</tr>
<tr>
<td>ECOG PS ≥ 2, n (%)</td>
<td>4 (22%)</td>
<td>3 (33%)</td>
<td>0.653</td>
</tr>
<tr>
<td>Stage III/IV, n (%)</td>
<td>12 (67%)</td>
<td>7 (78%)</td>
<td>0.676</td>
</tr>
<tr>
<td>LDH &gt; normal, n (%)</td>
<td>11 (61%)</td>
<td>8 (89%)</td>
<td>0.201</td>
</tr>
<tr>
<td>Extramedal sites ≥2, n (%)</td>
<td>5 (28%)</td>
<td>3 (33%)</td>
<td>1</td>
</tr>
<tr>
<td>Risk factors ≥3, n (%)</td>
<td>10 (56%)</td>
<td>6 (67%)</td>
<td>0.692</td>
</tr>
<tr>
<td>Histology, B-NHL/other</td>
<td>16/2</td>
<td>6/3</td>
<td>0.295</td>
</tr>
</tbody>
</table>

CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; IPI, International Prognostic Index; B-NHL, B-cell non-Hodgkin lymphomas.
Distribution of perfusion parameters according to the timing of CEUS evaluation.

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR group (n=18)</td>
<td>CR group (n=17)</td>
<td>CR group (n=8)</td>
</tr>
<tr>
<td></td>
<td>Non-CR group (n=9)</td>
<td>Non-CR group (n=7)</td>
<td>Non-CR group (n=6)</td>
</tr>
<tr>
<td>Peak enhancement (dB)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR group, median (range)</td>
<td>15 (0.71–27.32)</td>
<td>12.26 (0.46–22.64)</td>
<td>9.63 (3.54–17.2)</td>
</tr>
<tr>
<td>Non-CR group, median (range)</td>
<td>16.22 (1.95–21.96)</td>
<td>20.9 (7.83–26.35)</td>
<td>19.3 (12.90–24.4)</td>
</tr>
<tr>
<td>Time to peak enhancement (s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR group, median (range)</td>
<td>9.33 (6.27–13)</td>
<td>9.07 (7.07–16.3)</td>
<td>9.9 (6.20–18.3)</td>
</tr>
<tr>
<td>Perfusion index (db/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR group, median (range)</td>
<td>1.39 (0.09–3.92)</td>
<td>1.28 (0.05–2.31)</td>
<td>1.18 (0.19–2.07)</td>
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<tr>
<td>Non-CR group, median (range)</td>
<td>1.57 (0.29–3.17)</td>
<td>2.26 (1.14–4.16)</td>
<td>2.28 (1.35–3.89)</td>
</tr>
<tr>
<td>AUC-in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR group, median (range)</td>
<td>1.228 (53–2,610)</td>
<td>1.112 (175–1,959)</td>
<td>831 (370–1,328)</td>
</tr>
<tr>
<td>Non-CR group, median (range)</td>
<td>1,412 (104–2,526)</td>
<td>1,527 (471–1,678)</td>
<td>1,208 (823–2,310)</td>
</tr>
<tr>
<td>Total AUC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR group, median (range)</td>
<td>7,395 (803–15,401)</td>
<td>5,509 (687–11,464)</td>
<td>4,072 (1,445–8,064)</td>
</tr>
<tr>
<td>Non-CR group, median (range)</td>
<td>8,753 (568–10,163)</td>
<td>9,450 (2,277–13,222)</td>
<td>10,409 (5,044–12,220)</td>
</tr>
</tbody>
</table>

| neintensity curve. |

Table 2

Discussion

The present study demonstrated that changes in tumour perfusion parameters evaluated with CEUS at 1 or 2 weeks after the treatment initiation were significantly different between lymphoma patients who achieved CR and those who did not. By contrast, the changes in the ratio of the target lesion size were not significantly different between these two groups. These findings suggest that decreases or increases in blood flow volume and velocity in the lesion 1 week after the start of chemotherapy could be predictors of treatment response and the other clinical outcomes such as PFS among patients with lymphomas.

Recently, the utility of quantitative CEUS for determining early response to antiangiogenic therapies has been reported in various solid tumours such as hepatocellular carcinoma,11 renal cancer,12 liver metastasis of various cancers,13,16 and gastric cancer.17 Although several studies have investigated the utility of CEUS for the diagnostic evaluation of lymphomas,20–25 studies evaluating CEUS for early response evaluation in lymphomas are exceedingly rare. Little has been known that chemotherapy causes changes in the haemodynamics of lymphoma and that the changes themselves are directly linked to therapeutic effects. A study performed by Wei et al.26 revealed that a decrease in peak intensity was associated with treatment response and survival outcomes in 42 patients with aggressive B-cell lymphoma who were evaluated after two cycles of R–CHOP. Another study by Xin et al.27 showed that a decrease in peak intensity and AUC after the first three cycles of chemotherapy well predicted the overall response in 43 lymphoma patients. The present findings further support that such alterations in intratumour blood perfusions could be detectable using CEUS in a much earlier period during treatment and that changes in these parameters could predict the clinical outcomes in patients with lymphoma. In addition, unlike CT/PET, because CEUS is low-cost, portable, and free of radiation exposure, it can be used frequently, which is an advantage for patients with severe lymphoma.

The role of interim imaging analysis during the treatment of lymphomas has been considered, but optimal timing remains unclear. In contrast to most studies on interim PET whereby it was usually performed after 2–4 cycles of chemotherapy, the novelty of the present study is that interim imaging analysis was used during the early treatment period of lymphoma (i.e., 1 week after the treatment initiation). This period is one of the earliest reported in studies of lymphoma prognosis. Another preliminary study of 20 lymphoma patients conducted by Horger et al.28 focusing on image changes in 1 week used whole-body diffusion-weighted magnetic resonance imaging and the apparent diffusion coefficient (ADC) was calculated at baseline and within a median of 7 days after therapy onset. ADC values in the responder group increased significantly after the initiation of chemotherapy, whereas those in the non-responder group remained unchanged. In addition, there have been several studies on other tumours, which reported that changes in CEUS imaging within 1 week could predict response to chemotherapy. Response to bevacizumab could be predicted via perfusion parameters obtained using CEUS on day 3 in hepatocellular carcinoma12 or on day 7 in several metastatic cancers.30 These findings also support the present hypothesis that evaluating metabolic and/or vascular alteration at 1 week after the
treatment initiation may not be too early for interim analysis for predicting long-term clinical outcomes of malignant tumours. Interestingly, most patients in the non-CR group in the present study showed increased intratumour blood volume and velocity only at 1–2 weeks after the treatment. Furthermore, in the non-CR group, there were some cases in which even if such haemodynamic changes were shown at CEUS, CT/PET was evaluated as a PR.

In conclusion, the present findings suggest that conducting CEUS evaluations during the early treatment period could be useful for predicting long-term clinical outcomes in patients with lymphoma and has the advantage of low

Figure 3 Change ratios of perfusion parameters compared to the baseline. Change ratio of (a) PE, (b) TTP, (c) PI, (d) AUC-in, and (e) total AUC.

Figure 4 PFS according to change ratio of PE on day 7 to PE on day 0. (a) The PE change ratio < 1.09 group had significantly better PFS than the PE change ratio ≥ 1.09 group. PFS according to change ratio of PI on day 7 to PI on day 0. (b) The PI change ratio < 1.65 group had significantly better PFS than the PI change ratio ≥ 1.65 group.
costs and no radiation exposure. Besides, as a result of further studies, if CEUS is judged to be ineffective 1 week after the treatment, switching to another treatment immediately may improve the prognosis of lymphoma.

There are some limitations to the present study. The number of samples in the current study was insufficient to conduct additional analysis, and thus further investigations are required to clarify the relationship between the increase of blood flow and poor response to therapeutic effect. Moreover, the present study included only a small number of patients with heterogeneous characteristics and treatments. Therefore, the changes in CEUS before and after chemotherapy could not be considered separately for HL and NHL. Similarly, the present study did not analyse differences in CEUS imaging between B-cell lymphoma and T-cell lymphoma and between indolent lymphoma and aggressive lymphoma, before and after chemotherapy. Multicentre prospective studies involving a larger number of patients are necessary to confirm and expand the clinical implications of the present findings. Finally, there remains a

**Figure 5** Clinical example from the CR group. Targeted right neck lymph node in a 63-year-old female patient with anaplastic large cell lymphoma Stage IV treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone. The treatment response was evaluated as PR by computed tomography after 3 weeks. (a) CEUS images of target lesion measuring 43 × 21 mm before treatment, (b) strong vascularisation after bolus injection of perfluorobutane microbubbles before treatment, (c) target lesion measuring 26 × 12 mm on day 7, and (d) strong vascularisation after bolus injection on day 7. The reduction rate was 47.62% and treatment response evaluated as PR using CEUS. (e) TICs acquired via perfusion analysis of this lesion before treatment (parameters: PE: 27.32 dB, TTP: 9.47 seconds, PI: 2.89 dB/s, the AUC-in: 2,610.42, the total AUC: 15,400.57) and (f) day 7 (parameters: PE 10.7126 dB, TTP 12 seconds, PI 0.89 dB/s, AUC-in 1,118.23, the total AUC 4,961.60). This case still remains a CR.
point at the issue of interobserver agreement. Razec et al. reported excellent interobserver agreement of whole-body computed tomography for staging and treatment assessment in lymphoma according to the Lugano classification29; however, the US imaging technique depends largely on experience. So, it is difficult to numerically prove inter- and intra-observer variability. Therefore, it may be difficult to reproduce these assessments unless the facility has physicians with high experience for US, above all for lymphoma.

**Conflicts of interest**

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Matsumoto received personal fees from Daiichi-Sankyo and Eisai. Dr. Miura received personal fees from Chugai, Kyowa Kirin, and Nippon Shinyaku. Dr. Ogawa received personal fees from Daiichi-Sankyo, and Canon Medical Systems Corporation. Dr. Nakagawa received personal fee from

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**Figure 6** Clinical example of non-CR group. Targeted right neck lymph node in a 49-year-old male patient with anaplastic large cell lymphoma Stage IV treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone. The treatment response was evaluated as SD by computed tomography after 4 weeks. (a) CEUS images of target lesion measuring 19 × 8 mm before treatment, (b) strong vascularisation after bolus injection of perfluorobutane microbubbles before treatment, (c) target lesion measuring 16 × 6 mm on day 7, and (d) strong vascularisation after bolus injection on day 7. The reduction rate was ~12.5% and treatment response evaluated SD by CEUS. (e) TICs acquired via perfusion analysis of this lesion before treatment (parameters: PE 8.21 dB, TTP 8.53 seconds, PI 0.99 dB/s, the AUC-in 588.20, the total AUC 3,432.05) and (f) day 7 (parameters: PE 18.09 dB, TTP 9.27 seconds, PI 1.95 dB/s, AUC-in 1,526.76, the total AUC 9,117.30). This patient died 16 weeks later.
Bristol-Myers Squibb. Dr. Takahashi received personal fees from Chugai, Kyowa Kirin, Bristol-Myers Squibb, and Eisai; and research grants from Daiichi-Sankyo, Shionogi, Nippon Kayaku, Chugai, Kyowa Kirin, Nippon Shinyaku, Nichi-iko, Eli Lilly, Bristol-Myers Squibb, and Eisai; and research grants from Daiichi-Sankyo, Shionogi, Nippon Kayaku, Chugai, Kyowa Kirin, Nippon Shinyaku, Nichi-iko, Eli Lilly, and Eisai. Prof. Moriyasu received personal fees from Daiichi-Sankyo, Shionogi, Nippon Kayaku, Chugai, Kyowa Kirin, and Eisai; and research grants from Daiichi-Sankyo, Shionogi, Canon Medical Systems Corporation, Shionogi, Chugai, Kyowa-Kirin, Nippon Shinyaku, Nichi-iko, Eli Lilly, and Eisai. Prof. Moriyasu received personal fees from Daiichi-Sankyo, Shionogi, Kyowa Kirin, and Eisai; and research grants from Daiichi-Sankyo, Shionogi, Chugai, Bristol-Myers Squibb, and Eisai. All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

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References


