Brentuximab vedotin maintenance after autologous stem cell transplantation for refractory gray zone lymphoma with long-term remission

TOSHIKI TERAO[1,2], JUNICHIRO YUDA[1], NOBUHIKO YAMAUCHI[1], YONG-MEI GUO[1], KAORU SHIMADA[3], MASATO SUGANO[4], GENICHIRO ISHII[4] and YOSUKE MINAMI[1]

[1]Department of Hematology, National Cancer Center Hospital East, Kashiwa, Chiba 277-8577; [2]Division of Hematology/Oncology, Department of Internal Medicine, Kameda Medical Center, Kamogawa, Chiba 296-8604; Departments of [3]Radiology and [4]Pathology, National Cancer Center Hospital East, Kashiwa, Chiba 277-8577, Japan

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Abstract. Gray zone lymphoma (GZL) is a rare type of B-cell lymphoma characterized by features of both diffuse large B-cell lymphoma and classical Hodgkin lymphoma (cHL). The prognosis of GZL is poorer than that of cHL and mediastinal large B-cell lymphoma. However, an optimal treatment strategy for relapsed/refractory (R/R) GZL has not been established in the clinical setting. The current study reported an excellent clinical response in a patient with R/R CD30-positive GZL who received brentuximab vedotin (BV) maintenance after autologous stem cell transplantation (ASCT). Although the patient was resistant to prior treatments, BV maintenance after ASCT achieved long-term remission. Hence, BV was determined to be a safe and effective therapeutic option for CD30-positive R/R GZL.

Introduction

Gray zone lymphoma (GZL) is a rare type of B-cell lymphoma, with features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL) (1). Despite advancements in immunophenotyping and molecular diagnostics in addition to the conventional morphologic approach, the diagnosis of GZL remains complex and challenging (2). Although GZL is commonly observed in young adults, the survival of patients with GZL is worse than that of patients with DLBCL or cHL. That is, one-third of patients present with primary refractory disease, and the 2-year progression-free survival (PFS) rate is ~40% (3,4). Although its outcomes are inferior, an optimal treatment strategy for relapsed/refractory (R/R) GZL has not yet been identified. Allogenic stem cell transplantation (SCT) for R/R GZL may be a treatment option. However, the incidence of transplant-related mortality (TRM) or graft-versus-host disease is still a major problem. Therefore, more effective and less toxic therapy should be developed for patients with R/R GZL.

Brentuximab vedotin (BV), an anti-CD30 antibody drug conjugate, is highly effective for different types of lymphomas, including CD30-positive non-Hodgkin lymphoma and cHL (5-7). Recently, in the AETHERA trial, BV maintenance after autologous SCT (ASCT) had a statistically significant prognostic impact in patients with R/R cHL (8). However, only few studies showed that BV + conventional chemotherapy is effective for treatment-naïve GZL or BV maintenance therapy for R/R GZL (5,9,10). Herein, we report a patient with R/R GZL that is highly resistant to conventional chemotherapy and radiation therapy (RT). The patient achieved long-term remission after receiving BV maintenance treatment after ASCT.

Case report

A 19-year-old male patient was referred to our institution for further examination of left neck and right axillary lymphadenopathy and anterior mediastinal mass without B symptoms. The patient's lactate dehydrogenase and soluble interleukin-2 receptor levels were high at 317 U/l (normal upper limit: 245 U/l) and 2,040 U/ml, respectively. With consideration of malignant lymphoma, the patient underwent left neck lymph node biopsy. The pathological finding showed morphologic proliferation of atypical large lymphoma cells and the presence of few polynuclear Reed-Sternberg (RS)-like cells surrounded by infiltrating inflammatory cells (Fig. 1A). On immunohistochemical studies, the large lymphoma cells were positive for CD15, CD20 (Fig. 1C), CD30 (Fig. 1E), CD79a, PAX-5, and PD-L1 and were negative for CD5 and EBER. The Ki-67 index was 80%. Collectively, after a cautious review, the patient was diagnosed with GZL. Positron emission tomography (PET)/computed tomography (CT) scan was performed prior to treatment. Results revealed that the maximum standardized uptake value (SUVmax) was 11.4 (Fig. 2A). After completing eight cycles of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin,

Correspondence to: Dr Junichiro Yuda, Department of Hematology, National Cancer Center Hospital East, 6-5-1 Kashiwano-ha, Kashiwa, Chiba 277-8577, Japan
E-mail: jyuda@east.ncc.go.jp

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and rituximab (DA-EPOCH-R), PET/CT scan revealed a residual fluorodeoxyglucose (FDG)-uptake lesion, with an SUVmax of 6.8, in the mediastinum. Lymph node biopsy was performed with a mediastinoscope to identify the pathological characteristics of the residual mediastinal lesion. It showed the presence of CD15 and CD30-positive RS-like cells (Fig. 1B and F) surrounded by various inflammatory cells, but not CD20 and CD79a-positive atypical large lymphoma cells (Fig. 1D). This result indicated a phenotypic change from GZL to cHL. Consolidative involved-field RT to the mediastinal lesion at a dose of 41.4 Gy was performed. However, after 2 months, PET/CT revealed a new FDG-uptake lesion in the lymph node in front of the liver. Then, CT-guided lymph node biopsy was performed, and this new lesion was found to have pathological features similar to those of CD15 and CD30-positive cHL, but not DLBCL. The patient underwent additional three cycles of ifosfamide, cisplatin, and etoposide (ICE) and sequentially received high-dose chemotherapy with ranimustine, etoposide, cytarabine, and melphalan, followed by ASCT. PET/CT scan prior ASCT revealed the residual lymph node in the mediastinum with FDG uptake (SUVmax=3.53, partial metabolic response), scored as 4 by Deauville 5-point scales (5-PS). However, the patient eventually achieved complete metabolic remission (CMR) with 5-PS score of 3 on PET/CT scan on day 90 after ASCT. Based on the clinical course showing treatment resistance, this patient was at extremely high risk of GZL recurrence. To decrease such a risk, the patient was treated with BV maintenance targeting CD30 expression in lymphoma cells. BV monotherapy maintenance (1.8 mg/kg every 3 weeks) was initiated 3 months after ASCT. After 16 cycles of BV maintenance therapy, the patient was still on CMR and reached 5-PS of 1 on PET/CT scan on day 410 after BV initiation (Fig. 2B). Any adverse effects (AEs), such as peripheral neuropathy and neutropenia, were not observed during BV maintenance treatment.

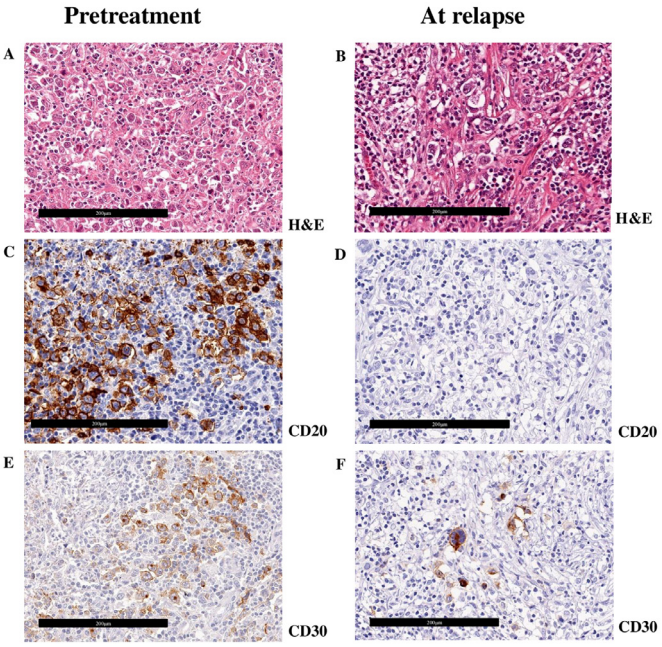

Figure 1. Pathological findings. Hematoxylin and Eosin Staining at (A) Pretreatment and (B) relapse revealed morphologic proliferation of atypical large lymphoma cells and the limited presence of polynuclear Reed-Sternberg-like cells surrounded by infiltrating inflammatory cells at pretreatment and relapse. These large lymphoma cells were positive for CD20 at (C) pretreatment; however, they became negative at (D) relapse. Lymphoma cells were positive for CD30 at both (E) pretreatment and (F) relapse. Scale bar, 200 μm.

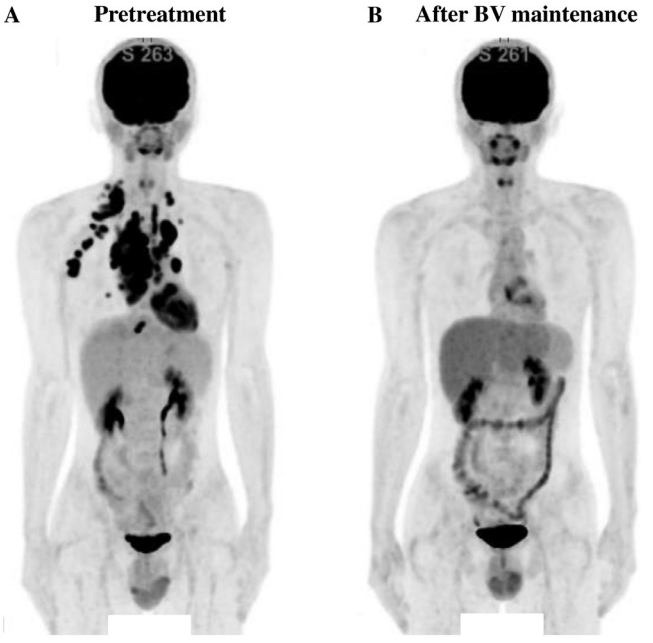

Figure 2. PET/CT. PET/CT images at pretreatment and after BV maintenance are presented. (A) Pretreatment PET/CT revealed hypermetabolic cervical, supraclavicular and anterior mediastinal masses (maximum standardized uptake value, 11.4). (B) After 16 cycles of BV maintenance, PET/CT demonstrated complete metabolic response. PET, Positron emission tomography; CT, computed tomography.

Discussion

This report showed that BV maintenance after ASCT might be effective in a patient with R/R GZL. GZL is pathologically composed of cHL and primary mediastinal B-cell lymphoma (PMBL), and its component may change between cHL and PMBL during the clinical course (4). Our case showed the phenotypic change from GZL to cHL after DA-EPOCH-R and RT with sustaining CD30-positivity of lymphoma cells, therefore, BV targeting CD30 was considered to be a promising therapeutic agent in our case. However, GZL showed negative for CD30 in some cases (2,4). Thus, re-biopsy of lymphoma lesion should be performed to confirm CD30 expression in lymphoma cells.

Previous reports showed that BV had a better prognostic impact on both R/R cHL and CD30-positive DLBCL. That is, the overall response rate (ORR) of R/R cHL and CD30-positive DLBCL were 75 and 44%, respectively (6,7). In the AETHERA trial, the PFS and 5-year PFS of patients who received treatment with BV maintenance after ASCT for R/R cHL were 42.9 months and 59%, respectively (8,11). On the other hand, although a small number of cases, two patients with treatment-naïve CD30-positive GZL have been shown to benefit from combination of BV and chemotherapy (5). In other previous reports, BV was administered to 4 patients with R/R GZL, resulting in achieving complete remission in 2 patients and presenting resistant for BV in another 2 patients (9,10). Although these results showed the efficacy of BV for R/R GZL, this has been still unknown due to the rarity of this disease. Allogenic SCT is another salvage

option for potentially achieving cure, however, it is concerned about transplant-related mortality and long-term toxicity. Our patient was at high risk of recurrence due to resistance to various chemotherapy (DA-EPOCH-R and ICE) and radiation, and the pathological diagnosis of residual disease prior ASCT showed a phenotypic change from GZL to cHL. Moreover, the prognosis of GZL is reported to be poorer than that of cHL or DLBCL (3). Considering of these points, our patient had received BV maintenance therapy after ASCT to lower the risk of recurrence based on the AETHERA study (11), and achieved long-term remission.

To date, our patient has maintained long-term remission after BV maintenance therapy. However, due to the history of resistance for treatment, he is still at risk of recurrence. At the time of recurrence after BV maintenance, the chemotherapy sensitivity of GZL is extremely low. Therefore, checkpoint inhibitors (CPIs) could be another therapeutic option. In patients with R/R cHL who received nivolumab, the ORR and 6-months PFS were 66.3 and 76.9%, respectively (12). In patients with R/R PMBL who received pembrolizumab, the ORR and 1-year PFS were 46% and ~40%, respectively (13). These data showed that CPIs might be an alternative therapeutic option for R/R GZL and could be a potential therapeutic option for our patient in future recurrence.

In summary, despite achieving CMR after ASCT, BV maintenance after ASCT was considered effective in a patient with GZL refractory to chemotherapy and RT, and severe AEs were not observed. Although a fraction of patients with R/R GZL is often difficult to treat, the change in morphology and immunophenotype, including CD30 expression, at the time of recurrence should be confirmed. Hence, BV maintenance after ASCT could be an extremely effective therapeutic modality for transplant-eligible patients with CD30-positive GZL.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TT and JY wrote and edited the manuscript, provided patient care and reviewed the literature. NY, YMG and YM provided patient care and acquired the clinical data. KS analyzed and evaluated PET-CT images. MS and GI conducted pathological reviews. All authors read and approved the final manuscript. TT and JY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present case study was approved by the Ethics Committee of the National Cancer Center Hospital East (approval no. 2018-416). The patient provided consent for inclusion in this study.

Patient consent for publication

The patient in this case provided consent to have this case published with removal of all identifying information to remain anonymous and retain privacy.

Competing interests

The authors declare that they have no competing interests.

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