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Vasculitis associated with myelodysplastic syndrome and chronic myelomonocytic leukemia: French multicenter case-control study.

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Brief report

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Abstract

Introduction: Our objective was to evaluate characteristics, treatment and outcome of vasculitis associated with myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML)

Patients and Methods: Retrospective descriptive analysis of MDS/CMML-related vasculitis and comparison with MDS/CMML patients without dysimmune features.

Results: Seventy patients with vasculitis and MDS/CMML were included, with median age of 71.5 [21-90] years and male/female ratio of 2.3. Vasculitis was diagnosed prior to MDS/CMML in 31 patients (44%), and after in 20 patients. In comparison with MDS/CMML without autoimmune/inflammatory features, vasculitis with MDS/MPN showed no difference in MDS/CMML subtypes distribution nor International Prognostic Scoring System and CMML-specific prognostic (IPSS/CPSS) scores. Vasculitis subtypes included Giant cell arteritis in 24 patients (34%), Behçet's-like syndrome in 11 patients (20%) and polyarteritis nodosa in 6 patients (9%). Glucocorticoids (GCs) were used as first-line therapy for MDS/CMML vasculitis in 64/70 patients (91%) and 41 (59%) received combined immunosuppressive therapies during the follow-up. After a median follow-up of 33.2 months [1-162], 31 patients (44%) achieved sustained remission. At least one relapse occurred in 43 patients (61%). Relapse rates were higher in patients treated with conventional Disease Modifying Anti-Rheumatic Drug (DMARDs) (odds ratio 4.86 [95% CI 1.38 - 17.10]), but did not differ for biologics (odds ratio 0.59 [95% CI 0.11-3.20]) and azacytidine (odds ratio 1.44 [95% CI 0.21-9.76]) than under glucocorticoids. Overall survival in MDS/CMML vasculitis was not significantly different from MDS/CMML patients without autoimmune/inflammatory features ($p=0.5$), but acute leukemia progression rates were decreased (log rank <0.05).

Conclusion: This study shows no correlation of vasculitis diagnoses with subtypes and severity of MDS/CMML, and no significant impact of vasculitis on overall survival. Whereas conventional DMARDs seem to be less effective, biologics or azacytidine therapy could be considered for even low-risk MDS/CMML vasculitis.

Introduction

Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) are clonal hematopoietic malignancies characterized by ineffective hematopoiesis and frequent progression to acute myeloid leukemia (1). In 10 to 25% of cases, MDS or CMML (MDS/CMML) are associated with autoimmune and/or inflammatory manifestations, among which vasculitis is a frequent manifestation (2). Various vasculitis have been reported with MDS and CMML, mainly polyarteritis nodosa and leukocytoclastic skin vasculitis. The prognosis and management of these autoimmune and/or inflammatory disorders associated to MDS remain to be determined in large case series (3). Here, we report a French nationwide study that describes 70 patients with different types of vasculitis occurring in the context of MDS and/or CMML (MDS/CMML vasculitis), compare the overall survival and acute leukemia progression to patients with MDS/CMML without vasculitis.

Patients

Patients' selection

Patients with systemic vasculitis and MDS or CMML were included in this retrospective study from databases of “Groupe Francophone des Myélodysplasies” (GFM), “Société Nationale Française de Médecine Interne” (SNFMI) and “French Network of Dysimmune Disorders Associated with Hemopathies” (MINHEMON) groups. MDS or CMML were diagnosed according to the WHO 2016 classification (4), and vasculitis according to the revised Chapel Hill nomenclature (5). We included only patients diagnosed with MDS or CMML and vasculitis less than ten years apart. MDS or CMML secondary to previous immunosuppressive treatment, infectious-, or neoplasm-related immune disorders were excluded. Some patients with MDS/CMML-related giant cell arteritis (GCA) were previously reported (3).

Controls with MDS or CMML without any autoimmune or inflammatory disease were extracted from GFM prospective nationwide database and matched by age.

MDS/CMML definitions

MDS were classified using WHO classification: MDS with single lineage dysplasia (MDS-SLD), MDS with multilineage dysplasia (MDS-MLD), MDS with ring sideroblasts (MDS-RS), MDS-RS with single lineage dysplasia (MDS-RS-SLD), MDS-RS with multilineage dysplasia (MDS-RS-MLD), MDS with isolated del(5q), MDS with excess blasts (MDS-EB) EB-1 and EB-2, and unclassifiable (MDS-U). CMML were classified as CMML-0 (for cases with 2% blasts in the blood and 5% blasts in the bone marrow), CMML-1 (2 to 4% blasts in the blood and/or 5 to 9% blasts in the bone marrow) and CMML-2 (5 to 19% blasts in the blood and 10 to 19% blasts in the bone marrow).

Data collection

Data were collected using a standardized case report form. Clinical data included fever, weight loss, arthralgia and arthritis, cephalic manifestations (headache, jaw claudication), visual impairment, respiratory, kidney and neurological symptoms, as well as histological features at baseline, follow-up and last visit. Laboratory data included blood cell counts, C-reactive protein level, liver enzymes, serum creatinine level, cryoglobulinemia, anti-neutrophil cytoplasmic antibodies (ANC subtype and titers, proteinuria and hematuria

analysis. Birmingham Vasculitis Activity (BVAS) and Five Factors (FFS) scores were applied to vasculitis at baseline and during the follow-up. All type of treatment, such as glucocorticoids (GCs), conventional disease-modifying anti-rheumatic drugs (DMARDs), biologics and azacytidine, as well as the number of lines of therapy per patient were recorded. Regarding underlying MDS or CMML, data collection included bone marrow cytology and cytogenetic analyses, International Prognostic Scoring System (IPSS), revised-IPSS (IPSS-R) scales and its components, treatments and the incidence of evolution into acute myeloid leukemia. The presence and the type of somatic mutations by next-generation sequencing (NGS) were recorded if available.

Definitions of treatment response and relapse

Complete response to treatment was defined by a complete disappearance of clinical symptoms (BVAS=0), normalization of acute-phase reactants and immune analysis if applicable with a stable low dose of prednisone of < 7.5 mg per day. Partial response was defined by a minimal 50% improvement of clinical manifestations from baseline and at least 50% decrease of acute-phase reactants (6,7). Relapses and GCs-dependency were recorded during follow-up. Relapses were defined as the recurrence of disease-specific manifestations requiring treatment intensification and were considered as major if patients needed to be admitted to the hospital and minor in the remaining cases (6).

Statistical analysis

Data are expressed as medians (ranges) for quantitative variables and numbers (percentages) for qualitative variables. Student *t* test or Mann Whitney test (as appropriate) were used to compare quantitative data and Chi-square or Fisher's exact tests for qualitative variables. Overall relapse-free and GCs-free survivals were estimated using Kaplan Meier curves, and log-rank test was used to compare patients with MDS/CMML with and without vasculitis. We used a mixed logistic regression model to analyze the relationship between the probability of a relapse, defined as above, during the duration of treatment and the different treatments (DMARDs, biotherapy, azacytidine, steroids), adjusting for age, sex and number of previous lines administered as fixed effects. Patients were treated as random effects (random intercept) to take into account treatment sequences for the same patient. Cause-specific risk is reported as odds ratios (OR) and 95% confidence intervals. All tests were 2-sided and a *p*-value over 0.05 was considered statistically significant.

Statistical analyses were performed using GraphPad Prism v7.00 for Windows (GraphPad Software, La Jolla, CA USA) and R v3.4.3 for Windows (R Foundation for Statistical Computing, Vienna Austria).

Results

Baseline characteristics of MDS/CMML-associated vasculitis

Seventy patients with vasculitis and MDS/CMML were included, with a median age of 71.5 [21-90] years and male/female ratio of 2.3 (**Table 1**). The vasculitis subtypes included Giant-cell arteritis (GCA) in 24 patients (34%) among which 17 (71%) completely fulfilled ACR 1990 criteria for GCA (at least 3/4 criteria), and 8 (33%) had a positive temporal artery biopsy. The 7 remaining patients were all aged 50 years or over, with elevated acute-phase

reactant levels and unexplained fever, polymyalgia rheumatica and/or aortitis. Eleven patients (20%) had Behçet's-like syndrome among which four (6%) fulfilled complete criteria for Behçet's disease (4 points according to the international Behçet's criteria). Seven patients (10%) presented with at least 2 criteria (oral aphthosis, cutaneous or ocular symptoms), gastrointestinal involvement and/or venous thrombosis, and 7/11 patients have trisomy 8 karyotype abnormality. Six patients (9%) presented with polyarteritis nodosa (ACR criteria), seven (10%) with ANCA-associated vasculitis (AAV) among which 5 were diagnosed with microscopic polyangiitis and 2 with granulomatosis with polyangiitis (ANCA positive in 5 cases, with anti-PR3 and 4 anti-MPO). Three patients (4%) had cryoglobulinemia vasculitis and 2 (3%) biopsy-proven IgA vasculitis. Seventeen patients (24%) presented with symptoms suggestive of vasculitis without fitting with a specific entity, mainly unexplained fever (n=7; 41%), weight loss (n= 8; 47%), arthritis (n= 9; 53%), purpura (n= 4; 24%), deep vein thrombosis (n= 6; 32%) and/or eye involvement (n=4, 24%), with histological evidence of leukocytoclastic vasculitis. Median C-reactive protein levels at diagnosis were 60 mg/L [0-380], with BVAS score at 6 [0-24].

Vasculitis was diagnosed prior to MDS/CMML in 31 patients (44%), with a median time lapse of 27 months [1-120] between both diagnoses, concomitant to MDS or CMML diagnosis in 19 cases (27%) and after in 20 patients (median interval 6 months [1-59]).

MDS/CMML subtypes

Underlying MDS/CMML was MDS in 54 patients (77%) - mostly MDS with multilineage dysplasia (MDS-MLD, n=23, 33%), while 23% of patients presented with CMML (n=16). Patients were at low or intermediate risk IPSS/CPSS in 40 cases (74%) (**Table 1**). The NGS analysis of myeloid somatic mutations was negative in 5/25 cases and showed somatic mutations mainly of TET2 (n=4), ASLX1 (n=4), SF3B1 (n=4), NRAS (n=3), CBL (n=3), U2AF1 (n=2), SRSF2 (n=1), DNMT3A (n=1), KRAS (n=1), ZRSR2 (n=1), and P53 (n=1).

In comparison to 183 MDS/CMML without autoimmune and/or inflammatory features, patients with MDS/CMML vasculitis showed no difference in MDS/CMML subtypes distribution nor median IPSS/CPSS scores (**Supplementary Table 3**). Comparison between MDS-vasculitis and CMML-vasculitis showed no differences for age, gender, vasculitis subtypes and BVAS (**Table 1**). Whereas no significant difference in treatment response and relapse rates was noted in vasculitis with MDS and those with CMML, patients with CMML-associated vasculitis had significantly lower GCs-dependency (**Table 2**).

Vasculitis treatment and outcome

GCs (60 mg/day [0-500] of prednisone equivalent) were used as first-line therapy for MDS/CMML vasculitis in 64/70 patients (91%). Second and 3rd line therapies were required for GCs-dependency or refractory patients in 56% and 31%, respectively. Forty-one (59%) received combined immunosuppressive therapies during follow-up (**Table 2**). Complete or partial response was observed in 50 MDS/CMML patients (71%) overall, with 56% of response at first line (39 patients), 8 % at second line (6 patients), 6 % (4 patients) at third line therapies. There was a trend to more treatment failure rates under GCs alone versus first-line combined immunosuppressive therapies (6/12 (50%) versus 13/49 (26%); p=0.07) (**Supplementary Figure 1**). Median BVAS, C-reactive protein levels and daily prednisone

dose significantly decreased from baseline to 6 and 12 months visits (**Supplementary Figure 2**). After a median follow-up of 33.2 months [1-162], 31 patients (44%) finally achieved sustained remission.

Nineteen MDS/CMML vasculitis (27%) were treated with azacytidine, a hypomethylating drug, among which 5 patients with low or intermediate-1 MDS risk receiving azacytidine for GCs- dependency or refractory vasculitis. Response of MDS/CMML vasculitis to azacytidine was noted in 9 (47%) patients with prednisone equivalent dose decreasing from 50 mg/day [30-80] at baseline to 5 mg/day [0-20] ($p=0.0006$) after 6 cycles of azacytidine, while hematological response was noted in 7 (37%) cases.

At least one relapse occurred in 43 patients (61%) during follow-up, with a median number of relapse of 1 [0-4] and a time to first relapse of 13 months [1-70]. GCs-dependency was observed in 32 patients (46%), at a median prednisone dose of 20 [12-45] mg/day. No factor was significantly associated with GCs-dependency. Relapse rates were higher in patients treated by conventional DMARDs (odds ratio at 4.86 [95% CI 1.38 - 17.10]), but did not differ from biologics (odds ratio 0.59 [95% CI 0.11-3.20]) and azacytidine (odds ratio 1.44 [95% CI 0.21-9.76]) (steroids considered as reference) (**Figure 1 and (Supplementary Figure 3)**).

Comparison to MDS/CMML patients without vasculitis

MDS/CMML patients with vasculitis ($n=70$) were compared to MDS/CMML patients without any autoimmune and/or inflammatory features ($n=183$) (**Supplementary Table 3**). Overall survival were not different between the two groups ($p=0.5$), even in patients with MDS low-risk disease (**Supplementary Figure 4**). Risk of AML occurrence was significantly reduced in patients with vasculitis (log rank=0.02), with median of time to acute myeloid leukemia (AML) not reached in patients with vasculitis versus 4.68 years [IC95% [3.68; 5.62] in MDS without vasculitis (**Figure 2A-B and Supplementary Table 3**). Twenty patients (29%) among MDS/CMML vasculitis died during follow-up versus 47 (26%) in MDS/CMML without autoimmune and/or inflammatory disease ($p=0.75$).

Discussion

This largest study of MDS/CMML-associated vasculitis describes the pattern, outcome and management of patients with this rare condition. We show no association between vasculitis diagnoses and subtypes and severity of the underlying MDS/CMML. Whereas there was no significant impact of vasculitis on overall survival, time to progression to acute myeloid leukemia was significantly longer in patients with vasculitis. The high rates of relapse and GCs dependence raise the question of combined therapies use to spare steroids. MDS/CMML azacytidine therapy could be considered for even low-risk MDS/CMML vasculitis, as an alternative to conventional DMARDs and biologics.

Vasculitis have been previously described in the context of MDS/CMML, mostly polyarteritis nodosa and leukocytoclastic vasculitis (8-16). In our previous study on 123 MDS-related autoimmune and/or inflammatory diseases, vasculitis was noted in 32% of the patients, with mainly polyarteritis nodosa and giant-cell arteritis (7). In another retrospective study (17), patients presented mostly with isolated cutaneous manifestations (67%) and 4 patients with systemic vasculitis (granulomatosis with polyangeitis, microscopic polyangeitis, relapsing

polychondritis and eosinophilic granulomatosis with polyangiitis). In the present study, GCA represented the most frequent vasculitis, which could be consistent with more frequent GCA in patients with older ages similar to MDS. Hence, the possibility of an underlying MDS or CMML should be discussed in GCA and polyarteritis nodosa patients, especially in case of GCs dependent or refractory vasculitis.

Overall survival was not negatively impacted by the presence of vasculitis in MDS/CMML patients. These data are consistent with our previous results, showing in 123 patients with MDS/CMML various associated diseases no difference in comparison to patients without autoimmune and/or inflammatory features. One study showed that vasculitis could negatively impact the overall survival in MDS, but with a limited number of patients (17, 18). Furthermore, less vasculitis-MDS/CMML patients progressed to acute myeloid leukemia which could be partly explain by more frequent low and intermediate risk MDS in the subset of these patients.

The most challenging question is the management of these patients, with the goal to control autoimmune and/or inflammatory manifestations while maintaining a satisfactory hematological response (13). In the absence of specific guidelines, GCs and conventional DMARDs are commonly used, but this strategy can be limited due to MDS-related cytopenias, the risk of infectious events and DMARDs-induced MDS. Among MDS/CMML vasculitis, relapse rates were as high as 61%, with 59% requiring combined therapies during follow-up. The large number of vasculitis subtypes did not allow any comparison according to the type of vasculitis, as important differences could be considered in various idiopathic forms of vasculitis. Conventional DMARDs should be probably avoided in these patients, as they seem to be associated with higher relapse rate and because of their inherent risk of aggravating cytopenias. The question of azacytidine benefit as a GCs-sparing agent (19-21), at least in some patients, and is currently being evaluated in tested for the management of GCs-dependent or refractory vasculitis in a French non-randomized clinical trial (ClinicalTrials NCT02985190) (22).

Our study have several limitations, especially the retrospective design, the absence of standardized and homogeneous therapies, various types of vasculitis and MDS/CMML subtypes and the lack of comparison to vasculitis without MDS/CMML. Another point is the tendency to have more males in MDS/CMML patients with vasculitis, which could have some bias for the overall survival analysis. However, this large case-series provides new insights into this rare condition and could help the physicians to better manage these patients.

Conclusion

In this study of MDS/CMML-related vasculitis high rates of relapse and GCs-dependency raise the question of combined therapies to GCs, and early use of MDS specific therapies, such as azacytidine should be discussed.

Figure 1. Relapse-free survival rates with azacytidine, biologics, steroids and DMARDs
Figure 2. Overall survival and time to progression to acute leukemia in MDS/CMML vasculitis and MDS without vasculitis.

Table 1. Characteristics of MDS/CMML-related vasculitis according to MDS/ CMML subtypes.

Characteristics at baseline	Vasculitis-MDS/CMML (n=70)	Vasculitis-MDS (n=54)	Vasculitis-CMML (n=16)
Age (years)	71.5 [21-90]	71 [22-90]	66.5 [21-79]
Males (n;%)	49 (70)	37 (68)	12 (75)
Vasculitis before MDS/CMML Time between 2 diagnosis (months)	31 (44.3) 27 [1 - 120]	26 (48) 29.5 [1 - 120]	5 (31) 22.5 [2 - 51]
Vasculitis after MDS/ CMML Time between 2 diagnosis (months)	20 (28.5) 6 [1-59]	12 (22) 4.5 [1-59]	8 (50) 14.2 [1-59]
Type of vasculitis			
Giant cell arteritis (n;%)	24 (34)	19 (36)	5 (31)
Polyarteritis nodosa (n;%)	6 (9)	3 (5)	3 (19)
Behçet / Behçet like disease (n;%)	4 (6) / 7 (10)	3 (5) / 5 (9)	1 (6) / 2 (13)
Unclassified vasculitis (n;%)	17 (24)	14 (26)	3 (19)
ANCA-associated vasculitis (n;%)	7 (10)	7 (13)	0
IgA / Cryoglobulinemic vasculitis (n;%)	2 (3) / 3 (4)	1 (2) / 3 (4)	1 (6) / 3 (4)
C-reactive protein (mg/L)	60 [0-380]	60 [0-333]	60 [3-380]
BVAS at diagnosis	6 [0-24]	6.5 [0-24]	6 [0-14]
MDS/ CMML features			
Hemoglobin (g/dL)	10 [7-15]	9.5 [7-12] *	11 [8.2-15] *
Platelets (G/l)	159 [25-1780]	159 [25-1780]	160 [59-421]
Neutrophils (n/mm ³)	2350 [300-21490]	2035 [300-21490]*	6880 [1290-18000]*
MDS with multilineage dysplasia (MDS-MLD) (n;%)	23 (33)	23 (43)	-
Refractory anemia with excess blasts-1 (RAEB-1)/ RAEB-2(n;%) /	9 (13) / 7 (10)	9 (17)/ 7 (13)	-
MDS with ring sideroblasts (MDS-RS) (n;%)	4 (6)	4 (7)	-
MDS-RS with single lineage dysplasia (MDS-RS-SLD) / MDS-RS with multilineage dysplasia	1 (1) / 1 (1)	1 (2) / 1 (2)	-

(MDS-RS-MLD) (n;%)			
MDS, unclassifiable (MDS-U)/ del 5 q- (n;%)	2 (3) /3 (4)	2 (4) /3 (5)	-
IPSS / CPSS (n, %) - Low / intermediate-1 - Intermediate-2 / high	-	18 (33) / 22 (41) 6 (11) / 3 (6)	9 (56) / 4 (25) 3 (19) / -
Blood / Bone marrow blasts (%)	0 [0-5] / 2 [0-29]	0 [0-5] / 2 [0-29]	0 [0-3] / 4 [0-16]
Acute myeloid leukemia (n;%)	9 (13)	7 (13)	2 (12.5)

Values are medians with ranges and numbers with frequencies.

*p<0.05 vasculitis-MDS vs vasculitis-CMML

Table 2. Treatments and outcomes of MDS/CMMLMPN-related vasculitis.

Characteristics	Vasculitis-MDS/CMML (n=70)	Vasculitis-MDS (n=54)	Vasculitis-CMML (n= 16)
Steroids (mg/day)	60 [0-500]	60 [0-500]	60 [0-80]
Lines of therapy	2 [0-6]	2 [0-6]	1 [0-4]
Immunosuppressive therapy (n, %)	41 (59)	35 (65)	6 (38)
- Methotrexate / Azathioprine	8 /10	8 /7	0 /3
- Tocilizumab	3	3	0
- Cyclophosphamide	8	6	2
Complete/partial response (n, %)	50 (71)	39 (72)	11 (69)
Relapse (n, %)	43 (61)	33 (61)	10 (62.5)
Steroid dependence (n, %)	32 (46)	31 (58)	4 (25)*
Deaths (n, %)	20 (29)	15 (28)	5 (31)
Follow-up (months)	33.2 [1-162]	34.8 [1-161]	17 [1-162]

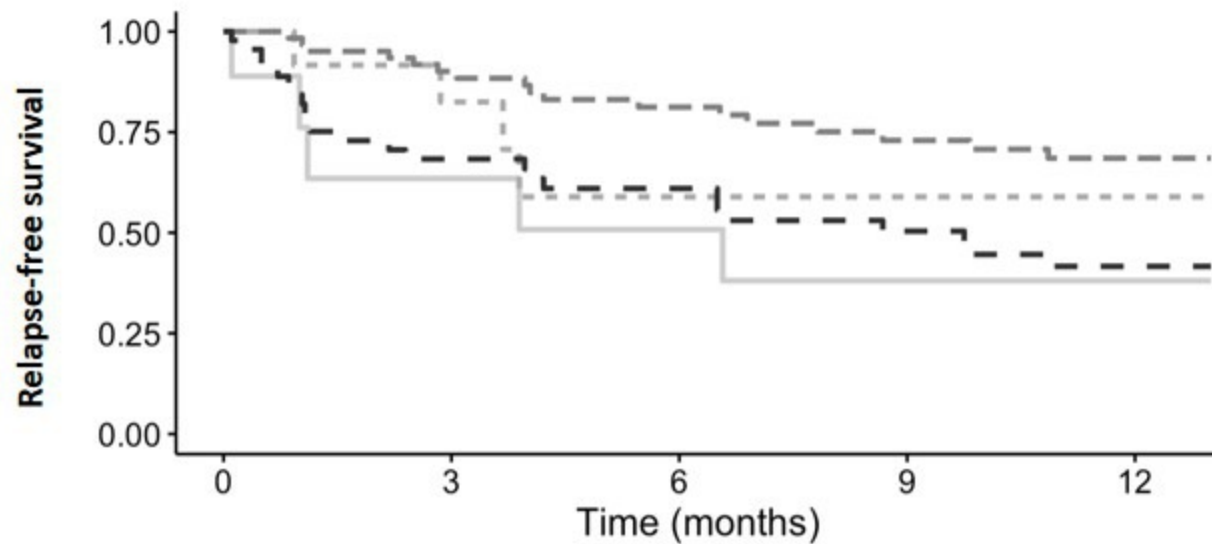
Values are medians with ranges and numbers with frequencies.

*p<0.05 vasculitis-MDS vs vasculitis-CMML

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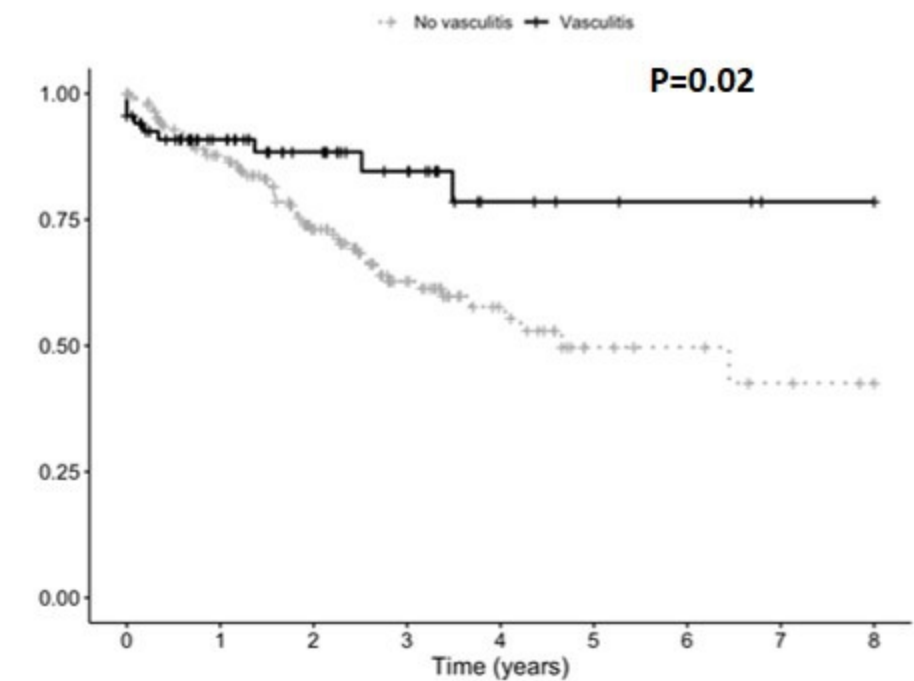
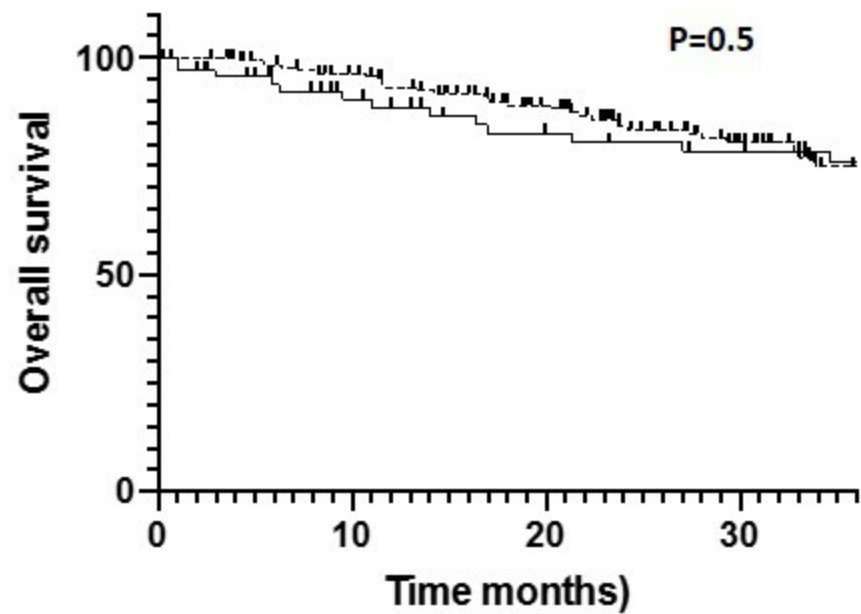


Number at risk

Azacytidin	11	5	4	3	3
Biologics	17	9	5	5	5
Steroids	67	53	43	34	30
DMARDs	53	30	23	18	14

— Azacytidin ··· Biologics - - - Steroids - · - DMARDs

Fig.1 – Relapse-free survival rates with azacytidine, biologics, steroids and DMARDs



Number at risk

vasculitis	174	131	85	47	25	10	8	5	3
no vasculitis	68	44	30	21	10	8	7	5	5
	0	1	2	3	4	5	6	7	8

Figure 2A and B