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Central nervous system relapse after combination therapy including polatuzumab vedotin in patients with diffuse large B-cell lymphoma

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ABSTRACT

Preventing central nervous system (CNS) relapse is a major challenge in the treatment of diffuse large B-cell lymphoma (DLBCL). However, no previous studies have examined the efficacy of polatuzumab vedotin (PV)-containing regimens in preventing CNS relapse in patients with DLBCL. Here, we report two cases of CNS relapse after PV-containing chemotherapy for DLBCL. CNS relapse developed during combination therapy with PV, bendamustine, and rituximab (PV-BR) in one patient and six months after PV-BR in the other patient. PV-containing chemotherapy may be ineffective as a prophylaxis against CNS relapse; therefore, additional strategies for preventing CNS relapse in DLBCL patients are required.

1. Introduction

Central nervous system (CNS) relapse in patients with diffuse large B-cell lymphoma (DLBCL) can be devastating. Preventing CNS relapse is currently one of the greatest challenges in the treatment of DLBCL [1]. When patients with newly diagnosed DLBCL receive R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone)-based chemotherapies, prophylactic treatment against CNS relapse, including intrathecal and high-dose methotrexate, is employed in those with adverse CNS International Prognostic Index (CNS-IPI) classifications [1]. In addition, it is important to prevent CNS involvement in relapsed DLBCL.

Recently, novel antibody drugs, such as brentuximab vedotin (BV) and polatuzumab vedotin (PV), have been combined with cytotoxic agents in treating malignant lymphomas. PV has shown efficacy in patients with DLBCL. PV comprises an antibody-drug conjugate that targets CD79b. Although BV was reported to be effective against CNS lesions in combination chemotherapies, the effect of PV on CNS lesions has not been elucidated [2,3]. Combination therapy with PV, bendamustine, and rituximab (PV-BR) has been reported to be effective at treating relapsed/refractory DLBCL [4]. However, the effectiveness of PV-containing chemotherapies in preventing CNS relapse remains unclear. Here, we report two patients who developed CNS relapse after receiving PV-containing chemotherapy for DLBCL.

2. Case report

Patient 1, a 72-year-old Japanese male, was diagnosed with DLBCL, involving primary lesions in the oral cavity, bilateral maxillary sinuses, right frontal bone, and both lungs (Fig. 1a). His-CNS-IPI was intermediate. He received six cycles of R-CHOP therapy. After six months, 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) confirmed a complete metabolic response (CMR) (Fig. 1b). Three years after the R-CHOP therapy, he developed swelling of the left testis, and total left orchiectomy confirmed DLBCL recurrence. PET/CT revealed FDG accumulation in the right testis (Fig. 1c). He received six cycles of PV-BR as salvage chemotherapy without any CNS-directed prophylactic therapy. At the end of the PV-BR treatment, PET/CT showed no FDG accumulation in the right testicular tumor. However, a new lesion appeared in the right temporal lobe (Fig. 1d and e). The brain lesion was clinically diagnosed without a biopsy as a relapse of the DLBCL. Three cycles of rituximab, methotrexate, procarbazine, and vincristine (R-MPV) therapy were administered for the brain lesion, and PET/CT showed a CMR two months after the R-MPV. After busulfan and thiotepa conditioning, autologous peripheral blood stem cell transplantation (PBSCT) was performed as a consolidation therapy. One year after the autologous PBSCT, the patient's DLBCL had not relapsed.

Patient 2, a 72-year-old Japanese male, was diagnosed with DLBCL, involving lesions extending from the mediastinal to the supraclavicular lymph nodes, stomach, and right atrium (Fig. 2a). His-CNS-IPI was

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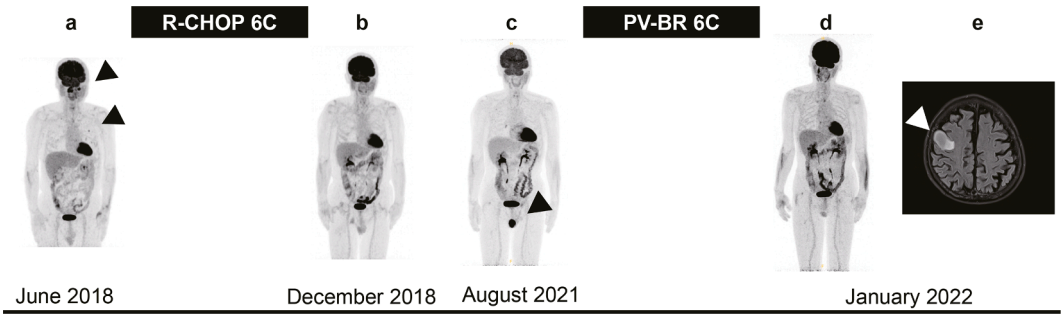

Fig. 1. PET/CT and brain MRI findings of case 1
18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) maximum intensity projection showed (a) oral cavity and lung lesions (arrowheads) at the initial diagnosis; (b) a complete metabolic response (CMR) after six courses of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone) therapy; and (c) the relapse in the right testis. (d) PET/CT and (e) MRI showed a relapse in the right temporal lobe (arrowheads) of the brain immediately after polatuzumab vedotin, bendamustine, and rituximab (PV-BR) therapy. C, cycles.

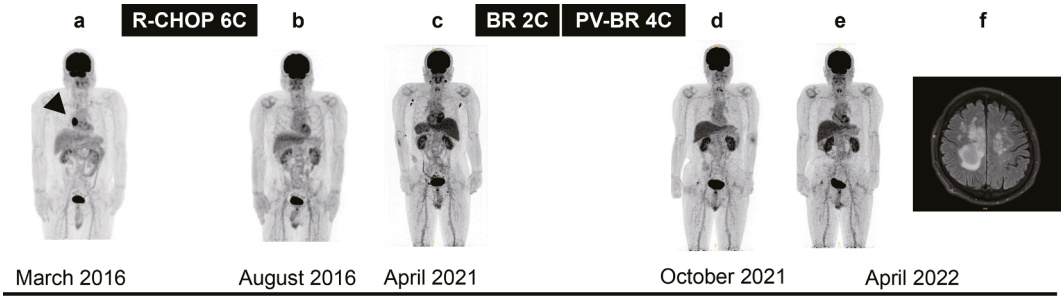

Fig. 2. PET/CT and brain MRI findings of case 2
PET/CT showed (a) a lesion in the right atrium (arrowheads) at the initial diagnosis; (b) a CMR after R-CHOP therapy; (c) relapses in the bilateral cervical, axillary, and inguinal lymph nodes; and (d) a CMR after BR and PV-BR therapy. (e) PET/CT and (f) MRI showed a brain relapse after BR and PV-BR therapy. C, cycles.

intermediate. He received six cycles of R-CHOP therapy. PET/CT showed a CMR (Fig. 2b). Five years after the R-CHOP therapy, PET/CT revealed a left lower abdominal subcutaneous tumor and FDG uptake in the bilateral cervical and axillary lymph nodes, and an inguinal lymph node (Fig. 2c). A biopsy of the subcutaneous tumor confirmed that the DLBCL had relapsed. Combination therapy with 120 mg/m2 bendamustine and rituximab (BR) was started. After PV was approved by the Japanese national health insurance system, two cycles of BR therapy were followed by four cycles of PV-BR (90 mg/m2 bendamustine) therapy. Upon the completion of the BR and PV-BR therapies, a PET/CT scan showed a CMR (Fig. 2d). No CNS relapse-directed prophylaxis was administered. Six months after the completion of the PV-BR therapy, PET/CT and brain MRI showed a relapse in the right frontal lobe (Fig. 2e and f). A brain biopsy confirmed that the DLBCL had relapsed. Six cycles of R-MPV therapy were administered. Autologous peripheral blood stem cell collection using plerixafor and granulocyte colony-stimulating factor was planned, but the patient was a poor mobilizer. After the R-MPV therapy, a residual tumor was seen in the C7/Th1 intervertebral space. Consequently, local radiotherapy was performed. Two months after the radiotherapy, the CNS lymphoma relapsed, and the patient received the best supportive therapy.

3. Discussion

PV has been used in combination with BR for relapsed/refractory DLBCL and with R-CHP (rituximab, cyclophosphamide, doxorubicin, and prednisolone) for newly diagnosed DLBCL. Although PV has been shown to improve the outcomes of DLBCL, the ability of PV-containing regimens to prevent CNS relapse remains an important issue in DLBCL management. In our patients, early CNS relapse developed after PV-BR therapy. The disease status of the CNS lesions was “refractory” during the PV-containing therapy in patient 1 and “relapsed” at six months after the PV-containing therapy in patient 2. Neither patient received any prophylaxis against CNS relapse during the first-line or salvage chemotherapies. Although PV, a large protein agent with a molecular weight of 153 kDa, is not expected to penetrate the CNS, there have been no reports in clinical practice on the prophylactic effect of PV against CNS relapse. Our cases suggest that PV-containing therapy may be ineffective as a prophylaxis against CNS relapse in DLBCL patients.

Prophylactic strategies for preventing secondary CNS lymphoma are important for patients who are at high risk of CNS relapse. However, no such strategies have been established. Intrathecal chemotherapy and high-dose methotrexate therapy have been used to treat patients with high CNS-IPI who had received R-CHOP chemotherapy [1]. In a study of patients who received PV-R-CHP therapy, the administration of intrathecal chemotherapy as a prophylaxis against CNS relapse was considered acceptable at the discretion of each institution [5]. The results showed that 16.4 % of patients received prophylactic intrathecal chemotherapy, and 3 % developed CNS relapse [5]. The latter study suggests that the CNS relapse rate of patients treated with PV-R-CHP is comparable to that of patients treated with R-CHOP. In addition, our cases suggest that PV may be insufficient for preventing CNS relapse. Therefore, CNS prophylaxis should be considered for patients receiving PV-containing regimens as well as for patients receiving R-CHOP-based therapies.

Identifying patients who should receive prophylaxis against CNS relapse, including those undergoing PV-containing chemotherapy, remains a challenge. The CNS-IPI is a widely used predictor of and risk stratification scoring system for CNS relapse in patients with newly diagnosed DLBCL that are treated with R-CHOP or similar regimens [1]. Although the CNS-IPI of our patients was intermediate, patient 1 had a testicular lesion. The most appropriate prophylaxis against CNS relapse during the initial and salvage treatment for patients who are at relatively high risk of CNS relapse remains unclear. In one report, the addition of

intrathecal methotrexate to first-line R-CHOP therapy did not prevent CNS relapse [6]. The efficacy of high-dose methotrexate for preventing CNS relapse is being debated. In some types of lymphoma, such as intravascular large B-cell lymphoma, a combination of high-dose methotrexate and intrathecal chemotherapy successfully reduced the rate of secondary CNS recurrence. On the other hand, two retrospective analyses reported that incorporating high-dose methotrexate prophylaxis into the initial standard R-CHOP treatment for DLBCL did not reduce the CNS relapse rate [7,8]. While no established prophylactic strategies against CNS recurrence for patients receiving R-CHOP therapy have been developed, the optimal CNS prophylaxis for patients receiving PV-containing regimens also needs to be determined.

Recently, PV-BR was reported to be effective in treating neurolymphomatosis [9]. However, the effect of PV on CNS lesions has not been reported. PV has a large molecular weight and is probably unable to cross the blood-brain barrier (BBB). A study investigating the pharmacokinetics of PV in rats demonstrated that the drug does not distribute to the brain [10]. Similar to PV, BV is an antibody-drug conjugate containing monomethyl auristatin E, which targets CD30. BV alone was reported to be insufficient for controlling CNS lesions [11]. On the other hand, other case reports have reported that combination chemotherapies, including BV, may be effective against CNS lesions when CNS lesions disrupt the BBB [2,3]. Although our case suggests that PV-BR chemotherapy may not prevent CNS relapse, further studies are warranted to determine the efficacy of PV in combination with other cytotoxic agents for treating CNS relapse involving disruption of BBB in DLBCL patients.

In conclusion, our cases suggest that additional prophylaxis against CNS relapse should be considered when patients at high risk of CNS relapse receive PV-containing chemotherapy, such as PV-BR, for DLBCL.

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Informed consent

Written informed consent was obtained from the patients for publication of this case report.

CRediT authorship contribution statement

Yoshikazu Hori: Conceptualization, Data curation, Investigation, Writing – original draft. **Hiroki Hosoi:** Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. **Toshiki Mushino:** Conceptualization, Data curation, Investigation, Writing – review & editing. **Yuka Okabe:** Data curation, Writing – review & editing. **Ayaka Sakaki:** Data curation. **Kikuaki Yoshida:** Data curation. **Yuichi Tochino:** Data curation. **Yusuke Yamashita:** Data curation. **Takashi Sonoki:** Supervision.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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