# Long-term remission in idiopathic Castleman's disease with tocilizumab followed by consolidation with high-dose melphalan-two case studies.

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# Long term remission in idiopathic Castleman's disease with tocilizumab followed by consolidation with high dose melphalan – two case studies

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## Abstract

Multicentric Castleman's disease (MCD) is an uncommon lymphoproliferative disorder, often associated with a clinically aggressive behavior. No standard treatment has been established, but patients are usually treated with lymphoma-type regimens such as rituximab or combination chemotherapy. Recently, immunotherapies targeting IL-6 have proven effective and have been approved for this indication. However, these agents require long-term administration. Here, we describe the clinical course of two patients, refractory to rituximab and chemotherapy, showing long-term remission (18 and 24 months), following an induction phase with tocilizumab (an anti-IL-6 receptor antibody) and a consolidative phase with high-dose melphalan accompanied by autologous stem cell support. This may prove to be an effective option for this group of patients with an orphan disorder.

**Key words**

Castleman´s disease, tocilizumab, autologous stem cell transplantation

## Introduction

Castleman's disease, an uncommon non-clonal lymphadenopathic disorder, was first described by Dr Benjamin Castleman in 1956[1], and is divided into unicentric and multicentric forms, based on the extent of local lymph node involvement[2]. The unicentric form usually manifests as an asymptomatic mass lesion with a benign course, most often in young adults, and may be treated with surgical resection. Multicentric Castleman's disease (MCD), on the other hand, is normally seen in adults in their sixties, is frequently associated with systemic manifestations such as fever, night sweats, and malaise, and multiple organ system impairment as a result of excessive production of interleukin-6 (IL-6) and other proinflammatory cytokines.

The disease is associated with Human herpes virus-8 (HHV-8) in all HIV-positive patients and in some HIV-negative patients. However, another, probably larger group of HIV-negative MCD patients, who are HHV-8 negative has recently been described and referred, in which the disease is referred to as idiopathic MCD (iMCD)[3].

There is currently no standard treatment for iMCD, and patients have have been given various forms of lymphoma-type treatment, including rituximab or combinations of chemotherapy  such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)[4], as well as high dose chemotherapy (melphalan) with autologous stem cell support[5]. However, rituximab has mainly been used in the HIV-associated population [6]. Based on the observation that IL-6 hypercytokinemia is central in the pathogenesis of this disorder, prospective trials have been performed using antibodies targeting the IL-6 signaling cascade, such as tocilizumab[7] and siltuximab, showing efficacy[8]. However, these antibodies require long-term administration and are not effective in all patients.

Here, we describe long-term control in two patients with multiple relapsed iMCD using anti-IL6 receptor immunotherapy (tocilizumab), consolidated with high dose melphalan.

## Patients

### Patient A

Patient A is a female patient, born in 1966, diagnosed with Crohn´s disease in 2004, who has been treated with mesalizine per os. In August 2011, she experienced progressive fatigue, abdominal pain, dyspnea and intermittent fever. A CT scan showed general lymphadenopathy, hepatosplenomegaly, and pericardial and bilateral pleural effusion. Her CRP was elevated to 100 mg/L. A lymph node biopsy showed MCD, plasma cell variant, negative for HHV-8 ORF26. Serology for HIV was negative.

Due to the aggressive clinical picture, treatment with R-CHOP-21 was started in October 2011. The patient received three cycles, followed by four weekly courses of single-agent rituximab. No improvement in symptoms was seen as a result of this therapy, and an FDG-PET-CT showed unchanged lymphadenopathy and hepatosplenomegaly, and an elevated creatinine level. She suffered from repeated episodes of epistaxis, that were difficult to control despite of her platelet count was 70 or above. Lymph nodes showed a moderate FDG uptake. She received corticosteroids, and in February 2012 treatment with tocilizumab 8 mg/kg at 2-week intervals was initiated. After one cycle, her symptoms resolved completely, and her CRP level normalized. An FDG PET-CT scan after 3 months of treatment showed complete resolution of pleural effusion, and normal FDG uptake in lymph nodes.

lymph nodes and spleen had decreased in size, whereas hepatomegaly was unchanged (Deauville 1). She received in total 17 doses of tocilizumab. In October 2012, the patient underwent a peripheral stem cell harvest, after G-CSF mobilization, of 4.1 x $10^6$ CD34+ cells/kg. In November 2012, the patient received high-dose melphalan (200 mg/$m^2$), with autologous stem cell support. The treatment course was uneventful, with a total hospital stay of 12 days. CT scans performed at 3-month intervals show gradual normalization of the lymph nodes and spleen, but the liver has remained enlarged.

At the most recent follow-up visit in April 2015, 30 months post therapy, the patient was asymptomatic, no longer taking steroids and her CRP and s-albumin were normal.

**Patient B**

Patient B is a male of Chinese origin, born in 1958. In 1979, he had a stroke causing left-sided hemiparesis. In 2003, he was diagnosed with cutaneous plasmocytosis. In 2009, he experienced progressive fatigue and weight loss, and a CT scan showed general lymphadenopathy. Lymph node biopsies (cervical and inguinal) showed follicular hyperplasia with prominent plasma cell infiltration, consistent with MCD and PCR was negative for HHV-8. Serological testing showed positivity for anti-HBc, but negativity for HIV. His CRP was markedly elevated, 150 mg/L and polyclonal IgG was elevated, 41 g/L. After diagnosis, he initially received four doses of rituximab, 375 mg/$m^2$, but without any effect on his symptoms, skin lesions, or lymphadenopathy, and only a marginal decrease in CRP level (Figure 1).

In 2011, the fatigue worsened, and was accompanied by profuse nightly sweats, and elevation of CRP to 200 mg/L. In addition, an elevation in s-creatinine was noted, to 280 μM. A renal biopsy showed IgA mesangioproliferative glomerulopathy, but no plasma cell infiltration, and was thought to be secondary to MCD. The patient then received six courses of R-CHOP-21, completing his treatment in April 2012. During this course of treatment, his renal function improved and his s-creatinine fell from 280 to 180 μM, but there was no improvement in symptoms, or in CRP or S-albumin levels. The patient was bedridden >75% during the daytime. A second renal biopsy now showed prominent plasma cell infiltration with Russell bodies. An FDG-PET scan showed enlarged, metabolically active lymph nodes bilaterally (SUV max 5.9 units) on the neck and in the axillae.

In October 2012, treatment was started with tocilizumab 8 mg/kg at two-weeks intervals. After two courses, the fatigue was markedly improved, his CRP level was normalized, and s-creatinine was reduced from 154 to 138 μM. An FDG-PET scan after three months of treatment showed complete resolution of hypermetabolic lesions (Deauville 1). In total, 12 courses of tocilizumab were given. In April 2013, the patient received 2000 mg/m$^2$ cyclophosphamide, followed by peripheral stem cell harvest of 16.7 x 10$^6$ CD34+ cells/kg. In May 2013, the patient received high-dose melphalan (200 mg/m$^2$), with autologous stem cell support. The treatment course was without unexpected complications, and the total hospital stay was 18 days.

At the most recent follow-up visit in January 2015, 18 months post-therapy, the patient was asymptomatic, and CRP and s-albumin were normal, while his S-creatinine remained slightly elevated at, 127 μmol/L.

## Discussion

These two cases demonstrate that a combination of anti-IL-6R immunotherapy and melphalan consolidation, can induce long term remission in patients with iMCD, refractory to rituximab and CHOP. It is perhaps not surprising that rituximab shows little efficacy in this disorder, as plasma cells, which constitute the main component of the disease-specific cells in the plasma cell variant of MCD, are CD20 negative. The use of high-dose melphalan in refractory MCD has been described previously in four cases[5, 9], in two of these in conjunction with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes)[10, 11]. Tocilizumab as a single agent has been shown to provide effective treatment for MCD in alleviating symptoms and producing objective remissions [7], and has been approved for this indication in Japan. Similarly, an antibody against IL-6, siltuximab, has recently been approved for the treatment of MCD in Europe and the U.S. based on a phase III trial, comparing this agent to best supportive care[8]. However, both these agents need to be administered for an indeterminate time, making it a very costly treatment. With the present approach, using an anti-IL-6R antibody for remission induction followed by consolidation with high-dose melphalan, patients with MCD may instead be free from treatment for a considerable period of time. Further studies are required to determine whether this treatment could develop into a curative treatment.

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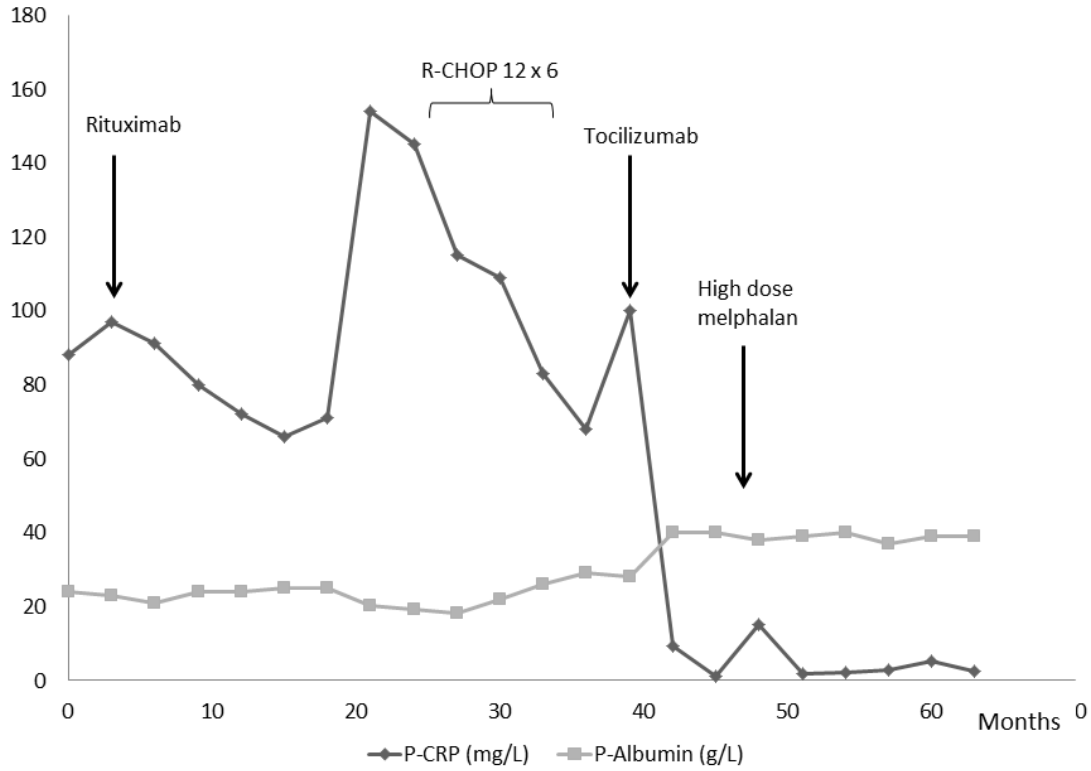
**Figure legend**

Plasma levels of C reactive protein (CRP) and albumin in Patient B during the course of disease and in relation to treatment interventions.

**Figure 1**


180
160
140
120
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60
Months
R-CHOP 12 x 6
Rituximab
Tocilizumab
High dose
melphalan
P-CRP (mg/L)
P-Albumin (g/L)