Review article

Myelodysplastic syndromes

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Abstract

The authors review the epidemiological biological, diagnostic, prognostic and therapeutic aspects of myelodysplastic syndromes.

Myelodysplastic syndromes (MDS) are clonal disorders of pluripotent hematopoïetic stem cells, of generally unknown aetiology, occurring predominantly in the elderly, characterized by ineffective hematopoïesis leading to blood cytopenias, a high incidence of progression to acute myeloid leukemia (AML) and overall by limited response to most available treatments.
We will review here epidemiological, biological, diagnostic, prognostic and therapeutic aspects of MDS.

Epidemiology

Incidence, age and sex [1,2,3,4]

MDS is a disorder of elderly people, occurring at a median age of about 70 years. Childhood MDS is rare, relatively often familial and often associated to monosomy 7 [3]. Among adults, only 8 to 10 % of the patients have less than 50 years at diagnosis [4]. The incidence of MDS is about 2-4/100 000/year, reaching 30/100 000/year in patients aged greater than 70. It has been suggested, but this has not been demonstrated, than the incidence of MDS had increased over the last 20 years. A male predominance is seen in all series (M/F ranging from 1.5 to 2).

Aetiology

The aetiology of MDS is generally unknown («de novo» MDS). However, in about 20 % of the cases, MDS are clearly «secondary», mostly to antineoplastic chemotherapy, or less often to occupational or environmental exposure to various chemicals, or finally constitutional disorders of childhood.
a) Antineoplastic drugs (therapy related MDS) [5,6,7]
About 80 % of the cases of AML occurring after exposure to antineoplastic drugs are preceded by a phase of MDS. The most frequently incriminated drugs are alkylating agents, mainly when used for prolonged periods. Some alkylating agents, like cyclophosphamide, could induce less MDS than others, especially when used in pulsed injections such as in CHOP cycles. Therapy related MDS usually develop 3 to 7 years after exposure to chemotherapy and are associated to complete or partial loss of chromosome 7 in more than one half of the cases. The epipodophyllotoxin agents VP_{16} and VM_{26} and, to a lesser extent, anthracyclines, have also been incriminated in the development of secondary AML, but these AML are generally not preceded by a preleukemic phase of MDS, and carry other genetic abnormalities, ie mainly rearrangements of 11q23 and 21q22 chromosome band [7].

After autologous marrow or stem cell transplantation, especially in lymphoma, an incidence of MDS of 3 to 5 % has been reported [8]. Total body irradiation in the conditioning regimen and a greater number of months on alkylating agents seem to be among the causative factors.

b) Occupational and environmental exposure to chemicals [9-11]

Exposure to benzene and its derivatives has clearly been associated to the development of MDS, or AML generally preceded by MDS [9].

For other compounds, data are less clear. The few case control studies performed in MDS, suggest a higher incidence of MDS not only in persons exposed to petrol and diesel compounds (which contain among others benzene derivatives) but also in persons using insecticides, pesticides and weed Killers [10, 11]. The latter findings would possibly explain the higher incidence of MDS observed in agricultural workers in some studies [11]. A higher incidence of MDS was also present in smokers or ex-smokers in our experience. It could be due to polycyclic hydrocarbons which are present in tobacco smoke [11]. Evidence for an association between MDS (or AML) and other exposures, including professional exposure to radiations, work in nuclear plants, and high magnetic fields appears undemonstrated.

c) Constitutional disorders of childhood [3, 12, 13]

A high incidence of antecedent constitutional disorders is seen in childhood MDS. These include Fanconi's anemia, Schwachman-Diamond syndrome, Down's syndrome mitochondrial cytopathies and neurofibromatosis. A large proportion of MDS occurring in these situations have monosomy 7.

d) MDS after acquired aplastic anemia [14]

28 cases of MDS were reported in 860 cases of aplastic anemia (AA) treated with immunosuppressive therapy, as compared to only 2 in 748 transplanted cases of AA [14]. However, it is still unclear whether this resulted from the presence in AA of an occult MDS clone eradicated by transplantation but not by immunosuppressive therapy, or from a link between immunosuppresion and secondary development of MDS.

Biology of MDS

Cytogenetic abnormalities [15-18]

Clonal cytogenetic abnormalities in marrow cells are seen in about 50 to 60 % of MDS (Table 1). Contrary to some other hematological malignancies, MDS are not associated to any specific chromosomal abnormality. However, the rare occurrence of translocations and the high incidence of complete or partial chromosomal loss or less often chromosome gain is typical of MDS and distinguishes MDS from AML. The most frequent abnormalities are by decreasing order del 5q, monosomy 7, trisomy 8, del 20q and loss of Y chromosome, the latter being clearly a clonal anomaly. Among translocations, unbalanced translocations, leading to loss of chromosomal material are relatively frequent. For example unbalanced t(5;17)(p11;p11) and t(7;17)(p11;p11) translocations lead to 17p deletion. Those translocations are more frequent in therapy related MDS than in «de novo» MDS. Complex cytogenetic findings (ie with at least 3 chromosome abnormalities) are seen in 15 to 20 % of MDS. They also predominate in therapy related MDS.

	Approximative incidence (%)	
	de novo MDS	Secondary MDS
Partial chromosomal deletion		
del 5q	20	20
del 20q	3-4	<1
del 7q	1-2	10
der or del 11q	2-3	<1
der or del 12p	1-2	3-4
del 13q	1	<1
Chromosome loss		
monosomy 7	10-15	50
loss of Y chromosome	3-4	10
monosomy 17	3	5-7
Chromosome gain		
trisomy 8	10-15	10
trisomy 11	3	1
trisomy 21	2	1
Translocations		
t(3;3)(q21;q26)	1-2	3
t(1;7)(p11;p11)	<1	4-5
t(5;17)(q11;p11)	1-2	4-5
t(7;17)(q11;p11)	1-2	2-3
t(5;7)(q11;p11)	<1	2
Others findings		
iso(17q)	<1	3-4
inv(3)(q21q26)	<1	3
Complex findings (> 3 chromosome abnormalities)	15-20	50

Table 1
Main cytogenetic abnormalities encountered in MDS

Fluorescence in situ hybridization (FISH) technique, performed on cytogenetic preparations (metaphase or interphase nuclei) or on bone marrow slides, appears to be more sensitive than conventional cytogenetic analysis in some situations, especially for the detection of monosomy 7 and trisomy 8. It is useful when low numbers of mitoses are obtained or when only one or two mitoses abnormal are found, questioning the clonality of the anomaly [19, 20].
The role of cytogenetic findings in the diagnosis of MDS, but more importantly for prognosis, will be stressed below.

Molecular abnormalities

Due certainly in part to the fact that recurring chromosomal translocations are rarely seen in MDS (as translocation breakpoints have the interest of pointing out precisely chromosomal regions of interest to discover new genes), few genes involved in the pathogenesis of MDS have been identified (Table 2).

Gene	Type of anomaly	Incidence
RAS (N or K)	Point mutation (codon 12, 13 or 61)	10 - 30 %
P53	Point mutation + deletion of other allele	5 %
FMS	Point mutation (codon 969 or rarely 301)	5 - 10 %
TEL	Fusion to PGDF-R gene (t(5;12) translocation)	< 1 %
MDS 1 EAP EVI 1	Fusion to AML_1 gene t(3;21) translocation	< 1 %

Table 2
Known molecular abnormalities in MDS

a) RAS, NF_1, FMS and p53 mutations in MDS

Point mutations involving codons 12 or 13 or 61 of members of the RAS gene family (mainly N-RAS, less often K-RAS and rarely H-RAS), leading to an activated RAS protein, certainly constitute the most frequent molecular anomaly identified in MDS [21,22,23]. Incidence of RAS mutations of about 30 % in MDS were reported in early series, but they often concerned patients with advanced MDS. The incidence of RAS mutations at diagnosis in MDS could rather be in the range of 10 to 15 %, with a higher incidence in chronic myelomonocytic leukemia (CMML), by comparison with other MDS subgroups. RAS mutation often appear during the disease course, as shown by longitudinal studies. They are usually detected by DNA amplification of exons 1 (codons 12 and 13) and exon 2 (codon 61) of RAS genes followed by hybridization with oligonucleotide probes specific for each possible mutation (dot blot technique). Cases of MDS occurring in children with neurofibromatosis are associated to NF_1 gene deletions and to a decrease in neurofibromin, the product of NF_1 gene [24]. Neurofibromin is active through the RAS pathway, and inactivation of neurofibromin, like RAS gene mutations, leads to RAS activation [25]. This suggests the importance of a deregulated RAS pathway in the pathogenesis of MDS. This importance is further substantiated by the fact that RAS mutations often occur in the absence of chromosomal abnormalities, suggesting the involvement of a limited number of genetic defects in pathogenesis. On the other hand, no abnormalities of the NF_1 gene have been found in adult MDS [26].

The FMS gene encodes for the M-CSF receptor. It is found mutated in about 10 % of MDS cases with a predominance in CMML, as for RAS mutations [27]. However, most mutations involve codon 969, a mutation that does not lead to activation of M-CSF receptor. Some mutations involve codon 301, leading to activation of the receptor, but they only account for 10 to 15 % of FMS gene mutations. The role of FMS gene mutations in MDS therefore still has to be more precisely established.

P53 gene mutations occur in about 5 % of MDS cases [28, 29]. As in other malignancies they predominate in exons 5 to 8 of the gene and are generally missense mutations inactivating p53. They can be detected by single stranded conformation polymorphism (SSCP) analysis of exons 5 to 8 of the gene, or immunocytochemistry on bone marrow slides (which detects p53 overexpression, almost synonymous with p53 missense mutation). p53 mutations are almost exclusively seen in RAEB, RAEB-T and CMML, and are generally associated to deletion of the non mutated allele, through chromosome 17p deletion (resulting from t (5;17) or t(7;17) unbalanced translocations, monsomy 17 or less often iso 17q) [28, 29]. Most MDS cases with p53 mutations have complex cytogenetic abnormalities. It is unknown whether this is secondary or not to the p53 mutation, as p53 inactivation can lead to chromosomal instability. In our experience, p53 mutations in MDS (and AML) were always found at diagnosis and were not acquired during the disease course. However, this does imply that they constitute an «early» event in pathogenesis. Furthermore, because they are generally associated to complex chromosomal abnormalities and therefore to many genetic defects, the precise role of p53 mutations in the pathogenetis of MDS is still unknown.

Finally, deletion and/or decreased expression of the retinoblastoma gene is very rare in MDS [30].

b) Other well characterized molecular anomalies in MDS

A few other gene abnormalities have been well characterized in MDS. However they appear to occur in very small subgroups of MDS. They have generally been found in the rare cases of MDS with balanced

translocations, whose molecular analysis lead to the discovery of fusion genes between a known gene and a new gene of interest, which could be subsequently cloned.
- *MDS with t(5;12)(q31;p13)* [31, 32]. A few cases of MDS, generally having features of atypical CMML with in particular, eosinophilia have been reported. Cloning of the translocation breakpoint allowed the identification in 12p13 of TEL gene, a member of ETS gene family. In this translocation the TEL gene was fused to the PDGF receptor gene in 5q31. Involvement of the TEL gene in other translocations, and/or TEL gene deletions have also subsequently been found in AML and, with a high incidence, in childhood ALL. However they seem to be very rare in MDS except in the rare cases with t(5;12).
- *MDS with t(3;21)(q26;q22)* [33]. A small number of MDS with t(3;21), generally occurring after antineoplastic drugs, has been reported. In those cases, the AML1 gene situated in 21q22 is fused to one of the following genes identified in 3q26 : EVI 1, MDS 1, EAP or both (AML MDS1 - EVI 1 complex fusion).
c) Unidentified genes : from cytogenetics to molecular biology of specific «entities» in MDS
In AML, specific morphological-cytogenetic entities such as M_2 AML with t(8;21), M_4 eosino AML with inv(16), M_3 AML with t(15;17) have been described. As in AML, specific entities with morphological-cytogenetic characteristics have been identified in MDS, including the «5q syndrome» and 17p deletions with dysgranulopoïesis (see below). In AML, specific gene abnormalities are being found in a growing number of those «entities». This search has been more elusive in MDS, due to a large extent to the fact that translocations, which offer a good opportunity to identify new genes, are so rare in MDS. Because chromosomal deletions are frequent in MDS, the role of inactivation of tumor suppressor gene(s) situated on deleted chromosomal fragments in the pathogenesis of MDS is strongly suspected. However, discovering new genes whose abnormalities could specifically be involved in MDS in those large chromosome segments has so far proved difficult, in spite of cytogenetic, FISH and molecular techniques.
In the case of del 5q, the deletion is always interstitial, but is of variable extent [34,35,36,37,38]. The first question was to demonstrate that a commonly deleted segment could be found in all cases. This proved to be the case as by cytogenetic analysis, involvement of 5q31 band in the deletion was found in 91 of 93 cases of del 5q analyzed [38]. The next step was to analyze known genes located in this region. However, none of the genes coding for growth factors or growth factor receptors situated in this region were found to be part of the common deleted segment. A third step was to identify genes in this segment, of which one allele was deleted through del 5q and the other allele inactivated on the remaining chromosome 5 (by deletion or mutation). By positional FISH and molecular biology techniques, 2 genes, IRF_1 and EGR_1, and a chromosomal locus (D_5S_{89}) were shown to play a possible role, but no consensus between scientists has been reached [34-38]. In fact, several genes could be involved. Another possibility is that loss of one allele of one or several genes could lead to impaired hematopoïesis (haploinsufficiency).
For other chromosome deletions, including del 20q, monosomy 7 and del 7q, several groups are also looking for tumor suppressor genes, but no candidate gene has been identified so far. Common deleted segments have been identified in 20q11 and 7q31, however [39, 40].

Clonality in MDS

The first demonstration that MDS were clonal disorders came from studies of G_6PD isoenzymes in hematopoïetic cells, although clonality was already strongly suspected when an abnormal clone was seen by chromosome findings. More recently, clonality studies have been made in female patients using X linked gene polymorphisms [41, 42]. The main genes studied were PGK, M27 beta and lately HUMARA gene. Their polymorphisms allow these genes to be informative in 50 % (PGK gene) or almost all females (M27 beta and HUMARA genes) [42]. Although there is still some controversy, it appears that in the majority of MDS cases, only myeloid but not lymphoid cells are part of the neoplastic clone [41-43]. In some cases, however, B and/or T cells may also be clonal. In a subgroup of patients, who have anemia with normal leukocyte and platelet counts, the clone could be restricted to the erythrocyte lineage, although this observation rests on a small number of cases.
Studies combining chromosome analysis (eg by FISH) and cell lineage determination (eg by immunophenotype) have shown that, in many cases of MDS, chromosome abnormalities such as monosomy 7 or trisomy 8 were present in only part of the circulating granulocytes [44]. In a study of MDS with del 20q, circulating granulocytes were shown not to carry the deletion [45]. These findings could reflect the persistance

of some non clonal granulopoïesis in MDS. However, in some well studied examples, it was demonstrated by X chromosome linked polymorphisms that granulocytes which did not carry the mutation were clonal. This suggests that chromosome abnormalities may be, in many cases, secondary genetic events in MDS. In the case of childhood MDS, several findings show that monosomy 7 is a secondary event, and could constitute a «common final pathway» to different conditions predisposing to MDS [12].

Immunological abnormalilies in MDS

Associations between auto-immune disorders (including Crohn's disease, ulcerative colitis, rheumatic disease, glomerulopathy, systemic lupus, etc...) and MDS have been reported, but it appears that their incidence is generally not higher in MDS than in the general population, with the possible exception of CMML [46, 47]. However vasculitis, seronegative arthritis and perhaps more importantly relapsing polychrondritis (RP) may constitutive exceptions, and be significantly associated to MDS. Indeed, in a series of 18 RP, 5 had clinical MDS. By systematic study of bone marrow samples in 7 cases of RP, 3 had morphological signs of MDS. This obviously suggests a pathophysiological link beetween the two disorders. As proposed by Hamblin [46], granulocyte and/or monocyte dysfunction, in MDS, could lead to impaired disposal of immune complexes and subsequent deposition in small blood vessels allowing the local activation of inflammatory mediators. Abnormalities of B cells including hypergammaglobulinemia, a higher incidence of monoclonal Ig and a higher incidence of autoantibodies than in a control age matched population are seen in CMML but not in other MDS [47]. Irrespective of the type of MDS, the number of circulating T cells is generally diminished, their function reduced, and impaired NK activity is found. Monocytes in MDS are derived from the abnormal clone, but only subtle functional impairment is generally seen.
Finally a higher than expected incidence of lymphoïd neoplasms, especially of immunoglobulin secreting tumors, is seen in MDS [46].
The relationship between impaired immunity and the clonal proliferation in MDS is unknown. Abnormal lymphoïd function could have an explanation in cases where lymphocytes are part of the abnormal clone. Conversely, although this would have to be demonstrated, primary immunological abnormalities could favour, by some kind of defective immunosurveillance, the emergence of abnormal myelodysplastic clones. Another model gives a major role to the mononuclear phagocytic cells. Monocytes are important antigen presenting cells which are in MDS part of the abnormal clone. Disordered monocyte/macrophage function could lead to persistant immune stimulation, by poor clearance of bacterial antigens, overactive antigen presentation, upregulated cytokine expression or a mixture of all three. This in turn would lead to B cell hyperplasia, hypergammaglobulinemia, production of auto antibodies and a greater risk of genetic errors in proliferating B cells, leading to noeplastic changes in some cases. This model could explain why CMML is the MDS sybtype with greatest immune disturbances.
A particular situation where autoimmunity could be implicated is MDS with thrombocytopenia. Indeed, the high incidence (>50 %) of antibodies directed against platelets in MDS, and some responses observed in this situation with therapeutic agents that are active in ITP (danazol steroids, high dose immunoglobulins) have suggested that peripheral autoimmune thrombocytopenia was frequent in MDS. However we found that, in MDS with platelets antibodies, the antibodies were in only 20 % of the cases autoantibodies directed at specific platelet antigens. Furthermore, platelet lifespan was generally normal, suggesting the central origin of thrombocytopenia in a great majority of the cases [48,49, 50, 51].

Cellular proliferation, differentiation and death in MDS

a) Erythropoïesis in MDS
Ferrokinetic study of erythropoïesis with 59Fe demonstrates, in MDS, high marrow iron turnover but low iron incorporation in erythrocytes, which is a characteristic feature of ineffective erythropoïesis [52]. A high proliferation of early erythroblasts, about 30 % of erythroblasts being in S phase has also been demonstrated. However, moderately shortened red cell lifespan is also often present in MDS. Finally, with evolution to RAEB and RAEB-T, MIT and percent ineffective erythropoïesis fall and a component of quantitative failure of erythropoïesis emerges [52].
Growth of mature erythroid progenitors (BFU-E and CFU-E) from bone marrow and peripheral blood is suboptimal in most cases of MDS and absent in 30 to 75 % of the cases [53]. Long term bone marrow

cultures show reduced progenitor recovery in MDS patients. Overall MDS erythroid progenitors appear to have reduced self renewal capability, reduced capacity to generate BFU-E from blast colonies, and a deficiency of BFU-E relative to CFU-E in most patients.
b) Growth factors and growth factor receptors in MDS.
Because cytopenias, in MDS, could have been due in part to a lack of growth factors (GF) or of response to growth factors, serum levels of GF were measured and analysis of GF receptors was made. Overall, very few abnormalities were found. Erythropoietin (EPO) concentration is usually appropriate for the degree of anemia but sometimes low or high [54]. In patients with low levels for the degree of anemia, some response to treatment with EPO is often observed [55]. GM-CSF is generally undetectable, and G-CSF and IL_3 occasionally elevated, whereas stem cell factor (SCF) concentration is often diminished in MDS. Local concentrations of IL_6, G-CSF and SCF secreted by stromal cells were not found impaired in MDS [56]. No rearrangement or abnormal expression of FMS, IL_3, GM-CSF genes (all situated in 5q) were seen and no mutation of C-KIT gene (which encodes for the receptor to SCF) was observed [57].
c) Apoptosis in MDS
Increased apoptosis (programmed cell death) of myeloid cells would provide an explanation to the ineffective hematopoïesis leading to blood cytopenias observed in MDS. In a recent study, in plastic embedded bone marrow biopsies, using in situ end labelling (ISEL) of DNA, RAZA et al. found that > 75 % marrow cells were apoptotic in most cases of MDS [58]. Other studies including ours have confirmed the increased incidence of apoptosis in MDS cells, but to a lesser extent that in the work of Raza et al, at least in fresh cells obtained from bone marrow aspirates (unpublished results). After short term cell incubation, the increased tendency of MDS cells to undergo apoptosis can be more easily demonstrated by morphological analysis, showing typical apoptotic features, by ISEL or similar techniques, and by DNA fragmentation (DNA laddering).

Diagnosis of MDS

The diagnosis of MDS is, in the majority of cases, relatively easy, and made by the combined examination of blood and bone marrow aspirate at least if the latter is examined by an experienced morphologist. Aplastic anemia and some diseases accompanied by marrow dysplasia, including vitamin B_{12} and/or folate deficiency, exposure to heavy metals, recent cytotoxic therapy, ongoing inflammation including HIV, and chronic liver disease/alcohol use, should however be ruled out before concluding to MDS. Bone marrow trephine biopsy and karyotype, and less often other tests, may be useful to ascertain diagnosis in difficult cases.

Clinical findings

They are non specific and are usually the consequences of cytopenias including : (i) symptoms of anemia; (ii) infections due to neutropenia but also to the frequently associated defect in neutrophil function. As in other types of neutropenia, infections are mainly due to gram negative bacilli or gram positive cocci and less often to deep fungal infections ; (iii) bleeding due to thrombocytopenia : it is usually seen in patients with very low platelet counts. However, bleeding may also occur in moderately thrombpocytopenic patients or even in patients with normal platelets counts, because of thrombocytopathy, with abnormal platelet function.
No organomegaly is generally found in MDS, except in CMML, where splenomegaly is found in 1/3 of the cases, sometimes associated to hepatomegaly. Specific infiltration of other organs is also observed in some cases of CMML, particularly infiltration of serous cavities (leading to pleural, pericardial or less often peritoneal effusions) or infiltration of the skin.

Peripheral blood findings [59]

MDS are characterized by cytopenias of variable importance, involving one or several myeloid lineages.
- Red cells. Anemia is present in about 85 % of the cases and usually macrocytic. The MCV rarely exceeds 120 μ^3, however, contrary to what is frequently observed in megaloblastic anaemias. Red cell shape abnormalities are frequent, including elliptocytosis and sometimes schizocytosis, and nucleated red cells can be found in about 10 % of the cases. Qualitative defects of erythrocytes, reflecting abnormal erythropoïesis, can be observed, including increased Hb F (or less often Hb H), decreased red cell enzyme activities

(especially of pyruvate kinase) PNH like disorder, and modification of red cell group antigens.
- Granulocytes and monocytes. Neutropenia is present in about 50 % of the cases at diagnosis and often associated to morphological anomalies of neutrophils including hypogranulation and less often hypolobulation with, in its extreme form pseudo Pelger Hüet anomaly. Qualiltative neutrophil defects include decreased myeloperoxidase, impaired chemotactic and bactericidal capability which can potentiate, as seen above, the risk of infections associated to neutropenia. The proportion of monocytes may be increased, and absolute circulating monocytosis (> 1000/mm^3) defines the CMML subtype of MDS.
- Platelets. Thrombocytopenia is present at diagnosis in about 30 % of the cases. Thrombocytosis can be observed, although rarely, in some situations. Platelets may be abnormally large, have poor granulation or large, fused central granulation. Platelet dysfunction, reflected by prolonged bleeding time and decreased aggregation to collagen or adrenaline, and secondary to dysthrombopoïesis, can be observed. It may clinically increase the bleeding tendency.
- Lymphocytes. As seen above, T cell lymphopenia and abnormal T cell function can be observed.

Bone marrow aspirate [59]

The bone marrow aspirate is usually normo or hypercellular, but is sometimes hypocellular, due to marrow fibrosis, poor aspiration, or true hypocellularity.
Myelodysplastic features are a characteristic finding of MDS. The different type of morphological abnormalities of myeloid precursors which can be observed are listed in Table 3. Among the most typical changes are megaloblastoid changes in erythroblasts, the presence of ringed sideroblasts (after Prussian blue staining), hypogranulation and hypolobulation of granulocytes, micromegacaryocytes and large mononuclear megakaryocytes. Of note is that myelodysplastic features do not always involve all 3 myeloid lineages, and that the megaloblastoid changes observed in erythroblasts in MDS are generally less pronounced than in vitamin B_{12} or folate deficiency. This characteristic, and the hyperlobulation of granulocytes seen in vitamin deficiencies, allow strong diagnostic orientation by morphology alone. On the other hand, none of the dysplastic features observed in MDS is specific.

MDS	Bone marrow and/or peripheral blood findings
Dyserythropoiesis	Bone marrow Multinuclearity Nuclear fragments Megaloblastoid changes Cytoplasmic abnormalities Ringed sideroblasts Peripheral blood Poikilocytosis Anisocytosis Nucleated red blood cells
Dysgranulopoiesis	Nuclear abnormalities including Hypolobulation Ring-shaped nuclei Hypogranulation
Dysmegakaryopoiesis	Micromegakaryocytes Large mononuclear forms Multiple small nuclei

Table 3
Myelodysplastic features in MDS

Prussian blue staining for iron should be systematically performed to reveal ringed sideroblasts where iron is stored in (abnormal) mitochondria, giving ring shaped staining around the nucleus.
An increased percentage of marrow blasts (defined by marrow blasts > 5 %) is seen in about about 50 % of MDS, and is very specific of MDS, in a context of myelodysplastic features of myeloid precursors. Because the percentage of marrow blasts form the basis of the FAB classification of MDS, it is important to clearly identify marrow blasts and distinguish them from more mature myeloid cells, especially promyelocytes. For

this purpose, the FAB group distinguishes type I blasts, which have no cytoplasmic granules, from type II blasts, which have a few primary azurophilic granules, and are termed by others myeloblasts. The blast percentage used for the FAB classification should include type I and type II blasts. Marrow blasts of MDS usually have morphological and immunological features of myeloid blasts (CD_{13}+, CD_{14}+, CD_{33}+, peroxidase+) but pure lymphoid (Tdt+, CD_{19}+, CD_{10}+) and biphenotypic patterns have been noted. They express CD_{34}, a marker of stem cells, more often than blasts of AML. Expression of Pglycoprotein product of the multidrug resistance (mdr) gene is found in blast cells of MDS at diagnosis in 50 % of the cases of MDS with an excess of marrow blasts (RAEB and RAEB-T), as compared to 20 to 30 % in de novo AML. This higher incidence of Pglycoprotein expression in MDS could explain in part the lower response rate to chemotherapy seen in MDS, by comparison to de novo AML (see below).

Bone marrow biopsy [60]

Because, in many cases, blood examination and bone marrow aspirate are sufficient for a diagnosis of MDS, we feel bone marrow biopsy should not be systematically performed in elderly MDS patients, especially if it does not lead to any treatment modification. However it is obviously important in cases of difficult diagnosis, and it could bring additional prognostic information in some cases.
It obviously assesses bone marrow cellularity better than MDS. Normal of increased cellularity is seen in 85 to 90 % of the cases, but authentic hypocellularity can be observed in 10 to 15 % of the cases (hypocellular MDS). Provided care is taken to fix and process the specimen properly, myelodysplastic features can be very well analyzed in marrow biopsies, and for many authors this method is superior to marrow aspirate for the analysis of dysmegakaryopoïesis.
Marrow biopsy can also allow the detection of clusters of immature granulocytes in the intertrabecular region, away from their normal sites along the osseous surface, termed ALIP («abnormal localization of immature precursors»). The presence of ALIP, even when it coexists with a normal percentage of blasts on bone marrow aspirates, could predict a poor outcome [60]. However, it may be difficult to distinghish true ALIP from clusters of early erythroblasts or megakaryocytes [61].
Finally, biopsy is needed to assess fibrosis in MDS. A mild degree of reticulin fibrosis has been reported in up to 50 % of patients with MDS, but only 15-20 % whow a significant in reticulin fibers, and collagen formation is rarely seen.

Other tests for diagnosis

Apart from tests aimed at ruling out differential diagnoses, other tests, with the exception of cytogenetic analysis of marrow cells, are rarely indicated.
a) Bone marrow karyotype [15]. It allows the diagnosis of MDS in difficult cases, with moderate cytopenias and/or myelodysplastic features, by showing a clonal abnormality typical of MDS, especially monosomy 7, trisomy 8, del 5q or del 20q. When the number of mitoses obtained is low, FISH analysis of those chromosomes may also be useful to demonstrate the anomaly.
b) Other tests.
- Magnetic resonance imaging (MRI). Two studies have shown that MRI of the spine or femur gave typical marrow patterns in MDS, that could be differentiated from those observed in aplasia. MRI could therefore be useful in some cases of difficult diagnosis [62].
- Isotopic studies. Normal platelet lifespan study using ^{111}In labelled platelets may be useful to demonstrate MDS and rule out autoimmune destruction in cases with isolated thrombocytopenia [51].
Isotopic study of erythropoïesis can sometimes be useful, by demonstrating ineffective erythropoïesis, which is typical of MDS [52].
- Bone marrow progenitor cultures. CFU-GM growth is characteristic of MDS when the number of colonies is diminished and small aggregates (clusters) predominate. A marked decrease of BFU-E and CFU-E is almost always observed in MDS [63].

Differential diagnosis [59]

Megaloblastic anaemias, due to vitamin B_{12} and/or folate deficiency always should be ruled out, by measuring serum and erythrocyte levels of those compounds.
When an excess of marrow blasts is present, diagnosis of MDS is generally easy, the only question being the border with AML, defined by a percentage of marrow blasts > 30 %.
In cases with numerous ringed sideroblasts, other sideroblastic anemias (due to alcohol abuse, lead poisining or very rarely congenital sideroblastinc anemias) can relatively easily be ruled out [59].
Chronic blood monocytosis is almost diagnostic of CMML (as chronic lymphocytosis in CLL) but causes of transient monocytosis should be eliminated in recent cases. [64]
In cytopenias without excess of marrow blasts, ringed sideroblasts and blood monocytosis, MDS is a diagnosis of exclusion. In particular, one should exclude several causes of myelodysplastic features of marrow precursors :
- vitamin B_{12} and folate deficiency.
- recent cytotoxic therapy.
- inflammation including viral infections and particularly HIV infection, which can lead to myelodypslastic features in the bone marrow, probably resulting from infection of myeloid cells, nutritional factors, autoimmunity and drug effects.
- chronic liver disease and alcohol use.
Aplastic anemia should be ruled out in hypocellular MDS.
In MDS with isolated neutropenia or thrombocytopenia, other causes of neutropenia and peripheral thrombocytopenia should be excluded.

Classification of MDS

FAB classification [65]

The French American British classification of MDS, proposed in 1982, has since progressively been widely accepted by hematologists (Table 4). It is based on a small number of variables (blood and marrow blasts, ringed sideroblasts and blood monocytes) and easy to apply, although discordances between groups have arisen, due to a large extent to the interpretation of the blast category on marrow smears. Some authors, for example, did not categorize until recently type II blasts among blasts, but counted them as promyelocytes.

FAB type	Frequency	Circulating blasts %		Marrow blasts %	Ringed sideroblasts %	Blood monocytes (10^9/l)
RA		< 1		< 5	< 15	< 1
RARS		< 1		< 5	> 15	< 1
RAEB		< 5		5-20	variable	< 1
RAEB-T		> 5	or	21-30	variable	< 1
			or	Auer rods		
CMML		< 5 (sometimes)[a]		< 30 [a]	variable	> 1
		>5				

Table 4
FAB classificaiton of MDS (65)

[a] Some authors classify patients with features of CMML but 21 to 30 % blasts or > 5% circulating blasts among RAEB-T

a) RAEB and RAEB-T. They account for about 30 and 10 % of MDS, respectively. Pancytopenia is usually present. Cytogenetic abnormalities, present in 60 % of the cases, are often of the unfavorable type (monosomy 7, trisomy 8, complex findings). About one half of the patients progress to AML and survival is short, with a median survival of about 9 months for RAEB-T and 15 months for RAEB.
b) RARS (66). It constitutes about 10 % of MDS and median age is higher than in other MDS (with the exception of CMML). Anemia is usually not associated to neutropenia or thrombocytopenia, and on the

contrary thrombocytosis is seen in 25 to 30 % of the cases. Cytogenetic abnormalities are less frequent than in RAEB and RAEB-T and, when present, are generally not unfavorable. Progression to AML occurs in only 10 % of the cases, and survival ranges between 5 and 10 years. The main complication of RARS is repetitive anaemia, requiring frequent RBC transfusions, which expose to the long term risk of iron overload.
c) CMML [64]. CMML, like RARS, occurs at an older age than most MDS, and has a more important male predominance than other MDS. It has characteristics of both MDS and myeloproliferative disorders (MPS). Characteristics of MPS result from the granulocytic and monocytic proliferation which tends to increase during evolution, leading to high leukocyte counts, and immature circulating granulocytes in addition to monocytosis, splenomegaly and sometimes visceral involvement (particularly of the skin and serous cavities). Some authors have attempted to separate «myelodysplastic» CMML, with no hyperleukocytosis and no organomegaly from «myeloproliferative» CMML, with hyperleukocytosis and frequent splenomegaly. However, the former often evolves to the latter and the disorder should be seen as a continuum rather than as composed of clear cut entities. About 25 % of CMML progress to AML and median survival is about 2 1/2 years.
d) Refractory anemia or refractory cytopenias [66]. This group is a diagnostic of exclusion among MDS, characterized by negative findings (no excess of marrow blasts, no blood monocytosis, no significant numbers of ringed sideroblasts). Although it is termed «refractory anemia», this group is relatively heterogeneous : it also includes patients with pancytopenia, and patients without anaemia but with neutropenia and/or thrombocytopenia. Therefore the term «refractory cytopenia(s)» would appear preferable to «refractory anemia». About 20 % of patients included in this group progress to AML, and median survival ranges from 4 to 6 years.

Atypical forms of MDS [67]

Most MDS cases can be classified according to FAB criteria. However, several types of MDS, with relatively specific features, were recognized after the FAB classification was proposed.
a) MDS with myelofibrosis [68]. They probably include about 5 % of MDS, and are more frequently seen in therapy related MDS. They can only be well recognized by marrow biopsy, which generally shows prominent dysmegakaryopoïesis. They can be distinguished from agnogenic myeloid metaplasia by the absence of splenomegaly, of teardrop-shaped RBC and leukoerythroblastosis, and from acute megakaryoblastic leukemia by the absence or small percentages of blasts of megakaryocytic origin.
b) Hypocellular MDS [69]. They include cases with bone marrow cellularity < 30 % (or < 20 % in patients older than 60 years) and represent about 10 % of MDS de novo, but are more frequent in therapy related MDS. They are often associated to chromosome abnormalities, especially to monosomy 7, which helps distinguish them from aplastic anemia (AA). However, the frontier between hypoplastic MDS and AA may not always be clear cut, as suggested for example by therapeutic response to antilymphocyte globulin in a few well documented cases of hypoplastic MDS (12 and personal findings).
c) MDS with erythroblastopenia [35]. In some cases of MDS, anemia may be associated with erythroblastopenia on marrow samples, confirmed by ferrokinetic studies of erythropoïesis. When other lineages are not involved, these cases should be distinguished from erythroblastopenia of autoimmune origin, particularly associated to thymoma. Del 5q is often observed in MDS with erythroblastopenia.
d) MDS with features of MPS. As seen above, CMML often have features of MPS. Another disorder at the MDS/MPS interface is «atypical CML» characterized in the blood by moderate hyperleukocytosis, granulocytic dysplasia with a moderate number of immature granulocytes, usually between 3 to 10 % of monocytes, no basophilia, no Ph 1 chromosome and no BCR rearrangement [70].
Finally, the thrombocytosis observed in some MDS may confine to thrombocytemia, especially in RARS, in MDS with 3q21, 3q26 abnormalities, del 5q or less often del 20q. Some cases of RARS or RA with del 20q can evolve to a typical MPS with myelofibrosis.

Specific morphological-cytogenetic «entities» in MDS

As seen above, the identification of morphological-cytogenetic subgroup in AML such as M_2 with t(8;21), M_3 with t(15;17) and M_4 eosino with inv(16) has allowed the discovery of specific cancer genes, which in at least

one case (M_3 with t(15;17)) response to a specific form of treatment. A few similar entities have also be identified in MDS, although no specific gene abnormality has as yet been identified in most of them, as seen above.
a) Del 5q syndrome [34-38]. Del 5q may be associated with other chromosomal abnormalities or with an important excess of marrow blasts and, in those cases, no typical features are generally seen. However, isolated del 5q in patients with RA (or RAEB) generally has very typical features, and can be recognized before cytogenetic results : most cases occur in elderly females, who have severe anemia, prominent macrocytosis, erythroblastopenia, normal leukocyte counts, thrombocytosis, and typical hypolobulated megakaryocytes in the bone marrow. The 5q deletion generally involves bands 5q13 to 5q33, progression to AML is rare and survival prolonged.
b) MDS with 17p deletion [71]. MDS with 17p deletion have characteristics of RAEB or RAEB-T, and are often therapy related. They generally have a specific type of dysgranulopoïesis with small granulocytes having prominent pseudo Pelger Hüet anomaly and cytoplasmic vacuoles, an association almost never seen in our experience in MDS or AML without 17p deletion. In 3/4 of the cases, those patients have mutation of the non deleted p53 allele (as the p53 gene is situated in 17p13 and one P53 allele is deleted in patients with 17p deletion). Although p53 inactivation may play an important role, it is suspected that other genes are involved in the pathogenesis of this syndrome.
c) MDS with t(3;3)(q21;q26) or inv(3)(q21;q26) [72, 73]. They are typically RAEB or RAEB-T, often therapy related, with thrombocytosis and micromegakaryocytes in the bone marrow. Gene(s) involved in these MDS variants are not yet known, but the c-mpl gene, located in 3q26 does not appear to be implicated
d) Other entities. Two of them, ie MDS with t(5;12) and MDS with t(3;21) are very rare, but their analysis has allowed the discovery of new genes whose disruption seems to play a role in pathogenesis, as seen above. No other chromosomal abnormality is associated to specific hematological features in MDS.

Childhood MDS *[3, 12, 13]*

Childhood MDS are rare, accounting for about 2 to 3 % of all MDS. They are often associated to constitutional abnormalities, including Down's syndrome, mitochondrial cytopathies, neurofibromatosis and Schwachman disease. They mainly occur in young children and are often not classifiable in the FAB classification. The most frequent entity in childhood MDS is «juvenile chronic myeloid leukemia» (JCML) which has many features in common with adult CMML, including hepatosplenomegaly, high leukocyte counts and monocytosis. It is also characterized by frequent elevation of Hb F. In mitochondrial cytopathies, the FAB type of MDS is usually RARS. The most frequent chromosomal abnormality in childhood MDS, including JCML, is monosomy 7, present in about 40 % of the cases. A subgroup of childhood MDS called «infantile monosomy 7 syndrome» has been described, but its feature largely overlap those of JCML cases associated to monosomy 7.
In JCML, spontaneous CFU-GM growth, which appears to be due to hypersensivity of CFU-GM to GM-CSF, has been observed. Because GM-CSF is particularly produced by monocytes, this phenomenom could participate to the myeloid proliferation, through an autocrine mechanism. 13 cis retinoic acid can inhibit CFU-GM growth in vitro in JCML, and preliminary results suggest its possible therapeutic role in vivo. [74]
On the whole, however, childhood MDS have a poor prognosis and allogeneic BMT should be proposed, whenever possible. Its results, as for other hematological malignancies, are somewhat better in childhood than in adult MDS.

Prognostic factors in MDS

Although a large number of prognostic factors have been reported in MDS, a small number of them are generally sufficient in clinical practice. The most important factors are the percentage of marrow blasts, the number and extent of blood cytopenias and cytogenetic data, and these factors can be grouped together in prognostic «scores» [15, 75-79].

Prognostic factors

They include prognostic factors for survival, but also for progression to AML.
a) Survival. Female sex and lower age are associated to more prolonged survival. However when the death

rate, in MDS, is adjusted on that of a sex and age matched population (standard mortality ratio), it appears that MDS per se is not less aggressive in females and younger patients, and that their better survival is related to a lower incidence of death from other causes [80].
Bone marrow blast percentage is certainly the most important prognostic factors, and it is inversely proportional to survival. The number and extent of cytopenias also has major prognostic value, independant from that of marrow blasts. FAB classification, largely based on marrow and circulating blasts, therefore has strong prognostic value, with RAEB and RAEB-T having short survival, RA and RARS relatively prolonged survival and CMML an intermediate outcome.
Apart from bone marrow blasts and cytopenias, the only factor having clearly shown independant prognostic value is cytogenetic analysis. Three or 4 prognostic groups can be identified by cytogenetics [15, 16]. Complex cytogenetics abnormalities have very poor prognosis, with survival rarely exceeding a few months ; isolated monosomy 7 and trisomy 8 also have poor prognosis, although they usually yield longer survival ; isolated del 5q and possibly isolated del 20q and loss of Y chromosome, although this is more disputed [76], are a favourable subgroup with prolonged survival ; patients with normal karyotype or with other single abnormalities have intermediate prognosis.
Other parameters have demonstrated prognostic value for survival, including ALIP [61], importance of myelodysplastic features on marrow analysis, CD34 expression by marrow blasts, serum LDH levels [70], results of marrow progenitor cultures, presence of RAS mutations, but it is unclear if those factors have independant prognostic value. Pglycoprotein expression by marrow blasts [81] and p53 mutations [29] are also associated to short survival.
b) Progression to AML. Prognostic factors for progression to AML are generally similar to those associated with survival. However 2 factors clearly emerge here, ie increased bone marrow blast percentage and the presence of complex cytogenetic rearrangements, which are associated to very high rates of progression to AML.
c) Prognostic factors in treated patients. Most prognostic factors have been established in cohorts of MDS that received supportive care only. Other prognostic factors could appear with the application of specific treatments. For example, Pglycoprotein expression, which was an unfavorable factor in MDS who received intensive chemotherapy, had no prognostic value on results of treatment with low dose Ara C in our experience [81]. Likewise, RAEB-T was the best prognostic subgroup in patients who received intensive chemotherapy, contrary to patients treated by supportive care only [82]. On the other hand, «unfavorable» karyotypes are associated to poor response to all available treatments, including intensive chemotherapy, low dose Ara C and growth factors [83].

Prognostic scores in MDS [15, 77-79]

They are based on parameters that have demonstrated prognostic value by multivariate analysis and their purpose is to provide useful guidelines to the clinician for the therapeutic approach. Several prognostic scores for survival have been designed, which combine the percentage of marrow blasts, cytopenias and sometimes an addtional factor like age or LDH. They include Bournemouth, Düsseldorf and Sanz's scores [77,78,80]. However, it was shown that karyotype could bring additional prognostic information to marrow blasts and karyotype leading to Lille's score (Table 5) and to an international prognostic score, recently designed after a meeting of major groups involved in MDS.

Survival

Score for each variable

Bone marrow blasts

0 if < 5 %

1 if 5-10 %

2 if > 10 %

Platelets

0 if > 75 X 109/l

1 if < 75 X 109/l

Karyotype

0 if normal diploid or single cytogenetic abnormalities

1 if complex abnormalities (ie at least three chromosomes involved)

Total score (addition of score for each variable)

0 «low risk» group (30 % of the 408 patients, median survival 55 months)

1 or 2 «intermediate risk» group (47 % of the 408 patients, median survival 24 months)

3 or 4 «high risk» group (19 % of the 408 patients, median survival 6 months).

Progression to AML

- Low risk : BM blasts < 10 % and no complex karyotype (238 patients —-> 34 AML)

- intermediate risk : BM blasts > 10 % or complex karyotype (126 patients —-> 40 AML)

- High risk : BM blasts > 10 % and complex karyotype (36 patients —-> 18 AML)

Table 5
Lille scoring system for survival and progression to AML in MDS

Prognostic factors for progression to AML, based on marrow blast percentage and cytogenetics, have also been designed, including Sanz's score and Lille's score (Table 5).

Treatment of MDS

It remains overall disappointing. The only really potentially curative available treatment so far is allogeneic bone marrow transplantation, which can however only be performed in a small proportion of patients, given the usual age of MDS cases. Intensive anthracycline-Ara C chemotherapy, when an excess of blasts is present, yield lower results than in de novo AML. However, these results are probably better than those obtained with low dose chemotherapy or so called «differentiating agents». Supportive care is an important component of the treatment and the role of growth factors still has to be determined.

Allogeneic bone marrow transplantation (BMT) [84-88]

Most reported series concern allogeneic BMT from familial donors (Table 6). About 40 % of the patients are alive in first long term remission, 30 % relapse and 30 % die from the procedure. The higher incidence of transplant related mortality is probably due to the age of the transplanted patients, with a high proportion of cases being older than 40. Relapses mainly occur in patients with an excess of marrow blasts and in patients with cytogenetic abnormalities. In order to prevent them, some authors have advocated the use of intensive anthracycline - Ara C chemotherapy before allogeneic BMT in RAEB and RAEB-T, but it is unknown whereas this can reduce the incidence of relapses post transplant. Another approach has been to reinforce the conditioning regimen (TBI + CY + BU instead of TBI + CY or CY + BU). This lead indeed to lower relapse rates but also to higher transplant related mortality [85,86,87].

Author	No. of patients	FAB type	Alive in CR	Relapse	Toxic death
Anderson (12)	93	RA: 10 RAEB(-T): 45 Others: 8	43 %	15%	42 %
Sutton (13)	86	RA: 20 RAEB(-T): 42 Secondary AML: 17 Others: 5	38 %	23 %	38 %
De Witte (14)	78	RA: 9 RAEB(-T): 36 Secondary AML: 32 CMML: 1	45 %	23 %	32 %

Table 6
Results of allogeneic BMT in MDS (3 main series)

The Seattle group performed unrelated donor marrow transplantation in 52 patients with MDS, with a median age of 33. The 2 year disease free survival, relapse and transplant related mortality were 38 %, 28 % and 48 %, giving the hope that this approach may cure some MDS without familial donor in the future [88].

Intensive chemotherapy with or without autologous stem cell transplantation

Large series of MDS treated with intensive anthracycline - Ara C protocols, in MDS phase or after progression to AML, have been published in the last few years [82, 89,90,91,92,93,94,95,96,97]. They clearly show that the CR rates obtained are lower than in de novo AML, and range between 40 to 60 % (Table 7). Furthermore, median CR duration is only about one year and less than 10 to 15 % of the patients have prolonged remission. Finally, median survival using intensive chemotherapy does not appear to be prolonged, by comparison with milder approaches.

Author	Patient number	FAB type at onset of treatment	CR rate (%)	Median CR duration (months)	Median survival from the onset of treatment
Mertelsmann (18)	45	MDS	51	7	
Hoyle (89)	36	AML	42	< 12	
Gajewski (90)	44	AML	41	10	
De Witte (91)	36	22 AML	62	6	
			63		
		14 MDS	64	7	
Fenaux (92)	58	21 AML	33	9	
			45	10	
		37 MDS	51	10	
Michels (93)	31	RAEB-T	63		> 25 (< 45 years) < 12 (> 45 years)
Estey (94)	85	MDS	66	< 12	35 % survival at one year
Aul (95)	76	33 AML	42	DFS = 29 %	13
			63	at 3 years	
		43 MDS	78		
De Witte (96)	42	AML ou MDS	60	11	18 % at 3 years
Bernstein (97)	38	MDS (29 RAEB-T)	76	14	

Table 7
Intensive chemotherapy in *de novo* MDS (treated before or after progression to AML)

On the other hand, several studies have shown that some subgroups of patients, including patients younger that 60, patients with RAEB-T at diagnosis and patients with normal karyotype have better results with intensive chemotherapy and that their survival can be prolonged with this approach, although probably only a small proportion can be cured. By contrast, the presence of abnormal karyotype, of p53 mutation and of Pglycoprotein expression predicts poor response to chemotherapy [81, 82, 98].
No type of induction regimen has proved any superiority over the other for inducing CR, or prolong CR duration. Preliminary results suggest that agents reverting mdr gene expression, such as quinine can increase

the CR rate in Pglycoprotein positive cases but they will have to be confirmed (personal results). G-CSF and GM-CSF can significantly reduce the duration of aplasia after intensive chemotherapy. This effect is important to consider because the duration of aplasia after chemotherapy is longer in MDS than in de novo AML, and addition of G or GM-CSF could also reduce the incidence of deaths due to hypoplasia.
In order to prevent relapse, several groups are attempting to perform autologous bone marrow (ABMT) or peripheral stem cell transplantation (APSCT) after CR achievement. The fact that, in a majority of MDS patients, lymphocytes do not appear to be part of the clone suggests the persistance of normal non clonal hematopoïetic cells that could reconstitute hematopoïesis after myeloablative treatment. Furthermore, it was recently shown that circulating progenitors obtained after mobilization with chemotherapy and growth factors in 5 cases of MDS in hematological remission after chemotherapy were polyclonal [99]. More than 50 autografted MDS cases have been reported so far. Hematological reconstitution does not seem to differ from that observed in AML, and is shorter after APSCT than ABMT [100, 101]. However, although results are preliminary, the incidence of relapse post transplant appears to be high, and it is uncertain whether this approach will cure a greater fraction of patients than intensive chemotherapy alone.

Low dose chemotherapy

Low dose chemotherapy has been initially advocated in MDS on the basis of a potentially «differentiating» effects. Low Ara C (3 to 10 mg/m^2/12h during 2 to 3 weeks) has been the most frequently used drug [83, 102, 103], while a few studies have used 5 deoxyazacitidine (decitabine) [104] or hexamethylene bisacetamide (HMBA) [105]. It is in fact unclear if these drugs have a differentiating effect ; in the case of Ara C, at least at 10 mg/m^2/12h, a cytotoxic effect is obvious and pancytopenia is generally observed.
Response rates are usually in the range of 30 to 40 %, about one half being CR and one half partial responses (PR). Toxicity is important, however and with Ara C at 10 mg/m^2/12h, the incidence of mortality due to hypoplasia is about 20 % [102]. For this reason, regimens combining low dose Ara C and G or GM-CSF have been proposed, but it is not known if they are superior to low dose Ara C alone in terms of response and survival [106]. Most responses to low dose Ara C do not exceed 12 to 18 months. A higher response rate to low dose Ara C has been reported in patients with normal karyotype [106]. Although in a randomized trial, treatment with low dose Ara C showed no superiority over supportive care only, this treatment is certainly beneficial to some MDS patients [103]. We also observed that although Pglycoprotein expression negatively influenced response to anthracycline - Ara C regimens, it did not modify response to low dose Ara C, so that mdr positive cases could be good candidates for this treatment [81].

Growth factors

a) G-CSF and GM-CSF. G-CSF and GM-CSF can correct neutropenia in about 75 % of the cases of MDS, using conventional doses of 5 µg/kg/day, and there is no evidence that they increase the incidence of progression to AML [107]. Preliminary results of a randomized study suggested that GM-CSF could reduce the incidence of severe infections in neutropenic cases [108]. However no study has so far analyzed if growth factors, by potentially reducing the risk of infection, could improve survival.
Furthermore, G-CSF and GM-CSF are expensive treatments, especially if they have to be applied for prolonged periods in patients where, as in MDS, neutropenia is chronic. Recently, it was shown that low dose G or GM-CSF, ie 0.25 to 0.5 µg/kg/day were almost as efficient as conventional doses in correcting neutropenia [109]. Such low doses, if their efficacy was confirmed, could allow wider use of G and GM-CSF in MDS, at reasonable cost.
In addition to improving neutropenia, granulocytic growth factors improve granulocytic function. Their stimulating effect on granulopoiesis seems to exert itself both on clonal and non clonal hematopoïesis in MDS.
b) Erythropoïetin. Erythropoïetin, even at very high dose (150 U/kg 3 times a week subcutaneously) can improve transfusion requirement in only about 15 % of the cases. In patients who require less than 2 RB C units per month, and who have a serum erythropoïetin level of less than 200 U/ml, however, the response rate may reach 50 % [55].
Interestingly, the addition of G or GM-CSF to erythropoïetin seems to increase the response rate to 40 % [110].

c) Other growth factors. No growth factor active on platelets is available for the thrombocytopenia of MDS. Interleukin 3 and 6 have shown limited efficacy and important toxicity. Thrombopoïetin is not yet available for clinical trials in MDS.
The role of early growth factors (ie SCF, IL1, FLT3 ligand) and of their combination with late acting growth factors has not been evaluated in MDS.

Other drugs in MDS

Alpha interferon, interleukin 2 and vitamin D derivatives have very limited efficacy, if any, in MDS. Retinoïds appear to improve cytopenias in a limited numbers of patients [111].
Our experience with danazol and other androgens is that these drugs can significantly improve thrombocytopenia in about 40 % of MDS with no major excess of blasts, a finding reproduced by some but not all groups. Their mechanism of action is uncertain but probably includes stimulation of megakaryopoïesis [50, 51].
In «proliferative» CMMML with hyperleucocytosis, and sometimes splenomegaly or visceral involvement, the most frequently used cytotoxic drugs used are Hydroxyurea or 6 mercaptopurine. Two preliminary reports suggested that the epipodophyllotoxin drug VP16 gave better response rates than those 2 drugs, especially in case of visceral involvement. However, this was not confirmed in a randomized study in advanced CMML, where hydroxyurea gave both higher response rates and more prolonged survival than VP16 [112].

Supportive care in MDS

Supportive care remains a major component in the management of MDS.
Repeated RBC cell transfusions expose to the risk of iron overload, which can be efficiently, as in thalassemias, prevented in patients who require frequent transfusions by prolonged subcutaneous infusions of desferoxamine during several nights every week.
Platelet transfusions can be useful in case of severe bleeding episodes. Broad spectrum antibiotics should be administered for all infectious episodes in neutropenic cases.

Therapeutic strategy in MDS

There is no clear consensus over the therapeutic strategy in MDS in many situations, given the limited number of efficient available treatments in these disorders. We have summarized in Table 8 the approach currently used by our group. In patients aged < 50 to 55 years with familial HLA identical donor, which constitute less than 5 % of MDS, allogeneic BMT is certainly the best treatment. It should however in our opinion not be performed in «low risk» MDS, ie MDS with no excess of marrow blasts and no unfavorable karyotype, until progression occurs. We suggest that it should not be preceded by intensive chemotherapy except in patients who present with RAEB-T and do not have an unfavorable karyotype (ie patients who have a good chance to achieve CR with chemotherapy).

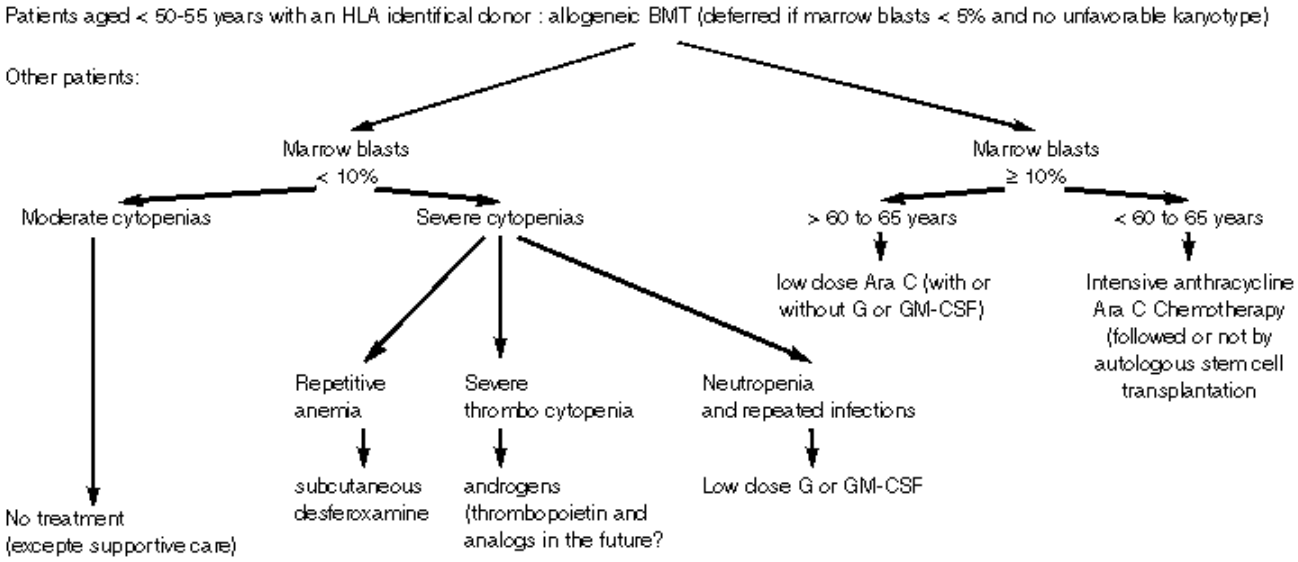

Table 8
Proposed therapeutic strategy in MDS

In other patients, we suggest the following attitude, also based on FAB classification, age and karyotype :
a) In case of no or only moderate excess of marrow blasts (ie < 10 % blasts). No treatment is useful in the absence of symptoms. Supportive care (transfusions, antibiotics) should be administered whenever required. In case of repetitive anemia, requiring multiple transfusions, subcutaneous desferoxamine (50 mg/kg/day, 2 to 5 nights every week) should be proposed, as soon as ferritinemia raises above 2500 to 3000 ng/ml and/or important hepatic or cardiac iron infiltration occurs.
In case of repeated infections in severely neutropenic cases, low dose G or GM-CSF can be envisaged, at least during infectious episodes and if a response on neutrophils is observed, in combination with antibiotics.
In patients with platelets below 50 to 60.10^9/l or in the presence of bleeding symptoms, we suggest a trial of danazol at the daily dose of 600 to 800 mg during at least 3 months.
b) In patients with marrow blasts > 10 %. Some kind of treatment aimed at reducing the blastic proliferation is required. In patients aged less than 60 to 65 years, capable of receiving intensive chemotherapy, we suggest an anthracycline Ara C course followed, in case of CR achievement, by consolidation chemotherapy and probably APSCT. In elderly patients, low dose Ara C, with or without growth factors, is warranted.

Conclusion

MDS are frequent disorders of the elderly whose pathophysiology remains poorly known. However, knowledge of the role of alkylating agents for instance has alrealy lead to diministry their prolonged use, and this should translate into fewer cases of therapy related MDS. A better knowledge of other occupational and environmental factors could also lead to preventive measures.
Further improvement in the comprehension of the mechanisms of ineffective hematopoiesis should lead to the design of new therapeutic approaches that, for instance, could reduce apoptosis.
In cases with a major excess of blasts, the major goal, as in AML remain eradication of blast cells.
As in AML, progress will be achieved by means of overcoming drug resistance, possibilities to isolate non clonal from clonal cells for autologous stem cell transplantation and improvements in allogeneic stem cell transplantation procedures.

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