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Brief Communication: Rituximab in HIV-Associated Multicentric Castleman Disease

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Background: HIV-associated multicentric Castleman disease is a rare lymphoproliferative disorder with marked systemic symptoms attributed to cytokine disarray. Many therapeutic approaches in small series of patients have proved largely unsuccessful to date.

Objective: To investigate the efficacy and clinicopathologic variables associated with first-line treatment for HIV-associated multicentric Castleman disease with the anti-CD20 monoclonal antibody rituximab.

Design: Single-group, open-label, phase II trial.

Setting: 3 teaching hospitals in England.

Patients: Previously untreated patients with histologically proven HIV-associated multicentric Castleman disease.

Intervention: 4 infusions of rituximab, 375 mg per m^2 of body surface area, at weekly intervals.

Measurements: Response was evaluated clinically and radiologically and by measuring plasma Kaposi sarcoma–associated herpesvirus viral load.

Results: 21 consecutive patients (18 men) with plasmablastic multicentric Castleman disease were recruited. The median follow-up was 12 months (range, 1 to 49 months). One patient died before completing therapy, 20 achieved remission of symptoms, and 14 (67%) achieved a radiologic response. The overall and disease-free survival rates at 2 years were 95% (95% CI, 86% to 100%) and 79% (CI, 49% to 100%), respectively. Plasma acute-phase proteins, immunoglobulins, and Kaposi sarcoma–associated herpesvirus viral load decreased after rituximab therapy. The main adverse effect was reactivation of Kaposi sarcoma.

Limitation: The study had no comparison group.

Conclusion: Rituximab may be clinically valuable as initial therapy for HIV-associated multicentric Castleman disease.

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Multicentric Castleman disease is a rare lymphoproliferative disorder that is increasingly occurring in people with HIV infection. It is associated with Kaposi sarcoma, sharing an etiologic agent, Kaposi sarcoma–associated herpesvirus (KSHV), also known as human herpesvirus-8 (1, 2).

The gold-standard therapy for HIV-associated multicentric Castleman disease is yet to be established. The use of an anti-CD20 monoclonal antibody, rituximab, to target KSHV-infected plasmablasts in multicentric Castleman disease is a novel and potentially beneficial approach. It has been the subject of case reports and clinical series, in which patients were often pretreated with chemotherapy and follow-up was brief (3–10). We investigated the efficacy and safety of rituximab as initial monotherapy and correlate clinical findings with immune subset, plasma cytokine, and HIV and KSHV virologic variables.

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Methods

Between 2003 and 2006, 21 patients (18 men) with multicentric Castleman disease were treated prospectively in a nonrandomized, open-label, phase II study with 4 infusions of rituximab at a standard dose of 375 mg per m^2 of body surface area at weekly intervals. All biopsy specimens were reviewed and confirmed to be plasmablastic variants of multicentric Castleman disease with no microlymphoma, as defined by previous studies (11, 12). The plasmablasts showed immunoglobulin light chain restriction, were KSHV latent nuclear antigen–positive, and expressed CD20 on immunohistochemistry. Patients were recruited from 3 HIV and cancer centers, where local ethics review committees approved the study and patients gave informed consent. Toxicity was recorded at each visit and was graded by using the Common Terminology Criteria for Adverse Events, version 3.0 (13).

We measured plasma KSHV DNA viral load at diagnosis and at 1 and 3 months after rituximab therapy by using Lightcycler quantitative polymerase chain reaction (Roche, Lewis, United Kingdom) on DNA extracted from whole blood using primers specific to KSHV *ORF-7* gene, as described elsewhere (14).

We assessed progression-free and overall survival by using the Kaplan–Meier method (15) and used the Wilcoxon rank-sum test to assess the statistical significance of changes in hematologic, biochemical, and immunologic

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variables. Summaries of data that were not normally distributed are presented as medians with interquartile ranges. All *P* values are 2-sided (Statview, version 4.57, Abacus Concepts, Berkeley, California).

Role of the Funding Source

Support for the cytokine assays was provided by St. Stephen's AIDS Trust, a national charity supporting clinical research in HIV/AIDS, which had no role in the design, conduct, or reporting of this review or in the decision to publish the manuscript.

RESULTS

We enrolled 21 patients with a histologically confirmed plasmablastic variant of multicentric Castleman disease without microlymphoma. Their median age was 37 years (range, 31 to 69 years), 9 (43%) patients had a previous AIDS-defining diagnosis, and 13 (62%) patients were receiving highly active antiretroviral therapy (HAART) at diagnosis of multicentric Castleman disease. The median CD4 cell count at diagnosis was 0.30×10^9 cells/L (range, 0.08 to 0.73×10^9 cells/L). Four patients had a plasma HIV-1 viral load less than 50 copies/mL, and 5 other patients had a viral load less than 400 copies/mL (**Table 1**).

At diagnosis, the median duration of symptoms was 4 months (range, 0.5 to 24 months), all patients had significant lymphadenopathy, 20 (95%) patients had fever of unknown origin, 18 of 20 (90%) patients had splenomegaly (1 had had splenectomy), and 11 (52%) patients had cutaneous Kaposi sarcoma. Ninety-five percent of the patients had an increased erythrocyte sedimentation rate (ESR) (>20 mm/h), 82% had an increased C-reactive protein (CRP) level (>10 mg/L), 67% were anemic (hemoglobin level <100 g/L), 67% were hypoalbuminemic (serum albumin level <30 g/L), and 14% were thrombocytopenic (platelet count $<100 \times 10^9$ cells/L). All patients had polyclonal hypergammaglobulinemia, and 2 patients had a serum IgG monoclonal paraprotein band (**Table 1**).

One patient who was receiving intensive care at diagnosis died of progressive disease before completing the rituximab course. All 20 remaining patients achieved resolution of symptoms and fever by the end of rituximab treatment. Of the 21 patients, 14 (67%) had a partial response and 6 (29%) had stable disease according to the radiologic Response Evaluation Criteria in Solid Tumors. The median follow-up was 12 months (range, 1 to 49 months). The 2-year overall survival rate was 95% (95% CI, 86% to 100%), and the relapse-free survival rate was 92% (CI, 75% to 100%) at 1 year and 79% (CI, 52% to 100%) at 2 years.

Context

Castleman disease is a rare lymphoproliferative condition. Risk for the condition is elevated in people with HIV infection. Case reports and series suggest that rituximab shows some therapeutic promise in patients previously treated with chemotherapy, but data on initial therapy with rituximab are lacking.

Contribution

This uncontrolled case series suggests that initial treatment with rituximab can achieve better overall and disease-free survival than that anticipated in untreated patients. Laboratory measures improved with therapy.

Caution

The absence of a control group precludes definitive assessment of the efficacy or safety of rituximab in treating HIV-associated Castleman disease.

—The Editors

Table 1. **Hematologic, Biochemical, and Immunologic Variables at Presentation and Change from Baseline 1 Month after Completion of Rituximab Therapy***

Variable	Median Value before Rituximab Therapy (IQR) (*n* = 21)	Median Change 1 mo after Rituximab Therapy (IQR) (*n* = 20)	*P* Value†
Hemoglobin level, *g/L*	92 (80 to 105)	48 (23 to 60)	<0.001
Platelet count, × 10^9 *cells/L*	195 (137 to 235)	75 (19 to 112)	0.011
Serum albumin level, *g/L*	26 (21 to 33)	9.0 (7.0 to 18)	<0.001
CRP level, *mg/L*	79 (17 to 130)	−59 (−7 to −124)	0.003
ESR, *mm/h*	97 (79 to 120)	−65 (−26 to −88)	<0.001
Serum IgG level, *g/L*	33 (27 to 38)	−2.0 (−0.5 to −6.5)	0.007
Serum IgA level, *g/L*	3.8 (2.7 to 4.7)	−0.06 (0.2 to −0.2)	0.86
Serum IgM level, *g/L*	1.7 (1.1 to 1.9)	−0.3 (−0.1 to −0.9)	0.002
CD4 cell count, × 10^9 *cells/L*	0.30 (0.12 to 0.39)	0.08 (0.003 to 0.17)	0.011
CD8 cell count, × 10^9 *cells/L*	0.12 (0.78 to 0.12)	0.24 (−0.08 to 0.53)	0.017
CD19 cell count, × 10^9 *cells/L*	0.28 (0.07 to 0.37)	−0.19 (−0.07 to −0.38)	<0.001
Plasma KSHV DNA viral load, *copies/mL*	700 (237 to 64 425)	−700 (−150 to −88 425)	0.018

* CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IQR = interquartile range; KSHV = Kaposi sarcoma–associated herpesvirus.
† *P* values obtained from Wilcoxon rank-sum test.

Table 2. **Proportion of Patients with Elevated Plasma Cytokine Levels at Diagnosis and Changes during Treatment***

Cytokine (Normal Range)	Elevated at Diagnosis (n = 11)	Elevated at End of Rituximab Therapy (n = 9)	Elevated at 3 mo after End of Rituximab Therapy (n = 9)
IL-1β (0–6 pg/mL)	45	66	44
IL-2 (0–3 pg/mL)	64	55	44
IL-4 (0–10 pg/mL)	54	55	44
IL-5 (0–5 pg/mL)	73	66	55
IL-6 (0–5 pg/mL)	54	11	22
IL-8 (0–8 pg/mL)	82	100	100
IL-10 (0–9 pg/mL)	100	55	77
IL-12 (50–92 pg/mL)	73	66	55
IL-13 (0–10 pg/mL)	36	44	44
IL-15 (0–5 pg/mL)	45	55	44
IL-17 (0–14 pg/mL)	18	33	44
GM-CSF (0–19 pg/mL)	45	55	44
TNF (0–12 pg/mL)	0	0	11
IFN-α (0–31 pg/mL)	27	44	44
IFN-γ (0–4 pg/mL)	73	88	55

* Values reported are percentages. GM-CSF = granulocyte macrophage colony-stimulating factor; IFN = interferon; IL = interleukin; TNF = tumor necrosis factor.

One month after completion of rituximab therapy, 0 of 20 patients were anemic, 0 of 20 were thrombocytopenic, 11 of 17 had an increased ESR, 2 of 16 had an increased CRP level, and 1 of 20 had hypoalbuminemia. Hemoglobin level, platelet count, and serum albumin level increased, whereas ESR and CRP level decreased, 1 month after rituximab treatment (**Table 1**).

Quantitative polymerase chain reaction for KSHV was available for 11 patients at diagnosis and was detectable in 9 patients (median, 700 copies/mL; range, 0 to 400 000 copies/mL). One month after treatment, only 2 of 10 (20%) patients had detectable KSHV (**Table 1**). In both cases, the titer was only 100 copies/mL. Three months after rituximab therapy, only 1 of 10 (10%) patients had detectable KSHV DNA, and once again the titer was only 100 copies/mL ($P = 0.018$).

Serum IgG and IgM levels decreased 1 month after rituximab therapy, but IgA levels did not change (**Table 1**). Similarly, the CD19 cell count decreased, which persisted at 3 months (median decrease from baseline, 104 cells/mL; interquartile range, 14 to 350 cells/mL; $P = 0.002$), but the CD19 cell count had recovered to prerituximab levels by 12 months. We performed immune subset analysis on the 13 patients who were already receiving HAART at the time of rituximab therapy. The CD4, CD8, CD56 (natural killer) cell subsets, or HIV viral load did not change during this period.

No Common Terminology Criteria for Adverse Events grade 3 or 4 toxicities were recorded with rituximab therapy; however, Kaposi sarcoma progressed during rituximab therapy in 4 of 11 (36%) patients who had cutaneous Kaposi sarcoma at diagnosis.

We also measured 15 plasma cytokines: interleukin (IL)–1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 p40/p70, IL-13, IL-15, IL-17, interferon-α, interferon-γ, tumor necrosis factor-α, and granulocyte macrophage colony-stimulating factor, before and after rituximab therapy and again 3 months after the completion of rituximab therapy. Most patients had elevated plasma cytokine levels at presentation, and the proportion with increased levels declined on completion of therapy (**Table 2**).

DISCUSSION

Rituximab therapy seems to be a promising first-line treatment for HIV-associated multicentric Castleman disease: Patients completing 4 weekly infusions achieved a clinical and biochemical remission within 1 month, and the radiologic response rate was 67%. Plasma KSHV viral load significantly decreased in individuals with this measurement ($P = 0.018$). The 2-year overall survival rate was 95% (CI, 86% to 100%), and the relapse-free survival rate was 79% (CI, 52% to 100%). This compares favorably with the median survival of 14 months recorded for 20 patients from the pre-HAART era (16).

The clinical response to rituximab occurred within 1 month of completing therapy, and normalization of acute-phase inflammatory markers, such as ESR, CRP, and albumin, occurred by this point. Plasma KSHV DNA viral load was measured before, during, and after treatment and decreased dramatically with treatment and increased at relapse. The high plasma titers of KSHV reflect lytic replication, which is not a feature of Kaposi sarcoma but correlates with disease activity in multicentric Castleman disease. Indeed, KSHV-infected B-lymphocytes from lymph nodes in patients with multicentric Castleman disease are known to express KSHV lytic gene products (17, 18).

Rituximab produced a decrease in CD19-positive B-lymphocytes, as would be expected, but was well tolerated in patients with HIV-related multicentric Castleman disease, with no grade 3 or 4 toxicities. In addition, rituximab did not seem to cause exacerbation of HIV infection, with no adverse effect on the immune T-cell subsets, including CD4 cell count or HIV viral load. However, Kaposi sarcoma progressed in 36% of patients with this disease, a phenomenon that has been recorded previously (4). The reason for this is unclear, but the rapid decrease in B-lymphocytes observed with rituximab therapy may play a role in the progression of Kaposi sarcoma (19). Because rituximab has also been associated with an increased risk for death from infection in AIDS-related non-Hodgkin lymphoma (20), the data we present should provide reassurance to clinicians. A recent trial in patients with chemotherapy-dependent, HIV-associated multicentric Castleman disease reported that 4-weekly rituximab infusions resulted in sustained remission off treatment at day 60 (the

primary end point) in 92% of individuals (10). Again, exacerbation of Kaposi sarcoma was the most frequent side effect.

We measured 15 plasma cytokines described earlier. Levels of most were elevated at presentation and normalized on completion of therapy. The most prominent change in plasma cytokine concentration was seen with IL-10, which is produced by KSHV-infected and HIV Tat–induced cell lines and has been linked to B-lymphocyte activation, and polyclonal hypergammaglobulinemia in HIV-1 infection (21–23). These data are consistent with previous findings, which suggested a close relationship between elevated IL-10 and symptomatic multicentric Castleman disease in patients receiving HAART, and that IL-10 was a better marker of disease activity than IL-6 (16).

Although no standard treatments have been established, many clinicians have favored the use of chemotherapy for managing HIV-associated multicentric Castleman disease. Our data and the aforementioned recent trial (10) show that rituximab results in sustained clinical, biochemical, and radiologic response. Prolonged follow-up after treatment is required as relapses occur. The main adverse event is reactivation of Kaposi sarcoma.

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