Castleman's Disease: From Basic Mechanisms to Molecular Therapeutics

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ABSTRACT

Castleman's disease is a rare lymphoproliferative disorder in which there has been recent progress in elucidating underlying mechanisms with potential therapeutic implications. Unicentric Castleman's disease is an indolent condition that is often treated with local approaches. In contrast, patients with multicentric Castleman's disease (MCD) have a less favorable prognosis and require systemic treatment. Cytotoxic chemotherapy, with its attendant risk for toxicity, has been widely used to treat MCD,

with variable efficacy. The discovery of putative etiologic factors and targets in MCD, particularly human herpes virus 8, CD20, and interleukin (IL)-6, has been translated into the use of rituximab and anti-IL-6-based therapy, as well as antiviral agents. In this article, we review the current state of the art of our understanding of Castleman's disease and its treatment and we provide insight into future treatment strategies based on disease biology. *The Oncologist* 2011;16:497–511

INTRODUCTION

Castleman's disease (CD) is an uncommon lymphoproliferative disorder characterized by enlarged hyperplastic lymph node(s). It was first described by Dr. Benjamin Castleman in 1954 in a patient who had a solitary hyperplastic mediastinal lymph node with a regressive germinal center [1]. To date, CD exhibits several different histological patterns. The hyaline vascular variant is characterized by abnormal follicles with regressed germinal centers surrounded by widened mantle zones comprised of small lym-

phocytes in an onion ring-like arrangement. The regressed germinal center may become hyalinized and contain follicular dendritic cells. The plasma cell variant is characterized by hyperplastic germinal centers and a massive accumulation of polyclonal plasma cells in the interfollicular region. Marked vascular proliferation in the interfollicular region is present in both CD variants. Mixed forms demonstrate the presence of both hyaline vascular and plasma cell elements [2]. The plasmablastic variant is less common and is associated with HIV infection. A subvariant of the plasma cell

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form, it is characterized by large plasmablasts harboring human herpes virus (HHV)-8 and it can progress to frank plasmablastic monoclonal lymphoma [3].

Two different clinical presentations can be distinguished. The localized or unicentric variant of CD (UCD) is the most common form of the disease, is confined to a single lymph-node chain or area, is usually of hyaline vascular histologically, and is often asymptomatic and curable by surgical excision of the mass. The systemic or multicentric variant of CD (MCD) is a less common and more aggressive form. Its corresponding histological pattern is the plasma cell variant, and rarely the plasmablastic type. It is frequently accompanied by systemic manifestations such as fever, night sweats, fatigue, anorexia, weight loss, organomegaly, diffuse polyadenopathy, and edema. A number of laboratory abnormalities are seen, including thrombocytosis, thrombocytopenia, anemia, leukocytosis, hypoalbuminemia, hypergammaglobulinemia, and increases in acute-phase proteins like C-reactive protein (CRP), sedimentation rates, fibrinogen, and interleukin (IL)-6 [2, 4, 5]. It presents usually later in the fifth to sixth decade of life. MCD can progress to severe pancytopenia, multiorgan failure [6], and lymphoma. It can rarely be associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, a devastating disease. Patients with MCD require systemic treatment and their prognosis is unfavorable [2, 4]. CD has some particularity if associated with HIV. It is almost always MCD of a mixed or plasma cell variant and associated with HHV-8. It occurs at a younger age, with a male preponderance. Constitutional manifestations are more prominent. Generalized lymphadenopathy is frequently encountered on physical examination [7]. Its incidence has been climbing recently [8]. It often runs an aggressive course and the median survival duration is about 14 months [9].

Although the mechanisms underlying MCD are not fully understood, recent advances in understanding the biological basis of the disease, particularly the pivotal role of HHV-8 and IL-6, have led to the development of promising targeted therapies. The roles of IL-1, the RAF pathway, and epidermal growth factor receptor (EGFR), and vascular endothelial growth factor (VEGF) expression have also been illustrated in limited anecdotal cases. Blocking these pathways therefore makes it another attractive therapeutic approach for this rare disorder.

The scope of this review is to cover the contemporary knowledge and the recent advances achieved in elucidating the pathophysiology of Castleman's disease, to present the efficacy of current treatment options, and to provide some

insight into future treatment strategies based on disease biology.

PATHOPHYSIOLOGY AND POTENTIAL THERAPEUTIC IMPLICATIONS

Although CD was discovered more than five decades ago, its pathophysiologic basis remained unknown until recently. Currently, MCD is considered to be mediated by the interplay among deregulated inflammatory mediators, particularly IL-6, which may be driven by HHV-8 in some cases, resulting in lymphovascular proliferation and systemic manifestations of the disease. Major biologic factors involved in disease pathogenesis are discussed in the following sections.

Role of IL-6

IL-6 is a multifunctional cytokine produced by various cells such as T cells, B cells, monocytes, fibroblasts, and endothelial cells. It induces the differentiation and proliferation of B cells and T cells, and can stimulate hematopoietic cells. It is involved in the synthesis of acute-phase reactant proteins by the liver and is associated with the development of constitutional symptoms accompanying many inflammatory diseases [10]. IL-6 also induces the secretion of the peptide hormone hepcidin by the liver, which interferes negatively with the absorption and use of iron, leading to the anemia of chronic disease [11]. Recently, its role in the growth of tumor cells and angiogenesis has suggested that it is a potential therapeutic target in cancer [12].

The contribution of IL-6 to the pathogenesis of CD has been demonstrated in animal models. Retroviral transduction of the coding sequence of murine IL-6 into mice bone marrow resulted in the development of a CD-like syndrome with fever, anemia, leukocytosis, hypoalbuminemia, polyclonal hypergammaglobulinemia, marked splenomegaly, and diffuse lymphadenopathy [13]. Katsume et al. [14] studied the effect of blocking IL-6 in transgenic mice carrying human IL-6 cDNA using an anti-IL-6 receptor (IL-6R) monoclonal antibody. Control mice developed plasmacytosis, mesangial proliferative glomerulonephritis, leukocytosis, thrombocytosis, and anemia. Mice who received the monoclonal antibody did not develop these symptoms and lived longer.

Yoshizaki et al. [15] noted an elevated concentration of IL-6 in a patient with UCD, which normalized after lymph node excision along with the disappearance of clinical and biologic abnormalities. The detection of IL-6 in germinal-center B cells implicates the generation of IL-6 by B cells in the pathogenesis of MCD.

Role of HHV-8

HHV-8 or Kaposi's sarcoma-associated herpesvirus (KSHV) is a human lymphotropic virus isolated for the first time from Kaposi's sarcoma tissue in 1994 [16]. It is etiologically linked with Kaposi's sarcoma, primary effusion lymphoma, and CD [17]. Nearly all cases of HIV-associated CD are HHV-8⁺, compared with 40%–50% of HIV[−] CD cases [18]. The correlation between the degree of proliferation of HHV-8 and symptom severity and symptom regression after administration of antiviral agents provides evidence of its critical role in CD.

KSHV encodes a number of putative proteins implicated in cell cycle regulation, apoptosis, and cytokine signaling, all associated with the pathogenesis of HHV-8–related diseases.

An important example is viral homolog of IL-6 (vIL-6), which shares a 25% homology with human IL-6 and is a particularly interesting protein. The region involved in receptor binding exhibits high homology with its human counterpart [19]. vIL-6 can bind to IL-6R and activate the downstream Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, leading to CD manifestations [17]. vIL-6 can activate human IL-6 signaling pathways independently of IL-6R via direct activation of glycoprotein (gp)130 [20]. However, vIL-6 has low affinity for IL-6R, compared with human IL-6. It is believed that vIL-6 induces VEGF production, which in turn induces human IL-6 production by endothelial cells in the lymph nodes [21]. Indeed, vIL-6–transduced murine fibroblast lines inoculated in athymic mice promoted hematopoiesis and, interestingly, induced VEGF production in the spleen and lymph nodes. In vitro, VEGF was detected at a higher level in the supernatant of vIL-6–expressing cells, an effect neutralized by the addition of anti-vIL-6 antibody [22].

Other virally encoded products might contribute to disease pathogenesis, including the latency-associated nuclear antigen, the viral G protein–coupled receptor, and the viral FLICE-inhibitory protein. These oncogenic proteins are characterized by their proangiogenic and antiapoptotic capabilities as well as their ability to activate many important intracellular pathways, particularly the phosphoinositide 3-kinase (PI3K)–mammalian target of rapamycin (mTOR), hypoxia inducible factor (HIF)- α , and nuclear factor (NF)- κ B signaling cascades [17, 23–27]. Based on these insights, these pathways may serve, at least theoretically, as targets in the treatment of MCD, even though their use in MCD has never been reported.

Role of Angiogenesis and VEGF

Blood vessel proliferation is an important histologic component of CD, although the role of angiogenesis in the

pathophysiology of CD has received scant attention. Nishi et al. [28] found the level of VEGF in sera and supernatants of cultured lymph nodes to be higher in two patients with CD than in normal controls. Immunohistochemical analysis showed a high expression level of VEGF in plasma cells of the interfollicular region [28]. In contrast, Foss et al. [29] showed VEGF mRNA overexpression in nonlymphoid cells in MCD patients, whereas Cohen et al. [30] demonstrated the role of IL-6 in the production of VEGF in vitro.

Role of EGFR

EGFR has been a therapeutic target in the treatment of various cancers. A recent study [31] evaluated EGFR expression in follicular dendritic cells and surrounding perifollicular fibroblastic reticular cells in patients with Castleman's disease and found EGFR expression in all 24 cases. However, the significance of overexpression of EGFR in relationship to therapeutic targeting is less clear than that for *EGFR* mutations.

Role of IL-1 and NF- κ B

The role of IL-1 in CD has been explored to a limited degree. Gheradi et al. [32] demonstrated elevated serum levels of IL-1b and IL-6 in five patients with POEMS syndrome, four of whom had concomitant MCD. In two of the patients, there were abundant IL-1b mRNA-producing cells in the interfollicular spaces, suggesting that lymph nodes might be a source of IL-1b. There are two distinct IL-1Rs: IL1RI and IL1RII. IL-1, by binding to IL1RI, triggers a signaling cascade in the cytoplasm leading to activation of I- κ B kinase (IKK). NF- κ B, normally bound in the cytoplasm to I- κ B, is a transcription factor for various proteins regulating the inflammatory process, cell growth, and apoptosis. Activated IKK phosphorylates I- κ B, which then is recognized and destroyed by the proteasome pathway. Consequently, NF- κ B is released and enters into the nucleus to turn on several genes that regulate cell growth and apoptosis and inflammation, particularly those encoding IL-1 and IL-6 [33, 34]. Therefore, it is conceivable that IL-1 and IL-6 are both overexpressed in CD because of a common aberrant upstream regulator or, alternatively, that upregulation of IL-1 stimulates IL-6. Recently, we observed a patient with MCD who responded well to administration of an IL-1R antagonist [35], a natural molecule that binds to IL-1RI and blocks its biologic effects, supporting further a role for that pathway in disease pathogenesis.

Role of B Lymphocytes and CD20

CD20 is a phosphoprotein expressed on the surface of mature B lymphocytes. Dupin et al. [3] demonstrated that lymph nodes from patients with HHV-8–related MCD har-

bor HHV-8 in IgM-restricted plasmoblasts localized in the mantle zone and marked by variable expression of CD20. Thus, the ability to eradicate HHV-8–infected B lymphocytes by targeting CD20 could provide a valid and appropriate approach for the treatment of some patients with MCD [3].

Rituximab, an anti-CD20 antibody, may cause durable remission of the disease, not only in HHV-8⁺ patients but also in HHV-8[−] ones, supporting a role for B lymphocytes in disease pathogenesis beyond their potential in providing a sanctuary for HHV-8 activation. Indeed, IL-6, a major mediator of CD symptomatology, can be produced by activated B lymphocytes [10]. In HHV-8[−] MCD patients, an unknown mechanism underlies the activation of B lymphocytes. B-cell lymphodepletion, leading to the inhibition of IL-6 production, could result in controlling disease activity.

Other Signaling Pathway Effectors: STAT, RAF, and Calcineurin

IL-6 signaling is mediated by its membrane-bound and soluble receptors. The binding of IL-6 to its receptor leads to homodimerization of gp130. Receptor activation results in transphosphorylation and activation of JAKs, which in turn triggers the phosphorylation of gp130 cytoplasmic tails, which serve as a docking site for STAT proteins, leading to the recruitment and activation of STATs. Phosphorylated STATs dimerize and translocate into the nucleus to promote the transcription of many key genes, such as the gene encoding the acute-phase reactant proteins, known to play a part in CD [10, 12]. Hence, interfering with IL-6 transduction by blocking downstream signals induced by the binding of IL-6 to its receptor, including STATs and JAKs, might have important implications in the management of MCD.

The role of the RAF in the MCD pathway is less clear. Akula et al. [36] demonstrated that VEGF expression by HHV-8–infected human B cells is mediated by the RAF pathway and that VEGF production can be aborted by using a mitogen-activated protein kinase/extracellular signal-related kinase kinase inhibitor [36]. Understanding whether the RAF pathway plays an essential role in the mechanism of CD requires further research.

Intracellular calcium mobilization in cell lines infected with HHV-8 can induce viral proliferation, an effect that could be blunted by a calcineurin inhibitor such as cyclosporine. Exploring the role of the calmodulin–calcineurin–nuclear factor of activated T cells pathway in the proliferation of HHV-8 [37] may make calcineurin a potential target for the antiviral proliferation of HHV-8.

SUMMARY

One simplified model for the pathophysiology of MCD is that HHV-8–infected cells, particularly plasmoblasts, secrete vIL-6, which in turn induces the production of VEGF, further enhancing vascular proliferation inside the tumor and human IL-6 production by endothelial cells. IL-6 excess results in lymphovascular proliferation and inflammatory systemic manifestations. In HHV-8[−] CD patients, uncharacterized factors can trigger IL-6 production. Among these factors, the activation of the IL-1–NF- κ B pathway appears to play a particularly important role in the production of its downstream target protein, IL-6, and hence warrants additional focused research effort (Fig. 1).

CURRENT THERAPEUTIC OPTIONS

In UCD patients, complete surgical excision of the affected lymph node affords a high cure rate [38, 39]. Radiotherapy could be a valuable alternative when complete resection of disease is technically difficult [40]. The management of MCD patients is more complicated and their prognosis is less favorable. Several therapeutic options have been employed in MCD patients with variable activity, although there is still no consensus regarding the gold standard therapeutic approach [2]. With a better understanding of the underlying biology of MCD, new approaches are under development.

Cytotoxic Chemotherapy

Most reports regarding the activity of antineoplastic agents in MCD patients are drawn from a few anecdotal cases and small case series. These data should be interpreted cautiously in the context of the nonuniformity of the response criteria, the infrequency of the disease, and the heterogeneity of the patient population.

In addition to the lack of randomized comparative trials, the scanty information available regarding duration of response and side effects of therapy confound interpreting the benefit of such treatment. Various single-agent cytotoxic drugs have been used to treat MCD patients, including chlorambucil, corticosteroids, cyclophosphamide, 2-chlorodeoxyadenosine, carmustine, vincristine, and bleomycin. Single-agent liposomal doxorubicin, oral etoposide, and vinblastine were reported to produce durable remission, predominantly in HIV⁺ patients [9, 41, 42]. Particular attention should be paid to this vulnerable population because of the risk for infection and the potential life-threatening interaction between antiretroviral therapy and antineoplastic drugs [4]. Multiple combinations of chemotherapy used to treat non-Hodgkin's lymphoma have also been tried in MCD patients, resulting in complete and partial responses (Table 1). These combinations include chlorambucil plus

Figure 1. Proposed unified model of the pathophysiology of CD representing the different known and suggested mechanisms involved in that disease. HHV-8–infected cells secrete vIL-6^a, which in turn enhances the production of VEGF by the nonlymphoid or plasma cell^b. VEGF induces vascular proliferation, a major component of MCD. The endothelium itself is a source of IL-6 production,^c thereby contributing to the systemic manifestations of MCD and further enhancing lymphocytic and vascular proliferation. In HHV-8[−] CD patients, an undefined upstream stimulus might be responsible for IL-6 production.^d We believe that the IL-1^e production by many cells, such as macrophage or follicular dendritic cells,^f induces the generation of IL-6 through the NF-κB signaling pathway. Dysregulation at any level can lead to overproduction of IL-6, which has a pivotal impact on the disease. Several key molecular functions may provide potential therapeutic targets in the management of Castleman's disease (i.e., siltuximab targeting IL-6, tocilizumab targeting IL-6R, steroid and bortezomib targeting the NF-κB pathway, rituximab targeting CD20⁺ lymphocytes, ganciclovir targeting HHV-8, cetuximab targeting EGFR on follicular dendritic cells, bevacizumab targeting VEGF receptor, anakinra targeting the IL-1 receptor). Of note, the black arrows represent an activation function, whereas the purple arrows represent blocking function.

Abbreviations: CD, Castleman's disease; EGFR, epidermal growth factor receptor; HHV-8, human herpes virus 8; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; IL-1R, IL-1 receptor; IL-6R, IL-6 receptor; MCD, multicentric Castleman's disease; NF-κB, nuclear factor κB; VEGF, vascular endothelial growth factor; vIL-6, viral IL-6.

prednisone; cyclophosphamide plus prednisone; cyclophosphamide plus procarbazine; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, doxorubicin, and dexamethasone; and high-dose melphalan followed by autologous stem cell transplantation [43, 44]. Complete remission resulting from the use of the antiparasitic agent suramin and an anti-H₂ agent was also reported [45].

Antiviral Agents

Anti-HHV-8 Therapy

Since its discovery in 1994, targeting HHV-8, a virus implicated in MCD, Kaposi's sarcoma and primary effusion lymphoma have been a research focus. The high degree of lytic replication of HHV-8 in MCD theoretically confers greater sensitivity to antiviral agents. Thus, targeting HHV-8 replication is another attractive approach for treating MCD patients

Table 1. Summary of studies of MCD patients treated with cytotoxic chemotherapy

Study	n of patients	Histology	HIV/HHV-8 status	Therapy	Response	Survival (mos)
Summerfield et al. (1983) [84]	1	HV	NA	Prednisone	PR	15+
	1	MV	NA	Prednisone	CR	61+
Frizzera et al. (1985) [85]	6	PC	NA	Steroid	6 PR	9, 10, 32, 39+, 42, 42+
	1	PC	NA	Steroid + COP	PR	5
	1	PC	NA	Steroid + COP, COP, vincristine	PR	14
	1	PC	NA	CHL	CR	116+
	1	PC	NA	Steroid, CVP	PR	30
	1	PC	NA	CVP	CR	138+
	1	PC	NA	CHL, CVP	PD	222
	1	PC	NA	CHL, CVP	PD	222
Weisenburger et al. (1985) [86]	6	PC	NA	Prednisone	4 PR, 2 PD	44+, 52+, 23, 29, 13, 36
	1	MV	NA	Prednisone	PR	8+
	1	HV	NA	COP + BLEO	CR	69
	1	PC	NA	CHL + prednisone	PR	5
Stanley et al. (1986) [87]	1	PC	NA	Prednisone	PR	15+
	1	PC	NA	CVP	PR	15+
Repetto et al. (1986) [44]	1	HV	NA	High-dose melphalan/PBSCT	CR	15+
Donaghy et al. (1989) [88]	1	PC	NA	COP + prednisolone	PR	53+
	1	PC	NA	Prednisolone	PD	1
	1	PC	NA	COP + Prednisolone	PR	2+
Pavlidis et al. (1990) [89]	1	PC	NA	CHL + prednisolone	CR	30+
Bordeleau et al. (1995) [90]	1	HV	NA	2-CDA	CR	9+
	1	PC	NA	2-CDA	PR	9+
	1	PC	NA	Fludarabine	SD	9+
Barbounis and Efremidis (1996) [45]	1	PC	NA	Cimetidine	CR	5+
Oksenhendler et al. (1996) [9]	9	MV	+/NA	VBN	9 PR	5+, 9, 10+, 14, 15+, 17, 25, 27+, 33+
	2	MV	+/NA	COP	2 PR	1, 25
	1	PC	+/NA	COP	1 PR	7
	4	3 PC, 1 MV	+/NA	ABV	3 PR, 1 PD	1, 7, 9, 39
Herrada et al. (1998) [38]	1	PC	NA	CHOP	CR	8+
	1	PC	NA	CHOP	PD	34
	1	HV	NA	CVAD	CR	58+
	2	MV	NA	Prednisone	CR	8+, 35+
	1	PC	NA	CHL + prednisone	CR	8+
Bowne et al. (1999) [39]	1	PC	N/A	Prednisone, VBN, COP, BCNU	PD	4
	1	HV	N/A	Pulse steroid, suramin	PR	46+
	1	HV	N/A	Prednisone	PD	70+

(continued)

Table 1. (Continued)

Study	n of patients	Histology	HIV/HHV-8 status	Therapy	Response	Survival (mos)
Chronowski et al. (2001) [40]	2	MV	NA	CVAD	2 PD	30+, 68+
	1	PC	NA	CVAD	CR	119+
	1	MV	NA	CVAD, CHOP	PD	12+
	1	HV	NA	CVAD, CHOP	PD	113+
					CR	
	1	PC	NA	CHOP, steroid	PD	30+
					PD	
	1	PC	NA	CHOP, MINE	PD	65+
					CR	
	2	MV	NA	CHL + prednisone	1 CR, 1 PR	100+, 32+
Scott et al. (2001) [41]	2	PC	+/+	Oral VP16	CR	12+, 6+
Colleoni et al. (2003) [91]	1	PC	−/−	2-CDA	CR	36
	1	HV	−/+	2-CDA	PD	19
	1	MV	−/+	2-CDA	CR	36
Loi et al. (2004) [42]	2	NA	+/NA	Liposomal doxorubicin	1 CR, 1 PR	10, 11
	1	NA	+/NA	CVP	PR	32
				Doxorubicin	CR	
	2	NA	+/NA	CHL	2 CR	9, 25
	1	NA	+/NA	VINC + BLEO + VBN	PR	43+
				Steroid	PD	
				Liposomal doxorubicin	CR	
	1	NA	+/NA	CHL + Prednisone	PD	1
	1	NA	+/NA	VINC + BLEO + VBN	CR	48+
Ogita et al. (2007) [43]	1	PC	−NA	High-dose melphalan + PBSCT	CR	42+
Park et al. (2007) [92]	1	HV	−/−	Prednisolone	PR	1+
Seo et al. (2009) [93]	1	PC	−/−	CHOP	CR	24+
Lee et al. (2010) [94]	1	PV	−/NA	CHOP, steroids	PD	0.5

Abbreviations: 2-CDA, cladribine; ABV, doxorubicin, bleomycin, and vinblastine; BCNU, carmustine; Bleo, bleomycin; CHL, chlorambucil; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; COP, cyclophosphamide; CR, complete response; CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; CVP, cyclophosphamide, vincristine, and prednisone; HHV, human herpes virus; HV, hyaline-vascular; MCD, multicentric Castleman's disease; MINE, mesna, ifosfamide, mitoxantrone, and etoposide; MV, mixed variant; NA, not available; PBSCT, peripheral blood stem cell transplantation; PC, plasma cell; PD, progressive disease; PR, partial response; SD, stable disease; VBN, vinblastine; Vinc, vincristine; VP16, etoposide.

[46–54]. Ganciclovir, foscarnet, and cidofovir are the only antiviral agents that have in vitro activity against HHV-8 [47–49]. In a series of three patients with HIV-associated CD, two achieved durable remission after treatment with valganciclovir and oral and i.v. ganciclovir. Although the third patient had

a good response to i.v. ganciclovir, he died a few days after treatment from a fungal infection. Interestingly, clinical responses in all three cases coincided with the suppression of viral replication parameters [50, 51]. In contrast, cidofovir failed to sustain remission in all five HIV⁺ chemotherapy-dependent

Table 2. Summary of studies of MCD patients treated with interferon

Study	n of patients	Histology	HIV/HHV-8 status	Associated treatment	Dose	Response	Survival (month)
Feremans and Khodadadi (1987) [56]	1	NA	NA/NA	None	5 MU 3× weekly	CR	4+
Rossi et al. (1988) [95]	1	NA	–/NA	None	9 MU daily	CR	3
Pavlidis et al. (1992) [96]	1	PC	NA	None	5 MU 3× weekly	CR	12+
Tamayo et al. (1995) [57]	1	PC	–/NA	None	3 MU 3× weekly	CR	45+
Oksenhendler et al. (1996) [9]	3	MV	+/NA	None	2 MU 3× weekly	2 CR, 1 PD	5+, 15+, 27+
Andrès and Maloïsel (2000) [59]	1	NA	–/NA	None	4.5 MU 3× weekly	CR	42+
Kumari et al. (2000) [58]	1	NA	+/+	None	5 MU 3× weekly	CR	24+
Nord et al. (2003) [97]	1	NA	+/NA	None	5 MU 3× weekly	CR	12+

Abbreviations: CR, complete response; HHV, human herpes virus; HV, hyaline-vascular; MCD, multicentric Castleman's disease; MV, mixed variant; NA, not available; PC, plasma cell; PD, progressive disease; PR, partial response.

patients in a subsequent series. More importantly, cidofovir failed to reduce the HHV-8 viral load in peripheral blood mononuclear cells [51]. Collectively, these data highlight the importance of HHV-8 replication in CD. The conflicting clinical results obtained thus far will require explanation through future controlled trials to define the place of antiviral treatment in the therapeutic armamentarium of the disease.

Highly Active Antiretroviral Therapy

The implementation of highly active antiretroviral therapy (HAART) to treat HIV/AIDS has altered the natural history of HIV and dramatically boosted survival. In patients with HIV and MCD, MCD exacerbation during the initiation of HAART has been reported and was attributed to immune reconstitution syndrome [52]. Nevertheless, the overall survival rate is remarkably higher and the progression rate to lymphoma has been 10–20 times lower in HIV-related MCD since the introduction of HAART therapy [53–55]. Whether this is a result of HAART or the use of new chemotherapy for CD remains unclear.

Immunomodulators

Interferon- α

Significant clinical benefits have been described from single-agent interferon- α for treating patients with Castleman's disease (Table 2). It was used initially in HIV⁺ patients, but later was found to be beneficial for HIV[–] patients. One case complicated by pancytopenia required treatment interruption [56],

even though interferon was well tolerated in most cases. Interestingly, interferon- α was successful in yielding long-term complete remission in patients off treatment for as long as 4 years [57]. The precise underlying mechanisms of these salutary outcomes have not been fully characterized but could be a result of several diverse biologic effects of interferon, including inhibition of trans-signaling via downregulation of IL-6R, antiviral effects such as inhibition of HHV-8 replication, and upregulation of human leukocyte antigen class 1 expression on HHV-8–infected cells leading to cell-mediated destruction [58, 59].

Corticosteroids

Variable benefit has been achieved with the use of corticosteroid agents. They are rarely administered as single agents to palliate symptoms before proceeding with more aggressive chemotherapy because steroid-induced remission is usually short lived [2, 60]. Assessing their benefit in MCD patients has been hampered by their use in combination with cytotoxic drugs. Moreover, the lack of information regarding the usual side effects of steroids, such as a higher risk for infection, osteoporosis, and metabolic abnormalities, make it difficult to estimate their impact in managing the disease.

Thalidomide

Thalidomide is part of the therapeutic arsenal in plasma cell malignancies, particularly multiple myeloma,

Table 3. Use of thalidomide for treating CD

Study	n of patients	Histology	HIV/HHV-8 status	Associated treatment	Dose	Response	Survival (mos)
Jung et al. (2004) [98]	1	NA	+ / +	VP16	200 mg qd	CR	9+
Starkey et al. (2006) [99]	1	NA	– / –	None	200 to 400 mg qd	PR	40+
Stary et al. (2008) [64]	1	Plasmablastic	+ / +	Rituximab	100 to 20 mg qd	CR	12+
Miltenyi et al. (2009) [63]	1	MV	– / –	Steroid and cyclosporine	200 mg qd	PR	48+

Abbreviations: CD, Castleman's disease; CR, complete response; HHV, human herpes virus; MV, mixed variant; PR, partial response; qd: once daily; VP16, etoposide.

wherein IL-6 plays a central role in disease activity [61]. Several encouraging reports indicate a beneficial effect of thalidomide in patients with MCD (Table 3). Thalidomide was shown to selectively downregulate the expression of IL-6 and tumor necrosis factor in peripheral blood monocyte cells from healthy volunteers [62]. Its therapeutic value in CD patients might therefore result from disrupting IL-6 production. In a patient with CD associated with pemphigus vulgaris, the IL-6 level decreased significantly concordantly with clinical improvement [63]. Other reports demonstrated a decline in the level of CRP, a surrogate of IL-6 activity [64].

Targeted Therapy

Targeting CD20 by Rituximab

Rituximab is a monoclonal chimeric antibody that targets CD20 on B cells, leading to B-cell lymphodepletion via activating complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity [65]. Rituximab was first introduced as a treatment for HIV⁺HHV-8⁺ patients with MCD. To date, treatment with rituximab has been effective in both HIV⁺ and HIV[–] patients (Table 4). Durable responses were achieved with rituximab used as a single agent and in combination with cytotoxic chemotherapy. In a prospective study of 24 HIV⁺ patients with chemotherapy-dependent MCD, rituximab was administered once weekly for four doses. At day 60, 22 patients had a sustained remission (92%), and 17 had a sustained remission at 1 year (71%). One patient died during treatment from disease progression, another died following acute respiratory failure. Five patients relapsed, one during treatment. Rituximab was well tolerated and most adverse events were mild-to-moderate infection and minor exacerbation of cutaneous lesions in eight of 12 patients with Kaposi's sarcoma (66%) [66].

A more recent prospective study included 21 HIV⁺ patients with plasmoblastic type MCD. One patient died before completing the trial, 14 achieved a partial response (67%), and 29% had stable disease. The 2-year overall survival rate was 95% and the progression-free survival rate was 92% at 1 year and 79% at 2 years. Interestingly, rituximab therapy in that study was associated with a decline in the HHV-8 viral load, as well as in IL-10 and IL-6 levels after treatment completion. No severe toxicity was recorded, even though Kaposi's sarcoma progressed during treatment in four of 11 patients (36%) with cutaneous disease [67].

For that reason, some investigators recommend avoiding, or at least delaying, the use of rituximab in patients with uncontrolled HIV replication or active Kaposi's sarcoma lesions [54].

Similarly, Marcelin et al. [65] investigated the therapeutic effect of rituximab in five HIV⁺ and HHV-8⁺ patients. Of these, two patients died quickly after initiation of treatment, and three had complete remissions after a follow-up period of 4–14 months. Clinical response was associated with a decrease in viral load.

Rituximab has also been used successfully in other circumstances, such as in UCD [68], MCD associated with autoimmune phenomenon [69], and POEMS [70].

Targeting IL-6 or IL-6R

In recent years, the promising preclinical and clinical efficacy exhibited by targeting IL-6 or IL-6R has confirmed IL-6 as an important target in the treatment of CD. Initial evidence was examined by Beck et al. [71], who reported a case of MCD associated with elevated IL-6 levels and treated with BE-8, a murine anti-IL-6 monoclonal antibody. All clinical and laboratory abnormalities improved rapidly after initiation of treatment. However, the disease relapsed after termination of treatment [71]. The short half-

Table 4. Summary study of MCD patients treated with rituximab

Study	n of patients	Histology	HIV/HHV-8 status	Associated treatment	Response	Survival (mos)
Corbellino et al. (2001) [100]	1	NA	+/+	None	CR	14+
Hudnall et al. (2003) [70]	1	HV	NA/+	None	PR	NA
Marcelin et al. (2003) [65]	5	NA	+/+	None	3 CR, 2 PD	4+, 6+, 14+, 1, 1
Marrache et al. (2003) [101]	1	PC	+/+	None	CR	6+
Abdou and Salib (2004) [102]	1	HV	–/NA	COP	CR	24+
Gholam et al. (2003) [103]	1	PC	–/–	None	PR	2
Kofteridis et al. (2004) [104]	1	NA	+/-	None	PR	12+
Newsom-Davis et al. (2004) [105]	1	HV	+/+	None	PR	4+
Estephan et al. (2005) [68]	1	HV	N/A	None	CR	2+
Neuville et al. (2005) [106]	2	NA	+/+	VP16	2 PD	22+, 32+
Ocio et al. (2005) [69]	1	MV	–/–	None	CR	14+
Casquero et al. (2006) [107]	1	MV	+/NA	None	CR	10+
Ide et al. (2006) [108]	2	HV	–/–	None	2 CR	40+, 16+
Bower et al. (2007) [67]	1	PC	–/–	None	1 PR	10+
	21	Plasmablastic	+/9+, 2–, 10 NA	None	14 PR, 6 SD	24+ (n = 20), 1 (n = 1)
Gérard et al. (2007) [66]	24	NA	+/+	None (all had chemotherapy-dependent remission)	22 SR	12+ (n = 22), 1 (n = 1), 4 (n = 1)
Fragasso et al. (2008) [109]	1	MV	–/+	CVP	CR	16+

Abbreviations: COP, cyclophosphamide; CR, complete response; CVP, cyclophosphamide, vincristine, and prednisone; HHV, human herpes virus; HV, hyaline-vascular; MCD, multicentric Castleman's disease; MV, mixed variant; PC, plasma cell; PD, progressive disease; PR, partial response; SD, stable disease; SR, sustained remission; VP16, etoposide.

life of the murine monoclonal antibody and its neutralization by human anti-mouse antibody could explain why murine monoclonal antibodies produced only a transient response. To overcome these limitations, humanized and chimeric monoclonal antibodies with longer half-lives and a lesser degree of immunogenicity were later developed.

Immediate symptom relief and improvement in biochemical abnormalities were seen with the use of the humanized anti-IL-6R rhPM-1 in seven patients with CD, three of whom had amyloidosis. Treatment was well tolerated with only transient leukopenia. However, the disease

flared up right after discontinuation of treatment [72]. In another trial conducted by Nishimoto et al. [73], tocilizumab, a humanized anti-IL-6R monoclonal antibody, was studied in 28 patients with HIV[–] CD. Reversal of inflammatory parameters, alleviation of constitutional symptoms, and reduction in the degree of lymphadenopathy were observed. Treatment was well tolerated, with only some minor-to-moderate reactions, and 27 patients (96.4%) continued to receive tocilizumab treatment for >3 years. Of 15 patients taking corticosteroids at the initiation of treatment, 11 were able to reduce the dose of or discontinue corticosteroid

treatment [73]. This molecule is approved in Japan for Castleman's disease.

Another anti-IL-6-based therapy that has been tried is siltuximab, a chimeric murine monoclonal antibody neutralizing IL-6. Interim results from a phase I trial with siltuximab in patients with HIV⁺HHV-8⁺ CD are available from 23 patients, all but one of whom had MCD [74]. None of those patients had drug-limiting toxicity and the treatment was well tolerated at a dose of up to 12 mg/kg weekly. Eighteen of the 23 patients (78%) achieved a clinical benefit response. Objective tumor responses were seen in 12 patients (52%). In the subgroup of patients treated at the 12-mg/kg dose level every 1, 2, or 3 weeks, eight of 12 patients achieved an objective tumor response (73%). A separate report described a striking complete response in a patient with a refractory cutaneous form of CD after receiving six doses of CNTO-328 [75].

Targeting the Proteasome by Bortezomib

Bortezomib was approved in 2003 for the treatment of relapsed and refractory multiple myeloma. Encouraging outcomes with the use of bortezomib in CD patients were illustrated in two case reports. A 48-year-old female patient with refractory MCD had a complete remission for >1 year after treatment with bortezomib [76]. A 49-year-old male patient with POEMS associated with MCD was treated with six cycles of bortezomib along with dexamethasone [77]. He experienced a complete remission, which was sustained >4 years after treatment discontinuation. Bortezomib was well tolerated in both patients. A key finding in both reports was that lower IL-6 levels after treatment with bortezomib correlated with treatment response, indicating that the therapeutic benefit of bortezomib results partly from the inhibition of IL-6 production. Indeed, bortezomib, by inhibiting the proteasome pathway, blocks the degradation of I- κ B, which in turn inhibits the NF- κ B pathway that induces the expression of numerous proinflammatory proteins, including IL-6 [78]. Both cases were HHV-8⁺. The safety of its use in HHV-8-associated MCD remains to be defined.

Targeting IL-1 or IL-1R

Targeting the IL-1 pathway was shown to be effective in several IL-6-driven diseases such as Still's disease and systemic onset juvenile rheumatoid arthritis [79]. IL-1 activates the NF- κ B pathway once it is bound to its receptor. This, in turn, upregulates the expression of multiple inflammatory proteins implicated in the pathogenesis of CD, particularly IL-6 [33]. An attractive approach would be to antagonize the IL-1 pathway to control disease by decreasing IL-6 production.

Anakinra, a recombinant IL-1R antagonist, is approved

by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis. It has a good adverse events profile. It was reportedly used with success for the first time in a 13-year-old boy with refractory MCD [80]. Our group showed that treatment of a 62-year-old patient with refractory MCD using anakinra led to a rapid and durable resolution of clinical symptoms and laboratory abnormalities [35].

THERAPEUTIC APPROACH FOR PATIENTS WITH MCD AND FUTURE DIRECTIONS

Defining firm recommendations to approach the treatment of MCD is difficult for a disease that is rare and heterogeneous, in which the literature is confined to case reports and small case series. Clinical judgment, physician experience, and patient preferences are of major importance in the treatment-planning process.

In HIV⁺ MCD patients, our approach is to initiate treatment with an IL-6R monoclonal antibody based on its remarkable tolerability and efficacy in the disease and to continue such treatment as far as a clinical benefit is derived. In cases of nonresponse, many options are available. Aggressive combination chemotherapy such as CHOP might be used to induce remission in a selected subset of patients with a good performance status and aggressive disease. Otherwise, the use of single-agent chemotherapy with or without steroids could be pursued. Rituximab can be combined with cytotoxic chemotherapy or used as a single agent when the disease is not life threatening, given the delay in action. It can also be used for maintenance treatment for chemotherapy-dependent disease.

In refractory cases, the use of other drugs proven to be effective in case reports or referral for a clinical trial, if available, is recommended. Autologous stem cell transplantation can be discussed in transplant candidate patients refractory to other treatment.

A particular approach in the HIV⁺ population was recently proposed—induction by i.v. etoposide followed by rituximab, etoposide, and valgancyclovir if CD4 is >50/mm³, HIV-RNA is <50 copies/ml, and there is no active Kaposi's sarcoma. Rituximab should be avoided in patients with uncontrolled HIV replication, a low CD4 count, or active Kaposi's sarcoma lesions. Early initiation of HAART is warranted, and maintenance treatment with valgancyclovir can be considered [54]. The use of liposomal doxorubicin for induction is also a reasonable approach that deserves further exploration [42].

Recently, several other molecular targets implicated in the pathogenesis of CD were identified, including IL-1, EGFR, VEGF, RAF, NF- κ B, STAT3, HIF- α , the mTOR-PI3K pathway, and calcineurin. A more personalized ap-

proach using targeted therapy directed at the underlying molecular abnormalities driving the disease can hopefully lead to more optimal and less toxic promising therapeutic strategies in the future.

CONCLUSION

CD is an example of a disease for which understanding the biology has informed effective drug development. To date, deregulated overproduction of IL-6 is suspected to drive the disease. HHV-8 is also apparently involved in the pathophysiology of MCD via production of vIL-6. Other promising molecular targets were recently identified but not exploited yet. Cytotoxic chemotherapy with or without steroidal agents has been widely used, with varying degrees of response. Currently, good results have been realized through targeting HHV-8 replication, CD20, and IL-6 pathways. The anti-IL-6R antibody tocilizumab is an effective treatment that has been approved in Japan for CD treatment [81]. Siltuximab, an anti-IL-6 antibody, is also highly effective and is currently in prospective trials in the U.S. and elsewhere [82, 83]. Side effects are few to none. Rituximab has produced durable responses.

Many other targeted agents, particularly the recombinant IL-1R antagonist anakinra, bortezomib, and thalidomide, have been used with success and with minimal side effects, albeit in a small number of cases. Future strategies may involve combining effective agents, and determining whether patients with concomitant POEMS require a distinct approach.

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REFERENCES

- 1 Castleman B, Towne VW. Case records of the Massachusetts General Hospital; weekly clinicopathological exercises; founded by Richard C. Cabot. *N Engl J Med* 1954;251:396–400.
- 2 Casper C. The aetiology and management of Castleman disease at 50 years: Translating pathophysiology to patient care. *Br J Haematol* 2005; 129:3–17.
- 3 Dupin N, Diss TL, Kellam P et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. *Blood* 2000;95:1406–1412.
- 4 Dham A, Peterson BA. Castleman disease. *Curr Opin Hematol* 2007;14: 354–359.
- 5 Larroche C, Cacoub P, Godeau P. [Castleman's disease]. *Rev Med Interne* 1996;17:1003–1013.
- 6 Waterston A, Bower M. Fifty years of multicentric Castleman's disease. *Acta Oncol* 2004;43:698–704.
- 7 Nasti G, Talamini R, Antinori A et al. AIDS-related Kaposi's sarcoma: Evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group Staging System in the HAART Era—the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naïve From Antiretrovirals. *J Clin Oncol* 2003;21:2876–2882.
- 8 Powles T, Stebbing J, Bazeos A et al. The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. *Ann Oncol* 2009;20:775–779.
- 9 Oksenhendler E, Duarte M, Soulier J et al. Multicentric Castleman's disease in HIV infection: A clinical and pathological study of 20 patients. *AIDS* 1996;10:61–67.
- 10 Nishimoto N, Kishimoto T. Interleukin 6: From bench to bedside. *Nat Clin Pract Rheumatol* 2006;2:619–626.
- 11 Vinzio S, Ciarloni L, Schlienger JL et al. Isolated microcytic anemia disclosing a unicentric Castleman disease: The interleukin-6/hepcidin pathway? *Eur J Intern Med* 2008;19:367–369.
- 12 Hong DS, Angelo LS, Kurzrock R. Interleukin-6 and its receptor in cancer: Implications for translational therapeutics. *Cancer* 2007;110:1911–1928.
- 13 Brandt SJ, Bodine DM, Dunbar CE et al. Dysregulated interleukin 6 expression produces a syndrome resembling Castleman's disease in mice. *J Clin Invest* 1990;86:592–599.
- 14 Katsume A, Saito H, Yamada Y et al. Anti-interleukin 6 (IL-6) receptor antibody suppresses Castleman's disease like symptoms emerged in IL-6 transgenic mice. *Cytokine* 2002;20:304–311.
- 15 Yoshizaki K, Matsuda T, Nishimoto N et al. Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. *Blood* 1989;74:1360–1367.
- 16 Chang Y, Cesarman E, Pessin MS et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994; 266:1865–1869.
- 17 Sullivan RJ, Pantanowitz L, Casper C et al. HIV/AIDS: Epidemiology, pathophysiology, and treatment of Kaposi sarcoma-associated herpesvirus disease: Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. *Clin Infect Dis* 2008;47:1209–1215.
- 18 Soulier J, Grollet L, Oksenhendler E et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. *Blood* 1995;86:1276–1280.
- 19 Radkov SA, Kellam P, Boshoff C. The latent nuclear antigen of Kaposi sarcoma-associated herpesvirus targets the retinoblastoma-E2F pathway and with the oncogene Hras transforms primary rat cells. *Nat Med* 2000; 6:1121–1127.

- 20 Friborg J Jr, Kong W, Hottiger MO et al. p53 inhibition by the LANA protein of KSHV protects against cell death. *Nature* 1999;402:889–894.
- 21 Sullivan R, Dezube BJ, Koon HB. Signal transduction targets in Kaposi's sarcoma. *Curr Opin Oncol* 2006;18:456–462.
- 22 Field N, Low W, Daniels M et al. KSHV vFLIP binds to IKK- γ to activate IKK. *J Cell Sci* 2003;116:3721–3728.
- 23 Sun Q, Zachariah S, Chaudhary PM. The human herpes virus 8-encoded viral FLICE-inhibitory protein induces cellular transformation via NF- κ B activation. *J Biol Chem* 2003;278:52437–52445.
- 24 Neipel F, Albrecht JC, Ensser A et al. Human herpesvirus 8 encodes a homolog of interleukin-6. *J Virol* 1997;71:839–842.
- 25 Adam N, Rabe B, Suthaus J et al. Unraveling viral interleukin-6 binding to gp130 and activation of STAT-signaling pathways independently of the interleukin-6 receptor. *J Virol* 2009;83:5117–5126.
- 26 Aoki Y, Jaffe ES, Chang Y et al. Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. *Blood* 1999;93:4034–4043.
- 27 Bais C, Santomasso B, Coso O et al. G-protein-coupled receptor of Kaposi's sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator. *Nature* 1998;391:86–89.
- 28 Nishi J, Arimura K, Utsunomiya A et al. Expression of vascular endothelial growth factor in sera and lymph nodes of the plasma cell type of Castleman's disease. *Br J Haematol* 1999;104:482–485.
- 29 Foss HD, Araujo I, Demel G et al. Expression of vascular endothelial growth factor in lymphomas and Castleman's disease. *J Pathol* 1997;183:44–50.
- 30 Cohen T, Nahari D, Cerem LW et al. Interleukin 6 induces the expression of vascular endothelial growth factor. *J Biol Chem* 1996;271:736–741.
- 31 Sun X, Chang KC, Abruzzo LV et al. Epidermal growth factor receptor expression in follicular dendritic cells: A shared feature of follicular dendritic cell sarcoma and Castleman's disease. *Hum Pathol* 2003;34:835–840.
- 32 Gherardi RK, Bélec L, Fromont G et al. Elevated levels of interleukin-1 beta (IL-1 beta) and IL-6 in serum and increased production of IL-1 beta mRNA in lymph nodes of patients with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome. *Blood* 1994;83:2587–2593.
- 33 Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol* 2009;27:519–550.
- 34 Hallegua DS, Weisman MH. Potential therapeutic uses of interleukin 1 receptor antagonists in human diseases. *Ann Rheum Dis* 2002;61:960–967.
- 35 El-Osta H, Janku F, Kurzrock R. Successful treatment of Castleman's disease with interleukin-1 receptor antagonist (anakinra). *Mol Cancer Ther* 2010;9:1485–1488.
- 36 Akula SM, Ford PW, Whitman AG et al. B-Raf-dependent expression of vascular endothelial growth factor-A in Kaposi sarcoma-associated herpesvirus-infected human B cells. *Blood* 2005;105:4516–4522.
- 37 Zoetewij JP, Moses AV, Rinderknecht AS et al. Targeted inhibition of calcineurin signaling blocks calcium-dependent reactivation of Kaposi sarcoma-associated herpesvirus. *Blood* 2001;97:2374–2380.
- 38 Herrada J, Cabanillas F, Rice L et al. The clinical behavior of localized and multicentric Castleman disease. *Ann Intern Med* 1998;128:657–662.
- 39 Bowne WB, Lewis JJ, Filippa DA et al. The management of unicentric and multicentric Castleman's disease: A report of 16 cases and a review of the literature. *Cancer* 1999;85:706–717.
- 40 Chronowski GM, Ha CS, Wilder RB et al. Treatment of unicentric and multicentric Castleman disease and the role of radiotherapy. *Cancer* 2001;92:670–676.
- 41 Scott D, Cabral L, Harrington WJ Jr. Treatment of HIV-associated multicentric Castleman's disease with oral etoposide. *Am J Hematol* 2001;66:148–150.
- 42 Loi S, Goldstein D, Clezy K et al. Castleman's disease and HIV infection in Australia. *HIV Med* 2004;5:157–162.
- 43 Ogita M, Hoshino J, Sogawa Y et al. Multicentric Castleman disease with secondary AA renal amyloidosis, nephrotic syndrome and chronic renal failure, remission after high-dose melphalan and autologous stem cell transplantation. *Clin Nephrol* 2007;68:171–176.
- 44 Repetto L, Jaiprakash MP, Selby PJ et al. Aggressive angiofollicular lymph node hyperplasia (Castleman's disease) treated with high dose melphalan and autologous bone marrow transplantation. *Hematol Oncol* 1986;4:213–217.
- 45 Barbounis V, Efremidis A. A plasma cell variant of Castleman's disease treated successfully with cimetidine. Case report and review of the literature. *Anticancer Res* 1996;16:545–547.
- 46 Hudson TJ, Edlund MJ, Steffick DE et al. Epidemiology of regular prescribed opioid use: Results from a national, population-based survey. *J Pain Symptom Manage* 2008;36:280–288.
- 47 Casper C. New approaches to the treatment of human herpesvirus 8-associated disease. *Rev Med Virol* 2008;18:321–329.
- 48 Friedrichs C, Neyts J, Gaspar G et al. Evaluation of antiviral activity against human herpesvirus 8 (HHV-8) and Epstein-Barr virus (EBV) by a quantitative real-time PCR assay. *Antiviral Res* 2004;62:121–123.
- 49 Neyts J, De Clercq E. Antiviral drug susceptibility of human herpesvirus 8. *Antimicrob Agents Chemother* 1997;41:2754–2756.
- 50 Casper C, Nichols WG, Huang ML et al. Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment. *Blood* 2004;103:1632–1634.
- 51 Berezne A, Agbalika F, Oksenhendler E. Failure of cidofovir in HIV-associated multicentric Castleman disease. *Blood* 2004;103:4368–4369; author reply 4369.
- 52 Zietz C, Bogner JR, Goebel FD et al. An unusual cluster of cases of Castleman's disease during highly active antiretroviral therapy for AIDS. *N Engl J Med* 1999;340:1923–1924.
- 53 Aaron L, Lidove O, Yousry C et al. Human herpesvirus 8-positive Castleman disease in human immunodeficiency virus-infected patients: The impact of highly active antiretroviral therapy. *Clin Infect Dis* 2002;35:880–882.
- 54 Oksenhendler E. HIV-associated multicentric Castleman disease. *Curr Opin HIV AIDS* 2009;4:16–21.
- 55 Oksenhendler E, Boulanger E, Galicier L et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood* 2002;99:2331–2336.
- 56 Feremans WW, Khodadadi E. Alpha-interferon therapy in refractory angioimmunoblastic lymphadenopathy. *Eur J Haematol* 1987;39:91.
- 57 Tamayo M, Gonzalez C, Majado MJ et al. Long-term complete remission after interferon treatment in a case of multicentric Castleman's disease. *Am J Hematol* 1995;49:359–360.
- 58 Kumari P, Schechter GP, Saini N et al. Successful treatment of human immunodeficiency virus-related Castleman's disease with interferon-alpha. *Clin Infect Dis* 2000;31:602–604.
- 59 Andrs E, Maloisel F. Interferon-alpha as first-line therapy for treatment of multicentric Castleman's disease. *Ann Oncol* 2000;11:1613–1614.

- 60 Dispenzieri A, Gertz MA. Treatment of Castleman's disease. *Curr Treat Options Oncol* 2005;6:255–266.
- 61 Singhal S, Mehta J, Desikan R et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999;341:1565–1571.
- 62 Shannon E, Noveck R, Sandoval F et al. Thalidomide suppressed interleukin-6 but not tumor necrosis factor-alpha in volunteers with experimental endotoxemia. *Transl Res* 2007;150:275–280.
- 63 Miltenyi Z, Toth J, Gonda A et al. Successful immunomodulatory therapy in Castleman disease with paraneoplastic pemphigus vulgaris. *Pathol Oncol Res* 2009;15:375–381.
- 64 Stary G, Kohrgruber N, Herneth AM et al. Complete regression of HIV-associated multicentric Castleman disease treated with rituximab and thalidomide. *AIDS* 2008;22:1232–1234.
- 65 Marcelin AG, Aaron L, Mateus C et al. Rituximab therapy for HIV-associated Castleman disease. *Blood* 2003;102:2786–2788.
- 66 Gérard L, Bérezné A, Galicier L et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 Castlemab Trial. *J Clin Oncol* 2007;25:3350–3356.
- 67 Bower M, Powles T, Williams S et al. Brief communication: Rituximab in HIV-associated multicentric Castleman disease. *Ann Intern Med* 2007;147:836–839.
- 68 Estephan FF, Elghetany MT, Berry M et al. Complete remission with anti-CD20 therapy for unicentric, non-HIV-associated, hyaline-vascular type, Castleman's disease. *Cancer Invest* 2005;23:191.
- 69 Ocio EM, Sanchez-Guijo FM, Diez-Campelo M et al. Efficacy of rituximab in an aggressive form of multicentric Castleman disease associated with immune phenomena. *Am J Hematol* 2005;78:302–305.
- 70 Hudnall SD, Chen T, Brown K et al. Human herpesvirus-8-positive microvenular hemangioma in POEMS syndrome. *Arch Pathol Lab Med* 2003;127:1034–1036.
- 71 Beck JT, Hsu SM, Wijdenes J et al. Brief report: Alleviation of systemic manifestations of Castleman's disease by monoclonal anti-interleukin-6 antibody. *N Engl J Med* 1994;330:602–605.
- 72 Nishimoto N, Sasai M, Shima Y et al. Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. *Blood* 2000;95:56–61.
- 73 Nishimoto N. Clinical studies in patients with Castleman's disease, Crohn's disease, and rheumatoid arthritis in Japan. *Clin Rev Allergy Immunol* 2005;28:221–230.
- 74 Van Rhee F, Fayad L, Voorhees P et al. Siltuximab, a novel anti-interleukin-6 monoclonal antibody, for Castleman's disease. *J Clin Oncol* 2010;28:3701–3708.
- 75 Ahmed B, Tschen JA, Cohen PR et al. Cutaneous Castleman's disease responds to anti-interleukin-6 treatment. *Mol Cancer Ther* 2007;6:2386–2390.
- 76 Hess G, Wagner V, Kreft A et al. Effects of bortezomib on pro-inflammatory cytokine levels and transfusion dependency in a patient with multicentric Castleman disease. *Br J Haematol* 2006;134:544–545.
- 77 Sobas MA, Alonso Vence N, Dias Arias J et al. Efficacy of bortezomib in refractory form of multicentric Castleman disease associated to POEMS syndrome (MCD-POEMS variant). *Ann Hematol* 2010;89:217–219.
- 78 Rajkumar SV, Richardson PG, Hideshima T et al. Proteasome inhibition as a novel therapeutic target in human cancer. *J Clin Oncol* 2005;23:630–639.
- 79 Kalliolias GD, Liossis SNC. The future of the IL-1 receptor antagonist anakinra: From rheumatoid arthritis to adult-onset Still's disease and systemic-onset juvenile idiopathic arthritis. *Expert Opin Investig Drugs* 2008;17:349–359.
- 80 Galeotti C, Tran TA, Franchi-Abella S et al. IL-1 RA Agonist (anakinra) in the treatment of multifocal Castleman disease: Case report. *J Pediatr Hematol Oncol* 2008;30:920–924.
- 81 Medical News Today. 'Actemra(R)' - World's First Drug for Castleman's Disease - Launched in Japan. Available at <http://www.medicalnewstoday.com/articles/26049.php>, accessed March 8, 2011.
- 82 Vermeulen J, Qi M, Herring JB et al. A randomized, double-blind, placebo-controlled, study to assess siltuximab (CNTO-328, an anti-IL6) in patients with multicentric Castleman's disease [abstract TPS186]. Presented at the 2010 American Society of Clinical Oncology Annual Meeting, Chicago, IL, June 4–8, 2010.
- 83 ClinicalTrials.gov. A Study of the Safety and Efficacy of CNTO 328 in Combination With Best Supportive Care Compared to Best Supportive Care in Patients With Multicentric Castleman's Disease. Available at <http://www.clinicaltrials.gov/ct2/show/NCT01024036>, accessed March 8, 2011.
- 84 Summerfield GP, Taylor W, Bellingham AJ et al. Hyaline-vascular variant of angiofollicular lymph node hyperplasia with systemic manifestations and response to corticosteroids. *J Clin Pathol* 1983;36:1005–1011.
- 85 Frizzera G, Peterson BA, Bayrd ED et al. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease: Clinical findings and clinicopathologic correlations in 15 patients. *J Clin Oncol* 1985;3:1202–1216.
- 86 Weisenburger DD, Nathwani BN, Winberg CD et al. Multicentric angiofollicular lymph node hyperplasia: A clinicopathologic study of 16 cases. *Hum Pathol* 1985;16:162–172.
- 87 Stanley MW, Frizzera G, Dehner LP. Castleman's disease, plasma-cell type. Diagnosis of central nervous system involvement by cerebrospinal fluid cytology. *Acta Cytol* 1986;30:481–486.
- 88 Donaghy M, Hall P, Gawler J et al. Peripheral neuropathy associated with Castleman's disease. *J Neurol Sci* 1989;89:253–267.
- 89 Pavlidis NA, Skopouli FN, Bai MC et al. A successfully treated case of multicentric angiofollicular hyperplasia with oral chemotherapy (Castleman's disease). *Med Pediatr Oncol* 1990;18:333–335.
- 90 Bordeleau L, Bredeson C, Markman S. 2-Chloro-deoxyadenosine therapy for giant lymph node hyperplasia. *Br J Haematol* 1995;91:668–670.
- 91 Colleoni GW, Duarte LC, Kerbaux FR et al. 2-Chloro-deoxyadenosine induces durable complete remission in Castleman's disease but may accelerate its transformation to non-Hodgkin's lymphoma. *Acta Oncol* 2003;42:784–787.
- 92 Park JB, Hwang JH, Kim H et al. Castleman disease presenting with jaundice: A case with the multicentric hyaline vascular variant. *Korean J Intern Med* 2007;22:113–117.
- 93 Seo HY, Kim EB, Kim JW et al. Complete remission in a patient with human herpes virus-8 negative multicentric Castleman disease using CHOP chemotherapy. *Cancer Res Treat* 2009;41:104–107.
- 94 Lee JH, Kwon KA, Lee S et al. Multicentric Castleman disease complicated by tumor lysis syndrome after systemic chemotherapy. *Leuk Res* 2010;34:e42–e45.
- 95 Rossi JF, Fegueur N, Calvet B et al. Alpha-interferon in angioimmunoblastic lymphadenopathy. *Ann Intern Med* 1988;109:512–513.
- 96 Pavlidis NA, Briassoulis E, Klouvas G et al. Is interferon-a an active agent in Castleman's disease? *Ann Oncol* 1992;3:85–86.
- 97 Nord JA, Karter D. Low dose interferon-alpha therapy for HIV-associated multicentric Castleman's disease. *Int J STD AIDS* 2003;14:61–62.

- 98 Jung CP, Emmerich B, Goebel FD et al. Successful treatment of a patient with HIV-associated multicentric Castleman disease (MCD) with thalidomide. *Am J Hematol* 2004;75:176–177.
- 99 Starkey CR, Joste NE, Lee FC. Near-total resolution of multicentric Castleman disease by prolonged treatment with thalidomide. *Am J Hematol* 2006;81:303–304.
- 100 Corbellino M, Bestetti G, Scalapogno C et al. Long-term remission of Kaposi sarcoma-associated herpesvirus-related multicentric Castleman disease with anti-CD20 monoclonal antibody therapy. *Blood* 2001;98:3473–3475.
- 101 Marrache F, Larroche C, Mémain N et al. Prolonged remission of HIV-associated multicentric Castleman's disease with an anti-CD20 monoclonal antibody as primary therapy. *AIDS* 2003;17:1409–1410.
- 102 Abdou S, Salib H. An extra ordinary response of Castleman's disease to Rituximab. *Blood* 2004;104:49b–49b.
- 103 Gholam D, Vantelon JM, Al-Jijakli A et al. A case of multicentric Castleman's disease associated with advanced systemic amyloidosis treated with chemotherapy and anti-CD20 monoclonal antibody. *Ann Hematol* 2003;82:766–768.
- 104 Kofteridis DP, Tzagarakis N, Mixaki I et al. Multicentric Castleman's disease: Prolonged remission with anti CD-20 monoclonal antibody in an HIV-infected patient. *AIDS* 2004;18:585–586.
- 105 Newsom-Davis T, Bower M, Wildfire A et al. Resolution of AIDS-related Castleman's disease with anti-CD20 monoclonal antibodies is associated with declining IL-6 and TNF-alpha levels. *Leuk Lymphoma* 2004;45:1939–1941.
- 106 Neuville S, Agbalika F, Rabian C et al. Failure of rituximab in human immunodeficiency virus-associated multicentric Castleman disease. *Am J Hematol* 2005;79:337–339.
- 107 Casquero A, Barroso A, Fernández Guerrero ML et al. Use of rituximab as a salvage therapy for HIV-associated multicentric Castleman disease. *Ann Hematol* 2006;85:185–187.
- 108 Ide M, Kawachi Y, Izumi Y et al. Long-term remission in HIV-negative patients with multicentric Castleman's disease using rituximab. *Eur J Haematol* 2006;76:119–123.
- 109 Fragasso A, Mannarella C, Ciancio A et al. Complete remission and virologic response to combined chemoimmunotherapy (R-CVP) followed by rituximab maintenance in HIV-negative, HHV-8 positive patient with multicentric Castleman disease. *Leuk Lymphoma* 2008;49:2224–2226.