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ORIGINAL ARTICLE

# Treatment outcome of relapsed/refractory primary central nervous system diffuse large B-cell lymphoma: a single-center experience of autologous stem cell transplantation

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**Abstract** No salvage treatment strategy has been established for relapsed or refractory primary central nervous system lymphoma (PCNSL). We compared treatment outcomes of patients who underwent salvage chemotherapy with or without autologous stem cell transplantation (ASCT). We retrospectively analyzed PCNSL patients who were histologically diagnosed with diffuse large B-cell lymphoma. All patients relapsed after high-dose methotrexate (MTX)-based chemotherapy, or were refractory to high-dose MTX. Patients were treated with salvage chemotherapy, such as ICE/D (ifosfamide, carboplatin, etoposide, and dexamethasone) or high-dose MTX. High-dose chemotherapy containing thiotepa and busulfan followed by ASCT was performed if patients were eligible for ASCT after salvage treatment. Forty-five patients (35 relapsed and 10 refractory) received ICE/D or high-dose MTX. Despite the important difference that ICE/D was used predominantly for early relapsed or refractory patients, the two salvage treatments produced similar overall response rates [84.4 % (38/45) for ICE/D and 81.3 % (13/16) for high-dose MTX re-treatment]. Eighteen patients underwent ASCT, whereas 27 patients received salvage chemotherapy alone. The median progression-free survival of patients who underwent ASCT (19.5 months) was significantly better than that of patients who did not receive ASCT (6.7 months, $P = 0.023$). Multivariate analysis showed that refractoriness to initial treatment and no ASCT were significantly associated with poor survival outcome. Our study suggested that the combination of ifosfamide, carboplatin, etoposide, and dexamethasone may represent a feasible salvage treatment option for relapsed or refractory PCNSL, and that high-dose chemotherapy containing thiotepa and busulfan followed by ASCT may be effective for patients with a favorable toxicity profile.

**Keywords** Primary CNS lymphoma · Salvage treatment · Autologous stem cell transplantation

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## Introduction

Primary central nervous system (CNS) lymphoma is a rare but aggressive non-Hodgkin lymphoma (NHL) that is confined to the brain, leptomeninges, and eyes [1]. The majority of cases have diffuse large B-cell lymphoma (DLBCL) histopathology [2]. Primary CNS lymphoma (PCNSL) represents 2–7 % of all primary tumors of the

CNS and 1–2 % of all NHLs [1, 3]. High-dose methotrexate (MTX) is now recognized as an effective primary treatment for PCNSL [4, 5], and its use with or without whole brain radiotherapy (WBRT) has resulted in reported response rates of 70–90 % and median survival of 3–5 years [6–10]. However, up to 50 % of patients relapse after initial remission and 10–15 % become refractory to conventional chemotherapy [10, 11]. Although various salvage treatments with chemotherapy and radiotherapy have been tried for these patients [12–14], standard treatment strategy for relapsed or refractory PCNSL is not established because there are no data from a randomized phase III trial owing to the rarity of the disease. A previous phase II study reported a 2-year overall survival rate of 69 % with thiotepa, busulfan, and cyclophosphamide followed by autologous stem cell transplantation (ASCT) in relapsed or refractory PCNSL [15]. This study demonstrated that ASCT could be effective and feasible as a part of salvage treatment for relapsed or refractory PCNSL, as shown for relapsed or refractory systemic NHL [16]. However, there is still a limited amount of data supporting the benefits of ASCT in patients with relapsed or refractory PCNSL. Therefore, we analyzed relapsed or refractory PCNSL patients who were treated with salvage chemotherapy, and compared their treatment outcomes according to the use of ASCT after salvage chemotherapy.

## Materials and methods

### Patients

We retrospectively analyzed 45 patients with relapsed or refractory PCNSL at the Samsung Medical Center. All patients were histologically diagnosed with DLBCL by stereotactic or open brain biopsy between 2007 and 2012. The initial evaluation to determine the extent of disease was performed according to the International Primary CNS Lymphoma Collaborative Group recommendations [17]. As a primary treatment for newly diagnosed PCNSL, patients received high-dose MTX-based chemotherapy with or without WBRT. Relapsed disease was defined as disease recurrence in patients without evidence of disease after cessation of therapy, whereas refractory disease was defined as stable or progressive disease during the primary treatment. After patients relapsed or progressed, evaluations were performed to explore the systemic involvement of disease including CT scan of the thorax and abdomen, bone marrow biopsy, and blood tests. To examine leptomeningeal or ocular invasion, cerebrospinal fluid (CSF) analysis and ophthalmic examination were also performed. This retrospective study was approved by the Institutional Review Board of Samsung Medical Center.

### Salvage treatment and stem cell transplantation

All patients had received at least one cycle of salvage chemotherapy after they were diagnosed with relapsed or refractory PCNSL. The most commonly used salvage regimen was ICE/D (ifosfamide 1500 mg/m$^2$ per day on days 1–5, carboplatin AUC 5.5 on day 1, etoposide 100 mg/m$^2$ on days 1–5, and dexamethasone 40 mg/day on days 1–4 every 3 weeks). It has been used as salvage chemotherapy for relapsed or refractory PCNSL in our institute since 2008. However, high-dose MTX-containing chemotherapy (MTX 3.5 g/m$^2$ on day 1, procarbazine 100 mg/m$^2$ on days 1–7, and vincristine 1.4 mg/m$^2$ on day 1 every 2 weeks for 10 weeks) was mainly used before 2008 accounting for the second most common regimen. However, if patients relapsed 12 months after the initial HD MTX treatment, re-treatment with HD MTX was tried even after 2008. After salvage treatment, patients who were eligible for stem cell transplantation as a consolidation treatment underwent high-dose chemotherapy followed by ASCT as follows. Peripheral stem cell collection was performed after administration of 1.5–2.5 g/m$^2$ of cyclophosphamide and 10 μg/kg of G-CSF for mobilization. The conditioning regimen consisted of busulfan (3.2 mg/kg, days −8 to −5) and thiotepa (5 mg/kg, days −4 and −3). Stem cells were infused on day 0, and G-CSF was administered until bone marrow recovery. The eligibility for ASCT was determined by following factors. First, the age of patients at the time of ASCT should be 65 years or younger because the Korean Health Insurance system reimbursed the cost of ASCT only for patients ≤65 years. Second, patients' health status should be adequate for high-dose chemotherapy including the Eastern Cooperative Oncology Group performance status of 0–2, and adequate renal, cardiac, pulmonary and hepatic functions. Lastly, patients should show at least partial response to salvage chemotherapy.

### Treatment response

Response evaluation was performed after the completion of salvage chemotherapy, and the post-ASCT response was determined after the completion of ASCT. During the follow-up, response was evaluated by brain MR imaging and examination of CSF and eyes. Response was assessed according to the response criteria for PCNSL recommended by the International Primary CNS Lymphoma Collaborative Group [17]. Thus, complete response (CR) was defined as no contrast enhancement in brain MR imaging and negative findings of ocular and CSF examination, partial response (PR) was defined as at least 50 % decrease in enhancing tumor lesion, progressive disease (PD) was defined as at least 25 % increase in lesion or any new lesion in CNS or systemic sites, and stable disease (SD) was defined as less than a PR but not PD.

### Statistical analysis

Clinical features and treatment outcomes were compared between patients with and without ASCT. The differences between these two treatment groups were estimated by Fisher's exact test. Progression-free survival (PFS) was calculated from the date that salvage treatment began until the date of disease progression or relapse, the last follow-up visit, or death as a result of any cause. Alive patients without evidence of disease progression were censored on the date of their last follow-up visit. Overall survival (OS) was measured from the date of first salvage treatment to the date of death or the last follow-up visit. The OS and PFS were estimated using the Kaplan–Meier method with log-rank analysis. A two-sided $P$ value $<0.05$ was considered significant. All analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Characteristics of patients

The median age of patients at initial diagnosis of PCNSL with histology of DLBCL was 57 years (range 19–72 years). All patients received high-dose MTX-based chemotherapy, and 12 patients received WBRT adjuvant to high-dose MTX. Thirty-five patients responded to high-dose MTX chemotherapy while 10 were refractory to initial treatment. The median time from initial diagnosis to relapse or refractoriness was 7.7 months (range 1.4–95.5 months). Thus, more than 60 % of patients showed relapse or progression within 12 months from the initial diagnosis (Table 1). As a result, the age at the time of relapse or progression differed from time of diagnosis by only a 1-year interval (median age 58, range 20–73 years). The relapsed site was predominantly the CNS; 38 patients showed relapse or progression as brain parenchymal lesion, whereas four patients had parenchymal and leptomeningeal invasion. Another two patients showed only leptomeningeal and ocular invasion, respectively, at the time of relapse. The remaining patient showed systemic progression involving multiple lymph nodes. The characteristics of patients at relapse or progression were not significantly different between patients who received ASCT and patients who did not ($P > 0.05$, Table 1). Only age was significantly different between the two groups (mean age 49.8 versus 58.1 years, $P = 0.038$).

### Response to salvage treatments

For patients who failed to respond to initial high-dose MTX chemotherapy or relapsed within 12 months from the initial diagnosis, ICE/D (ifosfamide, carboplatin, etoposide, and dexamethasone) was predominantly used as salvage chemotherapy (Table 2). However, re-treatment with high-dose MTX chemotherapy was also performed for patients whose disease was controlled for more than 12 months after the initial high-dose MTX chemotherapy. Ten patients who were refractory to initial treatment received ICE/D ($n = 9$) and other regimen ($n = 1$). In 35 patients diagnosed with relapsed disease, salvage chemotherapy were ICE/D ($n = 16$), HD MTX ($n = 1$ 6), and other regimens ($n = 3$). Thirteen out of 16 patients who received ICE/D relapsed within 12 months. In contrast, 12 out of 16 patients who received HD MTX as salvage chemotherapy relapsed after 12 months. The remaining 4 patients who relapsed within 12 months in 2007 were treated with HD MTX because ICE/D was not used as salvage chemotherapy for PCNSL in our institution before 2008. Four patients received other salvage regimens including high-dose cytarabine ($n = 3$) and rituximab-CHOP ($n = 1$). One patient who developed ocular relapse received HD MTX with intrathecal MTX. Other characteristics at relapse or progression were not significantly different between patients that received ICE/D and those that received high-dose MTX (Table 2). The responses to ICE/D and high-dose MTX were not significantly different; 12 and 8 patients achieved CR after ICE/D and high-dose MTX, respectively (Table 2). The overall response rate to salvage treatment was 84.4 % (38/45), including 23 CR (51.1 %) and 15 PR (33.3 %). However, seven patients were refractory to salvage treatments (Table 2).

### High-dose chemotherapy followed by ASCT

After salvage chemotherapy, 27 patients could not receive ASCT due to age older than 65 years ($n = 8$), refractoriness to salvage treatment ($n = 4$), physicians' discretion or poor performance status/inadequate organ function ($n = 14$), or salvage treatment-related death ($n = 1$). Thus, 18 patients underwent high-dose chemotherapy followed by ASCT (18/45, 40.0 %, Fig. 1) including 17 patients who had received ASCT as a consolidation treatment after they achieved CR or PR to salvage treatment. Only one patient underwent ASCT even in the state of progressive disease due to a physician's decision (Table 3). High-dose chemotherapy regimen consisted of busulfan and thiotepa. Post-ASCT response included 15 CR and 3 PR; however, all patients with PR progressed during follow-up and four patients with CR relapsed. Thus, at the time of analysis seven patients had developed progression or relapse after ASCT. Although six patients died, including one case of non-disease related death, there was no transplantation-related death. The median time to neutrophil engraftment and platelet recovery after stem cell infusion was 10 days

**Table 1** Characteristics of patients with primary CNS lymphoma at relapse or progression ($n = 45$)

| Characteristics | All patients ($n = 45$) | Salvage treatment + ASCT ($n = 18$) | Salvage treatment ($n = 27$) | *P* |
|---|---|---|---|---|
| Sex | | | | |
| Male | 27 | 11 | 16 | >0.99 |
| Female | 18 | 7 | 11 | |
| Age | | | | |
| ≤60 | 24 | 13 | 11 | 0.066 |
| >60 | 21 | 5 | 16 | |
| Performance status | | | | |
| <ECOG grade 2 | 25 | 12 | 13 | 0.359 |
| ≥ECOG grade 2 | 20 | 6 | 14 | |
| Serum LDH | | | | |
| Normal | 35 | 14 | 21 | >0.99 |
| Increased | 10 | 4 | 6 | |
| Initial treatment | | | | |
| HD MTX | 33 | 14 | 19 | 0.735 |
| HD MTX + WBRT | 12 | 4 | 8 | |
| Response to initial treatment | | | | |
| CR/PR | 28/7 | 10/3 | 18/4 | 0.884 |
| SD/PD | 2/8 | 1/4 | 1/4 | |
| Relapse vs. refractory | | | | |
| Relapse | 35 | 13 | 22 | 0.489 |
| Refractory | 10 | 5 | 5 | |
| Time to relapse/progression | | | | |
| ≤12 months | 29 | 11 | 18 | 0.758 |
| >12 months | 16 | 7 | 9 | |
| Salvage treatment | | | | |
| ICE/D | 25 | 13 | 12 | 0.096 |
| HD MTX | 16 | 5 | 11 | |
| Others | 4 | 0 | 4 | |
| Response to salvage treatment | | | | |
| CR/PR | 23/15 | 10/7 | 13/8 | 0.313 |
| PD | 7 | 1 | 6 | |
| Evidence of disease at analysis | | | | |
| No | 21 | 11 | 10 | 0.138 |
| Yes | 24 | 7 | 17 | |
| Survival status | | | | |
| Alive | 24 | 12 | 12 | 0.223 |
| Dead | 21 | 6 | 15 | |

*CNS* central nervous system, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ECOG* Eastern Cooperative Oncology Group, *LDH* lactate dehydrogenase, *HD MTX* high-dose methotrexate, *WBRT* whole brain radiotherapy, *ICE/D* ifosfamide, carboplatin, etoposide, dexamethasone; *ASCT* autologous stem cell transplantation

(range 8–12 days) and 10.5 days (range 7–17 days), respectively. This result was consistent with the fact that there was no case of stem cell mobilization failure (median number of CD34-positive cells per recipient body weight: $3.4 \times 10^6$/kg, range $2.0–11.0 \times 10^6$/kg). However, in some cases bacterial infections occurred during the recovery period after ASCT, including bacteremia ($n = 2$), and pneumonia ($n = 1$). One patient developed veno-occlusive disease, but recovered with supportive care. Another patient experienced hematuria immediately after stem cell infusion, but this was successfully managed with bladder irrigation. Frequently observed non-hematological toxicities of ASCT included stomatitis, nausea, and diarrhea. However, these toxicities were manageable and not life-threatening.

## Survival analysis

Twenty-one patients had died at the time of analysis, with a median follow-up duration of 53.4 months [95 %

**Table 2** Comparison of patient characteristics based on the type of salvage treatment

| | ICE/D ($n = 25$) | HD MTX ($n = 16$) | Others ($n = 4$)[a] | *P* |
|---|---|---|---|---|
| Age at relapse/progression | | | | |
| ≤60 | 15 | 9 | 0 | 0.079 |
| >60 | 10 | 7 | 4 | |
| PS at relapse/progression | | | | |
| <ECOG grade 2 | 15 | 8 | 2 | 0.799 |
| ≥ECOG grade 2 | 10 | 8 | 2 | |
| Response to initial treatment | | | | |
| CR/PR | 10/6 | 15/1 | 3/0 | 0.006 |
| SD/PD | 1/8 | 0/0 | 1/0 | |
| Relapse vs. refractory | | | | |
| Relapse | 16 | 16 | 3 | 0.012 |
| Refractory | 9 | 0 | 1 | |
| Time to relapse/progression | | | | |
| ≤12 months | 22 | 4 | 3 | <0.001 |
| >12 months | 3 | 12 | 1 | |
| Response to salvage treatment | | | | |
| CR/PR | 12/9 | 8/5 | 3/1 | 0.847 |
| PD | 4 | 3 | 0 | |
| ASCT | | | | |
| Yes | 13 | 5 | 0 | 0.096 |
| No | 12 | 11 | 4 | |
| Evidence of disease at analysis | | | | |
| No | 10 | 9 | 2 | 0.590 |
| Yes | 15 | 7 | 2 | |
| Survival status | | | | |
| Alive | 13 | 9 | 2 | 0.956 |
| Dead | 12 | 7 | 2 | |

*CR* complete response, *PR* partial response, *PD* progressive disease, *ECOG* Eastern Cooperative Oncology Group, *LDH* HD MTX, high-dose methotrexate; *ICE/D* ifosfamide, carboplatin, etoposide, dexamethasone; *ASCT* autologous stem cell transplantation

[a] Others included high-dose cytarabine ($n = 3$) and rituximab-CHOP ($n = 1$)

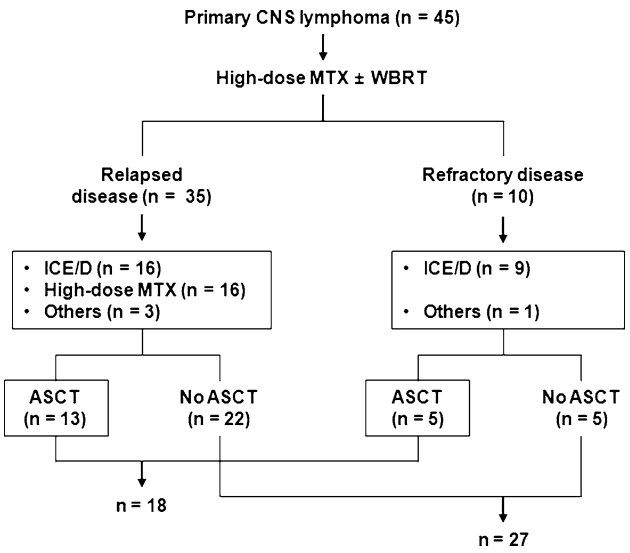


**Fig. 1** Summary of treatment for relapsed or refractory primary CNS lymphoma patients

confidence interval (CI) 34.9–71.8 months] from the date of initial diagnosis. Among the 24 patients who relapsed or progressed during the follow-up period, 19 patients died due to PCNSL and 5 were still alive with disease. The other two deaths were not associated with PCNSL. One patient died due to gastrointestinal sepsis during neutropenia after ICE/D chemotherapy and the other due to pneumonia that developed 5 months after ASCT without evidence of disease and neutropenia (Table 3, patient no. 5). The median OS and PFS from the date of first salvage treatment was 26.6 months (95 % CI 9.3–43.9) and 10.8 months (95 % CI 6.6–15.0), respectively. The survival outcomes of patients who were initially refractory to primary treatment with high-dose MTX were worse than those of patients who relapsed after high-dose MTX (Fig. 2a, b). When we compared the type of salvage treatment, there was no significant difference in OS and PFS between ICE/D and high-dose MTX (Fig. 2c, d) even though refractory patients were predominantly treated with ICE/D regimen (Table 2). However, the PFS of patients who underwent ASCT after salvage treatment was

**Table 3** Summary of patients who underwent ASCT

| No. | Sex/ age[a] | Site of invasion | Response to induction treatment | Relapse or refractory | Salvage chemotherapy | Response to salvage treatment | Post-ASCT response | Relapse/ progression after ASCT | Survival |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M/55 | Brain, leptomeninges | CR | Relapsed | ICE/D | PR | CR | No | Alive |
| 2 | F/51 | Brain | CR | Relapsed | ICE/D | CR | CR | No | Alive |
| 3 | F/47 | Brain | CR | Relapsed | ICE/D | CR | CR | No | Alive |
| 4 | M/61 | Brain | CR | Relapsed | HD MTX | CR | CR | Relapse | Dead |
| 5 | M/63 | Brain | CR | Relapsed | HD MTX | CR | CR | No | Dead |
| 6 | M/57 | Brain | CR | Relapsed | ICE/D | CR | CR | Relapse | Dead |
| 7 | M/19 | Brain | PR | Relapsed | HD MTX | PR | PR | Progression | Alive |
| 8 | F/42 | Ocular | CR | Relapsed | HD MTX | PR | CR | No | Alive |
| 9 | M/55 | Brain | SD | Refractory | ICE/D | CR | CR | Relapse | Dead |
| 10 | F/34 | Brain, leptomeninges | PR | Relapsed | ICE/D | PR | CR | No | Alive |
| 11 | M/63 | Brain | PD | Refractory | ICE/D | PD | CR | No | Alive |
| 12 | M/24 | Brain | PD | Refractory | ICE/D | PR | PR | Progression | Alive |
| 13 | M/47 | Brain | CR | Relapsed | HD MTX | PR | CR | No | Alive |
| 14 | F/38 | Brain | PR | Relapsed | ICE/D | CR | CR | No | Alive |
| 15 | M/47 | Brain | PD | Refractory | ICE/D | PR | PR | Progression | Dead |
| 16 | F/56 | Brain | PD | Refractory | ICE/D | CR | CR | Relapse | Dead |
| 17 | F/62 | Brain | CR | Relapsed | ICE/D | CR | CR | No | Alive |
| 18 | M/62 | Brain | CR | Relapsed | ICE/D | CR | CR | No | Alive |

*CR* complete response, *PR* partial response, *PD* progressive disease, *HD* MTX, high-dose methotrexate; *ICE/D* ifosfamide, carboplatin, etoposide, dexamethasone; *ASCT* autologous stem cell transplantation

[a] Age at relapse/progression

significantly better than that of patients who did not receive ASCT ($P = 0.023$), although ASCT failed to show a significant benefit in OS (Fig. 2e, f). Multivariate analysis for OS and PFS after salvage treatment showed that refractoriness to initial treatment and no ASCT were significantly associated with poor OS and PFS (Table 4).

## Discussion

We have used two kinds of salvage chemotherapy regimens, ICE/D and high-dose MTX, for PCNSL patients who were previously exposed to high-dose MTX chemotherapy. Based on a previous study reporting a 91 % overall response rate for high-dose MTX re-treatment in patients with relapsed PCNSL [12], we used high-dose MTX in one group of patients, predominantly those who relapsed more than 12 months from the initial diagnosis. However, patients who showed early relapse or refractoriness to high-dose MTX received ICE/D chemotherapy as a salvage treatment. The rationale for the use of ifosfamide in this clinical setting was based on reports that a protocol containing ifosfamide was effective for newly diagnosed and relapsed PCNSL patients [18, 19]. Although etoposide is known to have low blood–brain barrier permeability in a standard dose of <300 mg/m$^2$ [20], it was reported that higher doses of etoposide could reach a sufficient concentration to kill tumor cells [21]. Accordingly, a recent study with the DeVIC (dexamethasone, etoposide, ifosfamide and carboplatin) regimen also showed 95.2 % overall response rate and median PFS of 37.4 months in 21 patients with newly diagnosed PCNSL [22]. In our study, the overall response rate of ICE/D (84.4 %, 38/45) was comparable to that of high-dose MTX re-treatment (81.3 %, 13/16, Table 2) even though ICE/D was predominantly used for early relapsed or refractory patients (Fig. 1). Thus, the similar survival outcome of the ICE/D group to that of the HD MTX group might imply that ICE/D could be used as a salvage treatment for this clinical setting, even for refractory PCNSL.

After salvage treatment, patients who were determined as eligible for ASCT underwent high-dose chemotherapy followed by ASCT. As a conditioning regimen for ASCT, we have used thiotepa and busulfan because both agents are known to have excellent blood–brain barrier permeability with CSF levels >90 % of those in serum [23, 24].

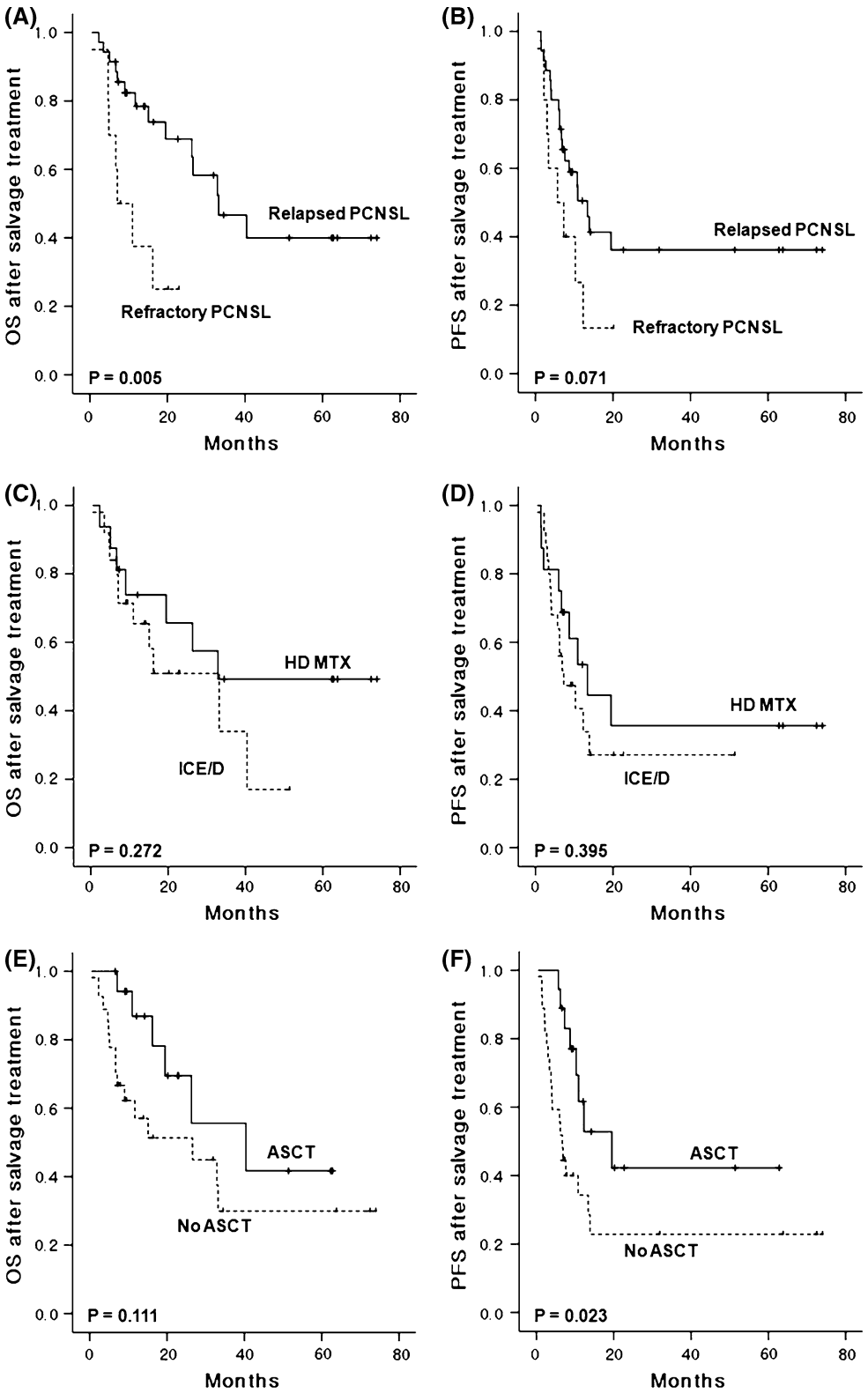


**Fig. 2** **a**, **b** Comparison of OS and PFS after salvage treatment shows better survival outcomes of patients that relapse after initial treatment compared with patients that are refractory to initial treatment. **c**, **d** Comparison of ICE/D and high-dose MTX shows no significant difference in OS and PFS. **e**, **f** Patients who underwent ASCT showed a significantly superior PFS compared with patients without ASCT, but ASCT failed to show a benefit on OS

Furthermore, given the dose–response correlation of these drugs, they can be used as high-dose chemotherapy in the setting of transplantation. A recent large retrospective study with a thiotepa, busulfan, and cyclophosphamide conditioning regimen for 79 patients with relapsed or refractory PCNSL and intraocular lymphoma showed a 5-year OS of 51 % in the total population and 62 % in patients who responded to the salvage treatment, with four

**Table 4** Multivariate analysis of survival outcomes according to clinical and treatment-related characteristics

| Characteristics | PFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|
| | HR | 95 % CI | | *P* | HR | 95 % CI | | *P* |
| Female | 0.862 | 0.374 | 1.985 | 0.727 | 0.944 | 0.377 | 2.364 | 0.902 |
| Age at relapse >60 | 0.981 | 0.413 | 2.331 | 0.966 | 1.423 | 0.535 | 3.790 | 0.480 |
| PS at relapse ≥ECOG grade 2 | 2.026 | 0.877 | 4.676 | 0.098 | 2.296 | 0.884 | 5.962 | 0.088 |
| Refractory to initial treatment | 3.050 | 1.037 | 8.969 | 0.043 | 5.895 | 1.681 | 20.678 | 0.006 |
| Relapse/PD ≤12 months | 1.064 | 0.386 | 2.936 | 0.904 | 0.965 | 0.303 | 3.077 | 0.952 |
| Salvage treatment | 0.445 | 0.196 | 1.013 | 0.054 | 0.543 | 0.223 | 1.323 | 0.179 |
| Refractory to salvage treatment | 0.941 | 0.351 | 2.521 | 0.904 | 0.932 | 0.299 | 2.905 | 0.904 |
| No ASCT | 5.952 | 1.931 | 18.346 | 0.002 | 4.550 | 1.238 | 16.718 | 0.022 |

*PFS* progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *PS* performance status; *ECOG* Eastern Cooperative Oncology Group, *PD* progressive disease, *ASCT* autologous stem cell transplantation

deaths associated with transplantation [25]. This result was comparable to that of the previous phase II study conducted by the same group that included 43 patients with relapsed/refractory PCNSL or intraocular lymphoma and reported 2-year overall survival rate of 45 % in the total population and 69 % in patients who received ASCT [15]. However, this phase II study also showed a 16 % rate of transplantation-related mortality. The fact that there was no transplantation-related mortality in our study suggests that the addition of cyclophosphamide, resulting in triple alkylating agent therapy, might increase the toxicity of the conditioning regimen. Indeed, a recent study combining busulfan, melphalan, and thiotepa has shown excessive toxicity and transplantation-related mortality [26]. Our study demonstrated that the combination of thiotepa and busulfan was both feasible and effective for conditioning in ASCT.

Previous studies have shown that age over 60 years is a risk factor for poor survival outcome in PCNSL because elderly patients are more susceptible to treatment-related complications [25, 27]. In this study, five patients aged over 60 years at relapse or progression underwent ASCT and completed the course of ASCT without mortality. Among these five patients, three were alive without evidence of disease at the time of analysis although one patient died due to disease relapse (patient no. 4, Table 3) and the other patient died due to pneumonia without neutropenia 5 months after ASCT (patient no. 5, Table 3). Thus, ASCT can be helpful for selected elderly patients with a good performance status. As expected, comparison of survival outcomes showed that patients with refractory PCNSL had a worse OS than patients with relapsed PCNSL (Fig. 2a, b). Consistent with this finding, four out of five patients with refractory PCNSL who underwent ASCT showed disease relapse (Table 3), suggesting that a more effective treatment strategy should be established for refractory PCNSL patients. Multivariate analysis showed that administration of ASCT and initial responses to primary treatment were independent predictive factors for better PFS and OS, rather than age and performance. Although the possibility of selection bias exists because more patients with favorable characteristics were able to undergo ASCT, these results implied the usefulness of ASCT as a part of salvage treatment for relapsed PCNSL. Furthermore, active application of salvage treatment may improve survival outcomes even in elderly patients.

In conclusion, our study suggested that ifosfamide, carboplatin, and etoposide combination might be a feasible salvage treatment option for relapsed or refractory PCNSL. In addition, high-dose chemotherapy with thiotepa and busulfan followed by ASCT showed antitumor activity and a favorable toxicity profile in refractory or relapsed PCNSL. Further development of salvage treatment strategy including ASCT is warranted for this rare but life-threatening clinical setting.

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