# Rituximab decreases the risk of lymphoma in patients with HIV-associated multicentric Castleman disease

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**HIV-associated multicentric Castleman disease (MCD) is associated with a high risk of developing nonHodgkin lymphoma (NHL). Rituximab is effective in HIV-MCD, but its impact on NHL incidence remains unknown. From a single-center prospective cohort, 113 patients were identified with a diagnosis of HIV-MCD for the present study. To compare the incidence of NHL between patients who had received a rituximab-based treatment (R+ group) and those who had not (R− group), data were analyzed before and after matching on propensity scores and after multiple imputation. The mean follow-up was 4.2 years. In the R− group (n = 65), 17 patients developed NHL (incidence, 69.6 of 1000 person years). In the R+ group (n = 48), only 1 patient developed NHL (incidence, 4.2 of 1000 person years). Based on the propensity score-matching method, a significant decrease in the incidence of NHL was observed in patients who had been treated with rituximab (hazard ratio, 0.09; 95% confidence interval, 0.01-0.70). Ten Kaposi sarcoma (KS) exacerbations and 1 newly diagnosed KS were observed in 9 patients after rituximab therapy. Rituximab was associated with an 11-fold lower risk of developing lymphoma. KS exacerbation was the most challenging adverse event after rituximab therapy. (*Blood*. 2012;119(10):2228-2233)**

## Introduction

In the context of HIV infection, multicentric Castleman disease (MCD) is a rare but potentially fatal lymphoproliferative disorder.[1] Human Herpes Virus-8 (HHV-8) can be detected in the plasmablastic cells that characterize the disease and is considered to be a causative agent.[2-4] MCD clinical course is characterized by recurrent attacks, with systemic symptoms, lymphadenopathy, splenomegaly, cytopenia, and inflammation associated with high HHV-8 viral load in the PBMCs.[1,2,5,6]

The HIV-MCD diagnosis is based on clinical features and lymph node pathology, which is characterized by angiofollicular hyperplasia and interfollicular plasma cell infiltration.[2] HHV-8–infected cells are large cells with plasmacytic differentiation that are predominantly present within the mantle zone and can be identified using immunohistochemical staining, which reveals HHV-8–associated latent nuclear antigen-1 (LANA-1) present in these cells.[7] These plasmablastic cells exhibit a restricted monotypic mu/λ phenotype and may express the CD20 surface Ag.[3,7,8] Although these HHV-8–positive cells are multiclonal, they may coalesce in sheets of cells to form "microscopic lymphoma."[8,9]

MCD is considered to be a nonmalignant disease, and the clinical course can be self-limited at the onset. However, attacks can also be severe and life-threatening, either through multiple organ failure or because of the development of non-Hodgkin lymphoma (NHL).[10,11] The prognosis for MCD has improved dramatically in recent years. Whereas the median overall survival (OS) was 14 months before the widespread use of combination antiretroviral therapy (cART), recent publications reported a 2-year OS probability of more than 80%.[6,12,13] This improvement was associated with the introduction of cART in the mid-1990s, but also with the development of rituximab-based therapies after 1999.[6,12] Two prospective trials have demonstrated the efficacy of rituximab in controlling the systemic symptoms as a first-line therapy or after the initial control of MCD by single-agent chemotherapy in patients with severe disease.[14,15] Recent studies have reported a possible benefit of rituximab on OS.[6,12]

Despite this improvement, some patients are still dying with active MCD or evolution toward HHV-8–associated NHL.[10,11,16] The occurrence of NHL has been identified as a major concern in HIV-MCD, with an incidence 15-fold higher than that in the HIV-infected population without MCD, and is the major cause of death in these patients.[10] In most cases, the lymphoma cells are infected with HHV-8.[10,16,17]

In the present study, we addressed whether rituximab may prevent the risk of developing NHL in the context of HIV-MCD. We examined the long-term incidence and risk factors for NHL in HIV-MCD patients from a French cohort of patients with HIV-associated lymphoproliferative disorders.

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## Methods

### Patients

Patients were included in a single institution prospective cohort that was established in 1987, collecting data on all consecutive HIV-infected adults with a first episode of HIV-associated lymphoma or MCD treated in the Clinical Immunology Department of Hôpital Saint-Louis in Paris. In the present study, we focused on patients with a MCD diagnosis during the cART era (ie, after July 1996). The study was approved by the Hôpital Saint-Louis ethics review board, and all patients gave written informed consent in accordance with the Declaration of Helsinki. The diagnosis of MCD was based on histopathological examination of tumor tissue with immunostaining for HHV-8 LANA-1 in patients with clinical features of active disease. For a few patients (n = 8), MCD was not histologically proven, but these patients were included in the cohort on the basis of typical presentation associated with high blood HHV-8 viral load and high serum C reactive protein (CRP) level. Patients with NHL diagnosed before the diagnosis of MCD or within 3 months after the diagnosis of MCD were excluded from analysis.

### Data collection

Baseline characteristics were collected at the time of MCD diagnosis. Thereafter, data were collected at scheduled follow-up visits at 1, 3, 5, and 10 years. Vital status was recorded until death, last follow-up visit, or April 15, 2011. Data collected at diagnosis included information on patient demographics, use of cART, CD4 cell count, nadir CD4 cell count before the diagnosis of MCD, plasma HIV-RNA, AIDS-defining events. Body mass index (ie, weight in kilograms divided by the square of the height in meters) values were categorized using World Health Organization cut-off points as follows: underweight, $< 18.5$; normal, 18.5-24.9; and overweight, $\geq 25$. Eastern Cooperative Oncology Group performance status and laboratory assessments, including cell blood counts, serum CRP, LDH, albumin and gammaglobulin level, prothrombin time level, and, when available, evaluation of circulating HHV8 DNA. Lymphoma cases were classified according to the World Health Organization classification.[18] Information regarding Kaposi sarcoma (KS) development was collected at each visit and classified as absent, healed, stable, or active. Occurrence of new KS lesions or progression of preexisting lesions were registered as KS flare.

### Treatment

Patients were classified into 2 groups according to the use of rituximab in the treatment of MCD. Rituximab therapy consisted of 4 IV infusions at the standard dose of 375 mg/m$^2$ once weekly for 4 weeks. The R+ group included patients who had received at least one infusion of rituximab as MCD therapy and the R− group included patients who never received rituximab. Patients who received rituximab as part as NHL treatment were censored at the time of NHL diagnosis. Rituximab was associated with single-agent chemotherapy in almost all patients.

### Statistical methods

The primary end point of this retrospective analysis was to assess the impact of rituximab on long-term incidence of NHL in a large, single-institution cohort of HIV-MCD patients. In the descriptive analysis, results are reported as medians with interquartile range (IQR) or number (%), and incidence rates per 1000 person-years. Person-years were calculated from the date of MCD diagnosis to the earliest date of NHL, death, last follow-up visit, or April 15, 2011. OS and MCD flare-free survival after rituximab therapy were estimated according to the Kaplan-Meier method. The rate of malignancies other than NHL was compared using the Fisher exact test between the R+ group and the R− group.

### Propensity-score analysis

As an observational study, the rituximab therapy assignment was not random, and may be influenced by patient characteristics. The R+ group and the R− group may differ in variables that influence occurrence of NHL. In an attempt to reduce the effect of potential bias in the decision to treat patients with rituximab, propensity-score matching was used. A propensity score is the estimated probability of receiving rituximab versus not receiving rituximab based on observed pretreatment covariates. This method allows balancing of all measured relevant variables between the 2 groups. Covariates included in the propensity-score model were a set of sociodemographic covariates, HIV-associated covariates, MCD-associated covariates, and numerous 2-way interactions. Briefly, the propensity score was estimated using a logistic regression model in which receipt of rituximab was regressed on patient pretreatment risk factors.[19] The estimated propensity score was then used to match 1:1 patients with similar propensity to receive rituximab based on nearest neighbor matching without replacement using calipers of width equal to 0.2 SD of the logit of the propensity score. Success in achieving balance in measured baseline covariates between R+ and R− patients was assessed using the standardized difference in covariates between subjects in the matched sample, with imbalances tested by 2-tailed paired *t* tests. The standardized difference is defined as a percentage of the average SD for dichotomous variables.

### Multiple imputation

The estimation of propensity score assumes fully observed covariates. However, in this cohort study, if outcome was available for all patients, some baseline covariates had missing values (Table 1). Exclusion from analysis of patients with at least one missing variable decreases the power of analysis and may introduce bias. To avoid this, multiple imputation was used, with 5 datasets being imputed using chained regression, under the assumption of missing at random.[20] This method imputes missing values of a variable from a posterior distribution based on a regression of the nonmissing values of the variable on all other predictors in the model. After this calculation, each of the simulated complete datasets was independently analyzed by standard methods and the results combined in a straightforward manner to produce estimates and confidence intervals (CIs) that incorporate missing-data uncertainty, using the Rubin rules.

### Cox proportional hazard model

An extended Cox proportional hazards model was used to estimate the association between rituximab therapy and occurrence of NHL. For the multivariate analyses, the regression model was set with the covariates that yielded $P < .1$ by univariate analyses. In addition, the CD4 cell count and the plasma HIV-RNA level were introduced in the model. To examine possible effect modification by the period of inclusion, periods of inclusion were categorized into three 5-year duration categories and introduced in the multivariate analyses. In a first analysis, survival was evaluated on the imputed datasets. Rituximab therapy was imputed in a time-dependent manner. Hazard ratios (HRs) were averaged across the 5 imputations and 95% CIs include the variability between and within imputations. A Cox proportional hazard model was then fit to each dataset and the results were pooled using the combining rules of multiple imputation. An analysis that excluded patients with missing covariates was also performed (nonimputation analysis). In a second analysis, NHL incidence was evaluated in matched pairs of treated and untreated patients after matching on propensity score. The matching was run separately within each complete dataset, and then the multiple imputation combining rules were used to obtain final effect estimates.

All analyses were performed with the statistical software Stata Version 11.1 (StatCorp) and the companion package PSMATCH2 for matching between R+ and R− patients.[21] All *P* values were 2-sided, with $P < .05$ considered statistically significant.

## Results

### Patient characteristics

From July 1996 to April 2011, 127 patients with HIV-associated MCD were included in the cohort. Fourteen patients had developed NHL either before or concomitantly to the diagnosis of MCD and

**Table 1. Major baseline characteristics of 113 HIV-infected patients at MCD diagnosis**

| | No. with complete data | R− group (n = 65) | R+ group (n = 48) |
|---|---|---|---|
| **Date of MCD diagnosis , n (%)** | 113 | | |
| 1996-2000 | | 27 (41.5) | 9 (19) |
| 2001-2005 | | 15 (23) | 16 (33) |
| 2005-2011 | | 23 (35) | 23 (48) |
| **Demographic characteristics** | | | |
| Sex, M:F | 113 | 56:9 | 36:12 |
| Median age, y (IQR) | 113 | 42 (36-48) | 43 (35-51) |
| Body mass index, n (%) | 96 | | |
| Underweight | | 14 (28) | 4 (9) |
| Normal | | 32 (64) | 36 (78) |
| Overweight | | 4 (8) | 6 (13) |
| **HIV characteristics** | | | |
| Median HIV duration, y (IQR) | 113 | 3.0 (0.6-9.2) | 3.6 (0.6-9.2) |
| Prior AIDS, n (%) | 113 | 44 (68) | 27 (56) |
| Prior KS, n (%) | 113 | 40 (61.5) | 20 (42) |
| cART, n (%) | 113 | 34 (52) | 33 (69) |
| Median cART duration, mo (IQR) | | 14.3 (1.7-23.9) | 31.3 (10.2-45.4) |
| HIV-RNA ≤ 500 copies/mL, n (%) | 111 | 20 (31) | 26 (55) |
| $CD4^+$ cell count | 112 | | |
| median, $\times 10^6$/L, median (IQR) | | 168 (73-264) | 213 (138-360) |
| ≤ 200 $\times$ $10^6$/L, n (%) | | 39 (61) | 21 (44) |
| nadir < 100 $\times$ $10^6$/L, n (%) | | 27 (47) | 15 (33) |
| **MCD characteristics, n (%)** | | | |
| ECOG > 2 | 110 | 29 (46) | 20 (42.5) |
| Hemophagocytosis | 109 | 24 (39) | 15 (32) |
| ICU stay | 105 | 15 (24) | 16 (37) |
| Hemoglobin ≤ 8 g/dL | 109 | 32 (52) | 20 (42.5) |
| Platelets < 50 $\times$ 109/L | 108 | 18 (29.5) | 13 (28) |
| LDH > normal | 103 | 26 (37) | 30 (68) |
| Serum albumin ≤ 25 g/L | 104 | 24 (41) | 19 (42) |
| Gammaglobulin ≥ 20 g/L | 103 | 37 (63) | 30 (68) |
| Prothrombin time ≤ 70% | 100 | 30 (53) | 22 (51) |

ECOG indicates Eastern Collaborative Oncology Group performance status score; KS, Kaposi sarcoma; ICU, intensive care unit; and LDH, serum lactate dehydrogenase.

were excluded from analysis. Data from the remaining 113 patients were analyzed in the present study. At MCD diagnosis, the median age was 43 years, and most patients were male. The median CD4 cell count was 188 $\times$ $10^6$/L and 41% of patients had an undetectable plasma HIV viral load. More than one-half of the patients received cART for a median of 21 months. For the other patients, cART was introduced within 2 months from diagnosis and 80% were on cART 1 year after diagnosis. The median duration between onset of MCD symptoms and diagnosis was 2.5 months (IQR, 1.1-5.7), and 61 patients (67%) reported spontaneously regressive flares before diagnosis. At the time of diagnosis, all patients had constitutional symptoms, with an Eastern Cooperative Oncology Group performance status > 2 in 49 cases. In more than one-third of patients, MCD attack was life-threatening, with the development of hemophagocytic syndrome in 39 patients and hospitalization in an intensive care unit in 31 patients. The median serum CRP level was 160 mg/L (IQR, 94-220), and the blood HHV-8 viral load was detectable in the 96 tested patients, with a median value of 5.5 log copies/mL in whole blood, and 5.3 log copies/$10^5$ cells in PBMCs.

### Rituximab therapy

Rituximab was administered in 48 patients (42%) after a median time of 6.9 months (IQR, 0.9-11.3) from the diagnosis of MCD. All patients had received single-agent chemotherapy as a first-line treatment. Table 1 shows a comparison of the 48 patients in the R+ group with the 65 patients in the R− group. R+ patients were less likely to have prior KS, had a low body mass index (< 18.5) and a higher baseline CD4 cell count, and were more likely to have undetectable plasma HIV-RNA than R− patients. The 2 groups did not differ in regard to MCD characteristics.

Rituximab was used in 48 patients and all but 2 patients received the 4 scheduled infusions; 1 patient died with MCD at day 15 after the second infusion, and the other 1 stopped rituximab therapy after 2 infusions for investigation of a rectal ulceration. Four patients experienced MCD flare-up during or just after rituximab treatment when rituximab was administered alone. When weekly oral etoposide was administered during the 4 weeks of rituximab therapy, no further patients developed MCD flares during therapy. Twenty-four patients had prior KS, which was considered stable or in complete remission at the time of rituximab infusions. Ten reactivations of KS were recorded in 8 patients and, in 8 of 10, KS exacerbation occurred within 6 months after rituximab therapy. One other patient developed a newly diagnosed KS. Only 2 KS exacerbations required specific treatment.

Response of MCD symptoms to rituximab was evaluated at 3 months. Thirty-six of the 46 patients were considered to be responsive to rituximab. Subsequent MCD flares were observed in 8 of 36 patients after a median of 10.5 months (IQR, 4.6-15.3). No patient relapsed after 2 years. After a median follow-up of 28 months, the 2-year MCD flare-free survival in patients who were in complete remission at 3 months after rituximab therapy was 74.7% (95% CI, 55.4-86.6).

### Incidence rates and risk factors for developing NHL

Within a mean follow-up of 4.2 years, 18 patients developed NHL, 1 in the R+ group and 17 in the R− group. The median time for NHL occurrence was 1.8 years (IQR, 1.1-4.3). The incidence rate was 4.2 per 1000 person-years (95% CI, 0.6-30.0) in the R+ group and 69.6 per 1000 person-years (95% CI, 43.3-112.0) in the R− group ($P < 10^{-3}$). The estimated 5-year probability of developing lymphoma was 3% (95% CI, 1-20) in the R+ group, and 31% (95% CI, 19-47) in the R− group. The overall incidence rate of NHL decreased over time, from 47.6 per 1000 person-years (95% CI, 26.4-86.0) in the 1996-2000 period, to 32.2 per 1000 person-years (95% CI, 13.4-77.3) in the 2001-2005 period, and 21.3 per 1000 person-years (95% CI, 5.3-85.0) in the 2006-2011 period. All further analyses were adjusted for period time of inclusion.

Among the 17 NHL cases that occurred in the R− group, 9 were classified as primary effusion lymphoma, 7 as large B-cell lymphoma and 1 as peripheral T-cell lymphoma not otherwise specified. Fifteen cases were evaluated for the presence of HHV-8 in the tumor cells, and all except the T-cell lymphoma case were positive. The only NHL that occurred in the rituximab group was not histologically proven. The patient developed diffuse tumoral infiltration with a compressive mediastinal mass associated with biologic symptoms suggesting tumor lysis and very high HHV-8 DNA copy numbers in PBMCs. In addition, 6 patients developed other hematologic neoplasias: 2 patients (1 in each group), developed Hodgkin lymphoma; 1 T-cell chronic lymphocytic leukemia, 1 acute lymphoblastic leukemia, and 1 acute myeloid leukemia were observed in the R+ group and 1 chronic myelocytic leukemia in the R− group ($P = .40$). None of these neoplasias were associated with HHV-8.

A statistical analysis was performed to evaluate the specific role of rituximab in reducing the risk of developing lymphoma. Using a standard Cox proportional hazard model on the imputed dataset with no covariates, the crude NHL rate ratio for rituximab was 0.11 (95% CI, 0.01-0.85). The addition of the covariates to the model provided a similar rate ratio to 0.11 (95% CI, 0.01-0.93). Risk factors for NHL were almost similar when analysis was restricted to patients with complete data (ie, the nonimputed dataset), with an adjusted HR of 0.14 (95% CI, 0.02-1.11) for rituximab. There was no evidence for a difference in risk for NHL according to demographics or HIV-associated covariates. Other MCD characteristics were also not associated with the risk of NHL.

### Association of rituximab therapy and NHL in propensity score–matched cohort

To avoid bias due to patient selection, the risk of NHL was analyzed in the 2 groups using the propensity score approach. A matched dataset was constituted from the 38 R+ patients who were successfully matched to 1 of the 65 available controls. Based on standardized differences, treated and untreated patients differed mainly in date of inclusion, history of KS, CD4 cell count, plasma HIV-RNA, hemophagocytosis, and intensive care unit requirement before matching. Propensity-score matching resulted in well-balanced cohorts of R+ and R− patients, which were similar in all observed characteristics except hemoglobin level. The median standardized difference decreased from 24.0 in the original unmatched sample to 2.5 in the propensity score–matched sample, demonstrating evidence of decreased treatment-selection bias. Based on these matched pairs, the crude estimated HR of NHL was 0.09 (95% CI, 0.01-0.70) for R+ compared with R− patients.

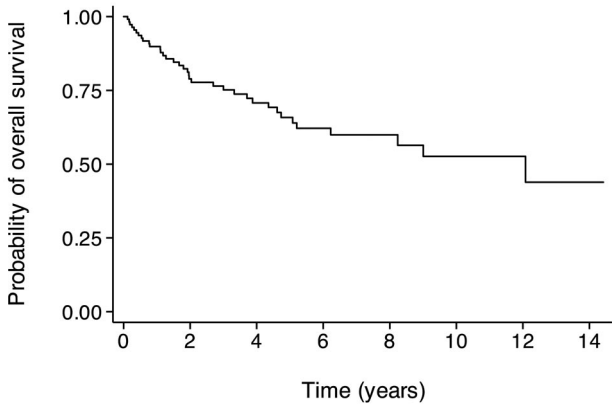


**Figure 1. OS in 113 HIV-infected patients with MCD.**

### OS

Thirty-six patients died during follow-up, 8 patients in the R+ group and 28 in the R− group. Overall median survival was 12.1 years (95% CI, 3.3 to not reached; Figure 1). Causes of death are reported in Table 2. Most of the patients died from NHL or MCD. The 2- and 5-year survival rates were 93.2% (95% CI, 80.1-97.8) and 90.2% (95% CI, 75.8-96.3), respectively, in the R+ group. The 2- and 5-year survival rates were 67.9% (95% CI, 53.8-78.5) and 47.3% (95% CI, 32-61.2), respectively, in the R− group.

## Discussion

HIV-MCD is a rare but potentially severe lymphoproliferative disorder, with a median OS of 14 months in the pre-cART era.[1] At that time, despite the effectiveness of single-agent chemotherapy, most patients experienced relapse after discontinuation of chemotherapy.[1,15] The prolonged use of chemotherapy raised the problem of toxicity; indeed, in the present study, 2 patients who had received etoposide developed acute leukemia. However, major causes of death remain MCD-related multiple organ failure and the development of HHV-8 associated lymphoma.[10] In the cART era, mortality in the general population of HIV-infected patients has been dramatically reduced, although lymphoma incidence remains high.[22,23]

In a recent study, Bower et al reported a dramatic improvement in the OS of patients with MCD diagnosed in recent years. In a cohort of 61 patients, the estimate 5-year OS was 77% and reached 90% in the subset of 49 patients who had been treated with rituximab-based therapy.[6] Moreover, only 1 patient developed lymphoma in a total of 61 patients with a median follow-up of

**Table 2. Cause of death in 36 patients with HIV-associated MCD**

| | R− group | R+ group |
|---|---|---|
| **Cause of death, n** | | |
| MCD | 4 | 3 |
| NHL | 10 | 1 |
| AIDS | 6 (KS = 1) | 0 |
| Non-AIDS–defining infection | 0 | 2 |
| Acute leukemia | 0 | 1 |
| Hodgkin lymphoma | 1 | 0 |
| NHL treatment | 2 | 0 |
| Cancer | 1 | 1 |
| Other | 1 | 0 |
| Unknown | 3 | 0 |
| Total | 28 | 8 |

4.2 years. In a German study, Hoffmann et al reported on the occurrence of 5 lymphoma cases in a total of 117 patient-years, an incidence very close to that observed in the present study.[12]

Rituximab was shown to be effective in preventing MCD relapse,[14,15] and subsequently might have an impact on OS. In the present study, the 3-month response rate to rituximab on MCD was 78.3% and the 2-year MCD flare-free survival was 74.7%. Because mortality in these patients was often associated with the development of aggressive lymphoma, we speculated on the possible preventing effect of rituximab against this lymphoma risk. However, patients who received rituximab or not may differ in covariates that may influence the occurrence of NHL. Some HIV-associated factors, such as CD4 cell count, HIV-RNA, and history of KS, are known to be associated with an increased risk of NHL,[24,25] and some MCD-associated characteristics can also be suspected. Therefore, a direct comparison of NHL incidence will not reflect the effect of rituximab treatment. In an attempt to reduce the effect of this potential treatment-selection bias in the decision to treat patient with rituximab, we used a more appropriate statistical method that was based on propensity-score matching. This method is relevant for treatments for which randomized, controlled trials are unlikely to be conducted, and allows balancing of almost all measured relevant baseline potential confounders between the 2 groups.[19] The limitation of propensity-score analysis is that it cannot adjust for unmeasured characteristics, and we cannot exclude that some covariates that were risk factors for NHL and predictor of subsequent initiation of rituximab therapy were not measured. However, whatever the methods of analysis (standard on complete data or after multiple imputation and propensity score-based), rituximab therapy remained associated with an 11-fold reduction of NHL risk and could be associated with a potential beneficial impact on OS.

Almost all lymphomas developing in patients with MCD were HHV-8–associated NHLs. Pathophysiology of these lymphomas may associate proliferation of the HHV-8–infected cells from the MCD lesion and/or proliferation of HHV-8–infected postgerminal center cells favored by the high levels of huIL10, huIL6, and vIL6 in active Castleman lesions.[2,5] The protective effect of rituximab on lymphoma risk could therefore be secondary to the depletion of the HHV-8–infected B cells and/or an indirect effect on the production of cytokines involved in B-cell proliferation. In the present study, 6 additional patients developed other hematological malignancies with no statistical differences according to rituximab therapy.

The possible occurrence of MCD or KS flares after rituximab therapy is a limitation of this therapy. The mechanism for KS flare because of rituximab is undefined. Low B-cell counts have been shown to be associated with an increased risk of KS development[26] and with advanced-stage KS.[27] In addition, increased expression of HHV-8–lytic gene products in KS lesions after rituximab therapy suggests a reactivation process.[28] Therefore, B-cell depletion and active HHV-8 replication may promote KS growth. MCD flares can be avoided when maintaining single-agent chemotherapy such as etoposide during the 4 cycles of rituximab. KS flares had already been observed in 4 of 11 patients, and in 8 of 12 patients, respectively, in the 2 initial prospective studies that had demonstrated the efficacy of rituximab.[14,15] In the present study, flares occurred in one-third of the R+ patients with previous stable KS lesions. Therefore, the presence of active KS lesions should still be considered to be a serious limitation to the use of rituximab therapy. This might explain why, even in recent years, only half of the patients of the present series were treated with rituximab.

OS has markedly improved since our initial study.[1] However, the mortality rate, which remains more than 30% at 5 years, is higher than that observed in other smaller cohort studies from the United Kingdom,[6] the United States,[13] and Germany.[12] Our series included all consecutive patients with a diagnosis of MCD followed in a single institution and included patients for whom the diagnosis was performed while they were initially hospitalized in an intensive care unit. Indeed, many of our patients presented with a severe disease; 28% presented with hemophagocytic syndrome and 29% required intensive care. In the present study, the median CD4 cell count was below $200 \times 10^6$/L; in the British study, it was $248 \times 10^6$/L, and in the German study, it was $284 \times 10^6$/L. Because CD4 cell count remains an independent prognosis covariate for both survival and risk of lymphoma in the general HIV-infected population, these differences may account for the worst overall prognosis and the highest rate of lymphoma observed in our cohort study.

## Conclusion

Despite improvement in OS in the cART era, the risk for developing lymphoma remains high in HIV-infected patients with MCD. However, the results of the present study suggest that the recent introduction of rituximab therapy could be associated with long-term protection against lymphoma risk. MCD flare-up and KS flare remain possible adverse events.

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## Authorship

Contribution: E.O. and L. Galicier designed and supervised the overall conduction of the study; L. Gérard and S.C. conducted the statistical analysis; L. Gérard, J.-M.M., C.F., E.O., and L. Galicier collected the data; F.A. performed the virologic analysis; V.M. performed the pathologic analysis; S.B., C.F., L. Galicier, and E.O. enrolled and cared for the patients; P.L. and V.D. referred the largest numbers of patients; L. Gérard, J.-M.M, and E.O. drafted the manuscript; L. Galicier and S.C. critically reviewed the manuscript; and all authors approved the final manuscript.

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