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Short Communication

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Siltuximab in Idiopathic Multicentric Castleman Disease: Real-World Experience

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Abstract

Background: Castleman disease (CD) is a very rare, non-malignant lymphoproliferative disorder that can be classified as unicentric or multicentric (MCD). MCD is associated with systemic symptoms, including organ dysfunction due to cytokine dysregulation, primarily interleukin-6 (IL-6). The anti-IL-6 monoclonal antibody siltuximab is recommended as a frontline treatment for idiopathic MCD (iMCD), but real-world data on its use in routine clinical practice are limited. This study aimed to assess disease response and survival outcomes in patients with iMCD treated with siltuximab therapy in real-world settings in Greece and Romania.

Methods: This retrospective cohort study included adult patients with iMCD treated with siltuximab in clinical practice across Greece and Romania between January 2017 and December 2022. The primary endpoint was overall response rate and secondary endpoints included survival and safety outcomes. Response assessments were performed according to the Castleman Disease Collaborative Network guidelines. Patients were followed until death, loss to follow-up or study conclusion (October 2023).

Results: Forty-eight patients with iMCD were included in the study. Mean age at baseline was 65 years, with significant age differences between patients from Greece (74 years) and Romania (54 years). The majority of patients were male (68.8%) and received one prior line of therapy (75%). Patients included in the study received a median of nine cycles of siltuximab. Response data were available for 38 patients. The overall response to siltuximab was 71.1%, with 55.3% of patients achieving a complete response, and 15.8% a partial response. The estimated overall survival rate at 3 years was 74% and the median survival was 123 months. The most common adverse events (> 5%) included elevated liver enzymes, anxiety, allergic reactions and nausea/diarrhea. Serious adverse events were experienced by 16.7% of the patients.

Conclusions: Our results suggest that siltuximab-based therapy is effective in treating iMCD in real-world settings in Greece and Romania. To our knowledge, this study represents the largest real-world analysis of siltuximab in European patients with iMCD so far.

Keywords: Idiopathic multicentric Castleman disease; Siltuximab; Anti-interleukin-6; Real-world evidence

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Introduction

Castleman disease (CD) is an extremely rare, non-malignant, lymphoproliferative disorder [1, 2]. Its estimated worldwide incidence is 5 - 16 per million people a year, depending on

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region [3], although accurate incidence rates in low- and middle-income countries are lacking. Until 2016, CD was poorly diagnosed and classified due to the lack of specific evidence-based diagnostic criteria [2].

CD can be unicentric (UCD) or multicentric (MCD), with the latter representing about 50% of diagnosed CD cases [4]. UCD has almost no symptoms, whereas MCD is characterized by systemic symptoms, enlarged lymph nodes, systemic inflammation, and organ dysfunction due to dysregulated secretion of cytokines (e.g., interleukin-6 (IL-6)) [5]. While the pathogenesis of UCD is thought to be driven by clonal expansion of lymph node stromal cells [2, 5], the etiology of MCD is less well understood. Infection with human herpes virus-8 (HHV-8) is considered to be the cause of 50% of MCD cases, and the remaining cases are either idiopathic MCD (iMCD) due to negative HHV-8 status and no other identified cause, or associated with polyneuropathy, organomegaly, endocrinopathy, M proteins, and skin changes (POEMS) [5]. IL-6 is known to play an important role in the pathogenesis of iMCD; many patients with iMCD overexpress IL-6 and respond to IL-6 inhibitors [2]. However, not all patients with iMCD have increased IL-6 levels and/or respond to anti-IL-6 therapy, suggesting the involvement of other cytokines [2].

The anti-IL-6 monoclonal antibody siltuximab is approved in over 40 countries for the treatment of iMCD [2] and is recommended by the Castleman Disease Collaborative Network (CDCN) as frontline therapy for iMCD, with or without adjunctive steroids, depending on severity [6]. Second-line treatment recommended by the CDCN includes rituximab plus steroids with or without an immunomodulatory agent in non-severe cases, or combination chemotherapy in severe cases of iMCD [6].

Due to the rarity of iMCD, it is important to report real-world data for patients treated with siltuximab in regions where modern therapies are available. Here, we report disease response and survival outcomes of patients with iMCD following therapy with siltuximab in a retrospective, real-world study conducted in Greece and Romania.

Materials and Methods

Study design and patient population

This retrospective cohort study included adult patients diagnosed with iMCD in Greek and Romanian centers between January 2017 and December 2022 and treated with siltuximab. The primary endpoint was overall response rate and secondary endpoints included survival and safety.

Diagnosis of iMCD was confirmed by expert pathologists who cross-checked all features of CD. Response to therapy was assessed in accordance with CDCN consensus guidelines. Treatment failure was defined as a newly appearing disease-related grade > 3 symptom according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE (version 4.0)), Eastern Cooperative Oncology Group score elevation of > 1 point, persistence of NCI-CTC-AE grade > 2 symptoms for ≥ 3 weeks, or radiological progression.

Patients were followed longitudinally until death, loss to follow-up, or end of study period (October 2023), whichever occurred first.

The study was conducted in accordance with the Declaration of Helsinki and approved by the respective Institutional Review Boards of the participating centers.

Study variables

Patient medical charts were checked for complete medical history, whole-body computed tomography (CT) or initial positron emission tomography, with MCD being confirmed when two or more lymph nodes were detected. Presenting symptoms were evaluated, with an emphasis on those related to IL-6 inflammatory response, such as prolonged fever, fatigue, weight loss and night sweats, in accordance with the NCI-CTCAE.

Laboratory examinations included a complete blood count with a differential count, human immunodeficiency virus and HHV-8 infections, using real-time polymerase chain reaction assessment.

Statistical analysis

Data are reported as mean and standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables. Differences in baseline characteristics were tested by Pearson's Chi-squared test, Wilcoxon rank sum exact test or Fisher's exact test. Differences in patient outcomes were tested by Fisher's exact test. Survival analysis was performed using the Kaplan-Meier method. P-values of < 0.05 were considered statistically significant and confidence intervals (CIs) were set to 95%. All analyses were performed using the R software (version 4.2.2 R).

Results

Patient characteristics

Overall, 48 patients with iMCD were included. All patients received siltuximab treatment at 11 mg/kg as a 1-h intravenous infusion administered every 3 weeks until treatment failure. Baseline characteristics of patients with iMCD are presented in Table 1. Overall, the mean (± SD) age of patients was 65 (± 19.0) years, with the mean age higher in Greece (74 (± 18.0) years) than in Romania (54 (± 14.0) years) ($P < 0.001$). There was a relative predominance of male patients (68.8%). The cohort had received a median of 1.5 prior lines of therapy, with 75% of patients receiving one prior line.

B symptoms were present in most patients at baseline: overall, 39.6% of patients had fever, 39.6% experienced night sweats, 62.5% reported weight loss and 68.8% asthenia, probably linked to the high presence of anemia (56.3%). Most patients had lung involvement (33.0%) as internal organ dissemination; other affected organs included the gastrointestinal tract (20.8%), kidney (8.3%) and thyroid gland (6.2%). All patients received supportive care, including treatment of constitution-

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Table 1. Baseline Characteristics and Details of Treatment

Variable	Cohort			P-value[a]
	Overall (N = 48)	Greece (n = 28)	Romania (n = 20)	
Sex, n/N (%)				0.082
Male	33/48 (68.8)	22/28 (78.6)	11/20 (55.0)	
Female	15/48 (31.3)	6/28 (21.4)	9/20 (45.0)	
Age (years), mean (SD)	65 (19.0)	74 (18.0)	54 (14.0)	< 0.001
Fever, n/N (%)				< 0.001
Yes	19/48 (39.6)	17/28 (60.7)	2/20 (10.0)	
No	27/48 (56.3)	9/28 (32.1)	18/20 (90.0)	
Unknown	2/48 (4.2)	0/20 (0.0)	2/28 (7.1)	
Night sweats, n/N (%)				0.47
Yes	19/48 (39.6)	12/28 (42.9)	7/20 (35.0)	
No	27/48 (56.3)	14/28 (50.0)	13/20 (65.0)	
Unknown	2/48 (4.2)	0/20 (0.0)	2/28 (7.1)	
Weight loss, n/N (%)				0.27
Yes	30/48 (62.5)	19/28 (67.9)	11/20 (55.0)	
No	16/48 (33.3)	7/28 (25.0)	9/20 (45.0)	
Unknown	2/48 (4.2)	2/28 (7.1)	0/20 (0.0)	
Asthenia, n/N (%)				0.67
Yes	33/48 (68.8)	19/28 (68.9)	14/20 (70.0)	
No	13/48 (27.1)	7/28 (25.0)	6/20 (30.0)	
Unknown	2/48 (4.2)	2/28 (7.1)	0/20 (0.0)	
Threatened end organ function: bowel ischemia due to bowel obstruction from enlarged node, n/N (%)				0.15
Yes	2/48 (4.2)	0/28 (0.0)	2/20 (10.0)	
No	44/48 (91.7)	26/28 (92.9)	18/20 (90.0)	
Unknown	2/48 (4.2)	2/28 (7.1)	0/20 (0.0)	
Threatened end organ function: renal failure/impairment due to ureteral obstruction by enlarged node, n/N (%)				0.63
Yes	3/48 (6.2)	2/28 (7.1)	1/20 (5.0)	
No	43/48 (89.6)	24/28 (85.7)	19/20 (95.0)	
Unknown	2/48 (4.2)	2/28 (7.1)	0/20 (0.0)	
Threatened end organ function: liver impairment, n/N (%)				0.50
Yes	7/48 (14.6)	3/28 (10.7)	4/20 (20.0)	
No	39/48 (81.5)	23/28 (82.1)	16/20 (80.0)	
Unknown	2/48 (4.2)	2/28 (7.1)	0/20 (0.0)	
Single mass, n/N (%)				0.42
Yes	2/48 (4.2)	0/20 (0.0)	2/28 (7.1)	
No	44/48 (91.7)	20/20 (100.0)	24/28 (85.7)	
Unknown	2/48 (4.2)	0/20 (0.0)	2/28 (7.1)	
Two or more masses, n/N (%)				0.17
Yes	40/48 (83.3)	21/28 (75.0)	19/20 (95.0)	
No	6/48 (12.5)	5/28 (17.9)	1/20 (5.0)	
Unknown	2/48 (4.2)	2/28 (7.1)	0/20 (0.0)	

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Table 1. Baseline Characteristics and Details of Treatment - *(continued)*

Variable	Cohort			P-value[a]
	Overall (N = 48)	Greece (n = 28)	Romania (n = 20)	
Splenomegaly, n/N (%)	29/48 (60.4)	9/20 (45.0)	20/28 (71.4)	0.065
Method for splenomegaly assessment n/N, (%)				< 0.001
Clinician	6/48 (12.5)	0/28 (0.0)	6/20 (30.0)	
Radiology	2/48 (4.2)	0/28 (0.0)	2/20 (10.0)	
Clinician and radiology	37/48 (77.1)	26/28 (92.9)	11/20 (55.0)	
Unknown	3/48 (6.2)	2/28 (7.1)	1/20 (5.0)	
Pleural or peritoneal serous effusion (irrespective of cell content), n/N (%)	17/48 (35.4)	12/28 (42.8)	5/20 (25.0)	0.20
Anemia, n/N (%)	27/48 (56.3)	21/28 (75.0)	6/20 (30.0)	0.002
Lymphopenia, n/N (%)	12/48 (25.0)	8/28 (28.6)	4/20 (20.0)	0.50
Transformation to aggressive lymphoma, n/N (%)				0.073
Yes	4/48 (8.3)	4/28 (14.3)	0/20 (0.0)	
No	43/48 (89.6)	24/28 (85.7)	19/20 (95.0)	
Unknown	1/48 (2.1)	0/28 (0.0)	1/20 (5.0)	
Malignancies, n/N (%)	7/48 (14.6)	5/28 (17.9)	2/20 (10.0)	0.68
Autoimmune diseases, n/N (%)	5/48 (10.4)	3/28 (10.7)	2/20 (10.0)	> 0.99
Cardiovascular diseases, n/N (%)	21/48 (43.8)	14/28 (50.0)	7/20 (35.0)	0.30
Diabetes, n/N (%)	8/48 (16.7)	7/28 (25.0)	1/20 (5.0)	0.12
HHV-8 infections, n/N (%)	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	> 0.99
HIV infections, n/N (%)	2/48 (4.2)	1/28 (3.6)	1/20 (5.0)	> 0.99
Hepatomegaly, n/N (%)				0.27
Yes	24/48 (50.0)	14/28 (50.0)	10/20 (50.0)	
No	22/48 (45.8)	14/28 (50.0)	8/20 (40.0)	
Unknown	2/48 (4.2)	0/28 (0.0)	2/20 (10.0)	
Gastric manifestation, n/N (%)	4/48 (8.3)	4/28 (14.3)	0/20 (0.0)	0.13
Thyroid manifestation, n/N (%)	3/48 (6.2)	3/28 (10.7)	0/20 (0.0)	0.26
Pancreas manifestation, n/N (%)	1/48 (2.1)	0/28 (0.0)	1/20 (5.0)	0.42
Hepatic manifestation, n/N (%)	5/48 (10.4)	2/28 (7.1)	3/20 (15.0)	0.64
Renal manifestation, n/N (%)	4/48 (8.3)	2/28 (7.1)	2/20 (10.0)	> 0.99
Pulmonary manifestation, n/N (%)	16/48 (33)	12/28 (42.9)	4/20 (20.0)	0.10
Radiation therapy, n/N (%)				0.046
Yes	3/48 (6.2)	1/28 (3.6)	2/20 (10.0)	
No	37/48 (77.1)	25/28 (89.3)	12/20 (60.0)	
Unknown	8/48 (16.7)	2/28 (7.1)	6/20 (30.0)	
Previous therapeutic strategies, n/N (%)				0.030
CFA-DEXA	1/48 (2.1)	0/28 (0.0)	1/20 (5.0)	
CHOP	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
Corticosteroids	4/48 (8.3)	3/28 (10.7)	1/20 (5.0)	
CVP	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
CVP, R-CHOP	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
CVP/Etoposide	3/48 (6.2)	0/28 (0.0)	3/20 (15.0)	
Melphalan-Vc-methylprednisolone	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	

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Table 1. Baseline Characteristics and Details of Treatment - *(continued)*

Variable	Cohort			P-value[a]
	Overall (N = 48)	Greece (n = 28)	Romania (n = 20)	
None	3/48 (6.2)	3/28 (10.7)	0/20 (0.0)	
R-CFA-DOXO-PREDNISON	1/48 (2.1)	0/28 (0.0)	1/20 (5.0)	
R-CHOP	11/48 (22.9)	8/28 (28.6)	3/20 (15.0)	
R-CHOP/etoposide	1/48 (2.1)	0/28 (0.0)	1/20 (5.0)	
R-CVP	5/48 (10.4)	4/28 (14.3)	1/20 (5.0)	
R-CVP + R maintenance	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
R-CVP/etoposide	2/48 (4.2)	0/28 (0.0)	2/20 (10.0)	
Rituximab	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
Siltuximab	10/48 (20.8)	3/28 (10.7)	7/20 (35.0)	
Tocilizumab	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
Number of prior lines of treatment before siltuximab, n/N (%)				0.006
0	3/48 (6.2)	3/28 (10.7)	0/20 (0.0)	
1	36/48 (75.0)	16/28 (57.1)	20/20 (100.0)	
2	6/48 (12.5)	6/28 (21.4)	0/20 (0.0)	
3	2/48 (4.2)	2/28 (7.1)	0/20 (0.0)	
Unknown	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
Number of siltuximab cycles, n/N (%)				0.10
0	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
1	7/48 (14.6)	5/28 (17.9)	2/20 (10.0)	
2	2/48 (4.2)	2/28 (7.1)	0/20 (0.0)	
4	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
6	11/48 (22.9)	4/28 (14.3)	0/20 (0.0)	
7	4/48 (8.3)	1/28 (3.6)	3/20 (15.0)	
8	8/48 (16.7)	6/28 (21.4)	2/20 (10.0)	
9	1/48 (2.1)	0/28 (0.0)	1/20 (5.0)	
10	1/48 (2.1)	0/28 (0.0)	1/20 (5.0)	
12	2/48 (4.2)	2/28 (7.1)	0/20 (0.0)	
14	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
16	1/48 (2.1)	0/28 (0.0)	1/20 (5.0)	
17	1/48 (2.1)	0/28 (0.0)	1/20 (5.0)	
18	1/48 (2.1)	0/28 (0.0)	1/20 (5.0)	
24	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
33	1/48 (2.1)	0/28 (0.0)	1/20 (5.0)	
48	1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
Unknown	3/48 (6.2)	3/28 (10.7)	0/20 (0.0)	

[a]Pearson's Chi-squared test; Wilcoxon rank sum exact test; Fisher's exact test. CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; CFA: complete Freund's adjuvant; CVP: cyclophosphamide, vincristine, prednisolone; DEXA: dexamethasone; DOXO: doxorubicin; HHV-8: human herpesvirus-8; HIV: human immunodeficiency virus; R: rituximab; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP: rituximab, cyclophosphamide, vincristine, prednisolone; SD: standard deviation.

al symptoms with antipruritics, antipyretics, pain medicines and antihistamines. Therapeutic strategies prior to siltuximab treatment included observation, surgical resection, steroid pulse therapy, combination therapy with cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (oncovin) and prednisolone (CHOP) with or without rituximab, combination therapy with cyclophosphamide, vincristine, and prednisone (CVP) with or without rituximab, and radiotherapy.

Table 2. Patient Outcomes

Variable	N	Cohort			P-value[a]
		Overall (N = 48)	Greece (n = 28)	Romania (n = 20)	
Best response, n/N (%)	38[b]				0.17
Complete response		21/38 (55.3)	10/19 (52.6)	11/19 (57.9)	
Partial response		6/38 (15.8)	3/19 (15.8)	3/19 (15.8)	
No response or stable disease		6/38 (15.8)	4/19 (21.1)	2/19 (10.5)	
Progressive disease		5/38 (13.2)	2/19 (10.5)	3/19 (15.8)	
Disease status at last known follow-up, n/N (%)	48				0.031
Disease progression		19/48 (39.6)	14/28 (50.0)	5/20 (25.0)	
Progression free		23/48 (47.9)	9/28 (32.1)	14/20 (70.0)	
Unknown		6/48 (12.5)	5/28 (17.9)	1/20 (5.0)	
Survival status at last known follow-up, n/N (%)	48				0.003
Alive		28/48 (58.3)	11/28 (39.3)	17/20 (85.0)	
Dead		19/48 (39.6)	16/28 (57.1)	3/20 (15.0)	
Unknown		1/48 (2.1)	1/28 (3.6)	0/20 (0.0)	
Primary cause of death, n/N (%)	48				0.029
Death from AE		3/48 (6.2)	3/28 (10.7)	0/20 (0.0)	
Death from malignant disease under study		6/48 (12.5)	5/28 (17.9)	1/20 (5.0)	
Death from other causes		10/48 (20.8)	8/28 (28.6)	2/20 (10.0)	
Alive		29/48 (60.4)	12/28 (42.9)	17/20 (85.0)	

[a]Fisher's exact test. [b]Response data were unknown for 10 patients. AE: adverse event.

Disease response and survival

Patients received a median of nine cycles of siltuximab. Response data were available for 38 patients. Overall response to siltuximab was 71.1%, with 21 out of 38 (55.3%) patients achieving complete response and six (15.8%) patients' partial response. No response or stable disease was observed in six (15.8%) patients, while progressive disease was observed in five (13.2%) patients (Table 2). At a median follow-up of 3.9 years, 28 out of 48 (58.3%) patients were alive, 23 (82.1%) of whom were progression-free; 19 (39.6%) patients had died, 10 (52.6%) of whom had died due to reasons unrelated to CD; and one patient (2.1%) was lost from follow-up. Overall, three out of 19 deaths (15.7%) were due to adverse events (cardiopulmonary events). The estimated overall survival rate at 3 years was 74% and the median survival was 123 months (95% CI: 52 - NA) (Fig. 1). The median progression-free survival (PFS) for patients with siltuximab was not reached. Patients from the Greek cohort had a higher incidence of disease progression and mortality rate at the end of the follow-up than the Romanian cohort (Table 2). In addition, four patients from this cohort reported transformation to aggressive lymphoma during treatment with siltuximab.

Safety

Adverse events included raised alanine aminotransferase, aspartate aminotransferase or bilirubin level (10.4% (n = 5)), anxiety (10.4% (n = 5)), allergic reactions (6.3% (n = 3)), nausea/diarrhea (6.3% (n = 3)), anemia (4.2% (n = 2)), thrombocytopenia (4.2% (n = 2)), hypertension (4.2% (n = 2)), bleeding (2.1% (n = 1)) and atrial fibrillation (2.1% (n = 1)) (Table 3). Overall, eight (16.7%) patients experienced serious adverse events.

Discussion

Prognosis and survival rates for patients with MCD were very poor before siltuximab-based therapies became available in Greece and Romania, with prior treatments being based on interferon alpha or chemotherapy; only one-third of patients survived more than 3 years [7, 8]. Siltuximab was originally evaluated in a randomized, double-blind, placebo-controlled phase 2 study in patients with iMCD who also received best supportive care [7]. Durable disease and symptom responses occurred in 34.0% of patients in the siltuximab group compared with 0% in the placebo group (P = 0.0012) [7]. At a later follow-up, PFS was significantly longer for patients treated with siltuximab versus placebo (P = 0.0001), with median PFS not reached for siltuximab versus 14.5 months for placebo [8]. The 2-year estimates for PFS were 91% versus 37% for siltuximab and placebo, respectively [8]. In our real-world cohort of patients with iMCD, treatment with siltuximab resulted in an estimated 3-year overall survival rate of 74%. Siltuximab therapy generally has a more acceptable safety profile than

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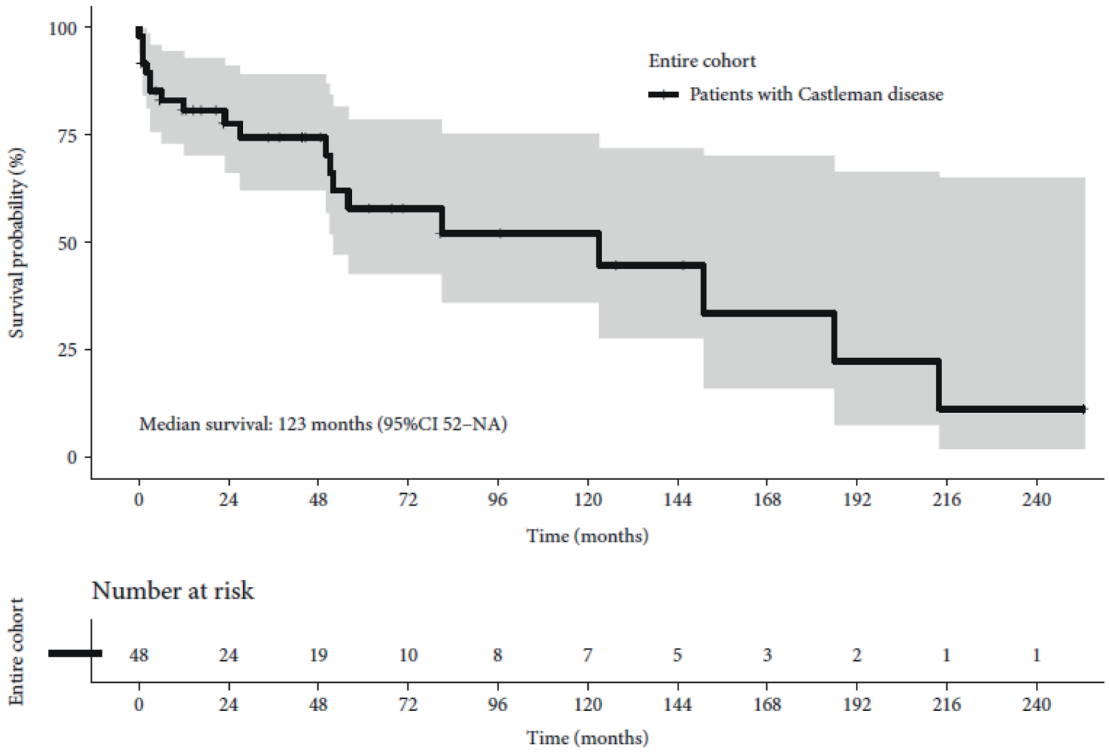

Figure 1. Kaplan-Meier curve of overall survival. CI: confidence interval; NA: not available.

classic chemotherapy, which is associated with severe hematological, gastrointestinal, and renal adverse events [9-11]. In our study, 16% of patients treated with siltuximab experienced severe adverse events and 6.3% of patients died due to adverse events. Still, the toxicity following siltuximab-based therapy is much lower than other therapeutic alternatives that include chemotherapy-based regimens and/or immunomodulatory agents [11].

MCD is very rare and real-world data for patients with iMCD treated with siltuximab are currently scarce, with only two publications related to European patients (from Italy [12] and Poland [13]) published so far. In the Italian study, nine patients with iMCD received siltuximab treatment for a median of 285 days (range, 104 - 1,113 days) [12]. The overall response and complete response rates were both 33.3% (3/9), with response durations of 20 - 37 months at the time of analysis [12]. In the Polish study, 11 patients with iMCD received siltuximab treatment for a median of 16 months (range, 3 - 65 months) [13]. The overall response rate was 72.7% (8/11), with two patients achieving complete response and six achieving partial response [13]. Our findings are broadly consistent with these reports [12, 13], and we believe that our analysis represents the largest real-world study of European patients with iMCD treated with siltuximab conducted to date. While the previous study in Italy included nine patients and the Polish study 11 patients, we now report data for 48 patients treated with siltuximab in routine clinical practice in Romania and Greece. We noticed some differences in baseline characteristics between our cohorts and those previously reported. The Greek cohort in the current study shows poor prognosis, older age, and more complications of malignancy compared with patients of the previously published Polish study as suggested by the presented signs and symptoms, organ manifestations and number of previous therapies at baseline [13]. These differences might be related to regional characteristics. However, it should be noted that the rate of complete response was higher in the current study (over 50% in both cohorts) than in the Italian and Polish cohorts (18% and 33%, respectively) [12, 13]. Compared to the Italian and Polish studies, our study reported a higher rate of serious adverse events: these were reported for over 16% of patients in our study, but for no patients in the previous reports as all adverse events were either grade

Table 3. Adverse Events in the Overall Study Population (N = 48)

Adverse event	n (%)
Raised ALT, AST or bilirubin level	5 (10.4)
Anxiety	5 (10.4)
Allergic reactions	3 (6.3)
Nausea/diarrhea	3 (6.3)
Anemia	2 (4.2)
Thrombocytopenia	2 (4.2)
Hypertension	2 (4.2)
Bleeding	1 (2.1)
Atrial fibrillation	1 (2.1)

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

1 or 2 [12, 13]. Furthermore, the rate of death due to adverse events was higher in the current study than in the Italian and the Polish studies, but this difference seems to be driven by the Greek cohort and might be related to the higher mean age of this group compared to both the Romanian cohort and the Italian and Polish populations [12, 13]. The difference in age between the two cohorts in the current study is likely related to the newly approved National Plan for Cancer Management, introduced by the Romanian government, in which large screening programmes for all cancers have been implemented [14].

Overall, the safety data of the current study are broadly in line with the ones reported in the pivotal phase II trial of siltuximab, with only anxiety, bleeding and atrial fibrillation reported as newly identified events and similar rates of serious adverse events (16.7% vs. 23%) [15].

Despite limitations such as the relatively small sample size, the retrospective nature of the study, and the potential inclusion of bias and confounding factors, this study provides valuable insights into the effectiveness and safety/tolerability of siltuximab when used in clinical practice. Further data are required to optimize therapy and improve therapeutic outcomes in patients with iMCD.

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Conflict of Interest

None of the authors has any conflict of interest to declare.

Informed Consent

Informed consent was obtained from all patients involved in the study.

Author Contributions

CJ, AS, SB, EK, AC, AM, AB, BT, PR, LU, IR, DD, AB, MD, VL, MSM, DF, BF, BP, AD, DD, SB, CC, MZ, MAD, CT, and ET contributed to the patient management. CJ gathered all of the clinical data. ET and CT coordinated the project.

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Abbreviations

CD: Castleman disease; CDCN: Castleman Disease Collaborative Network; CI: confidence interval; HHV-8: human herpes virus-8; IL-6: interleukin-6; iMCD: idiopathic multicentric Castleman disease; MCD: multicentric Castleman disease; NA: not applicable; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; UCD: unicentric Castleman disease; PFS: progression-free survival; POEMS: polyneuropathy, organomegaly, endocrinopathy, M proteins, and skin changes; SD: standard deviation

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