Cytomegalovirus infection in patients with malignant lymphomas who have not received hematopoietic stem cell transplantation

Kazuya Sato1*, Sho Igarashi1, Nodoka Tsukada1, Junki Inamura1, Masayo Yamamoto2, Motohiro Shindo2, Kentaro Morichi2, Yusuke Mizukami2, Mikihiro Fujiya2 and Yoshihiro Torimoto2

Abstract

Background: Life-threatening cytomegalovirus infection (CMVI) has been reported even in patients with malignant lymphoma (ML) who have not received hematopoietic stem cell transplantation (w/o HSCT) but had been treated with chemotherapy or radiotherapy. However, the CMVI incidence and risk factors (RFs) in patients with ML w/o HSCT have not been fully elucidated. This study aimed to evaluate the clinical aspects, including incidence and RFs, of CMVI in patients with ML w/o HSCT.

Methods: We retrospectively reviewed all patients with ML who received chemotherapy or radiotherapy in our department from 2005 to 2013. The overall survival (OS), incidence and RFs of CMVI, and other characteristics of patients with CMVI were analyzed.

Results: Overall, 236 patients with ML w/o HSCT were evaluated. Of these, 5.5% (13/236) developed CMVI; 54% (7/13) received steroid pretreatment before primary therapy (PT) for ML; and 62% (8/13) received > 2 therapeutic regimens for ML. The OS curve of patients with CMVI was significantly worse than that of patients without CMVI (p < 0.0001, log-rank test). A univariate analysis identified B symptoms (p = 0.00321), serum albumin < 3.5 g/dL (p = 0.0007837), C-reactive protein level > the upper limit of normal (p = 0.0006962), steroid pretreatment before PT for ML (p = 0.0004262), > 2 therapeutic regimens for ML (p = 0.0000818), T cell lymphoma (p = 0.006406), and non-complete remission (p = 0.02311) as RFs for CMVI. A multivariate analysis identified steroid pretreatment before PT for ML [odds ratio (OR): 4.71 (95% confidence interval [CI]: 1.06–21.0); p = 0.0419] and > 2 therapeutic regimens for ML [OR: 9.25 (95% CI: 2.33–36.8); p = 0.00159] as independent RFs for CMVI in patients with ML w/o HSCT.

Conclusions: Attention should be paid to CMVI development in patients with ML w/o HSCT pretreated with steroids or who had multiple therapeutic regimens.

Keywords: Malignant lymphoma, Cytomegalovirus infection, Steroid pretreatment, Multiple therapeutic regimens

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transplantation (HSCT) [1–3]. Factors associated with HSCT, such as transplantation from a CMV-seropositive donor, recipient CMV seropositivity, presence of chronic graft-versus-host disease, use of alemtuzumab or high-dose corticosteroids, or duration of neutropenia, are known risk factors (RFs) for the development of CMVI [4–6].

Several retrospective studies of CMVI in populations that included patients with ML who have received HSCT have reported the incidence rates of CMVI ranging from 3.9 to 16% [6–8]. Tay et al. reported that the incidence rate of CMVI in patients with ML who have received chemoimmunotherapy, but not HSCT, was 9.0% [9]. However, the clinical aspects, including CMVI incidence, survival, and RFs for CMVI, have not been fully elucidated in patients with ML who have not received HSCT but who had been treated with chemotherapy or radiotherapy. It is essential to clarify the clinical aspects of CMVI development in this population to ensure safe administration of chemotherapies and radiotherapies. Therefore, we performed a retrospective clinical analysis to evaluate these clinical aspects, including RFs, of CMVI in patients with ML who had not received HSCT but who had been treated with chemotherapy or radiotherapy.

Methods
Patients
We reviewed data of all patients with ML who received chemotherapy or radiotherapy in our department from April 2005 to March 2013 and identified 236 patients (B cell ML:T/NK cell ML:Hodgkin lymphoma [HL] ratio = 195:25:16) who had not received autologous or allogeneic HSCT. Diagnoses of lymphomas were made according to the 4th edition of the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues [10]. The clinical backgrounds, incidence of CMVI, treatments, overall survival (OS), RFs for CMVI, causes of death, and other characteristics of patients with or without CMVI were analyzed. This study was approved by our institutional ethics review board and was conducted in accordance with the Declaration of Helsinki. The requirement for obtaining patient informed consent was waived due to the retrospective design of the data collection.

Treatment and outcome
Patients with ML were treated with conventional chemotherapeutic regimens according to the physicians’ discretion; these included R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) for B cell MLs, CHOP for T cell lymphomas, and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) for HLs. Steroid pretreatment means a steroid treatment temporarily used before the chemotherapy to maintain the patients’ condition. OS was calculated from the first date of diagnosis until death from any cause, or the date of the last contact for surviving patients. The last date of censoring for patients who did not die, but who developed a censoring event, was May 4, 2013.

Data collection
Clinical or laboratory data, histological findings, treatment, and outcome of every patient were extracted from the electronic medical record system and medical charts at our institute. Histological findings were based on pathology reports. CMVI was defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen [11–13]. Screening for CMV antigenemia was not done routinely but mainly performed in patients with clinical symptoms and signs, such as fever, abdominal pain, diarrhea, liver dysfunction, bone marrow suppression, or interstitial pneumonia, which cannot be fully explained by other pathogens; this screening procedure was also done during the observation period of CMVI. CMV antigenemia was determined by measuring CMV antigen-positive cells per 5×10⁴ leukocytes with an anti-pp65 peroxidase-conjugated monoclonal antibody C7-HRP (Teijin antigenemia kit; Teijin, Osaka, Japan) [14]. This study did not assess the CMV serostatus because serum anti-CMV antibodies were not routinely tested in our department. To review cases of CMVI in patients with ML who have not received HSCT, we searched related literatures in PubMed by using the keywords “cytomegalovirus disease,” “cytomegalovirus infection,” and “lymphoma.” Case reports were excluded. Then, we checked and extracted papers reporting on relatively large-scale studies that described the incidence of CMVI, RFs for CMVI, and presence or absence of HSCT for lymphoma. Based on the extracted papers, we summarized the number of patients, incidence of CMVI, RFs for CMVI, and disadvantages in survival prognosis in patients with ML with CMVI in Table 4.

Statistical analysis
OS was estimated using the Kaplan–Meier method [15], and time-to-event distributions were compared with the log-rank test [16]. RFs for CMVI were initially identified through a univariate analysis. The Fisher’s exact test and t-test were used for categorical and continuous data, respectively; these identified RFs were subsequently evaluated in a multivariate Cox proportional hazards regression analysis using stepwise selection. A t-test was used to compare continuous variables. We divided all parameters into two groups so that it is easy to use the indicators for clinicians. Therefore, all comparisons were performed between

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two groups, and multiple comparisons were not used. A \( p \)-value of \(< 0.05\) was considered to indicate statistical significance in all analyses. All statistical analyses were performed using the EZR software package (Saitama Medical Center, Jichi Medical University) [17].

**Results**

**Patient characteristics**

The clinical background information of all patients with ML is shown in Table 1. The median age of the study participants was 69 years, and 53\% (126/236) of the patients had extranodal involvement.

| Characteristic                        | All patients, \( n = 236 \) | Patients with CMVI, \( n = 13 \) | Patients without CMVI, \( n = 223 \) |
|---------------------------------------|-----------------------------|----------------------------------|-------------------------------------|
| Median age (range), years             | 69 (23–94)                  | 64 (42–85)                       | 69 (23–94)                          |
| Male (%)                              | 126 (53)                    | 8 (62)                           | 118 (53)                            |
| Performance status (%)                |                             |                                  |                                     |
| 0–1                                   | 173 (73)                    | 6 (46)                           | 167 (75)                            |
| 2–4                                   | 63 (27)                     | 7 (54)                           | 56 (25)                             |
| Presence of B symptoms (%)            | 71 (30)                     | 9 (69)                           | 62 (28)                             |
| Ann Arbor stage (%)                   |                             |                                  |                                     |
| I, II                                 | 90 (38)                     | 2 (15)                           | 88 (39)                             |
| III, IV                               | 146 (62)                    | 11 (85)                          | 135 (61)                            |
| Involved extranodal sites (%)         |                             |                                  |                                     |
| 0–1                                   | 145 (61)                    | 6 (46)                           | 139 (62)                            |
| ≥2                                    | 91 (39)                     | 7 (54)                           | 84 (38)                             |
| Diagnosis (%)                         |                             |                                  |                                     |
| B cell lymphoma                       | 195 (83)                    | 8 (62)                           | 187 (84)                            |
| DLBCL                                 | 128                         | 5                                | 123                                 |
| FL                                    | 47                          | 2                                | 45                                  |
| Others                                | 20                          | 1                                | 19                                  |
| T/NK cell lymphoma                    | 25 (11)                     | 5 (38)                           | 20 (9)                              |
| Hodgkin lymphoma                      | 16 (7)                      | 0 (0)                            | 16 (7)                              |
| Treatment for lymphoma (%)            |                             |                                  |                                     |
| Rituximab                             | 180 (76)                    | 7 (54)                           | 173 (78)                            |
| R-CHOP (like)                         | 163 (69)                    | 7 (54)                           | 156 (70)                            |
| CHO (like)                            | 20 (8)                      | 6 (46)                           | 14 (6)                              |
| Bendamustine or fludarabine           | 21 (9)                      | 1 (7.7)                          | 20 (9)                              |
| Steroid pretreatment (%)              | 32 (14)                     | 7 (54)                           | 25 (11.2)                           |
| Radiation                             | 92 (39)                     | 5 (38)                           | 87 (39)                             |
| Median therapeutic regimens (range)   | 1 (0–7)                     | 3 (1–7)                          | 1 (0–6)                             |
| Dose reduction of primary therapy (%) | 55 (23)                     | 5 (39)                           | 50 (22)                             |

Median CMV cells among 50,000 WBCs (range) 3 (1–636) N/A

Median regimen with initial CMVI development 3 (1–6) N/A

Treatment for CMVI (%) 12 (92) N/A

Ganciclovir or valganciclovir 12 (92) N/A

Gamma globulin + methylprednisolone 2 (15) N/A

Intubation 2 (15) N/A

Death in the patients with CMVI (%) 11 (85) N/A

Cause of death of a patient with CMVI (%) N/A

Lymphoma 9 (69) N/A

Pneumonitis 2 (15) N/A

Abbreviations: ML Malignant lymphoma, DLBCL Diffuse large B-cell lymphoma, FL Follicular lymphoma, R-CHOP Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, CMVI Cytomegalovirus infection, WBC White blood cells
were men. Most patients had a good Eastern Cooperative Oncology Group performance status (73%; 173/236), B symptoms (30%; 71/236), and advanced-stage disease (62%; 146/236). B cell lymphomas (83%; 195/236), including diffuse large B cell lymphomas (n = 128) and follicular lymphomas (n = 47), comprised the largest subcategory of MLs, followed by T/NK cell lymphomas (11%; 25/236) and Hls (7%; 16/236). Most patients were treated with rituximab (76%; 180/236); this included R-CHOP (like) regimens (69%; 163/236). Moreover, 9% (21/236) of the patients received treatment with bendamustine or rituximab (76%; 180/236); this included R-CHOP (like) and HLs (7%; 16/236). Most patients were treated with MLs, followed by T/NK cell lymphomas (11%; 25/236) and HLs (7%; 16/236). The characteristics of patients with CMVI

### Characteristics of patients with CMVI

The characteristics of patients with CMVI are shown in Table 1. CMVI developed in 5.5% (13/236) of patients with ML; this group included 8 (62%) men, featured 8 (62%) cases of B cell ML and 5 (38%) of T cell ML, and had a median age of 64 (range: 42–85) years. Approximately half (54%; 7/13) of these patients had received steroid pretreatment before PT for ML, and 62% (8/13) had received >2 therapeutic regimens for ML. Twelve (92%) patients had received anti-CMV treatments. The median number of CMV antigen-positive cells per 5 × 10⁴ leukocytes at the initial development of CMVI was 3 (range: 1–636). Most patients (92%; 12/13) with CMVI received ganciclovir or valganciclovir, and 2 (15%) were intubated because of pneumonitis. The majority (85%; 11/13) of patients with CMVI eventually died from lymphoma progression (n = 9) or pneumonitis (n = 2). The putative affected organs by CMV were the liver (hepatitis) in seven and the lung (pneumonitis) in five, whereas four patients had fever only. The median duration of treatment for CMV was 15.5 (range: 0–35) days. Regarding the response to treatment for CMV, 7 out of 13 patients recovered, but the rest did not recover from CMVI. Regarding the treatment of lymphoma after CMVI, of the five patients who developed CMVI during the first-line treatment, two received no treatment, and each of the remaining three patients received CHASE, consisting of cyclophosphamide, cytosine arabinoside, etoposide, and dexamethasone; ESHAP, consisting of etoposide, methylprednisolone, cytarabine, and cisplatin, or oral etoposide. Both patients who developed CMVI during the second-line treatment received oral etoposide, but one died without recovering from CMVI. Of the six patients who developed CMVI after the third-line treatment, four patients died without recovering from CMVI during the final treatment regimen for lymphoma (methylprednisolone, rituximab, CHASE, or EPOCH, consisting of etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, respectively). However, the remaining two patients recovered from CMVI; then, FCM, consisting of fludarabine, cyclophosphamide, and mitoxantrone, or radiotherapy was performed.

In addition, patients with CMVI had a higher C-reactive protein (CRP) level (5.659 vs. 1.913 mg/dL; p = 0.0002) and lower hemoglobin (10.862 vs. 12.039 g/dL; p = 0.0493) and serum albumin levels (3.1 vs. 3.7 g/dL; p = 0.0005) at diagnosis than those without CMVI (Table 2).

### OS and RFs in patients with CMVI and cumulative incidence of CMVI during follow-up period

A comparison of OS between patients with and without CMVI revealed significantly worse OS in the former (3-year OS: 10% vs. 76%, p < 0.0001 by log-rank test; Fig. 1). To identify the RFs associated with CMVI, the clinical characteristics and background data were compared between patients with and without CMVI in a univariate analysis (Table 3). A significantly higher incidence of CMVI development was observed in patients with B symptoms [odds ratio (OR): 5.79 (95% confidence interval [CI]: 1.55–26.7); p = 0.00321], T cell lymphoma [OR: 6.26 (95% CI: 1.47–24.2); p = 0.006406], steroid pretreatment before PT for ML [OR: 9.08 (95% CI: 2.40–35.6); p = 0.004262], >2 therapeutic regimens for ML [OR: 11.4 (95% CI: 3.04–47.8); p = 0.000818], achievement of first remission [OR: 0.26 (95% CI: 0.07–0.98); p = 0.02311], serum albumin level <3.5 g/dL [OR: 8.02 (95% CI: 1.98–46.8); p = 0.007837], and CRP level of more than the upper limit of normal [OR: infinity (95% CI: 2.57–infinity); p = 0.006962]. The use of rituximab was not a significant RF for CMVI [OR: 0.34 (95% CI: 0.09–1.28); p = 0.08545]. These independent seven parameters were subsequently included in a multivariate analysis to determine the independent RFs for CMVI development, which identified steroid pretreatment before PT for ML [OR: 4.71 (95% CI: 1.06–21.0); p = 0.0419] and >2 therapeutic regimens for ML [OR: 9.25 (95% CI: 2.33–36.8); p = 0.00159] (Table 3). A cumulative incidence of CMVI during follow-up in the total cohort was 5.5%. In addition, each cumulative incidence of CMVI in patients pretreated with steroid before PT for ML or received >2 therapeutic regimens for ML was 21.9% (7/32) or 22.9% (8/35), respectively.

### CMVI in patients with ML according to the literature

Several investigators had previously reported retrospective studies of CMVI in patients with ML, as shown in
Table 2  Laboratory data of patients with and without CMV infection at the time of malignant lymphoma diagnosis

|                      | CMV (+)       | CMV (-)       | P value |
|----------------------|---------------|---------------|---------|
| Neutrophils (/µL)    | 5316 ± 1026   | 4178 ± 164    | 0.1162  |
| Lymphocytes (/µL)    | 945 ± 186     | 1430 ± 76     | 0.1239  |
| Hemoglobin (g/dL)    | 10.862 ± 0.53 | 12.039 ± 0.14 | 0.0493  |
| Platelets (×10⁴/µL) | 22.2 ± 3.65   | 23.3 ± 0.68   | 0.6982  |
| LDH (IU/L)           | 390 ± 99      | 327 ± 20      | 0.4830  |
| Total protein (g/dL) | 6.6 ± 0.27    | 6.7 ± 0.51    | 0.4961  |
| Albumin (g/dL)       | 3.1 ± 0.16    | 3.7 ± 0.04    | 0.0005  |
| CRP (mg/dL)          | 5.659 ± 1.52  | 1.913 ± 0.22  | 0.0002  |

Abbreviations: CMV Cytomegalovirus, LDH Lactate dehydrogenase, CRP C-reactive protein

Fig. 1  OS of patients with malignant lymphoma, with or without CMV infection. The OS of patients (n = 13) with malignant lymphoma who developed CMVI (a) was significantly worse (p < 0.0001, log-rank test) than that of patients (n = 223) without CMVI (b). The estimated 3-year OS rates of patients with and without CMVI were 10 and 76%, respectively. CMVI, cytomegalovirus infection; OS, overall survival.
Table 3 Univariate and multivariate analysis of risk factors for CMV infection

| Characteristic                              | Total CMV (+) n (%) | CMV (-) n (%) | univariate analysis | multivariate analysis |
|---------------------------------------------|---------------------|---------------|---------------------|-----------------------|
|                                             |                     |               | Odds ratio (95% CI) | P value               |
|                                             |                     |               |                     |                       |
| **Sex**                                     |                     |               |                     |                       |
| Male                                        | 126 (53)            | 8 (62)        | 118 (53)            | 1.42 (0.40-5.70)      | 0.5822                |
| Female                                      | 110 (47)            | 5 (38)        | 105 (47)            |                       |                       |
| **Age, years**                              |                     |               |                     |                       |
| >60                                         | 169 (72)            | 7 (54)        | 162 (73)            | 2.27 (0.60-8.23)      | 0.202                 |
| ≤60                                         | 67 (28)             | 6 (46)        | 61 (27)             |                       |                       |
| **Ann Arbor stage**                         |                     |               |                     |                       |
| III, IV                                     | 146 (62)            | 11 (85)       | 135 (61)            | 3.83 (0.81-36.6)      | 0.0815                |
| I, II                                       | 90 (38)             | 2 (15)        | 88 (39)             |                       |                       |
| **B symptoms**                              |                     |               |                     |                       |
| Yes                                         | 71 (30)             | 9 (69)        | 62 (28)             | 5.79 (1.55-26.7)      | 0.00321               |
| No                                          | 165 (70)            | 4 (31)        | 161 (72)            |                       | 0.317                 |
| **ECOG performance status**                 |                     |               |                     |                       |
| 2-4                                         | 63 (27)             | 7 (54)        | 56 (25)             | 3.46 (0.95-13.0)      | 0.04596               |
| 0-1                                         | 173 (73)            | 6 (46)        | 167 (75)            |                       |                       |
| **Number of extranodal sites**              |                     |               |                     |                       |
| >1                                          | 91 (39)             | 7 (54)        | 84 (38)             | 1.92 (0.53-7.19)      | 0.256                 |
| ≤1                                          | 145 (61)            | 6 (46)        | 159 (62)            |                       |                       |
| **Diagnosis**                               |                     |               |                     |                       |
| B cell                                      | 195 (83)            | 8 (62)        | 187 (84)            | 0.31 (0.08-1.28)      | 0.5445                |
| Non-B cell                                  | 41 (17)             | 5 (38)        | 36 (16)             |                       |                       |
| T-cell                                      | 25 (11)             | 5 (38)        | 20 (9)              | 6.26 (1.47-24.2)      | 0.006406              |
| Non-T cell                                  | 211 (89)            | 8 (62)        | 203 (91)            |                       | 0.564                 |
| HL                                          | 16 (7)              | 0 (0)         | 16 (7)              | 0 (0-4.72)            | 1                     |
| Non-HL                                      | 220 (93)            | 13 (100)      | 207 (93)            |                       |                       |
| **Bendamustine or fludarabine treatment**   |                     |               |                     |                       |
| Yes                                         | 21 (9)              | 7 (77)        | 20 (9)              | 0.85 (0.02-6.31)      | 0.84642               |
| No                                          | 215 (91)            | 12 (92)       | 203 (91)            |                       |                       |
| **Steroid pretreatment**                    |                     |               |                     |                       |
| Yes                                         | 32 (14)             | 7 (54)        | 25 (11)             | 9.08 (2.40-35.6)      | 0.000426              |
| No                                          | 204 (86)            | 6 (46)        | 198 (89)            | 4.71 (1.06-21.0)      | 0.0419                |
| **Rituximab treatment**                     |                     |               |                     |                       |
| Yes                                         | 180 (76)            | 7 (54)        | 173 (78)            | 0.34 (0.09-1.28)      | 0.08545               |
| No                                          | 56 (24)             | 6 (46)        | 50 (22)             |                       |                       |
| **Radiation**                               |                     |               |                     |                       |
| Yes                                         | 92 (39)             | 5 (38)        | 87 (39)             | 0.98 (0.24-3.52)      | 1                     |
| No                                          | 144 (61)            | 8 (62)        | 136 (61)            |                       |                       |
| **Dose reduction of PT for ML**             |                     |               |                     |                       |
| Yes                                         | 55 (23)             | 5 (38)        | 50 (22)             | 2.14 (0.53-7.86)      | 0.188                 |
| No                                          | 181 (77)            | 8 (62)        | 173 (78)            |                       |                       |
| **Therapeutic regimens for ML**             |                     |               |                     |                       |
| >2                                          | 35 (15)             | 8 (62)        | 27 (12)             | 11.4 (3.04-47.8)      | 0.0000818             |
| ≤2                                          | 201 (85)            | 5 (38)        | 196 (88)            | 9.25 (2.33-36.8)      | 0.00159               |
| **Achievement of first remission**          |                     |               |                     |                       |
| Yes                                         | 176 (75)            | 6 (46)        | 170 (76)            | 0.26 (0.07-0.98)      | 0.02311               |
| No                                          | 60 (25)             | 7 (54)        | 53 (24)             | 1.31 (0.30-5.78)      | 0.717                 |
| **Serum albumin < 3.5 g/dL**                |                     |               |                     |                       |
| Yes                                         | 75 (32)             | 10 (77)       | 65 (29)             | 8.02 (1.98-46.8)      | 0.0007837             |
| No                                          | 161 (68)            | 3 (23)        | 158 (71)            | 2.45 (0.42-14.4)      | 0.317                 |
| **CRP > ULN**                               |                     |               |                     |                       |
| Yes                                         | 132 (56)            | 13 (100)      | 119 (53)            | Inf. (2.57-Inf.)      | 0.0006962             |
| No                                          | 104 (44)            | 0 (0)         | 104 (47)            | 2.71 (0.51-14.4)      | 0.242                 |
| **Hemoglobin <12 g/dL**                     |                     |               |                     |                       |
| Yes                                         | 98 (42)             | 8 (62)        | 90 (40)             | 2.36 (0.66-9.46)      | 0.1545                |
| No                                          | 138 (58)            | 5 (38)        | 133 (60)            |                       |                       |

Abbreviations: CMV Cytomegalovirus, HL Hodgkin lymphoma, PT Primary therapy, ML Malignant lymphoma, n Number, CRP C-reactive protein, ULN Upper limit of normal, Inf Infinity

Table 3. The reported incidence rate of CMVI ranged from 3.9 to 16% in those studies, which were not limited to patients with ML who had not received HSCT. Although our study included only patients with ML who had not received HSCT, the incidence (5.5%) of CMVI was within the range reported in those earlier studies. In addition, 2 of the 4 previous studies reported RFs of CMVI or CMV disease, such as the use of rituximab-containing regimens [7, 9] or hyper-CVAD (cyclophosphamide, vincristine, adriamycin, and dexamethasone) [9]. However, the authors did not identify the use of steroid pretreatment or number of therapeutic regimens for ML as RFs for CMVI. Two studies have reported the use of rituximab as an RF of CMVI development in patients
with ML [7, 9], and CMVI-related fatalities have been reported among patients with ML who were treated with rituximab [1]. Although the use of rituximab-containing regimens was not identified as an RF for CMVI in our study, further investigations are required to clarify whether rituximab use is an RF for CMVI development in patients with ML. In addition, the disadvantages in survival prognosis in patients with ML with CMVI were not obviously reported, except in our study.

Discussion
This retrospective study determined that CMVI occurred in 5.5% (13/236) of the included patients with ML who had received chemotherapy or radiotherapy but not HSCT. In addition, we demonstrated that CMVI development might contribute to poor survival, and that pretreatment with steroids and >2 therapeutic regimens were independent predictive RFs of CMVI development in these patients. To the best of our knowledge, this is the first report to evaluate the clinical aspects, such as the incidence or RFs, of CMVI in patients with ML who had not received HSCT but who had been treated with chemotherapy or radiotherapy.

We also demonstrated that patients with ML who developed CMVI had a significantly worse OS ($p < 0.0001$, log-rank test) than those who did not develop CMVI, and we noted several potentially related factors. First, patients who developed CMVI had higher rates of advanced-stage disease and poor performance status than those without CMVI (85% vs. 61% and 54% vs. 25%, respectively; Table 3). Second, patients with CMVI had lower levels of hemoglobin and albumin than those without CMVI (10.862 vs. 12.039 g/dL and 3.1 vs. 3.7 g/dL, respectively).

These findings might suggest a greater likelihood of CMVI development in patients who already presented with more significant survival disadvantages; accordingly, patients with CMVI exhibited reduced survival. In addition, of the 11 deceased patients, 2 (15%) who had been intubated died of pneumonitis. Therefore, CMVI itself might contribute to reduced survival.

We also indicated that pretreatment with steroids and >2 therapeutic regimens were independent RFs of CMVI development among patients with ML. In patients with ML with some clinical concerns, such as poor general condition including fever or aggressiveness of lymphoma, steroid pretreatment is used before PT with the expectation of an anti-lymphoma and/or anti-inflammation effect. Therefore, steroid pretreatment and multiple chemotherapeutic regimens might inhibit host immune responses, including CMV-specific T and B cell responses, thus promoting the reactivation of CMV. Given the development of CMVI after steroid pretreatment, standard chemotherapy should be given without steroid pretreatment as much as possible. However, prophylactic treatment for CMVI is not appropriate considering adverse events. Closely monitoring CMV antigen is needed, and antiviral drug treatment should be started at an appropriate timing. The advantages and disadvantages of steroid pretreatment should be confirmed in patients with ML.

Although the duration of steroid treatment was very limited when it was used as a prephase treatment before chemotherapy, steroid pretreatment before PT for ML increases the risk of development of CMVI in this study. We speculate that patients with systemic symptoms, such as fever, or with an aggressiveness of lymphoma may

| Authors                  | Patients, N | Rate of CMVI (%) | Risk factors for CMVI | Disadvantages in survival prognosis in patients with CMVI |
|--------------------------|-------------|------------------|-----------------------|----------------------------------------------------------|
| Marchesi et al [6]       | MLs after autologous SCT, 188 | 16              | T-cell lymphoma       | Not mentioned                                             |
| Lee et al [7]            | Relapsed MLs after autologous SCT, 46 | 6.5             | Rituximab             | Not mentioned                                             |
| Damaj et al [8]          | B cell lymphomas, 207       | 3.9             | N/A                   | Not mentioned                                             |
| Tay et al [9]            | MLs who have received chemoimmunotherapy, but not SCT, 534 | 9.0             | Rituximab, Hyper CVAD (for CMV disease)                  | Not mentioned                                             |
| Our study                | MLs who have not received SCT, 236 | 5.5             | Therapeutic regimens for ML>2, steroid pretreatment for ML | yes                                                       |

Abbreviations: CMVI Cytomegalovirus infection, ML Malignant lymphoma, N Number, SCT Stem cell transplantation, N/A Not available, CVAD Cyclophosphamide, vincristine, doxorubicin, and dexamethasone
require steroid pretreatment in clinical practice. In these patients, the higher activity of lymphoma rather than the steroid administration itself may lead to immunosuppressive conditions due to progression of lymphoma or an increase in the number of chemotherapeutic regimens. As a result, CMVI might more likely develop.

In the current study, we analyzed patients who were treated for ML between 2005 and 2013. It is interesting to know recent data on the effects of CMV infection in patients with ML who have been treated with drugs with strong immunosuppression such as bendamustine. However, our present study data cannot reveal this. Pezzullo et al. [18] reported an increased incidence of CMV reactivation in older adults (age > 60 years) with non-HL who were treated with bendamustine-containing regimens, especially after the third course of bendamustine accompanied by a significant depression of circulating CD4-positive T cell count and anti-CMV IgG levels. Whether a bendamustine-containing regimen would be an RF for CMVI in our patient cohort needs to be clarified by further analysis in the future.

Several limitations of this study should be acknowledged. First, this was a retrospective study; accordingly, various physician-related selection biases might have existed, such as the frequency or timing of CMV antigenemia testing or treatment strategies for CMVI and ML. Therefore, the incidence of CMVI development and the usefulness of the identified independent RFs for CMVI development should be validated through a prospective analysis of patients with ML who have not received HSCT. Second, CMVI development was not confirmed to be an independent RF for survival among patients with ML who have not received HSCT. Third, the association of the total steroid dose with CMVI development was not confirmed in this study because some relevant data were not available. Fourth, this study had many censored patients with short-term observation in the survival group. It cannot be denied that the risk of CMVI might be underestimated. These issues will require further clarification.

Conclusion

We retrospectively analyzed patients with ML who had not received HSCT to evaluate the clinical aspects related to CMVI development, including RFs. We demonstrated that the prognosis of patients who developed CMVI was poor and identified two independent RFs for CMVI. Attention should be given to CMVI development in patients with ML who have not received HSCT but who have been pretreated with steroids or multiple therapeutic regimens. Further investigation into the development of CMVI in patients with ML is needed to ensure that chemotherapy and radiotherapies are safely administered.

Abbreviations

CMVI: Cytomegalovirus infection; ML: Malignant lymphoma; HSCT: Hematopoietic stem cell transplantation; RFs: Risk factors; OS: Overall survival; PT: Primary therapy; HL: Hodgkin lymphoma; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; CVAD: Cyclophosphamide, vincristine, adriamycin, and dexamethasone.

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Authors’ contributions

KS and YT designed the study. KS, SL, NT, JI, MY, MS, and YT contributed to patient recruitment and data acquisition. KS, KM, YM, and MF analyzed and interpreted the data. KS drafted the manuscript. MF substantively revised the manuscript. All authors read and approved the final manuscript.

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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.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Review Board of Asahikawa Kosei Hospital and was conducted in accordance with the Declaration of Helsinki. The requirement for obtaining patients’ informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Author details

1 Department of Hematology/Oncology, Asahikawa Kosei Hospital, 1-24, Asahikawa 078-8211, Japan. 2 Division of Metabolism and Bioisystemic Science, Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, Asahikawa, Japan.

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