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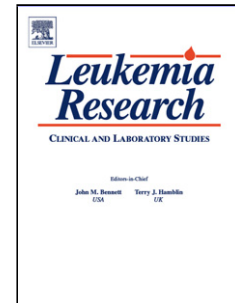
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Efficacy of Azacitidine in Autoimmune and Inflammatory Disorders associated with Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia

Running title: Azacitidine in autoimmune disorders associated with MDS/CMML

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Highlights

- 1) AID associated to MDS/CMML is difficult to manage
- 2) Azacitidine can improve the control of AID associated with MDS/CMML.
- 3) Azacitidine allows to reduce steroid dose in most MDS patients with concurrent AID
- 4) Azacitidine can be beneficial on AID, even when inactive on the underlying MDS/CMML.

Summary

This retrospective study describes efficacy of Azacitidine on autoimmune disorders (AID) associated with MDS/CMML in 22 patients. Response of AID to Azacitidine was observed in 19 patients (86%). Reduction or discontinuation of steroids and/or immunosuppressive therapy (IST) was possible in 16 cases (73%). Hematologic response was seen in 55% of the patients. MDS/CMML and AID evolution was concordant in 13 cases (59%): both favorable (n=11), both unfavorable (n=2), but AID improved while MDS/CMML worsened (n=8) and vice versa (n=1). Azacitidine frequently seems effective in controlling steroid-dependent AID associated with MDS/CMML, but prospective studies are necessary to confirm those findings.

Key words: Azacitidine, myelodysplastic syndromes, auto immune disorders.

Introduction

Autoimmune disorders are observed in 10 to 30% of MDS and CMML, typically diagnosed concomitantly or shortly before or after MDS/CMML [1].

Most common AID associated with MDS/CMML include relapsing polychondritis, vasculitis, non-erosive and seronegative arthritis [2,3] and Sweet's syndrome [4]. While AID associated with MDS/CMML usually respond to corticosteroids [2], many patients remain steroid dependent or resistant, requiring additional IST, a situation which increases the risk of severe cytopenias and infections in the context of MDS/CMML [1].

Azacitidine significantly improves survival in higher risk MDS [5] and in myelodysplastic type CMML [6,7] and is also approved outside Europe for the treatment of lower risk MDS. Seven patients with MDS/CMML and AID treated with Azacitidine have been reported to our knowledge [8–11].

Methods

We retrospectively analyzed the efficacy of Azacitidine in MDS/CMML patients with concomitant AID seen between 2007 and May 2014 in registries of the Société Nationale Française de Médecine Interne (SNFMI) and of the Groupe Francophone des Myélodysplasies. The SNFMI registry included 123 MDS/CMML patients with AID in 26 centres) [13], while the GFM registry included 4202 MDS/CMML in 30 centres of whom 80 also had documented AID. The GFM registry has been so far the basis for many publications of the GFM or that included the GFM [14–16].

Inclusion criteria for the present study were (i) complete or atypical AID according to usual international criteria [17], (ii) MDS or non-proliferative CMML (ie with WBC<13G/L), classified according to WHO 2008 criteria [18] but also including

patients with up to 30% marrow blasts, (iii) treatment with at least one cycle of Azacitidine.

Patients were excluded if AID were caused by infectious disease, AID were in remission without steroids or IST at Azacitidine onset, or if IST was administered more than 12 months before diagnosis of MDS, suggesting MDS secondary to IST.

Complete/ partial remission (CR/PR) of AID after Azacitidine were defined by complete/partial disappearance of clinical or biological signs with stable dose or decrease/discontinuation of steroids or IST, as previously defined [2]. Hematological response to Azacitidine was classified according to IWG 2006 criteria [18].

For statistical analysis, Wilcoxon test was used for analysis of paired quantitative variables and Fisher's exact test for paired qualitative variables using R 3.2.1 (2015) with package Rcmdr 2.1-7 (2007).

Results

Among patients with both MDS/CMML and AID included in the 2 registries, twenty eight patients had received Azacitidine (flow chart in figure 1). Six were excluded, because AID were in remission without IST at Azacitidine onset (n=2), of inadequate follow-up (n=3) and as vasculitis was post-infectious (n=1). Median age of the 22 remaining patients was 70 years (range 41-84), including 6 females and 16 males (73%). (Table 1)

Diagnosis of MDS/CMML preceded AID diagnosis (n=8; by a median of 17 months), was concomitant with (n=7) or followed AID diagnosis (n=7; by a median of 20 months).

AID and MDS characteristics

At MDS/CMML diagnosis, 14 patients had low or int-1 IPSS and 8 had int-2 or high IPSS. The 2 cases of CMML with WBC below 13G/L were classifiable by IPSS. AID diagnosis included: Behçet's disease (n=4), polymyalgia rheumatica (n=3), polymyalgia rheumatica with giant cell arteritis (n=1), giant cell arteritis (n=1), relapsing polychondritis (n=3), polychondritis with Sweet's syndrome (n=1), Sweet's syndrome (n=1), systemic lupus erythematosus (n=2), seronegative polyarthritis (n=2), Sjögren's syndrome with anti-phospholipid syndrome (n=1), adult onset Still's disease (n=1), large vessel vasculitis (n=1) and unclassified small vessel vasculitis (n=1). Twelve (55%) AID were considered atypical and 10 (45%) fulfilled complete diagnostic criteria.

AID features at Azacitidine onset

At Azacitidine onset, AID was still active (n=15), in PR (n=5) and in CR (n= 2). Nineteen patients still reported clinical symptoms related to AID including asthenia (n=17), weight loss (n=8), fever >38.5°C (n=8), rheumatologic signs (n=15), skin involvement (n=10), oral aphthosis (n=4) (Table 1). Twenty (91%) patients were receiving steroids (median: 23 mg/day) for a median duration of 11 months (range 1-101) with no efficacy (n=13), partial efficacy (n=5) and full efficacy on AID (n=2). In patients where steroids were ineffective, they were however generally continued to avoid AID flare. The median duration of steroid use, in the 18 good responders on AID, was 16 months (range 1-101) versus 9 (range 8-9) in the non-responders. Thirteen patients were non-responders to IST and 11 received concomitant treatment with IST and steroids: without efficacy in 7 patients, partial efficacy in 2 and full efficacy in 2 (Table 1). Onset of IST preceded that of Azacitidine by a median of 7

months (range 1-50); the 3 patients who did not have a good response on AID did not receive IST.

Median interval between MDS/CMML diagnosis and Azacitidine onset was 9 months (range 1-93). Azacitidine was the first-line treatment of MDS/CMML in 16 patients (73%) and was in 6 patients preceded by lenalidomide (n=2), hydroxyurea (n=2), idarubicin (n=1) and low dose cytarabine (n=1), treatments to which AID had not responded in any patient.

MDS features at Azacitidine onset

At Azacitidine onset, 11 patients had int-2 or high IPSS, and Azacitidine was used according to the drug label in EU; in the 11 low or int-1 IPSS, reasons to start Azacitidine were RBC transfusion dependence or severe thrombocytopenia in 8 patients (6 of whom also had AID flare) and AID flare alone in 3 patients (Table1).

AID response

Patients received a median of 6 cycles of Azacitidine (range 3-14). CR of AID was observed in 16 patients (73%), PR in 3 cases (14%) and no effect or worsening of AID in 3 cases (14%). All responses were observed within 3 cycles, but 8 PR after 3 cycles became CR after 6 months. In the 3 patients treated with Azacitidine for AID flare alone, one achieved CR, one PR and the last patient did not respond. Steroids were tapered from 40 mg/day to 16 mg/day in one patient and IST was discontinued in another patient.

Median prednisone dose was reduced from 23 mg/day to 9 mg/day ($p=0.001$), including prednisone discontinuation in 3 patients (14%) and dose reduction in 14 patients (64%) (Table1). IST discontinuation was possible in 7 patients (32%). In the 9 steroid-dependent or resistant patients, median prednisone dose was decreased from 50mg/day to 5mg/day ($p=0.01$) and prednisone discontinuation was possible in

3 patients. IST discontinuation was possible in the 3 patients who received them. After Azacitidine treatment, median CRP levels decreased from 40 (range 0-300) to 15 mg/L (range 0-146) ($p=0.28$).

MDS response

Response of MDS/CMML to Azacitidine was seen in 12 patients (55%), including CR in 9 patients (41%), PR in 1, stable disease with erythroid response in 1, marrow CR in 1, stable disease without response of cytopenias in 8 and progression in 2.

MDS/CMML and AID evolution were concordant in 13 cases (59%): both improved ($n=11$) or worsened ($n=2$). In the other patients, AID improved while MDS worsened ($n=8$) and vice versa ($n=1$).

Side effects/ Evolution

Adverse events occurring during Azacitidine treatment included: 9 grade 2-3 infections (6 of them occurred in Int-2 or high IPSS patients), 1 fatal CNS bleeding, 1 deep vein thrombosis, 1 Interstitial lung disease.

Only 3 relapses of AID were seen after 3, 19 and 19 months respectively, and 5 patients had response duration ≥ 12 months, but median follow-up from response to Azacitidine was only 8 months (Table1).

Seven patients (32%) progressed to AML and 10 patients (45%; including 80% of IPSS int-2 and high risk patients) had died, from CNS bleeding ($n=3$), severe infection ($n=5$), progression in AML ($n=1$) and myocardial infarction ($n=1$). Among the 10 patients who died, 6 had progressed to AML. Severe infections were more frequently linked to AML progression than to Azacitidine. Median survival from Azacitidine onset was 16 months in IPSS high or int-2 MDS, and was not reached in IPSS low and int-1 MDS.

Discussion

Azacitidine improved clinical signs of AID in 86% of the cases (73%CR, 14%PR) in patients with MDS/CMML. Azacitidine also allowed to reduce the steroid dose in 64% of the patients and discontinuation of other IST in 32% of them.

In patient n°5, Azacitidine allowed to discontinue both MMF and hydroxychloroquine without having an AID flare. In patient n°10, prolonged clinical and biological complete response was maintained under Azacitidine without requirement of new IST or steroids.

In the only 7 cases of AID with MDS/CMML treated with Azacitidine published so far to our knowledge, 6 were refractory to steroids and/or IST and 4 had higher risk IPSS. MDS and AID evolution were concordant in six cases (Table 2) [8–11].

In our series, all responses of AID to Azacitidine were seen by the third cycle, although about one third of responses improved and became complete between 3 and 6 cycles. Furthermore, although less than 50% of the patients received more than 6 cycles of Azacitidine, only 3 relapses were observed (but with a median follow-up from response of AID to Azacitidine of only 8 months).

Most of the MDS/CMML included in the present study required some treatment because of high or int-2 IPSS in 11 cases, RBC transfusion dependence or severe thrombocytopenia in 8 cases. In the last 3 patients, however AID flare refractory to IST and/or high dose steroids was the only reason to start Azacitidine.

The concordant evolution of AID and MDS/CMML we observed in 59% of the cases further supports a pathophysiological link between MDS/CMML and AID. However, it often remains unclear, in MDS/CMML associated with AID, which of the 2 diseases is the cause and which is the consequence. While immunological defects may potentially trigger MDS/CMML, they may also be in some cases the consequences of

MDS/CMML, when some cells of the immune system are part of the MDS/CMML clone [1,11]. In addition to its direct pro-apoptotic activity on MDS cells, Azacitidine also has immunomodulatory functions which could explain at least in part its effect in MDS-related AID. Azacitidine can indeed expand CD4+CD25+/FOXP3+ regulatory T cells which are decreased with impaired suppressive function in many AID [19]. Azacitidine also increases expression of anti-inflammatory molecules like IFN γ and could inhibit CD4+ T-cells and reduce immune-mediated cytotoxicity [11]. Azacitidine could finally decrease the synthesis of inflammatory cytokines like IL-6 [20]. In some cases, Azacitidine therefore could have a positive immunomodulatory effect, even when it is not active on MDS/CMML.

In conclusion, our results suggest that Azacitidine can improve the control of AID associated to MDS/CMML and allow to reduce steroid dose in most patients with MDS and concurrent AID. Prospective studies are necessary to confirm this beneficial effect and the safety of Azacitidine in AID associated with MDS/CMML.

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Contributions

FJB performed the research; MA, FP, FO and BT designed the research study; FJB analysed the data; GE, KJE, AJB, DO, DG, BAL, OM, MG, AA, LN, BS, LE, PS, GC, LO, RJ, FP, FO and BT share data on patients; and FJB wrote the paper.

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FIGURE 1

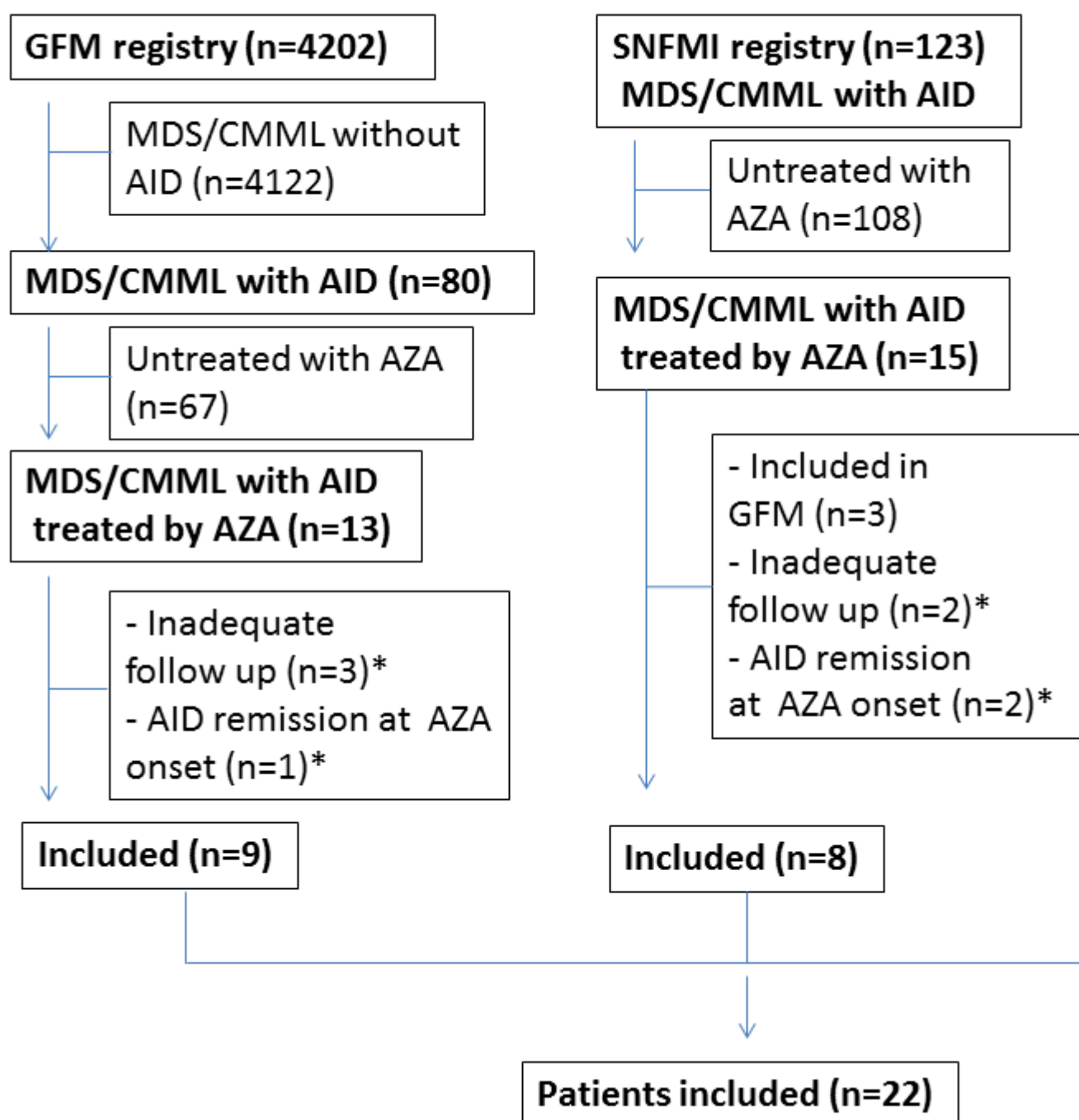


Table 1: Patient characteristics at baseline and after AZA treatment

Gender, Age	WHO classification karyotype	IPSS	Interval from MDS diagnosis to AZA treatment (months)	Type of AID	IST failure	AID status at AZA onset	Clinical signs of AID at AZA onset	Steroids (mg/d) before/ after AZA	IST Before/ after AZA	CRP (mg/L) before/ after AZA	Response of MDS to AZA	Response of AID to AZA	Clinical signs after AZA	Duration of AID response (months)
1, F 57	RAEB2 48,XX,+8,+9	Int-2	2	Behçet	Thal	F	As Fe Sk, Ap Thr	0/0	Thal/Thal	40/60	CR	CR	None	7+
2, F 82	RCMD 49,XX, del(7q),+8, +14,+21	High	11	Behçet	Col	PR	WL As Ap	5/5	Col/ None	10/30	SD	CR	WL As	5+
3, F 79	RAEB1 46,XX, del(20q)	Int-1	5	PA	SLZ	PR	As JI	15/5	SLZ/ SLZ	15/0	SD HI-E	CR	None	7+
4, M, 78	RAEB2 46,XY	Int-2	8	PMR	None	PR	JI	25/15	None/ None	12/15	SD	CR	None	19
5, M, 76	RAEBt 46XY	Int-2	1	SLE	RTX	CR	As	10/10	HCQ, MMF / None	5/25	SD	CR	None	13+
6, M, 66[10]	CMML 46,XY	Int-1	4	SS / APLS	MTX CYC MMF	F	As Sk JI Lu	20/8	MMF/ None	NA/5	CR	CR	None	10+
7, F, 61	RAEB2 46,XX, del(5q), del(17p)	High	0	Sweet	None	F	WL As Fe Sk JI	50/0	None/ None	54/3	Prog	CR	None	8+
8, M, 41	RCMD 50,XY,+7,+7,+8,+8	Int-1	0	Behçet	ANA	F	WL As Fe Sk Ap JI GI	20/20	ANA/ ANA	300/50	SD	PR	Sk	4+
9, M, 69	RAEB2 47,XY,+8	High	22	Behçet	None	F	WL As Fe Sk Ap JI GI	60/0	None/ None	8/5	SD	CR	None	23+
10, M, 74	RAEB1 46,XY	Low	23	SLE	HCQ MTX	CR	None	10/5	HCQ/ HCQ	0/0	CR	CR	None	9+
11, M, 81	Unclassified 47,XY,+8, t(3-5)	Int-2	16	SVV	Col	F	WL PN	0/0	None/ None	82/67	SD	NR	As JI PN	
12, F, 76	RCMD 46,XX	Int-2	9	Vasculitis	None	F	WL As Fe Sk JI	60/10	None/ None	20/NA	SD	CR	As, Fe	7+
13, M, 80	RAEB2 46,XY	Int-2	62	PMR	None	PR	As	13/13	None/ None	5/146	SD	NR	As	
14, F, 70	CMML 46,XX	Int-2	74	GCA & PMR	None	PR	As JI	40/8	None/ None	11/2	PR	CR	As	19

15, M, 67	RAEB1 46,XY	Low	59	PC	IFX ANA	F	As Sk JI	25/30	ANA/ None	50/60	CR	CR	None	
16, M, 57	RA 46,XY	Low	26	PC	IFX MTX CYC	F	As Sk JI ENT	15/18	None/ None	248/10	CR	PR	CNS	9+
17, M, 67	Del-5q MDS 46,XY,del(5q)	Int-1	93	PC & Sweet	CIC	F	WL As Fe Sk JI Lu ENT	80/5	None/ None	240/NA	CR	CR	None	8+
18, M, 66	RAEB1 46,XY	Int-1	0	GCA	ANA IFX MTX TCZ IVIG CIC	F	As Sk ENT	40/0	IVIG/ None	146/22	CR	CR	None	9+
19, M, 84	RCMD 46,XY	Int-1	8	PMR	Col	F	As Sk JI	17/15	None/ None	61/143	mCR	NR	Fe JI	3
20, M, 47	RCMD 47,XY, +8	Int-1	9	Still	Col MTX ANA TCZ HCQ	F	WL As Fe, JI ENT PN	40/16	ANA, HCQ / None	38/NA	CR	PR	JI	2+
21, M, 64	RAEBt 46,XY	Int-2	2	PC	ETC	F	JI	80/5	None/ None	161/14	Prog	CR	None	31+
22, M, 83	RA 46,XY	Int-1	11	PC	AZA	F	JI	14/10	AZAT/None	225/5	CR	CR	None	3+

RAEB: refractory anemia with excess of blasts, RCMD: Refractory cytopenia with multiple dysplasia, CMML: chronic myelomonocytic leukemia, RA: refractory anemia, Prog : progression, PA: polyarthritis, PMR: polymyalgia rheumatic, SLE: systemic lupus erythematosus, SVV : small vessel vasculitis, SS: Sjögren syndrome, APLS: antiphospholipid syndrome, GCA: giant cell arteritis, PC: Polychondritis, WL: weight loss, As: asthenia, Fe: fever, Sk: skin symptoms, Ap: oral aphthosis, Thr: deep vein thrombosis, JI: joint involvement, Lu: lung involvement, GI: gastro intestinal symptoms, PN: peripheral neuropathy, CNS : central nervous system involvement, ENT: ears nose and throat symptoms, HCQ: hydroxychloroquine, MMF: mycophenolate mofetil, IVIG: intravenous immunoglobulin, Thal: Thalidomide, CST: corticosteroids, Col: Colchicine, SLZ: salazopyrine, RTX: Rituximab, MTX, methotrexate, ANA: Anakinra, CYC: cyclophosphamide, IFX: infliximab, CIC: ciclosporine, TCZ: tocilizumab, ETC: etanercept, AZA: azathioprine. NA: not available, CR: complete response, PR: partial response, NR: no response, ±: absence of relapse at last follow-up.

Table 2: Published cases of MDS/CMML with AID treated with Azacitidine

Gender, Age	MDS/CMML	IPSS	AID	IST failure	Evolution
1, M 74[8]	RAEB2	High	Sweet		CR of MDS and AID
2, M 44[9]	RCMD	Int-2	SLE	CST, HCQ	CR of MDS and AID
3, M 69[10]	RCMD	Int-1	Polyarthritis & Sweet	CST (40/d), colchicine, disulone, thalidomide	CR of MDS and AID CST (8mg/d)
4, M, 66[10]	CMML	Int-1	SS & APLS	CST (20mg/d), MMF, MTX, CYC,	CR of MDS and AID CST (5mg/d) MMF stopped
5, M, 64[10]	RAEB-1	Int-1	Polyarthritis & Sweet	CST (10mg/d), thalidomide.	CR of MDS and AID CST stopped
6, F, 52[11]	RAEB-2	Int-2	Polyarthritis & Sweet	CST / MTX	CR of AID CST tapered ↓ transfusion
7, F, 73[11]	RAEB-2	Int-2	SLE	CST	CR of AID and MDS

RAEB: refractory anemia with excess of blasts, RCMD: Refractory cytopenia with multiple dysplasia, CMML: chronic myelomonocytic leukemia, SLE: systemic lupus erythematosus, SS: Sjögren syndrome, APLS: antiphospholipid syndrome, CST: corticosteroids, HCQ: hydroxychloroquine, MMF: mycophenolate mofetil, MTX, methotrexate, CR: complete response.