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## Autoimmune and inflammatory diseases associated with chronic myelomonocytic leukemia: A series of 26 cases and literature review

Eric Grignano<sup>1\*</sup>, Arsene Mekinian<sup>1\*</sup>, Thorsten Braun<sup>2</sup>, Eric Liozon<sup>3</sup>, Mohamed Hamidou<sup>4</sup>, Olivier Decaux<sup>5</sup>, Xavier Puéchal<sup>6</sup>, Jean Emmanuel Kahn<sup>7</sup>, Yoland Schoindre<sup>7</sup>, Julien Rossignol<sup>8</sup>, Olivier Lortholary<sup>9</sup>, Bertrand Lioger<sup>10</sup>, Olivier Hermine<sup>8</sup>, Sophie Park<sup>11</sup>, Lionel Ades<sup>13</sup>, François Montestruc<sup>12</sup>, Laure Ricard<sup>1</sup>, Claude Gardin<sup>2</sup>, Pierre Fenaux<sup>13\*\*</sup>, Olivier Fain<sup>1\*\*</sup>, on behalf of GFM, SNFMI and CRI

<sup>1</sup> DHU2B, Service de Médecine Interne, Hôpital Saint Antoine, APHP, Université Paris 6, 75012 Paris, France.

<sup>2</sup> Service d'hématologie clinique, Université Paris 13, AP-HP, Avicenne, 93000, Bobigny, France.

<sup>3</sup>Service de médecine interne, CHU Dupuytren, Limoges, France

<sup>4</sup>Service de médecine interne, Université Nantes, CHU de Nantes, Nantes, France

<sup>5</sup>Service de médecine interne, Université Rennes 1, Hôpital Universitaire de Rennes, Rennes, France

<sup>6</sup>Service de médecine interne, Université Paris 5, AP-HP, CHU Cochin, Paris, France

<sup>7</sup>Service de médecine interne, Université Versailles-Saint Quentin en Yvelines, Hôpital Foch, Suresnes, France

<sup>8</sup>Service d'hématologie clinique, Université Paris 5, AP-HP, Hôpital Necker, Paris, France

<sup>9</sup>Service de maladies infectieuses, Université Paris 5, AP-HP, Hôpital Necker, Paris, France

<sup>10</sup>Service de médecine interne, CHU Tours, Tours, France

<sup>11</sup>Service d'hématologie clinique, CHU Grenoble, Grenoble, France.

<sup>12</sup>eXYSTAT, Statistics, Malakoff, France

<sup>13</sup>Service d'hématologie clinique, Université Paris 7, AP-HP, CHU Saint-Louis, Paris, France

\*Both authors equally contributed to this work

\*\* Both authors equally contributed to this work

**Correspondance and reprint request to:** Arsène Mekinian, Service de Médecine Interne, Université Paris 6, AP-HP, Hôpital Saint Antoine, Paris, 75012. France

**E-mail:** [arsene.mekinian@sat.aphp.fr](mailto:arsene.mekinian@sat.aphp.fr)

### Highlights

Vasculitis are the most frequent autoimmune diseases associated with CMML

CMML features are worse when associated to SAIDs

Hypomethylating agents may represent an alternative therapy after steroids.

### Abstract

We wanted to describe the characteristics, treatment and outcome of autoimmune and inflammatory diseases (SAIDs) associated with chronic myelomonocytic leukemia (CMML), and conducted a French multicenter retrospective study and a literature review.

We included 26 cases of CMML (median age 75 years, 54% female), 80% with CMML-1. CPSS score was low (0 or 1) in 75% of cases. SAIDs was systemic vasculitis in 54%. Diagnosis of the 2 diseases was concomitant in 31% cases, and CMML was diagnosed before SAIDs in 12 cases (46%). First line treatment for SAIDs consisted mostly of steroid, with 85% of response. Second-line treatment was needed in 40% cases. Six patients received hypomethylating agents, with 66% response on SAIDs. A literature review found 49 cases of CMML-associated SAIDs, in whom SAIDs was systemic vasculitis in 29% cases.

Hence, vasculitis is the most frequent SAIDs associated with CMML. After initial response to steroids, recurrence and steroid-dependence were frequent. Hypomethylating agents may be interesting in this context.

**Keywords:** chronic myelomonocytic leukemia; autoimmune diseases; vasculitis; immunosuppressive agents ; hypomethylating agents ; outcome

## INTRODUCTION

Chronic myelomonocytic leukemia (CMML) is the most frequent subtype of the WHO 2008 classification defined group of myelodysplastic syndrome/myeloproliferative neoplasms (MDS/MPN). The disease is characterized by persistent monocytosis and variable features of myeloproliferative (high white blood cell [WBC] count and splenomegaly) and myelodysplastic features (anemia, thrombocytopenia and excess marrow blasts)(1).

Systemic autoimmune and/or inflammatory diseases (SSAIDs) have been reported in 15% to 25% of MDS/CMML patients, in series that included only few CMML cases, without focus on this disorder (2). In a recent report, we described 123 patients with MDS/CMML-associated SAIDs, mainly systemic vasculitis (32%), connective tissue diseases (25%) and inflammatory arthritis (23%)(3). The type of MDS/CMML was refractory anemia in 25% of cases, refractory anemia with blasts excess-1 in 15% and CMML in 15%.

Studies specifically analyzing CMML with SAIDs are lacking, as are data for SAIDs treatment response and outcome in those patients. Here we describe 26 cases of CMML with SAIDs (including 7 new cases), compare these cases to CMML without SAIDs, and report the literature review of CMML with SAIDs.

## PATIENTS AND METHODS

### Patients' selection

Case reports of patients with both CMML and SAIDs from 1993 to 2013 were collected retrospectively from 15 departments of hematology and internal medicine in France by using questionnaires submitted to members of the "Société Française de Médecine Interne" and the "Club Rhumatisme et Inflammation". Inclusion criteria were CMML diagnosis according to the 2008 WHO classification (persistent monocytosis  $> 1$  G/L, without any evidence of infection, absence of BCR-ABL and/or PDGFR $\alpha$  mutations, marrow blasts  $< 20\%$ ) and one of dysplasia of at least one cell line, or evidence of a clonal genetic or molecular mutation). We excluded cases with a  $>5$ -year interval between diagnosis of CMML and SAIDs, patients with immunosuppressive treatment  $> 12$  months before CMML diagnosis, or who experienced infectious or drug-induced SAIDs.

**CMML prognostic score and response assessment**

The CMML-Specific Prognostic Scoring System (CPSS) was used to retrospectively classify cases by 4 prognostic categories: low, intermediate-1, intermediate-2 and high (1). Response of CMML to treatment was retrospectively defined by recently proposed response criteria for MPN/MDS (4).

**SAIDs definition**

SAIDs (incomplete/incomplete forms) were diagnosed and classified by using international diagnostic criteria for each SAIDs type (1996 American College of Rheumatology for systemic lupus erythematosus, Chapel Hill classification for systemic vasculitis, etc.). Steroid dependence was defined as a daily equivalent prednisone amount  $\geq 20$  mg at least during 2 months which could not be decreased because of SAIDs (at diagnosis of SAIDs and any time when the steroid were needed for SAIDs).

**CMML patients without SAIDs**

We selected a control group of 103 CMML patients without any autoimmune/inflammatory features followed prospectively from 2003 to 2013 in the hematology department of Hôpital Avicenne (Paris 13 University), and included in the registry of the “Groupe Francophone des Myélodysplasies” (GFM).

**Literature review: search strategy**

Two investigators (AM and EG) searched for articles in MEDLINE via PubMed (January 1989 to August 2015) with the keywords “chronic myelomonocytic leukemia”, “arthritis”, “vasculitis”, “connective tissue disease”, “autoimmune disease”, “paraneoplastic syndrome”. The literature search yielded 14 citations (5–13). Five reports were excluded because of incomplete data concerning SAIDs features.

**Statistical analysis****Sample size**

The primary objective of the study is to estimate the prevalence of SAIDs in a population of patients with CMML. For an expected prevalence of 20%, 126 CMML are required for an accuracy of 7%. With 126 patients, the 95% two-sided confidence interval of a 20% prevalence is expected to be [13%; 27%]. With this sample size, a two group chi square test with a 5% two-sided significance level will have 80% power to detect the difference between a CMML patients with SAIDs and CMML patients without SAIDs with and odd ratio at 0.2 (corresponding to proportions of 10% in CMML patients with SAIDs and 25% in CMML patients without SAIDs).

Data were described with mean $\pm$ SD and/or median (ranges) for continuous variables and number with frequencies (%) for categorical variables. To account for missing data, results were expressed as observed data (missing data not replaced). Fisher's exact or chi-square test were used to compare categorical variables and Student's *t* or Kruskal Willis test for continuous variables. Overall survival was defined from the duration between diagnosis of

CMML and last available visit or death. Time to event data was analysed with Kaplan Meier methodology and associated log-rank test. Statistical analyses involved use of SAS 9.4 (SAS Inst., Cary, NC).  $p < 0.05$  was considered statistically significant.

## RESULTS

### CMML and SAIDs characteristics

Twenty six patients with CMML and SAIDs (median age 75 years [range 16–82]; M/F ratio 12/14) were included with 21 CMML-1 (81%) and 5 CMML-2 (**Table 1**). At CMML diagnosis, median monocytes count was 3000/mm<sup>3</sup> [range 160–10000/mm<sup>3</sup>] and proportion of marrow blasts 4% [range 0-20%]. CPSS score was 0 (n=6, 37.5%), 1 (n= 6, 37.5%), 2 or 3 (n=3, 19%), and 4 (n=1, 6%) (**Table 1**). According to the French-American-British classification of CMML, 55% of patients had a myelodysplastic form (WBC <13000 /mm<sup>3</sup>) and 45% a myeloproliferative form (WBC >13000 /mm<sup>3</sup>).

The type of SAIDs was systemic vasculitis (n=14, 54%, including polyarteritis nodosa (n=6), connective-tissue disease (n=2, 8%), inflammatory arthritis (n=4, 15%) (polymyalgia rheumatica, n=2; undifferentiated arthritis, n=2), neutrophilic dermatosis (n=2, 8%), retroperitoneal fibrosis (n=1), immune thrombocytopenia (n=1) and unclassified forms (n=2, 8%) (**Supplementary Table 1**). Connective tissue diseases consisted of relapsing polychondritis (n=1) and Sjögren's syndrome (n=1).

Median interval between diagnosis of SAIDs and CMML was 0.5 months [range 0-44]. Diagnosis of the 2 diseases was concomitant in 8 cases (35%), diagnosis of CMML preceded SAIDs in 12 cases (46%) and followed diagnosis of SAIDs in 6 (23%).

### Comparison between CMML with and without SAIDs

Compared with the 103 CMML patients without SAIDs included in the GFM registry, CMML with SAIDs were younger (median age 75 vs 79 years;  $p < 0.01$  Student test), more frequently had CMML-2 (19% vs 7%,  $p = 0.06$  Fisher test), a greater percentage of marrow blasts (median 4% vs 2%, mean (std) 3.2 (4.9) versus 6.7 (6.1)  $p < 0.01$  Student test) and greater incidence of poor karyotype, including trisomy 8, abnormalities of chromosome 7 or complex karyotype (15% vs 2%,  $p = 0.04$  Fisher test); however, the relative frequency of CPSS categories did not differ between the 2 groups ( $p = 0.43$  Fisher test) (**Table 1**).

### CMML and SAIDs treatments and outcomes

In the 26 patients with CMML and SAIDs, frontline hematological treatment was used in 15 cases (58%) and consisting of azacytidine (n=2) and hydroxyurea (n=13). SAIDs were treated in 25 cases, including steroids in 24, with a median daily prednisone dose of 32.5 mg/day, associated with immunosuppressive drugs in 2 cases (cyclophosphamide). One patient with unclassified disease received colchicine alone. Overall, 20/23 cases with available data (87%) showed complete (n=15) or partial SAIDs response, including 17 (74%) treated with steroids alone. Second-line treatment was needed in 10 cases (40%) because of SAIDs relapse (n=5), steroid dependence (n=4) or non-response (n=1); and 6/8 cases (75%) showed SAIDs response after second-line treatment, including 4 complete responses (**Figure 1**).

Of 14 patients with vasculitis, 12 received first-line treatment with steroids, associated with cyclophosphamide in 1 patient. The last patient with pseudo-Behcet disease received

anakinra. Twelve of the 13 cases (92%) showed complete (n=7) or partial SAIDs response. Second-line treatment was needed in 7 cases (54%) because of SAIDs relapse (n=3), steroid dependence (n=3) or non-response (n=1); 6/7 cases (86%) showed SAIDs response after second-line treatment, including complete responses in 2 cases.

SAIDs outcome and treatment responses were not correlated with CMML baseline hematological characteristics. Among 15 patients treated for CMML (hydroxyurea in 13 cases and azacytidine or decitabine in 6 cases, 4 patients with both hydroxyurea and hypomethylating agents), 8/13 patients with sufficient data have SAIDs remission and no SAIDs remission in 5/13 cases (p=0.4). Among our 6 cases treated with 5-azacytidine or decitabine, 4 showed SAIDs remission at the last follow-up associated with hematological response.

During the follow-up (median 30.7 months [range 14.5–61.9]), the number of involved organs and C-reactive protein levels significantly decreased (from 3 to 1 and 87 to 9 mg/l, respectively), as did the prednisone daily amount (37 mg/day at diagnosis to 19 mg/day at the last visit) (**supplementary Table 3**).

### **Patient outcome**

Acute myeloid leukemia developed in 26% of CMML patients with SAIDs, compared with 16% of the CMML without SAIDs (p=0.17 Fisher test).

We observed 4 deaths in the CMML with SAIDs group and 25 in the CMML without SAIDs group. Survival rates at 1 and 5 years were 95% (95% CI 70-99) and 78% (44-93) in CMML with SAIDs, and 87% (77-93) and 50% (32-66) in CMML without SAIDs. Median overall survival was 58 months in patients without SAIDs and not reached (greater than 72 months) in patients with SAIDs (p=0.07 Log-rank test), with Hazard ratio estimated to 2.6 [0.9; 7.5].

### **Literature review**

A literature review revealed 49 cases of CMML with SAIDs. Their median age was 67.7 years; 65% were males (**Table 3**). In patients with available data, 24% had proliferative CMML (WBC count > 13 g/L), 8% CMML-2 and 35% abnormal karyotype, including 17% complex karyotypes. SAIDs were systemic vasculitis in 26.5% (polyarteritis nodosa in 16%), connective-tissue disease in 2%, inflammatory arthritis in 8%, and autoimmune thrombocytopenia in 32.5%. Diagnosis of the 2 diseases was concomitant in 25%; diagnosis of CMML preceded that of SAIDs in 37.5% and occurred after SAIDs in 37.5%. Treatment of SAIDs consisted of steroids in 80% of cases, with first-line response obtained in 76%. Second-line treatment was needed in 64% of the cases (including cyclophosphamide in 8 patients; VP16 in 3; romiplostin, in 3). Overall, 78% of patients achieved remission of SAIDs (complete response in 45%), including 72% of patients with vasculitis. Acute myeloid leukemia developed in 12% of the patients.

### **Discussion**

In this largest series of CMML-related SAIDs to our knowledge, we found that systemic vasculitis was the most frequent SAIDs associated with CMML, with higher prevalence of



systemic vasculitis, mostly periarteritis nodosa. Previous studies described SAIDs in patients with MDS, but CMML was rarely included (7,8,14,15). Only one series of 8 cases of medium-vessel vasculitis associated with CMML was reported, with SAIDs diagnosed after CMML, and a fatal course in 7 cases (7). Overall good response to first line treatment was showed (87%), even mostly steroid dependence and relapse needed retreatment.

The clinical SAIDs associated with CMML could be as various as systemic vasculitis, connective tissue diseases and ITP. Even the frequencies are different from various case series, as 26% of ITP in recent study by Peker et al, and 3.5% in our study, the various inclusion criteria could explain this differences and prospective studies are needed to determine the real prevalence of SAIDs associated with CMML. As compared with CMML without SAIDs, our CMML patients with SAIDs showed unfavorable CMML features: more frequently CMML-2, poor karyotype and greater proportion of medullar blasts. No previous study has focused on survival of patients with CMML-associated SAIDs, and the impact of the SAIDs on survival remains controversial (16,17). Several reports showed that in patients with various SAIDs types, survival was similar in comparison with MDS without SAIDs.(14) Even the presence of vasculitis could be associated with poor outcome; (15) in a 4-year prospective study, only IPSS score was relevant for MDS prognosis(9). In our large series of 123 patients with MDS-associated SAIDs, survival did not differ from that in 665 patients with MDS without SAIDs(3).; The limited number of patients and deaths events in CMML-SAIDs group, the difference in patients age between CMML with and without SAIDs did not allow us to have definite conclusion whether the presence of SAIDs could affect the overall survival.

Response to SAIDs specific treatment, mostly steroids alone, was obtained in 87% of cases. No previous studies focused on CMML-associated SAIDs treatment and outcomes, and response rates to steroids alone was similar comparing to our larger cohort of MDS-associated SAIDs (80%)(3). Despite this initial good response, 40% of patients needed a second-line treatment for relapse or steroid dependence, comparing to 48% in other MDS-associated SAIDs (3). The effect of MDS treatment on SAIDs outcome is not established, and few case-reports described SAIDs remission with hypomethylating agents(18–20). Among our 6 cases treated with 5-azacytidine or decitabine, 4 showed SAIDs remission associated with hematological response. In 20 MDS/CMML patients with steroid-refractory or dependent SAIDs, we recently showed a 80% overall response with 5-azacytidine, with significantly decreased steroid amounts and steroid dependence rates, suggesting a potential interest for HMAs in this context(21).

### **Conclusion**

In this case-series of CMML-associated SAIDs, various diseases could be associated with CMML, mostly vasculitis and immune thrombocytopenia. Even though SAIDs was usually responsive to steroids, recurrence and steroid-dependence indicate the need to determine a better treatment strategy and the value of CMML-specific treatment for SAIDs remission.

**Conflicts of interest and funding:** none.

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**Authors contribution**

All authors were involved in drafting the article. Olivier Fain had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

<sup>3</sup>**Study conception and design.** AM, TB, PF, OF.

**Acquisition of data.** AM, TB, EL, MH, OD, XP, JEK, YS, JR, OL, BL, OH, SP, LA, FM, CG, PF, OF.

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All authors had access to the data and play a role in writing the manuscript.

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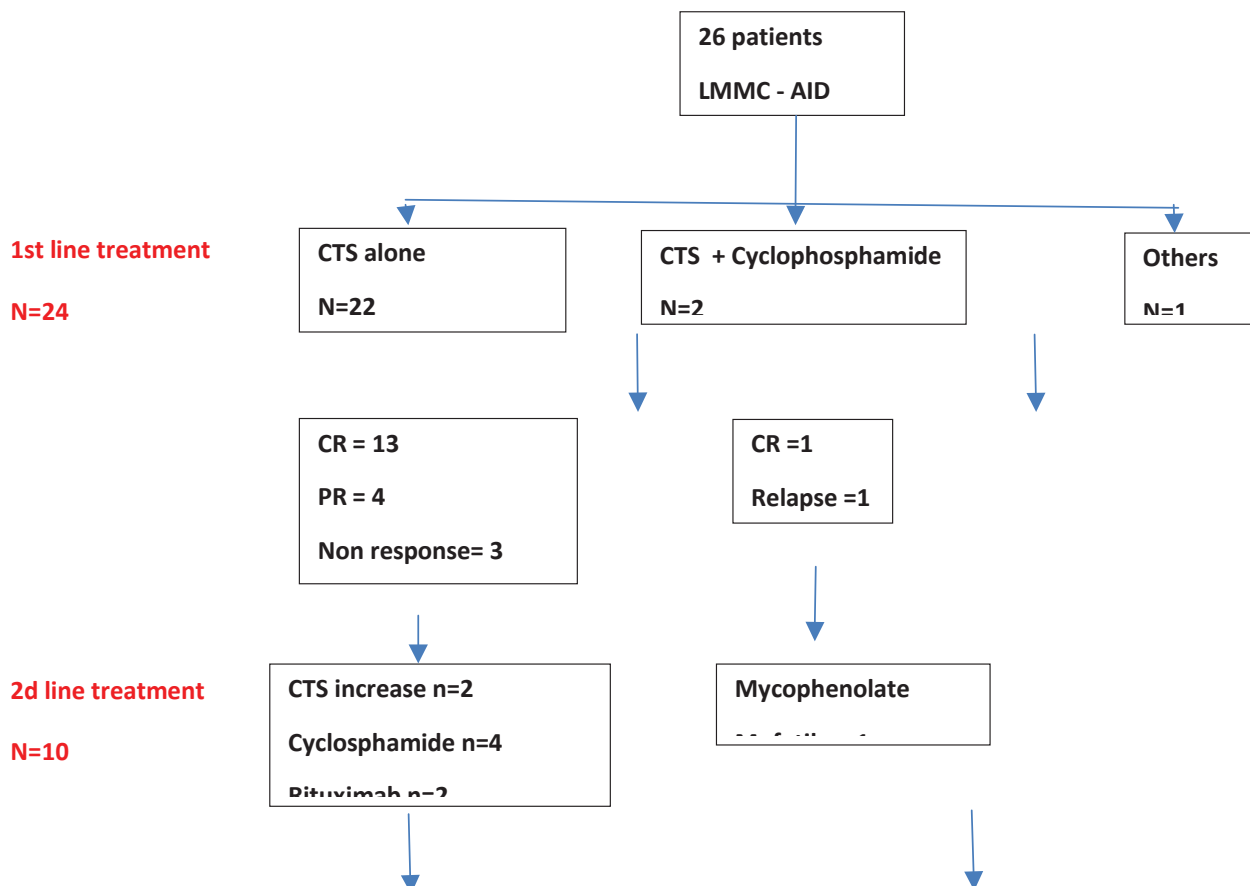
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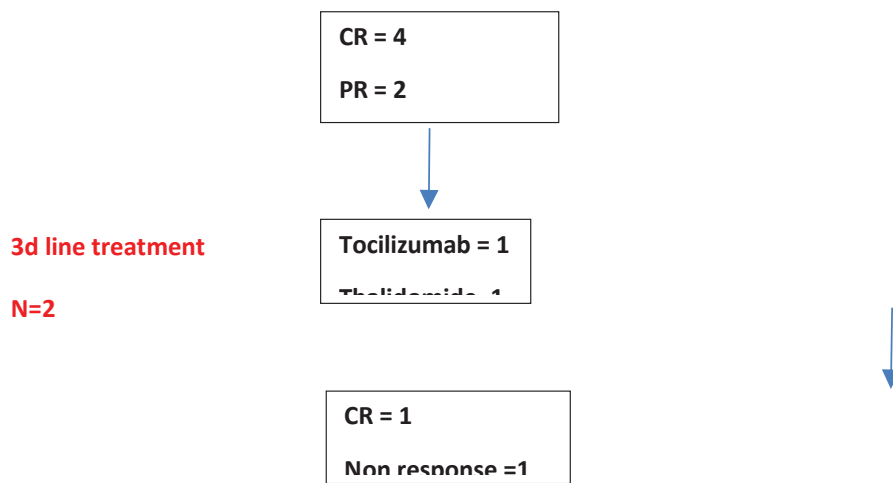


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**Figure 1. AIDs treatments and response.**





CR=complete response; PR = partial response; CTS = corticosteroids

**Table 1. Characteristics of chronic myelomonocytic leukemia (CMML) in patients with and without autoimmune and inflammatory diseases (SAIDs).**

	With SAIDs	Without SAIDs	P value
<b>CMML subtype</b>	n= 26	n=103	Fisher p=0.06
CMML 1	21 (81%)	96 (93%)	
CMML 2	5 (19%)	7 (7%)	
<b>Karyotype</b>	n=20	n=89	Fisher p=0.04
Good or intermediate	17 (85%)	87 (98%)	
Poor	3 (15%)	2 (2%)	
<b>CMML-Specific Prognostic Scoring System score</b>	n=16	n=55	Fisher p=0.41
Low			
Intermediate1/2	6 (37.5%)	28 (51%)	

High	9 (56,5%)	20 (36%)	
	1 (6%)	7 (13%)	
<b>Acute myeloid leukemia</b>	n=23	n=71	Fisher
Progression	6 (26%)	11 (16%)	p=0.17
Deaths	4 (17%)	25 (35%)	p=0.23
<b>Marrow blasts (mean std)</b>	3.2 (4.9)	6.7 (6.1)	Student
<b>(min median max)</b>	0 – 2 - 28	0 – 4 -20	p=0.01

**Table 2. Types of CMML-associated AID.**

Type	No. (%)	Type (n)
<b>Systemic vasculitis</b>	14 (54%)	Polyarteritis nodosa (6) Giant cell arteritis (3) Cryoglobulinemia (2) Behcet's disease (1) Granulomatosis with polyangeitis (2)
<b>Connective tissue diseases</b>	2 (8%)	Relapsing polychondritis (1) Sjogren's syndrome (1)
<b>Neutrophilic dermatosis</b>	2 (8%)	Sweet syndrome (2)
<b>Inflammatory arthritis</b>	4 (15%)	Polymyalgia rheumatica (2) Undifferentiated (2)
<b>Unclassified</b>	2 (8%)	-
<b>Retroperitoneal fibrosis</b>	1 (3.5%)	-
<b>Immune thrombocytopenia</b>	1 (3.5%)	-

**Table 3. CMML-associated SAIDs cases from the literature.**

Author	Cases	MDS cytogenetics	SAID features	SAID treatment	SAID, MDS and general outcome
Smail, 1989	1 F	NA	GPA	CS, Cy	SAID remission, death from AML
Leung, 1986	1 M	NA	PAN	CS, Cy	SAID remission, AML, death from infection
Hamidou, 2001	n=8 (6 M/ 2 F)	Del12 45-46 XX 3p-	PAN=7 ANCA (+) vasculitis	CS =8, Cy=4, VP16=2, MTX= 1, HA= 1	1 remission 3 deaths from vasculitis 2 deaths from infection 2 deaths unexplained
Saif, 2002	n=3 (1 M/ 2 F)	5q-; +8 1N 1 NA	Pyoderma gangrenosum Vasculitis ITP	CS,Cy, VP16 CS CS, IVIg	SAID remission, stable CMML AID remission, death from cerebral bleeding ITP transient response, no AML
Giannouli, 2004	n=2 (1 M/ 1 F)	1N 44XY; del7, del5, del 3q	Leucocytoclastic vasculitis	CS =1, ATG = 1	Refractory on SAID and MDS, deaths from infection
Isoda, 2009	1 F	46 XY t(3;8)	CIDP	IVIg, CS	SAID remission, AML
Park, 2011	1 F	N	Large vessel vasculitis	CS, Cy	SAID response, AML, death after alloASCT
Hadjadj, 2014	n=8 (5 M/ 3 F)	5N, 47 XY; +21	ITP	CS=4, Romiplostin = 3 Rituximab =1, IVIg = 2	7 chronic ITP, no AML, 1 death from infection
Peker, 2015	n=24 (18 M/6 F)	MLL mutation =2 monosomy 7 Trisomy 8 Del20q (=2) 15 N	7 ITP, Gout disease = 6 Psoriasis = 5, RA = 3 MS = 2, Sjogren =1 IBD = 1, Polymyalgia rheumatica =1	CS = 24 Rituximab = 4	NA

NA: not available, N: normal, CS: corticosteroids, Cy: cyclophosphamide, MTX: methotrexate, IVIg: intravenous immunoglobulin, CIDP: chronic inflammatory demyelinating polyneuropathy, ITP: immunologic thrombocytopenia, RA: rheumatoid arthritis, MS: multiple sclerosis, IBD: inflammatory bowel disease ; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome

