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# 2-Chloro-deoxyadenosine Induces Durable Complete Remission in Castleman's Disease but may Accelerate its Transformation to Non-Hodgkin's Lymphoma

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There is currently no consensus on the best treatment for unresectable hyaline-vascular variant or for multicentric Castleman's disease (MCD), because none of the reported regimens have consistently produced complete response or durable remission in the majority of patients. In the present study, we report on the use of 2-CdA (2-chloro-deoxyadenosine) in three patients, two of them with MCD and one with unresectable hyaline-vascular type disease. Relapse-free survival of the responding patients was 24 and 20 months. Later, both patients evolved to non-Hodgkin's lymphoma (NHL) (diffuse large B-cell lymphoma and peripheral T-cell NHL, respectively). 2-CdA typically causes a long-lasting state of immunodeficiency and the profound influence of this drug on the immune system has raised questions concerning the emergence of secondary neoplasms after its use. Therefore, it is reasonable to conclude that: 1) 2-CdA can induce durable complete remission in MCD patients but unfortunately it cannot cure the disease; 2) the possibility that 2-CdA may accelerate the transformation of MCD to NHL cannot be ruled out.

Castleman's disease (CD) is a lymphoproliferative disorder with benign hyperplastic lymph nodes characterized histologically by follicular hyperplasia and capillary proliferation with endothelial hyperplasia (1). Three basic histopathologic subtypes have been described: hyaline-vascular, plasma-cell and mixed variant subtypes (2). Two clinical entities have also been described: 1) a unicentric presentation, with disease confined to a single anatomic lymph-node-bearing region; and 2) a multicentric CD (MCD), characterized by systemic manifestation with fever, anemia, hypergammaglobulinemia, hypoalbuminemia, and an increase in acute-phase proteins with a more aggressive clinical course (3). MCD generally occurs in patients with plasma-cell or mixed (hyaline-vascular and plasma-cell) subtypes. Patients with MCD often develop secondary tumors such as Kaposi's sarcoma (KS), plasmacytoma and Hodgkin's disease, and the development of aggressive non-Hodgkin's lymphoma (NHL) is not a rare outcome in patients with this disorder (4). Most cases of MCD are associated with infection by KS-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), which occurs in almost 100% of human immunodeficiency virus (HIV) associated cases and in 40% to 50% of HIV-negative cases (5). Some recent studies have suggested that dysregulation of IL-6 production from affected lymphocytes may be responsible for the systemic manifestation of the disease (5, 6). Surgery has long been considered the standard therapy for the unicentric type (3, 4) and some case reports have documented favorable responses to radiotherapy in selected patients with this localized disease (7). The optimal treatment of MCD or unresectable localized CD is unknown. Many therapies have included extended courses of high-dose glucocorticoids alone or in combination with vinca alkaloids, alkylating agents, azathioprine and monoclonal antibodies against IL-6 or 2-chloro-deoxyadenosine (2-CdA) (8, 9). Considering that lymph nodes of patients with KSHV-related MCD specifically harbor the virus in B cells located in the mantle zone, which stain positively for the CD20 surface antigen, Corbellino et al. (10) treated a MCD HIV-positive patient with a single dose of anti-CD20 monoclonal antibody, which was well tolerated and allowed a 14-month remission of clinical symptoms and KSHV viremia. Corbellino et al.

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proposed that rituximab should be added to the therapeutic armamentarium for KSHV-related MCD. However, at this moment, there is no consensus regarding the best treatment for unresectable hyaline-vascular variant or for MCD, because none of the reported regimens have consistently produced durable remission in the majority of patients (9).

*Patient 1*

A 46-year-old white male who had suffered night sweats, sporadic fever and weakness for the preceding 8 months was admitted to our hospital in February 1999. He presented with cervical lymph nodes measuring 1–3 cm, spleen enlargement and anemia. A lymph node biopsy was compatible with plasma-cell CD. CT scans showed a mediastinal mass and splenomegaly with solid nodules. Bone marrow biopsy did not show infiltration by disease (see Table 1). The patient was HIV and HHV-8 negative. CD4/CD8 ratio was 0.49 (normal ratio 0.9–3.3) at diagnosis but we could not find any cause of this immunosuppression. The patient was treated with 3 cycles of 2-CDA (0.1 mg/kg/day × 7) between April and July 1999 resulting in complete clinical and radiological remission. In June 2001, he presented with B-symptoms and a bulky mediastinal mass. Biopsy of the mass showed diffuse, large, B-cell lymphoma, CS IIIB. After 6 cycles of anthracyclin-based chemotherapy (11), he went into partial remission, but the B-symptoms and residual mediastinal mass persisted. The patient did not achieve remission after 3 cycles of salvage therapy DHAP (dexametasone, cytarasine and cisplatin) and 1 cycle of MINE (mesna, ifosfamide, mitoxantrone, etoposide) (12) and died on April 2002 of sepsis and disease progression. We did not add anti-CD20 monoclonal antibody to any of the above chemotherapy regimens because in Brazil its high cost does not allow its routine use in public hospitals.

*Patient 2*

A 40-year-old white female presented with 6 years of progressive enlargement of a pelvic mass. In August 1999, a CT scan showed an 18 cm × 15 cm mass with involvement of the left iliac artery. There was no evidence of disease in other sites. A surgical approach led to partial resection of the tumor mass and left iliac artery injury. A histopathologic analysis showed hyaline-vascular CD. The patient was HIV negative and HHV-8 positive. Local radiation was not done because of the risk of left iliac artery anastomosis disruption. The patient was treated with 3 cycles of 2-CDA (0.1 mg/kg/day × 7) between November 1999 and July 1999 without improvement of the residual mass. In June 2000, she presented with skin lesions compatible with disseminated multiform erythema. Despite the use of corticosteroids (prednisolone 1 g/day for 5 days), cyclosporin and immunoglobulin, she evolved to multiple organ failure and death.

*Patient 3*

A 62-year-old white male was admitted to our hospital in January 2000 with weight loss, sporadic fever and weakness during the preceding 6 months. He presented with anemia, cervical, axillary, supraclavicular lymph nodes measuring

**Table 1**

*Clinical characteristics of 3 patients with Castleman's disease*

| Features | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Age (years) | 46 | 40 | 62 |
| Gender | Male | Female | Male |
| Localization | Systemic | Localized | Systemic |
| Histology | Plasma cell | Hyaline-vascular | Mixed variant |
| CBC Normal range | | | |
| Hemoglobin: 13.5–17.5 g/dL | Hemoglobin: 9.9 g/dL | Hemoglobin:13.3 g/dL | Hemoglobin: 8.5 g/dL |
| Platelets: 150–450 × 109/L | Platelets: $577 \times 10^9$/L | Platelets: $204 \times 10^9$/L | Platelets: $39 \times 10^9$/L |
| WBC: 3.5–10.5 × 109/L | WBC:$13.9 \times 10^9$/L | WBC: $7.8 \times 10^9$/L | WBC: $3.0 \times 10^9$/L |
| Bone marrow biopsy | No evidence of infiltration | No evidence of infiltration | No evidence of infiltration |
| HHV-8* | Negative | Positive | Positive |
| HIV | Negative | Negative | Negative |
| CD4/CD8 ratio at diagnosis | | | |
| Normal 0.9–3.3 | 0.49 | 1.70 | 1.79 |
| Albumin | | | |
| Normal 3.2–5.6 g/dL | 2.48 g/dL | 4.64 g/dL | 2.06 g/dL |
| Rheumatologic screening | Not done | Negative | Negative |
| Response to 2-CDA therapy | Complete remission | No response | Complete remission |
| Relapse-free survival | 24 months | No response | 20 months |
| Overall survival | 38 months | 84 months | 36 months |
| Evolution | B-cell NHL CD20+, CD45Ro − | Immunologic skin disease | T-cell NHL CD20 −, CD45Ro+, CD30 −, CD15 − |

Abbreviations: HHV-8* = antibodies against HHV-8 latency-associated nuclear antigen (IFA-Lana) and lytic phase antigens (IFA-lytic) detected by immunofluorescence assay, employing BCBL-1 cell line; CBC = complete blood count; WBC = white blood cells.

2–3 cm, and liver and spleen enlargement. CT scans confirmed the above clinical features. The result of a lymph node biopsy was compatible with mixed (hyaline-vascular and plasma-cell) CD. The patient was HIV-negative and HHV-8-positive. Bone marrow biopsy did not show disease infiltration (Table 1). The patient was treated with 2 cycles of 2-CDA (0.1mg/kg/day × 7) until October 2000 but refused the third cycle. CT scans showed persistence of mild hepatomegaly, probably due to chronic alcohol abuse. In June 2002 he presented with enlargement of the axillary and cervical lymph nodes, with spontaneous partial regression. CT scans showed enlargement of retroperitoneal lymph nodes. A cervical lymph node biopsy showed peripheral T-cell NHL. On January 2003, this patient died of sepsis and refractory NHL after two courses of chlorambucil/prednisone.

## DISCUSSION

Since the ideal treatment for MCD or unresectable localized CD is still unknown, we treated our three patients with 2 to 3 cycles of 2-CdA, based on the experience of Bordeleau et al. (9). In their report, one patient with unresectable localized hyaline-vascular CD had 9-month continuous complete remission after 2 cycles of 2-CdA and radiotherapy, while another patient with MCD of plasma-cell type had a partial response after 2 cycles of 2-CdA. In our experience, two patients with MCD had a complete remission but the unresectable localized disease did not respond to treatment. Relapse-free survival of the two patients who responded to 2-CdA was longer than that reported by Bordeleau et al. (9)—24 and 20 months. Patients with MCD often develop secondary tumors such as Kaposi sarcoma, Hodgkin's disease, plasmocytoma and NHL. In one study, 25% of patients with MCD developed NHL (13). In 70% of cases this is of B-cell origin, with advanced stage disease (III or IV) and a very poor prognosis. The diagnosis is usually concurrent with CD or occurs within 2 years of follow-up (4). Our cases are in line with these data.

It is well known that 2-CdA causes a long-lasting state of immunodeficiency (14). The profound influence of this drug on the immune system has raised questions concerning the emergence of secondary neoplasms or autoimmune disorders after its use (15). It is therefore reasonable to assume that 2-CdA may speed up transformation of CD into NHL. Robak et al. (16) reported a plasmablastic lymphoma in a patient with chronic lymphocytic leukemia heavily pretreated with 2-CdA. They suggested that this condition was caused by a second clone that emerged as a result of the prolonged and severe state of the host's immunosuppression. What would have been the evolution of our two cases that transformed to NHL if another treatment had been used? Would they have evolved to aggressive NHL as 25% of MCD patients do? Did 2-CdA speed up this transformation? At this moment, we are unable to answer these questions. Furthermore, we cannot rule out the possibility that the immunologic skin disease presented by patient 2 was an autoimmune disorder secondary to 2-CdA treatment (15).

We conclude that 2-CdA may be a possible alternative for temporary control of CD symptoms, but unfortunately it does not cure the disease. 2-CdA cannot prevent, and may even accelerate, the transformation of MCD into refractory NHL. Future studies are necessary to confirm the Corbellino et al. (10) data on the role of anti-CD20 monoclonal antibody in the treatment of MCD, even in non-HIV patients, since it is less toxic than combined chemotherapy or 2-CdA. It is also important to consider the role of autologous or allogeneic bone marrow transplantation in MCD, since the transformation to lymphoproliferative disorders is usually associated with refractoriness to standard and salvage therapy.

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