Spontaneous remission in adult patients with *de novo* myelodysplastic syndrome: a possible event

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Background and Objectives. Spontaneous remission (SR) in *de novo* myelodysplastic syndromes (MDS) is a rare event, which has been so far described only in children with monosomy 7. The phenomenon is extremely heterogeneous, perhaps depending on different pathogeneses of the disease.

Design and Methods. We retrospectively evaluated the outcome of 564 consecutive adult patients with primary MDS diagnosed at our Institution in a 12-year period. SR was defined as an unexpected improvement lasting more than 1 year without concomitant treatments other than vitamins or low-dose steroids (in patients with platelets < 50×10^9/L).

Results. Nine cases of SR were observed in 3 males and 6 females (median age 38.7 years). At diagnosis, all patients had Hb levels < 10 g/dL and 8/9 required packed red cell transfusions. The median time from diagnosis to SR was 18 months (range 4-46) and all patients had normalization of peripheral blood parameters: in 2 out of 3 patients with karyotypic abnormalities at onset, a cytogenetic remission was documented. The median duration of SR was 56 months; 5 patients are still in SR and 4 patients have relapsed (1 as MDS and 3 as acute myeloid leukemia).

Interpretation and Conclusions. SR is a rare (less than 2% in our experience) but possible event also in adult MDS patients. It should be kept in mind in the evaluation of experimental treatments for MDS in which very low rates of complete responses are expected.

Key words: myelodysplastic syndromes, spontaneous remission, trisomy 8.

Myelodysplastic syndromes (MDS) are clonal hematologic disorders characterized by pancytopenia, dysplastic features and high incidence of leukemic transformation. The introduction of the French-American-British (FAB) classification has facilitated the morphologic and prognostic definition of MDS by identifying 5 disease subgroups.[1]

Although the prognosis of MDS is generally poor, it shows a wide range of variation even in patients with the same FAB subgroup. Thus, while some patients die from complications of bone marrow failure or acute myelogenous leukemia (AML) transformation within a few months from diagnosis, others have a relatively stable course and survive for many years.[2–3]

The occurrence of spontaneous remissions (SR) during MDS has seldom been reported: all the cases were children or young people (< 20 years) and were characterized by the presence of monosomy 7.[4-9]

This paper deals with 9 cases of SR observed in adult MDS patients (>20 years old) at our Institution in a 12-year period.

Design and Methods

Patients

From January 1985 to December 1996, 564 consecutive patients (347 males and 217 females, median age 68.4 years) with a diagnosis of *de novo* MDS according to FAB criteria were observed at our Institution.

Definition of spontaneous remission (SR)

An unexpected improvement of the disease was retrospectively defined as *SR* if all the following characteristics were present: i) no treatment with growth factors, differentiating agents or cytosta-

Table 1. Clinical and biological characteristics at diagnosis of the 9 patients with MDS who entered spontaneous remission.

Pt. N°	*Age (yrs)*	*Sex*	*Karyotype (n° of cells)*	*Marrow blasts (FAB)*	*Marrow cellularity*	*HB (g/dL)*	*PMN (×10⁹/L)*	*PLTS (×10⁹/L))*	*PRC*/month*
1	27.7	F	Failed	2% (RA)	Normo	8.4	0.9	80	2
2	52.5	F	Failed	1% (RA)	Hypo	9.6	3.0	100	3
3	61	F	46, XX (25)	3% (RA)	Normo	9.5	2.6	8	2
4	34.3	F	46, XX (20)	1% (RA)	Normo	9.7	3.4	206	2
5	73.8	M	46, XY (27)	2%(RA)	Hyper	6.7	1.3	118	2
6	29.2	F	46, XX (32)	2% (RA)	Normo	3.4	1.0	108	2
7	72.6	M	46,XY,del(6q) (25)	10%(RAEB)	Normo	9.7	1.2	44	2
8	38.7	F	47, XX, +8 (20)	20%(RAEBt)	Hyper	3.8	2.0	368	2
9	26	M	47, XY, +8 (15) 46, XY (23)	2%(RA)	Hypo	9.5	1.5	40	None

**PRC: packed red cells.*

tic drugs in the previous 3 months; ii) no concomitant treatment other than vitamin therapy (folic acid and/or pyridoxine) or low-dose steroids (in patients with thrombocytopenia) started at least 3 months previously; iii) minimal SR duration of 1 year.

Three different types of SR were considered, according to the response criteria for MDS recently proposed by Cheson *et al.*:[10] i) peripheral SR: normalization of peripheral blood parameters (Hb > 11 g/dL, polymorphonuclear cells > 1.5 × 10^9/L, platelets > 100 × 10^9/L) with persistence of bone marrow dysplasia and/or marrow blasts; ii) morphologic SR: normalization of all peripheral and bone marrow parameters (marrow blasts < 5% with normal maturation of all cell lines) in patients without cytogenetic markers (diploid or not assessable karyotype); iii) karyotypic SR: normalization of all peripheral and bone marrow parameters with disappearance of the cytogenetic abnormality.

Bone marrow smears both at diagnosis and during SR were reviewed by 2 different pathologists.

Results

Among 564 adult patients with *de novo* MDS, 9 (1.6%) showed a SR during their follow-up. The clinical and biological characteristics of the 9 patients are shown in Table 1. There were 3 males and 6 females with a median age of 38.7 years (range 26 - 73.8). According to the FAB classification 7 had refractory anemia (RA), 1 had refractory anemia with excess of blasts (RAEB) and 1 had RAEB in transformation (RAEBt). Cytogenetic analysis was performed in all patients at diagnosis: three patients (1 RA, 1 RAEB and 1 RAEBt) had an abnormal karyotype [+ 8 in 2 patients and del (6q-) in 1 patient], 4 patients (all with RA) had a diploid karyotype and 2 patients had no evaluable metaphases.

At diagnosis, all patients had Hb levels < 10 g/dL and 8/9 required transfusional support with packed red cells. Three out of 9 patients had platelet levels < 50 × 10^9/L and 1/9 had PMN levels < 1 × 10^9/L (Table 1).

When SR occurred, 2 patients had not received any treatment, 3 patients were undergoing treatment with low-dose prednisone (0.25 mg/Kg/day) because of thrombocytopenia and the remaining 4 patients had been treated with vitamins for more than 3 months. None of the patients had suffered from infective episodes or revealed a positive history of abnormal alcohol intake before the spontaneous improvement. The median time from diagnosis to the spontaneous improvement was 18 months (range 4 - 46), while the median period of transfusional supportive care before the spontaneous improvement was 15 months (range 4 - 29). All patients had a normalization of peripheral blood parameters (Hb > 11 g/dL, PMNs > 1.0 × 10^9/L, platelets > 100 × 10^9/L) (Table 2) and became transfusion independent. Three patients showed a peripheral SR, 4 patients a morphologic SR and 2 out of the 3 patients with an abnormal karyotype at onset had a karyotypic SR.

The overall median duration of SR was 56 months (range +12 - +136). As for the follow-up, 4 patients relapsed (1 with a stable myelodysplastic disease and 3 with a leukemic phase of disease) after 21, 26, 29 and 114 months, respectively; in particular, 2 out of 3 patients with peripheral SR relapsed after 21

Table 2. Characteristics during disease improvement and follow-up of the 9 patients who had a spontaneous remission.

Pt. N°	*Time from diagnosis (months)*	*Type of SR*	*Hb (g/dL)*	*PMN (×10⁹/L)*	*PLTS (×10⁹/L)*	*Karyotype (n° of cells)*	*SR duration (months)*	*Outcome*
1	33	PSR	11.5	1.5	112	n.e.	26	Relapse (MDS)
2	18	MSR	14.8	2.6	117	n.e.	29	Relapse (AML)
3	18	MSR	12.5	5.1	125	n.e.	+ 98	SR
4	6	MSR	13.8	6.9	162	46, XX (20)	+ 136	SR
5	46	MSR	13.8	2.0	150	46, XY (19)	+ 12	SR
6	12	PSR	11.2	2.0	180	46, XX (25)	+ 56	SR
7	4	KSR	13.3	2.8	168	46, XY (22)	114	Relapse (AML)
8	21	PSR	12.0	5.3	319	47, XX, +8 (30)	21	Relapse (AML)
9	12	KSR	14.8	3.0	163	46, XY (25)	+ 132	SR

PSR: peripheral spontaneous remission (SR); MSR: morphologic SR; KSR: karyotypic SR.

and 26 months, 1 out of 4 patients with morphologic SR relapsed after 29 months and 1 out of 2 patients with karyotypic SR relapsed after 114 months. Both patients with excess of blasts relapsed after 21 and 114 months. Five patients are still in SR after 12, 56, 98, 132 and 136 months (Table 2).

Discussion

The natural evolution of MDS is towards a gradually worsening cytopenia or an overt leukemic phase: the occurrence of a spontaneous durable remission has been seldom reported in literature and only in patients aged less than 20 years.[4-9]

As *spontaneous remissions* during MDS course are so rare, we first of all need confirm a correct diagnosis: in fact, myelodysplastic features morphologically identical to those detected in primary MDS are reported in some chronic hepatic, renal or dysreactive diseases.

However, the presence of karyotypic abnormalities at onset and the disease evolution are hallmarks of a primary MDS. Among our SR cases, 3 displayed a karyotypic abnormality and 2 had a relapse of their disease (1 with a stable MDS phase and 1 with an evolution to AML) with evidence of a correct diagnosis of MDS. Of the other 4 patients (all with normal karyotype and persistent SR), none had evidence of chronic hepatic or renal impairment nor clinical signs of dysreactive diseases; moreover, they had a long-lasting dysplastic phase before SR occurrence (6, 12, 18 and 46 months). As a matter of fact, the diagnosis of primary MDS was highly probable also in these 4 patients.

Evidence exists that some clinical and therapeutic factors (infections, late response to previous treatments) may induce an improvement which might be misinterpreted as *spontaneous*.

None of the patients had infections between diagnosis and SR assessment nor had received treatment other than vitamins (4 patients) or low-dose steroids (3 patients) started more than 3 months before the SR. Some sporadic responses in MDS have been reported with both these treatments, but they occurred closely after the beginning of the treatment and, as for steroids, under high-dose (1-1.5 mg/Kg) schedules.

It is also common experience that MDS patients may have transient improvements in peripheral blood parameters, with no impact on prognosis and survival. To discriminate *durable* SR from only transient improvements, a cut-off duration of 1 year was chosen. In all our patients SR lasted more than 1 year, the median duration being 56 months.

In conclusion, a spontaneous improvement is rare (< 2%) but possible in adult and elderly MDS patients. Such an occurrence should also be kept in mind while evaluating experimental treatments of MDS,[11,12] in which only very low rates of stable complete responses are currently achieved. A longer follow-up of patients still in SR will provide further information about the nature of this phenomenon.

Contributions and Acknowledgments

MCP, RL and MB: designed the analysis, interpreted the data and wrote the paper; GA and AS: critically revised the draft; MDA, MM and MAAS: collected and revised the morphologic and karyotypic data; FM: approval of the version to be submitted.

Disclosures

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Manuscript processing

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Potential implications for clinical practice

Spontaneous remission is a rare but a possible event in adult MDS patients. This observation supports an initial "watchful-waiting" strategy, at least in those patients who do not need an immediate treatment. In addition, it should be kept in mind in the evaluation of experimental treatments with very low levels of complete stable responses.

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