

# **FRENCH CONSENSUS on MYELOYDYSPLASTIC SYNDROMES (MDS), and chronic MYELOMONOCYTIC leukemia: diagnosis, classification and treatment**

*2015 update*

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MDS are clonal pluripotent, stem cell disorders characterized by ineffective hematopoiesis resulting in blood cytopenias which contrast with a typically cellular marrow. MDS evolve frequently to acute myeloid leukemia (AML) and are the most frequent preleukemic states in adults.

MDS predominate in the elderly, with a median age at diagnosis of about 70 years. Their incidence is 4 to 5 per 100,000 persons per year. Their etiology is generally unknown. In 15 to 20% of cases, however, MDS are secondary to the use of chemotherapy and/or radiotherapy for a prior illness, usually cancer. More rarely, they are secondary to exposure to benzene or other aromatic hydrocarbons, or products used in agriculture (pesticides, herbicides, fertilizers, etc.).

This text tries to summarize a consensus between French hematologists for the diagnostic and prognostic tests to be performed when MDS is suspected, classifications to be applied, and finally treatment recommendations

## **I. DIAGNOSTIC ASSESSMENT**

### **A) *clinical aspects***

The medical history and clinical examination will assess the consequences of cytopenias:

- impact of anemia, especially compared to the patient's Hb level, also taking into account frequent comorbidities (cardiovascular complications, respiratory failure, etc...).

- history of infections and their severity

- history of bleeding

They will also seek:

- the date of onset of cytopenias (based on earlier blood counts)  
- possible etiological agents (radiotherapy, chemotherapy, immunosuppressive agents, occupational exposure to benzene and its derivatives or ionizing radiations, the 2 last being considered in France an occupational illness giving right to compensation)

- a familial history of MDS, AML, aplastic anemia, unexplained thrombocytopenia, that should lead to suspect an underlying germline mutation, especially of GATA 2, RUNX 1, CEBPa, TERT and TERC genes

- signs of underlying dysimmune disorders, particularly common in MDS (arthritis, generally seronegative, vasculitis, polyarthritides, inflammatory colitis etc.)

- lymphadenopathy, hepatosplenomegaly, (although they are rare except splenomegaly found in some cases of CMML, and more rarely in RARS)

-concomitant medications

### **B) *Biological tests (table 1)***

#### **1) level 1: tests considered as mandatory**

a) *Complete blood count* with reticulocyte count, manual WBC differential on blood smears (including a precise count of monocytes, careful research of a small number of blasts and myelodysplastic features) and *marrow aspirate (myelogram)* evaluating cellularity, the percentage of blasts (on 500 elements), myelodysplastic features and iron staining to determine the percentage of ringed sideroblasts are essential

Contrary to the recommendations made in the United States and most European countries, most French centers do not systematically perform *bone-marrow biopsy (BMB)*, except in case of difficult diagnosis or hypocellular marrow, for the differential diagnosis of aplastic anemia or primary myelofibrosis. According to some authors myelodysplasia, especially on the megakaryocytic lineage, is better described with the BMB. On the other hand, the assessment of the percentage of blasts should be performed on the marrow aspirate, as evaluation is less accurate in the biopsy, including after immunostaining with CD 34 (as not all blasts are CD34 positive)

b) *Marrow karyotype* should be systematic . In case of failure (less than 20 mitoses without any abnormality), it is important to repeat karyotype if this has some diagnostic or therapeutic implications for the patient. After two consecutive failures, it is important to perform FISH, assessing principally monosomy 7, trisomy 8 and in case of morphological suspicion 5q deletion and inversion 3q, because of the possible prognostic and therapeutic implications . FISH is also indicated when only one or 2 abnormal mitoses are found , in order to confirm the presence of an abnormal clone

In case progression is suspected (by worsening of cytopenias, appearance of new cytopenia, of a small circulating number blasts or of myelemia), it is necessary to perform a new marrow aspirate and a marrow karyotype. In case of failure, FISH analysis, particularly for monosomy 7, is strongly recommended.

*c) Additional mandatory tests:*

-serum ferritin should be measured before any transfusion support. It remains in routine the best parameter to evaluate and monitor transfusional iron overload.

- tests required for the differential diagnosis or to eliminate additional cause(s) of anemia: iron deficiency, erythrocyte and serum folates, serum vitamin B12 , serum creatinine, liver function assessment, anemia of chronic disease, hemolysis, thyroid dysfunction, HIV, hepatitis B and C serology;

In EPO-treated patients, it may be helpful to check regularly for iron and folate deficiency linked to chronic stimulation of erythropoiesis and supplement them if required (and possibly also look for the presence of antibodies to EPO, although their occurrence is quite exceptional).

-HLA typing of the patient and his siblings, systematic if the patient is aged 70 years or less except in case of obvious contraindication to an allograft, as the latter may be a treatment option at some point during evolution of MDS. HLA typing may also be useful when immunosuppressive treatment is considered, as the presence of HLA DR 15 seems to be a favourable prognostic factor of response to this treatment

-Red cell phenotyping (including for all antigens of the Rhesus system and Kell). In patients in whom chronic RBC transfusions are anticipated, further assessment or "extended" phenotype (including FY1, JK1, MNS3 et MNS4 systems), is strongly recommended

d) *material banking* is strongly advised, in order to be able to perform additional tests (especially somatic mutations ) for diagnosis and prognosis. This requires from the patients an informed consent which, in the current state of French legislation, is "general", allowing that samples be kept " for subsequent examinations, particularly for research". Samples may include mononuclear cells frozen in DMSO, RNA, DNA, serum

It is also recommended to include biological and clinical data of the patients in the GFM national registry of MDS ([www.myelodysplasie.net](http://www.myelodysplasie.net)), accessible via the internet and authorised by the CNIL

## **2) level 2: tests recommended** in at least in some situations

a) *Serum EPO level* in low and intermediate I risk MDS, as this is a prognostic factor for response to erythropoiesis stimulating agents (ESAs, including recombinant EPO alpha and beta and darbepoetin) was considered until recently as systematic before beginning this treatment. Based on the absence of standardized dosing technique, the fact that EPO levels >500U/l are rare in lower risk MDS unless they have a history of RBC transfusions, and as some patients with high (including greater than 500U/l) level respond to recombinant EPO, the French high health authority (HAS) has proposed not to require this assay as a prerequisite for treatment with EPO

b) *testing for a paroxysmal nocturnal hemoglobinuria (PNH) clone* characterized by the loss of expression of proteins to anchor glycosyl phosphatidylinositol (GPI) is recommended particularly in hypoplastic MDS forms, on granulocytic and/or erythrocytic blood populations

c) *germline mutations*: In a family context of MDS and/or AML or aplastic anemia and in the absence of known underlying genetic disease (especially Fanconi anemia), it is recommended to search for germline mutations of: GATA2, RUNX1, CEBPA, TERC, TERT, and even ANKRD26 genes

d) *somatic mutations*

They are currently specialized tests, not performed by many labs, and their possible impact on therapeutic decisions remains undemonstrated, with perhaps a few exceptions:

- lower risk MDS with del 5q, where presence of p53 mutation appears to be associated with worse response to lenalidomide, and a higher risk of AML progression, probably justifying treatment intensification in case of lenalidomide failure. In this situation, immunohisto or cytochemistry or bone marrow cannot substitute for mutation assessment, due to its possible false negative or positive results

- CMML with marrow blasts >10%, where presence of NPM 1 mutation or FLT3-ITD may suggest progression to AML and may be an incentive to administer intensive chemotherapy

- CMML in general, where presence of ASXL1 mutation appears to be independently associated to poorer prognosis, and may contribute to treatment decisions

- When MDS with myelofibrosis is suspected, the identification of JAK2, MPL or CALR mutations could rather suggest a diagnosis of primary myelofibrosis.

e) *material banking* is strongly advised, in order to be able to perform additional tests (especially somatic mutations) for diagnosis and prognosis. This implies asking the patient to sign an informed consent which, in the current French legislation, is « general », allowing that samples be kept "for purposes of subsequent examinations, particularly for research". Samples may include mononuclear cells frozen in DMSO, RNA, DNA, serum and the banking of cytogenetic pellets.

It is also recommended to include biological and clinical data of the patients in the GFM national registry of MDS ([www.myelodysplasie.net](http://www.myelodysplasie.net)), accessible via the internet and authorised by the CNIL, also after written informed consent

**3) level 3** : specialized tests, whose relevance to diagnosis and treatment of MDS remains to be confirmed

*a) testing for somatic mutations*

Somatic mutations are observed in approximately 80% of the MDS (or even 90%, if one uses expanded panels), and more than 90% of CMML. The most common genes are those involved in epigenetic regulation (TET2, ASXL1, EZH2, DNMT3A, IDH1, IDH2), splicing (SF3B1, correlated to RARS, SRSF2), transcription (RUNX1, ETV6, BCOR, TP53) and less often cohesin genes (STAG1, STAG2, RAD21, SMC1, SMC3A). Mutations of NPM1 gene and FLT3 duplication (FLT3 - ITD) are rare, unlike in AML, and mutations of JAK2 or CALR are also rare, unlike in MPN, except for JAK2 in RARS - T.

In CMML type 2, mutations of the Ras pathway (NRAS, KRAS, BRAF, NF1, CBL) are frequent.

.In some rare cases where morphological and cytogenetic diagnosis of MDS is uncertain but diagnosis still suspected, presence of at least 2 mutations may allow a diagnosis of MDS. Indeed, presence of isolated mutations of TET2 or DNMT3A genes (and to a lesser extent ASXL1) have been reported in rare healthy elderly persons

Presence of a mutation in most of these genes, except SF3B1 and possibly TET2 and JAK2, has a generally negative prognostic value, which in many studies is independent of other prognostic factors (including karyotype and IPSS, revised or not). This is particularly the case for ASXL1 mutations in MDS and CMML. In addition, prognosis is also worsened in case several mutations are present.

Presence of TET2 mutations (at least in the absence of ASXL1 mutations) also appears to be associated with better response to azacytidine.

TP 53 mutation is associated to worse response to chemotherapy, hypomethylating agents allogeneic stem transplantation and, as

already said above, with poorer response to Lenalidomide in lower risk MDS with del 5q

In addition to the situations described in level 2, the mutational profile could contribute to therapeutic decisions in the next future. Analysis may become particularly useful in relatively young patients with classical lower risk IPSS, as the presence of unfavorable mutation(s) in addition to other poorer prognostic factors (like being R-IPSS intermediate or greater), may lead to advocate more intensive treatments including allogeneic SCT.

Most specialized laboratories now use "next generation sequencing" (NGS) techniques analyzing simultaneously a panel of about 25 genes, widely shared between MDS, AML and MPN, and which include in particular: JAK2, KIT, CBL, FLT3 –ITD, SETBP1, RIT1, MPL, IDH1, IDH2, DNMT3A, TET2, EZH2, BCOR, BCORL1, TP53, RUNX1, SF3B1, CSF3R, ASXL1, NRAS, KRAS, U2AF1, SRSF2, PTPN11, CEBPA, WT1, ZRSR2

However, analysis of a small number of genes is still possible using classical Sanger methods which, although they have lower sensitivity than NGS, can detect a large proportion of mutations

### *b) flow cytometry(FCM) on marrow or blood cells*

In MDS, myeloid cells are generally immunophenotypically abnormal. In expert hands, immunophenotypic analysis of bone marrow or blood myeloid cells may help making a diagnosis of MDS in difficult cases with unobvious morphological abnormalities and a normal karyotype. Ogata's score can predict the diagnosis of MDS based on the decrease of CD34+ CD19+ B progenitors, the expression of aberrant markers on CD34+ blasts, the profile of CD45 and the diminution of granularity (SSC) with a sensitivity of 69% and a specificity of 92%. Bone marrow dyserythropoiesis can also be detected by abnormal fluorescence intensities of CD71 and CD36 ("RED-score"). The combination of RED-score and Ogata can improve MDS diagnosis prediction with a sensitivity of 88%.



FCM abnormalities may also have prognostic value, in particular for outcome treatment with ESA and azacitidine, although those data need confirmation in prospective multicenter studies

#### **4) *Diagnosis of CMML***

CMML is a disease with overlapping features between MDS and MPN, characterized by persistent monocytosis ( $>1\text{G/l}$ , also in principle accounting for  $> 10\%$  of the WBC differential)

Differential diagnosis includes CML (performed by molecular analysis of bcr-abl rearrangement) and, in case of eosinophilia, very rare cases of MPN with t(5,12) and PDGF-R rearrangement

About 90% of CMML patients carry somatic mutations, especially of TET 2, SRSF2, RUNX 1 and ASXL1. The last mutation appears to carry strong poor prognostic importance, and may soon be considered as a routine test

## **II. CLASSIFICATION , PROGNOSTIC FACTORS AND RESPONSE CRITERIA**

### **1. *diagnostic classifications***

It is recommended to classify patients according to WHO classification (table 2). Of note, this classification has excluded CMML and patients with 20-30% blasts (RAEB-T) from MDS. However, from a therapeutic standpoint, MDS , CMML and AML are a continuum. MDS with rapidly increasing marrow blasts, and/or Auer rods, normal karyotype, and CMML with greater than 10% marrow blasts and NPM 1 mutation may probably benefit from AML like chemotherapy, while on the contrary some patients with slow evolution to greater than 20% marrow blasts, multilineage dysplasia, complex karyotype, may behave

more like MDS and benefit from hypomethylating agents rather than intensive chemotherapy

## **2) prognostic classifications**

It is necessary to classify patients according to the 'classical' IPSS in low, intermediate I, intermediate II, and high risk (table 3). It is customary to combine low and intermediate risk I in 'lower risk' and intermediate risk II and high in 'higher risk', this separation being very often used for the choice of therapeutic approaches, particularly in clinical trials. 'Classical' IPSS also remains essential because the label given by health agencies for drugs in MDS is generally based on this classification

A revised version of the IPSS was recently published (R-IPSS, table 4). It takes into account the same parameters as the classical IPSS but with a different cytogenetic classification, different threshold values for bone marrow blasts and cytopenias, and it gives more weight to karyotype. It is important to also use it, especially for patients with low or int 1 classical IPSS, as about 25% of them are reclassified into more severe subgroups (intermediate or high) of the R-IPSS

The R-IPSS however still does not take into account some known prognostic factors including:

- multilineage dysplasia, whose assessment is however in part subjective
- Myelofibrosis which, when of grade  $\geq 2$ , is associated to poorer prognosis. Assessing myelofibrosis is a further incentive to performing a systematic bone marrow biopsy, at least at diagnosis

## **3) response criteria**

It is essential to use those of the IWG 2006 version that define, in addition to the conventional categories of complete and

partial remission (including of cytogenetics), a category of 'Hematological improvement' (HI) for each myeloid line (table 5). One may also take into account the improvement in quality of life, as measured by now commonly used tests (FACT-AN, QLQC30..).

### **III. THERAPEUTIC APPROACHES**

#### ***A) General approach***

There is a consensus over the fact that the therapeutic attitude must be guided by certain key elements:

- Only allogeneic stem cell transplantation (allo SCT) is potentially curative in MDS. However, it requires having a donor, being younger than 65-70 years, having no major comorbidities, and generally higher risk MDS (by conventional IPSS) where its benefit clearly outweighs potential toxicity of the transplant. If allo SCT is generally not indicated in conventional IPSS lower risk MDS there may be exceptions, particularly in patients who are intermediate or high by the revised IPSS, and/or in case of severe thrombocytopenia, of high RBC transfusion rate resisting to all treatments, although those indications will have to be tested prospectively. Overall, only about 15% of MDS are currently considered for allo SCT

- In other patients, treatment indications remain largely based on the classical IPSS. Although this may be a bit schematic, treatments having a potential impact on disease progression are applied whenever possible in higher risk patients, while in lower risk patients treatment mainly aims at correcting cytopenias, especially anemia. As seen above however, other prognostic factors and especially the revised IPSS may reclassify some lower risk patients in higher risk patients, possibly leading to more intensive treatments

-Symptomatic treatment, mainly RBC transfusions for anemia, rapid treatment of infections by broad-spectrum antibiotics in case of neutropenia and platelet transfusions in case of profound thrombocytopenia remain a mainstay in most MDS cases.

## ***B) Detailed approach***

Main therapeutic proposals of this consensus are listed in tables 7, 8 and 9. Several points can be stressed :

### **1) candidates for allo SCT (table 6)**

Although it remains the only potentially curative treatment of MDS at present , allo SCT still carries some uncertainties

a) *What conditioning regimen ?* As most MDS candidates for allo SCT are older than 45 to 50, they will generally receive reduced intensity conditioning (RIC) regimens. Other regimens like sequential regimens (intensive chemotherapy directly followed by conditioning) are being explored, but they require validation

b) *Should the allograft be performed upfront or be preceded by intensive chemotherapy or a hypomethylating agent?*

No prospective studies are available to answer this question, as the rare prospective studies that addressed this issue failed due to insufficient number of patient inclusion, and current recommendations are therefore mainly based on expert opinions:

- An excess of bone marrow blasts at the time of transplant (schematically if  $\geq 10\%$ ) increases the risk relapse of post-transplant, and treatment with chemotherapy or demethylating agents prior to transplant is generally considered necessary in

those patients (in the absence of prospective comparative studies, it is a consensus)

-Intensive chemotherapy is ineffective in case of abnormal karyotype, especially complex abnormalities. By contrast, it is more effective (CR rates of 50 to 60 % rate ) in case of major excess of blasts (RAEB 2 and RAEB-T/AML according to the WHO classification) and normal karyotype. In those patients, it remains the most effective way to obtain a rapid reduction in marrow blasts before transplant

-Hypomethylating agents appear to be particularly effective in case of abnormal karyotype, including monosomy 7 or complex karyotype, but yield a 'slower' reduction of marrow blasts, sometimes rendering difficult the optimal timing of allo SCT. Being less myelosuppressive than intensive chemotherapy, they may however bring the patient to the allograft in better general condition

c) *when should an allograft be performed?* Although they are retrospective, multicentre studies conducted in patients aged less than 60 years and 60 to 70 years support the contention that patients with IPSS intermediate 2 or high risk benefit (in terms "of years of life gained", even if this concept can be criticized) from early transplant (preceded or not by chemotherapy or hypomethylating agents). On the other hand, in patients with low IPSS, the risk to the allograft statistically generally outweighs the anticipated benefit. Data are less clear-cut for intermediate 1 risk patients , in whom the time to transplant should therefore be also discussed based on other risk factors, including reclassification in the intermediate or high group of the revised IPSS, presence of myelofibrosis ( $\geq$  grade 2), somatic mutations associated with poorer prognosis, severe thrombocytopenia and failure of several lines of treatment

e) *What donor ?* Results of allogeneic transplants from unrelated donors are now identical to those of allografts performed from sibling donors if HLA identity is 10/10. Results

of transplants with only 9/10 matched donors are associated with a 10% reduction in survival, and cord blood transplant using may also slightly less effective, while haplo identical transplant is currently being investigated in MDS

### **3) treatment of 'higher risk' SMD (IPSS high or intermediate II) who are not candidates for allo SCT (table 7)**

#### *a) intensive chemotherapy*

There is a consensus over the following:

- It gives 40 to 60 % CR rates, but short CR duration (median of 10 to 12 months), and less than 10% of very prolonged CR; those very prolonged remissions are in fact mainly seen in RAEB-T with normal karyotype, now classified as AML by the WHO classification.
- Those results are observed below 60 to 65 years. In subjects who are older or with comorbidities, this treatment is highly toxic, as in particular cytopenias induced by intensive chemotherapy tend to be longer in MDS, compared to de novo AML.
- No regimen appears superior to anthracyclines-Ara C combinations. For AraC, it is common to use intermediate or high doses, although it is unclear if they give better results than conventional doses.
- Abnormal cytogenetics, especially complex abnormalities, are associated with low CR rates, and very short CR duration if a response is obtained.
- There is no consensus regarding the optimal time to starting chemotherapy: as soon as cytopenias become important? after progression to AML has occurred?

Those restrictions, and the recent results obtained by azacitidine, now restrict indications of intensive chemotherapy to patients with marrow blasts generally > 10%, normal (or at least not complex) karyotype, age less than 60 to 65, especially with the aim to rapidly reduce the blast count before an allograft

*b) low-dose AraC (20 mg/m<sup>2</sup>/day, two weeks/ month)*

-This treatment induces about 15% CR and 20% CR, lasting 3 to 18 months

-Cytopenias induced are associated with substantial morbidity and mortality and require careful monitoring.

-The response rate is very low in case of unfavorable cytogenetic abnormalities.

-This treatment was associated with lower survival than azacitidine in AZA 001 study (clinical trial that led to approval of azacitidine in the treatment of higher risk MDS), particularly in case of complex karyotype, and it seems to be indicated any more in MDS

*c) Azacitidine (AZA)* (the other available hypomethylating agent, Decitabine, which has no marketing authorisation in Europe for the treatment of MDS, will not be discussed except in the case of CMML)

- AZA, following AZA 001 trial that led to its approval in Europe for higher risk MDS, has become the first line reference treatment in the vast majority of IPSS int 2 and high risk MDS
- AZA works slowly, and responses are often observed after only 3-4 or even 6 cycles. It is therefore recommended not to conclude to a failure prior to 6 cycles, except in case of overt progression or transformation to AML
- CR and PR rates obtained with AZA even after 6 cycles are modest, about 30% overall. The majority of responses correspond to "improvement hematological" (HI), with an improvement of cytopenias (reduction or disappearance of RBC transfusion need and/or improvement in platelet counts without reduction in the number of marrow blasts). Results of several studies suggest that achieving HI is

associated with a survival benefit, justifying the continuation of treatment. In fact, many responses of HI often evolve to PR or even CR after a few months of continued treatment

- The schedule of 75 mg/m<sup>2</sup>/day during 7 days every 4 weeks is the only schedule validated in higher-risk MDS. For practical reasons (absence of hospital day care facility during week-ends) many centres perform days 1 to 5, and days 8 and 9 schedules (so called "5-2-2 regimen"). Five day regimens administered every 4 weeks, on the other hand, are currently not validated in higher-risk MDS
- In the absence of studies having evaluated the optimal duration of treatment, it is currently recommended to treat responders after 6 cycles until relapse
- Response to AZA appears particularly favorable in patients with isolated monosomy 7, and to a lesser extent in patients with complex cytogenetic abnormalities, especially as those subgroups have very limited response to other treatments.
- The toxicity of AZA, in particular myelosuppression, is generally moderate, allowing outpatient treatment in most cases. Close (weekly during the first cycles ) monitoring of blood count is however essential and hospitalization for treatment of complications, including infections, may be necessary. Patients should be informed of those risks prior to the onset of treatment
- local reactions at injection points are frequent and may require local treatments (local steroids, primrose oil, etc...). In case of severe local reaction, AZA injections can be performed IV



#### *d) investigational treatments*

Many agents are currently being tested in higher-risk MDS:

- After failure of AZA (primary failure after 6 cycles, or relapse after an initial response) either as single agents, or in combination with AZA ( ' add on 'approach)
- or upfront in combination with AZA

None of these treatments can however be currently recommended outside clinical trials.

### **3) treatment of lower-risk MDS (table 8)**

-It is designed primarily to correct cytopenias, mostly anemia. When cytopenias are moderate and asymptomatic, no drug therapy is recommended.

- When anemia is symptomatic, it is preferable whenever possible to try to maintain a Hb level > 10-11 g by drug therapy, rather than treating patients only by regular RBC transfusion, as the latter maintain Hb levels generally below 9-10 g Hb, as chronic anemia is associated with more clinical symptoms , poorer quality of life (fatigue,etc...) and to a higher incidence of cardiovascular complications

#### *a. treatment of anemia*

- Erythropoiesis-stimulating agents (ESAs, including recombinant EPO or darbepoetin) . Many studies have shown erythroid response rates of 50 to 60 % in lower-risk MDS with endogenous EPO level < 500 U/l. It is therefore recommended to initiate treatment with ESAs in patients with less than 9-10 g Hb and poor clinical tolerance to anemia, even in RBC transfusion independent patients,

The effective doses are generally, for EPO alfa or beta, of 30000 to 60000 U weekly, and for darbepoetin alpha of 150 to 300 µg weekly. The addition of G - CSF ( at a dose adjusted to maintain between WBC between 5 and 10 G/l) can improve the effect of EPO and darbepoetin in about 20% of the cases

Responses are assessed after 12 weeks. In case of response, the treatment dose should be adjusted to maintain a Hb level between 10.5 and 12 g, complying with ANSM recommendations.

ESA therapy is less effective in patients with 5q deletion, particularly if they are RBC transfusion dependent. However, it is recommended to use it frontline in these patients, even if they often have to switch rapidly to Lenalidomide (see below)

EPO and darbepoetin are currently not formally approved for MDS in Europe, but their use is allowed in France by HAS and ANSM through specific programmes

- Lenalidomide

Transfusion-dependent anemia of lower risk MDS with del 5q responds in 70% of the cases to lenalidomide and a European marketing authorisation exists in this indication if del 5q is isolated, at a dose of 10 mg/day, 3 weeks every 4 weeks, after failure of ESA. Responses generally occur after 6 to 12 weeks

Lenalidomide is likely to induce in these patients, during the 8 to 12 first weeks of treatment, grade 3-4 neutropenia and and/or thrombocytopenia, justifying weekly monitoring of blood counts, and administration of G - CSF in case of neutropenia, broad-spectrum antibiotics in case of fever, and transient discontinuation if platelets < 25000/mm<sup>3</sup>.

Other treatments are considered for second line, after failure of ESA in patients without del 5q, and of lenalidomide in patients with del 5q, and they should preferably be used mainly in clinical trials:

-thalidomide (off label use for MDS)

It is effective on anemia in about 30% of patients resistant to ESAs, mainly if marrow blasts <5%, but is ineffective on neutropenia and thrombocytopenia. However, at daily doses > 100 mg/day (or sometimes even less) it is often poorly tolerated in this elderly population, leading to drowsiness, constipation, peripheral neuropathy and is difficult to use during more than a few months

- hypomethylating agents (off label use in lower risk MDS): they induce RBC transfusion independence in 30 to 40% of lower risk MDS resistant to ESA, also with also platelet responses. The RBC transfusion independence rate obtained in a GFM trial that included 93 low risk patients, generally with isolated anemia (60% had RARS) and in a similar smaller Nordic group trial was however of only approximately 20%,

-immunosuppressive therapy: It is based on the finding, in some MDS, of oligoclonal T cells with an inhibitory activity on myeloid progenitors, reversible after treatment by anti lymphocyte or thymocyte globulin (ALG or ATG). 30 to 35% responses are reported, often multilineage, and frequently durable in patients resistant to ESA. ATG is more effective in patients with the following characteristics: age less than 60 years, history of RBC transfusions of less than 2 years, presence of at least 2 cytopenias, no excess of marrow blasts, normal karyotype, HLA-DR15, and possibly hypocellular marrow, presence of a small asymptomatic PNH clone or isolated trisomy 8. ATG can be combined with Cyclosporine. Although not demonstrated in MDS but only in aplastic anemia, horse ATG is probably preferable to rabbit ATG in MDS

- Lenalidomide (in non del 5q patients). It yields about 25% of RBC transfusion independence in case of resistance to ESA. It can induce neutropenia and thrombocytopenia, however less pronounced than in the case of del 5q. In a GFM randomized study in patients resistant to ESA, a Lenalidomide - EPO beta

combination gave a significantly better erythroid response rate than single agent lenalidomide

### *b. treatment of neutropenia*

Long term use of G – CSF has demonstrated no significant effect on the risk of infection and on survival in MDS with neutropenia and is not recommended.

One may however propose G CSF for short periods of time in a few specific situations:

-in lower risk MDS with severe neutropenia in case of serious infectious episodes, or in patients treated with Lenalidomide

-in higher risk MDS treated with allo SCT, chemotherapy or AZA, during periods of neutropenia

### *c. treatment of thrombocytopenia*

-Therapeutic trials using the TPO receptor analogues Romiplostim and Eltrombopag are currently underway, including in France, in lower risk MDS with thrombocytopenia. Response rates of about 50% have been reported with high-dose Romiplostim (750ug/week). The main side effect of Romiplostim is a (generally transient) increase in marrow blasts, seen in about 15% of the patients. A phase III trial comparing Romiplostim and placebo in lower risk MDS with thrombocytopenia was prematurely stopped because concern was raised over a higher number of AML progressions in the Romiplostim arm, which was not confirmed with more long-term follow-up. Romiplostim and Eltrombopag (clinical experience with the latter is much more limited in MDS) can currently be used only in clinical trials in patients without excess of marrow blasts. Romiplostim has also proved capable, in randomized trials, to reduce the importance of thrombocytopenia and/or its duration and/or reduce the platelet transfusion need when combined with AZA and Decitabine in higher risk MDS, and with Lenalidomide in lower risk MDS

- Androgens, including Danazol (at a dose of 400 to 600 mg/day) provide about 30% of platelet responses, some of them durable and associated with androgen dependence. The mechanism of action of androgens on platelets in MDS remains uncertain, but is not restricted to cases with a peripheral platelet destruction component

-As previously seen, immunosuppressive drugs and hypomethylating agents may improve thrombocytopenia in 30% of lower-risk MDS.

-Finally when, in lower risk MDS, thrombocytopenia is severe and predominates over other cytopenias, looking for a peripheral component is relevant, and may justify a study of platelet lifespan by radioisotopic methods. If platelet lifespan is considerably reduced, ITP type treatments are sometimes applied with success, including splenectomy

#### **4) supportive care**

It remains very important in MDS

##### **a. RBC transfusions.**

They have no specificities compared to those administered in other blood disorders, except that they have to be considered in the long term, and that tolerance to anemia is usually poor in elderly MDS, while the risk of volume overload with pulmonary edema is also real in those patients. Recommendations of the ANSM, the HAS and the Société française d'hématologie (SFH) regarding chronic transfusions of red blood cell concentrates in general can therefore also be used in MDS :

- The usual threshold of Hb to trigger RBC transfusion is 8 g/dL. It does not seem necessary to have a higher threshold in MDS in the absence of additional cardiovascular risk factors, but a lower threshold is not desirable
- The transfusion threshold should however be greater than 8 g/dL in all circumstances which significantly increase oxygen consumption,

such as severe infection, bronchospasm, pulmonary complications, cardiac complications reducing cardiac output (myocardial ischemia, atrial fibrillation), etc... In patients aged over 65 to 70 years, ie the majority of MDS, it may therefore often be justified to maintain a higher transfusion threshold, ranging from 9 to 10 g/dl.

-The volume transfused, calculated on the basis of the total blood volume of the patient and the desired Hb level increase, is in general of 2 packed RBC concentrates per day, repeated in some cases the next day in order to reach the desired increase in Hb level, or 1 Packed RBC concentrate per day during 2-3 days when the risk of fluid overload and pulmonary edema appears high.

### *b. platelet transfusions*

Long term use of platelet transfusions is limited by the risks of rapid alloimmunization, and should be restricted, while shorter term use, especially in combination with myelosuppressive drugs, during a surgical gesture, or in patients with bleeding is the best indication.

Platelet transfusions in MDS can be based on the recommendations of the ANSM, HAS and SFH for platelet transfusions in general, which may however have to be adapted for prophylactic transfusions, because a platelet function defect is frequent in MDS, in addition to thrombocytopenia

-Prophylactic platelet transfusions are recommended for any treatment worsening thrombocytopenia (including for MDS: chemotherapy, hypomethylating agents, lenalidomide, allo SCT). The prophylactic transfusion threshold may, however, have to be adapted to 50 G/L in patients receiving anticoagulation or in case of coagulopathy (DIC-fibrinolysis). In elderly subjects treated by AZA at home, by far the most frequent situation of thrombocytopenia worsened by myelosuppressive treatment in MDS, a prophylactic threshold of 20 G/l seems reasonable, even if it has not been validated by prospective studies, as those patients often have platelet function

defects (in addition to thrombocytopenia ) and are not under constant hospital supervision

- in the absence of concurrent myelosuppressive treatment, only a curative transfusion attitude (ie solely in the presence of bleeding) is recommended in MDS

### *c) Prophylaxis and treatment of infections*

It is identical to that of infections occurring in other neutropenic patients. A neutrophil function defect is however frequent in MDS, in addition to neutropenia, potentially further increasing the risk of infection

It is therefore recommended for MDS patients with neutropenia (spontaneous or induced by myelosuppressive agents including chemotherapy, hypomethylating agents or lenalidomide) to have broad-spectrum antibiotics rapidly available in case of infectious problem. No specific antibiotic or combination has been studied prospectively in MDS. By analogy with patients with chemotherapy induced neutropenia (eg in lymphoma) and who are followed as outpatients, an amoxicillin – clavulanic acid 2-3 g/day + ciprofloxacin 0,75 g bid combination may be proposed, although it should be validated prospectively in MDS. Antibiotic prophylaxis (eg by broad spectrum fluoroquinolones and azoles) may also be interesting in AZA treated patients, especially during the first cycles, but this approach would have to be assessed prospectively

### ***c. Iron chelation therapy***

The deleterious role of iron overload in multitransfused MDS patients remains debated, and the indications for iron chelating treatment, in the absence of prospective studies, also disputed in MDS.

-Although less clearly demonstrated than in thalassemias and inherited hemochromatosis, it is very likely that iron overload has a deleterious effect on the liver, endocrine glands, and

most importantly the heart in heavily transfused MDS patients. It is also likely that iron chelation therapy may reduce this risk. The main current debate is to determine when, and in particular after how many transfusions and/or above which level of iron overload patients start to be at risk of complications and should receive chelation therapy

- Serum ferritin is a good parameter to evaluate iron overload in MDS. Liver and Cardiac MRI (with measurement of the T2 \*, influenced specifically by iron overload) are also non invasive and highly specific tests . Liver biopsy is contraindicated for this assessment in MDS, particularly because of the risk of bleeding (thrombocytopenia, platelet function defect...).

- In patients having received more than 60 to 70 RBC concentrates , or with a greater than 2000-2500 ng/ml ferritin level, the frequency of cardiac iron overload demonstrated by MRI becomes important, and those patients are at risk of cardiac failure , especially in case of underlying heart disease. Chelation therapy seems indicated in these patients if they have a relatively good prognosis, ie low or intermediate I IPSS, or higher IPSS but if they can benefit from a treatment potentially improving the disease course including chemotherapy or a hypomethylating agent.

- In allotransplanted patients, it has been shown by several studies, even if they are retrospective, that even moderate iron overload (with serum ferritin > 1000 ng/ml ) is associated with lower survival, due to an increase in transplant related mortality (and not to an increase in the frequency of relapses). Although the specific causes of this increased toxicity are unclear, it seems important prior to allo SCT to reduce such an iron overload if it exists, or prevent its occurrence in patients who might in the future be candidates for the allo SCT . This recommendation therefore also applies to all MDS patients aged less than 65 to 70 years, in the absence of a clear contra indication to allo SCT. In those patients, it is important to start chelation as soon as the serum ferritin exceeds 1000 ng/ml,



generally corresponding to the transfusion of 20 to 30 RBC concentrates

- For older lower risk MDS patients, who will never be candidates for allo SCT, ongoing prospective studies (particularly the international TELESTO trial randomizing chelation versus no chelation in regularly transfused lower risk MDS) will help determine if early chelation ( with the same thresholds as for potential allo SCT candidates) can improve survival

Currently, iron chelation is generally performed with oral deferasirox (Exjade). Parenteral chelation by deferoxamine (Desferal) is sometimes preferred to obtain rapid reduction in the iron overload, or in case of renal failure contra indicating deferasirox use (in practice, creatinine clearance less than 50 ml/min) . Deferiprone (Ferriprox) is another oral chelator agent, however not approved in Europe for MDS

- Deferasirox (Exjade)

It has a marketing authorisation for the prevention of transfusion hemochromatosis, including in MDS, in principle in case of intolerance (including possible anaphylactic shock even if it is rare) or inefficacy of desferal, at the daily dose of 20 to 40 mg/kg... Its side effects are mainly GI problems justifying adjustment of doses or sometimes progressive dose increase, and moderate renal impairment requiring regular monitoring of the renal function

-Deferoxamine

May be used:

-Either through subcutaneous continuous infusion 3-7 days/ week, through a portable infusor or over a period of 8 to 12 hours every night. The daily dose is usually of 40 mg/kg/day.

- Or by direct slow SC injection one or twice a day. The injected dose should not exceed 10 ml, ie 1 to 1.5 g/injection of the drug

- continuous IV infusion is restricted to symptomatic cardiac overload, with close monitoring because of the infectious risk

The use of Desferal requires annual testing for retinopathy and hearing loss or at the slightest clinical sign. Local hypersensitivity at injection sites reactions is not uncommon.

- Deferiprone

Used at a daily dose of 75 mg/kg , its overall chelating efficiency appears to be lower than that of Desferal, and it is responsible of rare cases of neutropenia. In hemoglobinopathies, its combination with desferoxamine can be interesting in case of severe cardiac iron overload

## ***5) treatment of CMML***

-in the absence of signs of myeloproliferation (splenomegaly, leukocytosis, immature circulating granulocytes, or extramedullary involvement ) treatment of the CMML does not seem to differ from that of MDS with similar cytopenias, marrow blasts and karyotype.

-AZA is approved in CMML with more than 10% bone marrow blasts and without major myeloproliferation (WBC < 13 G/l)

-in the presence of signs of myeloproliferation, Hydroxyurea remains the reference treatment, although its effectiveness is limited. Clinical studies with hypomethylants agents, including decitabine, have however given encouraging results, and a phase III trial comparing decitabine and Hydroxyurea in this context has just started in France and 2 other EU countries

- somatic mutations are seen in almost all cases of CMML, and presence of ASXL1 mutation appears to have an independent poor prognosis, which may have to be taken into account for therapeutic decisions