Inflammatory Disorders Associated with Trisomy 8-myelodysplastic Syndromes: French Retrospective Case-control Study

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Nadege Wesner[1], Louis Drevon[2], Alexis Guedon[3], Jean Baptiste Fraison[4], Salim Trad[5], Jean Emmanuel Kahn[6], Achille Aouba[7], Jerome Gillard[8], Matthieu Ponsoye[5], Thomas Hanslik[5], Clement Gourguechon[9], Eric Liozon[10], Khaled Laribi[11], Julien Rossignol[12], Olivier Hermine[12], Lionel Adès[2], Fabrice Carrat[3], Pierre Fenaux[2], Arsene Mekinian[1], Olivier Fain[1]. On behalf GFM and MINHEMON (French Network of dysimmune disorders associated to hemopathies)

[1]Department of Internal Medicine, Inflammation-Immunopathology-Biotherapy Department (DHU i2B), Assistance Publique - Hôpitaux de Paris, Hôpital Saint-Antoine, 184, rue du Faubourg Saint-Antoine, 75012 Paris, France UPMC University Paris 06, Paris, France
[2]Sorbonne Universités, UMPC University Paris 06, INSERM U938, Centre de Recherche Saint-Antoine (CRSA), Paris, France
[3]Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique IPLESP, AP-HP, Hôpital Saint Antoine, F75012 Paris, France
[4]Department of Internal Medicine, Assistance Publique - Hôpitaux de Paris, Hôpital Cochin, 27 rue du Faubourg St Jacques, 75014 Paris, France
[5]Department of Internal Medicine, Assistance Publique - Hôpitaux de Paris, Hôpital Ambroise Paré, 9 avenue Charles de Gaulle, 92100 Boulogne Billancourt, France
[6]Department of Internal Medicine, Hôpital Foch, 40 rue Worth, 92150 Suresnes, France
[7]Department of Internal Medicine, CH Caen, Avenue de la côte de nacre, 14033 Caen, France
[8]Department of Rheumatology, CH Lons le Saunier, 55 rue du Docteur Jean Michel 39016 Lons le Saunier, France
[9]Department of Internal Medicine, CHU Amiens-Picardie, Chemin de Longpré, 80080 Amiens, France
[10]Department of Internal Medicine, CHU Limoges, 2 Avenue Martin Luther King, 87000 Limoges, France
[11]Department of Internal Medicine, CH Le Mans, 194 Avenue Rubillard, 72037 Le Mans, France
[12]Department of Hematology, Assistance Publique - Hôpitaux de Paris, Hôpital Necker Enfants Malades, 149 rue de Sèvres, 75015 Paris, France

Correspondance: Dr Arsène Mekinian, Service de médecine interne, hôpital Saint Antoine, 184, rue du Faubourg Saint-Antoine, 75012 Paris, France.
Tel: +33 (0) 1 / Fax: +33 (0) 1
E-mail: arsene.mekinian@aphp.fr

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Abstract

Objective

We report myelodysplastic syndrome (MDS)-associated systemic inflammatory and autoimmune diseases (IADs) with cytogenetic trisomy 8, and describe their outcome, treatments efficacy and impact on MDS survival in a French multicenter retrospective study.

Methods

In this study, 21 patients with trisomy 8-MDS and IADs were analyzed and compared to 103 MDS patients with trisomy 8 without IADs.

Results

The median age was 67 [59 - 80] years and the male/female ratio 0.9. The IADs were Behçet's or Behçet's-like disease in 11 (52%) cases, inflammatory arthritis in 4 (19%) cases, Sjögren's syndrome, autoimmune hemolytic anemia, aseptic abscesses, periarteritis nodosa, Sweet's syndrome and unclassified vasculitis in one case each. Trisomy 8 karyotype was isolated in 8 cases (38%) and associated with other abnormalities in remaining cases. Seventeen (81%) IADs patients were treated (88% with steroids) with complete and partial response in 35% and 47%, respectively. A second-line therapy was required for steroid dependence or relapse in 38% of cases. The effect of MDS treatment on IADs could be assessed in 7 patients treated with azacytidine: 5/7 achieved remission and 2/7 partial response of IADs. Compared with 103 trisomy 8-MDS/CMML patients without IADs, IADs patients were more often non-Caucasian ($p = 0.004$), MDS subtype tended to have more frequently CRDM ($p = 0.09$) and poor karyotype ($p<0.001$). We found no difference in overall survival or acute myeloid leukemia progression between patients with trisomy 8-MDS-associated IADs and without IADs.

Conclusion

The spectrum of IADs associated to trisomy 8-MDS is dominated by Behçet's disease, but other various immune disorders can be also associated. Steroid therapy is often effective, but sparing therapies are mostly necessary and azacytidine could be an effective alternative.

Introduction:

Myelodysplastic syndromes (MDS) are clonal hematopoietic malignancies characterized by ineffective hematopoiesis and progression to acute myeloid leukemia. The cytogenetic abnormalities constitute one of major parameters to determine the risk of progression to acute myeloid leukemia. The trisomy 8 belongs to the IPSS intermediate-risk cytogenetic subgroups (alone or associated with other karyotype abnormalities) and ranges between 10% to 15% of MDS (1). In the presence of trisomy 8, the median survival is impaired to 25 months in comparison to 55 months in MDS with normal karyotype (2). The trisomy 8 can be find in various MDS subtypes, and is more frequent in CMML than MDS (3). MDS and CMML can be associated with inflammatory or autoimmune features in 15 to 25% of cases, with various rates in different MDS/CMML subtypes. In a recent case-series, we showed that trisomy 8 could be associated with Behcet's like disease, whereas we found no other phenotype-karyotype combinations (4). Previously several case-reports and case-series from asian groups reported Behçet's-like syndrome associated with trisomy 8 MDS, but larger data about the spectrum of inflammatory diseases associated with trisomy 8, outcome and treatments are not available (5).

In this French nationwide study from French Network on immune diseases associated to MDS/CMML (MINHEMON), we report 21 cases of MDS/CMML-related IADs with cytogenetic trisomy 8, describe their outcome, treatments efficacy and impact of associated IADs on overall survival and acute leukemia progression.

Patients and methods:

Patient's selection and data collection

From the French group MINHEMON, SNFMI and GFM, all cases of patients with MDS, CMML, trisomy 8 and associated IADs have been collected. Inclusion criteria were as follows: 1. MDS or CMML (2008 OMS); 2. Isolated or combined trisomy 8 on medullar karyotype; 3. Systemic inflammatory or autoimmune features; 4. Time between MDS and IADs less than 5 years. The exclusion criteria were secondary MDS to previous immunosuppressive drugs; infectious, drug or neoplasm-related immune disorders.

MDS prognosis was evaluated using the International Prognostic Scoring System (IPSS) and revised IPSS (IPSS-R). Response to specific hematological treatment was evaluated using IWG criteria (6).

IADs diagnosis was established using the usual international diagnostic and classification criteria (p.e ACR criteria for SLE, Chappel Hill classification for vasculitis, International

Behcet's criteria). The IADs was considered as incomplete or unclassified in the absence of sufficient criteria for well-defined IADs. For Behcet's disease diagnosis at least ≥ 3 criteria were needed, and Behcet's like disease was considered in the presence of at least 2 criteria, and/or because of frequent gastrointestinal involvement its combination with at least oral and/or genital aphtosis and/or thrombosis and/or characteristic ocular involvement in the absence of other features of another immune disease (The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria). Following clinical features were collected at the time of IADs diagnosis and during the follow-up: constitutional signs (non-infectious fever), skin abnormalities, arthritis, ocular manifestations, gastrointestinal features, neurological peripheral or central involvement, venous or arterial thrombosis. Laboratory data were recorded for blood count, C-reactive protein levels and serum creatinine, HCV, HIV serologies, ANCA and antinuclear antibodies, cryoglobulinemia and complement system. Response of IADs was defined as complete in the case of complete disappearance of all clinical signs, acute-phase reactants and immunological abnormalities, and partial if at least 50% improvement of clinical and biological signs was achieved.

The control group consisted of 103 patients with MDS associated to trisomy 8 without any systemic inflammatory or autoimmune features which were extracted from the "GFM" prospective registry.

Statistical analysis

Data are expressed as medians with interquartiles 25 and 75 for quantitative variables and numbers with frequencies for qualitative variables. Continuous variables were compared using Mann Whitney test or Kruskal-Wallis for analysis of more than 2 groups and Fischer's exact test was used to compare the qualitative variables. The overall survival and survival free of progression to acute myeloid leukemia were estimated using Kaplan Meier curves and compared between patients with and without IADs or according to treatment with the log-rank test. All tests were two-tailed and a $p \leq 0.05$ was considered statistically significant. Survival analyses and plots were performed using R version 3.4.3 for Windows (R Foundation for Statistical Computing, Vienna Austria) using the survminer package. All the other statistical analyses were performed using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla California USA).

Results :

Twenty-one patients with IADs associated to MDS/CMML with trisomy 8 and 103 trisomy 8-positive MDS without IADs have been included (**Table 1**). The IADs were Behçet's or Behçet's-like disease (n=11; 52%), inflammatory arthritis (n=4; 19%), Sjögren's syndrome, autoimmune hemolytic anemia, aseptic abscesses, periarteritis nodosa, Sweet's syndrome and unclassified vasculitis (n=1, each). Among the 11 patients with Behçet's disease, only 2 (18%) fulfilled the usual classification criteria, whereas all other patients with non Behçet's disease satisfied usual diagnostic criteria. Among patients with Behcets' disease, 10/11 (90%) had oral aphtosis, 4/11 (30%) genital aphtosis, 4/11 (30% characteristic skin lesions and 1/10 10% venous thrombosis, without any case of ocular involvement. Gastrointestinal involvement was present in 7/11 (64%) of patients with Behçets' syndrome. The main clinical features in 21 patients consisted in general signs (n=12, 63%), joint involvement (n=12, 60%), gastrointestinal (n=11, 52%) and skin signs (n=7, 37%). Median C-reactive protein levels at IADs diagnosis were at 36 mg/L (8 - 97). The median time from MDS and IADs diagnosis was 1 month (0 – 10). IADs occurred at the time of MDS diagnosis in 9 cases (47%), before MDS diagnosis in 6 cases (32%) and after MDS diagnosis in 4 cases (21%).The MDS subtype was mainly RAEB-1 (n=6; 28%), and multilineage cytopenias dysplasia (n=4; 19%), with 2 CMML. The CMML-associated diseases were Behçet's diseases (n=2). Trisomy 8 karyotype was isolated in 8 cases (38%) and associated with other abnormalities in the remaining cases (**Table 2**). In comparison to trisomy 8 with other abnormalities, patients with isolated trisomy 8 have similar frequencies of various MDS subtypes, median IPPSS and IPSS-R, acute myeloid leukemia progression and deaths. The distribution of IADs was significantly different, with 11/13 (85%) Behcet or Behcet like disease in trisomy 8 with other abnormalities versus none in isolated trisomy 8 (p=0.0067), without any differences for other IADs. The complete and partial responses to steroids were similar in patients with isolated trisomy 8 and others.

In comparison to trisomy 8-positive MDS without IADs, IADs patients were younger (p = 0.003), have similar demographic characteristics, median IPSS and IPSS-R, medullar blasts numbers, but frequency of non-Caucasians (all from North Africa) was most frequent in MDS associated with IADs (p = 0.004) (**Table 1**). MDS subtypes tended to be more frequently CRDM in MDS associated with IADs (19% versus 7%, p = 0.09), whereas other MDS subtypes distribution was similar between the 2 groups. Karyotypes were more frequently of intermediate group in MDS without IADs, and poor in MDS with associated IADs (**Table 1**). The median follow-up was 21 [8.5 – 43.5] and 20.5 [8–36] months in MDS/CMML with and without IADs, and the frequencies of acute leukemia and deaths were similar in 2 groups.

Seventeen patients (81%) received first line therapy for IADs which consisted of steroids in 88% cases, combined in 40% with other drugs (methotrexate, hydroxychloroquine, colchicine, tocilizumab, azathioprine and thalidomide (n=1 for each; 6%) (**Figure 1**). IADs complete and partial responses were obtained in 6 cases (35%) and 8 cases (47%), respectively (**Figure 1**). A second-line therapy was required for steroid dependence (n=6) or relapse (n=2) in 38% of cases and consisted mainly in biological-targeted drugs (tocilizumab, anakinra, infliximab). Complete or partial response to the 2nd line therapy occurred in 63% cases, but third-line therapy was used in 25% cases for steroid dependence (n=4) or inefficacy (n=1). During the 21 months [8.5 – 43.5] of median follow-up, the frequencies of IADs clinical features tended to decrease, and C-reactive protein levels remained stable (p=0.8; ANOVA test) (**Table 2**). Median steroids amounts decreased from 32 mg/day [20 - 52] at baseline to 2.5 mg/day [0 - 9.25] at the last visit (p=0.02), but 29% of patients were still steroid-dependent at the last visit. The IADs remission status did not correlate with stable MDS during the follow-up. At the last follow-up, 37.5% of patients in remission of IADs have MDS progression, and 50% of IADS which were not in remission have MDS progression.

First-line hematological therapy for MDS/CMML was initiated in 11/18 cases (61%) and consisted in azacytidine (n = 7; 39%), ciclosporin (n = 2; 9.5%) and lenalidomide, cytarabine or hydroxyurea (n= 1, each). In 4/11 (36%) cases the hematological treatment was initiated for steroids refractory or dependent IADs. Complete or partial hematological response to first-line treatment occurred in 2/10 cases (20%) and 5/10 evaluable cases (50%) respectively. Nine from 21 (43%) patients required a second-line hematological therapy: azacitidine (n = 6; 29%) and lenalidomide (n =1). Complete or partial response was achieved in 4/9 (44%) evaluable cases.

Among 13 patients treated with azacytidine (first or second line therapy for MDS/CMML), 7 patients under steroids alone and 3 patients without any treatment could be evaluated for IADs response to azacytidine. Among them, 2/10 (20%) patients have partial response at 3 and 12 months respectively, and 5/10 (50%) patients have complete IADs response at 6 (for two), 9, 10 and 12 months respectively. Azacytidine allowed steroids sparing effect in 40% of these patients after 6 to 12 months of treatment.

Among 11 patients with Behcet's disease, 3/11 (27%) received steroids alone in comparison to 1/10 (10%) of other IADs. Other immunosuppressive drug was associated to steroids in 4/11 (36%) of Behcet's disease in comparison to 5/10 (50%) of other IADs. Complete IADs treatment response rates were 55% and 20% in Behcet's disease and other IADs, respectively. Partial IADs treatment response rates were 27% and 50% in Behcet's disease and other IADs, respectively. One patient with severe gastrointestinal Behçet's disease with needed digestive surgery and was immediately treated with azacitidine, which allowed IADs and MDS

concomitant remissions after 6 months of treatment, and allowed the discontinuation of steroid therapy. The number of deaths and progression to acute myeloid leukemia were similar in Behcets' disease and other IADs (7 deaths vs 5 deaths and 2 acute myeloid leukemia each, respectively).

The median survival was similar in MDS patients with IADs and those without associated IADs (27 months in MDS patients with IADs versus 42 months in MDS patients without associated IADs; log rank=0.215) (**Figure 1**). The acute myeloid leukemia-free survival was also similar in MDS patients with and without IADs (log rank =0.96) (**Figure 2**). As expected, the hematological treatment significantly improved the overall survival (28 months in treated versus 19 months in untreated MDS (log rank =0.02)).

Discussion

In this study we report about a large spectrum of immune diseases associated with trisomy 8 in the subset of MDS/CMML. Most common IADs was Behçet's or Behçet's-like disease (52%), highlighting the previously reported link from asiatic groups between this cytogenetic abnormality and the clinical phenotype. Other various autoimmune manifestations were also reported, with a predominance of inflammatory arthritis. Another interesting feature is the predominance of non-European origin in these subsets. The IADs associated to MDS/CMML with trisomy 8 have similar survival and progression rate to acute myeloid leukemia than MDS/CMML without IADs. Steroid sparing effect have been shown with DSM specific azacytidine treatment, even studies with larger patients are necessary.

As far as we know, this is the first case-series that report a large various IADs associated to MDS/CMML, in particular in non-asian population. In our previous survey of French nationwide MDS/CMML-related diseases, among 6 patients with Behçet's disease 3 had trisomy 8 which was the only karyotype abnormality correlating with clinical subtype. Another study showed that 13/62 patients had trisomy 8 which also correlated with Behçet's disease (7). The relationship between trisomy 8-MDS/CMML and Behçet's disease was previously exclusively described in asian case-series and case-reports (8). Interestingly, children with constitutional trisomy 8 can develop Behcet's disease, and are also at risk of early myelodysplastic syndrome. The Behçet's disease in the context of MDS seems to have much higher prevalence of gastrointestinal involvement, with increased rates of digestive perforations and surgery need. Importantly, frequently Behcet's syndrome in this context did not fulfill usual diagnostic criteria, and in some case the differential diagnosis with Crohn's disease could be difficult. In our case-series none of patients with Behcets disease have isolated trisomy 8 and associated karyotype abnormalities have been shown in all these IADs,

whereas previous asiatic case reports showed isolated trisomy 8 with Behcet's disease in 14/21 available cases (67%). We report here that other immune disorders can be associated with trisomy 8 positive MDS/CMML, as usually shown in the subset of MDS/CMML. Such a various diseases like inflammatory arthritis, sweet's syndrome, vasculitis which are usually known to be associated with MDS/CMML can also be seen in MDS positive trisomy 8.

Treatment of MDS-associated IADs can be challenging, because of the underlying cytopenias related to MDS/CMML and the increased risk of infectious complications. Usually, steroids are used and allow complete response only in 30% of cases. As we previously shown in MDS/CMML associated IADs, most patients need steroids-sparing therapy, because of initially uncontrolled disease. As the use of DMARDs in the context of underlying MDS/CMML could be challenging, biological-targeted therapies are usually used. As we previously reported, in the subset of MDS/CMML the efficacy of biological-targeted drugs seem to be lower than usually seen in idiopathic IADs, except for rituximab in cryoglobulinemic vasculitis. Even if significant decrease of steroids has been shown during the follow-up, more than half of patients could not be went of steroids. The treatment of the underlying hematological disease has been reported to improve the outcome of associated IADs, even in low-risk MDS/CMML (9). As previously reported in MDS/CMML, treatment of the underlying hematological disease, in particular with azacytidine, seem also be beneficial for the IADs, in particular for steroid-sparing effect.
The impact of IADs on overall survival of MDS/CMML is controversial. Our previous data of 123 IADs with MDS matched to 665 MDS/CMML without IADs showed no impact on overall survival, deaths or progression to acute leukemia. Similar data have been shown in a prospective study of 13 MDS-related IADs and 57 MDS controls (10), whereas another study showed in 46 IADs with MDS decreased overall survival in two specific groups of patients : systemic vasculitis or cryoglobulin vasculitis, but only few cases of these patients could be analyzed (11). In our case-control study, no difference in overall survival, the rates of progression to acute myeloid leukemia have been shown in these specific subset of trisomy 8 positive MDS.

In conclusion, we show that trisomy 8 positive MDS/CMML can be associated with large spectrum of IADs, and among them mostly Behçet's syndrome with gastrointestinal involvement. IADs therapy with steroids in the context of MDS/CMML is not sufficient, and the benefit of specific hematological therapy could be discussed, independently of hematological indication. Gene candidate studies could help to determine the implicated mechanism related to trisomy 8 associated IADs.

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Table 1. Characteristics of IADs associated with MDS-trisomy 8 and MDS-trisomy 8 without IADs.

Characteristics	IADs with MDS N=21	MDS without IADs N=103	p
Age (years)	67 (59 – 80)	81 (72 – 88)	0.003
Females	11/21 (52%)	48/103 (47%)	0.77
Non Europeans	5/21 (24%)	3/103 (3%)	0.005
Refractory anemia	3/21 (14%)	13/103 (13%)	0.5
Refractory anemia with excess blasts -1	6/21 (28%)	27/103 (26%)	0.5
Refractory anemia with excess blasts -2	3/21 (14%)	18/103 (18%)	0.5
Multilineage cytopenias dysplasia	4/21 (19%)	7/103 (7%)	0,09
Chronic myelomonocytic leukemia	2/21 (8%)	0/103	NA
Unclassified MDS	2/21 (9.5%)	11/103 (11%)	0.5
SMD/SMP	1/21 (4.8%)	11/103 (11%)	0.7
AS	0	15/103 (15%)	0.2
IPSS	1 (1 – 1.9)	1 (0.5 – 1.5)	0,8
IPSS-R	4 (3 – 5.6)	4 (3 – 5.5)	0,8
Hemoglobin (g /dL)	10 (8,7 – 10,4)	9.55 (8.7 – 10.9)	0,4
Platelets (G/L)	137 (66 - 300)	113.5 (59.7 – 224)	0,36
Neutrophils (/mm3)	1900 (996 – 4200)	2115 (950 – 5035)	0,46
Monocytes (/mm3)	200 (182 – 500)	338 (126 – 527)	0,65
Blood blasts (%)	0 (0 – 2)	0 (0 – 0.5)	0,17
Medullar blasts (%)	4 (0 – 8)	4 (2 – 7.25)	0,5
Medullar richess (%)	15/19 (79%)	81/97 (84%)	0,75
Karyotype			
Very good	0/21	0/103	-
Good	0/21	0/103	-
Intermediate	11/21 (52%)	95/103 (92%)	<0.001
Poor	8/21 (38%)	0/103	<0.001
Very poor	2/21 (9.5%)	0/103	0.02
Follow-up (medians ; ranges)	21 (8,5 – 43,5)	20.5 (8 – 36.25)	0,62
Acute myeloid leukemia	4/16 (25%)	21/102 (21%)	0,7
Deaths	12/17 (71%)	53/94 (56%)	0,22

Table 2. Trisomy 8 and other associated cytogenetic abnormalities.

Karyotype	MDS with IADs	MDS without IADs
Trisomy 8 isolated	8 (38%)	95 (92%)
Microsomy 15	1	0
Trisomy 14	1	0
Trisomy 9	1	0
Trisomy 19	1	0
Trisomy 21	1	0
Tetrasomy 7	1	0
Tetrasomy 8	1	1
Translocation (13;2)	1	0
Del 1p	1	0
Del 5q	2	0
Del 20q	2	0
Del 7q	1	0
Monosomy 17	1	0
Monosomy 20	1	0
Monosomy 7	1	0
Monosomy X	1	1
Monosomy 13	1	0
Del 21q	1	0
+mar(20)	1	0

Table 3. Outcome of patients with IADs and MDS/CMML.

	At IADs diagnosis N = 21	At 6 months N = 14	At 12 months N = 14	At 24 months N = 6	Last visit N = 17
Hb (g/dL)	10 (8,7 – 10,4)	10 (9 – 11,5)	10 (7,8 – 11,3)	10 (8,7 – 10,5)	9,2 (8 – 11,5)
Platelets (G/L)	137 (66 - 300)	114 (38 – 234)	120 (80 – 201)	138 (102 – 240)	120 (44 – 207)
Neutrophils (/mm3)	1900 (996 – 4200)	3810 (1600 – 12125)	1249 (807 – 3160)	1000 (632 – 3873)	1500 (650 – 4962)
Monocytes (/mm3)	200 (182 – 500)	300 (100 – 800)	200 (175 – 462)	160 (110 – 400)	-
Stable MDS (n, %)	0	9/14 (64%)	6/14 (43%)	3/6 (50%)	6/15 (40%)
IADS clinical features (n, %)	21/21 (100%)	10/14 (71%)	11/11 (100%)	1/3 (33%)	4/13 (31%)
C-reactive protein (mg/L)	36 (8 - 97)	47 (4,5 – 71,5)	32 (11 – 48)	9,9 (7 – 136)	79 (5 - 242)
Steroids (n, %)	15/17 (88%)	10/14 (71%)	10/14 (71%)	5/6 (83%)	8/14 (57%)
Prednisone (mg/day)	32 (20 – 52)	11 (0 – 25)	7 (0 – 19)	11 (4 – 35)	2.5 (0 – 9.25)*
Steroid dependence (n, %)	-	4/14 (29%)	5/14 (36%)	3/6 (50%)	4/14 (29%)
Immunosupressive drugs (n, %)	7/17 (41%)	7/14 (50%)	6/14 (43%)	3/6 (50%)	2/14 (14%)
IADs remission (n, %)	-	6/14 (43%)	5/14 (36%)	2/6 (33%)	8/14 (57%)

*$p<0.05$ (ANOVA test from baseline to last visit)

Figure 2. Overall survival in MDS patients with and without IADs.

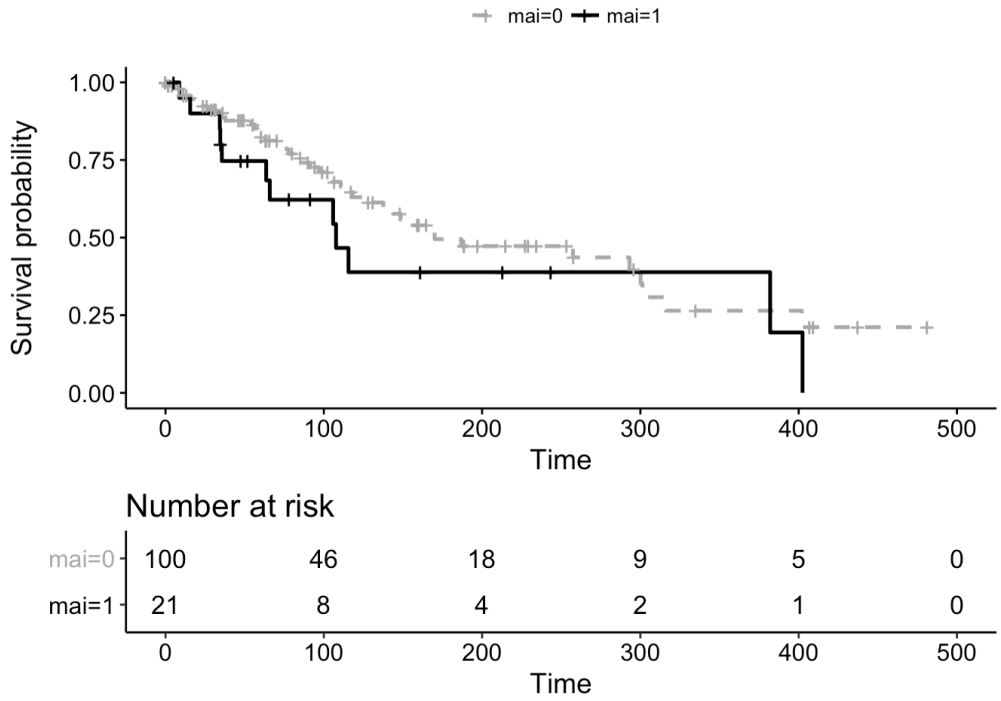

Figure 3. Acute myeloid leukemia-free survival in MDS patients with and without IADs

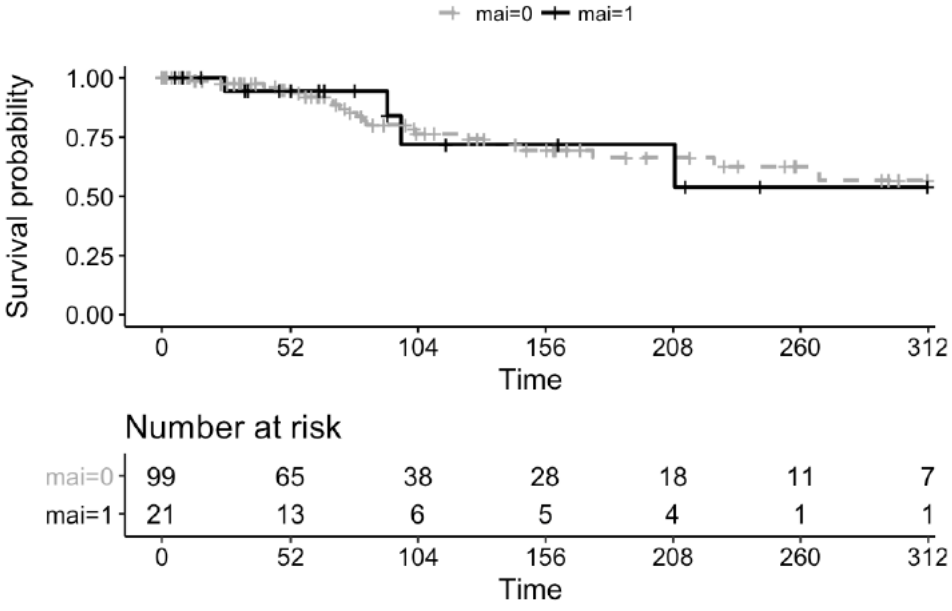

Figure 1. IADs treatments of MDS/CMML- trisomy 8- and associated IADs