Clinical management of myelodysplastic syndromes: update of SIE, SIES, GITMO practice guidelines

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ABSTRACT

Since 2002, date of publication of the previous Italian Society of Haematology (SIE) practice guidelines for management of myelodysplastic syndromes (MDS), novel disease-modifying treatments have been introduced and the SIE commissioned an update.

After a comprehensive review of the medical literature published since January 2001, the Expert Panel formulated recommendations for the management of adult and paediatric MDS, graded according to the available evidence.

The major updates are: first-line hypomethylating agents in patients with INT2-high-risk disease; controlled use of first-line lenalidomide in low-INT1 risk transfusion-dependent patients with 5q deletion; deferasirox in low-INT1 patients with a relevant transfusional load; first-line high-dose ESA in low-INT1 patients with Hb <10 g/dl and endogenous EPO <500 U/l; allogeneic HSCT first-line therapy for INT2- and high-risk patients <65 years without severe co morbidities.

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1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders associated with worsening cytopenias and leading to reduced survival and a compromised quality of life, especially in transfusion-dependent patients [1]. Moreover, most of the MDS patients experience complications due to infective and non-infective events with substantial clinical and economic consequences [2]. Finally, MDS occur mainly in older persons, who are likely to present co-morbidities which significantly worsen the natural history of MDS and limit the application of aggressive therapies.

In the year 2001, the Italian Society of Haematology (SIE) produced practice guidelines [3] based on the available evidence. Since 2001 more than 200 clinical trials in the setting of MDS have been...
reported as full papers and several others have been reported at international meetings. As a consequence, the treatment strategy for patients with MDS must be revised in view of new evidence. Here we report updated recommendations for treatment of MDS resulting from a critical systematic analysis of the new literature.

2. Methods

2.1. Organization and design

The methodology used for developing SIE guidelines was reported elsewhere [4]. Nine senior haematologists and three literature reviewers composed the working group. In brief, during the first meeting of the Expert Panel the key therapeutic questions for development of guidelines were identified. A systematic literature review was performed by selecting the relevant pieces of evidence and grading their quality. The grading system chosen for the present guidelines is the one produced by the Scottish Intercollegiate Guideline Network (SIGN) [5]. This system primarily classifies evidence according to the study design, thus assigns randomized trials to level 1, cohort and case control studies to level 2, and case reports to level 3. Studies belonging to levels 1 and 2 are further classified into three levels, namely ++, + and −, according to the study and reporting quality. We modified the original classification so as to account for phase II studies, which were assigned level 2, as for cohort studies. Relevant studies (i.e. randomized clinical trials) reported in abstract form only could not be assigned a quality level, but were uniquely classified according to their study design. Each member of the Expert Panel formulated recommendations pertinent to a specific key question. For all recommendations, the strength of supporting evidence is specified. When no evidence at all was available, the Panel suggested expertise-based recommendations.

In order to reach the final set of recommendations, an explicit approach to consensus methods was devised. A first round of consensus on the recommendations proposed by any individual expert was obtained through paper questionnaires, according to the Delphi Panel technique. The Expert Panel expressed the degree of agreement on any individual recommendation with comments.

The evidence bases were built through systematic search of common medical literature databases for relevant papers published up to end of 2008 and first months of 2009. The proceedings of ASH 2007–2008, ASCO 2008, EHA 2007–2008 were scanned for relevant abstracts. Finally, the major haematology, oncology and general medicine journals (Blood, Journal of Clinical Oncology, British Journal of Haematology, Bone Marrow Transplantation, Haematologica, New England Journal of Medicine, Leukemia, Lancet) were manually searched for relevant papers published from 2001 to 2008.

The Panel deemed essential to update Italian Guidelines by addressing 10 relevant questions, and not the entire body of the previous publication. The full body of recommendations was definitively approved during a meeting held in Bologna on 17th April 2009. The guidelines were reported according to the COGS checklist by the Conference on Guideline Standardization. Updating of the present guideline is expected in 2012.

2.2. Definitions

The present guidelines apply for patients with a diagnosis of MDS according to WHO classification (WHO 2008) [6]. Thereafter, the guidelines do not apply to patients with chronic myelomonocytic leukaemia and sideroblastic anaemia with thrombocytosis. Rather, the present guidelines do apply to patients with “severe refractory neutropenia” and “severe refractory thrombocytopenia”. The International Prognostic Scoring System (IPSS) was adopted throughout the guidelines due to large validation and international adoption [7]. Although the recent proposed and validated WPSS score [8,9], is mentioned and referred to, it is not adopted as standard prognostic score. Moreover, a relevant portion of MDS patients still currently lack cytogenetic information: for them a novel prognostic score could be applied [10]. Finally, dynamic prognostic score, which may be suitable irrespectively of prior therapy, is in the process of validation [11]. Standard definitions for response were adopted [12].

A patient is defined as “eligible” to HSCT if HSCT is a possible therapeutic option in his/her therapeutic pathway, but the availability of donors has not been checked, yet.

3. Results

3.1. Which investigations are to be performed before planning therapy?

Complete characterization of the disease is nowadays mandatory to guide therapeutic decisions. Present guidelines are addressed to MDS patients with complete diagnostic and prognostic evaluation.

Beside IPSS risk score, selection of MDS patients for specific options of therapy is based on diverse clinical and laboratory parameters. Therefore, the Panel indicated specific evaluations, like bone marrow biopsy as essential method to determine cellularity and fibrosis [13], and serum erythropoietin determination, as an essential test for guiding erythropoiesis stimulating agents (ESAs) treatment [14]. Assessment of iron status and transfusional history in patients receiving chronic red blood cell transfusions has been also recommended, in order to complete the process leading to decision making. Finally, the search for a nocturnal paroxysmic haemoglobinuria clone, reported in about 10% of patients with low-grade MDS [15] was not deemed to have sufficient evidence of relevance to be performed routinely. Analysis of MDS marrow cells by flow cytometry is not recommended, because of intrinsic difficulties in analysis and evaluation of data on a routine basis.

3.2. Which patients do not need any treatment and can just be followed?

The Expert Panel extensively discussed the criteria for selecting MDS patients candidates to watchful waiting.

Absence of treatment can be considered only for patients with no symptoms of anaemia or without any neutropenia-related infective episodes or thrombocytopenia-related bleeding. MDS patients with neutropenia and especially those with grade 2 neutropenia (neutrophil count lower than 1.0 × 10^9/L), are anyhow at increased risk of infection due to dysplastic neutrophils with altered function. The frequent presence of co-morbidities, such as diabetes, may worsen this infective risk. A warning regarding this issue was posed by the Panel.

3.2.1. Recommendations

Adults patients do not need any treatment and can just be followed when they belong to the IPSS low-INT1 group, are asymptomatic (no bleeding, no recurrent infections), are not severely anaemic (haemoglobin equal or greater than 10 g/dl, without symptoms), have a percentage of blasts in bone marrow <5%, do not carry poor-risk cytogenetics, and do not show other severe cytopenias (grade D).
As far as cytopenias are concerned, the Panel agreed that patients with an absolute neutrophil count greater than 1 × 10^9/L and a platelet count greater than 50 × 10^9/L, in the absence of symptoms, could be safely left without treatment (grade D). Patients with an absolute neutrophil count ranging from 0.5 to 1.0 × 10^9/L should be individually evaluated considering the other risk factors for infections, such as age and co-morbidities (grade D).

Due to inapplicability of the IPSS grading system in childhood MDS, children should be assessed with different criteria (see specific recommendations).

All children with refractory cytopenia, an absolute neutrophil count greater than 0.5 × 10^9/L, a normal karyotype, and without need of transfusions can be left without treatment (grade D). If untreated, patients should be monitored at least every 3 months with a full blood count and physical examination (grade D).

When eligible for allogeneic HSCT, patients should receive bone marrow examination for blast count and cytogenetics every 12 months (grade D).

### 3.3. Which patients are candidates to receive epigenetic therapy?

Epigenetic modifications play a role and cooperate with genetic alterations in the pathogenesis of MDS. The potential reversibility of chromatin remodelling renders epigenetic events ideal targets for therapy. The hypomethylating agents 5-azacitidine (AZA) and decitabine (DAC) can reverse epigenetic silencing and have been used extensively in the treatment of MDS patients. Although the efficacy of AZA and DAC was not definitely demonstrated to be based only on hypomethylation of DNA, yet these drugs are named epigenetic agents.

Three randomized trials (evidence level 1) consistently demonstrated that AZA and DAC are very active in MDS patients, and induced complete remissions (CR) (7–10% CALGB trial and 17% AZA-001 trial; 9% CR in D-0007 study) and a substantial percentage of partial responses in patients with MDS [16–20]. Re-analysis of CALGB trial by IWG 2006 criteria indicate 13% CR in azacitidine treated patients [17] and meta-analysis of several decitabine studies 24% CR [28] or more than 30% [29,30].

The earlier randomized study compared AZA therapy with best supportive care, but allowed crossover between the two treatment arms, therefore survival advantage with AZA was evident only when landmark analysis was performed [16]. In the same study, quality of life was significantly ameliorated in patients treated with AZA as compared with those given supportive care [21].

The most recent randomized study demonstrated that in INT2- and high-risk MDS patients AZA determines a significantly prolonged overall survival (24.5 months versus 15 months) compared to conventional care regimens, like low-dose Ara-C, high-dose chemotherapy or best supportive care [19]. Subgroup analysis performed in the same MDS population indicated that elderly MDS patients (>75 years old) respond equally well to treatment with no increase in side effects [22]. In parallel, the response to AZA was evaluated in MDS patients enrolled in the same study and carrying -7/del 7q. This group of patients usually prognostically at poor risk had significant prolongation of survival (13 months versus 5 months) and high percentage of haematological improvement (HI). Such findings were also confirmed by separate studies [23,24].

To note, although present in a substantial percentage of cases, the achievement of CR and PR was not determinant to obtain prolongation of survival, quite differently from what observed in AML patients. It appears that HI was essential to survival advantage in patients treated with AZA [25].

AZA schedule of administration through all the randomized published studies was 7 days subcutaneously at a dose of 75 mg/sqm/day. In outpatients with low-risk MDS different therapeutic schemes and doses of azacitidine induced HI and transfusion independence [26], but further studies aimed at establishing the activity of different doses and schedules of AZA are required. The Panel did not judge that at present there is evidence supporting the equal efficacy of different dose and schedule. The optimal duration of therapy with hypomethylating agents is unknown. However, continued AZA treatment was shown to further improve the quality of response [27]. In responding patients, the probability to achieve response was 50% after 2 cycles, but 87% after 6 cycles of AZA. Therefore, in the absence of disease progression, continued AZA treatment is appropriate and may maximize patient benefit.

Several studies were conducted with DAC, mainly in INT2- and high-risk MDS patients and indicated activity of this agent, with good percentage of haematological response, even in the worst prognostic subgroups (48% HI). CR and PR were quite variable among studies, ranging from 17% [28] to 35% [18,29]. Treatment-related mortality was reported to be 7% with DAC, probably due to a prolonged myelosuppression. The recently concluded EORTC trial reported no significant difference in survival in high-risk elderly MDS patients treated with DAC in comparison to those given supportive care only [20]. Lack of evidence on survival advantage, and considerations on toxicity guided the Panel to recommend a preferential use of azacitidine. The schedule of DAC employed in the EORTC trial was 15 mg/m² for 3 times/day continuous infusion for 3 consecutive days. Recently a monocentric [30] and a subsequent confirmatory trial [31] indicated as equally effective a 1 h intravenous administration for 5 days of DAC 20 mg/sqm/day.

About two thirds of the patients enrolled into the randomized trials belonged to the INT2- and high-risk score group and one third to the low and INT-1-risk one. However, similar response rates in the four IPSS risk groups were reported [16,18,32]. Moreover, recent data demonstrated that patients with low-INT1 MDS treated with AZA outside clinical trial achieved clinical benefits [26,33]. Similarly, 82 low-INT1 risk patients receiving AZA in the Italian National Patient Named Program achieved a response rate of 39% (12% CR) [34]. Therefore, the Expert Panel deemed that low and INT1-risk MDS may be candidate to receive treatment with AZA when resistant or intolerant to therapies such as ESAs or immunosuppressive agents.

#### 3.3.1. Recommendations

Patients belonging to the IPSS INT2-high groups and not eligible to allogeneic HSCT, or eligible to allogeneic HSCT but lacking an immediately available donor, are recommended to receive hypomethylating therapy (grade A).

Due to existing evidence of a lack of survival advantage and to a possible major myelosuppressive effect by decitabine, the Panel recommends the use of azacitidine in this clinical setting.

At least six courses of azacitidine are recommended, according to the following schedule: azacitidine 75 mg/sqm/day subcutaneously for 7 days q28d (grade A).

In patients with IPSS INT2-high risk and candidates for hematopoietic HSCT, the use of hypomethylating therapy before transplantation is recommended only within approved clinical trials (grade D).

Patients with IPSS low-INT1 risk disease are candidates for hypomethylating therapy first-line when they need a treatment, do not carry 5q deletion either alone or in combination with other chromosomal abnormalities, and have at least one of the following conditions: lack of recommendation to ESAs (i.e. serum erythropoietin level >500 mU/ml), presence of any other severe symptomatic cytopenia, more than 5% blasts in the bone marrow, or a poor-risk cytogenetics (grade D).

Patients with IPSS low-INT1 risk disease, included patients carrying 5q deletion, are candidates for hypomethylating agents also...
when they have been demonstrated resistant to first-line therapy with ESAs, immunosuppressive agents or lenalidomide (grade C).

3.4. Which patients are candidates to receive immunosuppressive therapy?

Immunosuppressive treatments have not been used extensively in MDS patients. Nevertheless, the available evidence includes clinical studies applying anti-thymoglobulin (ATG) alone (horse-ATG 40 mg/kg/day for 4 days) or ATG and cyclosporine-A (CysA) in overall 454 patients, mostly with low-INT1 disease. Only one published randomized phase II study [35] compared horse and rabbit ATG in MDS clinical subset and did not evidence clinically relevant differences. A randomized trial compared horse-ATG plus CysA with supportive care [36]. This and more recent reports consistently demonstrated a response rate ranging from 30% to 60% [37,38]. From these studies, ATG or ATG plus CysA resulted to be significantly more active than CysA alone. A scarce body of low-quality evidence (only 2 full papers reporting >10 MDS patients and published after 2001; overall 4 full papers published) consistently supports the efficacy (especially in terms of erythroid responses) of CysA single therapy in patients with hypocellular bone marrow, RA or low IPSS and good karyotype (included transfusion-dependent patients), provided that quite a high dose is tolerated (>3 mg/kg/day) [39].

Although the comparison of efficacy was performed in limited number of patients, the source of the ATG does not seem to influence outcome.

Several studies attempted to identify clinical parameters predictive of susceptibility to immunosuppressive therapy. The followings are products of consensus: younger age [38,40–42], hypocellular bone marrow [40,41,43], FAB diagnosis of refractory anaemia [35], lower IPSS score [38,43], normal karyotype [38], HLA-DR15 antigen was associated with a higher response rate in 2 studies [38,41]. Patients responding to ATG had longer overall survival and progression-free survival [40,43]. To note, infective complications were frequent in older patients (>60 years). Some members of the Panel argued that immunosuppressive therapy prior to HSCT would further increase infective complications after HSCT.

There are no published trials comparing new agents like hypomethylating drugs with ATG in lower risk MDS patients, thus no recommendation based on evidence can be given to select one of the two therapeutic options in this subset of patients.

3.4.1. Recommendations

Existing evidence indicates that the use of immunosuppressive therapy is appropriate for patients with MDS low-INT1 IPSS risk score who need a treatment, have <5% blasts in the bone marrow and do not have poor-risk cytogenetics (grade B).

The lack of clinical trials comparing immunosuppressive therapy with new agents, like hypomethylating drugs, makes the choice not feasible on the basis of evidence.

The Panel agreed that the best candidates for immunosuppressive treatments are those with an age <60 years (grade B), a normal karyotype (grade B), a hypocellular bone marrow (grade C) and the HLA-DRB1-15 antigen (grade C).

The use of ATG alone (grade C) or in combination with CysA (grade B) is recommended.

3.5. Which patients are candidates to receive immunomodulatory agents?

While in the 2001 guidelines the Panel found scarce evidence to support any recommendation concerning the use of thalidomide in MDS patients, literature is nowadays somehow different.

Ten retrospective or phase II studies (highest level 2+), enrolling at least 10 MDS patients each treated with thalidomide as single agent were reported. Overall, the selected studies included 419 patients, mostly with low-INT1 risk, who received thalidomide daily doses ranging from 50 to 1000 mg [44–49]. The rate of drop-out ranged from 15% to 67% at 12 weeks, mainly due to neurological toxicity. Thrombotic events were rarely reported and exclusively in patients treated with higher doses [48]. The reported intention-to-treat response and efficacy rates were highly variable (9–56%) and influenced by elevated drop-out rates and patients' selection. Only few cytogenetic responses were reported [44,45,48], however, hematologic responses, mainly erythroid, were not rarely long-lasting [45]. Prolonged survival in thalidomide responders versus supportive care treated-patients was reported in two studies [45,50]. Efficacy data in INT2- and high-IPSS risk patients were inconsistent [45,47]. The adjunct of ESAs [51,52] to thalidomide did not show significant advantages with respect to thalidomide as single agent. In particular, the association with darbepoetin induced a high rate of thrombotic events [53]. Overall, low-dose thalidomide has shown effectiveness in a subset of younger low-INT1 IPSS risk MDS patients with red cell transfusion-dependency, not otherwise cytopenic, who are not candidate to lenalidomide (i.e. without 5q deletion) or to ESAs (i.e. with a serum erythropoietin level higher than 500 mU/ml) or who failed previous ESAs therapy. Thalidomide dose should anyway be adjusted to the lowest effective in maintaining response. Moreover, thalidomide therapy should be adopted with caution in males and females patients with childbearing potential and strict monitoring should be performed. For the limited possible application of thalidomide, the Panel did not express specific recommendations about the use of this drug.

Lenalidomide is an oral agent with immunomodulating and antiangiogenic properties. Four phase II trials (evidence level 2+) investigated the efficacy of lenalidomide single therapy in more than 400 MDS patients [54–56]. Enrolled patients included low-INT1 risk patients with symptomatic or transfusion-dependent anaemia, refractory to ESAs. Patients with 5q deletion were peculiarly responsive to lenalidomide [54,55]. Erythroid response was achieved in 76% of 5q- positive patients (67% of whom achieved transfusion-independence); cytogenetic response in 50–77% of MDS patients carrying 5q deletion [55]. Best dose and schedule was 10 mg/day for 21 days every 28 [55]. Dose reduction is required in MDS patients with renal failure and altered drug metabolism [57], especially because responding patients may experience severe dose-related neutropenia and thrombocytopenia due to selective elimination of the 5q- positive cell clone [58]. The Panel recommends to follow advises for practical management during lenalidomide treatment [57], and in particular a regular weekly monitoring of full blood counts, especially in the first 2 months of treatment and the possible use of G-CSF in case of severe neutropenia. Periodical thyroid function and renal function must also be evaluated. Though median time to response was about 1 month, in some patients lenalidomide therapy may show effectiveness after several cycles, therefore it should be prolonged, and maintained in responders. Lenalidomide should be adopted with caution in males and females patients with childbearing potential [57].

Sporadic MDS patients treated with lenalidomide progressed to AML [59,60]. Although the percentage of progression to AML does not significantly differ from that reported in the cohort of MDS patients evaluated for establishing IPSS [6], this observation by itself constitutes a warning to the use of lenalidomide in MDS patients with deletion 5q and with complex karyotype, or when additional chromosomal abnormalities appear during treatment. Strict cytogenetic monitoring and the use of lenalidomide within controlled therapeutic programs (registries or clinical trials) are required. Lenalidomide therapy may show effectiveness after sev-
eral cycles, therefore it should be prolonged, and maintained in responders.

Sporadic haematological responses were observed also in INT2- and high-IPSS risk patients carrying 5q deletion [61], but almost exclusively in those without additional chromosomal abnormalities.

Two ongoing phase 3 randomized, placebo-controlled trials (MDS 004 and 005) are testing lenalidomide in MDS patients with or without 5q deletion, respectively. Combination trials of lenalidomide with ESA or azacitidine are also on-going.

3.5.1. Recommendations

Patients with a low-INT1 IPSS risk disease, transfusion dependent and carrying 5q deletion, either isolated or in combination with additional cytogenetic abnormalities, are candidates for a controlled treatment with lenalidomide as first-line therapy within a register or a clinical trial (grade B).

Patients with INT2- and high-IPSS risk disease and 5q deletion, either isolated or in combination with additional cytogenetic abnormalities, without an immediately available donor for allogeneic HSCT, should be considered for lenalidomide treatment only within approved clinical trials (grade C).

Patients with a low-INT1 IPSS risk disease, transfusion-dependent anaemia, without 5q deletion and not candidates for ESAs therapy (i.e. with a serum erythropoietin level higher than 500 mUI/ml) or who failed previous ESAs therapy, should be considered for lenalidomide only within approved clinical trials (grade D).

The currently recommended treatment schedule of lenalidomide in 5q- MDS patients is an initial dose of 5–10 mg/day orally for 21 days every month for at least 4 treatment cycles (grade B).

A regular (i.e. weekly) monitoring of full blood count is required, especially during first 2 months of treatment. In patients who develop severe neutropenia or severe thrombocytopenia, transient discontinuation of the drug, followed by dose reduction, should be adopted (grade D).

3.6. Which patients are candidates to receive AML-like chemotherapy?

High-dose chemotherapy regimens have been used to treat younger patients with high-risk MDS, and much less frequently elderly MDS patients. Although remissions have been observed in a relevant proportion of the patients, survival does not seem to be significantly improved when chemotherapy was not followed by allogeneic HSCT [62]. No controlled prospective study comparing the outcome of MDS patients treated either with standard-dose chemotherapy or with any other treatment is available. A recent randomized trial [19] compared AZA treated patients with those given conventional care regimen (among which high-dose chemotherapy), but the number of MDS patients treated with chemotherapy was limited and the study was not powered for such a direct comparative analysis. A retrospective study reported significantly longer OS in patients treated with DAC in comparison with historical group of matched patients treated with high-dose chemotherapy [63].

Retrospective analyses (evidence level 3) of MDS patient cohort reported similar efficacy for combination of citarabine with either idarubicin, fludarabine or topotecan [64–66]. No clinically relevant advantage was reported by adding GM-CSF, G-CSF, IL11, or multidrug-resistant modulators (level 1–1+) [67–73].

In current clinical practice, AML-like chemotherapy is administered to a portion of patients who are candidate to reduced intensity HSCT. Bone marrow blast percentage >10% is usually adopted as threshold for deciding the use of AML-like chemotherapy.

The randomized phase II CALGB 19803 study recently reported a modest response and relevant toxicity of oral topotecan in 90 low-INT1 risk patients with at least one severe cytopenia [74] (level 2–). The Panel judged that the use of Topotecan plus thalidomide, 9-nitro-captothecin, CPT-11 recently proposed should be restricted to experimental studies.

Even if low-dose chemotherapy is not strictly defined as an AML-like therapy option, we should spend some words to comment that, in view of the activity and scarce toxicity of hypomethylating agents, its use has at present little indication, with or without growth factor addiction [75]. In particular, there is no strong evidence to support the use of low-dose melphalan [76], a part a report of activity in hypoplastic-blastic MDS. Low-dose cytosine arabinoside could be considered in patients with INT2 or high-risk MDS [75], not candidate to any intensive treatment and for whom administration of AZA or DAC is not feasible. The addition of all-trans retinoic acid to low-dose cytosine arabinoside cannot be recommended.

3.6.1. Recommendations

According to the existing evidence, use of AML-like therapy is appropriate in patients with a bone marrow blast percentage >10% and aged less than 65 years (grade C).

Despite the absence of controlled trials comparing AML-like therapy with new drugs (i.e. hypomethylating agents), the Panel agreed that the most suitable candidates for AML-like chemotherapy are those who proved to be refractory to hypomethylating agents or for whom hypomethylating therapy is not feasible (grade D).

Standard or high-dose cytosine arabinoside-containing regimens are the recommended induction therapy (grade B) and cytosine arabinoside combined with anthracyclines is the recommended drug association (grade B).

Addition of fludarabine does not improve patients’ outcome with respect to regimens with cytosine arabinoside alone (grade B).

3.7. Which patients are candidates to receive allogeneic HSCT?

Allogeneic HSCT is the only treatment with curative potential for MDS. Co-morbidity, age, IPSS score, cytogenetics, conditioning regimen and donor selection are predictors of post transplant outcome [77–83].

At present, no direct high-quality evidence supports the decision when to offer allogeneic HSCT to a newly diagnosed MDS patient. Moreover, there are no comparative trials published nor MDS-specific score predictive of transplant outcome. A decision analysis employing clinical data from HSCT registries and from a large database of not transplanted MDS patients [84] calculated that probability of survival in patients with low-INT1 IPSS improve if HSCT is performed at progression. Nevertheless, over one-fourth of MDS patients currently transplanted have INT1-IPSS risk. In myeloablative allogeneic HSCT, busulfan containing regimens yield better results than TBI [81,83]. Although there are some evidences indicating better outcome in myeloablative HSCT using peripheral stem cells from matched siblings [81,86,87], other studies did not report a significant impact of stem cell source on the probability of survival [80]. Therefore, the Panel did not formulate any recommendation on this issue. HSCT from unrelated donor either matched or with only one allele disparity offered similar probability of long-term outcomes as compared to transplantation from matched siblings, after adjusting for age and disease status [80,81,88,89], provided an accurate matching by high-resolution molecular analysis is performed [90]. Only a small retrospective study reported positive outcomes of 22 MDS patients receiving cord blood SCT [91]. Reduced-intensity regimens have been evaluated...
by EBMT [92] and proved to decrease TRM after HSCT from sibling donors, as it has been recently confirmed [93], but are associated with an increased risk of relapse. The proposed reduced-toxicity regimens generally included fludarabine associated with thiotaope or busulfan and treosulfan-containing regimens [80,93–97].

Pre-transplant percentage of bone marrow blasts and response to induction chemotherapy were frequently, but not constantly shown to be associated with better DFS [92,94,97–99]. However, pre-transplant chemotheraphy seemed to select MDS patients with an expected better outcome after transplantation [98]. Therefore, the need for pre-SCT remission induction chemotherapy remains a debated issue and randomized studies are currently ongoing. Only small phase II studies investigated the feasibility of using AZA or DAC as induction therapy prior to allogeneic SCT [100–104]. The number of patients treated with hypomethylating agents before allogeneic SCT is still limited and sound conclusions cannot be drawn. Nevertheless, the major advantage is low toxicity, resulting in a better performance status at transplantation.

3.7.1. Recommendations

All patients with MDS aged less than 65 years should be evaluated for allogeneic HSCT eligibility (grade B). HLA identical (or single antigen mismatched) siblings or matched unrelated individuals are to be considered suitable donors (grade B).

The Panel agreed that the best candidates for allogeneic HSCT are patients with an IPSS score INT2 or high and patients with an IPSS score INT1 or low who have a sustained transfusion-dependent anaemia or another severe cytopenia, or a poor-risk cytogenetics or a blast percentage higher than 15% in the bone marrow (grade C).

Due to the high risk of relapse, patients with an IPSS risk INT2 or high should be offered a myeloablative HSCT if aged less than 55 years and without co-morbidities (grade C).

Novel conditioning regimens with reduced extramedullary toxicity are recommended in patients aged more than 55 years or with co-morbidities and in those with MDS at low risk of relapse because of both a low number of blasts in the bone marrow and absence of poor-risk cytogenetics (grade D).

In patients with INT2 or high-IPSS risk disease, allogeneic HSCT should be performed as a first-line therapy (grade B).

Alternative donors (i.e. mismatched-related, cord blood) HSCT should be performed only in centres with an active program in the field, in high-risk MDS patients without a matched (related or unrelated) donor and/or who urgently need transplantation (grade D).

No recommendation can be given on the long-term efficacy of AML-like therapy before HSCT.

3.8. Which patients are candidates to receive hematopoietic growth factors?

Since the publication of previous SIE guidelines, three meta-analyses (level 1+) addressed the efficacy of recombinant human erythropoietins (r-HuEPO) and darbepoetin in MDS patients [105–107]. The large majority of these studies referred to r-HuEPO alpha (22 studies, 925 patients) or darbepoetin (8 studies, 389 patients) and included more recent trials with higher ESAs dosing. The reported overall response rate was 57% and 59%, respectively, with three factors predicting a response to r-HuEpo: baseline serum erythropoietin level lower than 500 IU/l, FAB class (RA or RARS), and fixed, rather than weight adjusted dosages [106].

None of these two meta-analyses evidenced an increased risk of haematological or cardiovascular events or leukemic transformation in patients receiving ESAs. No direct comparison between the different ESAs could be done.

More recently, one retrospective study and phase III prospective, non-randomized trials reported rates of erythroid response of 50–71% in lower risk MDS patients treated with high doses r-HuEPO (60,000–80,000 U per week) [108,109], or darbepoetin (300 mcg once-weekly or 500 mcg every 2–3 weeks) (level 2++) [110,111].

Combination of r-HuEpo (or darbepoetin) and G-CSF has been tested in two large retrospective studies [108,112], a phase 2 prospective, dose-escalation trial [113] and 2 phase III randomized controlled trials (level 1−) versus supportive care [114] or “standard dose” r-HuEPO alone [115], respectively. Erythroid response was higher in patients with a lower baseline serum EPO level and a lower transfusion burden. A recent meta-analysis of 15 studies with 741 patients, indicated that erythroid response was equivalent (50%) in patients treated with alpha r-HuEPO as a single agent versus r-HuEPO plus G-CSF or GM-CSF [107]. Alpha r-HuEPO monotherapy 60,000–80,000 U weekly produced significantly higher response rates (65%) compared with the “standard” dose of 30,000–40,000 U weekly, either as a single agent (49%) or in combination with G-CSF/GM-CSF (51%), independently upon FAB subtypes and transfusion-dependency [107].

To note, quite recently, the use of ESAs was demonstrated to positively affect survival in comparison to supportive care [108,116]. The use of G-CSF as prophylaxis in severe neutropenic MDS patients was never shown to have an impact of survival and morbidity and was not recommended by this Panel. Likewise, the use of pegylated G-CSF is not recommended outside clinical trials.

The use of thrombopoiesis stimulating agents (romiplostim, eltrombopag) [117] in particular, but also of novel ESA (CERA, epoetin-delta, YM311) is currently being tested in phase I/II studies and is not recommended outside clinical trials.

3.8.1. Recommendations

Patients with low-INT1 IPSS risk disease, haemoglobin levels lower than 10 g/dl, and serum erythropoietin levels <500 mIU/ml should be considered for ESAs, i.e. erythropoietin alpha, erythropoietin beta or darbepoetin (grade B).

Fixed, rather than weight-adjusted, weekly subcutaneous doses of 60–80,000 U of erythropoietin (once-a-week or subdivided in two doses) (grade A) or 300 mcg darbepoetin (once-a-week) should be used (grade B) for at least 12 weeks, possibly more than 20 (grade B). During ESAs treatment iron supplementation should be considered for patients with a transferrin saturation lower than 20% (grade D).

If the patients respond to ESAs treatment, an attempt should be done to reduce the dose (or the frequency of administrations) to the lowest effective schedule able to maintain haemoglobin level between 10 and 12 g/dl (grade D).

The combination of ESAs and G-CSF should be considered only for not heavily (less than 2 U per month) red-cell transfusion-dependent patients with serum erythropoietin levels <500 mIU/ml and not responding to ESAs alone (grade C).

Daily use of G-CSF to modify disease course is not recommended (grade B).

The use of G-CSF in severely neutropenic patients with documented infection is not recommended routinely, but must be decided on a case-to-case basis (grade D).

3.9. Which patients are candidates to receive iron chelation therapy?

Low-INT1 MDS patients often receive regular red blood cell transfusion. Iron overload secondary to transfusion may lead to organ damage in these MDS patients [118]. Sanz and colleagues recently confirmed what previously reported by Malcovati et al. [8], namely that transfusion-dependency and elevated ferritin levels (possible indicators of transfusion-related iron overload) are both, independently, strongly associated with poorer OS and with AML transformation [10]. Moreover, transfusion-dependency and secondary iron overload are associated with a higher risk of cardiac complications [119], although detectable liver iron precedes cardiac iron deposition [120]. Finally, high ferritin predicts a higher transplant-related mortality and shorter survival post-transplant [121], and same poorer prognosis is observed in HCT recipient with relevant transfusion requirements [122].

Body iron content cannot be adequately assessed by serum ferritin, since inflammation and liver disease disproportionately elevate this circulating protein. Transferrin saturation is also of no value, since an isolated reticuloendothelial iron overload is associated with a normal saturation. According to SIE practice guidelines for the management of iron overload in thalassemic syndromes [123], the recommended non-invasive quantitative techniques to assess hepatic and cardiac iron content are R2 MRI and T2*MRI, respectively. T2*MRI has already been used to quantify heart and liver iron in transfusion-dependent MDS patients [120]. Serum ferritin may provide together with other parameters, a useful tool for dynamically monitoring iron status during iron chelation therapy [123].

Iron chelation therapy is aimed at preventing organ damage due to transfusional iron overload. Iron overload may be a concrete risk in MDS patients with longer life expectancy, such as pure erythroid cell dysplasia. Although still matter of debate, several guidelines and consensus conferences on iron chelation have been published and recommend to start such therapy in all MDS patients with low- and INT1 risk disease, life expectancy >1 year, who have received at least 20–30 red blood cell units and/or who show elevated serum ferritin levels (>1000 mcg/l) [124,125]. Suggestion of survival advantage for chelated MDS patients has been shown in two recent studies [126,127].

Iron chelation therapy has been disregarded in the past in MDS patients, because of the severity of the disease which rendered avoidance of organ damage by excess iron a superfluous measure and because of the subcutaneous route of administration of deferoxamine, which rendered therapy quite difficult in elderly and thrombocytopenic patients. Iron chelation has been neglected thus in reason of the short survival and lack of treatments in the majority of MDS patients. Quite recently, the oral iron chelator deferasirox has shown dose-dependent efficacy. In a multicentre trial, 341 MDS patients received deferasirox at a starting dose of 20 mg/kg/day obtaining a significant reduction in serum ferritin and improvement in quality of life [128–130]. A significant reduction of serum ferritin and liver iron content in MDS patients were reported also by other authors [131–133]. Deferasirox is effective in MDS patients; however, a proportion of patients in all studies discontinued therapy because of gastrointestinal and renal side effects. Although creatinine clearance increase of transient duration may be observed, a dose reduction (10 mg per kg body weight) is absolutely required in patients with renal failure [130]. Compared to the other chelators, namely deferoxamine and deferiprone, the Panel thought that deferasirox could be more widely administered to MDS patient population. In fact, its oral formulation allows treatment of severe thrombocytopenic patients and of elderly patients with reduced compliance. In these patients, however, special attention should be used for renal function. As deferiprone was reported to induce neutropenia in thalassemic patients, it is not an option for cytopenic MDS patients. In few optimally chelated MDS patients, an improvement in erythropoiesis was observed [134].

3.9.1. Recommendations

Iron chelation therapy is recommended in all patients with low- and INT1 IPSS risk disease who receive regular red-cell transfusion therapy; therapy should be started after the patients have received 20 packed red blood cell units (i.e. 4 g of iron) (grade B).

Iron chelation therapy should be considered for transfusion-dependent patients with INT2- and high-IPSS risk disease when they are responding to therapies able to modify their life expectancy or have a HSCT in their therapeutic program (grade D). Inception of iron chelation therapy should not be decided uniquely on the basis of the level of serum ferritin (grade D).

Due to proven efficacy, oral administration and favourable pharmacokinetics, deferasirox is the first-choice iron chelation therapy in MDS (grade B).

In patients timely starting iron chelation, the initial dosage of deferasirox should be low, i.e. 10 mg/kg. Deferasirox dosage should be adjusted according to the transfusional regimen, serum ferritin and iron-induced organ damage up to 20–30 mg/kg, if tolerated (grade C).

Patients with contraindications or intolerance to deferasirox therapy should be treated with deferoxamine. Subcutaneous administration of deferoxamine over 8–10 h daily is recommended.

Serum ferritin should be used as a routine monitoring measurement (grade C).

In case of confirmed increasing serum ferritin levels during iron chelation therapy, a quantitative measurement of hepatic and cardiovascular iron overload should be performed (grade D).

In polytransfused patients with an undetermined or unreliable history of transfusions and chelation therapy, a quantitative assessment of liver and heart iron overload should be performed by R2 MRI or liver biopsy and T2*MRI, respectively (grade D).

3.10. Therapeutic strategies in childhood

MDS account for less than 5% of all haematological malignancies of paediatric patients [134]. Childhood MDS include both variants shared with the adult population (i.e. RAEB) and other disorders more typical of the paediatric age, such as juvenile myelomonocytic leukaemia (JMML), which is classified within the mixed myelodysplastic/myeloproliferative disorders [134,135] RAEB-t still remains an accepted variant of childhood MDS [135].

JMML predominates in infants, median age at diagnosis being 2 years [136]. Hypersensitivity to GM-CSF and pathological activation of the RAS-RAF-MAP (mitogen-activated protein) kinase signalling pathway play an important role in the pathophysiology of JMML. Indeed, over 70% of children with JMML have mutations in the NFI, RAS, or PTPN11 genes, which encode proteins that are involved in RAS signalling [137].

Childhood MDS other than JMML often occur in the context of congenital bone marrow failure syndromes, this fact representing a peculiarity of myelodysplasia of the paediatric age [135] The most frequent variant of childhood MDS is represented by RC, a disorder often characterized in children by a reduced marrow cellularity rather than by a hypercellular bone marrow [138]. The IPSS grading system proved not to be useful for predicting outcome in childhood MDS [139]. Monosomy 7 is the most common chromosome aberration in childhood MDS [138–141]. Some studies showed that the cumulative incidence of progression from RC to
more advanced variants was significantly higher and survival was significantly poorer for patients with monosomy 7 than for patients with other chromosome aberrations or patients with normal karyotypes [138,140,141]. The impact of this cytogenetic abnormality on survival after HSCT is more controversial, as in some reports it was found not to influence patient’s outcome [138,142].

3.10.1.1. JMML

Allogeneic HSCT is the only curative approach for children with JMML, resulting in long-term survival in a significant proportion of patients given the allograft [143–146]. In the most recent study, which included the largest number of patients with JMML given allogeneic HSCT from either a histocompatible relative or from an HLA-matched/1-antigen disparate donor, the probability of LFS was in the order of 50% [145]. In multivariate analysis, age greater than 4 years and female sex predicted poorer outcome [145]. Available evidence indicates that, in more recent years, the use of an unrelated volunteer as donor offers minimal or possibly no significant disadvantage as compared to employing an HLA-identical sibling. Unrelated cord blood transplant (UCBT) is a suitable option for children with JMML lacking an HLA-compatible relative; the search for an unrelated CB unit should therefore be initiated at the same time as that for an unrelated BM donor [145].

Leukemia recurrence represents the main cause of treatment failure in children with JMML given HSCT, relapse rate being as high as 50% [144]. In patients with JMML harbouring the most common RAS pathway mutations (namely mutations of RAS or PTPN11), re-growth/expansion of leukaemia cells after the allograft can now be monitored in peripheral blood using an allele-specific minimal residual disease assay, this permitting therapeutic decisions aimed at preventing the occurrence of overt haematological recurrence [147]. For children with JMML experiencing leukemia relapse after allogeneic HSCT, donor leukocyte infusion proved to be largely ineffective [148], whereas a second allograft, from either the same or a different donor, together with reduction of the intensity of GVHD prophylaxis aimed at optimizing the GVL effect, is able to cure about one third of the patients [149].

Preparative regimens without TBI are particularly attractive for children with JMML since radiation-induced late effects, such as severe growth retardation, cataracts, hypothyroidism and neuropsychological sequelae may be especially deleterious for very young children. Moreover, in a retrospective analysis of the EWOG-MDS, busulfan-based myeloablative therapy offered a greater anti-leukemic efficacy than TBI [143]. Splenectomy before HSCT, as well as spleen size at time of the allograft, did not appear to have an impact on the post-transplantation outcome of children with JMML. Available data are not in favour of an indiscriminate use of splenectomy before transplantation, the potential advantages having to be weighed against the risks related to the procedure or to post-splenectomy infections [143,145].

3.10.1.2. RC, RAEB and RAEB-t

HSCT from either a related or an unrelated HLA-matched donor is routinely offered to all children with RAEB and RAEB-t, to paediatric patients with MDS secondary to chemo-radiotherapy, and to those with RC associated with poor-risk cytogenetic anomalies (namely monosomy 7 or complex karyotype) or transfusion-dependence or severe neutropenia [138,140–150]. Results on HSCT in children with advanced MDS other than JMML are scanty, the reported disease-free survival (DFS) being in the order of 60% when the donor is an HLA identical sibling [151]. Inferior results have been reported in a study for children with RAEB-t [152]. The outcome of children with MDS secondary to previous cytotoxic or radiation treatment remains particularly dismal, for both a high risk of disease recurrence and TRM, EFS probability at 3 years being below 20% [153].

The need for pre-HSCT remission induction chemotherapy remains a debated question in paediatric patients with RAEB and RAEB-t. In fact, whether cytoreductive therapy prior to HSCT for more advanced forms of MDS improves survival remains controversial. A study published by the Nordic Paediatric Haematology group, comparing the outcome of children with de novo MDS (including JMML) and children with de novo AML, documented that patients belonging to the former group had a lower rate of complete remission and a higher risk of death for treatment-related complications [154,155]. In an EWOG-MDS analysis on children with MDS other than JMML, the outcome of patients given intensive chemotherapy prior to the allograft was found to be comparable to that of children who were transplanted directly [156].

Patients with RC must be considered for an early allograft from either a related or an unrelated donor if they have cytogenetic abnormalities, in particular monosomy 7. In fact, in children with RC, it has been clearly demonstrated that the probability of progression to more advanced MDS (i.e. RAEB and RAEB-t), as well as to frank AML, is significantly higher in patients with monosomy 7 than in those with a normal karyotype [137–138]. Moreover, this study also showed that patients who had not progressed to advanced MDS prior to HSCT had a significantly better probability of survival than patients who experienced disease progression [137]. In the presence of a normal karyotype, a substantial proportion of children with RC may experience a long, stable course of their disease without any treatment. In view of the low TRM observed in patients transplanted from an HLA-compatible sibling, HSCT may be recommended if a suitable HLA-matched relative is available. A “watch and wait” approach with careful observation may be reasonable for children with RC lacking a compatible sibling in the absence of poor-risk cytogenetic anomalies, transfusion requirements, severe cytopenia or infections.

Since the risk of disease recurrence after the allograft in patients with RC is low, there is great interest in testing the safety and efficacy of reduced intensity regimens in this setting. In a recent EWOG-MDS report, patients with RC and normal karyotype transplanted from an unrelated donor following a fludarabine-based reduced-intensity regimen had a favourable post-transplant outcome, the overall and event-free survival at 3 years being 84% and 74%, respectively [156].

Immunosuppressive therapy may represent a treatment option for children with RC and normal karyotype or trisomy 8. A recent study reported 31 children with hypoplastic RC treated with immunosuppressive therapy including ATG and CycA [157]. At 6 months, 22 of 29 evaluable patients had a complete or partial response; 10 patients achieved complete response at varying time points. Six patients subsequently were given allogeneic HSCT because of non-response, progression to advanced MDS or evolution of monosomy 7. Three-year overall and failure-free survival rates were 88% and 57%, respectively [157].

3.10.2. Recommendations

HLA typing is recommended in all children with a diagnosis of MDS (grade C).

Myeloablative allogeneic HSCT from either a related or an unrelated volunteer is recommended to be performed as soon as possible in all children with JMML (grade C).

For children with JMML without an HLA-identical sibling the search for locating either an unrelated bone marrow donor or a suitable cord blood unit should start simultaneously (grade C).

Busulfan-based myeloablative therapy has to be preferred in children with JMML (grade C).

Monitoring of minimal residual disease through chimerism evaluation or an allele-specific assay in patients harbouroing the most common RAS pathway mutations (i.e. mutations of RAS or PTPN11) is recommended in all children with JMML in order to...
take clinical decisions, such as discontinuation of post-transplant immune-suppressive therapy, aimed at preventing overt relapse (grade C).

There are no data supporting a routine use of splenectomy before HSCT in children with JMML.

A second allograft from either the same donor or an alternative donor is the treatment of choice for children with JMML relapsing after a first HSCT (grade C). By contrast, DLI is not recommended in children with JMML relapsing after a first HSCT (grade C).

Allogeneic HSCT from an HLA-identical sibling is an acceptable therapeutic option in all children with a confirmed diagnosis of either primary or secondary RC, RAEB and RAEB-t (grade C).

Children with RC must be considered for an early allograft from an unrelated donor if they have monosomy 7 or a complex karyotype (grade C).

Children with RAEB, RAEB-t, therapy-related MDS should be offered an early allograft from an unrelated volunteer (grade C).

Allogeneic HSCT from alternative donors (i.e. mismatched-relative, mismatched unrelated cord blood unit) should be performed by centres with an active program in the field, in paediatric patients affected by RAEB, RAEB-t, therapy-related MDS or by RC associated with monosomy 7 or complex karyotype without a matched (related or unrelated) donor (grade C).

There are no data firmly supporting the routine use of pre-HSCT remission induction chemotherapy in paediatric patients with RAEB and RAEB-t.

Reduced intensity regimens can be employed before the allograft in children with RC not carrying monosomy 7 or complex karyotype (grade C).

Immunosuppressive therapy including ATG and CysA represents a possible treatment option for children with RC and normal karyotype or trisomy 8 (grade C).

A “watch and wait” approach is a reasonable option for children with RC in the absence of poor-risk cytogenetic anomalies, transfusion requirements, severe cytopenia or infections (grade D).

4. Discussion

The present updating of the Italian Guidelines for management of MDS has been prompted by the fact that in the last years a rapid and significant change in the therapeutic approach has occurred. More than other haematological neoplasias, MDS have experienced a renewed interest on the basis of clinical progresses. In recent years, low-toxicity and effective agents have become available, extending the portion of MDS patients eligible to be actively treated. In INT2- and high-risk MDS patients therapies modifying the natural history of the disease and delaying progression to AML have been identified, but also supportive care has significantly improved. Superior outcomes observed in the entire MDS population compel haematologists to dedicate more attention and to articulate better the diagnosis, in order to define optimally the treatment for MDS patients, independently from age. In fact, specific cytogenetic and prognostic subgroups have been re-defined, which allow a better tailoring of therapeutic strategies. This is evident for 5q- syndrome, and for -7/del7q MDS patients, for whom prognostic has been modified by the susceptibility to lenalidomide and hypomethylating agents, respectively.

Although several randomized trials are still ongoing, and could therefore further modify some of the perspectives in MDS therapy, the Panel judged that SIE guidelines were to be updated rapidly, in order to address the need of haematologists to have a reasoned approach to novel treatments based on evidence. The Panel feels that the medical attitude towards MDS patients should be modified radically: the knowledge of new therapies has to come in parallel with the awareness of the relevance and quality of responses among MDS and thus in the modality of treatment. In MDS it has in fact become clear that non-curative therapies like erythropoetin, hypomethylating agents and lenalidomide can, at any term, prolong survival, independently in some cases from achievement of complete responses. It has also been learned that such therapies must be maintained for a prolonged period of time to sustain haematological response, with the consequence of a “chronic” MDS. On the other hand, prolongation of survival and improvement of clinical outcome creates a wider bridge to transplant. The availability of RIC regimes and their applicability also to older MDS patients broaden the horizon for this population. These notions render MDS a quiet different disease to treat respect to AML.

Several recommendations presented in these SIE Guidelines for first-line therapy were updated based on solid clinical evidence with the aim of improving the quality of care for MDS patients in all clinical settings, included the non-specialist, smaller hospitals caring for most of the elderly MDS patients.

A new, rising issue is the pharmacoeconomic evaluation of the costs of caring for a growing, “chronized” MDS patient population. The economic impact of diagnostic and therapeutic changes is difficult to forecast, since scarce information are available on the economic burden of MDS. Moreover, the complete acceptance by the haematological community and the consequent adoption rate of novel drugs depends on several factors, included the diffusion of clinical practice guidelines. The therapeutic options introduced by the present updated guidelines, however, are recommended irrespectively of a formal economic evaluation, but are driven only by the evaluation of evidence of clinical improvements demonstrated.

When these updated recommendations of the Italian Society of Hematology were conceived and drafted, the 2009 update of the National Comprehensive Cancer Network (NCCN) guidelines was not yet published [158]. The here presented Italian guidelines address only some specific clinical questions and are therefore differently structured, not generating exhaustive indications for all possible MDS treatments. Notwithstanding this observation, produced recommendations are remarkably consistent. In particular, the indications for diagnostic and prognostic evaluation, for high-dose ESA treatment, for lenalidomide in 5q-, for immunosuppressive treatment and for HSCT are identical, and overcome broad discussions raised lately in the hematological community.

Iron chelation is recommended for the same group of MDS patients both in our guidelines and in NCCN ones, but in the present paper deferasirox is considered the first choice drug, while ferritin measurement is not a decisive parameter to start chelation, but a marker of efficacy in the follow up of therapy. High-dose chemotherapy, quite notably, is in both guidelines a treatment with marginal applications. The Italian Panel deemed important to give separate recommendations for paediatric patients.

Overall, it is quite noteworthy that two independent Panels of expert hematologists would conclude for exactly the same indications for treatment of MDS, irrespective of official drug approval, based only on data and evidence.

Because of the nature of the Panel work, only therapies for which there was novel evidence were discussed and updated. Low-dose cytosine arabinoside, as well as autologous stem cell transplant were not thoroughly discussed for these reasons. The Panel did not dedicate a chapter to new drugs and perspectives, again because it is not in keeping with the aim of Guidelines. Nevertheless, the Panel judges that some MDS patients who demonstrated resistant to several line of treatments and who are compliant, could be enrolled in investigational controlled trials performed in specialized haematological centres. Several new agents are under investigational evaluation for MDS. First of all, histone deacetylase inhibitors (HDACi); HDACi are promising agents, and their use in therapy of MDS is based on their epigenetic role, in modifying chromatin rearrangement due to histone deacetylation, frequently
associated with DNA methylation. Hundreds of new HDACi compounds are in the pipeline of pharmaceutical companies. Until now, few have demonstrated some activity and scarce toxicity as single drugs in MDS patients. There is no evidence, in fact, that valproic acid (VPA), which is the HDAC1 most easily available in Europe, although off label, may be recommended in MDS patients outside clinical trials. Several studies have demonstrated that VPA is relatively safe, but fail to demonstrate any additional activity when used in combination with AZA or DAC, at least at doses without major neurological side effects [159–161]. The potential benefit of HDACi, belonging to different classes, like SNX-D725 [162], both alone and in combination with hypomethylating agents has to be further evaluated in clinical trials. Vorinostat, a carboxylic acid HDACi which blocks classes I and II HDAC, and approved by FDA for cutaneous T cell lymphomas, has demonstrated single agent activity in patients with MDS and AML [163]. Most recent results [164] indicate that its association with AZA yields 83% rapid (2 cycles) responses in MDS/AML patients.

Clinical trials with combination of hypomethylating agents with other drugs which were demonstrated partially active in MDS indicate that its association with AZA yields 83% rapid (2 cycles) responses in MDS/AML patients.

Conflict of interest

VS, EA, EM, PM, GV, ST received honoraria from Celgene and Novartis.

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